

# Emergency Cardiovascular Hospitalization Risk Attributable to Cold Temperatures in Hong Kong

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**Background**—Associations between ambient temperature and cardiovascular morbidity have been well studied worldwide; however, few studies determined the cardiovascular disease burden attributable to temperature. We aimed to assess the risk attributed to temperature based on the exposure–lag–response relationship between temperature and circulatory diseases.

**Methods and Results**—We collected daily time series data of emergency hospital admissions, mean temperature, and air pollution concentrations from January 2005 to December 2012 in Hong Kong. The association with temperature was modeled using a distributed lag nonlinear model integrated in quasi-Poisson regression. The cumulated effects of cold/hot temperature were abstracted. Attributable risk measures because of below optimal temperature (OT) were calculated to summarize the disease burden, and further separated into contributions from moderate and extreme cold temperatures. We observed significant nonlinear and delayed cold effect but no apparent hot effect lasting for 3 weeks on emergency circulatory hospitalizations. Compared with the identified OT at 23.0°C, the cumulative relative risk during 0 to 21 lag days was 1.69 (95% confidence interval, 1.56–1.82) for extreme cold (first percentile) and 1.22 (95% confidence interval, 1.15–1.29) for moderate cold temperature (10th percentile). Cold temperatures were responsible for temperature-related circulatory emergency hospitalizations, with attributable fraction of 6.33% for moderate cold and 0.82% for extreme cold while inducing 33 030 and 4257 cases, respectively. Several specific causes of cardiovascular diseases showed higher vulnerability.

**Conclusions**—Moderate cold weather was responsible for a considerable attributable risk for cardiovascular diseases. The temperature-related hospitalizations risk found in this study may provide evidence for guiding the public health policies and preventions for cardiovascular diseases. (*Circ Cardiovasc Qual Outcomes*. 2016;9:135-142. DOI: 10.1161/CIRCOUTCOMES.115.002410.)

**Key Words:** air pollution ■ cardiovascular disease ■ epidemiology ■ risk ■ temperature

Associations between ambient temperature and mortality or morbidity have been studied worldwide.<sup>1,2</sup> Both cold and hot weather are associated with increased risk of mortality and morbidity with the minimal risk at an OT. In general, cold effects are delayed and last for longer days, whereas heat effects seem more acute and followed by harvesting, that is, heat affects mainly a pool of frail individuals whose disease onset or death is brought forward by a brief period of time.<sup>3</sup> Besides the whole range of temperature being examined, more specific attention has been paid to the effects of extreme temperature events, such as cold spells and heat waves.<sup>4-8</sup>

Although most studies have quantified the association with ambient temperature in terms of relative risk (RR), only a few studies have assessed the disease burden attributed to cold/hot temperatures.<sup>9-13</sup> The attributable fraction (AF) representing the fraction of cases or deaths from a specific disease that would be avoided in the absence of exposure to extreme

weather either in the exposed population or the population as a whole. AFs multiplied by the total number of cases of a given disease would obtain the absolute number (AN) of preventable cases because of extreme weather. AF and AN quantify the public health burden because of specific risk factors for specific diseases,<sup>14</sup> which has important policy implications for future interventions and prevention.

The approaches to assess the disease burden attributable to extreme weather were diverse without considering the possible nonlinear and delayed effect of temperature.<sup>11-13</sup> Until recently, Gasparrini et al<sup>9,10</sup> introduced an updated approach to estimate the attributable risk (AR) based on the distributed lag nonlinear model (DLNM) framework with consideration of the complex pattern of potentially nonlinear and delayed associations described through exposure–lag–response associations for time series study. Furthermore, no study has examined the AR of temperature on the morbidity

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**WHAT IS KNOWN**

- Associations between ambient temperature and cardiovascular mortality and morbidity have been studied.
- However, the risk of cardiovascular disease burden attributable to temperature is not known.

**WHAT THE STUDY ADDS**

- We assessed the risk attributed to temperature based on the distributed lag–nonlinear relationship between temperature and circulatory diseases.
- No effect was detected for hot temperature, but a nonlinear and delayed effect was noted for cold weather.
- Cold weather was associated with a substantial attributable risk for cardiovascular diseases because cold temperatures were responsible for temperature-related circulatory emergency hospitalizations, with attributable fraction of 6.33% for moderate cold and 0.82% for extreme cold.

end points, such as emergency hospitalizations, which was considered to better catch the effect of temperature change than mortality did.

In this time series ecological study, we aimed to examine the nonlinear and delayed association between temperature and emergency hospital admissions for circulatory diseases on population level, and quantify the risk of emergency hospitalizations attribute to temperature by calculating the AF and AN with extended definition of AR measures based on the DLNM framework.

**Materials and Methods****Data Collection****Emergency Hospital Admission Data**

The daily count of emergency hospital admissions for circulatory diseases as the principal diagnosis was obtained from the Hospital Authority Corporate Data Warehouse. Hospital Authority is the statutory body running all public hospitals in Hong Kong. The records of admission were taken from the publicly funded hospitals providing 24-hour accident and emergency services and covering 90% of hospital beds in Hong Kong.<sup>15</sup> For the study period of 2005 to 2012, the Hospital Authority provided daily counts of emergency hospital admissions aggregated for age, sex, date of admission, and principal diagnosis on discharge. We abstracted the overall daily circulatory emergency hospitalizations (*International Classification of Diseases Ninth Revision [ICD-9]*: 390–459), and some specific causes of circulatory diseases, such as ischemic heart disease (IHD, *ICD-9*: 410–414), acute myocardial infarction (AMI, *ICD-9*: 410), heart failure (HF, *ICD-9*: 428), and cerebrovascular diseases (stroke, *ICD-9*: 430–438). Because no studies in the literature showed the significant association between the onset of overall digestive diseases and ambient temperature, we also abstracted the diseases of digestive system (*ICD-9*: 520–579) as a negative control. Daily admissions for influenza (*ICD-9*: 487) were used to identify influenza epidemics, which were then treated as a potential confounder in the analysis.<sup>16</sup> Ethics approval and consent from individual subjects were not required by our institute because we used only aggregated data but not any individualized data. Mortality of the same disease categories collected from the Census and Statistics Department of Hong Kong was also examined as a secondary outcome measure.

**Temperature and Air Pollution Data**

The daily mean temperature and relative humidity from 2005 to 2012 was obtained from the Hong Kong Observatory. The extreme cold was defined as those days with daily mean temperature at or lower than the first percentile of its distribution in study period, whereas the moderate cold was those with daily mean temperature between the first percentile and OT that corresponds to a minimum circulatory hospitalization risk. The extreme hot and moderate hot was defined using the 99th percentile as the cut-off point.<sup>17</sup>

Air pollution concentrations in the same period were obtained from the Environmental Protection Department of Hong Kong. We calculated the daily 24-hour mean concentrations of nitrogen dioxide (NO<sub>2</sub>) and particulate matter with aerodynamic diameter <10 μm (PM<sub>10</sub>) and daytime 8-hour (10:00–17:00) mean concentrations of O<sub>3</sub> for each general monitoring, and then averaged them across the 10 stations.<sup>18</sup> Air pollutants would be acted as potential time varying confounders in the regression models.

**Statistical Modeling**

This is a time series ecological study on population level. A standard time series quasi-Poisson regression was applied to derive estimates of associations between temperature and emergency hospital admissions for circulatory hospitalizations and each specific cause, reported as RR.

The association with temperature was estimated using a DLNM. The temperature was included in the model as cross-basis function, which can describe complex nonlinear and lagged dependencies through the combination of 2 functions that define the conventional exposure–response relationship and the additional lag–response relationship, respectively.<sup>19</sup> The DLNM has the advantage of estimating cumulative effects of temperature over multiple days while adjusting for the collinearity of temperature on neighboring days.<sup>20</sup>

Specifically, we modeled the exposure–response curve with a natural cubic spline with 4 internal knots placed at equal spaces in the temperature range to allow for enough flexibility in the 2 ends of temperature distribution, and the lag–response curve with a natural cubic spline with an intercept and 3 internal knots placed at equally spaced values in the log scale to allow more flexible lag effects at shorter delays.<sup>21</sup> The lag period is extended to 21 days to capture the long delay in the effects of cold and adequately assess the hot effects after excluding emergency hospitalizations advanced only by a few days (harvesting effect). The short lags cannot adequately assess the hot effects, as the harvesting effects are ignored.<sup>21</sup> We included a natural cubic spline of time (*t*) with 8 degrees of freedom per year to control for seasonality and long-term trends, a natural cubic spline of relative humidity with 3 degrees of freedom, and dummy variables for day of the week, public holidays (Holiday), and influenza epidemics (Influenza) to control for these time varying confounders.<sup>22</sup> Air pollutants (PM<sub>10</sub>, NO<sub>2</sub>, and O<sub>3</sub>) were controlled by including third-degree constrained polynomial distributed lags with a maximum lag of 3 days.<sup>23</sup> Autocorrelation of the residuals of the model was checked by partial autocorrelation function, which showed no serial autocorrelations along the lags.<sup>24</sup> The model can be specified as follows:

$$\begin{aligned} \log(E(Y_t)) &= \alpha + \beta \times \text{Temp}_{t,l} + \text{ns}(t, \text{df}) \\ &= 8 / \text{yr} \times \text{no. of years} + \text{ns}(\text{RH}_t, \text{df} = 3) + \\ &\quad \beta_1 \times \text{DOW}_t + \beta_2 \times \text{Holiday}_t + \beta_3 \times \text{Influenza}_t + \\ &\quad \beta_4 \times \text{PM}_{10(t,3)} + \beta_5 \times \text{NO}_{2(t,3)} + \beta_6 \times \text{O}_{3(t,3)} \\ &= \alpha + \beta \times \text{Temp}_{t,l} + \text{COVs} \end{aligned} \quad (1)$$

Here,  $E(Y_t)$  means the expected daily counts of emergency hospital admission for circulatory diseases on day *t*;  $\text{Temp}_{t,l}$ , matrix obtained by applying the DLNM to temperature;  $\beta$ , vector of coefficients for  $\text{Temp}_{t,l}$ ; *l*, the lag days;  $\text{ns}(\cdot)$ , the natural cubic spline function for nonlinear variables; *df*, degrees of freedom; RH, relative humidity; DOW, day of the week; and COVs, all time varying covariates.

The OT, corresponding to a minimum circulatory hospitalization risk, was derived from the best linear unbiased prediction of the overall cumulative exposure–response association, using a constrained segmented distributed lag approach.<sup>25,26</sup> The minimum Bayesian information criterion was suggested to select the threshold, which is more probable to meet for segmented models.<sup>25</sup> This threshold value was used as the reference temperature (centering value) for fitting the exposure–lag–response relationship, both in the overall analysis and in the stratified analyses in cool and warm season separately. The association was then reduced to the overall temperature–circulatory hospitalizations relationship, cumulating the risk during the lag period. As previous studies indicated that the effects of hot temperatures were generally more short term than those from cold temperatures while including some harvesting a few days later, besides the cumulative effect during 0 to 21 lag days, we also estimated temperature effects during the following lag periods: 0 to 1, 2 to 6, and 7 to 21 to represent the acute, delayed, and long-lasting effects, respectively.<sup>27</sup> Because the temperature–mortality or morbidity relationship was generally “U” or “J” shaped, we calculated the RRs for cold and hot temperatures, respectively. Specifically, we abstracted the RRs for circulatory hospitalizations at the first percentile and 10<sup>th</sup> percentile of temperature distribution relative to the OT to represent the effect of extreme and moderate cold, and the RRs at the 99<sup>th</sup> percentile and 90<sup>th</sup> percentile relative to the OT to represent the effect of extreme and moderate hot, respectively.

### Computation of AR

The OT value corresponding to the minimum circulatory hospitalizations was also considered as the reference to compute the AR by centering the natural cubic spline that models the exposure–response association. For a specific disease category, the overall cumulative RR corresponding to each day’s temperature was used to compute the AF and number in the next 21 days, using a backward approach described by Gasparrini et al.,<sup>9</sup> which summarized the current burden because of the past exposures. These extended definitions of AR account for the additional temporal dimension in exposure–response associations, providing more appropriate attributable measures for the cold exposure with potentially complex temporal patterns.

The total attributable number of hospitalizations because of non-OT is given by the sum of the contributions from all the days of the series, and its ratio with the total number of hospitalizations provides the total AF. Because the overall hot effect on circulatory hospitalizations was not detected in Hong Kong, we computed the component attributable to cold by summing the subsets corresponding to days with temperatures lower than the optimum temperature. It was further separated into moderate cold and extreme cold contributions.<sup>9,10</sup>

Empirical confidence intervals were obtained by Monte Carlo simulations assuming a multivariate normal distribution of the reduced coefficients.<sup>9</sup> We derived empirical confidence intervals for total attributable numbers and fractions, computed overall and separated components, by simulating 5000 samples from the assumed distribution.

All analyses were conducted in R statistical environment version 3.1.3 (R Development Core Team, 2014), with its *dlm* package<sup>20</sup> to fit DLNM to estimate the temperature effect, and *modTempEff* package<sup>28</sup> to fit constrained segmented distributed lag model to identify the threshold temperature where hospitalizations reached minimum. The AR (AF and AN) was calculated by function *attrdl* provided by Gasparrini et al.<sup>29</sup>

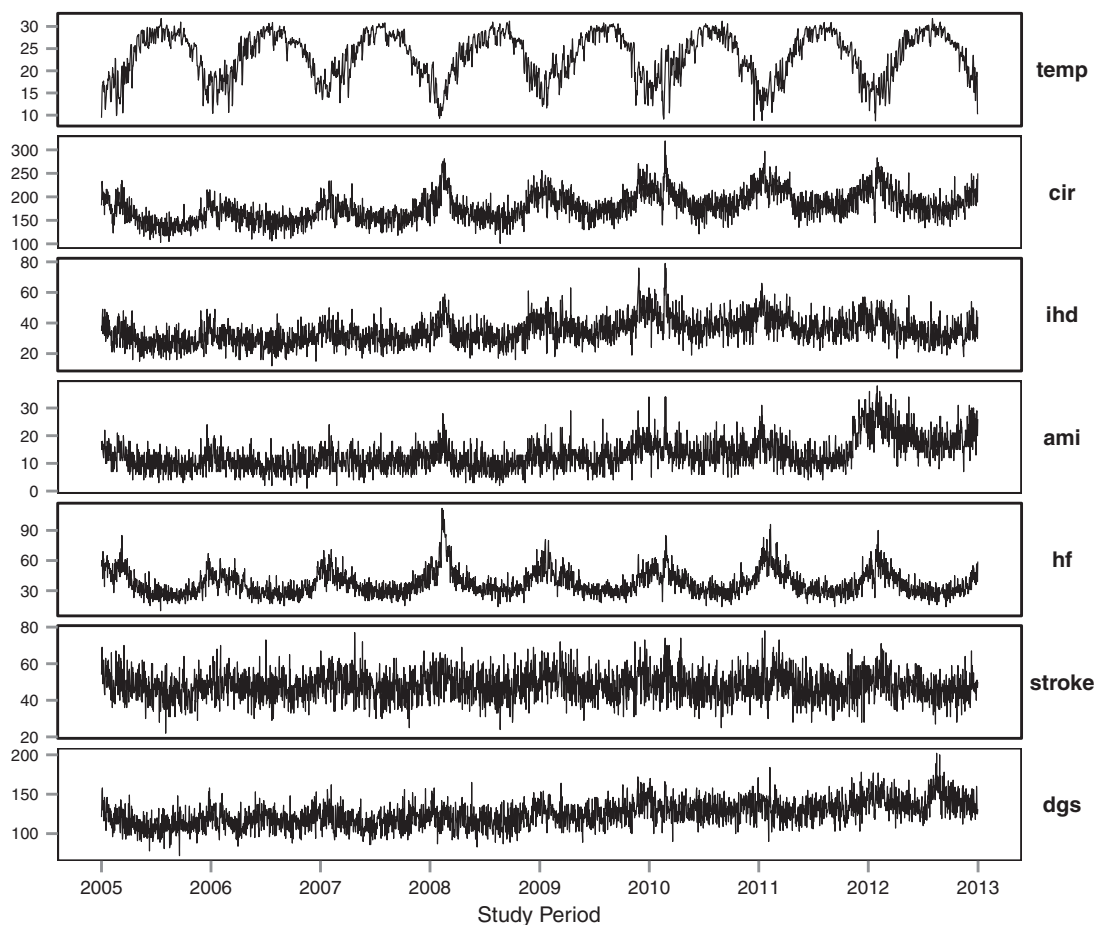
### Results

During the study period, a total of 521 575 emergency hospital admissions for circulatory diseases were recorded in Hong Kong. On an average, there were 179 emergency circulatory hospitalizations per day, of which 35 were IHD, 13 were AMI, 37 were HF, and 48 were stroke. The daily mean temperature was 23.4°C with range between 8.7°C and 31.8°C, and the relative humidity was 78%. The daily 24-hour mean concentration was 50.5 µg/m<sup>3</sup> for PM<sub>10</sub> and 55.9 µg/m<sup>3</sup> for NO<sub>2</sub>, whereas the daytime 8-hour mean concentration of O<sub>3</sub> was 47.1 µg/m<sup>3</sup> (Table 1). The time series plot shows the variation of daily mean temperature and emergency hospital admissions for circulatory diseases and each specific cause: both ambient

**Table 1. Descriptive Statistics of Daily Emergency Hospital Admissions for Circulatory Disease, Weather Conditions, and Air Pollution Concentrations in Hong Kong, 2005 to 2012 (2922 Days)**

Variables	Mean	SD	Percentiles				
			Min.	25th	50th	75th	Max.
Daily emergency hospital admissions							
Total circulatory	178.5	30.4	101	156	176	197	319
Ischemic heart diseases	34.8	8.6	12	29	34	40	79
Acute myocardial infarction	13.1	5.4	1	9	12	16	38
Heart failure	37.3	12.5	10	29	35	44	112
Stroke	48.0	7.8	22	43	48	53	78
Total digestive diseases	125.0	16.5	72	113	124	136	202
Weather conditions							
Mean temperature, °C	23.4	5.2	8.7	19.1	24.7	27.9	31.8
Relative humidity, %	78.4	10.5	31.0	74.0	79.0	85.8	99.0
Pollution concentration, µg/m <sup>3</sup>							
PM <sub>10</sub>	50.5	28.8	7.6	28.2	45.1	68.1	573.0
NO <sub>2</sub>	55.9	19.3	13.0	41.7	53.1	66.9	153.0
O <sub>3</sub>	47.1	30.2	4.8	23.2	39.7	64.9	203.2

Max. indicates maximum; Min., minimum; NO<sub>2</sub>, nitrogen dioxide; O<sub>3</sub>, ozone; and PM<sub>10</sub>, particulate matter with aerodynamic diameter <10 µm.



**Figure 1.** Time series plots for daily mean temperature (Temp, °C) and emergency hospitalizations (counts/d) for all circulatory diseases (CIR), ischemic heart disease (IHD), acute myocardial infarction (AMI), heart failure (HF), stroke, and all digestive diseases (DGS).

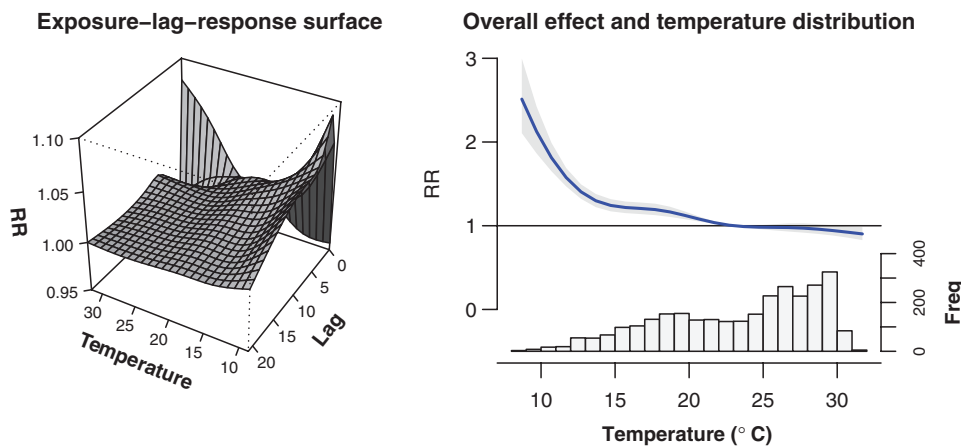
temperature and cardiovascular diseases follow apparent seasonal patterns and long-term trends (Figure 1).

Figure 2 shows the distributed lag–nonlinear relationship between temperature and total circulatory diseases, and the cumulative effect of temperature >21 lag days, using a natural cubic spline DLNM with 4 equal-spaced knots for temperature and 3 knots for lag. The exposure–lag–response surface revealed that the significant cold effect seemed on lag 1 day and lasted for 2 to 3 weeks, whereas acute hot effect occurred on the current day, followed by harvesting on lag 2 to 4 days and approached to null after 1 week. The overall temperature–hospitalization relationship was reversed ‘J’ shape with significant higher risk at low temperature and no apparent risk at high temperature.

The OT corresponding to the minimum circulatory hospitalizations in Hong Kong was identified as 23.0°C, close to the mean temperature in the study period. As indicated in Table 2, the temperature’s effects varied by lag periods. The overall RRs for extreme and moderate cold temperatures were non-significant on lag 0 to 1 days; the effects began on lag 2 day and generally increased with more lagged days. Compared with the OT, the RR during 0 to 21 lag days was 1.69 (95% confidence interval, 1.56–1.82) for extreme cold (first percentile) and 1.22 (95% confidence interval: 1.15–1.29) for moderate cold (10th percentile). The cold effects were stronger for IHD, AMI, and especially for HF, whereas weaker for

stroke. In contrast, the hot temperature showed some acute effects on total circulatory diseases and followed by harvesting. The overall effects of hot temperatures during 0 to 21 lag days for circulatory diseases and each subcategory were found to be nonsignificant (Table 2). The exposure–response curves show the consistent associations between cold and hospitalizations for all circulatory diseases and each specific cause (Figure 3). Mortality as a secondary outcome generated consistent results with the emergency hospitalizations (Figure I in the Data Supplement). Further stratified analyses in cool and warm seasons separately, which is an alternative approach to control for seasonality, also shows consistent significant associations in cool seasons but no apparent associations in warm seasons (Figures II and III in the Data Supplement). We did not observe any significant associations between all digestive diseases and both cold and hot temperatures. At the same time, the significant associations with air pollution were found in modified models, as the standard time series air pollution studies have been done previously.<sup>30</sup> (Table I in the Data Supplement).

The OT was also used as the reference point for the computation of the AR measures. Table 3 provides estimates of the AF and AN for total circulatory diseases and specific subcategories that attributed to cold temperature, with the components attributed to extreme cold and moderate cold separately. The comparison of the 2 contributions clearly indicates that



**Figure 2.** Distributed-lag-nonlinear relationship between temperature and emergency circulatory hospitalizations and the cumulative effect of temperature >21 lag days. RR indicates relative risk.

moderate cold is responsible for the major part of the temperature associated circulatory hospitalizations, with the AF=6.33% for moderate cold and 0.82% for extreme cold while inducing 33030 and 4257 cases during the 8 years' study period, respectively. Among the specific causes of circulatory diseases, AMI, HF, and IHD showed the higher risk of hospitalization attributed to cold temperature, with AF of 10.1% to 12.6% for moderate cold and 1.1% to 1.7% for extreme cold. The risk attributed to cold for stroke was less pronounced (Table 3).

### Discussion

In this study, we examined the nonlinear delayed association between ambient temperature and emergency hospital admissions for circulatory diseases and assessed the risk attributed to cold temperature. We observed significant positive effect of cold started on lag 2 day and lasted for 3 weeks. The hot effect was acute on lag 0 day, followed by harvesting and led to a null cumulative effect during 2 to 3 weeks. Hospitalization risk for cardiovascular diseases attributed to temperature was main because of the cold, and moderate cold was responsible for the major part of the AF and number of hospitalizations. Specific diseases such as AMI, HF, and IHD showed higher susceptibility to cold temperature exposure.

The association between cold temperature and CVD morbidity has been well documented in the literature.<sup>2</sup> Although the effect estimates were heterogeneous across geographical locations, the main finding was consistent as delayed and longer cold effects for  $\leq 2$  to 3 weeks. In this study, we observed similar exposure-lag-response relationship between cold and emergency CVD hospitalizations, and added to the literature the higher RRs for AMI, HF, and IHD. The associations with air pollutants were also estimated with the standard model<sup>30</sup> and presented in the in the Data Supplement for reference.

Biological processes underlying the cold-related morbidity has been explored. Exposure to cold would associate with cardiovascular stress by affecting blood pressure and plasma fibrinogen, increasing thrombosis, vasoconstriction and blood viscosity, and inflammatory responses.<sup>31,32</sup> These physiological responses can persist for longer than those effects from heat,<sup>32</sup> and seem to produce hospitalization risk after a

persistent response, so that the most of the AR occurred on moderately cold days.

The effect of hot temperatures on emergency hospital admissions for CVD was reported widely in regions<sup>2,4,12</sup>; however, we did not observe the positive associations between hot temperature and CVD in this study. The results were consistent with a previous study in Vietnam, which reported the nonsignificant association between hot temperature and CVD hospital admissions.<sup>33</sup> Even though some acute hot effect on lag 0 to 1 days was significant for stroke, the cumulative effect of hot temperature >1 week and longer period disappeared because of the harvesting. Hong Kong is a subtropical city located on the southern coast of China with hot and humid summer, whereas the mean temperature in summer (May to October) was 27.8°C, ranging between 18.7°C and 31.8°C. Although the mean temperature in summer was higher than the optimum for 98% of days, we did not find significant hot temperature effect for CVD and stroke hospitalizations, which may probably because of the population adaptation, high prevalence of air conditioner usage, and fewer outdoor activities. A previous study revealed that heat-related mortality declined and the population had become resilient to heat over time, especially in the elderly subjects >75 years of age.<sup>34</sup> High prevalence of air conditioner usage was also linked to the decreased extreme hot-related mortality or morbidity.<sup>35</sup>

Harvesting is the phenomenon that arises when a stressor affects mainly a pool of frail individuals, whose events are only brought forward by a brief period of time by the exposure.<sup>36</sup> Evidence of harvesting effect of hot temperature on mortality displacement has been well documented<sup>37-39</sup>; however, the impact of harvesting on morbidity has not been fully investigated. Schwartz et al<sup>3</sup> reported similar evidence of a short-term advance in emergency hospital admissions for heart diseases and myocardial infarction among people >65 years of age within a few days after hot temperature exposure, with a positive association on the day of admission followed by a period of lower-than-average admissions, returning to the baseline after a week. The temporal pattern for the effect of high temperatures suggested harvesting effects, whereas no evidence of harvesting effect was observed for cold weather for heart diseases, which was consistent with the findings in this study.

**Table 2. RR of Cold and Hot Temperatures on Emergency Hospital Admissions for Circulatory Diseases and Subcategories Over Multiple Lag Days in Hong Kong, 2005 to 2012 (RR With 95% CI)**

Diseases	Lag Days	Extreme Cold*	Moderate Cold†	Moderate Hot‡	Extreme Hot§
All CIR	0–1	0.98 (0.95–1.01)	0.97 (0.95–0.99)	1.04 (1.01–1.06)	1.04 (1.01–1.07)
	2–6	1.25 (1.21–1.29)	1.10 (1.08–1.13)	0.93 (0.91–0.96)	0.92 (0.89–0.94)
	7–21	1.38 (1.30–1.47)	1.14 (1.09–1.18)	0.98 (0.94–1.03)	0.97 (0.92–1.02)
	0–21	1.69 (1.56–1.82)	1.22 (1.15–1.29)	0.95 (0.89–1.01)	0.92 (0.86–0.99)
IHD	0–1	0.92 (0.87–0.98)	0.96 (0.92–1.00)	1.05 (1.00–1.11)	1.05 (0.99–1.12)
	2–6	1.39 (1.30–1.48)	1.17 (1.12–1.23)	0.92 (0.87–0.97)	0.90 (0.85–0.96)
	7–21	1.63 (1.44–1.83)	1.24 (1.14–1.35)	0.96 (0.87–1.06)	0.96 (0.86–1.06)
	0–21	2.08 (1.76–2.45)	1.39 (1.24–1.56)	0.93 (0.82–1.06)	0.90 (0.78–1.05)
AMI	0–1	0.99 (0.91–1.09)	0.97 (0.90–1.03)	1.02 (0.94–1.11)	1.04 (0.94–1.14)
	2–6	1.48 (1.35–1.64)	1.22 (1.13–1.31)	0.93 (0.85–1.01)	0.92 (0.83–1.01)
	7–21	1.62 (1.33–1.97)	1.27 (1.11–1.46)	1.04 (0.89–1.21)	1.03 (0.86–1.23)
	0–21	2.38 (1.83–3.10)	1.49 (1.24–1.80)	0.99 (0.80–1.22)	0.98 (0.77–1.25)
HF	0–1	0.96 (0.91–1.01)	0.91 (0.88–0.95)	1.04 (0.98–1.09)	1.01 (0.95–1.08)
	2–6	1.39 (1.31–1.48)	1.18 (1.12–1.23)	0.87 (0.82–0.92)	0.85 (0.80–0.91)
	7–21	1.95 (1.75–2.19)	1.33 (1.23–1.45)	0.99 (0.90–1.09)	1.03 (0.92–1.15)
	0–21	2.61 (2.24–3.04)	1.43 (1.28–1.60)	0.89 (0.78–1.02)	0.89 (0.76–1.03)
Stroke	0–1	1.00 (0.95–1.05)	0.99 (0.95–1.02)	1.04 (1.00–1.09)	1.07 (1.01–1.12)
	2–6	1.17 (1.11–1.24)	1.05 (1.01–1.09)	0.97 (0.92–1.01)	0.95 (0.90–1.00)
	7–21	1.13 (1.02–1.26)	1.05 (0.98–1.13)	0.95 (0.88–1.03)	0.90 (0.82–0.98)
	0–21	1.33 (1.15–1.53)	1.09 (0.99–1.20)	0.96 (0.86–1.07)	0.91 (0.80–1.02)
Digestive	0–1	0.93 (0.90–0.96)	0.98 (0.95–1.00)	1.04 (1.01–1.07)	1.04 (1.01–1.08)
	2–6	1.09 (1.05–1.13)	1.04 (1.01–1.07)	0.98 (0.95–1.01)	0.98 (0.95–1.01)
	7–21	1.06 (0.99–1.14)	1.01 (0.96–1.06)	1.02 (0.97–1.07)	1.02 (0.97–1.08)
	0–21	1.08 (0.98–1.18)	1.03 (0.96–1.10)	1.04 (0.97–1.11)	1.05 (0.97–1.13)

AMI indicates acute myocardial infarction; CI, confidence interval; CIR, circulatory disease; HF, heart failure; IHD, ischemic heart disease; and RR, relative risk.

\*The first percentile of temperature (11.2°C), compared with the optimal temperature at 23.0°C.

†The 10th percentile of temperature (15.8°C), compared with the optimal temperature at 23.0°C.

‡The 90th percentile of temperature (29.4°C), compared with the optimal temperature at 23.0°C.

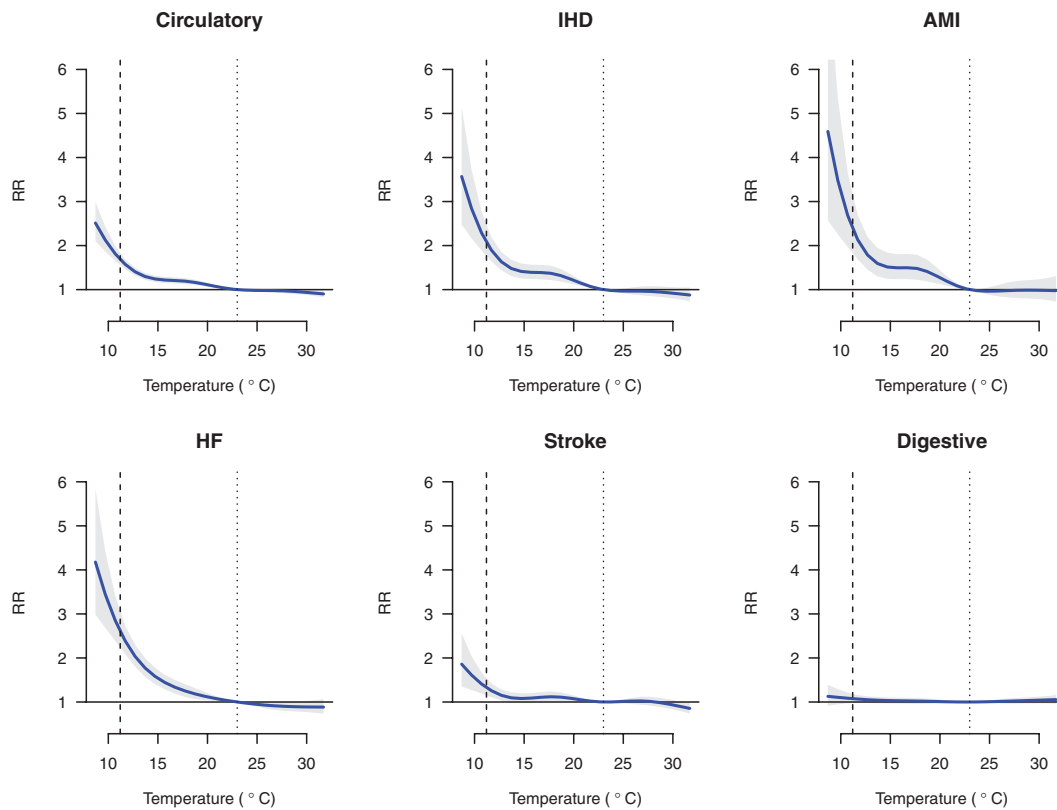
§The 99th percentile of temperature (30.6°C), compared with the optimal temperature at 23.0°C.

AF and AN quantify the disease burden because of specific risk factors for specific diseases, which has important public health implications pointing to the potential impact of an intervention or prevention.<sup>14</sup> In this study, we calculated AF and AN with extended definition of AR measures based on the DLNM framework. Results revealed that cold is mainly responsible for the temperature-related circulatory hospitalizations in Hong Kong, with 7.15% of total emergency circulatory hospitalizations attributed to cold. The AFs for moderate cold for specific causes of circulatory diseases were 7× to 9× of those for extreme cold. Most of the hospitalizations were in fact attributable to moderate cold in spite of the relatively lower RR compared with that of extreme cold, which may be explained that moderate temperature range included the majority of the days in the series.

The weather-warning system has been implemented in Hong Kong to alert the public for the dangers of extreme weather conditions.<sup>40</sup> The present assessment suggests that implemented public health policies and interventions

specifically designed for extreme weather conditions should be extended to consider the effects associated with cold temperature, and focused on the susceptible subpopulations.

The strength of this study is the application of updated flexible statistical model to characterize the temperature-hospitalization association and identified the OT. This is the first study to assess the AR of cold temperature on emergency circulatory hospitalizations, based on its nonlinear delayed relationship, and separated the attributable components into contributions from extreme and moderate cold temperatures. Meanwhile, some limitations should be noted. As in all other time series studies, personal exposure data were not available. The outdoor monitoring data were used to represent the population exposure to ambient temperature, which may induce exposure misclassifications. A study conducted in Greater Boston reported that the relationship between indoor and outdoor ambient temperature was different, with strong correlation only at warmer outdoor temperatures but weak correlation



**Figure 3.** The cumulative effect of temperature >21 lag days on emergency hospital admissions for all circulatory diseases and the specific causes. The dotted and dashed lines show the first percentile (11.2°C) and the optimal temperature (23.0°C), respectively. All digestive disease was used as a negative control. AMI indicates acute myocardial infarction; HF, heart failure; IHD, ischemic heart disease; and RR, relative risk.

at cooler temperatures.<sup>41</sup> But for the subtropical city of Hong Kong with high prevalence of air conditioner usage in summer but low prevalence of house heating in winter, the situation may be opposite. Outdoor fixed site measurement for ambient temperature may represent the average population exposure better in cool season than in hot season in Hong Kong. Another limitation was that we only include emergency hospital admissions for circulatory diseases but did not capture the less severe cases. However, the emergency hospitalizations could be assumed as less being influenced by health-seeking behaviors and were considered to be more sensitive and better reflect the acute effect of temperature change than mortality did. Finally, caution is warranted when the findings of this

single-city study are generalized to other places with different climates and population characteristics.

**Conclusions**

We observed significant nonlinear and delayed effect of cold temperature on emergency circulatory hospitalizations in this study. The OT corresponding to the minimum circulatory hospitalizations was 23.0°C in Hong Kong. Extreme cold weather showed a higher RR while moderate cold weather was responsible for a considerable fraction and number of emergency circulatory hospitalizations. Public health policies and preventions should consider the temperature-related hospitalizations risk on susceptible subpopulations.

**Table 3. Attributable Risk of Temperature on Emergency Hospitalizations for Circulatory Diseases, Contributing to Extreme and Moderate Cold Temperatures With 95% Empirical Confidence Intervals, 2005 to 2012**

Subgroup	Total No.*	Extreme Cold†		Moderate Cold‡	
		AF (%)	AN	AF (%)	AN
Total circulatory	521 575	0.82 (0.69–0.94)	4257 (3604–4922)	6.33 (4.72–7.75)	33 030 (24 465–40 510)
IHD	101 548	1.14 (0.87–1.39)	1157 (898–1429)	10.11 (7.27–12.76)	10 264 (7076–13 136)
AMI	38 292	1.44 (0.99–1.83)	552 (387–705)	12.56 (8.1–16.81)	4809 (2966–6424)
HF	108 961	1.74 (1.44–2.04)	1899 (1578–2199)	11.47 (7.81–14.51)	12 501 (8903–15 727)
Stroke	140 358	0.45 (0.24–0.64)	628 (307–905)	3.3 (0.42–5.93)	4638 (373–8092)

AF indicates attributable fraction; AMI, acute myocardial infarction; HF, heart failure; and AN, attributable number.

\*Total emergency hospital admissions for each disease category during the study period.

†Extreme cold was defined as those days with temperature at or lower than the first percentile of distribution.

‡Moderate cold was defined as those days with temperature range between the first percentile (11.2°C) and 23.0°C (the optimum).

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## Disclosures

None.

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## Emergency Cardiovascular Hospitalization Risk Attributable to Cold Temperatures in Hong Kong

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## SUPPLEMENTAL MATERIAL

### Supplemental Methods

#### *CVD mortality as a secondary outcome measure*

CVD mortality of the same disease categories as a secondary outcome measure was examined. We used the same approach that described in the main text <sup>1,2</sup> to identify the optimal temperature for CVD mortality, which was 26°C in Hong Kong and a little different from that for CVD hospitalizations (23°C). The exposure-lag-response relationship between ambient temperature and CVD mortality was examined using distributed lag non-linear model <sup>3</sup>. Figure-S1 below provides the consistent results with the emergency CVD hospitalizations.

#### *Stratified analyses by season*

Exposure-response relationships between ambient temperature and emergency CVD hospitalizations were estimated in cool seasons (November to April) and in warm seasons (May to October) separately. Stratified analyses by season were considered as an alternative approach to well control the seasonality. Figure-S2 and S3 below show the consistent significant associations in cool seasons but no apparent associations in warm seasons, the same as what we have found using the whole period data for analyses.

#### *Association with air pollution*

The associations between air pollution and emergency CVD hospitalizations were estimated using the same available data.

In the main text of the manuscript, we examined the emergency CVD hospitalizations risk attributed to ambient temperature. We extended the lag period to 21 days in order to capture the long delay in the effects of cold and adequately assess the hot effects while considering the harvesting effect <sup>4</sup>. We also adjusted for air pollution as the time-varying confounders and put PM<sub>10</sub>, NO<sub>2</sub> and O<sub>3</sub> in the model simultaneously to get the most conservative effect estimates for temperature <sup>5</sup>. However in these model specifications, the true effects of air pollutants would be underestimated due to the probably over-adjustment of ambient temperature.

To examine the effect estimates for air pollutants, we modified the statistical model used in the main text with the adjustment for the confounding effect of temperature in 0-3 lags (the mean temperature of current day, Temp<sub>0</sub>, and the moving average of previous 3 days, Temp<sub>1-3</sub>), as the standard air pollution time series studies have been done previously <sup>6</sup>.

The model specifications are as follows:

$$\begin{aligned} \log(E(Y)) &= \alpha + \beta * \text{Pollutant} + \text{ns}(t, \text{df}=8/\text{year} \times \text{no. of years}) \\ &\quad + \text{ns}(\text{Temp}_0, \text{df}=6) + \text{ns}(\text{Temp}_{1-3}, \text{df}=6) + \text{ns}(\text{RH}, \text{df}=3) \\ &\quad + \beta_1 * \text{DOW} + \beta_2 * \text{Holiday} + \beta_3 * \text{Influenza} \\ &= \alpha + \beta * \text{Pollutant} + \text{COVs} \end{aligned}$$

Here  $E(Y)$  means the expected daily counts of emergency hospital admission for circulatory diseases on day  $t$ ;  $ns(.)$  is the natural cubic spline function for nonlinear variables. Each pollutant was included in the model in third-degree constrained polynomial distributed lags with a maximum lag of 3 days, and presented as cumulative effect over 0-3 lag days.

### Supplemental Tables

We found the statistically significant associations between emergency hospitalizations for all circulatory diseases, IHD, HF and  $PM_{10}$ ,  $NO_2$  and  $O_3$ . And the association between AMI and  $NO_2$  was also found. We did not observe the significant effect of air pollution on stroke. (Table-S1)

Table-S1 The associations (RR (95%CI) per  $10\mu g/m^3$  increase of each pollutant) between air pollution and CVD hospitalizations\*

	$PM_{10}$	$NO_2$	$O_3$
<b>All Circulatory</b>	<b>1.003 (1.000, 1.005)</b>	<b>1.012 (1.008, 1.015)</b>	<b>1.003 (1.001, 1.005)</b>
<b>IHD</b>	<b>1.007 (1.003, 1.012)</b>	<b>1.017 (1.011, 1.024)</b>	<b>1.007 (1.002, 1.011)</b>
<b>AMI</b>	1.006 (0.998, 1.013)	<b>1.013 (1.003, 1.024)</b>	1.001 (0.994, 1.008)
<b>HF</b>	<b>1.008 (1.004, 1.013)</b>	<b>1.022 (1.015, 1.029)</b>	<b>1.009 (1.004, 1.013)</b>
<b>Stroke</b>	0.996 (0.993, 1.000)	1.004 (0.998, 1.009)	0.999 (0.995, 1.002)

\*: Generalized linear Poisson regression model and DLNM was used to estimate the cumulative effect of each pollutant distributed over 0-3 lag days in single-pollutant model, after adjusting for the time trend, seasonality, meteorological factors, calendar effect and influenza epidemics.

### Supplemental Figures and Figure Legends:

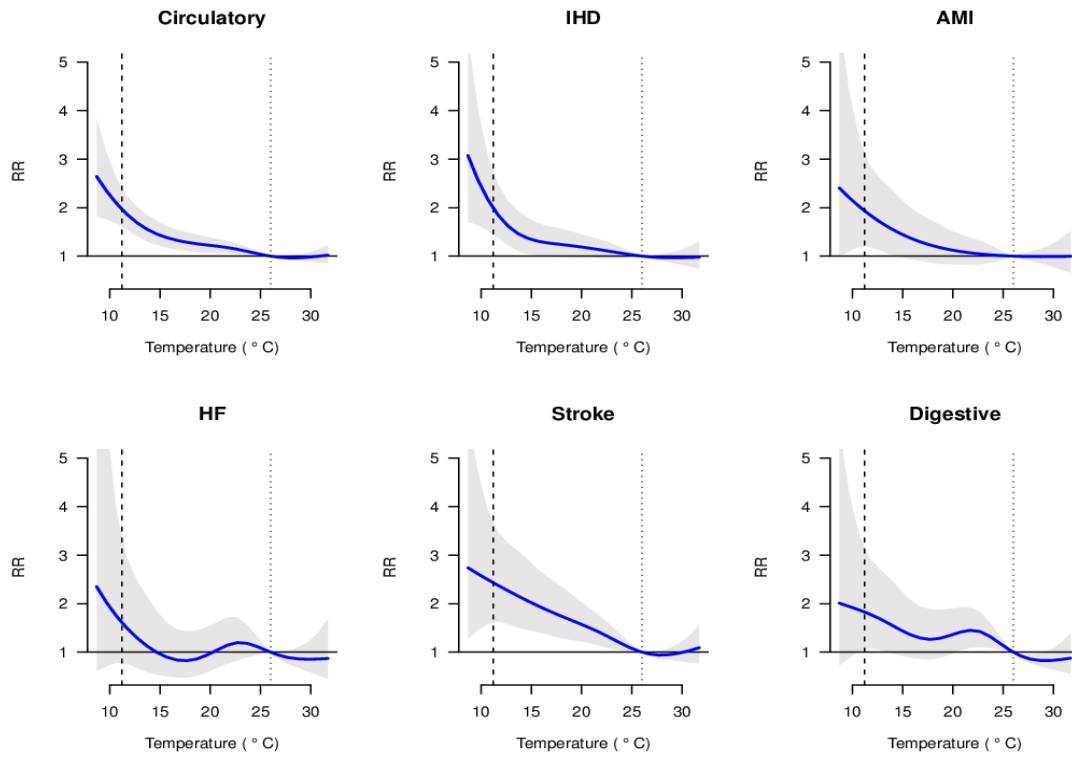


Figure-S1 The cumulative effect of temperature over 21 lag days on circulatory mortality and four specific categories. The dotted and dashed lines show the 1st percentile (11.2°C) and the optimal temperature (26.0°C), respectively. The digestive mortality is used as the negative control.

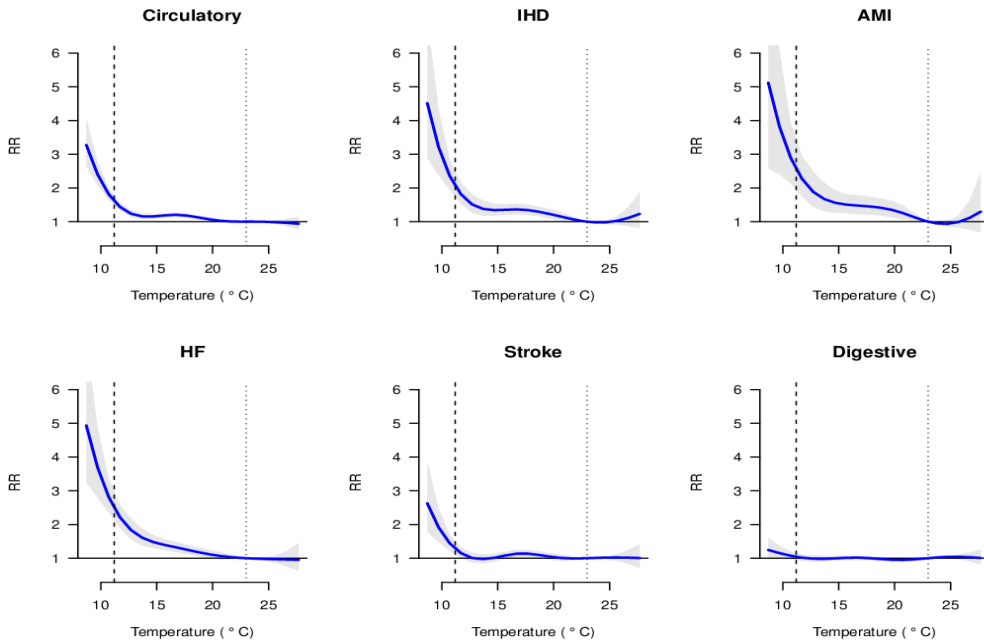


Figure-S2 The cumulative effect of temperature over 21 lag days on CVD hospitalizations **in cool seasons**. The dotted and dashed lines show the 1<sup>st</sup> percentile (11.2°C) and the optimal temperature (23.0°C), respectively. All digestive disease was used as a negative control.

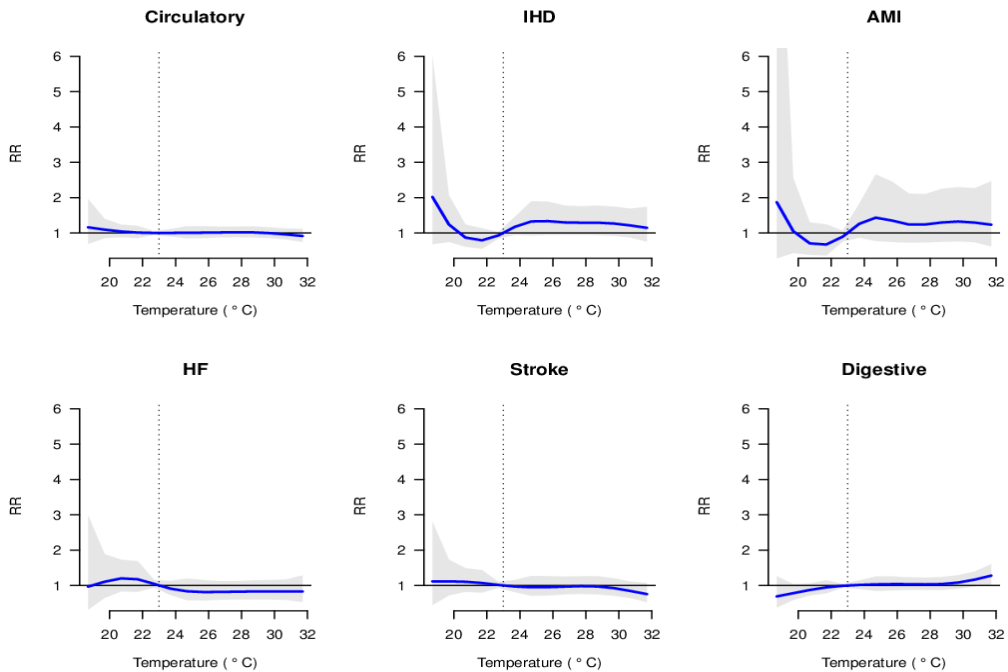


Figure-S3 The cumulative effect of temperature over 21 lag days on CVD hospitalizations **in warm seasons**. The optimal temperature (23.0°C) was used as the reference value and all digestive disease was used as a negative control.

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