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Bidirectional modification effects of non-optimal temperature and short-term exposure to fine particulate matter on cardiovascular diseases and their different subtypes: A time-case cross-design in multiple cities

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Abstract

Background Both fine particulate matter (PM_{2.5}) and non-optimal temperatures are well-recognized environmental hazard factors for cardiovascular diseases (CVD). However, the bidirectional modifying effects of these two factors on CVD mortality remain systematically understudied, particularly across different CVD subtypes and population strata.

Objective To examine the bidirectional modifying effects of PM_{2.5} short-term exposure and non-optimal temperatures on CVD and its subtype mortality risk, identify susceptible populations, and provide evidence for comprehensive environmental risk prevention strategies.

Methods Using 111,567 CVD deaths in Anhui Province, China, between 2019 and 2023, a time-stratified case-crossover design was carried out. To assess the independent

and bidirectional modifying effects of PM_{2.5} and non-optimal temperature, an analytical approach integrating conditional logistic regression with distributed lag non-linear models was utilized. To evaluate the bidirectional modifying effects of PM_{2.5} and temperature, stratification analysis was conducted based on the high, medium and low levels of PM_{2.5} concentration and temperature respectively, with 25% and 75% as cut-off values. The effects of extreme high temperature (EHT) and extreme low temperature (ELT) were estimated with The Minimum Mortality Temperature (MMT) as a reference at different PM_{2.5} exposure levels. Finally, two-sample Z-tests were performed to compare PM_{2.5}-associated effects between temperature strata, with the low temperature tertile as the reference.

Results Significant bidirectional modifying effects were observed between PM_{2.5} and low temperature on CVD mortality. High PM_{2.5} exposure amplified the ELT-related mortality risk, odds ratio (OR) rose from 1.03 (95%CI: 0.92, 1.14) to 1.90 (95%CI: 1.41, 2.58), while low temperature intensified the PM_{2.5}-related risk OR rose from 1.02 (95%CI: 0.98, 1.07) to 1.19 (95%CI: 1.18, 1.21). For high temperature, only a unidirectional amplification by PM_{2.5} was observed, with no evidence of reverse modification. These bidirectional effects were most pronounced in acute CVD subtypes, but not in chronic subtypes. The elderly and married people were identified as sensitive groups for the bidirectional modification effect.

Conclusion PM_{2.5} and low temperature exhibit synergistic bidirectional modifying effects on CVD mortality, particularly for acute CVD events and among vulnerable subgroups. Persistent progress in air quality can serve as a synergistic tactic to lessen

the cardiovascular health burdens associated with climate change.

Key words PM_{2.5}; Non-optimal temperatures; Cardiovascular diseases; Bidirectional modifying effect

Introduction

As the primary disease threatening human health, cardiovascular disease (CVD) exerts immense pressure on public health systems through its heavy morbidity and mortality burden (Ding et al., 2024; Zou et al., 2025). From 1990 to 2019, the global prevalence of CVD rose from 271 million to 523 million, as reported in the 2019 Global Burden of Disease Study, with 18.6 million annual fatalities representing over 31% of all global deaths (Cao et al., 2025). The situation is equally severe in China, according to official data, over 330 million people in China live with CVD, CVD-related deaths account for around 40% of all-cause mortality, and both incidence and mortality rates are on a continuous upward trend (Zhao et al., 2025).

Among the modifiable risk factors for CVD, ambient air pollution and climate-related factors are particularly prominent. Fine particulate matter (PM_{2.5}) and non-optimal temperatures, extreme high temperature (EHT) and extreme low temperature (ELT), are two types of widely coexisting environmental factors with significant hazards (Clark et al., 2025; Yu et al., 2025; Burkart et al., 2025; Burkart et al., 2025). Notably, short-term PM_{2.5} exposure is strongly associated with fatal outcomes of CVD, including heart failure, myocardial infarction (MI), and cerebrovascular accident (CVA) (Yang et al., 2025). Driven by global warming, extreme temperature events occur

frequently with continuously escalating intensity, which has become a prominent contemporary climate issue (Liu et al., 2026; Cheng et al., 2024). The exposure-response relationship between temperature and CVD mortality risk predominantly presenting a U-shaped or J-shaped pattern, deviating from the Minimum Mortality Temperature (MMT), high and low temperatures exert an increasing effect on CVD mortality risk (Huang et al., 2017; Jdidi et al., 2024).

Notably, PM_{2.5} and non-optimal temperatures do not act independently on CVD. Previous epidemiological studies often controlled for one of these factors as a confounder, but recent evidence suggests that there is a more complex bidirectional modifying effect between them. The two types of environmental factors can induce synergistic and even potentiated adverse health effects through shared pathophysiological signaling pathways, such as oxidative stress; increased exposure burden of either factor will modulate and alter the health risk associated with the other (Guo et al., 2025; Yazdi et al., 2023; Zhou et al., 2023). Accumulating epidemiological evidence has indicated that ambient temperature may substantially modify the exposure-response association between PM_{2.5} and CVD (Zhang et al., 2025; Zou et al., 2025). The risk of PM_{2.5}-induced acute coronary syndrome and MI is further elevated in cold seasons or ELT environments. In hot seasons, the synergistic effects to PM_{2.5} and high thermal conditions can significantly augment the adverse load exerted by electrolyte imbalances and dehydration in individuals with CVD (Liu et al., 2022; Xu et al., 2023; Pan et al., 2024). Nonetheless, PM_{2.5} may potentially alter the relationship between temperature and CVD. Excessive levels of pollutants can alter the dose-

response association between ambient temperature and CVD events. By compromising the body's thermoregulatory capacity, such exposures further augment physiological burden under heat or cold stress (Guo et al., 2025).

However, current study on the bidirectional modifying effect between PM_{2.5} and temperature on CVD mortality risk is relatively scarce, especially from the perspective of how pollutants modify the temperature-related health effects. In addition, analyses targeting different CVD subtypes (e.g., distinguishing acute and chronic CVD) are particularly insufficient. Due to the heterogeneity in the pathophysiological mechanisms of each subtype, their susceptibility to the bidirectional modifying effect of PM_{2.5} and non-optimal temperatures may vary significantly. This research gap limits the accurate assessment of combined environmental health risks and the formulation of targeted disease intervention strategies.

Anhui Province, characterized by significant PM_{2.5} pollution and distinct seasonal temperature changes (ELT in winter and EHT in summer), provides an ideal natural experimental setting for exploring such bidirectional modifying effects. This study intends to systematically evaluate the bidirectional modifying effects of non-optimal temperature and PM_{2.5} on overall CVD mortality as well as mortality from its major subtypes, clarify the direction of their modification effects, and identify susceptible diseases and population characteristics based on CVD mortality data from multiple cities in Anhui Province from 2019 to 2023. This study's findings are expected to provide scientific evidence for developing more accurate preventative and control measures for combined environmental health concerns, thereby alleviating the

simultaneous burden of severe temperatures and air pollution on CVD health.

Methods

Study region

Anhui Province features a subtropical monsoon climate and marked seasonal differences. The annual average temperature across the province varied between 16.6 °C and 17.2 °C from 2019 to 2023. In recent years, the PM_{2.5} pollution level in Anhui Province has declined, yet it still remains at a high pollution level. The 2024 Bulletin on the Ecological and Environmental Status of Anhui Province indicates that the annual average concentration of PM_{2.5} in 2024 was 35 µg/m³, considerably above stipulated by the World Health Organization's Air Quality Guidelines (WHO) (**Fig. 1**).

Mortality data

Information on CVD death cases in Anhui Province, China, between January 1, 2019, and December 31, 2023, were sourced from the Anhui Provincial Center for Disease Control and Prevention. Following the exclusion of people without physical location data, 111,567 cases were finally included in this study. Mortality from CVD (I00-I99) was delineated using the codes of the International Classification of Diseases, 10th Revision (ICD-10) (Pham et al., 2025; Mee et al., 2025). The present study identified representative subtypes of CVD according to ICD-10 codes, encompassing ischemic heart disease (IHD) (I20-I25), MI (I21-I22), chronic ischemic heart disease (CIHD) (I25), CVA (I60-I69), Ischemic Stroke (IS) (I61), Hemorrhagic Stroke (HS)

(I63), and sequelae of cerebrovascular disease (SCVS) (I69) (Fang et al., 2025; Chen et al., 2025).

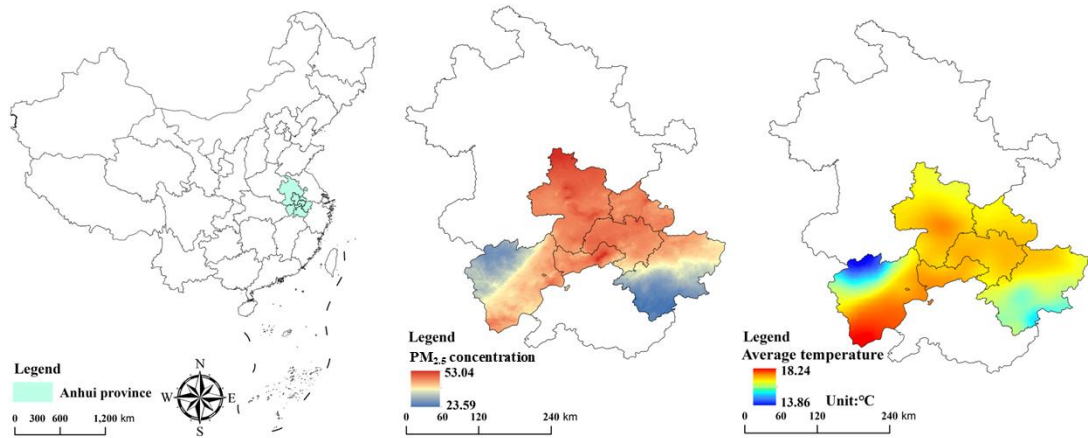


Fig. 1 Study area map with annual average distributions of PM_{2.5} and temperature during 2019–2023.

Environmental data

Environmental pollutant data in this study were derived from the China High Air Pollutants (CHAP) dataset (<https://weijing-rs.github.io/product.html>). This dataset was derived from integrating multi-source satellite remote sensing retrievals with ground-based monitoring measurements, employs spatial statistical methods like geographically weighted regression to generate high-precision gridded air pollutant data for the entire territory of China, with a spatiotemporal resolution of 1 km × 1 km. It offers a high-precision foundation for exposure assessment in atmospheric environmental research and has been extensively utilized (Huang et al., 2024; Wei et al., 2023; Wei et al., 2021). Daily temperature and relative humidity data were derived from the ERA5-Land dataset, characterized by a resolution of 0.1°×0.1°, which is a

globally comprehensive, physically coherent, high-resolution, and continuous dataset (Gong et al., 2026; Munoz-Sabater et al., 2021). For each case and control participant, spatial matching of environmental exposure data was carried out using the geographic coordinates of the patients' residential locations connected to the grid points in the exposure data (He et al., 2024).

Study design

This study utilized a time-stratified case-crossover design. We designated the death date of each case as the case day and selected control days that matched the case day by year, month, and weekday. Using the self as the control, each deceased person was paired with three to four control days (Zhang et al., 2025; Zhang et al., 2024; Ning et al., 2024a; Zhan et al., 2024). For instance, if a patient passed away on July 8, 2022, the time stratum would be July 2022 and the case day would be July 8 (Friday). Each deceased person was then paired with three to four control days on July 1, 15, 22, and 29 (other Fridays in this time stratum) (Yu et al., 2024).

The analytic sample ultimately consisted of 111,567 case days and 477,798 control days. This design enabled adjustment for confounding factors including age, gender, socioeconomic position, lifestyle behaviors, and potential seasonal effects (Cao et al., 2025). Bidirectional time-matched control can help mitigate the possible confounding influence of long-term temporal patterns. This method has been extensively employed in studies evaluating the short-term exposure to environmental pollutants and its impacts on health outcomes (Li et al., 2025).

Statistical analyses

Basic model

To assess the effect of acute PM_{2.5} short-term exposure on CVD mortality, a case-crossover design with time stratification was employed, and conditional logistic regression served as the analytical framework. For both case days and control days, short-term PM_{2.5} exposure was specified as the mean concentration of the current day and the preceding day (lag01) (Gong et al., 2026). In this study, the average values of ambient temperature and relative humidity for the current day and the three preceding days on both case days and control days were adopted, following the conventional approach to elucidate non-linear exposure-response relationships (Xu et al., 2014; Xu et al., 2025). Public holidays were also adjusted for in the model. The model equation in this study is as follows:

$$\begin{aligned} & \text{logit}[P(Y_{it} = 1)] \\ &= \alpha_i + \beta_1 PM_{2.5,it} + ns(Temp_{it}, 3) + ns(RH_{it}, 3) + \beta_2 Holiday_{it} \end{aligned}$$

where i indexes the matched case-control stratum and t indexes the day. The stratum-specific intercepts α_i condition out all time-invariant individual characteristics by design. $Temp$ and RH represent temperature and relative humidity, respectively.

In addition, the relationship between short-term temperature exposure and disease is typically nonlinear and often characterized by delayed effects (Liu et al., 2014; Lam et al., 2019). To account for the nonlinear and lagged nature of temperature exposure, we adopted a distributed lag non-linear model (DLNM), implemented via a cross-basis function. We additionally used a natural cubic spline function with 3 df to characterize

the non-linear exposure–response relationship and the distribution of lag effects (Fang et al., 2021; Chang et al., 2024). The MMT is defined as the temperature threshold on the exposure–response curve associated with the minimum CVD mortality risk.

Bidirectional modifying effect

An emerging study has shown that short-term environmental pollution and temperature may mutually modify each other's health effects (Guo et al., 2025). Therefore, we also investigated whether temperature and PM_{2.5} have bidirectional modifying effects on CVD and its subtypes.

When investigating the modification effect of PM_{2.5} on temperature-CVD relationships, PM_{2.5} was categorized into three groups (low, moderate, and high) using the 25% and 75% as cutoffs. Under different PM_{2.5} exposure levels, we estimated the effects of EHT and ELT with reference to the MMT, respectively. The two-sample *Z-tests* were performed to compare EHT/ELT-associated effects between PM_{2.5} strata, with the high PM_{2.5} level as the reference. *P-values* from the *Z-tests* reflected inter-PM_{2.5} stratum differences in temperature-CVD associations (i.e., whether modifying effects of PM_{2.5} are statistically significant) (Hu et al., 2025). The equation for *Z-tests* is presented as follows:

$$Z = \frac{\beta_1 - \beta_2}{\sqrt{SE_1^2 + SE_2^2}}$$

In this analysis, β_1 and β_2 denote the regression coefficients estimated by the conditional logistic model, whereas SE_1 and SE_2 represent the standard errors within the respective subgroups.

In the examination of the impact of temperature on PM_{2.5}-CVD relationships,

temperature was divided into low, medium, and high groups according to tertiles. Similarly, two-sample *Z-tests* were performed to compare PM_{2.5}-associated effects between temperature strata, with the low temperature tertile as the reference (Lei et al., 2026).

Subgroup analysis

This study also conducted subgroup analyses stratified by gender (male or female), age (<65 years or ≥65 years), educational level (junior high school and below or above junior high school), residential area (urban or rural), and marital status (married or unmarried) to assess whether the bidirectional modifying effects of PM_{2.5} and temperature on CVD mortality differ across population subgroups (Shupler et al., 2024). This subgroup analysis is helpful in identifying sensitive populations affected by bidirectional modification exposure to PM_{2.5} and temperature (Chu et al., 2025; Rau et al., 2024).

Sensitivity analyses

This study validated the findings' robustness using a series of sensitivity analysis. (1) In examining the influence of EHT and ELT on CVD mortality modified by PM_{2.5}, temperature exposure was determined using the 5th and 95th percentiles, while additional percentile thresholds (2.5th and 97.5th percentiles, 10th and 90th percentiles) were utilized to assess the effects on CVD mortality under varying definitions of extreme temperature exposure. (2) Multi-pollutant model analyses were conducted by

incorporating pollutants that have received extensive research attention and exert substantial impacts on CVD health, including PM₁₀, ozone (O₃), sulfur dioxide (SO₂), nitrogen dioxide (NO₂), and carbon monoxide (CO). (3) The lag periods of PM_{2.5} and temperature exposure were extended (lag 01–07) to capture more comprehensive exposure effects. (4) We tested model robustness by adjusting the df for temperature and relative humidity over a range of 4–6. A two-sided *P value* of < 0.05 was considered statistically significant, and all analyses were carried out using R software (version 4.4.3), with R packages including splines, survival, dplyr, lubridate, and dlnm.

Results

Descriptive statistics

This study comprised 477,798 controls and 115,670 CVD fatalities from Anhui Province, as indicated in **Table 1**. CVA and IHD constituted the largest numbers of cases, accounting for 51.32% and 32.63%, respectively. Males accounted for 52% and females for 47.96% of all cases, with a relatively balanced distribution. The elderly (≥ 65 years) accounted for a large proportion (89%), and individuals with Junior high school and below accounted for 88%. Urban residents accounted for slightly more than rural residents (61%). Married individuals accounted for 57%, while unmarried individuals and those with other marital statuses accounted for 43%, showing a balanced distribution.

During the study period (2019–2023), the study area in Anhui Province and the distribution of daily mean temperature and PM_{2.5} concentration are displayed in **Table**

2. The daily average PM_{2.5} concentration was 38.32 µg/m³, with a corresponding average daily temperature of 15.22 °C.

Table 1 Demographic characteristics of CVD deaths in Anhui Province, 2019–2023.

Characteristic	n	Percentage (%)
Case days	111567	
Control days	477798	
CVD Subtypes		
IHD	36409	32.63
MI	14079	12.62
CIHD	22028	19.74
CVA	57254	51.32
IS	18285	16.39
HS	12872	11.54
SCVS	21730	19.48
Sex		
Male	58059	52.04
Female	53508	47.96
Age		
< 65 years	11954	10.71
≥ 65 years	99613	89.29
Education		
Junior high school and below	98193	88.01
Junior high school or above	13374	11.99
Urban and rural		
Urban	68190	61.12
Rural	43377	38.88
Marital status		
Unmarried	48523	43.49
Married	63044	56.51

Abbreviations: CVD: Cardiovascular system diseases; IHD: Ischemic heart disease; MI: Myocardial infarction; CIHD: Chronic ischemic heart disease; CVA: Cerebrovascular accident; IS: Ischemic stroke; HS: Hemorrhagic stroke; SCVS: Sequelae of cerebrovascular disease.

Table 2 Distribution characteristics of PM_{2.5} lag01 and temperature lag03 for CVD and

its subtypes during 2019–2023.

CVD Subtypes	PM _{2.5} (ug/m ³)		Temperature (°C)	
	Mean (SD)	Median (P ₂₅ , P ₇₅)	Mean (SD)	Median (P ₂₅ , P ₇₅)
CVD	38.12 (22.78)	32.20 (22.65, 46.85)	15.33 (9.26)	15.13 (7.01, 23.94)
IHD	38.40 (23.03)	32.35 (22.70, 47.25)	15.25 (9.30)	15.01 (6.89, 23.93)
MI	38.13 (22.78)	32.25 (22.55, 46.90)	15.48 (9.17)	15.34 (7.12, 24.02)
CIHD	38.59 (23.19)	32.45 (22.80, 47.50)	15.09 (9.37)	14.79 (6.73, 23.86)
CVA	37.95 (22.62)	32.10 (22.60, 46.60)	15.40 (9.23)	15.23 (7.13, 23.98)
IS	37.96 (22.46)	32.15 (22.65, 46.85)	15.42 (9.25)	15.25 (7.19, 24.04)
HS	37.05 (21.81)	31.50 (22.40, 45.21)	16.09 (8.91)	16.13 (7.99, 24.25)
SCVS	38.68 (23.31)	32.60 (22.80, 47.50)	14.88 (9.38)	14.43 (6.49, 23.66)

Abbreviations: PM_{2.5}: particulate matter with aerodynamic diameter $\leq 2.5\mu\text{m}$; SD: standard deviation; Min: minimum value; Max: maximum value; CVD: Cardiovascular system diseases; IHD: Ischemic heart disease; MI: Myocardial infarction; CIHD: Chronic ischemic heart disease; CVA: Cerebrovascular accident; IS: Ischemic stroke; HS: Hemorrhagic stroke; SCVS: Sequelae of cerebrovascular disease.

Independent effects of temperature on CVD mortality

Fig. 2 illustrates a consistent U-shaped nonlinear correlation between temperature and overall mortality from CVD and its subtypes (including IHD, MI, CIHD, CVA, IS, HS, and SCVS). The MMT ranged from 17.9 °C to 20.5 °C. The mortality risk of CVD and most of its subtypes (e.g., IHD, MI, CVA, and SCVS) increased significantly when the temperature was either above or below the MMT. For the purpose of evaluating the mortality effects of EHT and ELT on overall CVD and its subtypes, we therefore selected the MMT for each respective disease as the reference.

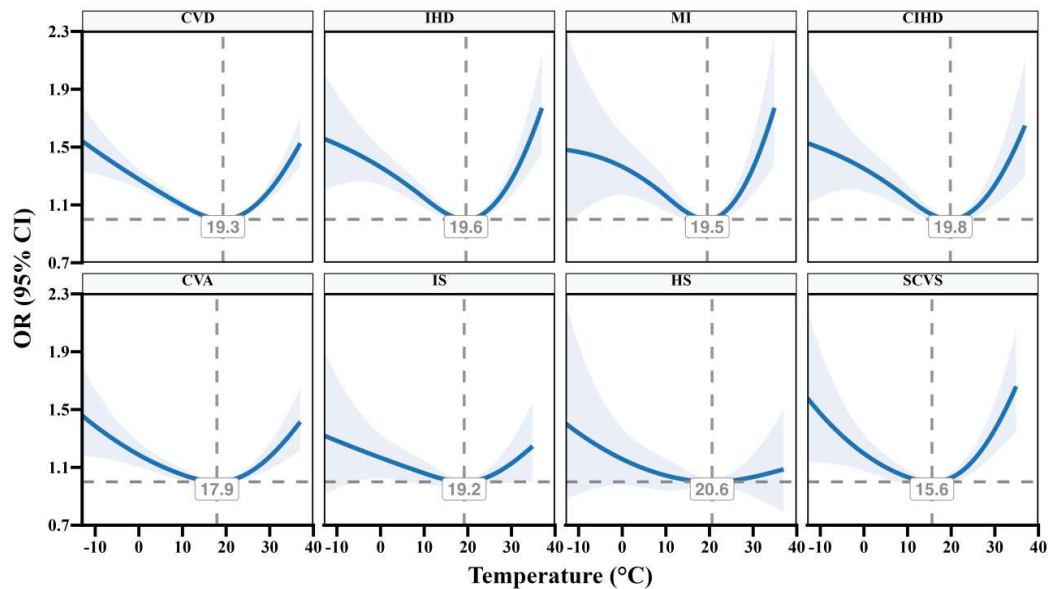


Fig. 2 Exposure-response curves for temperature and mortality from CVD and its subtypes.

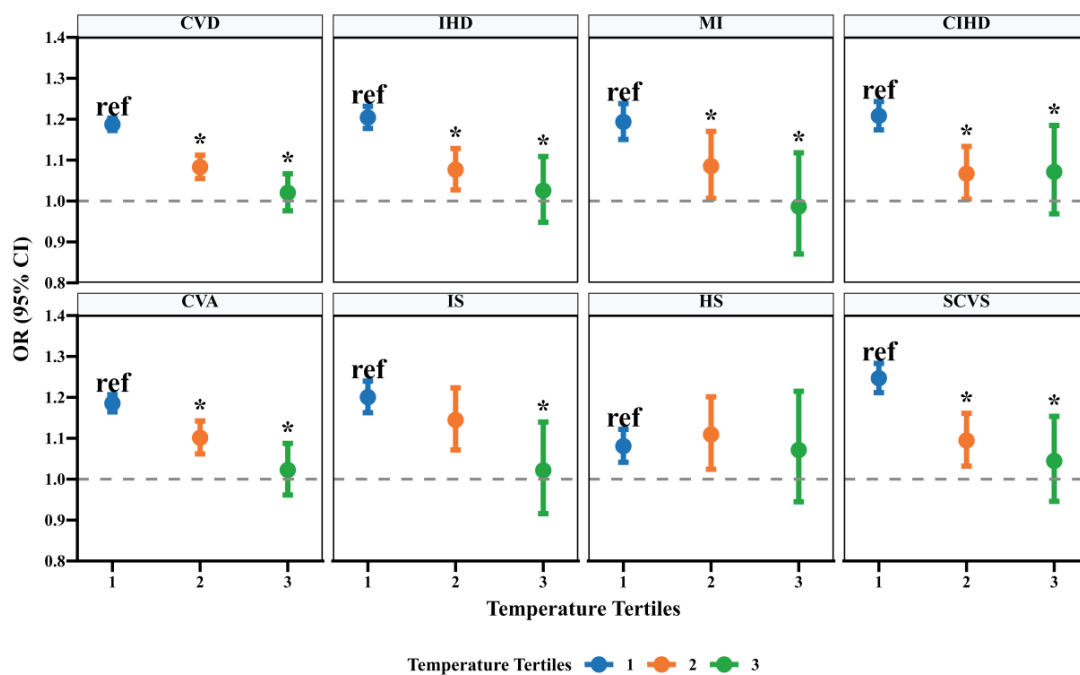
Bidirectional modifying effects of PM_{2.5} and temperature on CVD mortality

Table 3 and Fig. 3 illustrate that low temperature and short-term PM_{2.5} exposure have a substantial bidirectional regulatory effect on the risk of CVD death. With the increase of PM_{2.5} concentration, the risk of CVD death associated with ELT increased from 1.03 (95% CI: 0.92, 1.14) to 1.90 (95% CI: 1.41, 2.58). And with the decrease of temperature, the risk of CVD death related to PM_{2.5} showed a significant upward trend, increasing from 1.02 (95% CI: 0.98, 1.07) to 1.19 (95% CI: 1.18, 1.21), with significant differences between groups (P for Z test > 0.05). However, when the exposure level of PM_{2.5} increased, the risk of EHT-related CVD death rose from 1.12 (95% CI: 1.01, 1.25) to 2.13 (95% CI: 1.50, 3.02). However, with the increase of temperature level, the OR value of PM_{2.5} related CVD mortality risk decreased significantly (P for Z test > 0.05).

and high temperature had only a unidirectional moderating effect.

For different disease subtypes, IHD, MI, CVA and SCVS exhibit bidirectional modification patterns that match the overall CVD pattern. With the increase of PM_{2.5} exposure level, the OR of each subtype under ELT increased significantly: IHD increased from 1.05 (95% CI: 0.88, 1.25) to 2.14 (95% CI: 1.28, 3.56); MI increased from 0.99 (95% CI: 0.74, 1.32) to 3.23 (95% CI: 1.43, 7.28); CVA ranged from 0.95 (95% CI: 0.80, 1.11) to 2.27 (95% CI: 1.37, 3.75); SCVS ranged from 1.03 (95% CI: 0.76, 1.41) to 3.11 (95% CI: 1.31, 7.41) (*P for Z test* > 0.05). As the temperature drops, the risk of death related to PM_{2.5} increases significantly in all subtypes. Specifically, the OR of IHD increased from 1.03 (95% CI: 0.95, 1.11) to 1.20 (95% CI: 1.17, 1.23); MI increased from 1.08 (95% CI: 1.01, 1.17) to 1.21 (95% CI: 1.17, 1.24); CVA ranged from 1.02 (95% CI: 0.96, 1.09) to 1.19 (95% CI: 1.17, 1.21); for SCVS, from 1.06 (95% CI: 0.96, 1.17) to 1.25 (95% CI: 1.21, 1.28) (*P for Z test* > 0.05). In the context of EHT, PM_{2.5} has a single unidirectional effect on the temperature-related mortality risk of IHD, MI, CVA and SCVS. With the increase of PM_{2.5} exposure level, the OR of the above subtypes of EHT-related mortality risk also significantly increases, but the effect of PM_{2.5} does not enhance with the increase of temperature level.

For CIHD, IS and HS, only the one-way correction effect of low temperature on the PM_{2.5} effect was observed. With the increase of PM_{2.5} exposure level, the risk OR of ELT-related mortality associated with CIHD, IS, and HS showed an upward trend, but did not reach statistical significance (*P for Z test* > 0.05).



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326 Fig. 3 Effect modification of the PM_{2.5}-CVD mortality association by temperature and

327 analysis by disease subtype.

Table 3 Effect modification of PM_{2.5} on the association between temperature and mortality from CVD and their various subtypes.

Subgroup	PM _{2.5} level	EHT		ELT	
		OR (95% CI)	<i>P for Z test</i>	OR (95% CI)	<i>P for Z test</i>
CVD	Low	1.12 (1.01, 1.25) *	<0.01	1.03 (0.92, 1.14) *	<0.01
	Medium	1.05 (0.96, 1.16) *	<0.01	1.05 (0.96, 1.13) *	<0.01
	High	2.13 (1.50, 3.02)		1.90 (1.41, 2.58)	
IHD	Low	1.17 (0.98, 1.41) *	0.02	1.05 (0.88, 1.25) *	<0.01
	Medium	1.08 (0.91, 1.28) *	<0.01	1.07 (0.93, 1.23) *	0.01
	High	2.43 (1.35, 4.37)		2.14 (1.28, 3.56)	
MI	Low	1.10 (0.82, 1.48) *	0.01	0.99 (0.74, 1.32) *	<0.01
	Medium	1.31 (0.99, 1.72) *	0.03	1.23 (0.98, 1.55) *	0.03
	High	3.93 (1.53, 10.12)		3.23 (1.43, 7.28)	
CIHD	Low	1.25 (0.99, 1.59)	0.48	1.11 (0.88, 1.39)	0.35
	Medium	0.99 (0.80, 1.22)	0.20	0.99 (0.83, 1.19)	0.21
	High	1.67 (0.77, 3.62)		1.55 (0.79, 3.02)	
CVA	Low	1.01 (0.86, 1.19) *	<0.01	0.95 (0.80, 1.11) *	<0.01
	Medium	1.15 (1.00, 1.32) *	0.01	1.12 (1.00, 1.26) *	0.01
	High	2.27 (1.37, 3.75)		2.27 (1.37, 3.75)	
IS	Low	1.14 (0.88, 1.49)	0.25	1.09 (0.85, 1.41)	0.23
	Medium	1.03 (0.81, 1.30)	0.15	1.02 (0.84, 1.24)	0.15
	High	1.81 (0.87, 3.75)		1.67 (0.88, 3.16)	
HS	Low	0.98 (0.74, 1.29)	0.55	0.94 (0.72, 1.23)	0.50
	Medium	1.00 (0.76, 1.32)	0.59	1.01 (0.81, 1.26)	0.61
	High	1.28 (0.54, 3.04)		1.24 (0.59, 2.58)	
SCVS	Low	1.14 (0.83, 1.56) *	0.03	1.03 (0.76, 1.41) *	0.02
	Medium	1.37 (1.09, 1.73)	0.05	1.31 (1.08, 1.60)	0.06
	High	3.67 (1.38, 9.75)		3.11 (1.31, 7.41)	

Abbreviations: CVD: Cardiovascular system diseases; IHD: Ischemic heart disease; MI: Myocardial infarction; CIHD: Chronic ischemic heart disease; CVA: Cerebrovascular accident; IS: Ischemic stroke; HS: Hemorrhagic stroke; SCVS: Sequelae of cerebrovascular disease. PM_{2.5} level: Grouped levels of PM_{2.5} (Low: < 25%; Medium: 25%–75%; High: > 75%); EHT: Extreme high temperature above the 95th temperature percentile; ELT: Extreme low temperature below the 5th temperature percentile. Two-sample *Z-tests* were performed to compare EHT/ELT-associated effects

between PM_{2.5} strata, with the high PM_{2.5} level as the reference and P-values from the Z-tests reflect inter-stratum differences. *: $P < 0.05$.

Subgroup analysis

In the subgroup analysis covering all populations, temperature showed a similar U-shaped correlation with the risk of cardiovascular disease mortality (**Fig. 4**). The results in **Table 4** and **Fig. 5** show that heterogeneity of moderating effects was observed in the age and marital status groups. Among people over 65 years old, with the increase of PM_{2.5} concentration, the OR of ELT-related CVD mortality risk increased from 1.05 (95%CI: 0.93, 1.18) to 2.15 (95%CI: 1.53, 3.04). Meanwhile, when the temperature dropped, it increased from 1.02 (95%CI: 0.97, 1.07) to 1.21 (95%CI: 1.19, 1.23). Among married people, with the increase of PM_{2.5} exposure concentration, the OR of ELT-related CVD mortality risk increased from 1.01 (95%CI: 0.88, 1.14) to 1.97 (95%CI: 1.36, 2.83). The temperature decreased from 1.01 (95%CI: 0.94, 1.06) to 1.19 (95% CI: 1.17, 1.21). There was a significant difference between groups (***P for Z test*** < 0.05). However, in cases under 65 years old and unmarried, low temperature did not have a significant modifying effect on the risk of death from cardiovascular diseases related to PM_{2.5} (***P for Z test*** > 0.05). Consistent bidirectional moderating effects of PM_{2.5} and low temperature were observed in the subgroups of gender, residential area and educational attainment, with significant differences between the groups (***P for Z test*** < 0.05). Among the above subgroups, except for unmarried individuals, with the increase of PM_{2.5} concentration, the risk of EHT-related CVD death significantly

increased (*P for Z test* < 0.05), but with the increase of temperature, the risk of PM_{2.5} related CVD death significantly decreased. Therefore, high temperature has only a unidirectional regulatory effect.

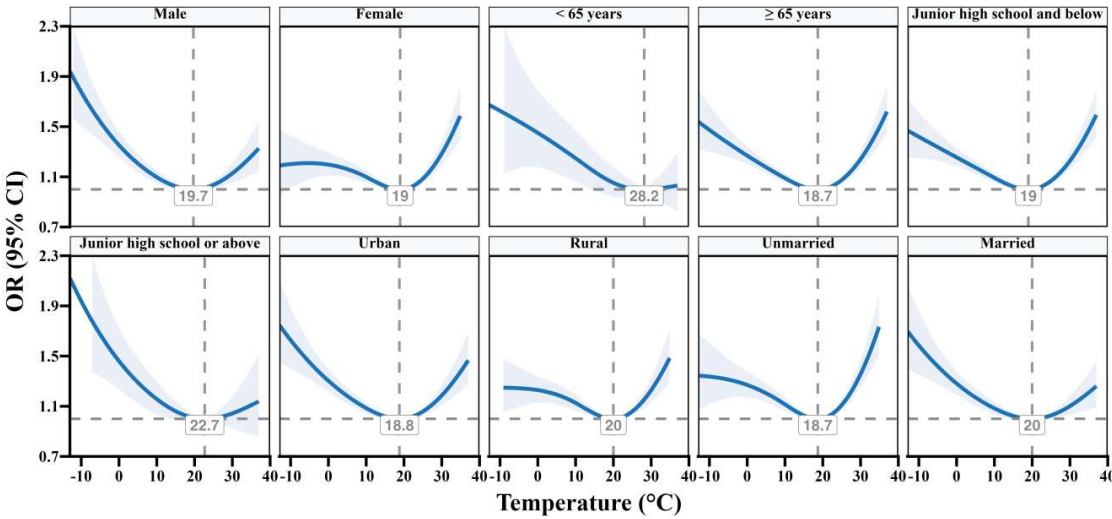


Fig. 4 Exposure–response curves for the temperature–CVD mortality association across population subgroups.

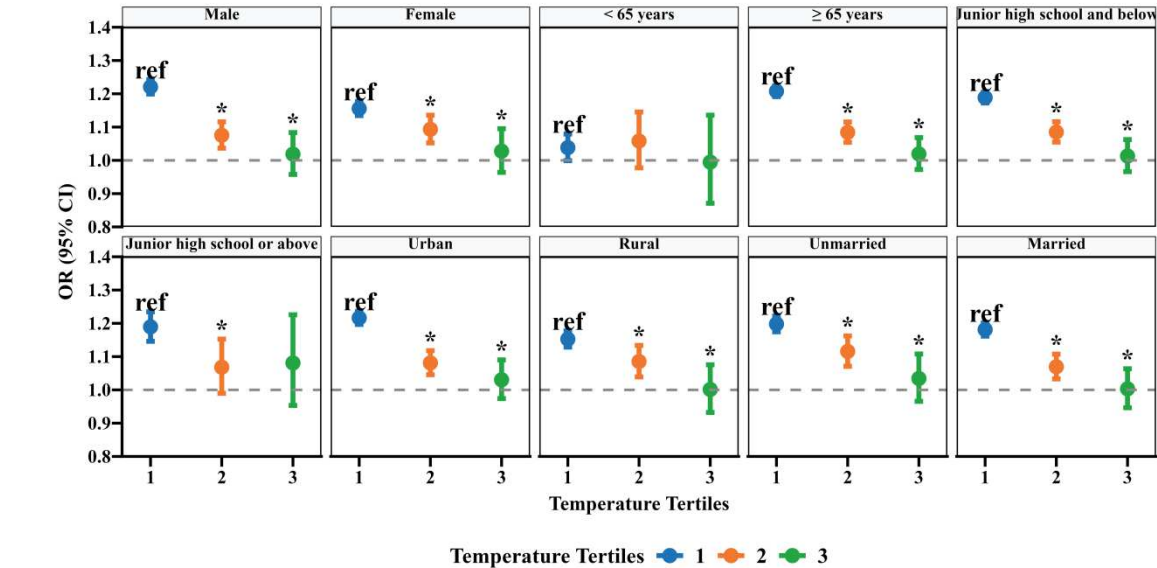


Fig. 5 Effect modification of the PM_{2.5}–CVD mortality association by temperature across population subgroups.

Table 4 Effect modification of PM_{2.5} on the temperature–CVD mortality association

370 across subgroups.

Subgroup	PM _{2.5} level	EHT		ELT	
		OR (95% CI)	<i>P for Z test</i>	OR (95% CI)	<i>P for Z test</i>
Male	Low	1.11 (0.96, 1.28) *	0.03	1.04 (0.90, 1.20) *	0.02
	Medium	1.03 (0.90, 1.18) *	0.01	1.03 (0.92, 1.15) *	0.02
	High	1.90 (1.19, 3.03)		1.72 (1.15, 2.57)	
Female	Low	1.14 (0.97, 1.34) *	<0.01	1.01 (0.87, 1.19) *	<0.01
	Medium	1.08 (0.94, 1.25) *	<0.01	1.07 (0.96, 1.21) *	<0.01
	High	2.50 (1.48, 4.20)		2.20 (1.40, 3.45)	
<65 years	Low	1.08 (0.93, 1.25)	0.37	1.02 (0.95, 1.11)	0.49
	Medium	1.03 (0.90, 1.17)	0.54	1.01 (0.93, 1.10)	0.55
	High	0.93 (0.68, 1.25)		0.95 (0.79, 1.15)	
≥65 years	Low	1.16 (1.02, 1.30) *	<0.01	1.05 (0.93, 1.18) *	<0.01
	Medium	1.07 (0.96, 1.18) *	<0.01	1.06 (0.97, 1.15) *	<0.01
	High	2.44 (1.64, 3.62)		2.15 (1.53, 3.04)	
Junior high school and below	Low	1.17 (1.04, 1.31) *	0.01	1.05 (0.94, 1.18) *	<0.01
	Medium	1.04 (0.94, 1.16) *	<0.01	1.04 (0.95, 1.13) *	<0.01
	High	2.01 (1.37, 2.95)		1.81 (1.30, 2.54)	
Junior high school or above	Low	0.89 (0.71, 1.11) *	0.01	0.91 (0.75, 1.10) *	<0.01
	Medium	1.12 (0.90, 1.40)	0.07	1.09 (0.92, 1.31)	0.07
	High	2.02 (1.12, 3.65)		1.79 (1.09, 2.91)	
Urban	Low	1.12 (0.96, 1.29) *	0.03	1.04 (0.90, 1.20) *	0.02
	Medium	1.05 (0.93, 1.19) *	0.02	1.05 (0.94, 1.16) *	0.02
	High	1.86 (1.18, 2.92)		1.70 (1.15, 2.52)	
Rural	Low	1.15 (0.98, 1.35) *	0.02	1.04 (0.89, 1.22) *	0.01
	Medium	1.05 (0.90, 1.23) *	<0.01	1.04 (0.91, 1.18) *	<0.01
	High	2.20 (1.29, 3.75)		1.96 (1.24, 3.11)	
Unmarried	Low	1.23 (1.03, 1.46)	0.17	1.07 (0.90, 1.27)	0.08
	Medium	1.13 (0.97, 1.31)	0.09	1.11 (0.97, 1.26)	0.10
	High	1.90 (1.05, 3.43)		1.74 (1.04, 2.90)	
Married	Low	1.06 (0.93, 1.21) *	<0.01	1.00 (0.88, 1.14) *	<0.01
	Medium	1.00 (0.89, 1.14) *	<0.01	1.00 (0.91, 1.11) *	<0.01
	High	2.22 (1.45, 3.40)		1.97 (1.36, 2.83)	

371 **Abbreviations:** EHT: Extreme high temperature above the 95th temperature percentile;
372 ELT: Extreme low temperature below the 5th temperature percentile. Two-sample Z-
373 *tests* were performed to compare EHT/ELT-associated effects between PM_{2.5} strata,
374 with the high PM_{2.5} level as the reference and P-values from the Z-tests reflect inter-
375 stratum differences. *: $P < 0.05$.

376

377 **Sensitivity analysis**

378 When temperature exposure was categorized using different percentile cutoffs, the
379 bidirectional modifying effects of non-optimal temperature and PM_{2.5} on CVD
380 mortality were unchanged and consistent (2.5th and 97.5th; 10th and 90th) (**Table S1**).
381 After adjusting for additional air pollutants (PM₁₀, O₃, SO₂, NO₂, and CO) as covariates,
382 the bidirectional modifying effects of PM_{2.5} and non-optimal temperature on CVD
383 mortality remained robust (**Table S2, Fig. S1**).

384 When the lag windows for PM_{2.5} and temperature were expanded to lag01–07, the
385 categorization of PM_{2.5} and temperature in this study remained anchored to PM_{2.5}-lag01
386 and temperature-lag03, in alignment with the primary model, and the outcomes were
387 nearly indistinguishable from those of the primary model (**Table S3, Table S4, Fig. S2,**
388 **Fig. S3**). When the df for temperature and relative humidity were altered, the results
389 were predominantly consistent with the fundamental model outcomes (**Table S5, Table**
390 **S6, Fig. S4, Fig. S5**).

391

392 **Discussion**

393 This study systematically investigated the bidirectional modification effects of
394 PM_{2.5} and non-optimal temperature exposure on CVD mortality risk in Anhui Province.
395 The primary findings are presented below: First, there was a significant bidirectional
396 modifying effect between PM_{2.5} and low temperature on CVD mortality risk; second,
397 at the disease subtype level, the bidirectional modifying effect of PM_{2.5} short-term

exposure and low temperature was more prominent in acute CVD, including IHD, MI, CVA, and SCVS; third, the elderly population aged ≥ 65 years and married individuals were vulnerable groups.

This study revealed that PM_{2.5} and low temperature interact synergistically to affect CVD mortality, corroborating earlier research (Song et al., 2017; Ye et al., 2012). Comparable findings have been documented in Europe, where elevated particulate matter levels were linked to stronger impacts of cold temperature on both total and CVD mortality (Yitshak-Sade et al., 2018). A study in China found that the mortality risk linked to PM_{2.5} was elevated during low-temperature conditions compared to moderate temperatures (Qiu et al., 2018). Temperature's modifying effect on air pollution-related health effects has long been a key research focus in environmental epidemiology. (Qi et al., 2025; Hsu et al., 2017; Qiu et al., 2013; Huang et al., 2016; Winquist et al., 2014; Ren et al., 2006; Zhao et al., 2025; Qiu et al., 2018). A study in Shenzhen confirmed that exposure to low temperatures and elevated levels of PM_{2.5} exhibited synergistic associations with the risk of hospitalization for stroke (Zhao et al., 2025), whereas research in Jiangsu demonstrated a synergistic effect of heatwaves and PM_{2.5} on MI mortality (Xu et al., 2023). Conversely, research investigating the inverse modifying effect of pollutants on temperature-related impacts is comparatively scarce (Ren et al., 2006; Zhao et al., 2025; Jin et al., 2022; Rai et al., 2023). Previous study has revealed that elevated PM_{2.5} levels modulated the relationship between high temperatures and CVD mortality (Rai et al., 2023). The findings of this study further validate and enhance these previous observations: PM_{2.5} stratification analysis showed that the effect of non-

optimal temperature was significantly enhanced under higher PM_{2.5} exposure; meanwhile, ELT also significantly exacerbated the harm of PM_{2.5} on CVD mortality, confirming a bidirectional modifying effect between the two, which was more stable and stronger at ELT.

From a biological mechanism perspective, low temperature and PM_{2.5} may act on CVD through similar pathophysiological pathways (Xu et al., 2023; Yazdi et al., 2023). Low temperature can elicit sympathetic nerve excitement, vasoconstriction, and a hypercoagulable state of the blood (Chen et al., 2024); whereas PM_{2.5} can trigger systemic inflammatory responses and oxidative stress (Ding et al., 2024; Costa-Beber et al., 2025; Muenzel et al., 2025). The superposition of the two may synergistically promote the increase of blood pressure, thrombosis, and the occurrence of acute ischemic events (Ning et al., 2024b). In this study, the bidirectional modifying effect was weaker at high temperatures than at low temperatures, and the possible reasons include: high temperature leads to vasodilation, reducing vascular resistance and cardiac load (Liu et al., 2015); the high usage rate of air conditioning in Anhui Province in summer weakens the health hazards of high temperature to a certain extent; While there is no centralized heating in winter and the temperature can drop below zero, residents are significantly exposed to cold during outdoor activities, combined with high PM_{2.5} concentrations, amplifies the combined effect on the CVD burden.

This study revealed that the bidirectional modifying effect of PM_{2.5} and low temperature was notably significant and consistent across acute CVD, including IHD, MI, CVA, and SCVS. This finding may be closely related to the underlying

pathophysiological mechanisms of acute CVD, which are often triggered by acute pathological processes such as plaque rupture and thrombosis. Low temperature and PM_{2.5} work in concert to promote endothelial damage, inflammation, and a hypercoagulable condition, which increases the likelihood of acute events (Kliengchuay et al., 2025). Similar to a Korean study, low temperatures greatly enhanced the association between PM_{2.5} short-term exposure and MI hospitalization risk. In contrast, the progression of chronic CVD involves more complex, multifactorial, and long-term cumulative mechanisms, which may attenuate the immediate effects of short-term environmental exposure combinations, making significant interactions more difficult to detect (Peralta et al., 2025).

In terms of population subgroups, this study further identified individuals aged 65 years and older, as well as married individuals, as susceptible populations to the bidirectional modifying effect of PM_{2.5} short-term exposure and low temperature. This finding corresponds with a national health and retirement longitudinal research, which indicated that elevated PM_{2.5} exposure coupled with ELT markedly heightened the prevalence of CVD among the elderly (Zhang et al., 2025). Due to declining cardiopulmonary reserve, reduced vascular elasticity, and the presence of multiple chronic underlying conditions, older adults exhibit substantially impaired physiological compensation and stress adaptation capabilities (Calciolari and Luini, 2023). Moreover, diminished thermoregulatory function and reduced efficiency in pollutant metabolism and clearance further heighten their health vulnerability under dual environmental stressors (Zhuang et al., 2025). In this study, married individuals constituted a relatively

high proportion of the susceptible group. Married men generally had higher body mass index (BMI) compared to their unmarried counterparts and bore a greater burden of CVD. Our findings also indicate that married individuals are more sensitive to ELT exposure, which may partly explain the elevated susceptibility of married individuals to co-exposure to ELT and PM_{2.5}. In line with a prior study, married males may exhibit greater susceptibility to ambient air pollution-related overweight and obesity, in addition to their higher BMI levels (Peng et al., 2025). Therefore, both the elderly and married populations should be prioritized as key targets in public health strategies targeted at reducing the detrimental CVD consequences of combined environmental exposures.

Several notable strengths characterize the present study. First, it constitutes the inaugural systematic assessment of the bidirectional modifying effect between non-optimal temperature and PM_{2.5} on CVD mortality at the regional scale in Anhui Province, clarifying the direction of this interaction and addressing a critical research gap in this area. Second, by conducting stratified analyses across different CVD subtypes and population characteristics, the study identified acute CVD, the elderly, and married individuals as high-risk groups, contribute to the formulation of targeted prevention and control strategies. Third, to guarantee the validity of the findings, this study performed various sensitivity analyses.

However, several limitations must be recognized in this study. As an ecological study, this study was unable to fully adjust for potential confounders, including individual-level behavioral factors and socioeconomic status, which may have

introduced residual confounding. Exposure misclassification may have occurred, as exposure assessment was based on data from stationary monitoring stations rather than personal exposure measurements; Additional research is required to corroborate whether our findings are generalizable to regions with varied climate and pollution backgrounds; our study concentrated exclusively on PM_{2.5} and did not account for the possible synergistic effects of co-exposure to several pollutants. Future research should integrate individual-level exposure monitoring, multi-pollutant assessment frameworks, and multicenter study designs to further validate and expand upon these findings.

To conclude, our findings carry important public health implications. They emphasize that when formulating health protection strategies, we must shift from one-way early warning to combined risk early warning. Especially in winter, a targeted health early warning framework for co-exposure to low temperature and elevated PM_{2.5} levels should be established, and key protection should be implemented for the elderly, married individuals, and those with existing chronic CVD. At the same time, the study results highlight that controlling PM_{2.5} pollution can not only directly reduce pollution-related deaths but also significantly weaken the health impacts of temperature extreme events, which provides strong scientific evidence for synergistically promoting air quality improvement and climate change adaptation. In the future, integrating individual exposure monitoring and health data will help more accurately identify high-risk populations and formulate targeted intervention measures.

Conclusion

This study demonstrates a notable bidirectional modifying effect between PM_{2.5} and non-optimal temperature concerning CVD mortality. These bidirectional modifying effects are particularly pronounced under low temperature conditions. In contrast, PM_{2.5} only exhibited a unidirectional enhancement of the effect of EHT, with no evidence of reverse modification. The bidirectional modifying effects were most prominent in acute CVD (IHD, MI, CVA, and SCVS), suggesting that acute pathological processes are more sensitive to such bidirectional modifying effects. The elderly (≥ 65 years) and married individuals were identified as susceptible populations, with their mortality risk significantly elevated under the bidirectional modification of PM_{2.5} and low temperature. These results indicate that PM_{2.5} and low temperature do not function separately in relation to CVD, but instead have intricate bidirectional modifying effects. This study provides critical regional evidence for health risk assessment of combined environmental exposures and highlights important public health implications. Furthermore, continued improvements in air quality may serve as a synergistic strategy to mitigate the health threats posed by extreme temperatures.

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Author contributions

Jiahui Zhou: Data curation; Formal analysis; Writing-original draft. Yueyue Zhu: Data curation; Formal analysis. Yingru Gong: Methodology; Formal analysis; Writing-

review & editing; Software. Meng Cheng: Data curation; Formal analysis. Haisheng Wu: Methodology; Formal analysis; Writing-review & editing; Software. Yanlong Xu: Data curation; Writing-review & editing; Supervision. Yuhui Wan: Resources; Writing-review & editing; Supervision. Jinping Ou: Conceptualization; Methodology; Writing-review & editing; Supervision; Funding acquisition. Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

Declarations

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

Competing interests

The authors declare no competing interests.

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