Cardiovascular Response to Thermoregulatory Challenges

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ABSTRACT

A growing number of extreme climate events are occurring in the setting of on-going climate change, with an increase in both the intensity and frequency. It has been shown that ambient temperature challenges have a direct and highly varied impact on cardiovascular health. With a rapidly growing number of literatures on this issue, we aim to review the recent publications regarding the impact of cold and heat on human populations with regards to cardiovascular diseases (CVD) mortality/morbidity while also examining lag effects, vulnerable subgroups and relevant mechanisms. Although the relative risk of morbidity/mortality associated with extreme temperature varied greatly across different studies, both cold and hot temperatures were associated with a positive mean excess of cardiovascular deaths or hospital admissions. Cause-specific study of CVD morbidity/mortality indicated that the sensitivity to temperature was disease-specific, with different patterns for acute and chronic ischemic heart disease. Vulnerability to temperature-related mortality was associated with some characteristics of the populations, including gender, age, location, socioeconomic condition and comorbidities such as cardiac diseases, kidney diseases, diabetes and hypertension. Temperature-induced damage is thought to be related to enhanced sympathetic reactivity followed by activation of the sympathetic nervous system, rennin-angiotensin system, as well as dehydration and a systemic inflammatory response. Future research should focus on multidisciplinary adaptation strategies that incorporate epidemiology, climatology, indoor/building environments, energy usage, labor legislative perfection and human thermal comfort models. Studies on the underlying mechanism by which temperature challenge induces pathophysiological response and CVD await profound and lasting investigation.
Key words: cardiovascular, cold, heat, vulnerability, mechanism
In view of the global climate change there has been a violent change in the frequency, intensity, and duration of extreme climate events such as heat waves and cold spells. Furthermore, global average surface temperature has risen at an average rate of 0.15°F per decade since 1901 in response to the increased concentrations of heat-trapping greenhouse gases in the Earth's atmosphere, with the United States having warmed faster than the global rate (1). The mortality or morbidity induced by the extreme climates is not necessarily caused directly by hypothermia or hyperthermia, but by other indirect causes such as respiratory diseases and cardiovascular disorders that are triggered when human body attempts to adapt to the excessive environment (44). Recently, special attention has been drawn by the temperature
effects on cardiovascular response. Undeniably, these endeavor is vital for planning before the occurrence of extreme heat or cold event to effectively reduce the mortality/morbidity induced by the climate variation. In this review, the recent evidence on the impact of temperature change on the cardiovascular diseases (CVD) and the relevant mechanisms were summarized.

Search Strategy

To review all studies directly describing the cardiovascular responses both in human and in animals, we used the keywords “cardiovascular” and “cold” with limiting the search to title and/or abstract for the literature about effects of cold, and used the keywords “cardiovascular” and “hot” with limiting the search to title and/or abstract for the literature about effects of hot. The initial search generated 1509 results and 801 results respectively. So, we limited the publications within 5 years and then afterwards selected the articles based on our aims from the 435 results and 265 results. To be included in the review, the articles had to be published on peer-reviewed journals in English. A total of 89 research articles and 3 website references were finally included in the review.

COLD TEMPERATURE AND CVD MORTALITY

The impact of temperature variations on human health in the context of systemic diseases has garnered a great amount of concern. Epidemiological studies have shown an association between cold (temperature) and adverse cardiovascular effects since the 1940s. In general, mortality is usually lowest around a certain temperature and will increase at lower or higher
temperatures. In other words, the association curve between temperature and CVD mortality is U-, V-, or J-shaped (35, 37, 38, 55, 79) (Figure 1). The relationship between temperature variation and hospital admission or mortality of CVD varies by location, climate, and socioeconomic status. Five years ago, most previous studies were conducted in developed countries such as the United States and European nations. Recently, new studies are emerging with thorough investigations in the cities of developing countries such as Vietnam (31), Thailand (36), and particularly China (35, 85, 92).

**Effects of cold on CVD mortality**

Various definitions of cold spell have appeared in the literature as a descriptor of extreme cold events (44, 61, 92). In the Czech Republic, a study was conducted in which cold spells were defined as periods of days during which air temperature does not exceed -3.5°C. The association between cardiovascular mortality and winter cold spells was evaluated in the population of the Czech Republic over a 21-year period from 1986–2006. Cold spells were associated with positive mean excess CVD mortality in all age groups (25–59, 60–69, 70–79 and 80+ years) in both men and women (44). A study was conducted in Italy in which cold spell episodes (happened in February 2012) were defined as days when mean temperatures were below the 10th percentile of February’s normal distribution for greater than three days. With the mortality data from a national mortality surveillance system, an overall 1578 (+25%) excess deaths, including 20% of CVD, 14% of ischemic heart disease (IHD) and 33% of other heart disease, among the 75+ age group was recorded in the 14 cities that registered a cold spell in February 2012 (23). Taken together, cold spell was positively associated with increased CVD
mortality in the developed countries.

This association linking cold spell and mortality of CVD was also studied in the developing countries, especially in China. The 2008 cold spell of South China, characterized by lower than normal temperatures, heavy precipitation and thick snow deposition, was widely considered to be the most extreme cold spell of the past five decades in China (99). Thus, it provided a unique opportunity to estimate the effect of cold on mortality in subtropical regions. In a study conducted in Guangdong, the southernmost province of China, three representative cities were selected; the northernmost city of Nanxiong, the centrally located city of Guangzhou and the southern coastal city of Taishan. For this study a cold spell was defined as occurring when the minimum daily temperature fell below the 5th percentile of temperatures recorded at that location from January 2006 through December 2009 for at least 5 consecutive days. The investigation showed 66.2%, 66.5%, and 39.7% more deaths than the average for the corresponding days of the three adjacent years in the three cities, respectively (92). In another study conducted from 2006 to 2010 in thirty-six communities across 4 geographical regions (eastern, central, southern and southwestern China) the average air temperature during the cold spell days was 2–4°C lower than that during the same period of neighboring years. The 2008 cold spell increased mortality from CVD by 52.9% (95% CI: 42.1%-64.5%) with the highest effects in southern and central China (99). A study conducted in Shanghai’s urban districts, defined a cold spell as a period of at least seven consecutive days with daily temperatures below the third percentile during the study period (2001–2009). Cold spells were observed to cause a statistically significant increase for cardiovascular mortality (RR-1.21,
The association of exposure to cold temperature with increasing CVD mortality was well observed in some other studies although the cold temperature was not defined as a cold spell. One study reported that the relative risk of total mortality associated with extreme cold temperature (1st percentile of temperature, −0.3 °C) over lags 0–14 days was 1.75 [95% confidence interval (CI): 1.43, 2.14]), compared with the minimum mortality temperature (26 °C) (85). Another study indicated the cumulative effect of cold-related CVD mortality was 6.6% (95% CI: 5.2%–8.2%) for 30 lag days (39). In addition, a 5°C decrease of 15-day average temperature in the cold period, was associated with a RR of 1.057 (95%CI: 1.022-1.094) for cardiovascular mortality, specifically, 1.123 (95%CI: 1.057-1.193) for mortality of IHD. The effects remained robust after considering particles as additional confounders (55). In a study conducted in 17 large cities, a 1 °C decrease from the 25th to 1st percentiles of temperature over lags 0–14 days was associated with increases of 2.49% (95%PI: 1.53%, 3.46%) in cardiovascular mortality(60). Although the magnitude of cold temperature’s cardiovascular effects varies greatly by geography or locations, the detrimental effects of cold on CVD mortality are consistent.

**Years of life lost (YLL) as a measure of CVD mortality**

YLL is a measure of disease burden. Instead of measuring relative mortality risk of all deaths
equally, both young and old people, it adopts the life expectancy at death. YLL gives more
weight to deaths among younger people and is more reasonable than the traditional measure
of mortality in all populations at different ages. The effects of temperature on YLL due to CVD
were reported to estimate the burden of temperature on CVD mortality using data from
Brisbane, Australia (38). They found that the association between temperature and YLL due to
CVD was U-shaped, with the lowest YLL at 24 °C and increased YLL attributable to cold and
hot temperatures(38). This study showed that the greatest effect of cold on YLL was not acute,
but occurred 2 days later. Understanding the lag time between temperature exposure and YLL
is important for health care providers to develop response plans for extreme temperature
events. Hence, health care providers should expect a time lag and sustained increase in
ambulance call-outs and hospital admissions during cold weather.

Effect of diurnal temperature range on CVD mortality

Diurnal temperature range refers to the difference between maximal and minimal
temperatures within 1 day, which is a meteorological indicator associated with global climate
change and urbanization. It may be a better indicator when analyzing temperature impacts on
human health. With single-day models, a 1.7% increase in CVD mortality for an increase of
1 °C in diurnal temperature range at lag 0-3 days was observed among the elderly in Hong
Kong (77). Compared to it, a distributed lag non-linear model is more flexible and biologically
plausible when quantifying individual lags, especially at short lag times. Luo et al. used a
distributed lag non-linear model to conduct a time-series study in Guangzhou, China to
examine the acute effect of diurnal temperature range on CVD mortality, and further
investigate the modification of season on the effect. Significant associations between extreme
diurnal temperature range (both extreme low and high diurnal temperature range) and
mortality were observed in both hot and cold seasons, which further indicated that extreme
diurnal temperature range was a risk factor for daily mortality regardless of season (59). In
particular, the effects on cardiac failure were most obvious, with a 3.0% (95% CI, 1.4–4.6)
increase in hospital admissions per 1 °C increment of diurnal temperature range, among 6
CVD (stroke, myocardial infarction, ischemic heart disease, cardiac failure, cardiac disease,
and arrhythmia) (51). Based on these findings, the extreme diurnal temperature range is
independent risk factor of daily mortality, besides cold or hot temperature per se. The
physiological adaptation and regulation may fall behind the huge temperature difference in a
short time, making the body in disorder and contributing to the CVD mortality.

**Cause-specific analysis of CVD mortality**

Specifically, the mortality impact of cold spells was more pronounced for acute myocardial
infarction (MI) than chronic IHD. Cardiovascular changes induced by cold stress may result in
death from acute coronary events rather than chronic IHD (22). When evaluating the mean
excess mortality for CVD including IHD, cerebrovascular disease, MI, and chronic IHD in the
population as a whole, only MI exceeded the expected level significantly in a study conducted
in the Czech Republic (southern Bohemia) (80). In a study of 99 US cities lasting 14 years
(1987 - 2000), there was no added cold wave effect on average that went beyond the known
increased risk of cold temperatures. Notably, evidence of reduction in daily death during the
most extreme cold waves was also found(9). This might be due to the fact that people took
better protective measures under extreme cold situation, such as avoiding work outside,

staying at home and clothing behavior. Table 1 depicts selected investigations of cold
temperature and CVD mortality.
COLD TEMPERATURE AND CVD MORBIDITY

Effect of cold on CVD morbidity

Although the impact of temperature on mortality is well documented, relatively few studies have evaluated the associations of temperature with morbidity outcomes such as hospital admissions. In Vietnam, Giang et al examined the effect of cold during the years 2008 to 2012 on elderly CVD hospital admission and showed that the average point of minimum CVD admissions was at 26°C. Below this threshold, the cumulative CVD admission risk over 30 lag days tended to increase with lower temperatures. The cumulative effect of cold exposure on CVD admission was statistically significant with a relative risk of 1.12 (95% confidence interval: 1.01-1.25) for 1 °C decrease below the threshold (31). In Hong Kong, the CVD admission was reported to be increased during cold temperatures, i.e., for every decrease of 1 °C within the 8.2-26.9 °C range, CVD admission- rose by 2.1% (18). Interestingly, the effects of temperature drop on total MI incidence were more pronounced in those years with higher average temperatures and were especially visible in the summer (88). It is suggested what really may be concerning is not a pure "cold effect" but the impact of unusual temperature decreases. Because peoples are already acclimated the “consistent temperature” in the certain season, they failed to physiologically adapt to the sudden, sharp temperature fluctuation, thus making the body in disorder.

Cause-specific analysis of CVD morbidity

The relationship between weather variables and the incidence of acute cardiovascular events, such as type A acute aortic dissection, acute MI, and acute presentation of abdominal aortic
aneurysms, has been examined. Two hundred and six patients suffered an acute aortic
dissection and underwent surgery during the years 1997 and 2007 at Toulouse University
Hospital, France. By reviewing the medical records of patients and the meteorological data
over the same period, analysis results demonstrated a decrease in ambient temperature
during the three days preceding the onset of symptoms (P=0.0009) and highlighted an inverse
association between spontaneous acute aortic dissection and low ambient temperature(11). In
regards to acute MI, Bhaskaran K et al. reviewed some relevant data from the winter season
and reported a statistically significant short-term increased risk of MI at lower temperatures(12).
Subsequently, Wolf K et al observed an inverse relationship between cold temperature and MI
occurrence in Germany. Looking closer at the total number of MI cases, including nonfatal and
fatal events, a 1°C decrease in 5-day average temperature was associated with a relative risk
of 1.10 (95% confidence interval, 1.04-1.15) (88). Finally, in a study conducted in Portugal,
Poisson regression analysis based on generalized additive models was applied to estimate the
influence of a human-biometeorological index on daily hospitalizations for MI. The results
revealed that for every degree fall during winter, there was an increase of up to 2.2% (95% CI
= 0.9%; 3.3%) in daily hospital admission (82). This influence of atmospheric temperature on
the CVD incidence may be due to the cold-enhanced sympathetic activity and circulation
regulation, which will be discussed in details in the “MECHANISTIC INSIGHTS INTO
TEMPERATURE CHALLENGE AND CVD” section.

Most of the studies only examined the effects of local weather on different cardiovascular
events in different populations. However, a survey in the Netherlands taken between 1998 and
2010 looked at the incidence of all three events in the same population in one topographic region with minimal differences in demographic profiles. During the study period, a total of 11,412 patients were admitted with acute MI, 212 patients with acute aortic dissection and 1,593 patients with abdominal aortic aneurysms. Although no significant correlation was found with the onset of abdominal aortic aneurysms, a significant correlation was found between the daily temperature and number of hospital admissions for both acute aortic dissection (p0.002) and acute MI (p0.02) (83). Given that all climate factors interact with each other and traditional epidemiological methods may not provide a sufficient explanation, Shiue et al proposed using a thermal index adopted from a biometeorological concept. Universal Thermal Climate Index or Physiologically Equivalent Temperature incorporates epidemiological, geographical and meteorological methods to better quantify the weather and to assess the effect of cold stress. They observed 5-6 more admissions per day for IHD and 8 more for hypertension during the cold stress days compared to acceptable weather conditions. Although the difference was not statistically significant, a higher number of stroke, MI, and total cerebrovascular disease admissions were also seen during the cold stress days (74). Table 2 depicts select investigations of the correlation of cold temperature to emergency room (ER) visits, hospital admission or CVD morbidity.
HOT TEMPERATURE AND CVD MORTALITY

Effect of heat on CVD mortality

Similar to cold spell, heat wave/hot spell was described variously with local definitions, characterized by daily temperatures over several consecutive days above an extreme temperature threshold or percentile. In North America, Barnett et al. examined the effect of heat waves in 99 US cities over 14 years (1987–2000), investigating the risk of death from cardiovascular issues and the relationship to temperature thresholds. Heat waves were defined as temperatures above heat thresholds for two or more days with a range of heat thresholds by using the 95–99 percentiles of temperature in each city. Heat waves generally increased the risk of death by 1.6%. Notably, the increase in deaths during heat waves was much greater for cardiovascular mortality rather than respiratory mortality at the two hottest thresholds (9). In the Czech Republic, for the population (regardless of ages or genders) as a whole, IHD mortality increased markedly from day D+1 to D+4 in response to hot spells, with a peak on D+2 (22). In this study, hot spell was defined as periods of at least two consecutive days with anomalies of average daily temperature from the mean annual cycle about the 90% quantile. Furthermore, the patterns for acute and chronic IHD were analyzed. A sharp increase in the mortality due to chronic IHD was noticed on the first day after the onset of a hot spell (excess mortality about 15% on D+1), followed by high excess mortality persisted for 5 days, nevertheless, significant excess mortality from acute MI was only observed on a single day of (D+2 with much lower increase (excess mortality about 8%) compared to chronic IHD mortality (22). A as long as seven consecutive days was used to define heat waves in a study on daily mortality between 2005 and 2008 in Suzhou, China, with daily maximum temperature above
The relative risk of 1.43 (95% CI: 1.31, 1.56) was shown to be associated with extremely hot temperature (99th percentile of temperature, 32.6 °C) over lags 0–3 days (85). Although different definitions may result in considerable difference in associations between heat and mortality, these findings consistently demonstrated the cardiovascular impact of heat waves,

Since the impact of heat on health may vary on how heat waves/hot spell are defined, D’Ippoliti et al compared the impact of heat waves (in summer, 2003) on mortality in different cities using a common heat wave definition, which defined as periods of at least two days with maximum apparent temperature exceeding the 90th percentile of the monthly distribution, or periods of at least two days in which minimum temperature exceeds the 90th percentile and the maximum apparent temperature exceeds the median monthly value (21). During the heat wave days a significant increase in daily CVD mortality was observed in all 9 European cities, with highest mortality of 39.2% in Milan (90% CI, 31.2-43.3), lowest mortality of 8.2% in Munich (90% CI, 2.8-13.9) (21). It is surprising that the greatest impact on mortality was observed in North-Continental cities but not in the Mediterranean cities. Since heat episodes are rare events and the temperatures were outside the usual meteorological conditions in the North-Continental cities, the poor ability to adapt to the unusual high temperatures may help to explain the greater impacts.

The association between ambient temperature and mortality was also assessed when hot temperature was not defined as heat waves or hot spell. Recent studies in Europe mostly focusing on cardiovascular mortality have documented heat-related excess deaths in large
cities (7, 21) as well as less urbanized regions such as England and Wales (30)). Consistently, a 5 °C increase of two-day average temperature was associated with a RR of 1.098 (95% confidence interval (95%CI): 1.057-1.140) for CVD mortality in Beijing (55), a 1 °C increase from the 75th to 99th percentiles of temperature was associated with corresponding increases of 3.02% (95%PI:1.33%,4.71%) in 17 large Chinese cities (60). Of particular interest was that the harvesting effect was observed in the heat effect, that is, an initial increase in mortality followed by a period of lower than average mortality. It can be interpreted as an early occurrence of deaths that would have happened in subsequent days regardless of the weather changes (60). Since the largest increases were for the most extreme hot temperatures (9), the public health burden of these extreme heat is very likely to increase with the rising global temperature. Considering getting relief from hot weather would be more difficult with least clothing layer and limited air conditioning in the developing countries, these findings may be useful for local government to develop intervention strategies to protect vulnerable subgroups, especially in under-developed regions.

**YLL as a measure of CVD mortality**

The association between temperature and YLL due to CVD was shown to be U-shaped, with increased YLL attributable to cold and hot temperatures. Added effect implies that an extra risk arises when the exposure to extreme temperature is sustained for more than 2 days.

Significant added effects of heat waves were also observed, with between 85 and 264 YLL per day depending on the severity of heat waves (38). However, there was no added effect of cold spells. It might be that people took better protective actions during prolonged cold weather.
The greatest effect of heat occurred on the day of exposure (38). Hence, health care providers should expect an immediate increase in ambulance call-outs and hospital admissions during hot weather. Table 3 depicts selected investigations of hot temperature and CVD mortality.

HOT TEMPERATURE AND CVD MORBIDITY

So far, little research examined the effects of heat on CVD morbidity and non-fatal health outcomes, although several studies have been conducted specifically to examine the relationship between ambient temperature and ambulance attendances. In Sydney, Australia, there was a statistically significant increase in the odds ratios of hospital admissions for several diseases, including CVD, respiratory diseases and dehydration et al. on hot days (95th percentile), with the largest number of hospital admissions due to CVD (38%) (81). A study from another city in Brisbane, Australia found that the exposure response relationship for cardiovascular attendances was described by a ‘V’ shape with a threshold temperature (of minimum attendance count) of 22 °C through the use of a distributed lag non-linear model with a linear threshold model for temperature (79). Consistently, the overall heat effect for CVD hospitalization or dispatches was observed in Korea (75), New York city, USA (54), Sydney, Australia (81), and a multicity analysis in Italy (4).

The sensitivity to ambient temperature may be disease-specific since the investigation of specific cardiovascular subsets showed the most frequent admissions of IHD (35%) and the least frequent of acute rheumatic fever (0.02%). In addition, when CVD as a collective group was analyzed, significantly higher admissions occurred on the third day after a hot day (95th
percentile) (81). When specific CVD was analyzed, admissions due to “other diseases of the circulatory system” were significantly higher one day after, and the admissions due to “other forms of heart disease” and “diseases of veins and lymphatics” occurred three days after a hot day. Different from some previous studies, which reported increases in IHD and in acute MI (69), no evidence of higher admissions due to any CVD subcategory was observed on the day of the extreme heat event (81). The authors explained that overall admissions in all ages may mask the increase in admissions in special populations such as the elderly (81). Future analysis of CVD admissions focusing on the elderly may help clarify this issue. Table 4 depicts selected investigations of hot temperature and ER visits, hospital admission or CVD morbidity.

LAG EFFECTS AND HARVESTING EFFECTS

Analysis of the lag effect of temperature has been pretty consistent. Most results showed the effects of heat were relatively immediate while the effects of cold became predominant with longer time lags. The lag effect for heat-related CVD mortality was just 0–3 days, whereas cold effects were found to be delayed, generally occurring 2-3 days following the exposure and within 10–25 lag days (8, 35, 38, 39, 55, 79, 85, 96). However, both hot and cold temperatures resulted in an immediate increase in all mortality types and age groups, which showed non-linear effects of cold temperature on cardiovascular mortality and all age groups (<=64, 65–74, 75–84, and >=85 years) (36). The acute cold effects might be due to the tropic climatic pattern in Chiang Mai city as people were not accustomed to cold weather. In addition, it was found that the hot effects on all groups displayed characteristically consistent with harvesting, with a significant decrease in attendances for cardiovascular (1.85%, 95% CI 3.06% to 0.64%)
categories over lags 2-15 days (79). This may be due to the mortality displacement for non-accidental, cardiopulmonary, and cardiovascular deaths (35) which followed the immediate increases in ambulance attendance observed over the first few days of exposure (79).

The characteristic such as duration of extreme temperature within the season is taken for granted important factors which affects the temperature effects. Keeping in line with it, a two-fold higher effect of heat waves of longer duration and high intensity was shown in both North-Continental regions and Mediterranean regions (21). However, there were conflicting results on this issue. For example, it was shown the cold effect was mainly from extreme low temperatures (intensity) rather than sustained cold days during the 2008 cold spell (99). Interestingly, instead of colder intensity or longer duration, cold waves earlier in the cool season were more dangerous, as were heat waves earlier in the warm season. The authors contributed it to a build-up in the susceptible pool or a lack of preparedness for extreme temperatures (9). Actually, it was shown as early as 1998, Geor et al examined effects of exercise training under acclimated ambient conditions on protective adaptation with horses and showed that both cold acclimation and heat acclimation resulted in physiologic adaptations which include expanded plasma volume, improved efficiency of evaporative heat loss as a result of alterations in the sweating response, and greater stability of cardiovascular function during exercise, conferring improved thermoregulatory ability. Furtherly, short-term heat acclimation training not only enhanced thermoregulatory adaptations, but also cardiovascular regulation, and metabolic adaptation such as reduction in anaerobic energy
release or elevation of the anaerobic threshold(17). Thus, it is not surprising to see early cold
or early heat is more dangerous than the intensity or duration and temperature acclimation
could serve to attenuate the risk of CVD attack.

VULNERABILITY AMONG SUBGROUPS

Vulnerability to temperature-related mortality has been associated previously with some
characteristics of the populations, including gender, age, location, socioeconomic condition,
workplace exposure, regional air quality and comorbid diseases.

Gender

When it comes to cold, although no effect modification by gender has been reported (18), a
number of studies have shown that men are more vulnerable to cold then women (73, 87). For
example, in Stockholm, Sweden, mortality was associated with a decrease in temperature
particularly in men (73). The excess IHD mortality associated with cold spells was more
significant and less lagged in males compared to females(22). Consistently, the estimated
mortality at lag 0-27 was more pronounced for males than for females (RR = 1.56; 95% CI:
1.07, 2.28 vs. RR = 1.31; 95% CI: 0.85, 2.02 in Guangzhou; RR = 1.93; 95% CI: 1.14, 3.27 vs.
RR = 1.27; 95% CI: 0.71, 2.27 in Taishan) during the 2008 cold spell (92). However, others
have reported differently. In one study that took place across eastern, central, southern and
southwestern China, more pronounced effects of the 2008 cold spell were noted for females
than for males(60). Similarly, higher excess winter mortality was observed in females in
several other studies (39, 65, 75). With respect to hot temperatures, the results of gender
vulnerability were not consistent. For example, males were generally found to be more susceptible than females to heat in a study in Tibet, China (8). To the contrary, females were more sensitive to heat than males (39, 75) and the heat-related excess IHD mortality was much larger in women than in men (more than 15% excess mortality on D + 2)(22). The inconsistency among these investigations may be due to regional or population factors. For example, men are more likely to engage in outdoor jobs and activities, which may increase men’s exposure to the extreme temperatures whereas health status, mean ages, and preexisting chronic diseases or mental disorders of the subjects themselves may contribute to the greater vulnerability of females to temperature challenges. In addition, women still participate some outdoor work in some relatively poor regions may also explain the more susceptible to extreme temperatures.

Age
Greater vulnerability of the elderly to cold temperatures has been shown. For example, the most sensitive populations to cold temperatures and hospitalization for CVD were among people aged 65-75 years or older (18, 60, 65, 73, 86, 87), which is consistent with a series of studies in Sweden (87), Italy (23), Australia (96) and several regions in China including Guangdong (92, 95), Tibet (8), and Changsha (39). However, a number of studies have reported the opposite. In a study conducted in Ibaraki, Japan, risk-stratified analysis identified subjects with an age of less than 80 years as being more influenced by cold temperature (6). Similarly, in the Czech Republic, the effects of cold spells on IHD mortality were more direct and more pronounced in the younger age group (0–64 years) (22). This is consistent with
previous findings for aggregated CVD mortality showing that low temperature extremes affect cardiovascular health more markedly in the 25–59 years of age population compared to the older age groups (44). The possible explanation as to why elderly people were less influenced by cold temperature might be occupational exposure to the cold in middle-aged population, whereas the elderly tended to stay indoors during the cold spell and thus avoided direct exposure to ambient extreme temperatures.

For hot spells, the elderly and infants within the perinatal period had consistently larger increases in death associated with heat waves. For instance, the acute heat effects on CVD mortality in elderly people (65 years and older) were observed in the United States (9), Sweden (73), the Czech Republic (22), Tibet (8), and Australia (96), supporting the general perception that the elderly have long been considered physiologically susceptible to extreme climate (13). In addition, heat contributes to increased mortality in infants. It is believed that the first week of life is the most critical window of vulnerability. The effect of heat was observed on the same day and was detected only in conditions originating during the perinatal period (relative risk = 1.53 [95% confidence interval=1.16-2.02]), within which, cardiovascular disorder was one of the causes of death with stronger effects (10).

Regional and Indigenous difference

A comparison between urban and rural populations in the Czech Republic showed that MI, cerebrovascular disease, and IHD cold-related mortality were (in the population as a whole) higher in southern Bohemia (rural region) than in Prague (city region) (80). Moreover,
metropolitan regions were found to have a substantially lower mortality than rural areas after cold and heat events (20, 89). The urban–rural differences in mortality impact may be caused by environmental factors such as the urban heat island effect and generally warmer climate of Prague as well as prolonged exposure to air pollution (89). People in urban areas have a higher socioeconomic status on average in addition to more medical resources potentially giving them greater adaptive capability. Other variables that go along with socioeconomic status such as different lifestyle and population structure may also contribute to the observable differences on mortality impact.

Except for the effects of urban and rural factors on the temperature-mediated CVD mortality, the effects of extreme temperature vary appreciably from city to city. For example, it showed larger heat effects in northern cities versus southern cities in China (60). The heterogeneity may be attributable to climatic, geographic and demographic characteristics, such as a lower prevalence of air conditioning in northern cities that may have hindered the ability of local residents to adapt to heat stress. Although the inverse association of CVD deaths with cold waves is well known, the opposite association was observed during a study conducted in 99 US cities in which there was evidence of a decreased risk during the coldest waves (9). Similarly, the inverse associations between apparent temperatures and mortality from cardiovascular or cerebrovascular causes were not found in Astana, Kazakhstan—the second coldest capital in the world (33) or in the eight major cities of Korea (75). Factors that may be behind the lack of association include well-equipped heating facilities (such as centrally heated houses) and preparedness for extreme cold stemming from a culture of wearing large volumes
of winter clothes outdoors.

In addition, the Indigenous population of the northern territory, Australia, was more sensitive to temperature change than the non-Indigenous people. Specifically, among the younger population (25-64 years old), Indigenous females were more adversely affected by very hot days than non-Indigenous ones, with admission rates for IHD increased by 32%. The pattern of response to temperature in the older age cohort (>65 years old) was different from that in the younger cohort. Instead of being sensitive to hot temperature, the Indigenous older male population was more sensitive to cold conditions than non-Indigenous cohorts, with IHD admissions increased by 52% and 29%, respectively. For older females, admissions for heart failure in the Indigenous population increased more than that in non-Indigenous people, by around 64% and 56%, respectively (86). The prevalence of diabetes, which is associated with IHD incidence, is three times higher in the Indigenous population than that in the non-Indigenous population. Thus, it is not surprising to observe the higher Indigenous admission rates. In addition, the Indigenous population was found to be over-crowded and with limited access to safe water supplies or health services (2, 3), tending to reduce adaptive capacity to climate change and increase the vulnerability to diseases. This is contrary to the theoretical result that the Indigenous population should be less sensitive to extreme temperatures since then adapted better than non-Indigenous people, so the role of adaptation in modifying climate-mortality/morbidity relationships is another major uncertainty and may be overwhelmed by factors such as comorbid diseases, nutrition and lifestyle. These findings indicate extensive concern over the observed disproportionate health impact on Indigenous
population from temperature variation, especially for cardiovascular conditions.

**Socioeconomic status**

Generally, people in low socioeconomic condition show a greater vulnerability to temperature-related mortality/morbidity. For instance, blue-collar workers were at significantly higher risk of temperature-related mortality than white-collar workers (95). This might be due to the populations’ poorer health status themselves, limited access to health care and poor housing conditions subsequently of lower wealth, behavior patterns such as smoking (8, 73, 85) and a lower adaptive capacity to extreme weather events (20, 92). In addition, a study conducted in Tibet found that cold temperatures had a stronger effect among illiterate persons compared to those who were literate (8). Keeping in line with this, residents in Suzhou and Guangzhou, China with lower educational levels were particularly vulnerable to temperature-related mortality (85, 95). It is suggested that education and occupation class are important factors which determines populations’ overall socioeconomic status and ability to cope with extreme climates. Thus building up health missionary in these vulnerable populations could help people pull through the climate extremes.

**Occupational exposure**

With predicted increasing frequency and intensity of heat waves, heat exposure is an increasingly severe challenge, especially to those susceptible occupations. According to the US Census of Fatal Occupational Injuries (2013), construction/extraction had the highest count of fatal injuries in industry sector (45). Except for the accidents happened during work, heat-related mortalities contributes most to the fatal injury, with ratio of 2.32 for
heat-associated death in association with construction/extraction (67). This may be due to their constant work with machinery tools, working aloft, heavy workload, hot accommodation, and constant and direct exposure to sunlight. The agricultural workers also showed high rate of heat-related deaths among all industries because of working in extreme outdoor heat in summer (41, 67). Miners are another at risk population varying according to the type of mining. The heat exposure in surface mines is similar to the outdoor workplace and the workers are apt to be dehydrated (40), whereas the underground mines are at higher risk since the additional heat from depth, air auto-compression for ventilation and humidity from water contribute markedly to the thermal load (91). Solar radiation, humidity and wind speed are all important factors which may deteriorate temperature-induced injury. Fire fighters are prone to heat-related diseases since they are required to be equipped with personnel protective equipment (fire-fighting protective clothing and self-contained breathing apparatus) regardless of environmental temperatures, leading to reduced heat dissipation and contributing more to the risk of heat stress (91). In a study, fire fighters performed a repeat work protocol in a heat chamber and their immune/inflammatory responses were examined. Accompanied with increases in core temperatures, significant increases in leukocytes, platelets and TNFα following work were observed and platelets continued to increase at 1 h and remained elevated at 24 h. The sustained increases in leukocytes and platelets may increase the risk of cardiac events in firefighters when performing repeat work tasks in the heat (84). Although there is little or no direct solar radiation, manufacturing workers in the workplace without air condition are suffering heat-related illness since they can be exposed to heat and/or humidity. For instance, the workplaces surrounding furnaces, ovens, hot machines or molten metal in
the steel plants place the workers at risk of heat injury, whereas workers in paper mill or printing and dyeing factory are suffering both heat and air humidity generated from work process or equipment. However, due to the underreporting of heat illness and lack of awareness of the heat-related injuries, the potential impacts of occupational heat exposure are to some extent underestimated. Thus, in one hand, workers need training to avoid heat illness and recognize the symptoms in themselves and coworkers. In the other hand, effective prevention measures for the occupational health and safety are required to be taken in the workplace.

**Regional air quality**

Air pollution has been demonstrated as a risk hazard for CVD and it is assumed that effects of air pollution and temperature on mortality confounds each other (90, 95). Earlier studies have reported the enhancing effects of temperature on the air pollution-mediated CVD mortality (63, 70). However, there were few studies to assess the modifying effects of air quality on temperature. A study was conducted in Germany for the period 1990-2006 to examine the modifying effects of air pollutant on temperature-mediated mortality. It is revealed that associations between heat, but not cold, and mortality were strongest under a high PM$_{10}$ level(15). Consistent with it, another study on nine cities in Europe revealed that the heat wave effect on CVD mortality in high PM$_{10}$ days was increased, especially in the 75-84 year and 85+ year age groups (5). Applying a distributed lag non-linear model combined with non-linear interaction terms, a newly published study by Li et al revealed that both hot and cold effects increased with the concentration of PM$_{10}$, and observed statistically significant interaction effects between PM$_{10}$ and mean temperature on CVD mortality. Specifically, the enhanced
The effect of PM10 on hot/cold-induced CVD mortality appeared immediately, independence of PM10 levels (50). The enhanced heat effect may be that high temperature increases respiratory rate, subsequently allowing more pollutants to be absorbed into the body. The augmented cold effects on CVD mortality could be explained that cold temperature may reduce mucociliary clearance and thus augmented the susceptibility of the respiratory tract to PM10. In addition, among people age 75-84 years, the increase in mortality during heat wave episodes was much higher on high ozone days compared with low ozone days (5), shedding new light on the extreme temperature-induced CVD mortality. However, the modified effect of air pollution merits to be generalized to other regions and further research need to be conducted to investigate the potential effect modification by PM2.5 or other pollutants. What concerned is, the heat wave effect was much smaller after adjustment for ozone or PM10 (5), indicating lack of adjustment for ozone or particulate matters overestimates effect parameters. This bias has implications for evaluating the data without adjustment for pollutant factors and constitutes an alarm to raises people's awareness to preserve the environmental and mitigate the climate change.
Comorbid diseases

**Hyperglycemia or diabetes**

In Ibaraki, Japan, subjects with hyperglycemia were vulnerable to cold temperature (6). Another study from Toronto showed that people with comorbid diabetes (7.3%) were more affected by the short-term effects of extreme heat and the risk of being admitted to the emergency department for a cardiovascular event was consequently increased (47). Diabetes is characterized by endothelial dysfunction and hypercoagulability. Several factors such as oxidative stress and protein kinase C may contribute to macrovascular injury from hyperglycemia. Cold temperature may more severely affect the patients with hyperglycemia in the setting of injured vasculature. Impaired thermoregulation due to reduced autonomic control and endothelial function may explain why diabetic patients are particularly vulnerable to heat during an extreme heat episode (47).

Cardiac diseases

A time series study with 292,666 emergency room visits was applied to examine the effect of extreme cold or hot temperature on CVD emergency attendance. The results showed that patients with comorbid cardiac diseases (6.5%) were vulnerable to the short-term effects of extreme temperature and consequently had an increased risk of being admitted to the emergency department for a cardiovascular event (8, 47, 73). Patients who had a prior acute MI were consistently more sensitive to extreme temperatures (47, 62, 73). In further support of this observation, ET-1, a serum indicator of vascular injury, showed greater elevation in response to cold air in the patient group, indicating that the effect of cold air on CVD patients
was greater than that in healthy people (57, 97), providing more evidence for the susceptibility of patients with vascular disease. The biological mechanisms that can lead to a CVD event include the association of cold temperature with an increase in blood pressures and a series of abnormal biomarkers, which may place people with comorbid cardiac diseases in a vulnerable state. This is described more in detail in the mechanism section below.

Kidney diseases

The cold-enhanced CVD emergency room visits were positively related to comorbid kidney disease (47). The biologic mechanism underlying this relationship may be related to the fact that renal disorders are commonly accompanied by increased blood pressure, which is also the added effect of extreme cold temperatures. The increased blood pressure may act synergistically in people with renal disorders towards an adverse cardiovascular response and CVD attack (47). This hypothesis, however, awaits further investigation and clarification.

Hypertension

The susceptibility of hypertension to temperature change has been evaluated in humans and animals. Among patients with a history of hypertension, a greater increase in blood urea nitrogen/creatinine, a dehydration marker, was observed in response to temperature change (53). Early last century, it was shown that the cardiovascular and sympathetic responses were more exaggerated in hypertensive rats than healthy rats under cold stimuli. This finding suggests that people with hypertension are more susceptible to temperature change. However, in another study significantly greater increases in CVD risk factors, particularly systolic blood
pressure, whole blood viscosity, and LDL/HDL, were demonstrated among the healthy rats rather than the hypertensive rats (58). The authors contributed this finding to compensatory mechanisms involved in normalizing blood pressure under continuously sustained sympathetic activation in cold, which may be more prominent in hypertensive rats. Nevertheless, this result does not mean that people with hypertension should pay less attention to cold-air stress.

Taken together, these results showed the association between temperature and adverse cardiovascular effects, with lowest around a certain temperature and will increase at lower or higher temperature. The effects of heat were relatively immediate while the effects of cold became predominant with longer time lags. There are some susceptible peoples who are prone to the temperature challenge, including those physiologically vulnerable populations (such as the elderly and children), occupationally exposed population or those who have already suffered from some comorbid diseases and those on certain medications (Figure 2). To elucidate the mechanism by which cold/hot leads to cardiovascular dysfunction and/or CVD would contribute to alleviating the cardiovascular injury induced by temperature challenge, in the next section, we will focus on the investigational studies that have explored how cold/hot triggered cardiovascular response and the underlying mechanisms.

**MECHANISTIC INSIGHTS INTO TEMPERATURE CHALLENGE AND CVD**

Compared to the great amount of studies showing the positive association between extreme temperature and CVD mortality/morbidity, the mechanisms by which cold/heat triggered cardiovascular response are less elucidated. Based on the current publications, the mechanisms underlying initiation of cardiovascular diseases in response to temperature...
challenges involve multiple physiopathology regulations, which include cold-enhanced sympathetic reactivity, cold-activated rennin-angiotensin system, both cold and heat-mediated dehydration, and heat stroke-induced systemic inflammatory response (Figure 3 and Figure 4).

**Sympathetic activity**

Enhanced sympathetic reactivity to stressful stimuli has been associated with the development of hypertension and CVD and is well established to be one of possible mechanisms underlying the increased risk of CVD in humans (Figure 3). Cold pressor test (CPT, done by submerging the participant’s hand up to the wrist in ice-cold water for 1 min), is a known sympathoexcitatory stimulus. Park et al made hemodynamic measurements and direct measurements of muscle sympathetic nerve activity (MSNA) using microneurography in healthy individuals, and found that, after the CPT, MSNA increased significantly from 26 burst/min to 40 bursts/min, accompanied with elevated systolic and diastolic blood pressures (66). Furthermore, overweight individuals (obese individuals excluded) were also examined. Although there was no significant difference in baseline MSNA, the magnitude of MSNA response to cold stress was observed to be significantly higher in overweight participants (+18.1 ± 2.8 bursts/min) compared with lean controls (+10.8 ± 1.2 bursts/min) (66). However, in another study on obese subjects, Lambert et al. found that the obese had higher MSNA than lean controls even at baseline (46), as were overall levels of MSNA during the sympathoexcitation (42). Thus, the chronic baseline sympathetic activity, as well as greater sympathetic responses to stressful stimuli, may contribute to increased risk of hypertension.
Many CVD events occur more frequently on winter mornings with the peak incidence at the end of the sleep period, prior to morning awakening, as compared to any other periods of the day. The morning blood pressure surge is an acute blood pressure change, which is a normal physiological response that occurs during the sleep-wake transition early in the morning. Based on the phenomenon that MSNA increased in response to cold, this leads to the hypothesis that during the last rapid eye movement sleep transition, low ambient temperature produces a higher sympathetic change and morning blood pressure surge, thus playing an important role in cold-related cardiovascular events. To verify this, Kuo et al. conducted a series of experiments and demonstrated that cold conditions resulted in a higher morning blood pressure surge accompanied with significant and greater sympathetic index changes during the sleep–wake transition than during cover-to-uncover and supine-to-sit position tests. In addition, the non-REM–REM transition-related sympathetic elevation during the cold conditions was significantly higher in late sleep period than in early sleep period. These results may explain the peak incidence of cardiovascular events that occur more frequently at the end of the sleep period of winter mornings. It also provides strong evidence for the role of cold-enhanced sympathetic activity in CVD (43).

Ambient temperature-mediated sympathetic activity was also supported by a study on heart rate variability; a noninvasive and sensitive measure of cardiac autonomic function. Heart rate variability is often used as a measure of cardiovascular function in physiologic and
epidemiologic studies, predicting sudden death from CVD. Heart rate variability was examined in a longitudinal analysis (2000–2008) of the Normative Aging Study population to clarify the association of ambient temperature changes with cardiac autonomic function, and showed that higher ambient temperature was inversely associated with heart rate variability measures (standard deviation of normal-to-normal intervals, low-frequency power, and high-frequency power) during the warm season but not during the cold season, indicating an activation of sympathetic activity and a withdrawal of vagal activity (72). Consistent with these results, Yamamoto et al. reported that after 6 healthy males were exposed to temperatures of 35 °C for half an hour, their high-frequency power percentage significantly decreased and the ratio of low-frequency power to high-frequency power significantly increased (94). These warm-season associations were significantly greater when ambient ozone levels were higher (>22.3 ppb). Given that both heat waves and ozone formation are likely to increase in response to global warming, such an interaction may be very important for peoples’ health concerns. On the contrary, Okamoto-Mizuno et al. reported that heart rate variability was related to low ambient temperature during sleep in humans (64). Furthermore, Kuo et al. evaluated the change in autonomic nervous system functioning in various different posture states after morning awakening and found that heart rate variability indices showed a significant change during the sleep–wake transition under cold conditions; thus, the sleep–wake transition would seem to be a major factor affecting HRV and the morning blood pressure surge when exposure to cold (43). The different response of heart rate variability following cold exposure may be related to different climates (Boston, US and Taiwan, China) or subjects examined (old people more than 70 and young people around 24 years old).
Rennin-angiotensin system (RAS) and sympathetic nervous system (SNS)

Angiotensin-II levels in plasma were found to be elevated during cold air exposure both in patients with cardiovascular or cerebrovascular diseases and in control groups, indicating the RAS was activated (76, 97). Similar to norepinephrine (indicator of SNS activation), the cold caused systemic vasoconstriction, thereby elevated the blood pressure. Therefore, the increase in blood pressure following cold air is caused by activation of the SNS and RAS (Figure 3). In addition, the epinephrine level showed no significant change in response to cold temperature, suggesting that norepinephrine in the plasma was not secreted by the adrenal medulla, but was released from sympathetic nerve endings. Since it is known that angiotensin-II can also promote this pathway to increase the release of norepinephrine, SNS and RAS should interact with each other and lead to the elevation in blood pressure.

Confirming these results were animal studies that showed high levels of norepinephrine and angiotensin-II in healthy Wistar rats exposed to artificial cold air under laboratory conditions (57). The sustained high blood pressure could increase myocardial load and oxygen consumption and even reduce blood supply to the brain, which could eventually induce myocardial and cerebral infarctions.

Dehydration

One of the mechanisms underlying temperature-related health effects is dehydration, which stresses the cardiovascular system. Because cardiovascular morbidity and mortality is
associated with the blood volume in circulation, body water loss could result in various cardiovascular health effects (78). Therefore, hydration status, which reflects the circulating blood volume, may be an important hemodynamic indicator of cardiovascular function. Hydration status was generally evaluated by measuring some dehydration markers including serum urea nitrogen-to-creatinine ratio, urine specific gravity, plasma tonicity and blood hematocrit. Until now, evidence regarding the effects of temperature on dehydration was limited. Lim et al. examined the association between temperature and dehydration markers using 43,549 hospital visits for physical examinations during a 14-year period in South Korea (53). Levels of these markers decreased linearly with an increase in the apparent temperature until a point between 22 and 27 °C, which was regarded as the flexion point of apparent temperature, and then increased with apparent temperature. This phenomenon fits well with the U shaped association curves between temperature and cardiovascular mortality. It is most likely that temperature-related changes in hydration status underlie the increased cardiovascular mortality and morbidity during high- or low-temperature conditions.

The pathophysiological mechanisms related to hot and cold weather conditions were investigated, both of which could induce dehydration (Figure 3 and Figure 4). In hot temperature, vasodilatation, increased peripheral circulation and increased sweating were induced, leading to water loss. Although the lower blood pressure due to vasodilation and reduced circulatory blood volume may reduce the risk of hemorrhagic stroke, the accompanying hemoconcentration and hyper-viscosity may cause thromboembolism, leading to an increased risk of ischemic stroke (52). When it is cold, blood pressure increases in
response to vasoconstriction and increased peripheral resistance accompanied by decreased peripheral circulation and increased urinary voiding which leads to dehydration (19). Together with hemoconcentration and hyper-viscosity from dehydration, it may increase the risk of hemorrhagic as well as ischemic stroke (19, 53). Thus, dehydration not only contributes to the cardiovascular burden by reducing circulatory blood volume but could also lead to coronary and cerebral thrombosis by causing hemoconcentration and hyper-viscosity (19). In addition, electrolyte and acid–base balance could also be impaired depending on dehydration status. Therefore, these disturbances in addition to fluid loss may contribute to the increased cardiovascular morbidity and mortality during hot and cold weather events (53).

Heat Stroke-induced Systemic Inflammatory Response

Heat stroke, characterized by an elevated core body temperature (>40), occurs during exposure to high ambient temperatures or while performing heavy physical labor and is classified as passive/classic or exertional in nature. The sequelae of heat stroke include thermoregulatory, cardiovascular, hemodynamic and immune disturbances that lead to systemic inflammatory response syndrome and organ (e.g., gut, liver, kidney) damage. It is thought that a systemic inflammatory response is related to heat-induced damage in individuals that are immune or physiologically compromised and exposed to climatic heat stress during summer heat waves. In actuality, the temperature-mediated inflammation involves a multi-organ system reaction. The process includes a series of issues. First off, the core temperature increases in response to heat stress, and then stimulates multiple reflexive adjustments. Vasodilatation is an important negative feedback pathway to limit hyperthermia
by increasing skin blood flow to facilitate heat loss to the environment. Accordingly, the body accommodates by decreasing in gut blood flow to facilitate the redistribution of blood to the skin surface. Prolonged reductions in gut blood flow cause the gut epithelial barrier membrane to become ischemic by inducing oxidative/nitrosative stress response. Tight junctions of the gut become leaky under ischemic status, allowing endogenous bacteria, its toxic cell wall component lipopolysaccharide (LPS) or endotoxin to leak from the gut lumen into the systemic circulation(49). Toll-like receptor 4 (TLR4) recognizes pathogen-induced LPS or other damage-associated molecular patterns, initiating the innate immune response to both infection and sterile injury. With a well-established murine model of heat stroke (mutant specific pathogen-free mice), Dehbi et al. demonstrated that another ligand of TLR4, HMGB1, was released very early at the onset of heat stroke in a sustained manner. Thus, LPS and HMGB1 together mediate cytokine or other immune modulators release through activation of TLR4, inducing tissue damage (24). In addition, high body temperature causes thermal injury to the vascular endothelium and initiates the coagulation/fibrinolysis pathways that lead to occlusion of the arterioles and capillaries (microvascular thrombosis) or excessive bleeding (consumptive coagulation). Thus, the systemic inflammatory response syndrome and coagulation pathways interacts each other, leading to multi-organ system failure including CVD (48). Figure 4 shows the hypothetical model for heat stroke induced inflammation and cardiovascular disorders.

**Molecular hypotheses**

Molecular mechanisms underlying the cold-associated high cardiovascular risk are far from
clear because only few studies conducted exploring the effects of cold. Figure 3 shows the hypothetical model for cold-induced cardiovascular disorders.

**Atherosclerosis, CVD risk factors and uncoupling protein (UCP) 1**

Plasma levels of some traditional CVD risk factors, such as whole blood viscosity, plasma fibrinogen, total cholesterol, and LDL were examined in both healthy and hypertensive rats. The CVD risk factors were found to be higher after cold air exposure (57, 58, 76) and even increase with cold-air ranks, that is with cold-air exposure intensities (58). The increase in whole blood viscosity may indicate increases in some coagulation factors, such as red cells, fibrinogen, blood lipids, platelet, and hemoglobin, thus increasing the risk of thrombosis in coronary and cerebral arteries. Fibrinogen, known as an indispensable coagulation factor, could directly induce pro-inflammatory responses in the process of atherosclerosis at high plasma levels by binding fibrin and its degradation products (32, 34). Increased total cholesterol and LDL, popular indicators of lipids profiles, are closely related to atherosclerosis by inducing manifestation of adhesion molecules and vascular endothelium dysfunction, particularly, the high LDL/HDL ratio, induced by increased LDL and decreased HDL, more accurately predicts risk of CVD than LDL or HDL alone (28). In addition, the increased uric acid in blood has been shown to enhance the proliferation of vascular smoothness and induce endothelial dysfunction by stimulation of inflammatory pathways [27–29], which may in turn promote atherogenesis. Together with whole blood viscosity, fibrinogen and lipid profiles, the increased uric acid in rats after cold air exposure may facilitate the atherosclerosis formation, aggravate any preexisting atherosclerosis, especially in coronary arteries(56), and increase
In two genetic atherosclerotic mouse models (apoE<sup>−/−</sup>, LDL<sup>−/−</sup>), persistent cold exposure stimulated atherosclerotic plaque growth. Further supporting this, cold temperature was found to alter plasma lipid profiles in a food-intake-independent way. Indeed, the level of plasma triglycerides significantly decreased in response to cold temperature. This effect may be attributable to the highly expressed lipolysis-associated genes, crucial enzymes for oxidative and lipid degradation, in inguinal white adipose tissue from cold-exposed mice. However, a marked increase in levels of cholesterol, LDL cholesterol, intermediate-density lipoprotein and the proportion of LDL by cold exposure were observed after cold stimulation. This may be explained by the increased level of cholesterol synthesis, hydroxymethylglutaryl-coenzyme A reductase (HMG-CoA reductase) and transcriptional factors essential for cholesterol synthesis such as sterol regulatory element-binding proteins (SREBPs) transcription factor and its partner protein SREBP cleavage-activating protein. These accumulating atherosclerosis-prone lipids increased lipid deposition, leading to an accelerated development of atherosclerotic lesions in mice. In addition, persistent cold exposure increased the necrotic areas but decreased fibrous cap thickness, indicating that cold exposure increased plaque instability and potential plaque disruption. Notably, marked increase of inflammatory cells and plaque-associated microvessels were detected in the cold-acclimated genetic mice, providing additional factors contributing to plaque instability. Taken together, persistent cold exposure not only stimulated atherosclerosis plaque growth, but also increased plaque instability and potential plaque disruption.
UCP1 is a key mitochondrial protein involved in thermogenesis in brown adipose tissue. In rodents, it has been shown that cold exposure can not only sufficiently activate brown adipose tissue, leading to increased levels of non-shivering thermogenesis via activation of the sympathetic system, but also stimulate phenotypic and functional conversion from white adipose tissue into brown-like adipose tissue (BRITE) in an UCP1-dependent manner (93). Thus, double knockout mice that lacked apoE and UCP1 were generated. Deletion of UCP1 in the apoE\(^{-/-}\) strain completely protected mice from the cold-induced atherosclerotic lesions and lipolysis in adipose tissue. In addition, deletion of the UCP1 gene in apoE\(^{-/-}\) mice resulted in a marked increase in the total amount of collagen I components and plaque fibrous cap thickness as well as a decrease of necrotic core area, indicating inhibited plaque growth and improved plaque stability. This may be related to UCP1 involvement in cold-triggered abnormal metabolism and awaits further investigation (93).

Atherosclerosis and adiponectin

Adiponectin, which has recently been reported to suppress lipolysis, was significantly decreased in cold-exposed mice (71). To examine whether adiponectin contributes to cold-mediated atherosclerosis development and further elucidate molecular mechanisms that may underlie cold-induced atherosclerotic plaque growth and instability, the circulating adiponectin levels were measured. Cold acclimation markedly reduced plasma levels of adiponectin, once again suggesting this adipokine might participate in regulation of lipid metabolism. Surprisingly, the systemic delivery of adiponectin protected ApoE\(^{-/-}\) mice from
plaque development and substantially decreased levels of the total cholesterol and LDL cholesterol in the plasma.

Given the essential role of UCP1 in the cold-induced atherosclerotic plaque development in apoE<sup>-/-</sup> mice (93), the relation between adiponectin and UCP1 expression was examined. Interestingly, UCP1 was almost completely inhibited by systemic delivery of adiponectin, at both mRNA levels and protein levels in brown adipose tissue, subcutaneous white adipose tissue and epididymal white adipose tissue, leading to ablation of cold-induced activation of brown adipose tissue and BRITe. These findings demonstrate that cold-induced suppression of adiponectin and subsequently upregulation of UCP1 is, at least in large part, responsible for cold-induced atherosclerosis plaque development and instability in the apoE<sup>-/-</sup> mouse model.

**Endothelium dysfunction and adiponectin**

Endothelium dysfunction plays a pivotal role in CVD. Contrary to the classic opinion that adiponectin expression is predominantly found in fat tissue, the expression of adiponectin has been extended to other tissues such as cardiomyocytes (68), fat-free vessel segments (27) and isolated vascular smooth muscle cells(25). Ebner et al. demonstrated expression of adiponectin isoforms, including the high-molecular-weight form (HMW, 12-18 multimer), medium-molecular-weight form (MMW, hexamer) and low-molecular-weight (LMM, trimer) in mouse aorta. Studies have shown that two days of cold storage resulted in an impairment of endothelium-dependent relaxation (26). Adiponectin mRNA expression was decreased in a vascular failure model of prolonged cold storage (27). Given the cold-induced lower level of
adiponectin expression in the aorta, it was tested whether re-establishing extracellular adiponectin concentrations can be beneficial for vascular function in cold conditions. Addition of full-length adiponectin (containing the HMW fraction, trimeric and truncated forms) to storage supernatant specifically improved the acetylcholine-induced vasorelaxation, whereas, addition of trimeric adiponectin further diminished the endothelium-dependent relaxation (26). This confirms the role of adiponectin in cold-impaired endothelium function and leaves the HMW fraction as the elicitor of the beneficial effects.

To evaluate the potential mechanism of how adiponectin mRNA is decreased during cold storage, analysis of miRNA that are known to regulate adiponectin mRNA expression (miR-369-5p, miR-292-3p or miR-145-5p) (14) was performed. Following 2 hour or 2 days of storage, only expression of miR-292-3p was significantly reduced. By down-regulation using respective miRNA-inhibitors, the adiponectin mRNA was significantly decreased by inhibition of miR-292-3p, proving miR-292-3p may be the reason for the reduction of adiponectin mRNA in murine aortic vascular smooth muscle cells. It’s interesting to notice that vessels stored for 2 days showed a significant five-fold higher adiponectin concentration in the supernatant compared with 1 h storage, indicating a net release of adiponectin (26). These results may provide explanation for the inconsistency of adiponectin levels between plasma and specific tissues. The impact of secreted adiponectin from non-fat sources in maintenance of plasma adiponectin and in vivo vascular tone regulations remains to be established.

To explore the potential mechanism of how adiponectin protects endothelium function during
cold storage, examination of endothelial nitric oxide synthase (eNOS) activity under multiple situations was conducted. It is well known that the product of eNOS activation, nitric oxide, plays a large part in acetylcholine-induced vessel relaxation. Studies have demonstrated that mice with targeted genetic deletion of adiponectin display impaired vascular function and a decreased Ser1177 phosphorylation of eNOS and that this can be reversed by in vivo application of recombinant human truncated adiponectin (16). Under the applied hypothermic conditions, a reduction of Ser1177-phosphorylation and NO production was observed (26, 76), whereas a trend for its elevation appeared only in presence of full-length and truncated adiponectin (26). Consistent with this, the following stimulated release of vasoactive nitric oxide was verified by the effect of eNOS inhibitor, L-NMMA, on acetylcholine-mediated relaxation. However, it should be taken into account that the full-length adiponectin does not only contain the HMW fraction but also trimeric adiponectin. Trimeric adiponectin may increase monomeric fraction of eNOS. Together with it, the phosphorylation at position Thr495 promotes superoxide production, and this will shift to conditions which favor the formation of reactive oxygen species over nitric oxide production following storage in the presence of trimeric adiponectin (26). Although the direct level of the trimeric adiponectin was not examined in the cold storage supernatant, the decreased adiponectin mRNA in aorta following cold storage, improved endothelium function by addition of adiponectin during cold exposure and the detrimental monomer/phosphorylation site of eNOS in presence of trimeric adiponectin provide valid evidence for role of adiponectin isoforms in cold-induced vascular impairment via dysfunctional eNOS signaling.
Cardiac injury and ETA receptor

Endothelin-1 (ET-1), which is endothelium-derived, is a key regulator for blood pressure, cardiac growth, myocardial contractility, and hemodynamics. In humans, significantly increased ET-1 in plasma during cold air exposure was reported (57, 97). Actually, circulating ET-1 usually represents the spillover from local tissues and poorly reflects the local ET-1 action under pathological conditions. Although increased plasma ET-1 levels were not found following low ambient temperature (4°C) for 2-5 weeks (98), it has been demonstrated that cold exposure increases levels of ET-1 in heart tissue (76, 98). Studies have shown that ET-1 mediated cold stress triggered cardiac injury. Keeping in line with this, Luo et al. showed that two well-known indicators of myocardial injury, Myoglobin (Mb, sensitive and specific to myocardial necrosis) and cardiac troponin I (cTnI, best marker for acute myocardial infarction) quickly elevated after cold air exposure (57). Cold air can induce a stress response in the body especially when temperature and pressure change sharply in a short time period. Meanwhile, it increased the blood flow in the heart which can cause damage to heart muscle cells, resulting in higher concentrations of Mb and cTnI. Moreover, it facilitates the formation of ET-1 in the damaged area, which activates a variety of messenger pathways by combining with the endothelin receptor. Therein, release of thromboxane A2 results in an influx of calcium flow and subsequently calcium overload, which brings about severe functional disturbance that eventually causes cell death.

Based on the function of ET-1 and cold-increased ET-1 levels in plasma or cardiac tissue, the cardiomyocyte-specific ETA receptor knockout (ETAKO) and wild-type (WT) mice were
exposed to low ambient temperature (4°C) to further elucidate the mechanism of ET-1 in cold stress induced cardiac dysfunction (98). In the heart, cold stress triggered cardiac hypertrophy and depressed myocardial contractile capacity, which was attenuated or ablated by ETA deletion, evidenced by fractional shortening, peak shortening, and maximal velocity of shortening/re-lengthening (98).

Furthermore, the signaling pathway involved in the cold-induced cardiac geometric and contractile dysfunction was explored. On one hand, ETAKO ameliorated cold stress induced hypo-phosphorylation of GSK3β and hyper-phosphorylation of GATA4 and CREB, supporting a role of these signaling molecules in ET-1 downstream, contributing to the beneficial effects of ETAKO. On the other hand, ETAKO reversed cold exposure induced down-regulation of TRPV1 expression. This is in concurrence with in vivo findings that temperature sensor protein transient receptor potential vanilloid (TRPV1) agonist (SA13353) rescued cold exposure-induced cardiac geometric and functional defects, and the in vitro data that TRPV1 agonist ablated ET-1-induced cardiomyocyte hypertrophy. Looking closer, the cold stress-induced GSK3β activity and MMP depolarization were nullified by ETA deletion and TRPV1 agonist, favoring preserved mitochondrial integrity. Thus, it prevented an unfavorable cellular cascade reactions triggered by mitochondria dysfunction, thereby ablating intracellular calcium mishandling and contractile dysfunction. Although the mechanisms behind the GSK3β–TRPV1 pathway-engaged regulation on some cardiac cellular events under cold stress, such as mitochondrial integrity, intracellular Calcium homeostasis and contractile function, are far from clear, these findings suggest that ETAKO protects against cold
exposure induced cardiac remodeling and dysfunction mediated through TRPV1 and mitochondrial function (98).
LIMITATION AND CONCLUSION

Our review unavoidably has some limitations. First, some studies might have been missed due to our search strategy. However, we believe that most of the recent, major studies on cardiovascular responses to cold or hot should have been included. Second, there are some variables, such as ozone, air pollution, solar radiation, wind speed, humidity and barometric pressure. These factors are the fundamental issues that may influence the effect of extreme temperature. However, the influence of these factors could not get controlled because such data even were not provided in many studies. Third, several points worth noting include the option of appropriate statistical models, the handling of the non-linear relationship (The statistic methods or models in the epidemiological studies are listed in Table 5), and the adjustment of confounding factors including public holiday, weekend, time-lag effects, long-term variation trend, wind speed, humidity, barometric pressure. The lack of a unified standard among different studies limit the accuracy of weighing all findings together. Although these concerns on such varied methodology and reporting should always be born in mind, our purpose was not to make a quantitative estimate of the effect of extreme temperature on CVD, but rather to give a qualitative overview of the evidence available.

Extreme climate events such as cold spells and heat waves have been associated with excess morbidity and mortality of CVD across various populations and geographic locations. There is a need to further investigate, quantify and explain the excess deaths and incidence related to temperature challenges. This is especially important in the global setting of severe air pollution and an increasingly elderly population and vulnerable groups of people such as those with
comorbid diseases. Adaptation to temperature change related health hazards could take place through improved strategies at various scales. The biometeorological forecasts and warnings would advance preparedness strategies, particularly in the vulnerable population, to minimize the health hazard induced by extreme temperature events. Improving labor protection laws to reduce outdoor occupational exposure to extreme ambient temperatures could help. Furthermore, individually or communally increasing outreach for education on protective adaptations in cold and hot weathers would help people pull through the extreme events, particularly those who are illiterate. Weatherization activities can help to save energy and reduce harmful greenhouse gas emissions. Improving housing conditions by equipping central heating and air conditioning would protect populations against extreme cold or heat. To explore strategies to minimize the hazard of temperature challenge, future research should incorporates multi disciplines including epidemiology, climatology, indoor/building environments, energy usage, labor legislative perfection and human/animal models. In addition, knowledge of the pathophysiology induced by cold/heat events is severely limited. Thus, the underlying mechanisms by which temperature challenge induces pathophysiological response and CVD await profound and further investigation.

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DISCLOSURES

The author(s) declare that they have no competing interests.
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Webb L, Bambrick H, Tait P, Green D, and Alexander L. Effect of ambient temperature on


FIGURE CAPTIONS

Figure 1. A. The estimated relative risks of mean temperature (°C) over lags 0-14 days on cardiovascular mortality. The black lines are the mean relative risks and the gray areas are the 95% Cis of risk estimates (85). B. Relative risks of cardiovascular mortality types by mean temperature (°C), using a natural cubic spline-natural cubic spline DLNM with 5 df natural cubic spline for temperature and 4 df for lag (35).

Figure 2. The effects of extreme temperatures on cardiovascular diseases (CVD) mortality and morbidity. Both heat and cold increase mortality and morbidity of CVD, with the effect of former immediate and short whereas the effect of latter delayed and long. Physiologically vulnerable populations are the elderly, the infants, those in low socioeconomic status (such as low educational level or blue collar workers) and with comorbid diseases (such as diabetes, hypertension, cardiac or kidney diseases). The gender vulnerability may depend on lifestyle of the population and being engaged in outdoor work or not. Physically vulnerable populations are those who live in rural regions, in low air quality regions and those who suffer occupational exposure or confront early cold/early hot in the season. Symbols: +, activation.

Figure 3. Summary of hypothesized mechanisms by which cold exposures induce cardiovascular disorders. Cold air exposure activated both sympathetic nervous system (SNS) and rennin-angiotensin system (RAS), which also interact with each other, thereby elevated the blood pressure (BP), leading to hypertension and cardiovascular disease (CVD) such as myocardial infarctions. Next, skin blood flow (SBF) decreased in response to cold exposure.
due to the vasoconstriction accompanied by increased urine voiding leads to dehydration,
increasing the risk of hemorrhagic as well as ischemic stroke by causing hemoconcentration
and hyper-viscosity. In addition, endothelium dysfunction, evidenced by eNOS inhibition, could
be induced by cold exposure, which may be in relation to cold-inhibited adiponectin expression
in the vascular system. As well, CVD risk factors were higher after cold exposure, contributing
to atherosclerosis by enhancing lipid deposition, plaque instability and plaque disruption.
Finally, plasma ET-1 levels increased during cold exposure, induced hypo-phosphorylation of
GSK3β and down-regulation of temperature sensor protein transient receptor potential
vanilloid (TPRV1) by activation of ETA receptor, triggering mitochondria dysfunction and
resulting in myocardial injury, cardiac hypertrophy and cardiac dysfunction.

Figure 4. Summary of hypothesized mechanisms by which heat and heat stroke induce
cardiovascular disorders. Increased skin blood flow (SBF) and sweating in response to heat
exposure lead to water loss and dehydration. The accompanied hemoconcentration and hyper
viscosity may cause thromboembolism, leading to increased risk of ischemic stroke. In
presence of heat stroke, increased core temperature redistributed the blood flow to the skin to
facilitate heat loss and limit hyperthermia. Accordingly, gut blood flow decreases and the
prolonged reduction in gut blood flow would cause increase in the gut epithelial membrane
permeability, allowing bacteria, its toxic cell wall component LPS or HMGB1 to leak from the
gut lumen into the systemic circulation. Toll-like receptor 4 (TLR4) recognizes these molecules,
stimulating the innate and adaptive immune systems and causing systemic inflammatory
response syndrome (SIRS). Together with it, the hyperthermia-impaired vascular endothelium
induces occlusion of arterioles and capillaries (microvascular thrombosis) or excessive bleeding (consumptive coagulation), leading to multi-organ system failure including cardiovascular dysfunction. Symbols: +, activation; ++, aggravation; —, inhibition.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study period</th>
<th>Study region</th>
<th>Population size</th>
<th>Outcome</th>
<th>Main findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ma et al</td>
<td>1996-2008</td>
<td>17 large cities, China</td>
<td>&gt;7,000,000</td>
<td>Mortality</td>
<td>A 1°C decrease from the 25th to 1st percentiles of temperature over lags 0-14 days associated with increases of 2.49% in CVD mortality</td>
<td>(60)</td>
</tr>
<tr>
<td>Zhou et al</td>
<td>2006-2010</td>
<td>15 provinces in China</td>
<td>&gt;200,000</td>
<td>Mortality</td>
<td>2008 cold spell increased mortality of CVD more pronounced for elderly females</td>
<td>(99)</td>
</tr>
<tr>
<td>Davidkovova et</td>
<td>1994-2009</td>
<td>The Czech</td>
<td>400,063</td>
<td>Mortality</td>
<td>Relative excess IHD mortality most</td>
<td>(22)</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Year(s)</td>
<td>Location</td>
<td>Population</td>
<td>Mortality</td>
<td>Findings</td>
<td></td>
</tr>
<tr>
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<td>------------------</td>
<td>------------</td>
<td>-----------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Huang et al</td>
<td>2008-2011</td>
<td>Changsha, China</td>
<td>6,570,000</td>
<td>Mortality</td>
<td>1. 6.6% of cumulative effects of cold-related CVD mortality for 30 lag days</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Females and older people more sensitive</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>counties, China</td>
<td></td>
<td></td>
<td>2. The vulnerable population tended to be men, the elderly and illiterate persons.</td>
<td></td>
</tr>
<tr>
<td>Wang et al</td>
<td>2005-2008</td>
<td>Suzhou, China</td>
<td>49,984</td>
<td>Mortality</td>
<td>1.75 of relative risk of total CVD mortality associated with extreme cold temperature</td>
<td></td>
</tr>
</tbody>
</table>
over lags 0–14 days compared with the minimum mortality temperature (26 °C)

<table>
<thead>
<tr>
<th>Study</th>
<th>Years</th>
<th>Location</th>
<th>Population</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urban et al</td>
<td>1994–2009</td>
<td>Prague and Bohemia, the Czech Republic</td>
<td>24,000,000</td>
<td>Higher cold-related mortality in rural region versus city region. (80)</td>
</tr>
<tr>
<td>Rocklov et al</td>
<td>1990-2002</td>
<td>Stockholm County, Sweden</td>
<td>1,600,000-1,800,000</td>
<td>Associated with a decrease in temperature particularly in men, population &gt; 80, population &gt;65 with myocardial infarction. (73)</td>
</tr>
<tr>
<td>Ou et al</td>
<td>2003-2011</td>
<td>subtropical city, Guangzhou,</td>
<td>213,737</td>
<td>1. 52% of excess winter death from CVD, higher in the elderly, females and those with low education level. (65)</td>
</tr>
</tbody>
</table>
2. Much larger winter increase in out-of-hospital mortality compared to in-hospital mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Period</th>
<th>Location</th>
<th>Population</th>
<th>Type</th>
<th>Outcome Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xie et al</td>
<td>2006-2009</td>
<td>Three subtropical cities in China</td>
<td>8,300,000</td>
<td>Mortality</td>
<td>CVD mortality at lag 0-27 more pronounced for males and for the elderly</td>
</tr>
<tr>
<td>Wichmann et al</td>
<td>1985-2010</td>
<td>Gothenburg, Sweden</td>
<td>49,297</td>
<td>IHD deaths</td>
<td>More deaths among men, &gt; 75 years during the cold period</td>
</tr>
<tr>
<td>de'Donato et al</td>
<td>2008-2012</td>
<td>27 cities, Italy</td>
<td>&gt;200,000</td>
<td>Mortality</td>
<td>Excess in mortality among &gt; 75 age for CVD, IHD and other heart disease</td>
</tr>
</tbody>
</table>

(92) (87) (23)
<table>
<thead>
<tr>
<th>Study</th>
<th>Years</th>
<th>Location</th>
<th>N/A Value</th>
<th>Type</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atsumi et al</td>
<td>1993-2008</td>
<td>Ibaraki, Japan</td>
<td>3593</td>
<td>Cardiovascular</td>
<td>Cold temperature had stronger effect on deaths those &lt;80 years and with hyperglycemia</td>
</tr>
<tr>
<td>Grjibovski et al</td>
<td>2000-2001, 2006-2010</td>
<td>Astana, Kazakhstan</td>
<td>3,206,832</td>
<td>Mortality</td>
<td>No association between temperatures and mortality from cardiovascular or cerebrovascular causes</td>
</tr>
<tr>
<td>Guo et al</td>
<td>1999-2008</td>
<td>Chiang Mai city, Thailand</td>
<td>151,839</td>
<td>Cause-specific</td>
<td>Resulted in immediate increase in all mortality types and age groups</td>
</tr>
<tr>
<td>Barnett et al</td>
<td>1987-2000</td>
<td>99 US cities</td>
<td>N/A</td>
<td>Mortality</td>
<td>1. No increased risk of death during cold waves, even evidence of a decreased risk observed during the coldest waves</td>
</tr>
</tbody>
</table>
2. Cold waves earlier in the cool season more dangerous

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Location</th>
<th>Population</th>
<th>Measure</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang et al</td>
<td>1996-2004</td>
<td>Brisbane, Australia</td>
<td>896,649</td>
<td>YLL</td>
<td>U-shaped exposure-response curve between temperature and YLL, with the lowest at 24°C</td>
</tr>
<tr>
<td>Guo et al</td>
<td>2005-2007</td>
<td>Tianjin, China</td>
<td>4,200,000</td>
<td>Mortality</td>
<td>U-shaped relationship between temperature and CVD mortality</td>
</tr>
<tr>
<td>Liu et al</td>
<td>2003-2005</td>
<td>urban area of Beijing, China</td>
<td>7,072,000</td>
<td>Mortality</td>
<td>In the cold period, 5°C decrease of 15-day average temperature associated with a RR of 1.057 for CVD mortality</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Study Period</td>
<td>Location</td>
<td>N</td>
<td>Study Type</td>
<td>Main Findings</td>
</tr>
<tr>
<td>------------</td>
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<td>------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Yu et al</td>
<td>1996-2004</td>
<td>Brisbane, Australia</td>
<td>22,805</td>
<td>Mortality</td>
<td>A significant effect of low temperature found in older people and all ages</td>
</tr>
<tr>
<td>Wu et al</td>
<td>1994-2003</td>
<td>Taiwan, China</td>
<td>358 townships</td>
<td>Mortality</td>
<td>Substantially lower CVD mortality in metropolitan regions than in rural areas after cold events</td>
</tr>
</tbody>
</table>

CVD, cardiovascular diseases; IHD, ischemic heart diseases; YLL, years of life lost
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study period</th>
<th>Study region</th>
<th>Population size</th>
<th>Outcome</th>
<th>Main findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giang et al</td>
<td>2008-2012</td>
<td>Thai Nguyen Province, Vietnam 18,975 Morbidity</td>
<td>1. Associated with increasing CVD admission risk among the elderly population 2. Cold effect occurred 4-5 days and peaked at a week following exposure</td>
<td>(31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lavigne et al</td>
<td>2002-2010</td>
<td>Toronto, Canada 292,666 ER visits</td>
<td>Extreme cold on CVD ER visits stronger for individuals with comorbid cardiac diseases and kidney diseases</td>
<td>(47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Webb et al</td>
<td>1992-2011</td>
<td>Australian Northern 176,000 Morbidity</td>
<td>Hospitalization higher for older, Indigenous, and</td>
<td>(86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Territory</td>
<td>male people</td>
<td>Territory</td>
<td>Hospital</td>
<td>5–6 more admissions per day for IHD, 8 more admission for hypertension during the cold stress days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Shiue et al</td>
<td>2010.1-2010.12 Plymouth, US</td>
<td>N/A</td>
<td>Hospital</td>
<td>(74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban et al</td>
<td>1994–2009 Prague and Bohemia, the Czech Republic</td>
<td>24,000,000</td>
<td>Morbidity</td>
<td>Weak excess CVD morbidity in cold days (80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan et al</td>
<td>1998-2009 Hong Kong, China</td>
<td>7,869, 661</td>
<td>Hospital</td>
<td>CVD admissions increased during cold temperatures by 2.1% for every decrease of 1°C (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wichmann et al</td>
<td>1985-2010 Gothenburg, Sweden</td>
<td>49,297</td>
<td>Acute MI</td>
<td>1.3% and 7% decrease in acute MI (87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>hospitalization</td>
<td>hospitalizations in a 2-day cumulative average</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
of temperature during the entire year (11°C) and the warm period (6°C)

2. More hospitalizations among men, > 75 years during the cold period

<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
<th>Location</th>
<th>Sample Size</th>
<th>Data Type</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>de' Donato et al</td>
<td>2008-2012</td>
<td>27 cities, Italy</td>
<td>&gt;200,000</td>
<td>ER visits</td>
<td>Excess in ER visits among &gt; 75 age for CVD, IHD and other heart disease</td>
</tr>
<tr>
<td>Vasconcelos et al</td>
<td>2003-2007</td>
<td>Lisbon and Oporto, Portugal</td>
<td>N/A</td>
<td>Daily</td>
<td>An increase of up to 2.2% in daily MI hospital admissions for every degree fall in during winter</td>
</tr>
<tr>
<td>Verberkmoes et al</td>
<td>1998-2010</td>
<td>Eindhoven, the Netherlands</td>
<td>13,217</td>
<td>Cause-specific morbidity</td>
<td>A significant correlation between daily temperature and hospital admissions for acute</td>
</tr>
</tbody>
</table>

(23) (82) (83)
aortic dissection or AMI

Turner et al 2000-2007 Brisbane, Australia 783,935 Attendances

1. V-shaped exposure–response curve between temperature and CVD attendance with the lowest attendance at 22°C

2. Cold effects delayed and lasted longer with a 1.30% increase in attendances for a 1°C decrease below the threshold

CVD, cardiovascular diseases; ER, emergency room; IHD, ischemic heart diseases; YLL, years of life lost; MI, myocardial infarction
### Table 3. Effect of hot temperature on CVD mortality

<table>
<thead>
<tr>
<th>Author</th>
<th>Study period</th>
<th>Study region</th>
<th>Population size</th>
<th>Outcome</th>
<th>Main findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ma et al</td>
<td>1996-2008</td>
<td>17 large Chinese cities, China</td>
<td>&gt;7000,000</td>
<td>Mortality</td>
<td>A 1°C increase from the 75th to 99th percentiles of temperature was associated with corresponding increases of 3.02% in cardiovascular mortality.</td>
<td>(60)</td>
</tr>
<tr>
<td>Davidkovova et al</td>
<td>1994-2009</td>
<td>The Czech Republic</td>
<td>400,063</td>
<td>Mortality</td>
<td>Chronic IHD for most IHD excess deaths, much more pronounced in &gt; 65 years.</td>
<td>(22)</td>
</tr>
<tr>
<td>Huang et al</td>
<td>2008-2011</td>
<td>Changsha, China</td>
<td>6,570,000</td>
<td>Mortality</td>
<td>0–3 days for heat-related CVD mortality lag effect. Females and older people more sensitive to extreme hot temperatures.</td>
<td>(39)</td>
</tr>
</tbody>
</table>
Bai et al 2008-2012 three Tibetan counties, China 5,610 Mortality Heat on CVD death immediate and strong (8)

Rocklov et al 1990-2002 Stockholm County, Sweden 1,600,000-1,800,000 Mortality Mortality by heat wave higher for people > 80 years, for the population <65 years with lower wealth or a previous MI and with chronic obstructive pulmonary diseases (73)

Wang et al 2005-2008 Suzhou, China 49,984 Mortality The relative risk associated with extremely hot temperature over lags 0–3 days was 1.43 (85)

Urban et al 1994–2000 Prague and 24,000,000 Mortality Higher relative excess CVD mortality on warm days (80)
<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th>Sample Size</th>
<th>Category</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>Bohemia, the Czech Republic</td>
<td>than on cold days in both rural and urban regions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guo et al 1999-2008</td>
<td>Chiang Mai city, Thailand</td>
<td>151,839</td>
<td>Cause-specific mortality</td>
<td>Hot temperatures resulted in immediate increase in all mortality types and age groups in a short-term time</td>
</tr>
</tbody>
</table>
2. Heat waves earlier in the warm season may be more dangerous. |
| Huang et al 1996-2004 | Brisbane, Australia | 896 649 | YLL | Significantly added effects of heat waves on years of life lost |
| Guo et al 2005-2007 | Tianjin, China | 4.200,000 | Mortality | 1. A U-shaped relationship between temperature and |

(36) (9) (38) (35)
CVD mortality.

2. Significantly increased mortality associated with high temperatures were acute and lasted for 3 days

<table>
<thead>
<tr>
<th>Study</th>
<th>Time Period</th>
<th>Location</th>
<th>Population</th>
<th>Mortality</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al</td>
<td>2003-2005</td>
<td>urban area of Beijing, China</td>
<td>7,072,000</td>
<td>Mortality In the warm period, a 5°C increase of two-day average temperature associated with a RR of 1.098 for acute CVD mortality; a 5°C decrease of 15-day average temperature associated with a RR of 1.040 for CVD mortality</td>
<td></td>
</tr>
<tr>
<td>Yu et al</td>
<td>1996-2004</td>
<td>Brisbane, Australia</td>
<td>22,805</td>
<td>Mortality Increase in mortality to be 3.7% for people aged ≥65 and 3.5% for all ages associated with an increase of 1°C above the threshold temperature of 24°C</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Time Period</td>
<td>Location</td>
<td>Sample Size</td>
<td>Mortality</td>
<td>Findings</td>
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<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Wu et al</td>
<td>1994-2003</td>
<td>Taiwan, China</td>
<td>358</td>
<td>Mortality</td>
<td>Substantially lower CVD mortality in metropolitan townships than in rural areas after heat events</td>
</tr>
<tr>
<td>Basagaña et al</td>
<td>1983-2006</td>
<td>Catalonia region</td>
<td>503,389</td>
<td>Mortality</td>
<td>Effect on CVD mortality observed on the same day of heat in the perinatal period in infants</td>
</tr>
</tbody>
</table>

CVD, cardiovascular diseases; IHD, ischemic heart diseases; YLL, years of life lost; MI, myocardial infarction
Table 4. Effect of hot temperature on CVD morbidity

<table>
<thead>
<tr>
<th>Author</th>
<th>Study period</th>
<th>Study region</th>
<th>Population size</th>
<th>Outcome variables</th>
<th>Main findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lavigne et al</td>
<td>2002-2010</td>
<td>Toronto, Canada</td>
<td>292,666</td>
<td>ER visits</td>
<td>Stronger associations of CVD ER visits for persons with diabetes with short term extreme hot temperatures</td>
<td>(47)</td>
</tr>
<tr>
<td>Webb et al</td>
<td>1992-2011</td>
<td>Australian Northern Territory</td>
<td>176,000</td>
<td>Morbidity</td>
<td>Among 25-64 year olds, Indigenous females more adversely affected by very hot days than the non-Indigenous females, with admission rates for IHD increased by 32%</td>
<td>(86)</td>
</tr>
<tr>
<td>Son et al</td>
<td>2003-2008</td>
<td>8 major cities, Korea</td>
<td>3,174,736</td>
<td>Hospital admissions</td>
<td>Overall heat effect for CVD hospitalization a 4.5 % increase</td>
<td>(75)</td>
</tr>
<tr>
<td>Study</td>
<td>Year Range</td>
<td>Location</td>
<td>Population/Sample Size</td>
<td>Outcome/Measure</td>
<td>Findings</td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
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<td>-------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Urban et al</td>
<td>1994–2009</td>
<td>Prague and Bohemia, Czech Republic</td>
<td>24,000,000</td>
<td>Morbidity</td>
<td>Weak excess CVD morbidity on warm days than on cold days in both rural and urban regions</td>
<td></td>
</tr>
<tr>
<td>Vaneckova et al</td>
<td>1991-2009</td>
<td>Sydney, Australia</td>
<td>1,561,231</td>
<td>Hospital admissions</td>
<td>Increase in the ORs of CVD hospital admissions on hot days, most due to IHD</td>
<td></td>
</tr>
<tr>
<td>Turner et al</td>
<td>2000-2007</td>
<td>Brisbane, Australia</td>
<td>783,935</td>
<td>Attendances</td>
<td>Acute heat effects with a 1.17% increase in total attendances for 1°C increase above threshold</td>
<td></td>
</tr>
</tbody>
</table>

CVD, cardiovascular diseases; ER, emergency room; IHD, ischemic heart diseases; YLL, years of life lost; OR: odds ratios
Table 5. The statistical methods or models in the epidemiological studies

<table>
<thead>
<tr>
<th>Statistical method or model</th>
<th>Confidence Interval Levels</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLNM and Poisson regression model</td>
<td>95%</td>
<td>(85)</td>
</tr>
<tr>
<td>Poisson generalized linear model</td>
<td>95%</td>
<td>(51)</td>
</tr>
<tr>
<td>Temperature-matched case-crossover design</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poisson regression model</td>
<td>95%</td>
<td>(82)</td>
</tr>
<tr>
<td>Time-stratified case cross over design</td>
<td>95%</td>
<td>(6)</td>
</tr>
<tr>
<td>DLNM</td>
<td>95%</td>
<td>(38)</td>
</tr>
<tr>
<td>Monte Carlo method</td>
<td>95% and 90%</td>
<td>(22)</td>
</tr>
<tr>
<td>Semi-parametric poisson regression model</td>
<td>95%</td>
<td>(55)</td>
</tr>
<tr>
<td>Polynomial distributed lag model</td>
<td></td>
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<tr>
<td>Univariate liner regression analysis</td>
<td>95%</td>
<td>(83)</td>
</tr>
<tr>
<td>Binary logistic regression analysis</td>
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<tr>
<td>Passion-distributed variable</td>
<td>95%</td>
<td>(80)</td>
</tr>
<tr>
<td>Two-stage hierarchical model</td>
<td>95%</td>
<td>(75)</td>
</tr>
<tr>
<td>Poisson regression model</td>
<td>95%</td>
<td>(18)</td>
</tr>
<tr>
<td>DLNM with 5 df natural cubic spline for temperature and 4 df for lag</td>
<td>95%</td>
<td>(35)</td>
</tr>
<tr>
<td>Polynomial distributed lag model</td>
<td>95%</td>
<td>(92)</td>
</tr>
<tr>
<td>Time-series regression models</td>
<td>95%</td>
<td>(60)</td>
</tr>
<tr>
<td>DLNM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayesian hierarchical models</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLNM</td>
<td>95%</td>
<td>(31)</td>
</tr>
<tr>
<td>Method</td>
<td>Percentage</td>
<td>Notes</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>------------</td>
<td>-----------</td>
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<tr>
<td>Linear description</td>
<td>95%</td>
<td>(73)</td>
</tr>
<tr>
<td>Poisson regression model</td>
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<td>(33)</td>
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<tr>
<td>Linear regressions</td>
<td>95%</td>
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<td>Poisson loglinear model</td>
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<td>(86)</td>
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<tr>
<td>Poisson regression model</td>
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<td>(39)</td>
</tr>
<tr>
<td>Farrington method</td>
<td>Not applied</td>
<td>(23)</td>
</tr>
<tr>
<td>Conditional logistic regression analysis</td>
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<td>(87)</td>
</tr>
<tr>
<td>A generalized linear model with a quasi-Poisson distribution analysis</td>
<td>95%</td>
<td>(65)</td>
</tr>
<tr>
<td>DLNM</td>
<td>95%</td>
<td>(99)</td>
</tr>
<tr>
<td>Multivariate meta-analyses</td>
<td></td>
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</tr>
<tr>
<td>Compared target data with a winter reference period</td>
<td>95%</td>
<td>(61)</td>
</tr>
<tr>
<td>No exact description. This approach consists in estimating excess daily mortality by calculating deviations of the observed number of deaths and the expected (baseline) number of deaths for each day of the examined period.</td>
<td>95%</td>
<td>(44)</td>
</tr>
<tr>
<td>Nonparametric methods</td>
<td>Not applied</td>
<td>(11)</td>
</tr>
<tr>
<td>Wilcoxon signed-rank test</td>
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<tr>
<td>Bonferroni correction</td>
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<td>Poisson regression analyses</td>
<td>95%</td>
<td>(88)</td>
</tr>
<tr>
<td>Bayesian model</td>
<td>95%</td>
<td>(9)</td>
</tr>
<tr>
<td>DLNM</td>
<td>95%</td>
<td>(8)</td>
</tr>
<tr>
<td>DLNM</td>
<td>95%</td>
<td>(36)</td>
</tr>
<tr>
<td>Poisson regression model</td>
<td>95%</td>
<td>(47)</td>
</tr>
<tr>
<td>Method</td>
<td>Percentage</td>
<td>Count</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>------------</td>
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<td>Generalised additive models</td>
<td>95%</td>
<td>(79)</td>
</tr>
<tr>
<td>a natural cubic spline with 4 degrees of freedom (df)</td>
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<tr>
<td>DLNM</td>
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<tr>
<td>DLNM</td>
<td>95%</td>
<td>(59)</td>
</tr>
<tr>
<td>Time-stratified case-crossover analysis</td>
<td>95%</td>
<td>(81)</td>
</tr>
<tr>
<td>GEE model</td>
<td>95%</td>
<td>(21)</td>
</tr>
<tr>
<td>Time series analysis</td>
<td>Not applied</td>
<td>(29)</td>
</tr>
<tr>
<td>Case-crossover design</td>
<td>95%</td>
<td>(10)</td>
</tr>
<tr>
<td>Spatial regression models</td>
<td>95%</td>
<td>(89)</td>
</tr>
<tr>
<td>Polynomial distributed lag models</td>
<td>95%</td>
<td>(96)</td>
</tr>
</tbody>
</table>

DLNM, distributed lag non-linear model

The elderly/the infant
People in low socioeconomic status
People with comorbid diseases
Male/female
Early cold/early hot
Rural regions
Occupational exposure
Regions in bad air quality
Figure 3

- **Blood Pressure (BP)**
  - Blood pressure
  - COLD
  - Heart
  - Artery
  - Hemodynamics
  - SNS activation
  - RAS activation
  - Adiponectin
  - eNOS
  - CVD risk factors
  - Lipid deposition
  - Plaque instability
  - Plaque disruption
  - ET1-ETA
  - GSK3β, TRPV1
  - Mitochondrial injury

- **CVD**
  - Hypertension
  - Myocardial infarction
  - Ischemic stroke (thromboembolism)
  - Hemorrhage stroke
  - Endothelium dysfunction
  - Atherosclerosis
  - Myocardial injury
  - Cardiac hypertrophy
  - Cardiac dysfunction

- **SBF**
  - SBF
  - Urinary voiding
  - Dehydration
  - Hemoconcentration
  - Hyper viscosity

- **CVD**
  - Blood pressure
  - COLD
  - Heart
  - Artery
  - Hemodynamics
  - SNS activation
  - RAS activation
  - Adiponectin
  - eNOS
  - CVD risk factors
  - Lipid deposition
  - Plaque instability
  - Plaque disruption
  - ET1-ETA
  - GSK3β, TRPV1
  - Mitochondrial injury
HEAT STROKE

Core temperature

Vascular endothelium injury

Consumptive coagulation

Microvascular thrombosis

Multiple organ failure

Cardiovascular dysfunction

TLR4

SIRS

Endotoxin, LPS, HMGB1, et al. leakage

Gut epithelial membrane permeability

Gut blood flow

Hemoconcentration

Hyper viscosity

Dehydration

Water loss

SBF

Sweating

(hemodynamics)

Ischemic stroke (thromboembolism)