CALL FOR PAPERS | Cardiovascular Responses to Environmental Stress

Cardiovascular response to thermoregulatory challenges

Cuiqing Liu,1 Zubin Yavar,2 and Qinghua Sun2
1Basic Medical College, Zhejiang Chinese Medical University, Hangzhou, China; and 2Division of Environmental Health Sciences, College of Public Health, The Ohio State University, Columbus, Ohio

Submitted 25 March 2015; accepted in final form 28 September 2015

Liu C, Yavar Z, Sun Q. Cardiovascular response to thermoregulatory challenges. Am J Physiol Heart Circ Physiol 309: H1793–H1812, 2015. First published October 2, 2015; doi:10.1152/ajpheart.00199.2015.—A growing number of extreme climate events are occurring in the setting of ongoing 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 amount of literature on this issue, we aim to review the recent publications regarding the impact of cold and heat on human populations with regard to cardiovascular disease (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 sex, 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, renin-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.

Address for reprint requests and other correspondence: Q. Sun, Div. of Environmental Health Sciences, College of Public Health, The Ohio State Univ., Columbus, OH 43210 (e-mail: sun.224@osu.edu).

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 (79b). 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 cardiovascular diseases (CVDs) 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” while limiting the search to title and/or abstract for the literature about effects of cold, and used the keywords “cardiovascular” and “hot” while limiting the search to title and/or abstract for the literature about effects of hot. The initial search generated 1,509 and 801 results, respectively. So, we limited the publications within 5 years and then afterward selected the articles based on our aims from the 435 and 265 results. To be included in the review, the articles had to be published on peer-reviewed journals in English. A total of 95 research articles and four 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) (Fig. 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 to 2006. Cold spells were associated with positive mean excess CVD mortality in all age groups (25–59, 60–69, 70–79, and 80+ yr) 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 3 days. With the mortality data from a national mortality surveillance system, an overall 1,578 (+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 Nanchong, 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 four 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% confidence interval (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 7 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 [rate ratio (RR): 1.21; 95% CI: 1.12–1.31] (61). In general, although the definitions of cold spell vary greatly across different studies, the cold spells were associated with positive mean excess cardiovascular mortality, nothing to do with the prosperity country of concerned.

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% 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, 1.12 (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% posterior intervals: 1.53%, 3.46%) in cardiovascular mortality (60). Although the magnitude of cold temperature’s cardiovascular effects varies greatly by geogra-

---

**Fig. 1.** A: estimated relative risks of mean temperature (in °C) over lags 0–14 days on cardiovascular mortality. Black lines are mean relative risks and gray areas are 95% Cis of risk estimates (85). B: relative risks of cardiovascular mortality types by mean temperature (in °C), using a natural cubic spline-natural cubic spline (DLNM) with 5 df natural cubic spline for temperature and 4 df for lag (35).
phy or locations, the detrimental effects of cold on CVD mortality are consistent.

Years of life lost as a measure of CVD mortality. Years of life lost (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). When compared with it, a distributed lag nonlinear model is more flexible and biologically plausible when quantifying individual lags, especially at short lag times. Luo et al. (59) used a distributed lag nonlinear 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 six CVDs [stroke, myocardial infarction (MI), IHD, 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 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 CVDs including IHD, cerebrovascular disease, MI, and chronic IHD in the population as a whole, only MI significantly exceeded the expected level in a study conducted in the Czech Republic (southern Bohemia) (80). In a study of 99 United States 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. (31) examined the effect of cold during the years 2008–2012 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% CI: 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. With the review of medical records of patients and the meteorological data over the same period, analysis results demonstrated a decrease in ambient temperature during the 3 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 regard to acute MI, Bhaskaran et al. (12) reviewed some relevant data from the winter season and reported a statistically significant short-term increased risk of MI at lower temperatures. Subsequently, Wolf et al. (88) observed an inverse relationship between ambient 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% CI: 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
<table>
<thead>
<tr>
<th>Authors</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>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 al.</td>
<td>1994–2009</td>
<td>The Czech Republic</td>
<td>400,063</td>
<td>Mortality</td>
<td>Relative excess IHD mortality most pronounced in the younger age group</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>1) 6.6% of cumulative effects of cold-related CVD mortality for 30 lag days 2) Females and older people more sensitive</td>
<td>(39)</td>
</tr>
<tr>
<td>Bai et al.</td>
<td>2008–2012</td>
<td>3 Tibetan counties, China</td>
<td>5,610</td>
<td>Mortality</td>
<td>1) The effect of cold on CVD death lasted longer 2) The vulnerable population tended to be men, the elderly and illiterate persons</td>
<td>(8)</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 over lags 0–14 days compared with the minimum mortality temperature (26°C)</td>
<td>(85)</td>
</tr>
<tr>
<td>Urban et al.</td>
<td>1994–2009</td>
<td>Prague and Bohemia, the Czech Republic</td>
<td>24,000,000</td>
<td>Mortality</td>
<td>Higher cold-related mortality in rural region versus city region</td>
<td>(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>Mortality</td>
<td>Associated with a decrease in temperature particularly in men, population &gt;80, population &gt;65 with myocardial infarction</td>
<td>(73)</td>
</tr>
<tr>
<td>Ou et al.</td>
<td>2003–2011</td>
<td>Subtropical city, Guangzhou,</td>
<td>213,737</td>
<td>Mortality</td>
<td>1) 52% of excess winter death from CVD, higher in the elderly, females and those with low education level 2) Much larger winter increase in out-of-hospital mortality compared to in-hospital mortality</td>
<td>(65)</td>
</tr>
<tr>
<td>Xie et al.</td>
<td>2006–2009</td>
<td>3 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>
<td>(92)</td>
</tr>
<tr>
<td>Wichmann et al.</td>
<td>1985–2010</td>
<td>Gothenburg, Sweden</td>
<td>49,297</td>
<td>HHD deaths</td>
<td>More deaths among men, &gt;75 yr during the cold period</td>
<td>(87)</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>
<td>(23)</td>
</tr>
<tr>
<td>Atsumi et al.</td>
<td>1993–2008</td>
<td>Ibaraki, Japan</td>
<td>3593</td>
<td>Cardiovascular deaths</td>
<td>Cold temperature had stronger effect on those &lt;80 yr and with hyperglycemia</td>
<td>(3)</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 mortality</td>
<td>Resulted in immediate increase in all mortality types and age groups</td>
<td>(36)</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 2) Cold waves earlier in the cool season more dangerous</td>
<td>(9)</td>
</tr>
<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>
<td>(38)</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>
<td>(35)</td>
</tr>
</tbody>
</table>

Continued
the relationship to temperature thresholds. Heat waves were investigating the risk of death from cardiovascular issues and waves in 99 United States cities over 14 years (1987–2000), North America, Barnett et al. (9) examined the effect of heat characterized by daily temperatures over several consecutive wave/hot spell was variously described with local definitions, visits, hospital admission, or CVD morbidity.

correlation of cold temperature to emergency room (ER) days (74). Table 2 depicts select investigations of the disease admissions were also seen during the cold stress days compared with acceptable weather conditions. For IHD and eight more for hypertension during the cold stress 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 (p = 0.002) and acute MI (p = 0.02) (83). Given that all climate factors interact with each other and traditional epidemiological methods may not provide a sufficient explanation, Shiue et al. (74) 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 five to six more admissions per day for IHD and eight more for hypertension during the cold stress days compared with 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 variously described with local definitions, characterized by daily temperatures over several consecutive days above an extreme temperature threshold or percentile. In North America, Barnett et al. (9) examined the effect of heat waves in 99 United States 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 2 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 sexes) as a whole, IHD mortality increased markedly from day 1 to day 4 in response to hot spells, with a peak on day 2 (22). In this study, hot spell was defined as periods of at least 2 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 day + 1), followed by high excess mortality persisted for 5 days; nevertheless, significant excess mortality from acute MI was only observed on a single day (day + 2) with much lower increase (excess mortality about 8%) compared with chronic IHD mortality (22). A time period of 7 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 35.0°C and daily average temperatures above the 97th percentile. 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 spells are defined, D’Ippoliti et al. (21) 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 2 days with maximum apparent temperature exceeding the 90th percentile of the monthly distribution, or periods of at least 2 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 the nine European cities, with highest mortality of 39.2% in Milan (90% CI: 31.2–43.3) and 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 2-day average temperature was associated with a RR of 1.098 [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% posterior intervals: 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.

<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>Ma et al.</td>
<td>1996–2008</td>
<td>17 large Chinese cities, China</td>
<td>&gt;7,000,000</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 yr 0–3 days for heat-related CVD mortality lag effect. Females and older people more sensitive to extreme hot temperatures</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>Mortality by heat wave higher for people &gt;80 yr, for the population &lt;65 yr with lower wealth or a previous MI and with chronic obstructive pulmonary diseases</td>
<td>(39)</td>
</tr>
<tr>
<td>Bai et al.</td>
<td>2008–2012</td>
<td>3 Tibetan counties, China</td>
<td>5,610</td>
<td>Mortality</td>
<td>Heat on CVD death immediate and strong</td>
<td>(8)</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>Mortality</td>
<td>Mortality by heat wave higher for people &gt;80 yr, for the population &lt;65 yr with lower wealth or a previous MI and with chronic obstructive pulmonary diseases</td>
<td>(73)</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>2005–2008</td>
<td>Suzhou, China</td>
<td>49,984</td>
<td>Mortality</td>
<td>The relative risk associated with extremely hot temperature over lags 0–3 days was 1.43</td>
<td>(85)</td>
</tr>
<tr>
<td>Urban et al.</td>
<td>1994–2009</td>
<td>Prague and Bohemia, the Czech Republic</td>
<td>24,000,000</td>
<td>Mortality</td>
<td>Higher relative excess CVD mortality on warm days than on cold days in both rural and urban regions</td>
<td>(80)</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 mortality</td>
<td>Hot temperatures resulted in immediate increase in all mortality types and age groups in a short-term time 1) Heat waves increased CVD death 2) Heat waves earlier in the warm season may be more dangerous</td>
<td>(36)</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>Significantly added effects of heat waves on years of life lost 1) A U-shaped relationship between temperature and CVD mortality 2) Significantly increased mortality associated with high temperatures were acute and lasted for 3 days</td>
<td>(38)</td>
</tr>
<tr>
<td>Huang et al.</td>
<td>1996–2004</td>
<td>Brisbane, Australia</td>
<td>896649</td>
<td>YLL</td>
<td>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>(55)</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>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>(96)</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>Mortality increase 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>(89)</td>
</tr>
<tr>
<td>Yu et al.</td>
<td>1996–2004</td>
<td>Brisbane, Australia</td>
<td>22,805</td>
<td>Mortality</td>
<td>Mortality increase 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>(89)</td>
</tr>
<tr>
<td>Wu et al.</td>
<td>1994–2003</td>
<td>Taiwan, China</td>
<td>358 townships</td>
<td>Mortality</td>
<td>Mortality increase 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>(89)</td>
</tr>
<tr>
<td>Basagaña et al.</td>
<td>1983–2006</td>
<td>Catalonia region of Spain</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>
<td>(10)</td>
</tr>
</tbody>
</table>
Hot Temperature and CVD Morbidity

So far, little research examined the effects of heat on CVD morbidity and nonfatal 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 (and others) 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 nonlinear 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 (54), Sydney, Australia (81), and a multicity analysis in Italy (1).

The sensitivity to ambient temperature may be diseasespecific since the investigation of specific cardiovascular subcategories showed the most frequent admissions of IHD (35%) and the least frequent of acute rheumatic fever (0.02%). In addition, when CVDs as a collective group was analyzed, significantly higher admissions occurred on the third day after a hot day (95th percentile) (81). When specific CVDs were analyzed, admissions due to “other diseases of the circulatory system” were significantly higher 1 day after, and the admissions due to “other forms of heart disease” and “diseases of veins and lymphatics” occurred 3 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, whereas 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 to 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 nonlinear effects of cold temperature on cardiovascular mortality and all age groups (≥64, 65–74, 75–84, and ≥85 yr) (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: 3.06-0.64%) categories over lags 2–15 days (79). This may be due to the mortality displacement for nonaccidental, 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 takes for granted important factors that affect the temperature effects. Keeping in line with it, a twofold higher effect of heat waves of longer duration and high intensity was shown in both north continental regions and Mediter-
Vulnerability Among Subgroups

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

Sex Difference. When it comes to cold, although no effect modification by sex difference has been reported (18), a number of studies have shown that men are more vulnerable to cold than 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 men compared with women (22). Consistently, the estimated mortality at lag 0–27 was more pronounced for men than for women (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 women than for men (60). Similarly, higher excess winter mortality was observed in women in several other studies (39, 65, 75). With respect to hot temperatures, the results of sex difference vulnerability were not consistent. For example, men were generally found to be more susceptible than women to heat in a study in Tibet, China (8). To the contrary, women were more sensitive to heat than men (39, 75), and the heat-related excess IHD mortality was much larger in women than in men (≥15% excess mortality on day + 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 women 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 yr 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 yr as being more influenced by cold temperature (3). 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 yr) (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 yr age population compared with 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 yr 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; and 95% CI: 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 United States 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 nonindigenous people. Specifically, among the younger population (25–64 yr old), indigenous women were more adversely affected by very hot days than nonindigenous ones, with admission rates for IHD increased by 32%. The pattern of response to temperature in the older age cohort (>65 yr 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 nonindigenous cohorts, with IHD admissions increased by 52 and 29%, respectively. For older women, admissions for heart failure in the indigenous population increased more than that in nonindigenous 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 nonindigenous population. Thus it is not surprising to observe the higher indigenous admission rates. In addition, the indigenous population was found to be overcrowded and with limited access to safe water supplies or health services (4, 5), 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 they adapted better than nonindigenous 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 conditions 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 with 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 determine 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 United States Census of Fatal Occupational Injuries (2013), construction/extraction had the highest count of fatal injuries in industry sector (79a). Except for the accidents happened during work, heat-related mortalities contribute 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 autocombustion for ventilation, and humidity from water markedly contribute to the thermal load (91). Solar radiation, humidity, and wind speed are all important factors which may deteriorate temperature-induced injury. Firefighters are prone to heat-related diseases since they are required to be equipped with personnel protective equipment (firefighting 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, firefighters 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, because of 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, on one hand, workers need training to avoid heat illness and recognize the symptoms in themselves and coworkers. On 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 confound 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 and 85+ yr age groups (2). Applying a distributed lag nonlinear model combined with nonlinear interaction terms, a newly published study by Li et al. (50) 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 effect of PM$_{10}$ on hot/cold-induced CVD mortality appeared immediately, independent of PM$_{10}$ 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 augment the susceptibility of the respiratory tract to PM$_{10}$. In addition, among people age 75–84 yr, the increase in mortality during heat-wave episodes was much higher on high-ozone days compared with low-ozone days (2), 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 needs to be conducted to investigate the potential effect modification by PM$_{2.5}$ or other pollutants. What is of concern is that the heat wave effect was much smaller after adjustment for ozone or PM$_{10}$ (2), 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 raise 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 (3). 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 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 ER 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, endothelin-1 (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 ER visits were positively related to comorbid kidney disease (47). The biological 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 toward 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, whereas 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 (Fig. 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

When compared to the great number 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 CVDs in response to temperature challenges involve multiple physiopathology regulations, which include cold-enhanced sympathetic reactivity, cold-activated renin-angiotensin system (RAS), both cold and heat-mediated dehydration, and heat stroke-induced systemic inflammatory response (Figs. 3 and 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 (Fig. 3). Cold pressor test (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. (66) made hemodynamic measurements and direct measurements of muscle sympathetic nerve activity (MSNA) using microneurography in healthy individuals and found that after the cold pressor test, MSNA increased significantly from 26 bursts/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. (46) found that the obese had higher MSNA than lean controls even at baseline, 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 and CVD.

Many CVD events occur more frequently on winter mornings with the peak incidence at the end of the sleep period, before morning awakening, compared with 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. (43) 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-rapid eye movement-rapid eye movement 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 non-invasive and sensitive measure of cardiac autonomic function. Heart rate variability is often used as a measure of cardiovascular function in physiological and epidemiological 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. (94) reported that after six 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. These warm-season associations were significantly greater when ambient ozone levels were higher (>22.3 parts/billion). 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. (64) reported that heart rate variability was related to low ambient temperature during sleep in humans. Furthermore, Kuo et al. (43) evaluated the change in autonomic nervous system functioning in various different posture states after morning awakening and found that heart rate variability indexes 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 heart rate variability and the morning blood pressure surge when exposure to cold. The different response of heart rate variability following cold exposure may be related to different climates (Boston, MA, and Taiwan, China) or subjects examined (old people, >70 yr; and young people, ~24 yr).

**RAS and 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 sympathetic nervous system (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 (Fig. 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 are 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. (53) examined the association between temperature and dehydration markers using 43,549 hospital visits for physical examinations during a 14-yr period in South Korea. 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 (Figs. 3 and 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 hyperviscosity 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 hyperviscosity 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 hyperviscosity (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°C), 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 multiorgan system reaction. The process includes a series of issues. First, 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. (24) demonstrated that another ligand of TLR4, high-mobility group box 1, was released very early at the onset of heat stroke in a sustained manner. Thus LPS and high-mobility group box 1 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 interact each other, leading to multiorgan 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 have been conducted exploring the effects of cold. Figure 3 shows the hypothetical model for cold-induced cardiovascular disorders.

**Atherosclerosis, CVD risk factors, and uncoupling protein 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 in-
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 proinflammatory 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-to-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 lipids profiles, the increased uric acid in rats after atherogenesis. Together with whole blood viscosity, fibrinogen, and lipids profiles, the increased uric acid in rats after atherogenesis. Together with whole blood viscosity, fibrinogen, and lipids profiles, the increased uric acid in rats after atherogenesis. Together with whole blood viscosity, fibrinogen, and lipids profiles, the increased uric acid in rats after atherogenesis.

In two genetic atherosclerotic mouse models [apolipoprotein E-knockout (ApoE<sup>−/−</sup>) and 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.

Uncoupling protein (UCP) 1 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 nonshivering thermogenesis via activation of the sympathetic system, but also stimulate phenotypic and functional conversion from white adipose tissue into brown-like adipose tissue in an UCP1-dependent manner (93). Thus double knockout mice that lacked ApoE and UCP1 were generated. Deletion of UCP1 in the ApoE<sup>−/−</sup>-strain completely protected mice from the cold-induced atherosclerotic lesions and lipolysis in adipose tissue. In addition, deletion of the UCP1 gene in ApoE<sup>−/−</sup> 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<sup>−/−</sup> 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 brown-like adipose tissue. These findings demonstrate that cold-induced suppression of adiponectin and subsequently up-regulation of UCP1 is, at least in large part, responsible for cold-induced atherosclerotic 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. (26) demonstrated expression of adiponectin isoforms, including the high molecular weight form (HMW, 12–18 multimer), medium molecular weight form (hexamer), and low molecular weight (trimer) in mouse aorta. Studies have shown that 2 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 reestablishing 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).
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 miRNAs that are known to regulate adiponectin mRNA expression (miR-369-5p, miR-292-3p, or miR-145-5p) (14) was performed. Following 2 h 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 is interesting to notice that vessels stored for 2 days showed a significant fivefold higher adiponectin concentration in the supernatant compared with 1 h of 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 nonfat 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 nitric oxide 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 N\textsuperscript{-}monomethyl-L-arginine on acetylcholine-mediated relaxation. However, it should be taken into account that the full-length adiponectin contains not only 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 provides valid evidence for role of adiponectin isoforms in cold-induced vascular impairment via dysfunctional eNOS signaling.

Cardiac injury and ET\textsubscript{A} receptor. 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 wk (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. (57) showed that two well-known indicators of myocardial injury, myoglobin (sensitive and specific to myocardial necrosis) and cardiac troponin I (best marker for acute MI), quickly elevated after cold-air exposure. 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 myoglobin and cardiac troponin I. 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 A\textsubscript{2} 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 ET\textsubscript{A} receptor knockout (ETAKO) and wild-type 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 ET\textsubscript{A} deletion, evidenced by fractional shortening, peak shortening, and maximal velocity of shortening/relengthening (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 hypophosphorylation of GSK3\textbeta and hyperphosphorylation of GATA4 and cAMP response element binding protein, 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 transient receptor potential vanilloid (TRPV)-1 expression. This is in concurrence with in vivo findings that temperature sensor protein 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. With a closer look, the cold stress-induced GSK3\textbeta activity and matrix metalloproteinase depolarization were nullified by ET\textsubscript{A} 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 GSK3\textbeta/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 because of 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, that are fundamental issues which may influence the effect of extreme temperature. However, the influence of these factors could not get controlled because such data were not even provided in many studies. Third, several points worth noting include the option of appropriate statistical models, the handling of the nonlinear relationship (the statistical 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, and 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 borne 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 weather 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 incorporate multidisciplines 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 are severely limited. Thus the underlying mechanisms by which temperature challenge induces pathophysiological response and CVD await profound and further investigation.

GRANTS

This work was supported by National Institutes of Health Grant ES018900 (to Q. Sun) and National Natural Science Foundation of China Grant 81402646, Zhejiang Provincial Natural Science Foundation of China Grant LQ13H070002, and Hangzhou Science and Technology Plan Project of China (to C. Liu).

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>DLMN and Poisson regression model</td>
<td>95 (85)</td>
<td></td>
</tr>
<tr>
<td>Poisson generalized linear model</td>
<td>95 (51)</td>
<td></td>
</tr>
<tr>
<td>Temperature-matched case-crossover design</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poisson regression model</td>
<td>95 (82)</td>
<td></td>
</tr>
<tr>
<td>Time-stratified case cross over design</td>
<td>95 (3)</td>
<td></td>
</tr>
<tr>
<td>DLMN</td>
<td>95 (38)</td>
<td></td>
</tr>
<tr>
<td>Monte Carlo method</td>
<td>95 and 90 (22)</td>
<td></td>
</tr>
<tr>
<td>Semiparametric poisson regression model</td>
<td>95 (55)</td>
<td></td>
</tr>
<tr>
<td>Polynomial distributed lag model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariate liner regression analysis</td>
<td>95 (83)</td>
<td></td>
</tr>
<tr>
<td>Binary logistic regression analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passion-distributed variable</td>
<td>95 (80)</td>
<td></td>
</tr>
<tr>
<td>Two-stage hierarchical model</td>
<td>95 (75)</td>
<td></td>
</tr>
<tr>
<td>Poisson regression model</td>
<td>95 (18)</td>
<td></td>
</tr>
<tr>
<td>DLMN with 5 df natural cubic spline for temperature and 4 df for lag</td>
<td>95 (35)</td>
<td></td>
</tr>
<tr>
<td>Polynomial distributed lag model</td>
<td>95 (92)</td>
<td></td>
</tr>
<tr>
<td>Time-series regression models DLMN</td>
<td>95 (60)</td>
<td></td>
</tr>
<tr>
<td>Bayesian hierarchical models</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLMN</td>
<td>95 (31)</td>
<td></td>
</tr>
<tr>
<td>Linear description</td>
<td>95 (73)</td>
<td></td>
</tr>
<tr>
<td>Poisson regression model</td>
<td>95 (33)</td>
<td></td>
</tr>
<tr>
<td>Linear regressions</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Poisson loglinear model</td>
<td>95 (86)</td>
<td></td>
</tr>
<tr>
<td>Poisson regression model</td>
<td>95 (39)</td>
<td></td>
</tr>
<tr>
<td>Farrington metho</td>
<td>Not applied (23)</td>
<td></td>
</tr>
<tr>
<td>Conditional logistic regression analysis</td>
<td>95 (87)</td>
<td></td>
</tr>
<tr>
<td>A generalized linear model with a quasi-Poisson distribution analysis</td>
<td>95 (65)</td>
<td></td>
</tr>
<tr>
<td>DLMN</td>
<td>95 (99)</td>
<td></td>
</tr>
<tr>
<td>Multivariate meta-analyses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compared target data with a winter reference period</td>
<td>95 (61)</td>
<td></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 (44)</td>
<td></td>
</tr>
<tr>
<td>Nonparametric methods</td>
<td>Not applied (11)</td>
<td></td>
</tr>
<tr>
<td>Wilcoxon signed-rank test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bonferroni correction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poisson regression analyses</td>
<td>95 (88)</td>
<td></td>
</tr>
<tr>
<td>Bayesian model</td>
<td>95 (9)</td>
<td></td>
</tr>
<tr>
<td>DLMN</td>
<td>95 (8)</td>
<td></td>
</tr>
<tr>
<td>DLMN</td>
<td>95 (36)</td>
<td></td>
</tr>
<tr>
<td>Poisson regression model</td>
<td>95 (47)</td>
<td></td>
</tr>
<tr>
<td>Generalised additive models a natural cubic spline with 4 df of freedom (df)</td>
<td>95 (79)</td>
<td></td>
</tr>
<tr>
<td>DLMN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLMN</td>
<td>95 (59)</td>
<td></td>
</tr>
<tr>
<td>Time-stratified case-crossover analysis</td>
<td>95 (81)</td>
<td></td>
</tr>
<tr>
<td>GEE model</td>
<td>95 (21)</td>
<td></td>
</tr>
<tr>
<td>Time series analysis</td>
<td>Not applied (29)</td>
<td></td>
</tr>
<tr>
<td>Case-crossover design</td>
<td>95 (10)</td>
<td></td>
</tr>
<tr>
<td>Spatial regression models</td>
<td>95 (89)</td>
<td></td>
</tr>
<tr>
<td>Polynomial distributed lag models</td>
<td>95 (96)</td>
<td></td>
</tr>
</tbody>
</table>

DLMN, distributed lag nonlinear model.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

C.L. and Q.S. conception and design of research; C.L. and Q.S. prepared figures; C.L., Z.Y., and Q.S. drafted manuscript; C.L., Z.Y., and Q.S. edited figures; C.L., Z.Y., and Q.S. drafted manuscript; C.L., Z.Y., and Q.S. edited
REFERENCES


3. Atsumi A, Ueda K, Irie F, Sairenchi T, Tumura K, Watanabe H, Iso H, Ota H, Aonuma K. Relationship between cold temperature and cardio-


17. Conlon KC, Rajkovich NB, White-Newsome JL, Larsen L, O’Neill MS. Preventing cold-related morbidity and mortality in a changing cli-


23. Ebner A, Poitz DM, Alexiou K, Deussen A. Secretion of adiponectin from mouse aorta and its role in cold storage-induced vascular dysfunc-


30. Grijphovski AM, Nurgaliyeva N, Kosbayeva A, Menne B. No association between temperature and deaths from cardiovascular and cerebrovas-

31. Guo Y, Punnasiri K, Tong S. Fibrinogen, fibrin, and FDP induce C-reactive protein generation in rat vascular smooth muscle cells: pro-


36. Huang J, Wang J, Yu W. The lag effects and vulnerabilities of tempera-


