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CLINICAL RESEARCH
Epidemiology and prevention

Low ambient temperature and temperature drop between neighbouring days and acute aortic dissection: a case-crossover study

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See the editorial comment for this article 'Ambient temperature and aortic dissection: do pipes burst in freezing weather?', by Makoto Hibino *et al.*, https://doi.org/10.1093/eurheartj/ehab792.

Aims The incidence of acute aortic dissection (AAD) has been shown to have seasonal variation, but whether this variation can be explained by non-optimum ambient temperature and temperature change between neighbouring days (TCN) is not clear.

Methods and results We performed a time-stratified case-crossover study in the Registry of Aortic Dissection in China covering 14 tertiary hospitals in 11 cities from 2009 to 2019. A total of 8182 cases of AAD were included. Weather data at residential address were matched from nearby monitoring stations. Conditional logistic regression model and distributed lag nonlinear model were used to estimate the associations of daily temperature and TCN with AAD, adjusting for possible confounders. We observed an increase of AAD risk with lower temperature cumulated over lag 0–1 day and this association became statistically significant when daily mean temperature was below 24°C. Relative to the referent temperature (28°C), the odds ratios (ORs) of AAD onset at extremely low (-10°C) and low (1°C) temperature cumulated over lag 0–1 day were 2.84 [95% confidence interval (CI): 1.69, 4.75] and 2.36 (95% CI: 1.61, 3.47), respectively. A negative TCN was associated with increased risk of AAD. The OR of AAD cumulated over lag 0–6 days was 2.66 (95% CI: 1.76, 4.02) comparing the extremely negative TCN (-7°C) to no temperature change. In contrast, a positive TCN was associated with reduced AAD risk.

Conclusion This study provides novel and robust evidence that low ambient temperature and temperature drop between neighbouring days were associated with increased risk of AAD onset.

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Key Question

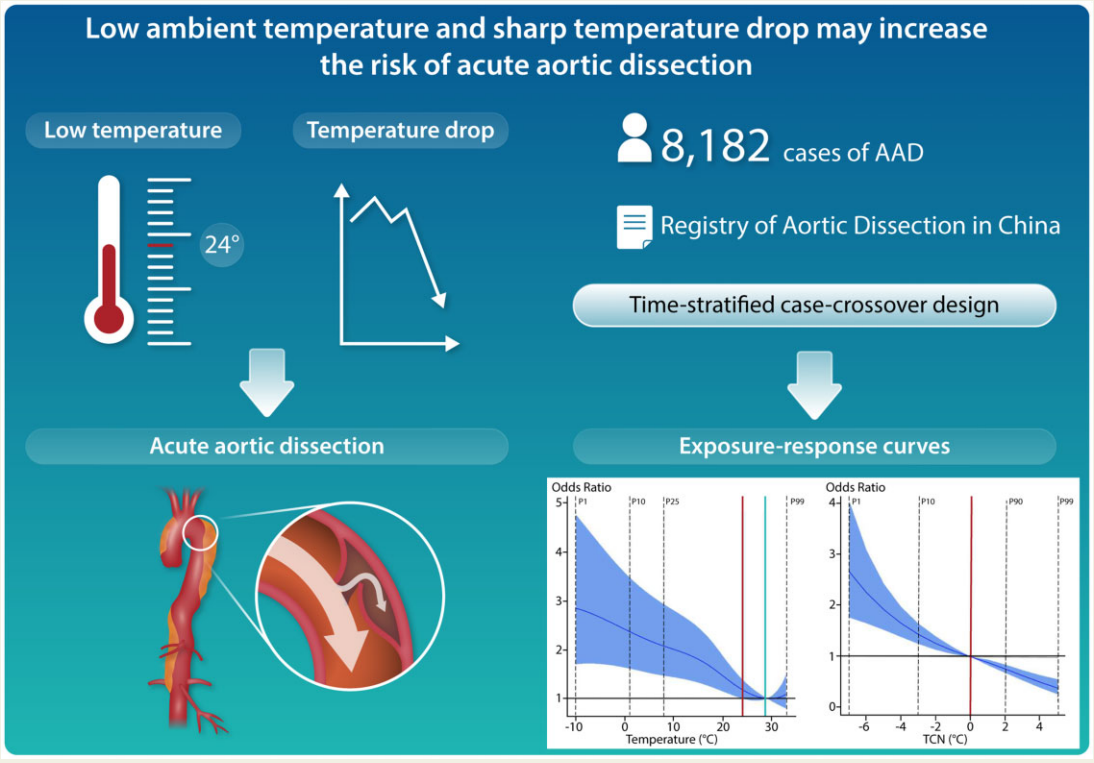
Incidence of acute aortic dissection (AAD) was reported to have seasonal trends, but it remains unclear whether non-optimum ambient temperature and temperature change between neighbouring days (TCN) is associated with AAD onset.

Key Finding

Daily mean temperature lower than 24°C was significantly associated with increased risk of AAD at lag 0–1 day. A negative TCN (temperature drop) was associated with increased risk of AAD, whereas a positive TCN was associated with decreased risk.

Take Home Message

This multi-centre, case-crossover study provides novel and robust evidence that low ambient temperature and temperature drop between neighbouring days were associated with increased AAD risk.



Structured Graphical Abstract Low ambient temperature and sharp temperature drop may increase the risk of acute aortic dissection.

Keywords Acute aortic dissection • Ambient temperature • Temperature change • Case-crossover study • Multi-centre study

Introduction

Acute aortic dissection (AAD) is one of the most life-threatening cardiovascular emergencies caused by tearing of the inner layer of the aortic wall and the consequential separation of the inner layer from the middle layer of the aorta.[1–3] Although AAD is rare with incidence rates between 3 and 8 per 100 000 person-years as reported previously,[4–6] the fatality rate of AAD is high even with advanced treatments.[7] Thus, identifying potential risk factors is especially critical for AAD prevention.

Incidence of AAD has been found to be highest in winter and lowest in summer.[8–11] Such seasonal variation suggested a possibility that ambient temperature may be an important environmental risk factor of AAD. In addition, temperature variability such as temperature change between neighbouring days (TCN) has also been linked with adverse cardiovascular outcomes in the literature.[12] So far, several studies have suggested the associations of meteorological factors, including ambient temperature, with AAD, but most studies were conducted in single cities, and may be subject to ecological bias and residual confounding such as long-term time trends and

seasonality.[8,11,13–19] Besides, to the best of our knowledge, no studies have considered TCN as a potential risk factor of AAD and no investigations have evaluated the lag pattern for the effects of temperature and TCN on AAD onset at individual level, which may have important implications for AAD prevention.

Therefore, we conducted a time-stratified case-crossover study using the multi-centre Registry of Aortic Dissection in China to quantitatively evaluate the association of ambient temperature and TCN with AAD onset. We also aimed to explore the lag pattern of these associations and to identify the susceptible population.

Methods

Study population

Incident cases of AAD from 1 January 2009 to 31 December 2019 were obtained from the ongoing Registry of Aortic Dissection (available at: www.Sino-RAD.com) in China, which was established to understand the clinical features and outcomes of AAD in the Chinese population.[20] This programme invited large cardiovascular centres from representative areas of China. Finally, 14 tertiary hospitals in 11 large Chinese cities (Beijing, Shanghai, Xi'an, Guangzhou, Wuhan, Fuzhou, Chongqing, Chengdu, Shenyang, Changsha, and Lanzhou) were included in this study. These hospitals spread over all seven geographical zones of China, including Northeast of China ($n = 1$), Northwest of China ($n = 2$), Northern China ($n = 2$), Central China ($n = 2$), Southern China ($n = 1$), Southwest of China ($n = 3$), and Eastern China ($n = 3$).

The suspected AAD cases admitted to above hospitals were evaluated and diagnosed based on clinical presentation and imaging findings from computed tomography angiography or echocardiography. Thereafter, the diagnosed AAD cases were recorded in the Hospital Information System and then a code under I71.0 according to the Chinese clinical modification of International Classification of Diseases-10 would be assigned to each patient. These codes include I71.000–I71.005 and I71.007, which cover all subclassifications of AAD.[11] I71.006 was not included because it represents intramural haematoma, which is essentially one of acute aortic syndromes rather than AAD.[21] When establishing the registry, the electronic medical records of AAD patients were retrieved from the Hospital Information System in each hospital based on the diagnosis name of AAD (in Chinese) and then inputted into the registry database by well-trained staffs.

Data on age, sex, onset time (the earliest time of symptoms reported by the patient or the patient's relatives), residential address, smoking, alcohol drinking, and comorbidities (diagnosed hypertension, type 2 diabetes, coronary artery disease, and connective tissue disorders) of AAD cases were extracted from the registry. Some AAD cases were excluded from the current analysis based on the following criteria: (i) AAD with unknown onset time, such as chronic aortic dissection and asymptomatic aortic dissection; (ii) AAD with no precise residential address; (iii) traumatic AAD; or (iv) iatrogenic AAD within 1 year following surgical intervention or endovascular repair. This study was approved by the Institutional Review Board of Zhongshan Hospital, Fudan University, with a waiver of informed consent.

Exposure assessment

It was reported that daily mean temperature may be a better predictor of population health than daily maximum or minimum temperatures.[22] Thus, we used the daily mean temperature as the indicator of ambient temperature in this study. The daily mean temperature and mean relative humidity were derived from the China Meteorological Data Sharing Service System (http://data.cma.cn/). TCN was defined as the difference of daily mean temperature on the current day minus that on the previous day. As ambient air pollution may confound the associations of temperature with AAD, we obtained air pollution data from 2013 to 2019 from the National Urban Air Quality Real-time Publishing Platform of China (http://106.37.208.233:20035). Each AAD case was assigned to weather and air quality data monitored at the nearest station to his or her residential address.

Study design

We used a time-stratified case-crossover design to explore the associations of ambient temperature and TCN on the onset of AAD. The case-crossover study design has been widely used to investigate acute effects of environmental exposures on various health outcomes.[23–25] By design, each AAD case served as his or her own control and so factors that were time-invariant or less likely to change in a short duration, such as age, sex, weight, socio-economic status, lifestyle, and comorbidities, were automatically controlled for. For each AAD case, the case day was the day of AAD onset. Control days were selected as days when the patient did not have an AAD onset. To avoid confounding by long-term trends and seasonality, we included control days in the same year, month, and day of week with the case day in this analysis. Each case was thus matched to 3 or 4 control days.

Statistical analysis

We used conditional logistic regression models to quantify the associations of AAD onset with daily temperature and TCN, respectively. To explore the possible nonlinear and lagged associations of temperature and AAD, we incorporated the distributed lag nonlinear model (DLNM) into the conditional logistic regression models.[26] This DLNM model can create a flexible cross-basis function for temperature or TCN allowing for nonlinear exposure-response relationships in each lag day and nonlinear lagged effects.[27] In this study, we used a natural cubic B-spline with 5 degrees of freedom (df) in the exposure-response curve in the cross-basis function for daily mean temperature and a natural cubic spline of 3 df for TCN.[28,29] Effects across different lag days were defined to have three equally-spaced internal knots by the log of lags for flexible lag effects at short delays.

We empirically incorporated several covariates into the model based on prior studies[30,31]: (i) a dummy variable of public holiday and (ii) a natural cubic spline with 3 df in the cross-basis function for relative humidity. The formula for the main model in this study was adopted as follows: $E(Y) = \alpha + cb.DMT/cb.DMTC + \beta \times stratum + cb.RHU + holiday$. $E(Y)$ refers to the case or the control, α is the intercept, *stratum* is defined as the same days of the week in the same month of the same year and same patient, *cb. DMT* is the cross-basis function for daily mean temperature, *cb. DMTC* is the cross-basis function for TCN, *cb. RHU* is the cross-basis function for daily mean relative humidity, and *holiday* is a binary variable to control for public holidays.

We first used a maximum lag of 6 days prior to AAD onset (lag 0–6 days, 1 week) to fully explore the lag pattern of short-term temperature exposure and then used the lag days till the AAD risk close to 1 for subsequent analyses.

We then plotted the exposure–response relationship curves after truncating the temperature or TCN distribution from the 1st to 99th percentiles to reduce statistical uncertainty associated with very small sample size at exposure extremes. To better interpret out results, we chose a referent temperature as the one corresponding to the lowest AAD risk in the exposure–response curve and reported the odds ratio (OR) and 95% confidence intervals (CIs) of AAD onset associated with the extremely low (1st percentile) and low (10th percentile)

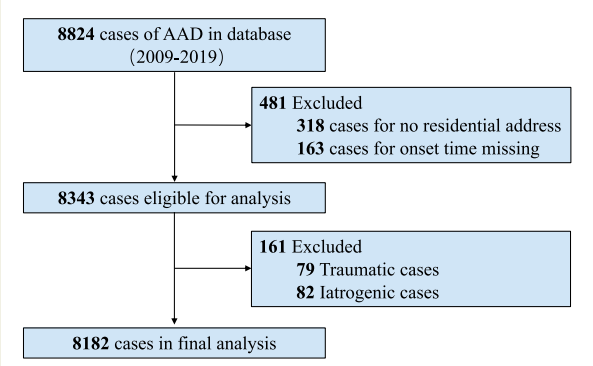


Figure 1 The flow diagram for the inclusion and exclusion of acute aortic dissection patients.

temperatures compared to the referent in main analyses. For TCN, we *a priori* determined a TCN of 0°C (i.e. no temperature difference between the current and the previous day) as the referent and reported the ORs and CIs associated with the extremely negative TCN (1st percentile), moderate negative TCN (10th percentile), moderate positive TCN (90th percentile), and extremely positive TCN (99th percentile) in main analyses.

We considered sensitivity analyses by adding the daily mean temperature and TCN simultaneously into the model to adjust for possible confounding by co-exposure. In addition, we further controlled for fine particulate matter ($PM_{2.5}$) and ozone (O_3) in the model using data collected during 2013–19 because air pollution data were first available in 2013.

To further identify the susceptible population, we conducted stratified analyses by fitting separate models by age (<60 or ≥60 years), sex, and history of hypertension, diabetes, coronary artery disease, smoking, alcohol drinking, and connective tissue disorders. Effect modification was examined by the difference and 95% CI of effect estimates by strata, calculated as $(\hat{Q}_1 - \hat{Q}_2) \pm 1.96\sqrt{\hat{SE}_1^2 + \hat{SE}_2^2}$, where $\hat{Q}_1$ and $\hat{Q}_2$ are regression coefficients by strata; and $\hat{SE}_1^2$ and $\hat{SE}_2^2$ are the standard errors.[32] We then calculated the *P*-value for effect modification using the CIs of the between-strata difference as calculated above.[33]

All statistical analyses were conducted in the R software (version 3.4.4, R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided, and a *P*-value of <0.05 was considered statistically significant.

Results

Descriptive statistics

In total, there were 8182 AAD cases in final analysis (*Figure 1*). The mean age was 52.2 [standard deviation (SD) 12.3) years] and 71.0% ($n = 5803$) patients were under age 60. Most of the AAD patients were male (79.5%, $n = 6502$) and had a history of hypertension (71.8%, $n = 5836$) (*Table 1*). The distributions of sex and age did not vary significantly by season (Supplementary material online, *Table S1*), supporting a balanced demographical distribution across season in our database. On average, the daily mean temperature and relative humidity were 15.7°C (SD 10.2) and 66.9% (SD 17.6), respectively,

Table 1 Characteristics of acute aortic dissection cases in this study

Population characteristics	Number	Proportion (%)
All	8182	100
Age, years		
<60	5803	70.9
≥60	2369	29.0
Sex		
Male	6502	79.5
Female	1680	20.5
Hypertension		
Yes	5836	71.3
No	2297	28.1
Type 2 diabetes		
Yes	231	2.8
No	7951	97.2
Coronary artery disease		
Yes	188	2.3
No	7994	97.7
Smoking		
Yes	2651	32.4
No	5496	67.2
Connective tissue disorders		
Yes	302	3.7
No	7880	96.3
Drinking		
Yes	1176	14.4
No	6969	85.2

Proportion (%) = Number/8182.

during the study period. The average TCN was 0.0°C (SD 2.2) (Supplementary material online, *Table S2*). The annual average daily $PM_{2.5}$ and O_3 concentrations were 62.7 ± 50.2 and 46.7 ± 31.3 μg/m^3, respectively.

The counts of AAD cases exposed to each degree of temperature and each degree of TCN are shown in Supplementary material online, *Figure S1*. The ratio of case to controls also increased with the differences of temperature and the differences of TCN between all case days and all control days, revealing possible negative associations of daily temperature and TCN with AAD onset (Supplementary material online, *Figures S2* and *S3*).

Regression results

The exposure–response relationship showed that a daily temperature of 28°C was associated with the lowest AAD risk and was used as the referent. *Figure 2* illustrates the associations with AAD onset for the extremely low (-10°C) and low (1°C) temperature to the referent temperature (28°C) by different lag days. We found the risk of AAD occurred on the concurrent day, attenuated on lag 1 day and thereafter became insignificant. Therefore, we reported the cumulative risks over lag 0–1 day in subsequent analyses.

We found an almost linear exposure-response relationship between lower daily mean temperature and AAD risk. As shown in

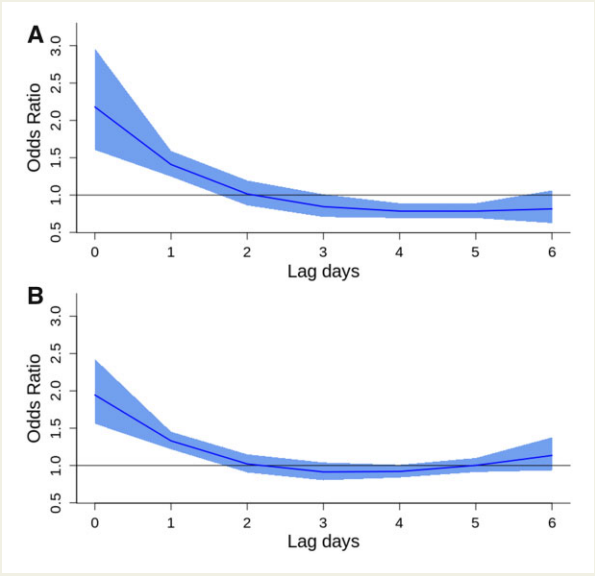


Figure 2 Lag–response curves for the risks of acute aortic dissection at different temperatures. Note: The risks were presented as odds ratios and 95% confidence intervals of acute aortic dissection at extremely low (*A*: P1, -10°C) and low (*B*: P10, 1°C) temperature compared to the referent temperature (28°C) on different lag days. The blue solid lines are mean risk estimates and the blue areas are their 95% confidence intervals.

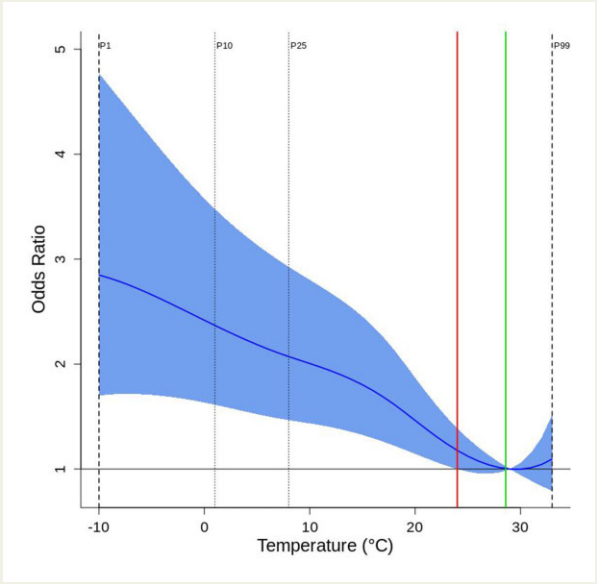


Figure 3 Exposure-response curve of daily temperature and risks of acute aortic dissection onset cumulated over lag 0–1 day. Note: Odds ratios and 95% confidence intervals were calculated based on a referent temperature of 28°C. The blue solid line is mean risk estimates and the blue areas are their 95% confidence intervals. The red vertical line is 24°C and denotes the cut-off below which temperature has a statistically significant risk. The green vertical line is 28°C and denotes the referent temperature that has the statistically lowest risk.

Figure 3, a lower daily temperature was associated with higher AAD risk cumulated over lag 0–1 day compared to the referent, and the ORs became statistically significant under 24°C (about 75th percentile). For example, compared to the referent temperature (28°C), the ORs of AAD onset were 2.84 (95% CI: 1.69, 4.75) for extremely low temperature (-10°C) and 2.36 (95% CI: 1.61, 3.47) for low temperature (1°C), respectively. Meanwhile, there was a very slightly increasing but statistically insignificant risk above 28°C. For example, compared to the referent, the OR of AAD onset was 1.10 (95% CI: 0.79–1.52) for temperature at the 99th percentile (33°C) (Supplementary material online, *Table S3*).

As for TCN, we found that a decrease in temperature from the previous day was associated with higher risk of AAD while an increase in temperature was associated with lower AAD risk. Associations of extreme TCN and AAD were found on the concurrent day (lag 0 day) until up to lag 6 days (*Figure 4* and Supplementary material online, *Figure S4*). Therefore, we reported the cumulative associations of TCN over lag 0–6 days thereafter.

There was also a clear inverse exposure–response relationship between TCN and AAD risk cumulated over lag 0–6 days (*Figure 5*). A negative TCN (i.e. a temperature drop from the previous day) was associated with increased risk of AAD, meanwhile a positive TCN (i.e. an increase in temperature from the previous day) was associated with lower risk of AAD. For example, the ORs of AAD for the extremely negative TCN (-7°C), moderate negative TCN (-3°C), moderate positive TCN (2°C), and extremely positive TCN (5°C) were 2.66 (95% CI: 1.76, 4.02), 1.43 (95% CI: 1.25, 1.64), 0.77 (95% CI: 0.69, 0.85), and 0.40 (95% CI: 0.28, 0.57), respectively, compared to no temperature difference from the previous day (Supplementary material online, *Table S4*).

Stratification analyses were performed about the cumulative risks of AAD onset associated with different cut-offs of temperature and TCN classified by different characteristics of patients (Supplementary material online, *Figures S5* and *S6*). Patients who were above age 60, female, or did not have a history of hypertension or connective tissue disorders tended to have higher AAD risk associated with extremely low and low temperature. Patients without connective tissue disorders also showed larger risk of AAD associated with extremely negative and negative TCN. Nevertheless, all between-strata differences in this study were not statistically significant.

Results from sensitivity analyses were in general comparable to our main analyses. The lag patterns and exposure–response curves for temperature (Supplementary material online, *Figures S7* and *S8*) and TCN (Supplementary material online, *Figures S9* and *S10*) did not change substantially when they were mutually adjusted for in the same model. Estimates for AAD risk with daily mean temperature and TCN were similar with slight attenuations to our main results after additionally controlling for $PM_{2.5}$ and O_3 (*Table 2*).

Discussion

In this study, we used a multi-centre registry database and a time-stratified case-crossover design to examine the associations of daily temperature and TCN with AAD onset. We found a daily mean temperature under 24°C was significantly associated with higher AAD risk in the concurrent day and in the lag 1 day. In addition, a sharp

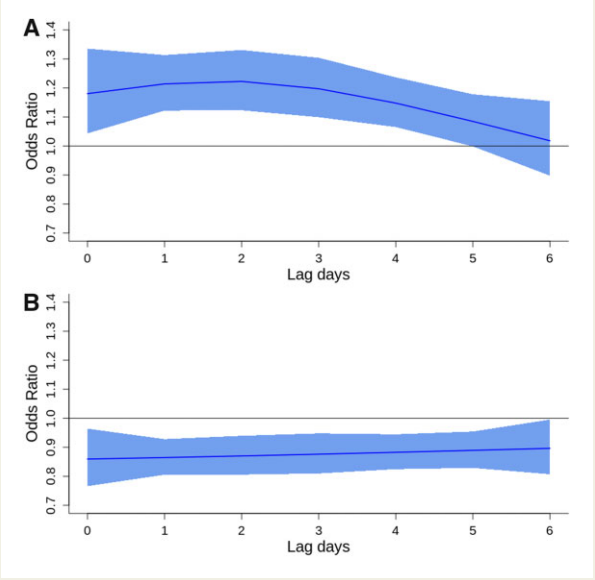


Figure 4 Lag-response curves for the risks of acute aortic dissection at extreme temperature change between neighbouring days. Note: The risks were presented as odds ratios and 95% confidence intervals of acute aortic dissection at extremely negative temperature change between neighbouring days (*A*: P1, -7°C) and extremely positive temperature change between neighbouring days (B: P99, 5°C) compared to the referent temperature change between neighbouring days (0°C) on different lag days. The blue solid lines are mean risk estimates and the blue areas are their 95% confidence intervals.

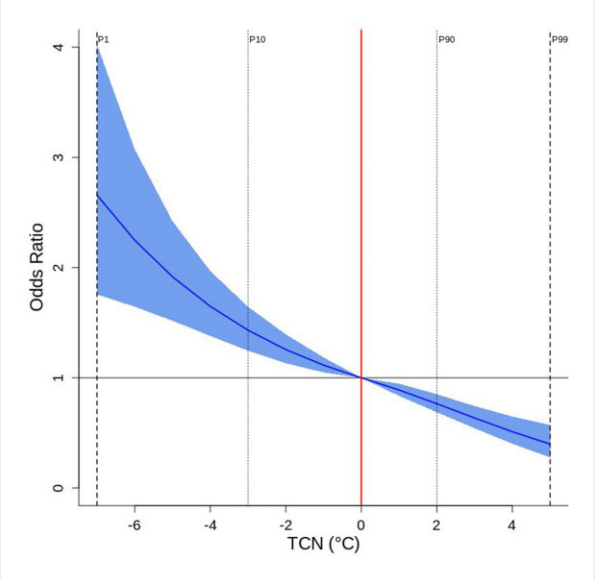


Figure 5 Exposure–response curve of temperature change between neighbouring days and risks of acute aortic dissection onset cumulated over lag 0–6 days. Note: Odds ratios and 95% confidence intervals were calculated based on a referent temperature change between neighbouring days of 0°C (denoted by the red vertical line). The blue solid line is mean risk estimates and the blue areas are their 95% confidence intervals.

temperature drop from the previous day was associated with increased AAD risk in the concurrent day and following 6 days, while a temperature rise may reduce AAD risk. Our study clearly demonstrated that low ambient temperature and temperature drop between neighbouring days may increase the risk of AAD onset (*Graphical Abstract*).

Previous studies reported that AAD incidence peaked in winter.[9,11,34] However, whether such seasonal variation can be explained by temperature or temperature variation warrants further investigation.[34] To the best of our knowledge, few studies have addressed this critical question. In this study, we found lower daily temperature was associated with higher AAD risk. This finding was consistent with the broad literature that suggested associations between low ambient temperature and higher risk of acute cardiovascular events such as sudden cardiac death, acute myocardial infarction, and stroke.[35–38] Besides, compared to these cardiovascular events, AAD showed stronger risks associated with low ambient temperature. In addition, our analysis on lag patterns showed that this association was restricted within the first 2 days with strongest risks on the concurrent day, which suggested the necessity of prompt precaution of immediate AAD surge after encountering cold days.

Acute and drastic temperature variation between neighbouring days may increase the risks of acute cardiovascular events as reported previously.[29,39] In this study, we found that a negative TCN, which indicates a temperature drop in the current day compared to the previous day, can lead to higher AAD risk. In contrast, a positive TCN (i.e. an increase in temperature in the current day compared to the previous day) was associated with lower AAD risk. In addition, we found a longer lag pattern for TCN with AAD risk than daily temperature, as TCN may affect AAD onset for up to 6 days after exposure. Our findings provide evidence of the association and lag pattern in the effects of TCN on AAD onset, which has rarely been considered in previous studies.

We conducted a range of stratified analyses according to patients' characteristics. It appears that patients with hypertension or connective tissue disorders had smaller risks of AAD associated with low temperature. These differences may be due to the fact that the history of hypertension or connective tissue disorders is a strong trigger for AAD, which may lead to the development of AAD in a manner probably irrelevant to ambient temperature. However, it should be noted that the sample size varied greatly in patients with or without pre-existing diseases, leading to unstable risk estimates in some strata and considerable statistical uncertainty when testing the between-strata risk differences.

Low temperature and temperature drop may increase the risk of AAD onset via several common pathways. First, low ambient temperature and sudden temperature drop may cause an increase of blood pressure as a common physiological response resulting from sympathetic activation.[10,40] Hypertension has been recognized as one of the most important risk factors of AAD as high blood pressure could deteriorate the aortic artery wall and thus increase the risk of tearing.[2] Therefore, the increase of blood pressure in response to low ambient temperature or a sharp temperature drop could lead to

Table 2 Odds ratios and 95% confidence intervals of acute aortic dissection with daily temperature and temperature change between neighbouring days with and without adjusting for air pollution

	Main model	Adjusted for $PM_{2.5}$ and O_3
Temperature (percentile)		
-10°C (P1)	3.12 (1.74–5.60)	2.76 (1.37–5.59)
1°C (P10)	2.53 (1.66–3.87)	2.14 (1.33–3.44)
TCN (percentile)		
-7°C (P1)	3.34 (2.09–5.34)	3.38 (1.96–5.83)
-3°C (P10)	1.50 (1.28–1.76)	1.54 (1.29–1.86)
2°C (P90)	0.75 (0.66–0.85)	0.74 (0.64–0.85)
5°C (P99)	0.35 (0.23–0.53)	0.36 (0.23–0.57)

This analysis was restricted within the period from 2013 to 2019 when air pollutant data were available. Odds ratios were estimated using a referent temperature of 28°C and a referent TCN of 0°C, respectively. Odds ratios and 95% confidence intervals of daily temperature and TCN were cumulated over lag 0–1 day and lag 0–6 days, respectively.
O_3, ozone; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; TCN, temperature change between neighbouring days.

higher risk of tearing in the aortic wall and AAD. Second, temperature decrease could be related to changes of hemodynamics, including higher blood viscosity, which can lead to greater arterial sheer forces on the aortic wall and intimal tear.[41] Third, cold weather can cause vasoconstriction in small vessels, which may reduce the blood flow in vasa vasorum and affect blood supply to aorta media, resulting in AAD.[42,43] Fourth, temperature variations may lead to changes of behavioural factors (e.g. physical activity) or intermediate health conditions that could eventually lead to greater AAD risk. However, evidence for the potentially biological mechanisms underlying the association of low temperature and negative TCN with increased AAD risk were still scarce and further toxicological investigations are warranted.

This study used a case-crossover design, which allows us to efficiently control for all time-invariant covariates at individual levels and time-varying covariates such as long-term time trends, seasonality, and day of week. Findings from our study showed that short-term exposure to low temperature and a sharp temperature drop may be important risk factors of AAD. Given that AAD is highly fatal, our results can help physicians and susceptible individuals to better manage the risk of this life-threatening condition and to take appropriate preventive measures. Possible mitigations include avoiding outdoor activities when encountering days of cold temperature or sharp temperature decline, staying indoors with appropriate air conditioning, strengthening blood pressure monitoring, using preventive hypertension treatments, and extending preventive measures to longer duration (e.g. for 7 days after a drastic temperature drop).

There were several limitations in this study. First, all AAD cases in this study were identified from medical records; therefore, AAD patients who died outside of hospitals were not included. Second, exposure measurement error was inevitable as all environmental exposure data were collected from fixed-site monitors rather than personal measurements. Moreover, as all exposures were measured at residential address, we had to assume all patients stayed at or close to their homes on the day of or several days preceding AAD onset and control days within a month, which may also lead to exposure measurement errors. However, these errors are considered likely to be random and to underestimate the effects.[44] Third, this time-stratified case-crossover study cannot fully exclude confounders (e.g. behavioural risk factors such as physical activity) that may vary within a time stratum by design, but we may assume that these factors are not likely to vary considerably for an individual within a month. Fourth, although our registry data included 11 Chinese cities, our results may have limited generalizability to the general Chinese population and to population from other countries or regions.

Conclusion

This multi-centre, case-crossover study provides novel and robust evidence that short-term exposure to low temperature and temperature drop between neighbouring days were associated with increased AAD risk. These observed associations started from the concurrent day of exposure and lasted for 2 days for low temperature and 7 days for temperature drop. As AAD is a life-threatening cardiovascular emergency, our findings provided important evidence for modifiable environmental risk factors of AAD that would be helpful for AAD prevention.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: none declared.

Data availability

Data will be made available upon request in adherence with transparency conventions in medical research and through requests to the corresponding authors.

References

1. Hagan PG, Nienaber CA, Isselbacher EM *et al.* The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. *JAMA* 2000; **283**:897–903.
2. Erbel R, Aboyans V, Boileau C *et al.* ESC Guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). *Eur Heart J* 2014;**35**:2873–2926.
3. Mody PS, Wang Y, Geirsson A *et al.* Trends in aortic dissection hospitalizations, interventions, and outcomes among Medicare beneficiaries in the United States, 2000-2011. *Circ Cardiovasc Qual Outcomes* 2014;**7**:920–928.
4. Howard DP, Banerjee A, Fairhead JF, Perkins J, Silver LE, Rothwell PM. Population-based study of incidence and outcome of acute aortic dissection and premorbid risk factor control: 10-year results from the Oxford Vascular Study. *Circulation* 2013;**127**:2031–2037.

5. DeMartino RR, Sen I, Huang Y *et al.* Population-based assessment of the incidence of aortic dissection, intramural hematoma, and penetrating ulcer, and its associated mortality from 1995 to 2015. *Circ Cardiovasc Qual Outcomes* 2018;**11**: e004689.
6. Smedberg C, Steuer J, Leander K, Hultgren R. Sex differences and temporal trends in aortic dissection: a population-based study of incidence, treatment strategies, and outcome in Swedish patients during 15 years. *Eur Heart J* 2020;**41**: 2430–2438.
7. Pape LA, Awais M, Woznicki EM *et al.* Presentation, diagnosis, and outcomes of acute aortic dissection: 17-year trends from the International Registry of Acute Aortic Dissection. *J Am Coll Cardiol* 2015;**66**:350–358.
8. Mehta RH, Manfredini R, Hassan F, Sechtem U *et al.* Chronobiological patterns of acute aortic dissection. *Circulation* 2002;**106**:1110–1115.
9. Ma WG, Li B, Zhang W *et al.* Chronologic and climatic factors of acute aortic dissection: study of 1642 patients in two continents. *Ann Thorac Surg* 2020;**110**: 575–581.
10. Benouaich V, Soler P, Gourraud PA, Lopez S, Rousseau H, Marcheix B. Impact of meteorological conditions on the occurrence of acute type A aortic dissections. *Interact Cardiovasc Thorac Surg* 2010;**10**:403–406.
11. Xia L, Huang L, Feng X, Xiao J, Wei X, Yu X. Chronobiological patterns of acute aortic dissection in central China. *Heart* 2021;**107**:320–325.
12. Lei X, Liu L, Chen R *et al.* Temperature changes between neighboring days and childhood asthma: a seasonal analysis in Shanghai, China. *Int J Biometeorol* 2021; **65**:827–836.
13. Luo Z-R, Yu L-L, Huang S-T, Chen L-W, Chen Q. Impact of meteorological factors on the occurrence of acute aortic dissection in Fujian Province, China: a single-center seven-year retrospective study. *J Cardiothorac Surg* 2020;**15**:178.
14. Xie N, Zou L, Ye L. The effect of meteorological conditions and air pollution on the occurrence of type A and B acute aortic dissections. *Int J Biometeorol* 2018; **62**:1607–1613.
15. Majd P, Madershahian N, Sabashnikov A *et al.* Impact of meteorological conditions on the incidence of acute aortic dissection. *Ther Adv Cardiovasc Dis* 2018;**12**: 321–326.
16. He X-N, Zhan J-L, Zhang C *et al.* Impact of meteorological conditions and PM2.5 on the onset of acute aortic dissection in monsoonal climate. *J Geriatr Cardiol* 2018;**15**:315–320.
17. Chen Z, Huang B, Yang Y *et al.* Onset seasons and clinical outcomes in patients with Stanford type A acute aortic dissection: an observational retrospective study. *BMJ Open* 2017;**7**:e012940.
18. Taheri Shahraiyni H, Sodoudi S, Cubasch U. Weather conditions and their effect on the increase of the risk of type A acute aortic dissection onset in Berlin. *Int J Biometeorol* 2016;**60**:1303–1305.
19. Law Y, Chan YC, Cheng SW. Influence of meteorological factors on acute aortic events in a subtropical territory. *Asian J Surg* 2017;**40**:329–337.
20. Wang W, Duan W, Xue Y *et al.*; Registry of Aortic Dissection in China Sino-RAD Investigators. Clinical features of acute aortic dissection from the Registry of Aortic Dissection in China. *J Thorac Cardiovasc Surg* 2014;**148**:2995–3000.
21. Clough RE, Nienaber CA. Management of acute aortic syndrome. *Nat Rev Cardiol* 2015;**12**:103–114.
22. Guo Y, Barnett AG, Pan X, Yu W, Tong S. The impact of temperature on mortality in Tianjin, China: a case-crossover design with a distributed lag nonlinear model. *Environ Health Perspect* 2011;**119**:1719–1725.
23. Li J, Liu C, Cheng Y *et al.* Association between ambient particulate matter air pollution and ST-elevation myocardial infarction: a case-crossover study in a Chinese city. *Chemosphere* 2019;**219**:724–729.
24. Liu Y, Pan J, Fan C *et al.* Short-term exposure to ambient air pollution and mortality from myocardial infarction. *J Am Coll Cardiol* 2021;**77**:271–281.
25. Polcaro-Pichet S, Kosatsky T, Potter BJ, Bilodeau-Bertrand M, Auger N. Effects of cold temperature and snowfall on stroke mortality: a case-crossover analysis. *Environ Int* 2019;**126**:89–95.
26. Gasparrini A, Guo Y, Hashizume M, Lavigne E *et al.* Mortality risk attributable to high and low ambient temperature: a multicountry observational study. *Lancet* 2015;**386**:369–375.
27. Gasparrini A. Modeling exposure-lag-response associations with distributed lag non-linear models. *Stat Med* 2014;**33**:881–899.
28. Ma W, Chen R, Kan H. Temperature-related mortality in 17 large Chinese cities: how heat and cold affect mortality in China. *Environ Res* 2014;**134**:127–133.
29. Cheng J, Zhu R, Xu Z *et al.* Temperature variation between neighboring days and mortality: a distributed lag non-linear analysis. *Int J Public Health* 2014;**59**:923–931.
30. Niu Y, Chen R, Liu C *et al.* The association between ambient temperature and out-of-hospital cardiac arrest in Guangzhou. *China. Sci Total Environ* 2016;**572**: 114–118.
31. Peng Z, Wang Q, Kan H, Chen R, Wang W. Effects of ambient temperature on daily hospital admissions for mental disorders in Shanghai, China: a time-series analysis. *Sci Total Environ* 2017;**590–591**:281–286.
32. Chen R, Peng RD, Meng X, Zhou Z, Chen B, Kan H. Seasonal variation in the acute effect of particulate air pollution on mortality in the China Air Pollution and Health Effects Study (CAPES). *Sci Total Environ* 2013;**450–451**:259–265.
33. Altman DG, Bland JM. How to obtain the confidence interval from a P value. *BMJ* 2011;**343**:d2090.
34. Mehta RH, Manfredini R, Bossone E *et al.*; International Registry of Acute Aortic Dissection (IRAD) Investigators. The winter peak in the occurrence of acute aortic dissection is independent of climate. *Chronobiol Int* 2005;**22**:723–729.
35. Sun Z, Chen C, Xu D, Li T. Effects of ambient temperature on myocardial infarction: a systematic review and meta-analysis. *Environ Pollut* 2018;**241**:1106–1114.
36. Thu Dang TA, Wraith D, Bambrick H *et al.* Short-term effects of temperature on hospital admissions for acute myocardial infarction: a comparison between two neighboring climate zones in Vietnam. *Environ Res* 2019;**175**:167–177.
37. Wang X, Cao Y, Hong D *et al.* Ambient temperature and stroke occurrence: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2016;**13**:698.
38. Lian H, Ruan Y, Liang R, Liu X, Fan Z. Short-term effect of ambient temperature and the risk of stroke: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2015;**12**:9068–9088.
39. Zhan Z, Zhao Y, Pang S, Zhong X, Wu C, Ding Z. Temperature change between neighboring days and mortality in United States: a nationwide study. *Sci Total Environ* 2017;**584-585**:1152–1161.
40. Modesti PA. Season, temperature and blood pressure: a complex interaction. *Eur J Intern Med* 2013;**24**:604–607.
41. Keatinge WR, Coleshaw SR, Cotter F, Mattock M, Murphy M, Chelliah R. Increases in platelet and red cell counts, blood viscosity, and arterial pressure during mild surface cooling: factors in mortality from coronary and cerebral thrombosis in winter. *Br Med J (Clin Res Ed)* 1984;**289**:1405–1408.
42. Haverich A, Boyle EC. Aortic dissection is a disease of the vasa vasorum. *JTCVS Open* 2021;**5**:30–32.
43. Calafiore AM, Katsavrias K, Di Marco M, Guarracini S, Di Mauro M. Commentary: vasa vasorum dysfunction and acute aortic syndromes: when guidelines do not follow the evolution of knowledge. *JTCVS Open* 2021;**5**:33–34.
44. Guo Y, Barnett AG, Tong S. Spatiotemporal model or time series model for assessing city-wide temperature effects on mortality? *Environ Res* 2013;**120**: 55–62.