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Research Article

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Posted Date: August 13th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10547139/v1

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Additional Declarations: No competing interests reported.

Nonlinear and Lagged Associations of Compound Cold Wave–$PM_{2.5}$ Pollution Exposure with Cardiovascular Emergency Ambulance Calls: A Time-Series Study in Shijiazhuang, China

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Funding Program:

The Hebei Natural Science Foundation (Project No. H2026106020)

2024 Shijiazhuang Municipal Science and Technology Plan (Project No. 2414605403)

Abstract

Background: Cold waves and fine particulate matter ($PM_{2.5}$) pollution are well-recognized environmental risk factors for cardiovascular health. However, evidence remains limited regarding the health effects of compound exposure to different cold-wave intensities and $PM_{2.5}$ pollution levels, as well as the potential interactions between these environmental stressors. This study aimed to establish a multi-level cold wave–$PM_{2.5}$ compound exposure framework to evaluate the associations of different exposure combinations with cardiovascular emergency ambulance calls and to investigate their lagged and interactive effects.

Methods: Daily cardiovascular emergency ambulance call records (n = 82,714), meteorological data, and air pollution data were collected in Shijiazhuang, China, from 1 January 2014 to 31 December 2023. Three cold-wave categories (T1–T3) were defined using temperature percentile thresholds, while four $PM_{2.5}$ pollution levels (P1–P4) were classified according to daily

mean $PM_{2.5}$ concentrations. Compound cold wave–$PM_{2.5}$ exposure events were subsequently constructed. A distributed lag non-linear model (DLNM) combined with quasi-Poisson regression was applied to estimate both single-day and cumulative lag effects of different exposure patterns. Additive interactions between cold waves and $PM_{2.5}$ were assessed using the relative excess risk due to interaction (RERI).

Results： A total of 82,714 cardiovascular emergency ambulance calls were recorded during the study period. Cold-wave exposure alone was consistently associated with an increased risk of cardiovascular emergency ambulance calls, with stronger cold waves (T3) showing more pronounced cumulative effects. In contrast, $PM_{2.5}$ exposure alone exhibited relatively weak associations, and no stable cumulative risk increase was observed. Compound cold wave–$PM_{2.5}$ exposure demonstrated substantial nonlinearity and heterogeneity, with considerable variation across different exposure combinations. The P2T3 event (moderate $PM_{2.5}$ pollution combined with a strong cold wave) was associated with the highest cumulative risk (RR = 1.137, 95% CI: 1.082–1.194). Interaction analyses further indicated that the joint effects of cold waves and $PM_{2.5}$ were not uniformly synergistic; instead, both positive and negative additive interactions were observed across different exposure combinations, suggesting that the health impacts of compound exposure varied according to cold-wave intensity, $PM_{2.5}$ pollution level, and population characteristics. Subgroup analyses additionally revealed differential susceptibility among males, older adults, and patients with different cardiovascular disease subtypes.

Conclusion： Cold waves may represent a more important environmental driver of cardiovascular emergency ambulance calls than $PM_{2.5}$ pollution, whereas the health effects of $PM_{2.5}$ appear to be modified by exposure combinations and meteorological conditions. The health impacts of compound cold wave–$PM_{2.5}$ exposure were characterized by nonlinear, lagged, and heterogeneous associations across exposure combinations. These findings highlight the importance of incorporating multiple environmental stressors into environmental health risk assessment and early warning systems, rather than focusing on single environmental factors alone.

Keywords: Cold wave; $PM_{2.5}$; Compound exposure; Circulatory diseases; Emergency ambulance calls; Distributed lag nonlinear model

1. Introduction

Climate change has increased the frequency, duration, and intensity of extreme weather events worldwide, posing substantial challenges to public health(**Error! Reference source not found.**). Among these events, cold waves are one of the most common and have been consistently associated with increased risks of cardiovascular diseases, respiratory diseases, and all-cause mortality (**Error! Reference source not found.-Error! Reference source not found.**). Although global average

temperatures continue to rise, the health burden attributable to low temperatures remains considerably greater than that associated with high temperatures (5,**Error! Reference source not found.**). Epidemiological studies have demonstrated that cold-wave exposure is associated with increased risks of cardiovascular mortality, hospital admissions, and emergency department visits, highlighting its importance as a public health concern worldwide (**Error! Reference source not found.**,**Error! Reference source not found.**-8).

Ambient air pollution is another major environmental determinant of human health (**Error! Reference source not found.**). Fine particulate matter ($PM_{2.5}$), because of its small aerodynamic diameter and large surface area, can penetrate deep into the respiratory tract and enter the circulatory system, thereby increasing cardiovascular risk through multiple biological pathways, including oxidative stress, systemic inflammation, endothelial dysfunction, and autonomic nervous system imbalance (**Error! Reference source not found.**-**Error! Reference source not found.**). According to the Global Burden of Disease Study, $PM_{2.5}$ remains one of the leading environmental risk factors for premature mortality and disability worldwide, with particularly substantial health impacts in developing countries such as China (13-**Error! Reference source not found.**).

Cold waves and $PM_{2.5}$ pollution are not independent environmental exposures. During winter, cold-air outbreaks can alter atmospheric boundary layer dynamics, pollutant dispersion, and regional transport processes, thereby increasing the likelihood of concurrent low-temperature and high-pollution events (**Error! Reference source not found.**,**Error! Reference source not found.**). This phenomenon is particularly pronounced in northern Chinese cities, where residential heating emissions and unfavorable meteorological conditions frequently result in compound exposure to cold waves and elevated $PM_{2.5}$ concentrations. Emerging evidence suggests that cold waves and $PM_{2.5}$ may affect cardiovascular health through overlapping biological mechanisms, including oxidative stress, inflammatory responses, endothelial injury, and coagulation abnormalities. Consequently, their combined health effects may exceed those associated with either environmental exposure alone(**Error! Reference source not found.**-**Error! Reference source not found.**).

Despite growing interest in compound environmental exposures, several important knowledge gaps remain. First, most previous studies have examined the independent effects of cold waves or air pollution, whereas evidence regarding their combined health impacts remains limited. Second, existing studies have generally relied on a single definition of cold waves or a single $PM_{2.5}$ threshold, with few systematically evaluating health risks across multiple combinations of cold-wave intensity and $PM_{2.5}$ pollution levels. Third, although joint exposure effects have been reported, whether cold waves and $PM_{2.5}$ interact synergistically or antagonistically has not been adequately investigated. Finally, current evidence is derived predominantly from mortality or hospital admission data, whereas studies using emergency ambulance call records remain scarce. Compared with mortality and hospitalization data, emergency ambulance calls provide a more timely and sensitive indicator of acute health events and fluctuations in healthcare demand.

Shijiazhuang, a major city located within the Beijing–Tianjin–Hebei air pollution transmission corridor, experiences frequent cold waves and persistently elevated $PM_{2.5}$ concentrations during winter, making it an ideal setting for investigating the health effects of compound cold wave–$PM_{2.5}$ exposure. Using cardiovascular emergency ambulance call records collected in Shijiazhuang between 2014 and 2023, this time-series study established a multi-level cold wave–$PM_{2.5}$ compound exposure framework. A distributed lag non-linear model (DLNM) was applied to quantify the single-day and cumulative lag effects of different compound exposure events, while additive interactions between cold waves and $PM_{2.5}$ were evaluated using the relative excess risk due to interaction (RERI). This study aimed to characterize the health impacts and potential interaction patterns of compound cold wave–$PM_{2.5}$ exposure on cardiovascular emergency ambulance calls and to provide evidence to support environmental health risk assessment, early warning systems, and targeted protection of susceptible populations under a changing climate.

2. Materials and methods

2.1. Health outcome data

Daily cardiovascular emergency ambulance call records from 1 January 2014 to 31 December 2023 were obtained from the Shijiazhuang Emergency Medical Center, China. The database contained demographic information (age and sex), chief complaints, and preliminary clinical diagnoses for all emergency ambulance dispatches during the study period. To ensure patient confidentiality, all personal identifiers, including names, residential addresses, and telephone numbers, were anonymized before data extraction (18).

Cardiovascular emergency ambulance calls were identified according to the International Classification of Diseases, Tenth Revision (ICD-10). The primary outcome was all cardiovascular diseases (ICD-10: I00–I99). Subgroup analyses were further conducted for cerebrovascular diseases (I60–I69), heart diseases (I20–I25, I05–I09, I26–I28, and I30–I52), and hypertension (I10). Daily counts of emergency ambulance calls were calculated for each disease category. The ICD-10 codes were assigned based on the preliminary clinical diagnoses recorded by emergency physicians during prehospital assessment rather than on final hospital discharge diagnoses.

2.2. Meteorological and air pollution data

Daily meteorological data and air pollution data covering the study period (1 January 2014 to 31 December 2023) were obtained from the Shijiazhuang Meteorological Service Center and the Shijiazhuang Environmental Monitoring Center, respectively. Meteorological variables included daily mean temperature (°C), relative humidity (RH, %), and wind speed (m/s). Air pollution data consisted of daily mean concentrations of fine particulate matter ($PM_{2.5}$) and ozone (O_3), which were obtained from the city's routine ambient air quality monitoring network.

Daily air pollution concentration data were obtained from seven fixed-site monitoringstations located across the main urban area of Shijiazhuang, covering five administrative districts (Xinhua, Chang′ an, Qiaoxi, Yuhua, and Gaoxin). These stations are distributed in areas with diverse land-use types, including residential, commercial, educational, and park zones. The spatial coverage of the monitoring network is considered representative of the population-weighted exposure to air pollution in the city′ s built-up area.City-wide average concentrations were calculated to represent population-level ambient exposure. The spatial distribution of the air quality monitoring stations used in this study is shown in **Figure S1**.

2.3. Definition of cold waves, $PM_{2.5}$ pollution episodes, and compound exposure events

There is currently no universally accepted definition of a cold wave. Because the exposure–response relationship between temperature and health outcomes varies geographically, epidemiological studies commonly define cold waves using a combination of location-specific temperature percentile thresholds and event duration. Consistent with previous studies (19), cold-wave events were defined as periods during which the daily mean temperature remained below the local 10th, 5th, or 2.5th percentile for at least two consecutive days, corresponding to mild (T1), moderate (T2), and strong (T3) cold-wave events, respectively.

To evaluate the health effects associated with different pollution intensities, $PM_{2.5}$ pollution was classified into four levels according to daily mean $PM_{2.5}$ concentrations. The classification was based on the World Health Organization (WHO) Air Quality Guidelines, the Chinese Air Quality Index (AQI), and the distribution of $PM_{2.5}$ concentrations during the study period. Specifically, P1 was defined as a daily mean $PM_{2.5}$ concentration of $75\mu g/m^3 \leq PM_{2.5} < 115\mu g/m^3$, with the lower threshold ($75\ \mu g/m^3$) corresponding to the first interim target (IT-1) of the 2021 WHO Air Quality Guidelines. P2 was defined as $115\mu g/m^3 \leq PM_{2.5} < 150\mu g/m^3$, corresponding to the moderate pollution category in the Chinese AQI. P3 was defined as $150\mu g/m^3 \leq$

$PM_{2.5}$<203μg/m³, corresponding to the heavy pollution category. P4 was defined as $PM_{2.5}$≥203μg/m³, representing the 95th percentile of daily $PM_{2.5}$ concentrations during the study period and serving as the threshold for extreme $PM_{2.5}$ pollution. A $PM_{2.5}$ pollution episode was defined as a period during which the daily mean $PM_{2.5}$ concentration remained at or above the corresponding threshold for at least two consecutive days.

A compound cold wave–$PM_{2.5}$ exposure event was defined when a $PM_{2.5}$ pollution episode and a cold-wave event overlapped temporally (20). To account for the potential health effects occurring immediately before and after exposure, a three-day moving window was applied during event identification. However, compound exposure events were defined exclusively by the days on which the two events actually overlapped. Compound exposure events were classified according to $PM_{2.5}$ pollution level (P1–P4) and cold-wave intensity (T1–T3), resulting in 12 exposure combinations: P1T1, P1T2, P1T3, P2T1, P2T2, P2T3, P3T1, P3T2, P3T3, P4T1, P4T2, and P4T3.

2.4. Statistical analysis

2.4.1. Association between compound exposure events and cardiovascular emergency ambulance calls

Daily cardiovascular emergency ambulance calls (EACs) were analyzed using a distributed lag non-linear model (DLNM) combined with a quasi-Poisson regression model to account for overdispersion in the count data and to estimate the delayed effects of cold waves, $PM_{2.5}$ pollution episodes, and compound exposure events. Cross-basis functions were constructed to simultaneously characterize the exposure–response relationship and the lag structure. Model parameters, including the maximum lag period and degrees of freedom, were selected according to the minimum Akaike Information Criterion (AIC). Based on this criterion, the maximum lag period was set to 21 days. The model is specified as follows:

$$\log[E(Y_t)] = \beta 0 + \beta 1 * cb_pm + \beta 2 * cb_cold + \beta 3 * cb_joint + ns(rhum, df=3) + ns(date, df=7*10) + weekdays + holiday$$

Equation (1)

Potential confounding factors were controlled using natural cubic splines, including relative humidity (natural spline, 3 degrees of freedom [df]) and calendar time (7 df per year) to account for long-term trends and seasonality. Indicator variables for the day of the week and public holidays were also included in the model.

Additive interaction between cold waves and $PM_{2.5}$ pollution was evaluated using the relative excess risk due to interaction (RERI). The reference exposure was defined as days with a $PM_{2.5}$ concentration <75 μg/m³ and a daily mean temperature above

the local 10th percentile. A positive RERI indicated a synergistic interaction, whereas a negative RERI indicated an antagonistic interaction. The RERI was calculated as follows:

$$RERI = RR_joint - RR_pm_only - RR_cold_only + 1$$

Equation (2)

2.4.2. Sensitivity analysis

Sensitivity analyses were performed to evaluate the robustness of the model. Candidate compound exposure combinations were first screened according to the AIC values presented in **Table S1**. The two representative exposure combinations with the lowest AIC values (P4T1 and P4T3) were subsequently selected for sensitivity analyses. Alternative lag structures, covariate adjustment strategies, and model specifications were examined to assess the stability of the estimated associations.

2.4.3. Other statistical analysis

All statistical analyses were performed using R software (version 4.4.3; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were summarized as the median and interquartile range (IQR) because they did not follow a normal distribution according to the Shapiro–Wilk test. The primary analyses were conducted using the dlnm and splines packages. All statistical tests were two-sided, and a P value <0.05 was considered statistically significant.

3. Results

3.1. Characteristics of study population

A total of 82,714 cardiovascular emergency ambulance call records were collected during the study period. Among these cases, males accounted for 55.7% and females accounted for 44.3%. Regarding age distribution, the proportion of patients aged ≥65 years was higher than that of patients aged <65 years.**(Table 1)**

Table 1 Descriptive statistics of daily emergency ambulance calls, meteorological variables, and air pollutants in Shijiazhuang, China, from 2014 to 2023

	Mean	Min	P_{25}	Median	P_{75}	Max
Cardiovascular diseases	22.65	4	18	22	26	68
Cerebrovascular disease	8.36	0	6	8	10	26

Ischemic heart diseases	5.06	0	3	5	7	21
Hypertension	3.71	0	2	3	5	22
Male	12.6	1	10	12	15	38
Female	10.02	1	7	10	12	35
<65 years	8.79	0	6	9	11	34
≥65 years	13.86	2	11	13	17	43
Average daily temperature /℃	14.95	-10.8	5	16	24.7	35.8
Average relative humidity /%	55.84	7	40	56	72	100
wind speed（m/s）	1.89	0.3	1.3	1.8	2.3	6.5
$PM_{2.5}$	73.24	6.3	31	51.4	89.62	625.3
O_3	93.90	1.9	49.25	82.8	128.18	1156.25

3.2. Associations between compound exposure events and cardiovascular emergency ambulance calls

3.2.1. Characteristics of compound exposure events

A total of 108 compound cold wave–$PM_{2.5}$ exposure event days were identified during the study period. The proportion of event days varied across exposure combinations, ranging from 0.71% for P1T1 to 0.12% for P4T3 of the total study period (**Table 2**).

Because some compound exposure combinations occurred infrequently, the estimated effects for combinations with a limited number of exposure days should be interpreted with caution.

Table 2 Basic characteristics of cold wave–$PM_{2.5}$ compound exposure events under different definitions

definition	Event Days (N)	Proportion of Study Days (%)
P1T1	26	0.71
P1T2	9	0.25
P1T3	8	0.22
P2T1	10	0.27
P2T2	2	0.05
P2T3	3	0.08
P3T1	4	0.12
P3T2	3	0.08
P3T3	7	0.19
P4T1	26	0.71
P4T2	6	0.16
P4T3	4	0.12
Total	108	2.96

3.2.2. Lag-specific effects of compound exposure events on cardiovascular emergency ambulance calls

The lag-specific associations between compound cold wave−PM2.5 exposure events and cardiovascular emergency ambulance calls showed evident delayed effects, with heterogeneous patterns across exposure combinations and population subgroups.

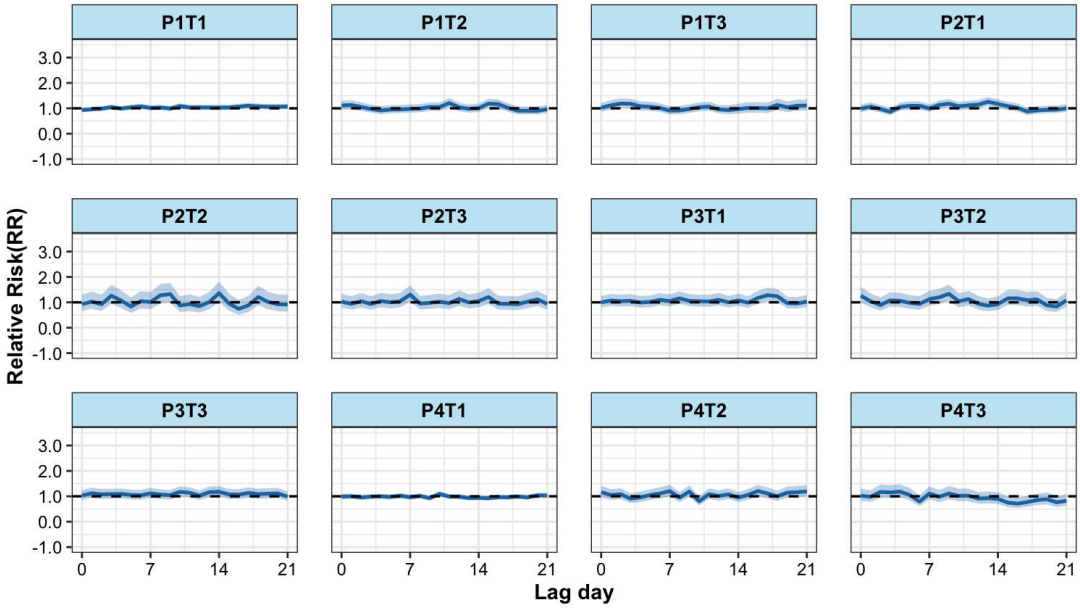
For overall cardiovascular emergency ambulance calls, significant associations were observed at different lag days, with risk peaks generally occurring several days to approximately two weeks after exposure. Specifically, the P1T3 compound exposure event showed the strongest effects at lag 2 (RR = 1.188, 95% CI: 1.011−1.395) and lag 3 (RR = 1.181, 95% CI: 1.006−1.385). The P1T2 event reached its maximum effect at lag 11 (RR = 1.205, 95% CI: 1.036−1.402). In addition, significant risk increases were observed for P2T1 at lag 13 (*RR* = 1.259, 95% *CI*: 1.097−1.446) and P2T3 at lag 7 (*RR* = 1.304, 95% *CI*: 1.025−1.659).

Sex-stratified analyses demonstrated different response patterns between males and females. Among males, P1T2 showed the strongest association at lag 11 (*RR* = 1.385, 95% *CI*: 1.156−1.660), while elevated risks were also observed for P1T3 at lag 3 (*RR* = 1.329, 95% *CI*: 1.098−1.608) and P3T1 at lag 18 (*RR* = 1.418, 95% *CI*: 1.099−1.829). Among females, significant associations were observed for P1T1 at lag 19 (*RR* = 1.146, 95% *CI*: 1.003−1.310) and P1T2 at lag 15 (*RR* = 1.306, 95% *CI*: 1.070−1.594).

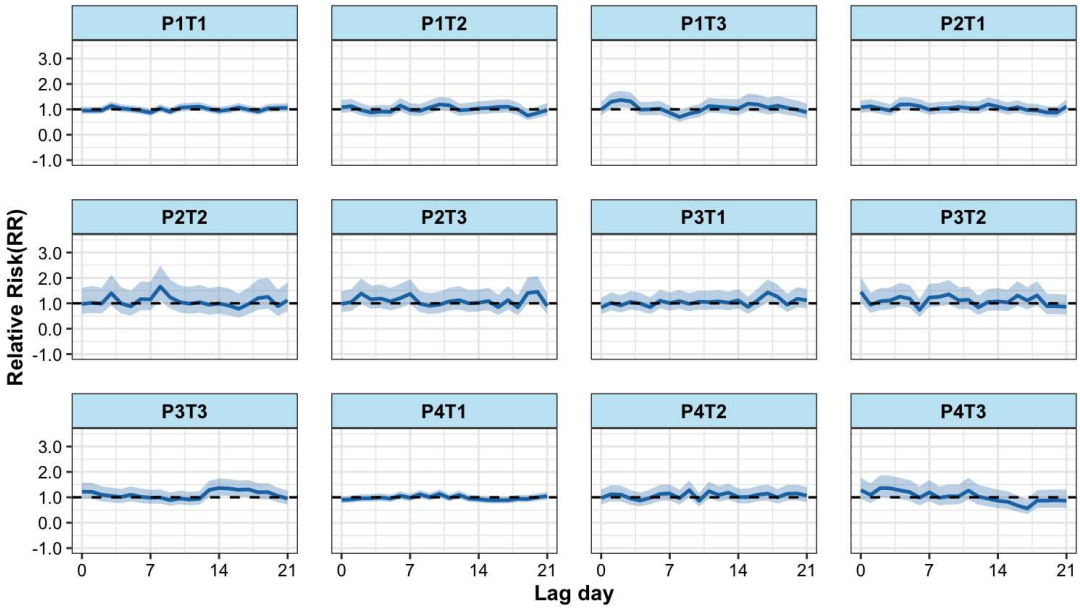
Age-stratified analyses indicated that individuals aged ≥65 years exhibited significant associations with several compound exposure combinations. The strongest effects were observed for P1T3 at lag 11 (*RR* = 1.323, 95% *CI*: 1.046−1.674), P2T1 at lag 13 (*RR* = 1.322, 95% *CI*: 1.077−1.623), and P3T3 at lag 10 *(RR* = 1.313, 95% *CI*: 1.017−1.694). Among individuals aged <65 years, the highest risks were observed for P4T2 at lag 0 (*RR* = 1.322, 95% *CI*: 1.054−1.656) and lag 16 (*RR* = 1.322, 95% *CI*: 1.062−1.645).

Disease-specific analyses demonstrated differential susceptibility across cardiovascular disease subtypes. Among individuals with hypertension, the highest risk was observed for P4T2 exposure (*RR* = 1.540, 95% *CI*: 1.034−2.294), with significant associations also observed for P1T1 at lag 20 (*RR* = 1.361, 95% *CI*: 1.112−1.666) and P2T1 at lag 8 (*RR* = 1.640, 95% *CI*: 1.217−2.211). For heart disease, the strongest associations were observed for P1T1 at lag 7 (*RR* = 1.312, 95% *CI*: 1.083−1.589) and P3T1 at lag 6 (*RR* = 1.609, 95% *CI*: 1.115−2.321). For cerebrovascular disease, significant associations were observed for P1T3 at lag 2 (*RR* = 1.368, 95% *CI*: 1.080−1.734) and P3T3 at lag 14 (*RR* = 1.367, 95% *CI*: 1.072−1.743).(**Figure 1**)

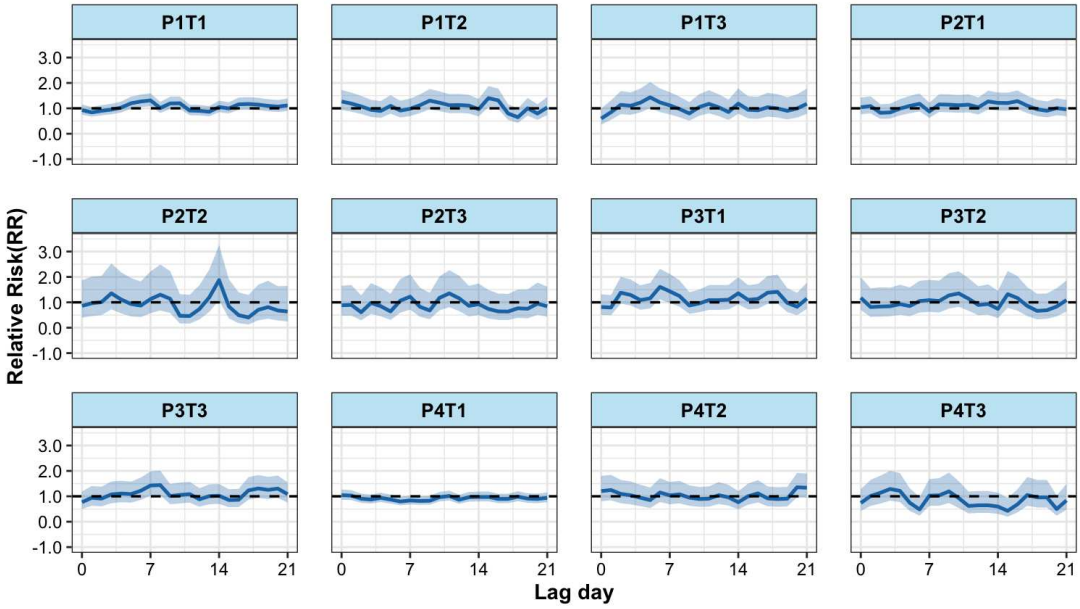
A.


P1T1
P1T2
P1T3
P2T1
P2T2
P2T3
P3T1
P3T2
P3T3
P4T1
P4T2
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Relative Risk(RR)
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-1.0
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14
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Lag day

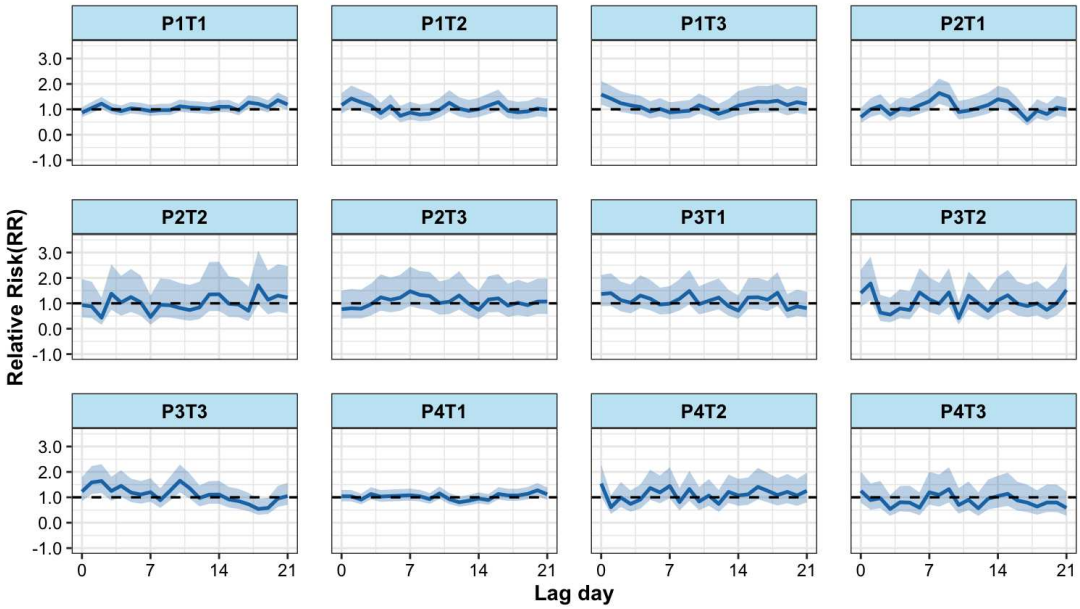
B.


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Relative Risk(RR)
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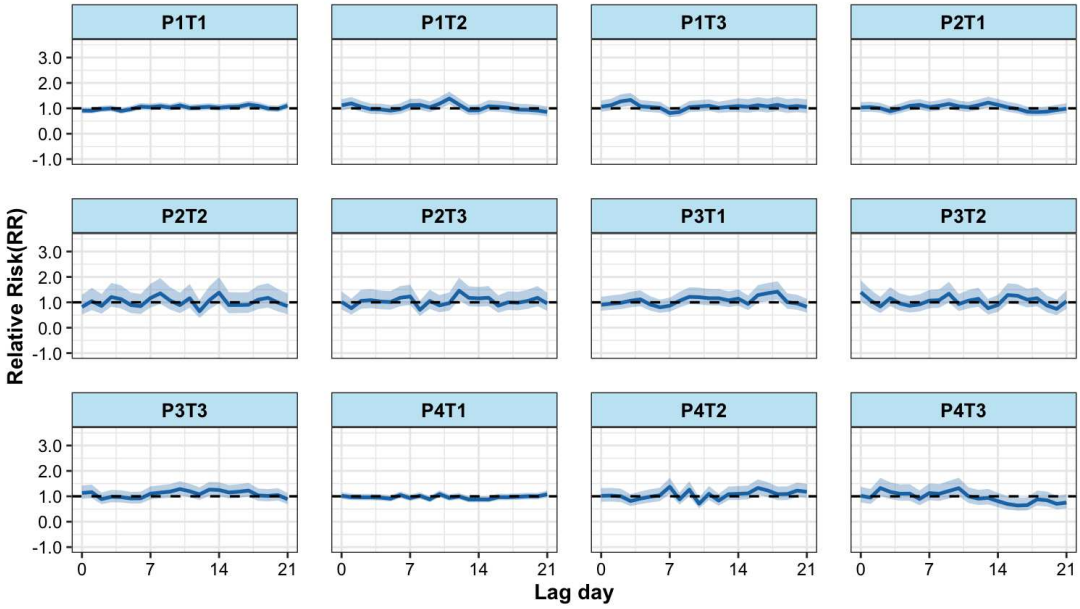
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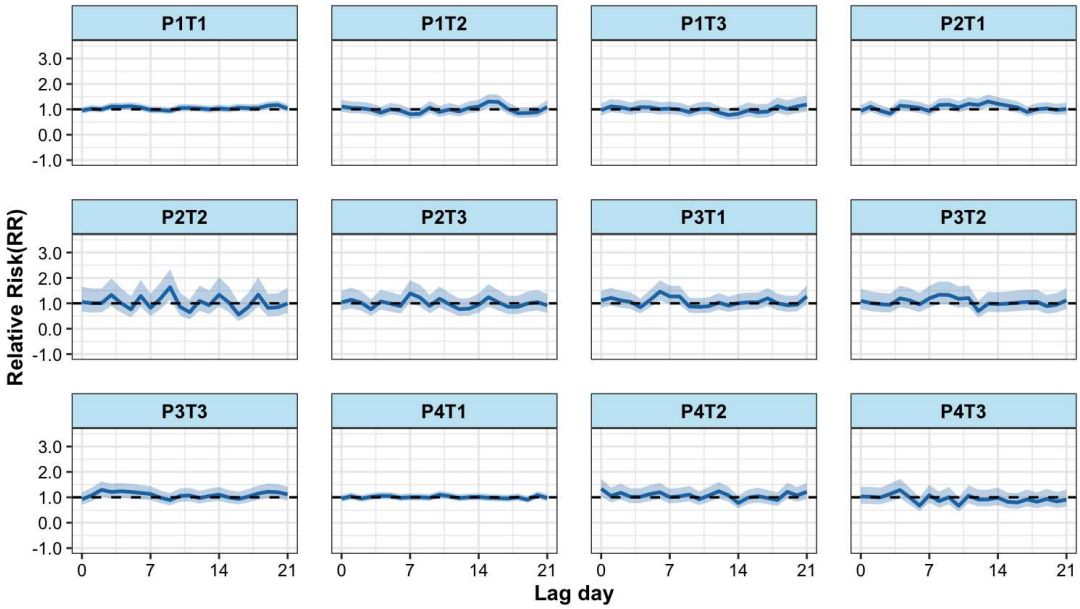
D.


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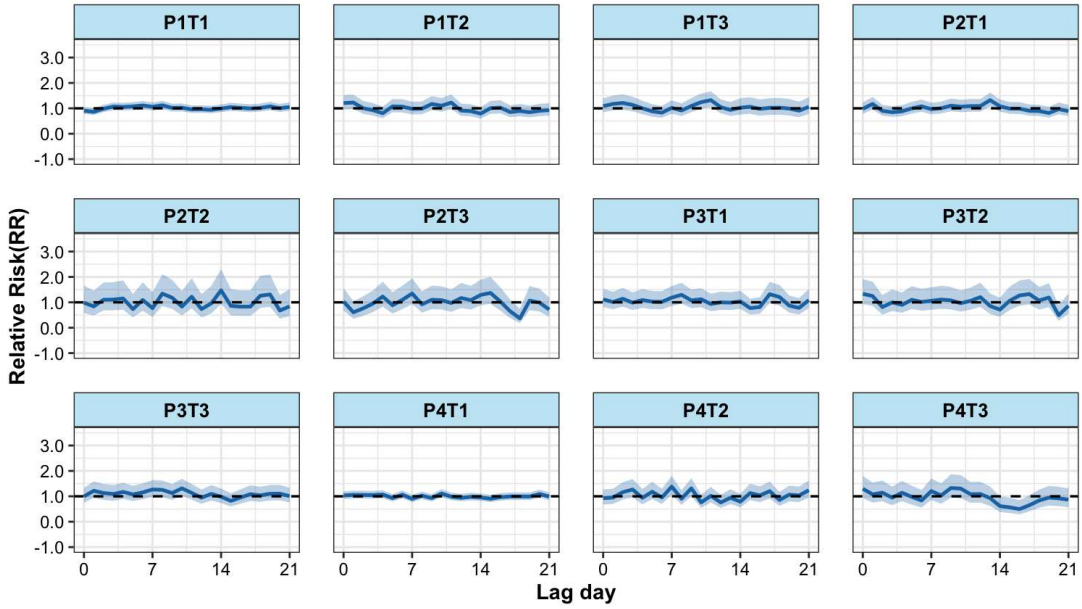
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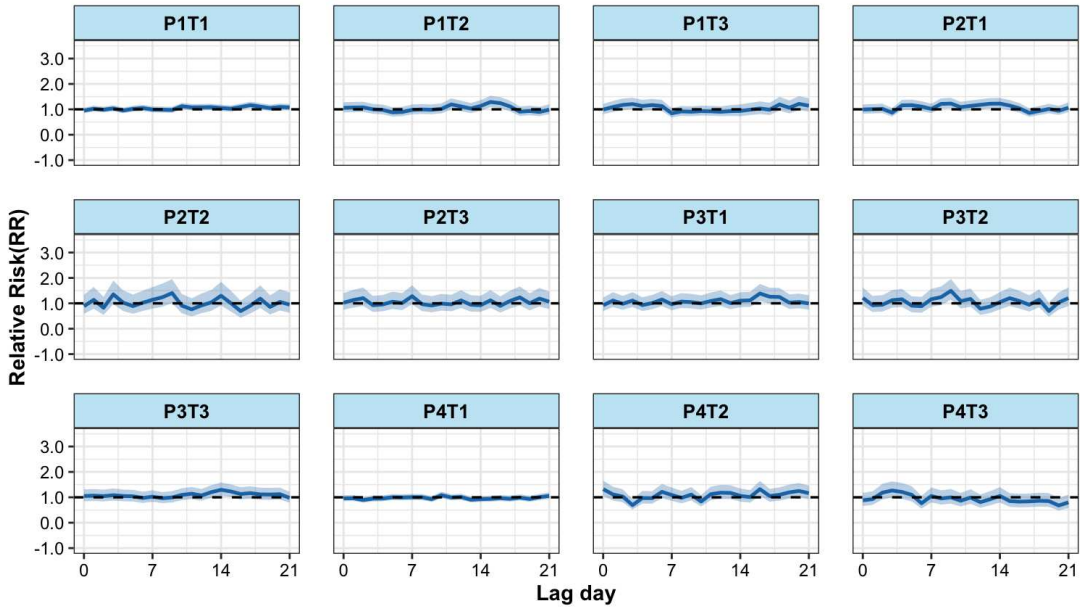
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Relative Risk(RR)
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Lag day

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H.



A：Cardiovascular diseases；B:Cerebrovascular disease；C：Heart diseases；D：Hypertension；E：Male；F：Female；G：<65 years；H：≥65years

Figure 1 Lag-specific associations between cold wave–$PM_{2.5}$ compound exposure events and cardiovascular emergency ambulance calls

3.2.3. Cumulative lag effects of compound exposure events on cardiovascular emergency ambulance calls

The cumulative lag effects over lag 0–21 days demonstrated distinct risk patterns associated with different environmental exposure scenarios (**Figure 2**). Overall, cold-wave-related exposures showed greater variations in risk estimates than $PM_{2.5}$ exposure alone. When cold waves co-occurred with $PM_{2.5}$ pollution episodes, several compound exposure combinations showed further increases in cardiovascular emergency ambulance calls.

For cold-wave exposure alone, different cold-wave intensities exhibited heterogeneous cumulative risk patterns. Among all cardiovascular emergency ambulance calls, stronger cold waves (T3) were generally associated with higher risk estimates, whereas weaker cold waves (T1 and T2) showed relatively smaller effects. Similar patterns were observed in some disease-specific and population subgroups. In particular, individuals with hypertension exhibited relatively higher risk estimates associated with cold-wave exposure.

In contrast, cumulative risk estimates associated with $PM_{2.5}$ exposure alone were generally weak, and no consistent concentration–response relationship was observed. For overall cardiovascular emergency ambulance calls and most subgroups, risk estimates across different $PM_{2.5}$ pollution levels (P1–P4) were generally close to the null value. Although some higher pollution levels showed RR estimates below 1, the confidence intervals were relatively wide, indicating substantial uncertainty in the short-term cumulative effects of $PM_{2.5}$ exposure under the pollution episode definitions and lag periods used in this study.

Notably, although $PM_{2.5}$ exposure alone did not demonstrate a stable cumulative risk increase, more complex risk patterns were observed when $PM_{2.5}$ pollution occurred concurrently with cold waves. Compared with $PM_{2.5}$ exposure alone, most cold wave–$PM_{2.5}$ compound exposure events showed higher risk estimates, with some combinations exceeding those observed for cold-wave exposure alone. Among the overall cardiovascular disease population, the P2T3 compound exposure event showed the highest cumulative risk (*RR* = 1.137, 95% *CI*: 1.082–1.194). Increased risks were also observed for P1T3 and P3T1 exposure combinations.

However, the effects of compound exposure events did not show a monotonic increase with increasing $PM_{2.5}$ concentrations, but instead exhibited clear non-linear patterns. The combined effects of $PM_{2.5}$ varied substantially across different cold-wave intensities. Exposure combinations involving stronger cold waves (T3) generally showed more consistent risk increases, whereas some T2-related combinations showed relatively lower risk estimates, with some RR values approaching or falling below 1.

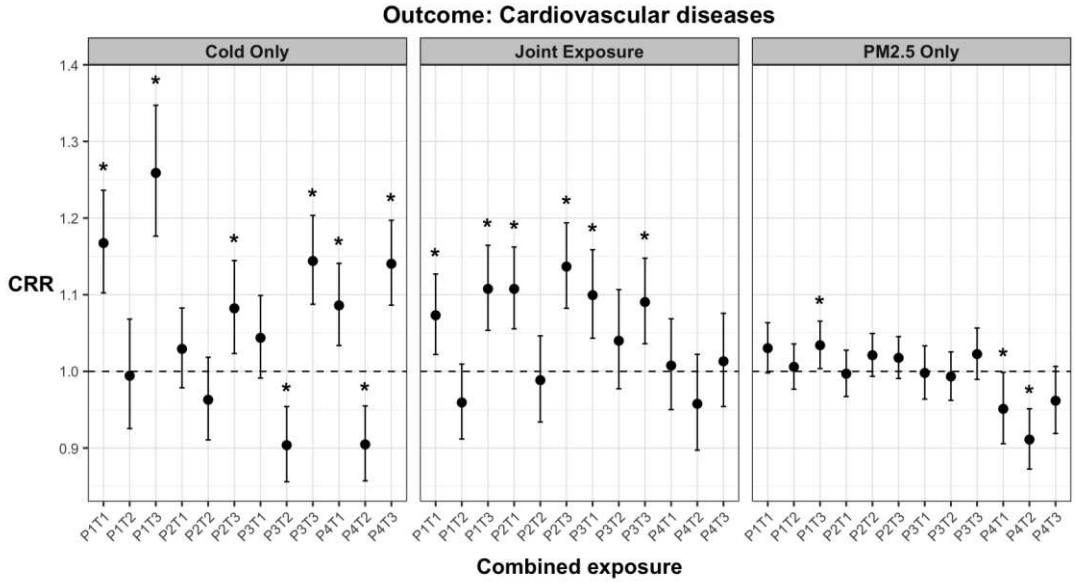
Disease-specific analyses further indicated differential responses across cardiovascular disease subtypes. Individuals with cerebrovascular diseases showed relatively increased risks under both cold-wave exposure alone and compound exposure

scenarios, with the P2T3 combination showing a particularly elevated risk estimate. Individuals with hypertension appeared to be more responsive to cold-wave-related exposures, with higher risk estimates observed for both cold-wave exposure alone and some compound exposure combinations. In contrast, overall risk variations among individuals with heart diseases were relatively smaller, although several T3-related compound exposure events remained associated with increased risks.

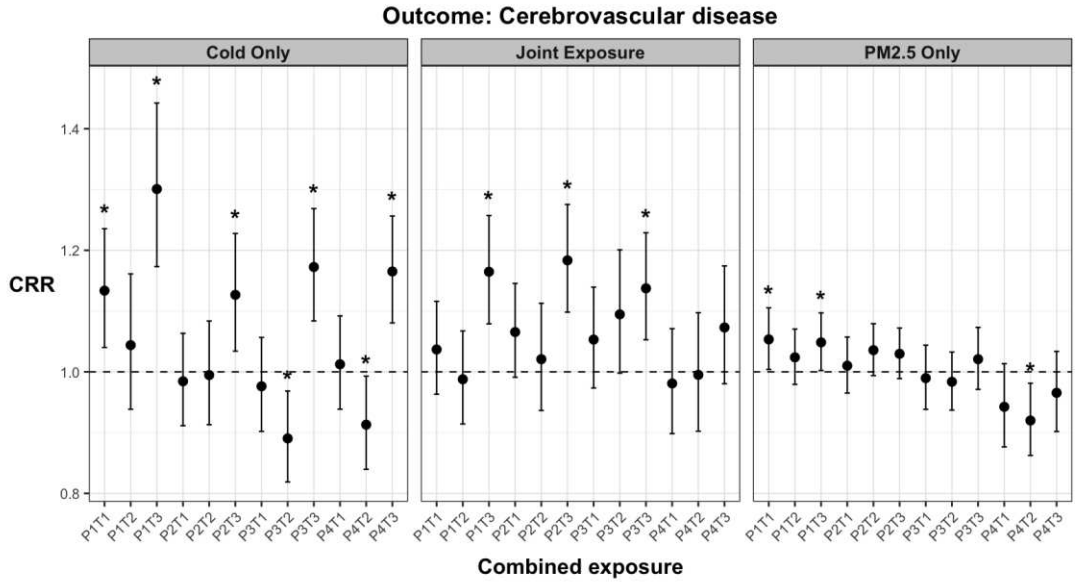
Stratified analyses by sex showed increased risks associated with cold-wave-related exposures in both males and females, although the specific exposure combinations differed. Among males, the P2T3 compound exposure event was associated with an increased risk (*RR* = 1.152, 95% *CI*: 1.083−1.226), whereas females showed a stronger association with the P3T1 combination (*RR* = 1.137, 95% *CI*: 1.057−1.223). Age-stratified analyses indicated that individuals aged <65 years showed a higher risk estimate for the P2T3 combination (*RR* = 1.164, 95% *CI*: 1.080−1.254), while individuals aged ≥65 years exhibited increased risks for several T3-related compound exposure combinations.

Overall, cumulative lag analyses demonstrated that cold waves represented an important environmental factor associated with cardiovascular emergency ambulance calls, whereas the short-term cumulative effects of $PM_{2.5}$ exposure alone were relatively unstable. Compound cold wave−$PM_{2.5}$ exposure further altered the risk patterns and exhibited clear non-linearity and exposure-combination dependence. Strong cold waves (T3) combined with $PM_{2.5}$ pollution were more consistently associated with increased risks, while some moderate-intensity cold-wave combinations showed different patterns compared with single environmental exposures.

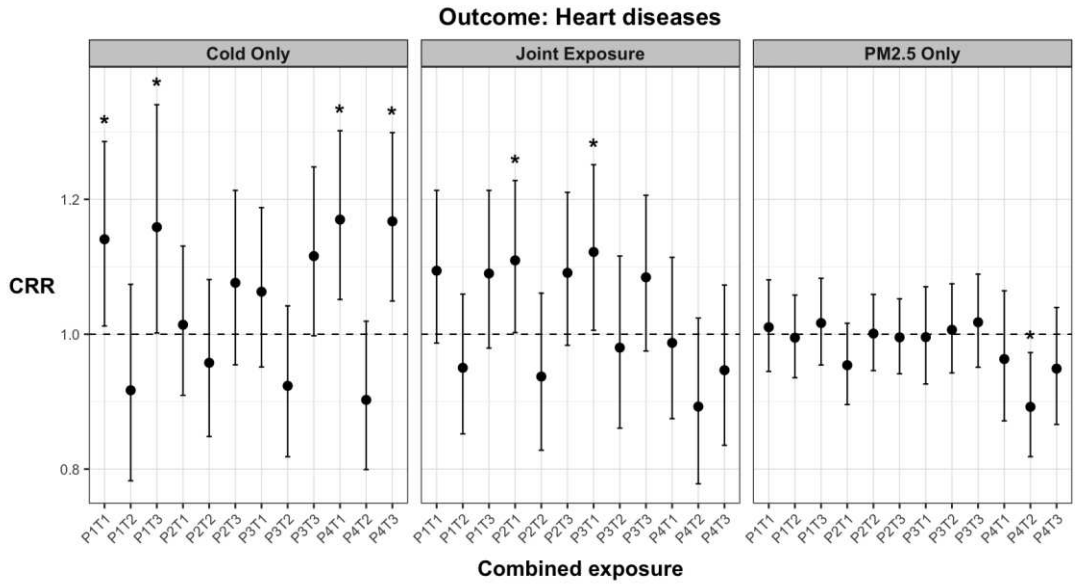
A.



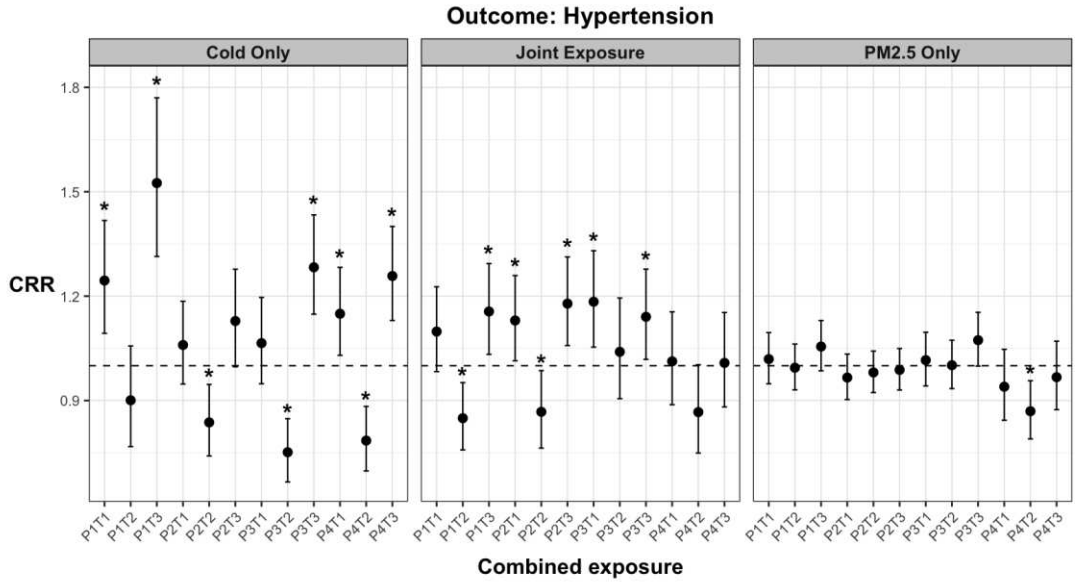
B.


Outcome: Cerebrovascular disease
Cold Only
Joint Exposure
PM2.5 Only
CRR
1.4
1.2
1.0
0.8
P1T1 P1T2 P1T3 P2T1 P2T2 P2T3 P3T1 P3T2 P3T3 P4T1 P4T2 P4T3
Combined exposure

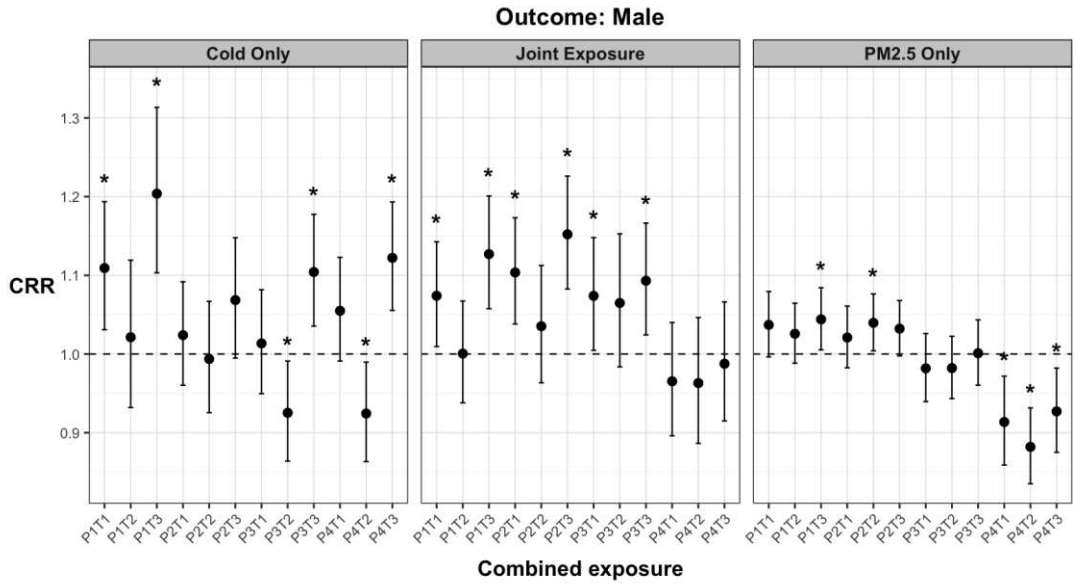
C.


Outcome: Heart diseases
Cold Only
Joint Exposure
PM2.5 Only
CRR
1.2
1.0
0.8
P1T1 P1T2 P1T3 P2T1 P2T2 P2T3 P3T1 P3T2 P3T3 P4T1 P4T2 P4T3
Combined exposure

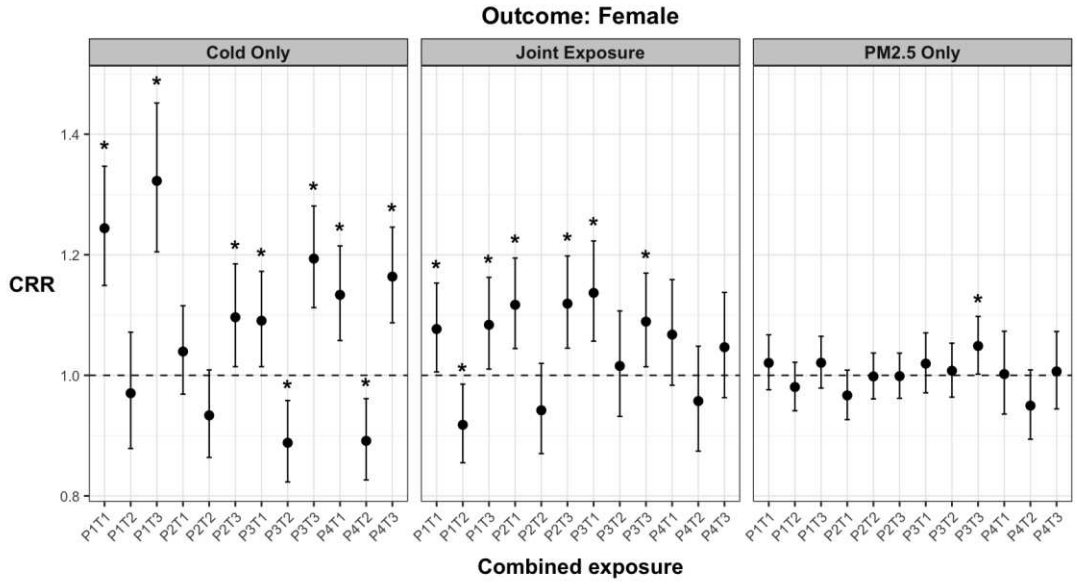
D.


Outcome: Hypertension
Cold Only
Joint Exposure
PM2.5 Only
CRR
1.8
1.5
1.2
0.9
P1T1 P1T2 P1T3 P2T1 P2T2 P2T3 P3T1 P3T2 P3T3 P4T1 P4T2 P4T3
Combined exposure

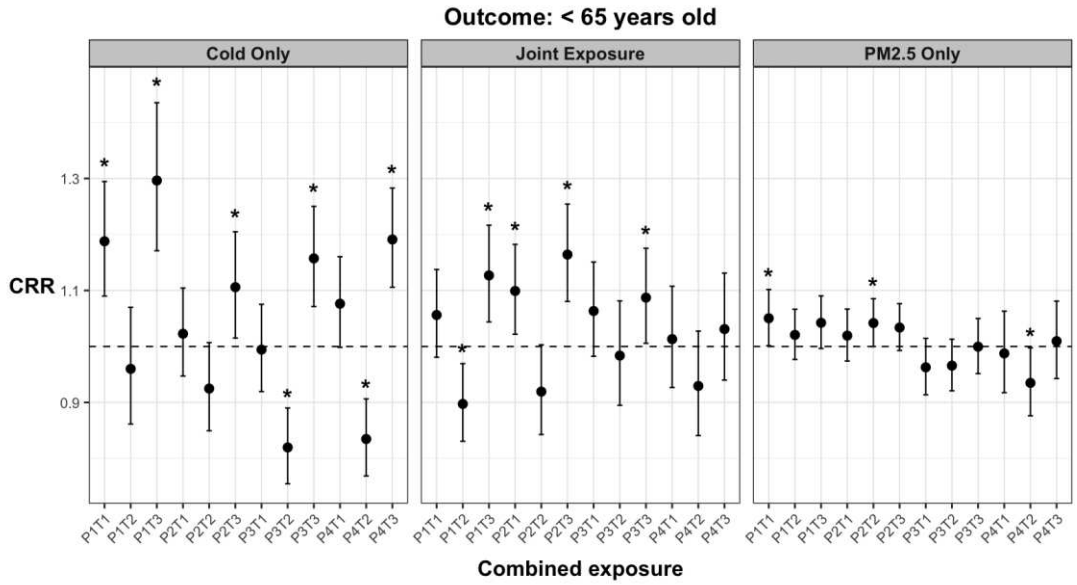
E.


Outcome: Male
Cold Only
Joint Exposure
PM2.5 Only
CRR
1.3
1.2
1.1
1.0
0.9
P1T1 P1T2 P1T3 P2T1 P2T2 P2T3 P3T1 P3T2 P3T3 P4T1 P4T2 P4T3
Combined exposure

F.


Outcome: Female
Cold Only
Joint Exposure
PM2.5 Only
CRR
1.4
1.2
1.0
0.8
P1T1 P1T2 P1T3 P2T1 P2T2 P2T3 P3T1 P3T2 P3T3 P4T1 P4T2 P4T3
Combined exposure

G.


Outcome: < 65 years old
Cold Only
Joint Exposure
PM2.5 Only
CRR
1.3
1.1
0.9
P1T1 P1T2 P1T3 P2T1 P2T2 P2T3 P3T1 P3T2 P3T3 P4T1 P4T2 P4T3
Combined exposure

H.

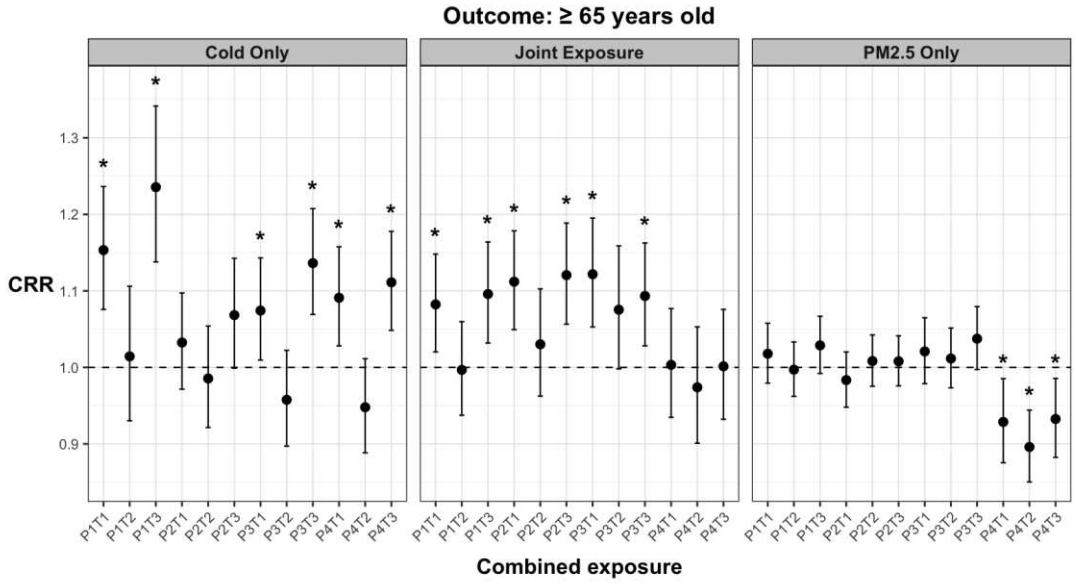


Figure 2 Cumulative relative risks associated with cold wave–$PM_{2.5}$ compound exposure events over lag days 0–14

3.2.4. Additive interactions between cold waves and $PM_{2.5}$ pollution

The additive interaction analysis showed that the interaction between $PM_{2.5}$ pollution and cold waves was highly dependent on exposure combinations and population characteristics. Different combinations of $PM_{2.5}$ pollution levels and cold-wave intensities exhibited varying directions of interaction.(**Figure 3**)

Among the overall cardiovascular emergency ambulance calls, several low-level $PM_{2.5}$ pollution combined with cold-wave events showed significant negative additive interactions. Specifically, the RERI values were −0.124 (95% *CI*: −0.187 to −0.062) for P1T1 and −0.185 (95% *CI*: −0.268 to −0.103) for P1T3, indicating that the combined effects were lower than the sum of their individual effects. Significant negative interactions were also observed for higher pollution levels combined with stronger cold waves, including P3T3 and P4T3 (RERI = −0.076 and −0.089, respectively). In contrast, several moderate-to-high $PM_{2.5}$ pollution and cold-wave combinations showed positive additive interactions, including P2T1, P3T2, and P4T2, with RERI values of 0.081, 0.143, and 0.142, respectively.

Sex-stratified analyses demonstrated different interaction patterns between males and females across compound exposure combinations. Among males, significant positive additive interactions were observed for P3T1 and P4T2 events (RERI = 0.079 and 0.157, respectively), whereas P1T3 showed a significant negative interaction (RERI = −0.121). Among females, significant negative interactions were observed for P1T1, P1T3, and P3T3 events (RERI = −0.188, −0.260, and −0.153, respectively), while positive interactions were observed for P2T1, P3T2, and P4T2 events (RERI = 0.111, 0.120, and 0.116, respectively).

Age-stratified analyses indicated that both positive and negative interactions existed among individuals aged ≥65 years and <65 years. Among individuals aged ≥65 years, significant negative interactions were observed for P1T1, P1T3, and P4T3 events (RERI = −0.182, −0.212, and −0.169, respectively), whereas P3T2 showed a positive interaction (RERI = 0.198). Among individuals aged <65 years, negative interactions were observed for P1T1, P1T3, and P3T3, whereas positive interactions were observed for P2T1, P3T2, and P4T2 (RERI = 0.096, 0.106, and 0.130, respectively).

Disease-specific analyses further revealed heterogeneous interaction patterns across cardiovascular disease subtypes. Among individuals with hypertension, significant negative interactions were observed for P1T1, P1T3, P3T3, and P4T3 events, whereas positive interactions were observed for P3T2 and P4T2 events (RERI = 0.287 and 0.213, respectively). Among individuals with heart diseases, a significant positive interaction was observed only for P2T1 (RERI = 0.141), while P4T1 and P4T3 showed negative interactions. Among individuals with cerebrovascular diseases, negative interactions were observed for P1T1 and P1T3, whereas positive interactions were observed for P3T1, P3T2, and P4T2 (RERI = 0.087, 0.220, and 0.162, respectively).

Overall, the RERI analysis demonstrated that cold waves and $PM_{2.5}$ pollution did not exhibit a consistent direction of additive interaction. Instead, the interaction patterns varied according to $PM_{2.5}$ levels, cold-wave intensity, disease subtype, and population characteristics, showing clear dependence on specific exposure combinations.

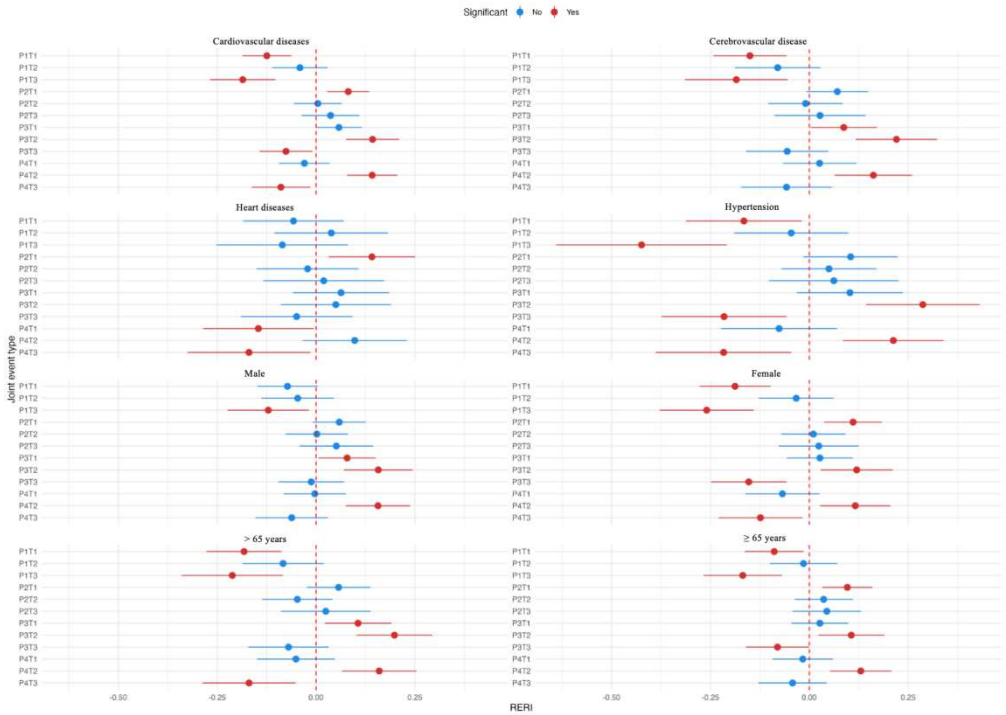


Figure 3 Additive interactions between cold waves and $PM_{2.5}$ pollution on cardiovascular emergency ambulance calls

3.3. Sensitivity analyses

The results of the compound exposure analyses remained consistent under different lag structures, model parameter settings, and covariate adjustment strategies (**Table S2**).

4. Discussion

In this study, we systematically evaluated the associations between compound exposure to cold waves and $PM_{2.5}$ pollution of different intensities and cardiovascular emergency ambulance calls using a 10-year time-series dataset from Shijiazhuang, China. We found that cold wave–$PM_{2.5}$ compound exposure exhibited substantial lagged effects, non-linear patterns, and heterogeneity across exposure combinations. The health effects varied considerably depending on the intensity of cold waves and $PM_{2.5}$ pollution levels, rather than showing a consistent exposure–response pattern. Overall, several compound exposure events were associated with increased risks, particularly combinations involving moderate-to-high $PM_{2.5}$ pollution levels (P2–P3) and stronger cold waves (T3), which showed relatively higher cumulative risks. The timing of peak effects differed across exposure combinations, with some events showing increased risks within several days after exposure, whereas most compound events reached their maximum effects during lag days 7–17. These findings suggest that the cardiovascular impacts of compound cold wave–$PM_{2.5}$ exposure may involve multi-stage physiological responses. Furthermore, additive interaction analyses demonstrated that cold waves and $PM_{2.5}$ did not exhibit a consistent direction of interaction; instead, both positive and negative additive interactions were observed across different exposure combinations, indicating that the health effects of compound environmental exposures may be jointly influenced by exposure intensity, exposure scenarios, and population susceptibility.

Our findings are generally consistent with previous studies investigating the combined health effects of cold waves and air pollution. Previous studies have demonstrated that concurrent exposure to cold waves and $PM_{2.5}$ pollution may increase the risks of cardiovascular mortality, coronary heart disease hospitalization, and ischemic heart disease, suggesting that ambient temperature may modify the health effects of air pollution (21,**Error! Reference source not found.**). Notably, $PM_{2.5}$ exposure alone did not demonstrate a stable cumulative increase in risk in our study, whereas stronger associations were observed under compound exposure conditions. This finding does not indicate that $PM_{2.5}$ lacks adverse health effects; rather, it may suggest that cold exposure increases susceptibility to $PM_{2.5}$-related cardiovascular stress, thereby making pollution-related risks more apparent under low-temperature conditions. Previous studies have also reported enhanced associations between air pollutants and cardiovascular outcomes under low-temperature conditions. For example, a study conducted in Istanbul found that associations between air pollutants and hospital admissions were strengthened during colder periods (**Error! Reference source not found.**).

Studies from other regions of China have similarly reported interactive effects between $PM_{2.5}$ and extreme temperatures on mortality and cardiovascular outcomes (**Error! Reference source not found.**,**Error! Reference source not found.**). Previous evidence further suggests that low temperatures may aggravate $PM_{2.5}$-related cardiovascular risks through enhanced oxidative stress, systemic inflammation, endothelial dysfunction, and sympathetic nervous system activation (26). These mechanisms are consistent with the compound exposure effects observed in the present study. However, differences in climatic conditions, pollution sources, $PM_{2.5}$ chemical compositions, and population adaptation behaviors may contribute to heterogeneity among studies.

From a biological perspective, cold waves and $PM_{2.5}$ may jointly influence cardiovascular health through interconnected pathological pathways. Cold exposure can activate the sympathetic nervous system, induce peripheral vasoconstriction and elevated blood pressure, increase myocardial oxygen demand, and promote increased blood viscosity and coagulation activity (**Error! Reference source not found.**), thereby increasing the risk of acute cardiovascular and cerebrovascular events. $PM_{2.5}$ exposure can induce oxidative stress, systemic inflammation, endothelial dysfunction, and autonomic nervous system imbalance, contributing to vascular injury and atherosclerotic progression (**Error! Reference source not found.**). When these two environmental stressors occur simultaneously, inflammatory responses, oxidative damage, and vascular regulatory dysfunction may interact and modify cardiovascular risks. However, the RERI analysis in this study demonstrated that the interaction between cold waves and $PM_{2.5}$ was not consistently synergistic but instead showed both positive and negative additive interactions across different exposure combinations. These findings suggest that the relationship between cold waves and $PM_{2.5}$ is complex and cannot be simply explained by additive accumulation of risks.

It is noteworthy that we did not observe a linear increase in cardiovascular risks with increasing $PM_{2.5}$ concentrations during cold wave–$PM_{2.5}$ compound exposure. Instead, higher cumulative risks were mainly observed for combinations involving moderate-to-high $PM_{2.5}$ pollution levels (P2–P3) and stronger cold waves (T3), whereas some extreme pollution-related compound events showed relatively lower risk estimates. This finding suggests that the health effects of compound exposure may exhibit non-linear characteristics and may not be determined solely by $PM_{2.5}$ mass concentrations. On the one hand, during periods of extreme air pollution combined with cold waves, residents may adopt more protective behaviors, such as reducing outdoor activities, increasing indoor stay time, and improving indoor air quality, which may reduce actual exposure levels (**Error! Reference source not found.**). Previous studies have suggested that behavioral changes during extreme environmental events may modify the observed associations between environmental exposures and health outcomes (**Error! Reference source not found.**). On the other hand, $PM_{2.5}$ from different emission sources may vary substantially in chemical composition, oxidative potential, and toxicity, indicating that higher $PM_{2.5}$ concentrations do not necessarily correspond to greater health hazards (31,32). In addition, under extremely adverse environmental conditions, some highly susceptible individuals may experience

acute cardiovascular events shortly after exposure, resulting in a reduced magnitude of risk increases during subsequent lag periods (33). Therefore, assessing cardiovascular risks during cold-wave conditions solely based on $PM_{2.5}$ concentrations may have certain limitations.

This study further demonstrated significant cumulative lag effects of cold wave–$PM_{2.5}$ compound exposure. For most compound exposure events, the risk peaks occurred approximately 7–17 days after exposure. This delayed pattern may be attributed to the combined effects of cold-induced vascular constriction, elevated blood pressure, altered coagulation status, and the persistent inflammatory responses, oxidative stress, and endothelial dysfunction induced by $PM_{2.5}$ exposure (34). The additive interaction analyses further indicated that cold waves and $PM_{2.5}$ did not exhibit a stable and consistent interaction direction, with both positive and negative interactions observed across different exposure combinations. These findings further suggest that the health effects of compound cold wave–$PM_{2.5}$ exposure cannot be simply interpreted as a linear accumulation of risks from two environmental factors. Instead, they may be influenced by multiple factors, including exposure intensity, exposure duration, pollution sources, and physiological adaptation (35).

Negative additive interactions should not be interpreted as protective effects of cold waves or $PM_{2.5}$ exposure. Instead, they may reflect several possible mechanisms, including diminishing marginal effects (36), behavioral adaptation among exposed populations, and limited statistical power due to the relatively small number of certain compound exposure events. In contrast, positive additive interactions observed for some moderate-to-high pollution levels combined with cold waves suggest that cold exposure may enhance $PM_{2.5}$-related cardiovascular risks under specific environmental conditions. These findings further highlight the context-dependent nature of compound environmental exposure effects and suggest that assuming a constant synergistic interaction between cold waves and $PM_{2.5}$ may oversimplify the underlying risk patterns.

Stratified analyses further indicated substantial population heterogeneity in the associations between cold wave–$PM_{2.5}$ compound exposure and cardiovascular emergency ambulance calls. Sex-stratified analyses showed different interaction patterns between males and females under various compound exposure scenarios. Males may be more susceptible to certain compound exposures due to differences in outdoor activity patterns, occupational exposure, and the distribution of underlying cardiovascular risk factors (37,38). In contrast, the observed patterns among females may be related to differences in exposure behaviors, health management practices, and baseline risk profiles (39,40).

Age-stratified analyses showed that older and younger populations both exhibited a coexistence of positive and negative additive interactions. Older adults generally have a higher prevalence of cardiovascular disease and reduced physiological adaptability, making them theoretically more vulnerable to cold and air pollution exposure (41-43). However, our findings indicated that both older and younger populations demonstrated heterogeneous interaction patterns, suggesting that age may influence overall susceptibility but may not completely determine the direction of compound exposure interactions.

Disease-specific analyses further revealed differential responses among cardiovascular disease subtypes. Individuals with hypertension may be more sensitive to cold and pollution exposure due to impaired vascular regulation (44), whereas individuals with cerebrovascular diseases may be particularly vulnerable to cold-induced vasoconstriction and coagulation changes (45,46). Nevertheless, the inconsistent directions of interaction across disease subtypes suggest that disease type may modify the manifestation of compound exposure effects rather than simply determine the direction of risk. Therefore, when evaluating the health impacts of combined cold wave and air pollution exposure, future studies should consider specific exposure combinations, temporal characteristics, and susceptible population groups rather than assuming a universal synergistic effect.

Compared with previous studies that mainly used mortality or hospitalization data to evaluate the health effects of environmental exposures, this study used emergency ambulance calls as the health outcome indicator, which provides several advantages. Compared with mortality and hospitalization records, emergency ambulance call data are more time-sensitive and may capture acute disease onset and changes in healthcare demand more promptly. In addition, we developed a multi-level cold wave–$PM_{2.5}$ compound exposure framework and integrated distributed lag non-linear models with RERI analysis to systematically evaluate the health effects of complex environmental exposures. This analytical framework may provide a more comprehensive understanding of cardiovascular risks under real-world conditions where multiple environmental stressors occur simultaneously.

Under the combined influence of climate change and air pollution, compound environmental exposure events have attracted increasing attention. Climate change may alter the frequency, duration, and intensity of extreme weather events while simultaneously affecting pollutant emissions, atmospheric dispersion, and accumulation processes, thereby increasing the likelihood of concurrent cold waves and air pollution episodes. For northern Chinese industrial cities such as Shijiazhuang, winter heating emissions, stagnant meteorological conditions, and cold-air outbreaks may jointly contribute to the occurrence of low-temperature and high-pollution compound exposure events. Our findings suggest that future environmental health warning systems should move beyond assessments based on single environmental factors toward integrated evaluations of compound environmental risks. Such systems should incorporate cold-wave intensity, $PM_{2.5}$ exposure levels, and population susceptibility characteristics into comprehensive prediction frameworks, while strengthening health protection strategies for vulnerable groups, including older adults and individuals with hypertension.

Several limitations should be acknowledged. First, as a single-city time-series study, the generalizability of our findings requires further validation in populations from different climatic regions. Second, environmental exposure assessment was based on fixed-site monitoring data, which may not accurately represent individual-level exposure and could introduce exposure misclassification bias. Third, emergency diagnoses were based on preliminary assessments made by emergency physicians at the scene rather than final clinical diagnoses after hospitalization, which may have resulted in potential disease classification errors.

Fourth, other air pollutants, such as NO_2 and SO_2, as well as seasonal confounders including influenza activity, were not included in the analysis; therefore, residual confounding cannot be completely excluded.

Furthermore, because cold wave–$PM_{2.5}$ compound exposure events occurred relatively infrequently, some extreme exposure combinations contained a limited number of event days. Therefore, the corresponding risk estimates and interaction analyses should be interpreted with caution. Future studies should extend this research through multi-city and multicenter designs and integrate individual-level exposure assessment, $PM_{2.5}$ chemical composition analysis, and biomarker measurements to further elucidate the underlying mechanisms through which compound exposure to cold waves and air pollution affects cardiovascular health.

Declaration

Clinical trial number

Not applicable.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Shijiazhuang Center for Disease Control and Prevention (approval date: March 6, 2024) and was conducted in accordance with the Declaration of Helsinki. The Ethics Committee that approved this study also approved a waiver of informed consent because the study used routinely collected emergency ambulance call records, and prospective informed consent was not feasible in the prehospital emergency setting. All data were anonymized before analysis to protect patient confidentiality.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request. Restrictions apply to the availability of these data because they contain potentially identifiable health information. The data are therefore not publicly available but may be shared upon reasonable request.

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.

Funding

The Hebei Natural Science Foundation (Project No. H2026106020)

2024 Shijiazhuang Municipal Science and Technology Plan (Project No. 2414605403)

Authors' contributions

S.Y.C. and M.N.L. conceived and designed the study. S.Y.C. conducted the statistical analyses, interpreted the results, and wrote the main manuscript text. Y.S.D., N.X., and F.G.C. assisted with data collection and quality control. J.W.T.contributed to manuscript revision and interpretation of the findings. M.Y.G. supervised the study and critically revised the manuscript. All authors reviewed and approved the final manuscript.

Acknowledgements

The authors would like to thank all participants for their cooperation and participation in this study.

Appendix A. Supplementary data

References

1. Zhao Q, Yu P, Mahendran R, et al. Global climate change and human health: pathways and possible solutions. Eco Environ Health. (2022) 1(2):53-62. doi:10.1016/j.eehl.2022.04.004
2. Ning Z, He S, Liao X, et al. Health impacts of a cold wave and its economic loss assessment in China's high-altitude city, Xining. Arch Public Health. (2024) 82(1):52. doi:10.1186/s13690-024-01284-7
3. Xu R, Huang S, Shi C, et al. Extreme temperature events, fine particulate matter, and myocardial infarction mortality. Circulation. (2023) 148(4):312-323. doi:10.1161/CIRCULATIONAHA.122.063504
4. Ning Z, He S, Liao X, et al. Cold waves and fine particulate matter in high-altitude Chinese cities: assessing their interactive impact on outpatient visits for respiratory disease. BMC Public Health. (2024) 24(1):1377. doi:10.1186/s12889-024-18896-x
5. Chen R, Yin P, Wang L, et al. Association between ambient temperature and mortality risk and burden: time series study in 272 main Chinese cities. BMJ. (2018) 363:k4306. doi:10.1136/bmj.k4306

6. Wang L, Liu J, Yin P, et al. Mortality risk and burden of sudden cardiac arrest associated with hot nights, heatwaves, cold spells, and non-optimum temperatures in 0.88 million patients: an individual-level case-crossover study. Sci Total Environ. (2024) 949:175208. doi:10.1016/j.scitotenv.2024.175208

7. Hanefeld C, Klaaßen-Mielke R, Miebach J, et al. Einfluss von Wetterextrema auf Einsatzzahlen im Notarztdienst [Influence of extreme weather conditions on the deployment volume of emergency medical services]. Med Klin Intensivmed Notfmed. (2021) 116(2):154-160. doi:10.1007/s00063-019-00641-7

8. Ponjoan A, Blanch J, Alves-Cabratosa L, et al. Effects of extreme temperatures on cardiovascular emergency hospitalizations in a Mediterranean region: a self-controlled case series study. Environ Health. (2017) 16(1):32. doi:10.1186/s12940-017-0238-0

9. Shen WT, Yu X, Zhong SB, et al. Population health effects of air pollution: fresh evidence from China Health and Retirement Longitudinal Survey. Front Public Health. (2021) 9:779552. doi:10.3389/fpubh.2021.779552

10. Liu K, Hua S, Song L. PM2.5 exposure and asthma development: the key role of oxidative stress. Oxid Med Cell Longev. (2022) 2022:3618806. doi:10.1155/2022/3618806

11. Wang Q, Liu S. The effects and pathogenesis of PM2.5 and its components on chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. (2023) 18:493-506. doi:10.2147/COPD.S402122

12. Hu T, Zhu P, Liu Y, et al. PM2.5 induces endothelial dysfunction via activating NLRP3 inflammasome. Environ Toxicol. (2021) 36(9):1886-1893. doi:10.1002/tox.23309

13. Apte JS, Marshall JD, Cohen AJ, et al. Addressing global mortality from ambient PM2.5. Environ Sci Technol. (2015) 49(13):8057-8066.

14. Huang W, Zhou Y, Chen X, et al. Individual and joint associations of long-term exposure to air pollutants and cardiopulmonary mortality: a 22-year cohort study in Northern China. Lancet Reg Health West Pac. (2023) 36.

15. Huang W, Li S, Guo Y. Enduring public health challenge: air pollution and the potential dominant risks of particulate matter. Environ Health. (2023) doi:10.1021/envhealth.3c00185.

16. Gao M, Carmichael GR, Wang Y, et al. Modeling study of the 2010 regional haze event in the North China Plain. Atmos Chem Phys. (2016) 16(3):1673-1691. doi:10.5194/acp-16-1673-2016.

17. Zscheischler J, Martius O, Westra S, et al. A typology of compound weather and climate events. Nat Rev Earth Environ. (2020) 1(7):333-347.

18. Gasparrini A, Guo Y, Hashizume M, et al. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. Lancet. (2015) 386(9991):369-375. doi:10.1016/S0140-6736(14)62114-0

19. Huang Y, Wang Y, Zhang T, et al. Exploring health effects under specific causes of mortality based on 90 definitions of PM2.5 and cold spell combined exposure in Shanghai, China. Environ Sci Technol. (2023) 57(6):2423-2434. doi:10.1021/acs.est.2c06461

20. Guo Y, Wang Y, Chen K, et al. Exploring health effects under specific causes of mortality based on 90 definitions of PM2.5 and cold spell combined exposure in Shanghai, China. Environ Sci Technol. (2023) 57(8):3019-3029. doi:10.1021/acs.est.2c04509

21. Han X, Wang Y, Li T, et al. Association between meteorological factors, air pollutants and daily hospitalizations of coronary heart disease in rural areas of southern Xinjiang, China. Front Public Health. (2025) 13:1123456. doi:10.3389/fpubh.2025.1123456

22. Ning Z, Ma Y, Chen R, et al. Effects of combined exposure to fine particulate matter and cold waves and on IHD hospitalizations at low and high altitudes. Ecotoxicol Environ Saf. (2024) 256:114876. doi:10.1016/j.ecoenv.2024.114876

23. Birinci E, Çeker AO, Çapraz Ö, et al. Lagged and temperature-dependent effects of ambient air pollution on COPD hospitalizations in Istanbul. Environments. (2026) 13:56. doi:10.3390/environments13010056

24. Zhou L, Wang Y, Wang Q, et al. The interactive effects of extreme temperatures and PM2.5 pollution on mortalities in Jiangsu Province, China. Sci Rep. (2023) 13:9479. doi:10.1038/s41598-023-62436635-x

25. Liu T, Zhu Q, Wei J, et al. The interactive and joint associations of ambient PM2.5 and temperature on the onset of acute coronary syndrome: findings from the Chinese Cardiovascular Association (CCA) Database-Chest Pain Center Registry. Environ Sci Technol. (2024) 58(50):21978-21988. doi:10.1021/acs.est.4c07508

26. Feng S, Huang F, Zhang Y, et al. The pathophysiological and molecular mechanisms of atmospheric PM2.5 affecting cardiovascular health: a review. Ecotoxicol Environ Saf. (2023) 249:114444. doi:10.1016/j.ecoenv.2022.114444

27. Chen K, Wolf K, Breitner S, et al. Two-way effect modifications of air pollution and air temperature on total natural and cardiovascular mortality in eight European urban areas. Environ Int. (2018) 116:186-196. doi:10.1016/j.envint.2018.04.021

28. Yang L, Zhang Y, Qi W, et al. Adverse effects of PM2.5 on cardiovascular diseases. Rev Environ Health. (2021) 37(1):71-80. doi:10.1515/reveh-2020-0155

29. Xu G, Feng X, Li Y, et al. Mediation effects of online public attention on the relationship between air pollution and precautionary behavior. J Manag Sci Eng. (2022) 7(1):159-172. doi:10.1016/j.jmse.2021.09.002

30. GBD 2023 Causes of Death Collaborators. Global burden of 292 causes of death in 204 countries and territories and 660 subnational locations, 1990-2023: a systematic analysis for the Global Burden of Disease Study 2023. Lancet. (2025) 406(10513):1811-1872. doi:10.1016/S0140-6736(25)01917-8

31. Thukham-Mee W, Wattanathorn J, Palachai N. SIRT1-Mediated Epigenetic Protective Mechanisms of Phytosome-Encapsulated Zea mays L. var. ceratinaTassel Extract in a Rat Model of PM2.5-Induced Cardiovascular Inflammation. Int J Mol Sci. 2025;26(12):5759. Published 2025 Jun 16. doi:10.3390/ijms26125759

32. Danesh Yazdi M, Wei Y, Sonntag A, et al. Long-term exposure to PM2.5components and cardiovascular admissions in medicare patients. Environ Res. 2025;286(Pt 1):122779. doi:10.1016/j.envres.2025.122779

33. Global Burden of Cardiovascular Diseases and Risks 2023 Collaborators. Global, Regional, and National Burden of Cardiovascular Diseases and Risk Factors in 204 Countries and Territories, 1990-2023. J Am Coll Cardiol. 2025;86(22):2167-2243. doi:10.1016/j.jacc.2025.08.015

34. Park S, Kario K, Chia YC, et al. The influence of the ambient temperature on blood pressure and how it will affect the epidemiology of hypertension in Asia. J Clin Hypertens (Greenwich). 2020;22(3):438-444. doi:10.1111/jch.13762

35. Cheng C, Liu Y, Han C, Fang Q, Cui F, Li X. Effects of extreme temperature events on deaths and its interaction with air pollution. Sci Total Environ. 2024;915:170212. doi:10.1016/j.scitotenv.2024.170212

36. Labib SM. Greenness, air pollution, and temperature exposure effects in predicting premature mortality and morbidity: A small-area study using spatial random forest model. Sci Total Environ. 2024;928:172387. doi:10.1016/j.scitotenv.2024.172387

37. Jin A, Park YM, Chen X, Liang L, Gong P. (2026). Leveraging real-time personal monitoring of air pollution and physical activity levels, and location tracking for mobility- and inhaled dose-based assessments of exposure and health risk. Environ Monit Assess. 198(3):242. Published 2026 Feb 23. doi:10.1007/s10661-026-15090-x

38. Sun, J., Qiao, Y., Zhao, M., Magnussen, C. G., & Xi, B. (2023). Global, regional, and national burden of cardiovascular diseases in youths and young adults aged 15-39 years in 204 countries/territories, 1990-2019: a systematic analysis of Global Burden of Disease Study 2019. BMC medicine, 21(1), 222. https://doi.org/10.1186/s12916-023-02925-4

39. Ferrín M. (2022). Reassessing Gender Differences in COVID-19 Risk Perception and Behavior. Social science quarterly, 103(1), 31–41. https://doi.org/10.1111/ssqu.13116

40. Potje, S. R., Martins, N. S., Benatti, M. N., Rodrigues, D., Bonato, V. L. D., & Tostes, R. C. (2023). The effects of female sexual hormones on the endothelial glycocalyx. Current topics in membranes, 91, 89–137. https://doi.org/10.1016/bs.ctm.2023.02.005

41. GBD 2023 Chronic Kidney Disease Collaborators. Global, regional, and national burden of chronic kidney disease in adults, 1990-2023, and its attributable risk factors: a systematic analysis for the Global Burden of Disease Study 2023. Lancet. 2025;406(10518):2461-2482. doi:10.1016/S0140-6736(25)01853-7

42. Achebak H, Rey G, Lloyd SJ, Quijal-Zamorano M, Méndez-Turrubiates RF, Ballester J. Ambient temperature and risk of cardiovascular and respiratory adverse health outcomes: a nationwide cross-sectional study from Spain. Eur J Prev Cardiol. 2024;31(9):1080-1089. doi:10.1093/eurjpc/zwae021

43. Zhang W, Wang Y, Xu Q, et al. Association of joint exposure to PM2.5 and extreme heat with cardiovascular disease: A population-based cohort study in Northwest China. iScience. 2026;29(7):116526. Published 2026 Jul 6. doi:10.1016/j.isci.2026.116526

44. Zhang, Y. Y., Tong, X. Z., Xia, W. H., Xie, W. L., Yu, B. B., Zhang, B., Chen, L., & Tao, J. (2016). Increased plasma neopterin levels are associated with reduced endothelial function and arterial elasticity in hypertension. Journal of human hypertension, 30(7), 436–441. https://doi.org/10.1038/jhh.2015.72

45. Alahmad B, Khraishah H, Royé D, et al. Associations Between Extreme Temperatures and Cardiovascular Cause-Specific Mortality: Results From 27 Countries. Circulation. 2023;147(1):35-46. doi:10.1161/CIRCULATIONAHA.122.061832

46. Li Y, Wei M, Gu Y, et al. Cold exposure promotes thrombotic risk in ischemic stroke by activating the platelet cGAS-STING pathway. Thromb Res. 2026;260:109663. doi:10.1016/j.thromres.2026.109663

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