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Sequential Exposure to Cold Waves and $PM_{2.5}$ Pollution and the Risk of Emergency Ambulance Calls for Circulatory Diseases: A Time series Study in Shijiazhuang, China

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Abstract

Background: The health impacts of compound environmental exposure have become an increasing public health concern under climate change. However, evidence regarding the health risks associated with different exposure sequences of cold waves and $PM_{2.5}$ pollution remains limited. This study aimed to evaluate the lag effects and interaction effects of sequential exposure to cold waves and $PM_{2.5}$ pollution on cardiovascular emergency ambulance calls (EACs) in Shijiazhuang, China.

Methods: Daily cardiovascular EAC, meteorological, and air pollution data from Shijiazhuang from 2014--2023 were collected. On the basis of four cold wave definitions and six $PM_{2.5}$ pollution definitions, 24 joint exposure definitions were constructed. Three sequential exposure scenarios were further established: overlapping exposure (Scenario A), cold wave-first exposure (Scenario B), and $PM_{2.5}$-first exposure (Scenario C). A quasi-Poisson regression combined with a distributed lag nonlinear model (DLNM) was applied to estimate the single-day and cumulative lag effects of joint exposure on cardiovascular EAC risk. Additive interaction effects were assessed via the relative excess risk due to interaction (RERI).

Results: Joint exposure to cold waves and $PM_{2.5}$ pollution significantly increased the risk of cardiovascular EACs, with substantial heterogeneity across exposure scenarios. Overall, Scenario C consistently presented the strongest and longest-lasting effects. Under the P2T4 definition, the cumulative relative risk (CRR) at lag0–21 days in Scenario C reached 1.243 (95% CI: 1.166–1.325), which was higher than that in Scenario B [1.137 (95% CI: 1.054–1.226)] and Scenario A [1.071 (95% CI: 1.001–1.145)]. The combined effects generally increased with increasing cold wave intensity and moderate-to-high $PM_{2.5}$ concentrations but weakened under extremely high pollution levels. Hypertension showed the strongest susceptibility among the disease subtypes. Males and individuals aged ≥65 years were more vulnerable to joint exposure. Interaction analyses revealed nonlinear patterns characterized by antagonistic effects under low-intensity exposure and synergistic effects under moderate-to-high-intensity exposure.

Conclusions: Joint exposure to cold waves and $PM_{2.5}$ pollution significantly increased cardiovascular emergency ambulance risk and exhibited evident lag characteristics, exposure-order dependence, and nonlinear interaction patterns. The strongest health effects were observed when $PM_{2.5}$ exposure preceded cold wave events, suggesting that prior air pollution exposure may increase vulnerability to subsequent cold stimulation. These findings provide epidemiological evidence for improving public health early warning systems and developing targeted intervention strategies for compound environmental exposures under climate change.

Keywords: Cold wave; PM2.5; Sequential exposure; Circulatory diseases; Emergency ambulance calls; Distributed lag nonlinear model

1.Introduction

According to the 2023 Lancet Countdown report on health and climate change in China, the health impacts of climate change continue to intensify [**Error! Reference source not found.**,**Error! Reference source not found.**]. However, existing assessments have focused mainly on extreme heat, whereas the health risks associated with extreme cold have received comparatively less attention [1,2]. In addition, most previous studies have been conducted in developed countries, with limited evidence from developing countries that may be more vulnerable to climate-related health risks [3,4]. Compared with high temperatures, low temperatures generally exert stronger and more prolonged health effects, particularly in relation to increased risks of cardiovascular and cerebrovascular mortality and acute events. Cold waves may also produce sustained health impacts through cumulative lag effects. For example, a study conducted in China by Lei et al. [5] reported that cold waves increased the risk of nonaccidental mortality to 1.39 (95% CI: 1.15–1.69). Therefore, a better understanding of the synergistic effects of cold waves, environmental factors, and individual vulnerability on population health in developing countries, as well as the underlying pathophysiological mechanisms, is essential for developing targeted and effective public health strategies.

Air pollution represents another major environmental challenge that threatens human health. According to the Global Burden of Disease (GBD) study, approximately 1.85 million deaths in China in 2019 were attributable to air pollution exposure, accounting for nearly 25% of all deaths, with an estimated 33.8 million years of life lost (YLL) due to premature mortality [7,9]. Air pollution, particularly fine particulate matter ($PM_{2.5}$), has been widely associated with increased morbidity and mortality from circulatory diseases [**Error! Reference source not found.**]. Globally, nearly 20% of circulatory disease deaths are attributable to air pollution and nonoptimal temperatures, while the corresponding proportion in China is as high as 30% [7,9]. Although extensive air pollution control measures have been implemented in China, data from the State of Global Air report indicate that China remains among the countries with a relatively high disease burden attributable to $PM_{2.5}$ exposure [**Error! Reference source not found.**–**Error! Reference source not found.**].

In recent years, the combined impacts of climate change and air pollution have become increasingly prominent, and the integrated health effects of extreme weather events and environmental pollution have emerged as important research topics in public health [14–16]. As typical extreme low-temperature events, cold waves are consistently associated with increased morbidity and mortality from cardiovascular and cerebrovascular diseases [**Error! Reference source not found.**]. Cold exposure may induce vasoconstriction, sympathetic nervous system activation, and increased blood viscosity, thereby triggering acute circulatory events [**Error! Reference source not found.**,20]. Moreover, $PM_{2.5}$, one of the major indicators of air pollution, may

adversely affect the cardiovascular system through multiple biological pathways, including oxidative stress, systemic inflammation, endothelial dysfunction, and coagulation abnormalities [**Error! Reference source not found.**–23].

Although substantial evidence has demonstrated the independent effects of cold waves and $PM_{2.5}$ on cardiovascular health, individuals in real-world settings are often exposed to multiple environmental stressors simultaneously or sequentially. Therefore, single-exposure models may not adequately reflect actual exposure scenarios. In recent years, increasing attention has been given to the health effects of compound environmental exposures, and several studies have suggested that low temperature and air pollution may exert additive or even synergistic effects [24], thereby further increasing the risk of cardiovascular events.

Nevertheless, several important research gaps remain. First, previous studies have primarily focused on the independent or simultaneous effects of low temperature and air pollution, while the potential health impacts of different exposure sequences and exposure intervals remain largely unclear. In reality, cold spells and air pollution episodes often occur sequentially rather than simultaneously, and prior exposure to one environmental stressor may alter individual susceptibility to subsequent exposure. Therefore, understanding sequence-dependent joint effects may provide more realistic evidence for assessing compound environmental health risks. Second, the joint health effects of cold waves and $PM_{2.5}$ under different exposure intensities and exposure sequences have not been systematically investigated. Third, most existing studies have relied on mortality and hospitalization data [25,26], whereas evidence based on cardiovascular emergency ambulance calls remains limited.

To address these gaps, the present study used emergency ambulance records for circulatory diseases in Shijiazhuang from 2014--2023, combined with meteorological and air pollution monitoring data, to construct novel cold wave–$PM_{2.5}$ combined exposure scenarios with different exposure sequences, including overlapping exposure, cold wave-first exposure, and $PM_{2.5}$-first exposure. A distributed lag model was further applied to systematically evaluate the lag effects and interaction effects of combined exposure on emergency ambulance risk for circulatory diseases. This study specifically investigated whether the temporal sequence of $PM_{2.5}$ pollution and cold wave exposure affects cardiovascular emergency risk, an issue that has rarely been systematically evaluated in previous environmental epidemiological studies.

2. Materials and methods

2.1 Emergency ambulance data for circulatory diseases

Daily emergency ambulance data from January 1, 2014, to December 31, 2023, were obtained from the Shijiazhuang Emergency Medical Center. The dataset included demographic characteristics (age and sex), chief complaints, and clinical diagnoses. All emergency calls initiated during the study period were systematically recorded. To ensure data confidentiality, sensitive personal identifiers, including patient names, residential addresses, and telephone numbers, were encrypted prior to data

extraction. According to the International Classification of Diseases, 10th Revision (ICD-10), daily emergency ambulance counts were classified and aggregated for circulatory diseases (I00–I99), cerebrovascular diseases (I60–I69), heart diseases (I20–I25, I05–I09, I26–I28, and I30–I52), and hypertension (I10).

2.2 Collection of meteorological and air pollution data

Concurrent air pollution and meteorological data were obtained from the Shijiazhuang Environmental Monitoring Center and the Shijiazhuang Meteorological Service Center, respectively. Routine air pollution monitoring data collected in Shijiazhuang between January 1, 2014, and December 31, 2023, were used in this study. The air pollution indicators included daily mean concentrations of $PM_{2.5}$ and O_3. The meteorological variables included daily mean temperature (T, °C), daily maximum temperature (tmax, °C), daily minimum temperature (tmin, °C), relative humidity (RH, %), and wind speed (m/s).

2.3 Definition of $PM_{2.5}$ pollution and cold wave joint exposure

This study referred to the cold wave warning standards established by the Expert Team on Climate Change Detection and Indices (ETCCDI), the Intergovernmental Panel on Climate Change, the World Meteorological Organization, and the Chinese cold wave warning system. Four cold wave definitions (T1–T4) were developed on the basis of either a decrease in minimum temperature of at least 8 °C within 24 h or daily mean temperatures below the 2.5th, 5th, or 10th percentiles for at least 48 h, among which T1 was defined according to the Chinese blue-level cold wave warning standard.

Different $PM_{2.5}$ exposure scenarios were constructed according to the transitional target IT-1 in the 2021 World Health Organization air quality guidelines (24-h mean $PM_{2.5}$ concentration of 75 μg/m³), as well as the moderate and severe pollution levels defined by the Chinese Air Quality Index (AQI) (115 μg/m³ and 150 μg/m³, respectively). By further incorporating the pollution duration (1 day and 2 days), six $PM_{2.5}$ pollution levels (P1–P6) were established [27].

Joint exposure events were defined as combinations of four cold wave definitions and six $PM_{2.5}$ pollution definitions, resulting in a total of 24 combined exposure definitions. PiTj represents a combined event defined by the $PM_{2.5}$ definition Pi and the cold wave definition Tj. Since both cold wave events and air pollution events may exert lagged health effects, three combined exposure scenarios were constructed in this study (Figure 1).

(1) Scenario A (concurrent exposure scenario): $PM_{2.5}$ pollution events and cold wave events temporally overlapped. The onset of the latter event was considered the beginning of the combined event, which lasted until the event ended.

(2) Scenario B (cold-first exposure scenario): A cold wave event occurred first, followed by an independent $PM_{2.5}$ pollution event within 7 days after the end of the cold wave event. The occurrence and duration of the $PM_{2.5}$ event were identified as the combined event.

(3) Scenario C ($PM_{2.5}$-first exposure scenario): A $PM_{2.5}$ pollution event occurred first, followed by an independent cold wave event within 7 days after the end of the $PM_{2.5}$ event. The occurrence and duration of a cold wave event were considered combined events.

Because some joint exposures lasted for fewer than 3 days and therefore did not satisfy the modeling requirements for effect estimation, corresponding results were not available for these scenarios. Therefore, joint exposure combinations without valid estimates in Scenario A were excluded from the subsequent AIC comparison to ensure consistency across exposure scenarios.

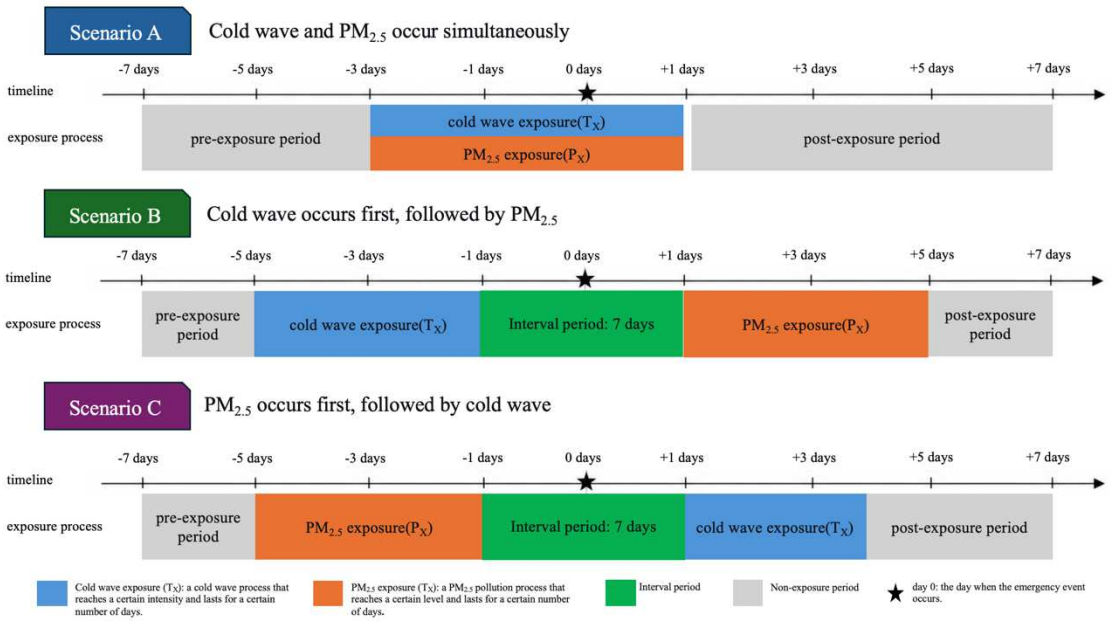


Figure 1 Schematic illustration of three joint exposure scenarios involving cold waves and $PM_{2.5}$ pollution

2.4 Statistical analysis

2.4.1 Analysis of joint exposure and emergency ambulance calls (EACs) for circulatory diseases

Given that the daily number of emergency ambulance visits (Yt) represented count data with evident overdispersion (variance greater than the mean), a quasi-Poisson regression model was applied. This model accommodates overdispersed count data by introducing a dispersion parameter to account for the actual degree of variability in the data. The model was specified as follows:

$$\log[E(Y_t)] = \beta0 + \beta1*cb_pm + \beta2 * cb_cold + \beta3 * cb_joint + ns(rhum, df=3) + ns(date, df=7*10) + weekdays + holiday \quad 式（5）$$

where Y_t represents the daily number of emergency ambulance calls (EACs) on day t and where cb_pm, cb_cold and cb_joint denote the cross-basis matrices for $PM_{2.5}$ pollution events, cold wave events, and combined exposure events, respectively. The term ns(rhum, df=3) represents the natural cubic spline function for relative humidity with 3 degrees of

freedom, whereas ns(time, df=7×10) represents the natural cubic spline function for calendar time to control for long-term trends and seasonality, using 7 degrees of freedom per year (70 degrees of freedom over the entire study period). Weekday represents the day-of-week variable, and holiday represents public holidays. The maximum lag period was set to 21 days. The maximum lag days and the degrees of freedom for the spline functions were determined according to the principle of minimizing the Akaike information criterion (AIC).

To evaluate the additive interaction between cold waves and $PM_{2.5}$ pollution, the relative excess risk due to interaction (RERI) and its 95% confidence interval (95% CI) were calculated in this study. A synergistic interaction was considered to exist when both the RERI estimate and its 95% CI were greater than 0, whereas an antagonistic interaction was considered when both the RERI estimate and its 95% CI were less than 0. If the 95% CI included 0, the interaction was considered statistically insignificant. The specific formula was as follows:

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

2.4.2 Other statistical analyses

Statistical analyses were performed via IBM SPSS Statistics. According to the Shapiro–Wilk test, air pollution data, meteorological variables, and daily emergency ambulance counts for circulatory diseases were all nonnormally distributed. Therefore, these variables were described using the median and interquartile range M ($P_{25,\ P75}$).

2.4.3 Sensitivity analyses

The Akaike information criterion (AIC) was used to evaluate the goodness-of-fit of the models under different definitions. The definition with the lowest average AIC value was considered to provide the best model fit and was identified as the optimal cold wave definition [28]. To assess the robustness of the model, sensitivity analyses were conducted by varying the degrees of freedom (dfs) for temperature and relative humidity, changing the maximum lag days, and additionally adjusting for air pollutants in the optimal combined-event model.

Because several joint exposure combinations in Scenario A did not yield valid model estimates due to limited event counts, those combinations were excluded when calculating AIC values for Scenario C. The optimal joint exposure definitions selected according to the lowest AIC values in Scenario C were subsequently applied to the sensitivity analyses for Scenarios A, B, and C.

All analyses were performed via R, and the “dlnm”, “ns”, and “lme4” packages were applied to examine the associations between combined exposure events and health outcomes. A two-sided $P<0.05$ was considered statistically significant.

3. Results

3.1 Descriptive results

During the study period from 2014--2023, a total of 82,714 emergency ambulance records for circulatory diseases were collected in Shijiazhuang. In terms of sex distribution, males accounted for approximately 55.7% of the cases, whereas females accounted for 44.3%. In terms of age distribution, the number of emergency ambulance cases was greater among individuals aged ≥65 years than among those aged <65 years (Table 1).

Table 1 Descriptive statistics of daily emergency cases, meteorological variables, and air pollutants in Shijiazhuang, China, from 2014--2023

	Mean	Min	P_{25}	Median	P_{75}	Max
Circulatory diseases	22.65	4	18	22	26	68
Cerebrovascular disease	8.36	0	6	8	10	26
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/°C	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 Effects of joint exposure to emergency ambulance calls (EACs) for circulatory diseases

3.2.1 Descriptive characteristics of joint exposure

Among the cold wave definitions, T2 (daily mean temperature ≤10th percentile for ≥2 consecutive days) occurred most frequently, with a total of 61 events. Among the $PM_{2.5}$ pollution definitions, P1 ($PM_{2.5}$ concentration ≥75 μg/m³ for ≥1 day) was the most common, occurring 333 times, whereas P6 ($PM_{2.5}$ concentration ≥150 μg/m³ for ≥2 consecutive days) occurred least frequently, with only 86 events. (Table 2)

For the combined exposure scenarios, the P1T2 definition in Scenario B presented the highest number of joint exposures (49 events). The maximum numbers of joint exposures in Scenarios A and C were 39 and 43, respectively, both corresponding to the P1T3 definition. To ensure the stability and comparability of the statistical analyses across exposure scenarios, combined event definitions with fewer than 3 event days or without valid model estimates in Scenario A were excluded from the subsequent AIC comparison and sensitivity analyses. (Figure 2).

Table 2 Number of independent exposure events

event	index	definition	
cold spell	T1	decrease more no less than 8 °C within 24 h	14
	T2	≤P10 with ≥2-day duration	61
	T3	≤P5 with ≥2-day duration	38
	T4	≤P2.5 with ≥2-days duration	20
$PM_{2.5}$ pollution	P1	≥75 μg/m3 with ≥1-day duration	333
	P2	≥75 μg/m3 with ≥2-days duration	234
	P3	≥115 μg/m3 with ≥1-day duration	309
	P4	≥115 μg/m3 with ≥2-days duration	135
	P5	≥150 μg/m3 with ≥1-day duration	142
	P6	≥150 μg/m3 with ≥2-days duration	86

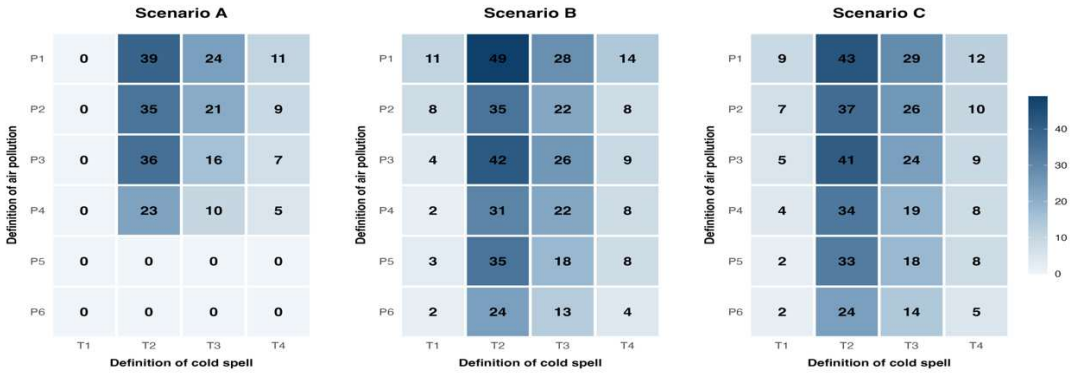


Figure 2 Number of joint exposures

3.2.2 Single-day lag effects of joint exposure on emergency ambulance calls (EACs) for circulatory diseases

Significant differences were observed in the effects of combined cold wave and $PM_{2.5}$ exposure on emergency ambulance risk for circulatory diseases across different exposure scenarios. Overall, Scenario C ($PM_{2.5}$ exposure preceding cold wave events) presented the highest relative risk (RR), followed by Scenario A, whereas most RRs in Scenario B were close to 1, suggesting relatively weak health effects.

In Scenario C, the combined effects clearly increased with increasing cold wave intensity. Under a fixed cold wave intensity, moderate-to-high $PM_{2.5}$ exposure levels further increased the risk; however, this increasing trend weakened or even disappeared under extremely high pollution levels (P5–P6). In contrast, Scenario A mainly exhibited short-term acute effects, whereas Scenario B demonstrated a relatively delayed risk pattern.

In terms of temporal distribution, the elevated risks in Scenario A were primarily concentrated within 0–3 days after exposure. In Scenario B, the risk remained relatively low during lag0–3 days and then slightly increased during lag4–10 days. In

Scenario C, the risk increased rapidly after lag 3 days and persisted until approximately lag 10 days, indicating a more pronounced and longer-lasting lag effect.

Marked differences in susceptibility were observed across disease subtypes. Hypertension exhibited the strongest and most stable risk increases under most combined exposure scenarios, followed by cerebrovascular diseases. The effects of heart disease were relatively weak; however, significant increases in risk were still observed under some high-intensity combined exposure conditions. Overall, all disease subtypes in Scenario C presented higher risks and longer risk windows (**Figures 3–6**).

Stratified analyses further demonstrated that, under most combined exposure conditions, individuals aged ≥65 years presented higher RRs than those aged <65 years did, and the increasing trend with increasing cold wave intensity was more pronounced in Scenario C. Sex stratification analyses revealed generally consistent patterns between males and females, although males presented greater risk increases under conditions of strong cold waves combined with high $PM_{2.5}$ pollution levels (**Figures S1–S4**).

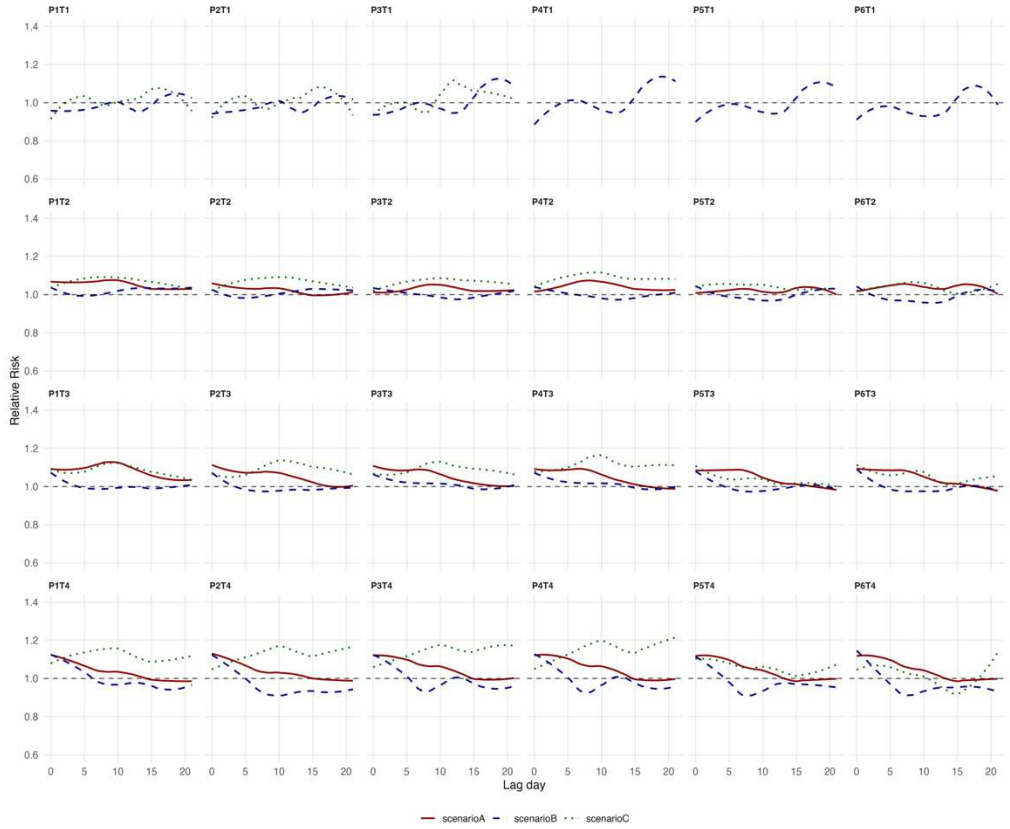


Figure 3 Relative risk of joint exposure (circulatory diseases).

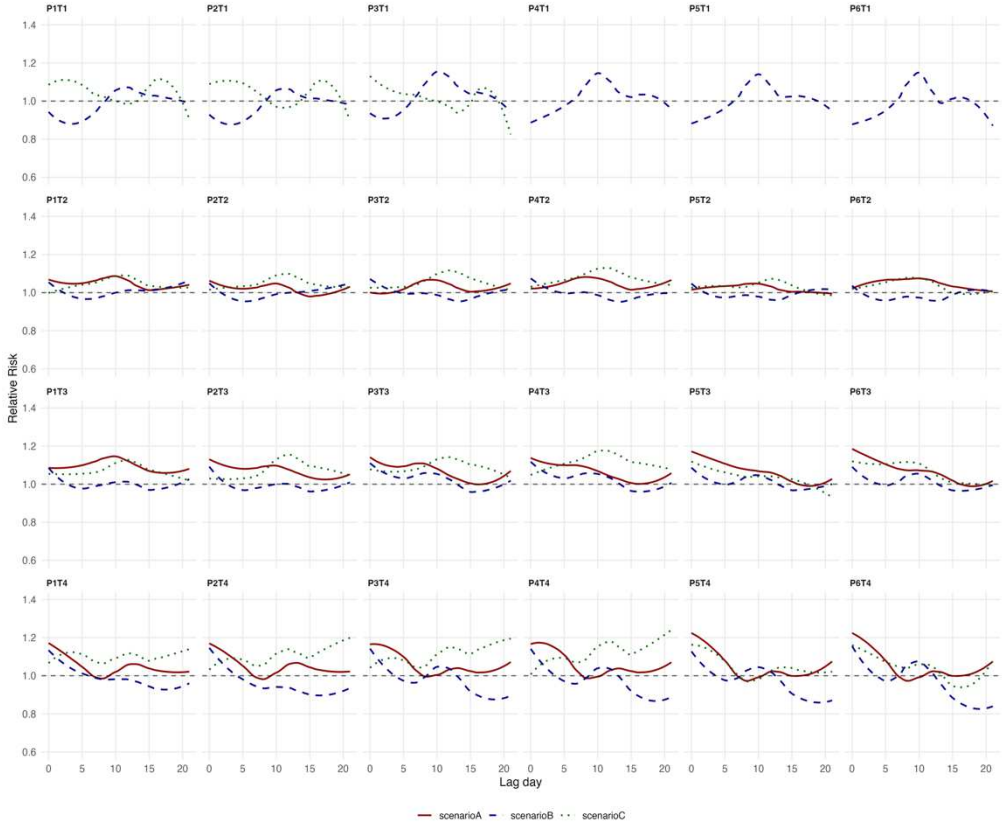


Figure 4 Relative risk of joint exposure (cerebrovascular disease).

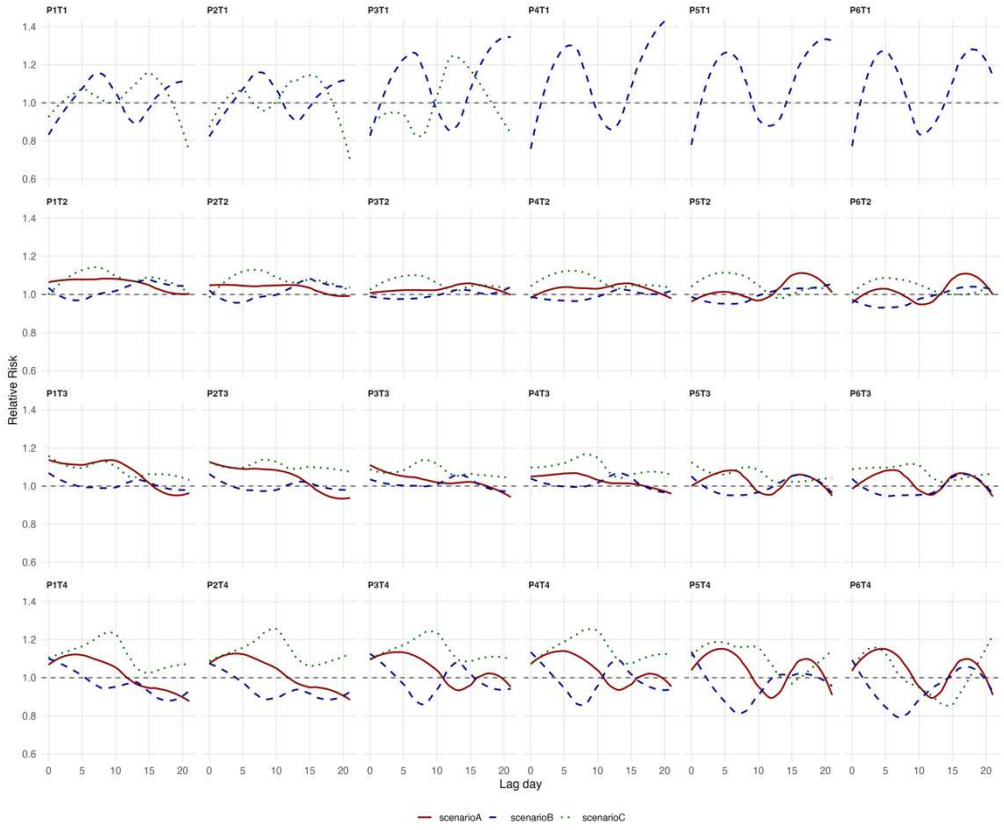


Figure 5 Relative risk of joint exposure (heart diseases).

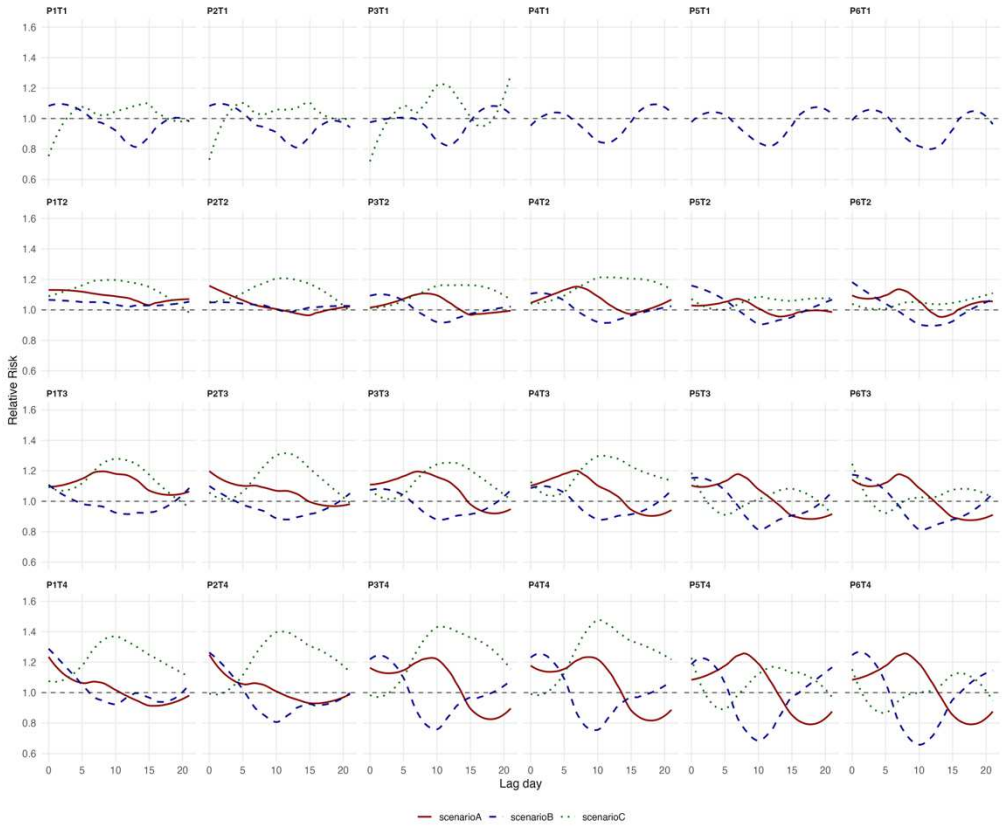


Figure 6 Relative risk of joint exposure (hypertension).

3.2.3 Cumulative lag effects of joint exposure to emergency ambulance calls (EACs) for circulatory diseases

Among the three combined exposure scenarios, Scenario C presented the highest cumulative relative risks (CRRs), with a clear increasing trend observed as the cold wave intensity increased, suggesting that $PM_{2.5}$ exposure preceding cold wave events may further increase the risk of circulatory diseases. Taking the P2T4 combination as an example, the CRR in Scenario C was 1.243 (95% CI: 1.166–1.325), which was higher than those in Scenario B [1.137 (95% CI: 1.054–1.226)] and Scenario A [1.071 (95% CI: 1.001–1.145)].

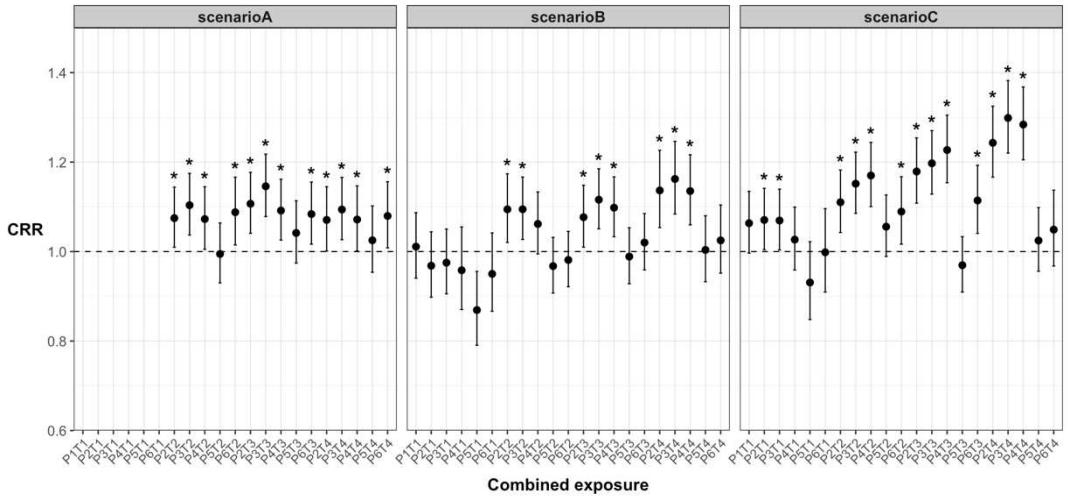
Under Scenario C, when the $PM_{2.5}$ level was fixed, the CRR increased continuously with increasing cold wave intensity. When the cold wave intensity was fixed, the CRR gradually increased at moderate-to-high $PM_{2.5}$ levels (P2–P4) but declined at extremely high pollution levels (P5–P6), with the 95% CIs of some combinations crossing 1. These findings suggest the presence of a nonlinear exposure–response relationship for the combined effects.

Substantial heterogeneity in combined effects was observed across disease subtypes. Hypertension had the strongest combined effects, followed by cerebrovascular diseases, whereas heart diseases had relatively weaker effects. For example, under

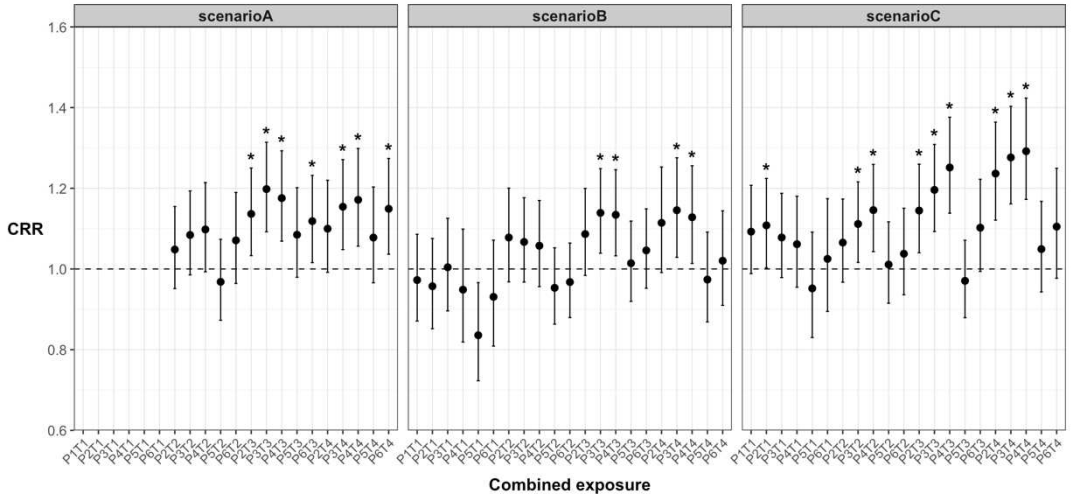
the P2T4 combination in Scenario C, the CRR for hypertension was 1.389 (95% CI: 1.208–1.597), which was higher than that for cerebrovascular diseases [1.237 (95% CI: 1.121–1.364)] and heart diseases [1.232 (95% CI: 1.074–1.414)].

Stratified analyses demonstrated that males generally presented higher CRRs than females did across most combined exposure combinations. In addition, under higher-intensity combined exposure conditions, individuals aged ≥65 years presented higher CRRs than those aged <65 years did, suggesting that males and older adults may be more susceptible to combined exposure to cold waves and $PM_{2.5}$ pollution (**Figure 7**; **Figures S5–S8**).

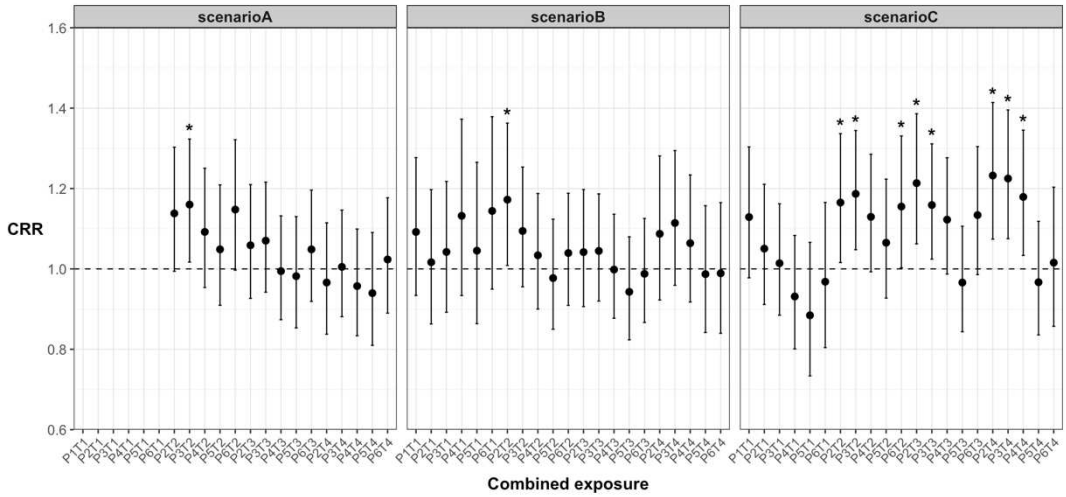
A.



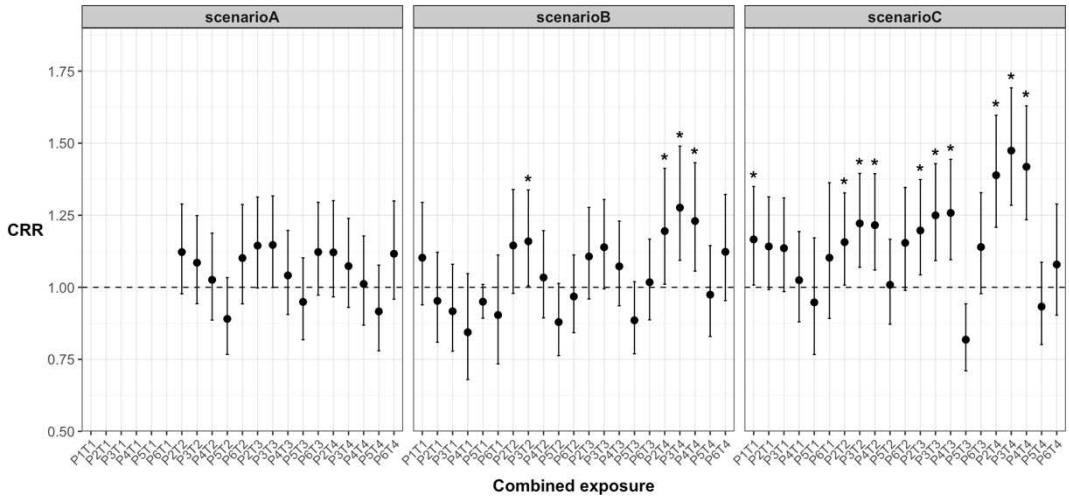
B.



C.



D.



A: Circulatory diseases; B: cerebrovascular disease; C: heart disease; D: hypertension

Figure 7 Cumulative relative risk of the joint event at lag days 0–21

3.2.4 Interaction effects of joint exposure to emergency ambulance calls (EACs) for circulatory diseases

Interaction analyses based on the relative excess risk due to interaction (RERI) demonstrated substantial differences in interaction patterns across the three combined exposure scenarios. Scenario A was characterized predominantly by negative interactions, whereas both positive and negative interactions were observed in Scenario B. In contrast, Scenario C presented the highest overall RERI levels, suggesting that synergistic health effects were more likely to occur when $PM_{2.5}$ exposure preceded cold wave events.

Further analyses revealed marked nonlinear characteristics in the interaction patterns across different exposure intensities. Low-intensity combined exposures were associated mainly with negative interactions, whereas moderate-to-high-intensity exposures gradually shifted toward positive synergistic effects. Under extremely high pollution levels, some combinations again

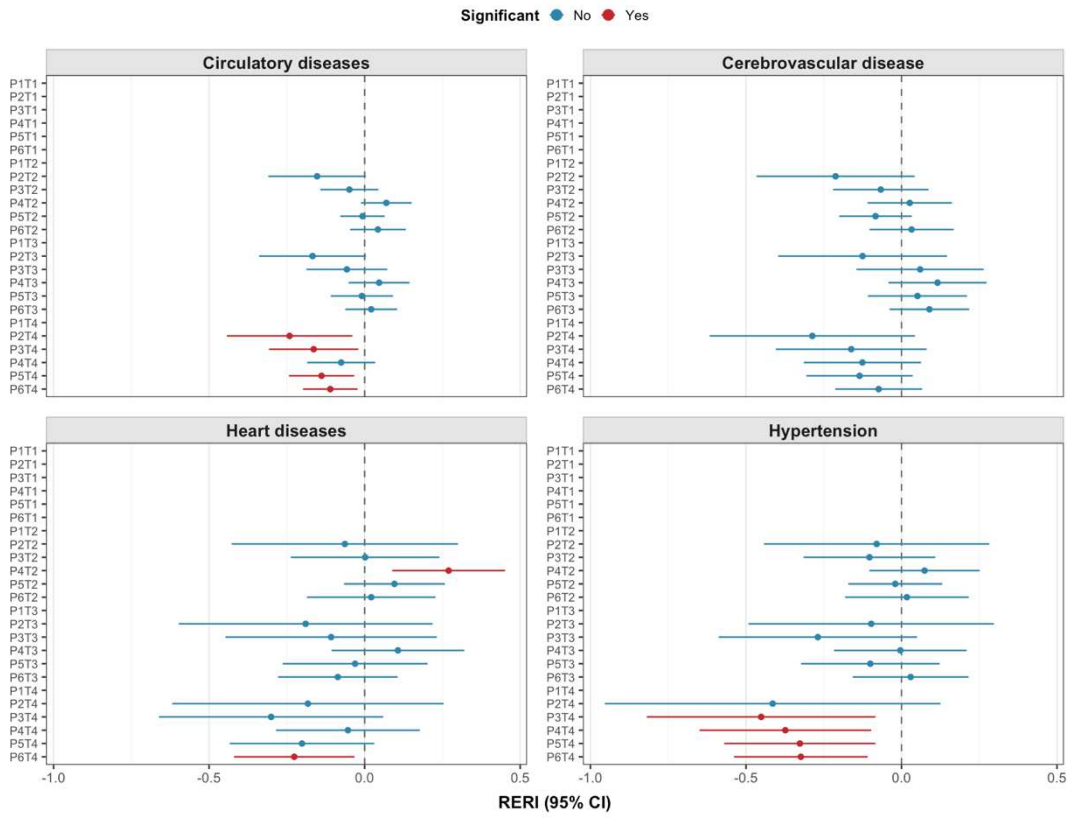
exhibited negative interactions. Significant positive interactions were primarily concentrated during the middle-to-late lag periods.

Distinct interaction responses to combined exposure were observed among the different disease subtypes. Hypertension had the strongest and most stable positive interaction effects. Under Scenario C, five combinations exhibited significant positive interactions, among which P2T4 presented the highest RERI value [0.658 (95% CI: 0.257–1.058)]. Cerebrovascular diseases also demonstrated relatively pronounced synergistic effects, whereas the interaction effects for heart diseases were comparatively weaker and showed greater heterogeneity in direction (**Figure 8**).

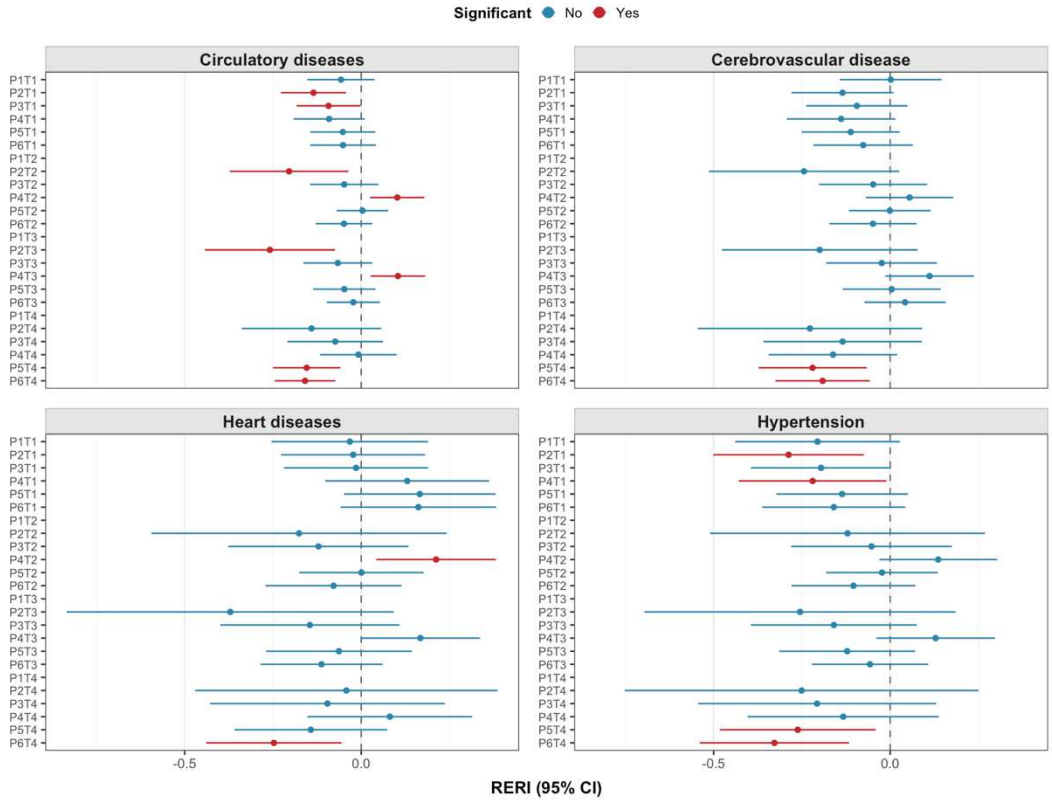
Stratified analyses further indicated that positive synergistic effects were stronger in males than in females. Under Scenario C, males presented a greater number of significant positive interaction combinations and generally higher RERI values than females did (**Figure S9**).

Overall, this study demonstrated that the effects of combined cold wave and $PM_{2.5}$ exposure on circulatory diseases exhibited exposure intensity-dependent interaction patterns. Low-intensity combined exposure was associated mainly with antagonistic interactions, whereas high-intensity combined exposure shifted toward significant synergistic effects. These synergistic effects showed evident lag characteristics, sex differences, and disease-specific heterogeneity.

Scenario A



Scenario B



Scenario C

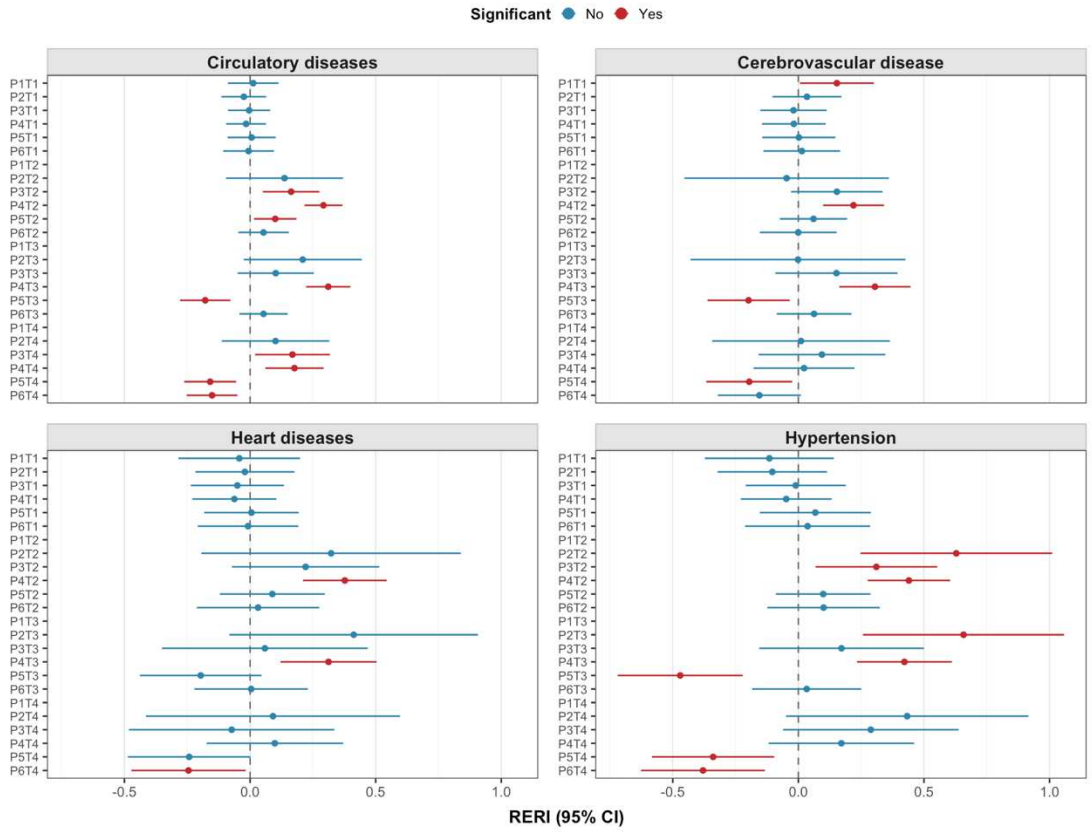


Figure 8 Interaction analysis of the joint event

3.3 Sensitivity analyses

Since several joint exposure combinations in Scenario A did not yield valid model estimates because of limited event counts, the AIC comparison was restricted to Scenario C, and the optimal joint exposure definitions for subsequent sensitivity analyses were determined according to the lowest AIC values in Scenario C.

The AIC values calculated under Scenario C (**Table S2**) indicated that the optimal combined exposure definitions differed across health outcomes. Joint exposure combinations without valid estimates in Scenario A were excluded from the AIC comparison to maintain consistency across the three exposure scenarios. The best-fitting definitions were P3T4 for circulatory diseases (AIC = 22851.8), P3T4 for cerebrovascular diseases (AIC = 18511.8), P2T3 for heart diseases (AIC = 17282.7), and P4T4 for hypertension (AIC = 15251.5).

Sensitivity analyses based on these optimal definitions (Table 3) demonstrated that the CRR estimates remained generally stable across different scenarios after adjusting the degrees of freedom for calendar time, temperature, and relative humidity, varying the lag days, and additionally controlling for air pollutants, including SO_2, NO_2, PM_{10}, and CO. Only minor changes were observed in the 95% confidence intervals, indicating good robustness of the model results. Similar effect estimates across different lag structures and model specifications indicate that the observed associations were not sensitive to modeling assumptions. (**Table 3**)

Table 3 Sensitivity analysis of the estimated cumulative effects of the joint event on the total number of emergency cases for a total of 0–21 lag days

Scenario	model choices	Circulatory diseases (P3T4)	Cerebrovascular disease (P3T4)	Heart diseases (P2T3)	Hypertension (P4T4)
A					
	main modle	1.09(1.03-1.17)	1.15(1.05-1.27)	1.06(0.93-1.21)	1.01(0.87-1.18)
	df for time: 6	1.09(1.02-1.16)	1.14(1.04-1.25)	1.09(0.96-1.23)	1.03(0.89-1.19)
	df for time: 8	1.08(1.01-1.16)	1.17(1.06-1.29)	1.06(0.93-1.22)	0.97(0.83-1.14)
	df for temp: 4	1.09(1.02-1.16)	1.15(1.04-1.27)	1.06(0.92-1.21)	1.01(0.87-1.18)
	df for temp: 5	1.09(1.02-1.16)	1.15(1.04-1.27)	1.06(0.93-1.21)	1.01(0.87-1.18)
	df for relative humidity: 4	1.09(1.03-1.16)	1.15(1.05-1.27)	1.06(0.92-1.21)	1.01(0.87-1.18)
	df for relative humidity: 5	1.09(1.03-1.17)	1.15(1.05-1.27)	1.06(0.92-1.21)	1.02(0.87-1.18)
	model + SO2	1.09(1.02-1.16)	1.15(1.05-1.27)	1.05(0.91-1.20)	1.00(0.86-1.16)
	model + SO2 + NO2	1.09(1.02-1.16)	1.16(1.05-1.27)	1.05(0.92-1.20)	0.99(0.85-1.16)
	model + SO2 + NO2+ PM10	1.09(1.02-1.16)	1.16(1.05-1.27)	1.06(0.92-1.21)	1.00(0.86-1.17)
	model + SO2 + NO2+ PM10 + CO	1.08(1.02-1.16)	1.15(1.04-1.27)	1.06(0.93-1.21)	1.00(0.86-1.17)
	lag 0-14	1.10(1.04-1.18)	1.13(1.03-1.25)	1.15(1.02-1.30)	1.12(0.97-1.31)
	lag 0-28	1.10(1.03-1.18)	1.13(1.02-1.25)	1.11(0.97-1.27)	1.12(0.95-1.32)
B					
	main model	1.16(1.08-1.25)	1.15(1.03-1.28)	1.04(0.91-1.20)	1.24(1.06-1.44)

	df for time: 6	1.13(1.06-1.21)	1.10(0.99-1.21)	1.08(0.95-1.23)	1.22(1.06-1.40)
	df for time: 8	1.16(1.07-1.25)	1.18(1.05-1.33)	1.04(0.90-1.20)	1.20(1.02-1.41)
	df for temp: 4	1.16(1.08-1.24)	1.14(1.02-1.27)	1.04(0.90-1.19)	1.22(1.05-1.43)
	df for temp: 5	1.16(1.08-1.24)	1.14(1.02-1.27)	1.04(0.90-1.20)	1.23(1.05-1.43)
	df for relative humidity: 4	1.16(1.08-1.25)	1.15(1.03-1.28)	1.04(0.90-1.20)	1.24(1.06-1.44)
	df for relative humidity: 5	1.16(1.08-1.25)	1.15(1.03-1.28)	1.04(0.90-1.20)	1.24(1.06-1.44)
	model + SO2	1.17(1.09-1.25)	1.15(1.03-1.28)	1.04(0.90-1.20)	1.25(1.07-1.46)
	model + SO2 + NO2	1.17(1.09-1.25)	1.15(1.04-1.29)	1.04(0.91-1.20)	1.26(1.08-1.47)
	model + SO2 + NO2+ PM10	1.17(1.09-1.25)	1.15(1.03-1.28)	1.05(0.91-1.20)	1.27(1.09-1.48)
	model + SO2 + NO2+ PM10 + CO	1.16(1.08-1.24)	1.14(1.02-1.27)	1.05(0.91-1.21)	1.27(1.09-1.48)
	lag 0-14	1.13(1.06-1.21)	1.14(1.03-1.26)	1.05(0.92-1.19)	1.14(0.99-1.32)
	lag 0-28	1.18(1.09-1.27)	1.16(1.03-1.30)	1.07(0.93-1.23)	1.33(1.13-1.57)
C					
	main model	1.30(1.22-1.38)	1.28(1.16-1.40)	1.21(1.06-1.39)	1.42(1.23-1.63)
	df for time: 6	1.28(1.21-1.36)	1.25(1.15-1.37)	1.22(1.08-1.39)	1.41(1.24-1.61)
	df for time: 8	1.30(1.22-1.39)	1.31(1.18-1.45)	1.24(1.08-1.42)	1.37(1.19-1.58)
	df for temp: 4	1.29(1.21-1.37)	1.26(1.15-1.39)	1.21(1.06-1.38)	1.39(1.21-1.60)
	df for temp: 5	1.29(1.21-1.37)	1.26(1.15-1.39)	1.21(1.06-1.39)	1.39(1.21-1.60)
	df for relative humidity: 4	1.30(1.22-1.38)	1.28(1.16-1.40)	1.21(1.06-1.38)	1.41(1.23-1.63)
	df for relative humidity: 5	1.30(1.22-1.38)	1.28(1.16-1.40)	1.21(1.06-1.38)	1.42(1.23-1.63)
	model + SO2	1.30(1.22-1.38)	1.28(1.16-1.40)	1.21(1.06-1.38)	1.42(1.24-1.64)
	model + SO2 + NO2	1.30(1.22-1.38)	1.28(1.16-1.40)	1.21(1.06-1.38)	1.42(1.24-1.64)
	model + SO2 + NO2+ PM10	1.30(1.22-1.38)	1.28(1.16-1.41)	1.21(1.06-1.38)	1.43(1.24-1.64)
	model + SO2 + NO2+ PM10 + CO	1.29(1.21-1.37)	1.27(1.16-1.40)	1.21(1.06-1.39)	1.42(1.24-1.63)
	lag 0-14	1.26(1.18-1.34)	1.22(1.11-1.35)	1.17(1.04-1.33)	1.46(1.28-1.67)
	lag 0-28	1.25(1.17-1.34)	1.21(1.09-1.34)	1.15(1.00-1.32)	1.48(1.27-1.73)

4. Discussion

This study systematically evaluated the lag effects and interaction effects of combined exposure to cold waves and $PM_{2.5}$ pollution on the risk of circulatory disease emergency ambulance calls under different exposure sequences in Shijiazhuang, China, from 2014--2023. The findings showed that combined exposure to cold waves and $PM_{2.5}$ significantly increased the risk of circulatory disease emergency ambulance calls, and the health effects exhibited evident exposure-order dependence. Among the three exposure scenarios, the scenario in which $PM_{2.5}$ exposure preceded cold wave events (scenario C) consistently presented the strongest and most stable risk increases, suggesting that prior air pollution exposure may increase susceptibility to subsequent cold stimulation.

Overall, the combined effects tended to increase with increasing cold wave intensity and moderate-to-high $PM_{2.5}$ concentrations, whereas the effects weakened under extremely high pollution conditions, indicating potential nonlinear interactions between these environmental stressors. Hypertension patients, males, and older adults were identified as particularly

susceptible populations. These findings further highlight the temporal dependence characteristics of compound environmental exposure and provide new epidemiological evidence for assessing the health impacts of compound environmental risks.

This study identified evident lag characteristics of combined cold wave and $PM_{2.5}$ exposure, with most health risks concentrated within short-term cumulative lag periods. Similar findings have been reported in Shanghai, Xinjiang, and other regions, where combined exposure to low temperature and air pollution significantly increased cardiovascular mortality and hospitalization risk [28,30-32].

The underlying mechanisms may be related to the combined damage caused by cold waves and $PM_{2.5}$ to the circulatory system. Cold exposure may induce sympathetic nervous system activation, peripheral vasoconstriction, elevated blood pressure, and increased blood viscosity [33–35], whereas $PM_{2.5}$ exposure may affect the cardiovascular system through oxidative stress, systemic inflammation, endothelial dysfunction, and coagulation abnormalities [36]. Simultaneous or sequential exposure to these environmental stressors may therefore further increase cardiovascular burden through shared inflammatory and vascular injury pathways.

Considerable heterogeneity was observed across disease subtypes. Hypertension showed the strongest and most stable associations across most combined exposure scenarios, suggesting that blood pressure regulation may be particularly sensitive to the combined stimulation of cold waves and $PM_{2.5}$. Cold waves may rapidly increase blood pressure through sympathetic activation and vasoconstriction [37–38], whereas $PM_{2.5}$ may further impair endothelial function and vascular regulation [39–40], thereby aggravating short-term blood pressure fluctuations and vascular burden.

Cerebrovascular diseases also show relatively high sensitivity to combined exposure, possibly due to increased blood viscosity and enhanced coagulation under cold conditions, together with $PM_{2.5}$-induced inflammatory responses and thrombosis [33–36]. In contrast, the associations for some heart diseases were relatively weaker or less stable, which may reflect differences in pathological mechanisms and sensitive exposure windows across disease subtypes.

In Scenario C, where $PM_{2.5}$ exposure preceded cold waves, the health effects were consistently stronger and more persistent, suggesting that the exposure sequence may critically modify compound environmental health risks. Prior $PM_{2.5}$ exposure may induce persistent oxidative stress, endothelial dysfunction, and systemic inflammation, thereby increasing vulnerability to subsequent cold stimulation [34,36,39,40]. In contrast, cold exposure preceding $PM_{2.5}$ may partly trigger adaptive physiological responses, which could partially explain the relatively weaker effects observed in Scenario B [34,41]. Similar findings were also reported in a recent study from Tianjin, China [42].

This study also revealed evident nonlinear interaction patterns between cold waves and $PM_{2.5}$. Low-intensity combined exposure was characterized mainly by antagonistic interactions, whereas moderate-to-high-intensity exposure gradually shifted toward synergistic enhancement effects. Similar findings have also been reported in previous environmental epidemiological studies [32,42–44].

The nonlinear interaction patterns observed in this study may reflect different physiological responses across exposure intensities. Under low-intensity exposure conditions, overlapping inflammatory and oxidative stress pathways may limit the incremental effects of combined exposure, resulting in antagonistic interactions [33]. In contrast, under moderate-to-high-intensity exposure, physiological compensatory capacity may be exceeded, thereby aggravating vascular dysfunction and inflammatory responses and leading to synergistic effects [45].

The combined effects increased at moderate-to-high $PM_{2.5}$ concentrations but weakened at extremely high pollution levels, suggesting a potential nonlinear exposure–response relationship. This phenomenon may be related to physiological saturation, depletion of susceptible populations, behavioral adaptation, and limited event counts under extremely high-exposure conditions.

Stratified analyses indicated that males and older adults were more susceptible to combined cold wave and $PM_{2.5}$ exposure. Older adults may be more vulnerable to acute circulatory events because of impaired thermoregulatory capacity, reduced cardiovascular compensatory function, and a greater burden of underlying diseases [46–48]. The greater risk observed among males may be associated with greater occupational exposure, higher smoking prevalence, and longer durations of outdoor activity.

From a public health perspective, these findings suggest that health warning systems based solely on single environmental factors may underestimate the actual health burden associated with compound environmental exposure. In particular, greater attention should be given to the sequential exposure characteristics of $PM_{2.5}$ and cold waves under persistent air pollution conditions, and targeted protection strategies should be strengthened for susceptible populations such as older adults and patients with hypertension. Under climate change, compound exposure to extreme weather events and air pollution may become increasingly common. Therefore, establishing precise early warning and intervention strategies on the basis of compound environmental exposure characteristics is important for public health.

This study has several strengths. First, on the basis of long-term emergency ambulance call data, this study comprehensively evaluated the short-term health effects of combined cold wave and $PM_{2.5}$ exposure. Second, this study innovatively constructed different exposure-sequence scenarios and simultaneously evaluated lag effects and interaction effects, thereby providing a more

comprehensive assessment of the health risks associated with compound environmental exposure. In addition, analyses across disease subtypes and population groups enhanced the public health relevance of the findings.

Several limitations should also be acknowledged. First, the exposure assessment was based on fixed-site monitoring data and may not accurately reflect individual-level exposure. Second, as an ecological time series study, individual behavioral characteristics and underlying diseases could not be incorporated into the analyses, and residual confounding may remain unavoidable. Third, this study did not further evaluate differences in the chemical composition of PM2.5, although different components may have distinct toxicological effects. Therefore, caution is warranted when these findings are generalized to regions with different climatic conditions or pollution characteristics.

In conclusion, combined exposure to cold waves and $PM_{2.5}$ significantly increased the risk of circulatory disease emergency ambulance calls and exhibited evident lag characteristics, exposure-order dependence, and nonlinear interaction patterns. The strongest health effects were observed when $PM_{2.5}$ exposure preceded cold wave events, suggesting that prior air pollution exposure may increase susceptibility to subsequent cold stimulation. Our findings suggest that the cardiovascular health impacts of compound cold and $PM_{2.5}$ exposure may be strongly influenced by exposure sequence and temporal interval, highlighting the importance of incorporating sequential exposure patterns into environmental health risk assessment and early warning strategies.

Declaration

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. Due to the emergency setting of prehospital care, it was not feasible to obtain prospective informed consent from patients. The Ethics Committee granted a waiver of informed consent for this study. All data were anonymized prior to analysis.

Consent for publication

Not applicable.

Availability of data and materials

The data supporting the findings of this study are available from the corresponding author 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.

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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. M.F.K. prepared the figures and tables. 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.

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Appendix A. Supplementary data

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