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The Interactive and Joint Associations of Ambient $PM_{2.5}$ and Temperature on the Onset of Acute Coronary Syndrome: Findings from The Chinese Cardiovascular Association (CCA) Database-Chest Pain Center Registry

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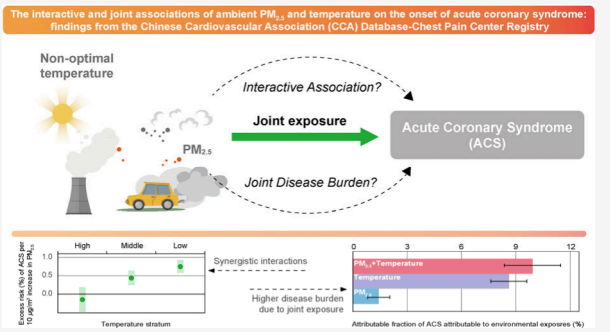
ABSTRACT: Environmental factors are important exposures that trigger acute coronary syndrome (ACS) onset. However, the interactive and joint associations of multiple exposures on ACS onset remain unknown. A time-stratified case-crossover study was conducted including 1,292,219 ACS patients who were selected from 1,895 districts/counties across China during 2015−2020. The ACS conditions included ST-segment-elevation myocardial infarction (STEMI), non-ST-segment-elevation myocardial infarction (NSTEMI), and unstable angina (UA). Conditional logistic regression models were applied to estimate the interactive and joint associations of particulate matter with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) and temperature (TM) with the ACS onset. The ACS onset risks increased by 0.38% for each 10 $\mu g/m^3$ increment in $PM_{2.5}$ concentration, and an inverse U-shaped curve of TM and risk of ACS onset was observed. The associations of $PM_{2.5}$ with the ACS onset were greater on colder days. The jointly attributable fractions (AF) of $PM_{2.5}$ and nonoptimal TM was 9.93% in all ACS patients, 10.31% in females, 12.91% in patients aged ≥65 years, 17.54% in NSTEMI patients, and 12.43% in Southern China. This study suggested that joint short-term exposures to ambient $PM_{2.5}$ and moderate cold TM may substantially increase the onset of ACS. Furthermore, there are synergistic interactions among higher $PM_{2.5}$ and lower TM peaks on the ACS onset.



KEYWORDS: *Acute coronary syndrome, air pollution, ambient temperature, joint association, interaction*

INTRODUCTION

Acute coronary syndrome (ACS) is an important subcategory of cardiovascular disease (CVD), and includes ST-segment-elevation myocardial infarction (STEMI), non-ST-segment-elevation myocardial infarction (NSTEMI), and unstable angina (UA).[1,2] ACS can be life-threatening, and also substantially decrease the quality of life for survivors.[3] Although the diagnosis and treatment of ACS have substantially improved over the past decade, ACS is still an important contribution to mortality from CVD worldwide.[4] The Global Burden of Disease study reported that CVD was the leading cause of death worldwide, and more than 19.4 million people died of CVD globally in 2021, in which 9.0 million deaths were due to ischemic heart diseases (IHD).[5] ACS accounts for a substantial portion of total IHD deaths.[6] More importantly, the age-standardized prevalence and mortality rate of IHD are still increasing in many low- and middle-income countries, such as China.[7]

Although ACS is a preventable disorder, more than 90% of the population attributable risk could be accounted by a limited number of risk factors and health behaviors, including abnormal lipids, smoking, hypertension, abdominal obesity, alcohol consumption, etc.[8] In recent years, many studies have identified the associations of short-term exposures to air pollutants and ambient temperature with the risk of ACS-related events.[9,10] However, most previous studies focused on the individual associations between a single environmental factor and health outcomes. In practice, people in daily life are simultaneously exposed to multiple environmental factors, which may jointly affect human health. To the best of our knowledge, no study has systematically estimated the joint

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effects of air pollutants and ambient temperature on the onset of ACS conditions.

Environmental factors are usually closely correlated with each other, and one factor may modify the health effect of other factors.[11] In the context of climate change, assessing the interactive effects of air pollutants and the temperature has attracted growing scientific concerns. Some studies reported greater associations of air pollution with risk of CVD in low-temperatures conditions or during winter,[12−14] indicating the synergistic interaction between low temperature and air pollutants on cardiovascular health. However, some studies have observed that high temperatures may have additive interaction effects with air pollutants on cardiovascular health.[15,16] The possible reasons for the inconsistent results may be related to the study settings, exposure assessments, and outcome measurements. Most previous studies were based on a single-city/region.[17,18] Their results may be largely impacted by local climate.[19] Low-quality exposure assessments, such as those with low spatial resolution, could contribute to heterogeneity in effect estimates of associations between environmental factors and health outcomes. It has been illustrated that exposure measurement error may lead to an attenuation of effect estimates and reduced statistical power.[20] In addition, most previous evidence of the interactive effects of multiple environmental exposures on cardiovascular health is based on mortality data rather than morbidity data. Compared with mortality data, hospital admission of ACS conditions could be more sensitive to environmental exposures and capture the early damage of environmental factors. Therefore, more research at the individual level information in wider study settings is needed to clarify the interactive effects of environmental factors on ACS conditions.

In this study, we applied an individual-level time-stratified case-crossover design based on a nationwide registry database across China to comprehensively investigate the interactive and join associations of particulate matter with aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$) and temperature with the onsets of ACS conditions. We also aimed to identify the potential modifications and estimate the morbidity burden of ACS patients attributable to environmental exposures.

METHODS

Study Design. This study employed a time-stratified case-crossover design to explore the associations of short-term exposures to $PM_{2.5}$ and ambient temperature with ACS onset. For each patient with ACS, the date of ACS symptomatic onset was defined as the case day, and dates sharing the same year, calendar month, and day of week with the case day were selected as their self-control days. Therefore, each case day could be matched to 3 to 4 control days, and several factors that are constant (e.g., sex and family history) and less likely to change (e.g., age, health behavior, economic condition, and diet) in the short term could be controlled automatically.

Study Population. All data of ACS onset were obtained from the Chinese Cardiovascular Association (CCA) Database-Chest Pain Center, which was established in 2015 as a national, multicenter, and representative registry in China. The Chest Pain Center is an integrated medical rescue model in hospitals of China that provides more optimized treatment procedures and diagnostic measures for patients with acute chest pain.[21] Records of admitted patients with acute chest pain visiting the Chest Pain Center were collected and reported to the CCA-Chest Pain Center by well-trained staffs. Reported information included demographic data (e.g., sex and age), clinical information (e.g., medication use and electrocardiogram), laboratory examination (e.g., blood routine examination), disease diagnosis (e.g., admission and discharge diagnosis, occurrence date of symptom), and so on.

In this study, we extracted data on ACS cases reported from January 1, 2015 to December 31, 2020 in the CCA Database-Chest Pain Center. An ACS case was identified as a patient discharged with a diagnose of STEMI, NSTEMI, or UA. The discharge diagnosis was implemented by cardiologists according to standard guidelines combined with patient's clinical symptoms and medical examination.[22] Occurrence date of symptom for each patient was reported by the patient or his (her) near relatives. After excluding data with missing records of occurrence date of symptom and discharge diagnosis, and further removing cases with key variables missing (including age, sex and information on district/county), a total of 1,292,219 ACS cases from 3,017 Chest Pain Centers in 1,895 districts/counties were included in our final analyses (Figure S1, Figure S2).

Exposure Assessment to Environmental Variables. Daily air pollution data including particulate matter with $PM_{2.5}$, nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO) and daily maximum 8 h average ozone (MDA8 O_3) from January 1, 2015 to December 31, 2020 were collected from the National Earth System Science Data Center, National Science & Technology Infrastructure of China (http://www.geodata.cn). An artificial intelligence technology was used to product daily air pollution concentration data, which simultaneously integrated multidomain information including ground-based observations, satellite remote sensing products, atmospheric reanalysis et al. Finally, grided daily air pollution concentration data with high spatial resolution (1km × 1km for $PM_{2.5}$ and 10km × 10km for other four air pollutants) across China were modeled, and accuracies of models were assessed using cross-validation coefficient of determination (CV-R^2) and root-mean-square error (RMSE) ($PM_{2.5}$: CV-R^2 = 0.92, RMSE = 10.76 $\mu g/m^3$; NO_2: CV-R^2 = 0.84, RMSE = 7.99 $\mu g/m^3$; SO_2: CV-R^2 = 0.84, RMSE = 10.07 $\mu g/m^3$; CO: CV-R^2 = 0.80, RMSE = 0.29 mg/m^3; MDA8 O_3: CV-R^2 = 0.87, RMSE = 11.70 $\mu g/m^3$).[23−26]

Daily mean temperature (TM) and daily relative humidity (RH) during January 1, 2015 to December 31, 2020 were obtained from the fifth generation of European Reanalysis (ERA-5). Produced by the Copernicus Climate Change Service (C3S) at European Centre for Medium-Range Weather Forecasts (ECMWF), ERA-5 provided global TM and RH data with a spatial resolution of 0.25° × 0.25° and a temporal resolution of hours. The 24 h average TM and RH were calculated as the daily TM and RH values. A previous study has suggested ERA-5 data set was a reliable substitute when high-quality station data were not available.[27] We also compared the daily TM and RH from ERA-5 with station data from 698 climate monitoring station of China, and observed good goodness-of-fit (TM: CV-R^2 = 0.95, RMSE = 2.87 °C; RH: CV-R^2 = 0.84, RMSE = 7.59%) (Figure S3), which demonstrated the reliability of ERA-5. Detailed methodology of data validation can be found in Supporting Information (SI Method 1.1).

Based on the above predicted data, we extracted the daily air pollution and meteorological data of all grids covered by each county/district where the Chest Pain Center is located. Then we calculated the average level across all included grids in each

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county or district, which was applied to represent the environmental exposures on the case and control days of each ACS case.

STATISTICAL ANALYSIS

Associations of Environmental Factors with ACS Onset. We applied conditional logistic regression models to explore the associations of exposure to $PM_{2.5}$ and TM with onset of ACS. According to previous studies,[28−30] we estimated the associations of $PM_{2.5}$ and ACS onset with 4-day moving average (lag03 days), and associations of TM with 22-day moving average (lag021 days). In the regression models, current-day RH (lag0) was controlled as a confounding factor in this study.

We first conducted a single-exposure model to separately estimate the associations of $PM_{2.5}$ and TM with ACS onset. We fitted their nonlinear effects using a natural splines (*ns*) function with three degrees of freedom (*df*), and the likelihood ratio test was used to test potential nonlinearity for each factor. Linear associations of $PM_{2.5}$ were estimated by removing the *ns* function in the models. We further employed multiple-exposure models to estimate joint associations of $PM_{2.5}$ and TM on ACS onset, which could be specified as following:

$$\log it(P(case = 1 instratum i)) = \alpha_i + PM_{2.5}(lag03 days) + ns(TM(lag021 days), df = 3) + ns(RH, df = 3)$$

where $P(case = 1 \text{ in stratum } (i))$ denoted the conditional probability of ACS onset in the i stratum, and α_i denotes the intercept of stratum i. To explore potential effect modifications, stratified analyses were conducted by sex (males and females), age (<65 and ≥65 years), subtype of ACS (STEMI, NSTEMI, and UA), region (Southern and Northern, divided by Huai River and Qinling Mountain).[31] Differences of estimates among subgroups were test by z tests following the formula:[32]

$$z = \frac{\beta_1 - \beta_2}{\sqrt{se_1^2 + se_2^2}}$$

where β_1 and β_2 were the regression coefficients from conditional logistic models, and se_1 and se_2 were the corresponding standard errors. For subtype of ACS, Bonferroni correction was used to adjust P values when the difference was tested (SI Method 1.2). We reported the main results of associations using excess risk (ER), which could be calculated by $[(e^{\beta}\text{-}1) \times 100\%]$.

Estimations of Morbidity Burdens of ACS. Attributable fraction (AF) was used to assess the disease burdens of ACS attributable to environmental factors. We separately calculated the individual and joint AFs of ACS onset attributable to $PM_{2.5}$ and TM. First, the individual AF was calculated using the formula:[33]

$$AF(\%) = \frac{\left[\sum (P_{ij} \times RR_{ij}) - 1\right]}{\sum (P_{ij} \times RR_{ij})} \times 100\%$$

where P_{ij} represents the proportion of ACS onset in exposure level i of environmental factor j; RR_{ij} indicates the relative risk value of factor j in level i on ACS onset, in which the RRs could be obtained in the single-exposure and multiple-exposure models. Then, we calculated the joint AF of ACS onset attributable to multiple environmental factors using the formula below:[33]

$$AF_{joint}(\%) = \left[1 - \prod_{j=1}^{J} (1 - AF_j)\right] \times 100\%$$

We used the Monte Carlo method to calculate the 95% confidence intervals (CIs) of joint AFs. We simulated 10,000 samples of individual AFs from multiple-exposure models for each factor under normal distribution. Next, simulations were aggregated to calculate the joint AFs. The 2.5th and 97.5th percentiles of a series of joint AFs were extracted as the lower and upper bound of 95% CIs, respectively.

Interactive Associations Analyses of $PM_{2.5}$ and TM. To explore the potential interactive associations of $PM_{2.5}$ and TM on ACS onset, we applied stratified analyses by categorizing TM into three groups: low TM (<25th percentile), middle TM (25th-75th percentile) and high TM (>75th percentile). To ensure comparability, the category thresholds of different TM strata were calculated based on the distribution of TM in each county. Then, we estimated the associations of $PM_{2.5}$ at different TM strata, respectively. To compare the associations of $PM_{2.5}$ between different TM strata, we calculated P values using z tests, and the Bonferroni correction was used to adjust P values. Further, we also calculated the proportion attributable to the interaction (AP) to estimate potential additive interaction between $PM_{2.5}$ and TM, and the detailed methodology could be found in SI Method 1.3.

Sensitivity Analysis. Several sensitivity analyses were conducted to test the robustness of our results. We changed the lag days of $PM_{2.5}$ and TM, and also conducted two-pollutants models additionally adjustment for MDA8 O_3, SO_2, and NO_2. However, we did not consider CO in two-pollutant models due to high correlation between CO and $PM_{2.5}$ (r = 0.71, Figure S4). Finally, we removed RH in the regression model.

Data analysis in this study was performed with R software (version 4.2.1, R Development Core Team). We used "*survival*" package to conduct conditional logistic regression models. And two-sides P values <0.05 denoted statistical significance.

RESULTS

Characteristics of Study Participants. This study included 1,292,219 ACS patients from 3,017 hospitals across China, out of which 569,309 (44.1%) were STEMI patients, 263,947 (20.4%) were NSTEMI patients, and 458,963 (35.5%) were UA patients. Moreover, 895,119 (69.3%) were male patients, 644,592 (49.9%) were aged 65 years or over, and 666,601 (51.6%) were resided in Northern China (Table 1). In addition, differences existed in the proportions of sex, age, and region among three subtypes of ACS (Table S1). For example, compared with NSTEMI and UA, STEMI had higher proportions in males and people aged 65 years or over. And UA had a higher proportion in population from Northern China than the other two subtypes of ACS. Compared with control days, case days had higher $PM_{2.5}$ concentration (38.07 ± 23.54 $\mu g/m^3$ vs 37.83 ± 18.89 $\mu g/m^3$) and ambient TM (16.33 ± 9.14 °C vs 16.28 ± 8.71 °C), with P values <0.05 (Table S2). Result from Pearson's correlation analysis showed

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Table 1. Characteristics of the ACS Onset Population in the Study

Characteristics	Case (n, %)
Total ACS onset	1 292 219 (100.0)
Type of ACS	
STEMI	569 309 (44.1)
NSTEMI	263 947 (20.4)
UA	458 963 (35.5)
Sex	
Male	895 119 (69.3)
Female	397 100 (30.7)
Age (years)	
<65	647 627 (50.1)
≥65	644 592 (49.9)
Region	
Southern	625 618 (48.4)
Northern	666 601 (51.6)

low and negative correlation between $PM_{2.5}$ concentration with TM ($r = -0.39$) and RH ($r = -0.11$) (Figure S4).

Associations of Ambient $PM_{2.5}$ and TM with Onset of ACS Conditions. Single-exposure modeling analyses showed positive associations of short-term exposures to $PM_{2.5}$ (lag03 days) (Figure 1A, Table S3). Exposure-response curve showed higher risks of ACS onset with increases in $PM_{2.5}$ concentration. Although the increasing trend in the risk of ACS onset became attenuated when exposed to extremely high levels of $PM_{2.5}$, the result of the nonlinearity test indicated that the association between $PM_{2.5}$ and the risk of ACS was almost linear (P for nonlinear = 0.056). An inverse U-shaped curve of short-term exposure (lag021 days) to ambient TM with risks of ACS onset was observed (P for nonlinear <0.001) (Figure 1B). Setting 32.2 °C as the reference, the greatest risk of ACS onset was observed at 3.5 °C (ER = 19.43%, 95%CI: 17.81%, 21.07%). Similar inverse U-shaped exposure-response curve of TM and ACS onset could also be observed from several stratified analyses (Figure S5).

Results from multiple-exposure models showed that each 10 $\mu g/m^3$ increment in $PM_{2.5}$ concentration was associated with 0.38% (95%CI: 0.21%, 0.54%) increase in the risk of ACS onset based on linear assumption (Figure 1C, and Table S3). Although there were no statistically significant differences among subgroups, the results of the stratified analyses showed slightly greater associations between PM2.5 and ACS onset in males (ER = 0.45%, 95%CI: 0.25%, 0.65%), patients aged less than 65 years (ER = 0.53%, 95%CI: 0.30%, 0.76%), NSTIME patients (ER = 0.64%, 95%CI: 0.27%, 1.02%), and patients living in Southern China (ER = 0.43%, 95%CI: 0.15%, 0.70%) (Figure 1C and Table S3). In results of multiple-exposure models, analogous inverse U-shaped exposure-response curves of TM with that from single-exposure models were also observed (Figure 1D, Figure S5). Compared with 32.2 °C which had the lowest onset risk of ACS, the risks were greater in moderate cold TMs, with the greatest risk in 4.0 °C (ER = 18.17%, 95%CI: 16.57%, 19.79%).

Morbidity Burdens Attributable to Ambient $PM_{2.5}$ and TM. Based on the above multiple-exposure modeling results, the AFs of $PM_{2.5}$ and TM on overall ACS onset were 1.43% (95% CI: 0.81%, 2.04%) and 8.62% (95% CI: 7.62%, 9.62%) (Figure 2 and Table S4). Here, joint AFs were calculated to quantify the burden of disease attributable to simultaneous exposure to $PM_{2.5}$ and TM. The joint AF of

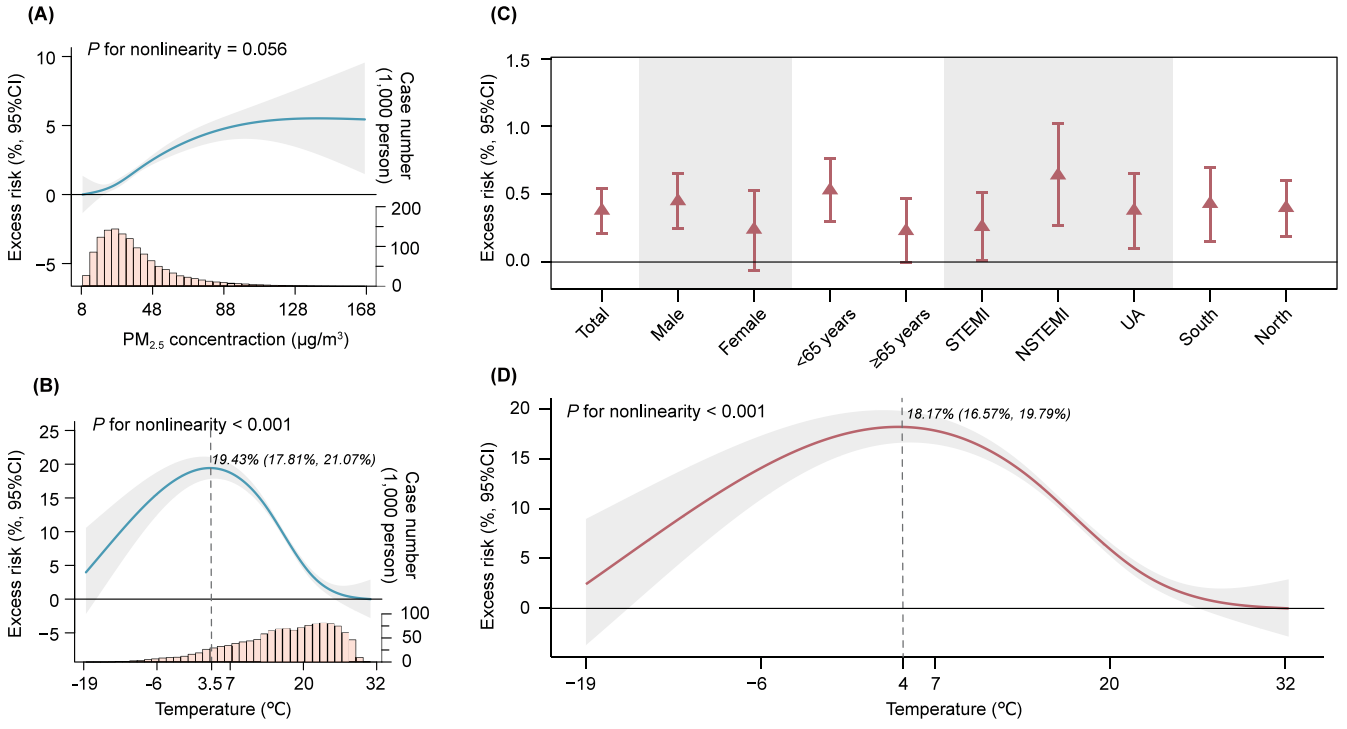

Figure 1. Excess risk of $PM_{2.5}$ and TM with ACS onset in single-exposure and multiple-exposure models. Note: (A) and (B) showed the nonlinear and single-exposure association of environmental factors with ACS onset, and nonlinearity was tested using likelihood ratio test. Single-exposure models were only adjusted for relative humidity; (C) showed the associations of $PM_{2.5}$ with ACS onset for 10 $\mu g/m^3$ increasing after linearization from multiple-exposure models; (D) showed the nonlinear and multiple-exposure association of TM with ACS onset. The peaks of ACS risks and corresponding TM were shown. In multiple-exposure models, ambient $PM_{2.5}$ and TM were mutually controlled for.

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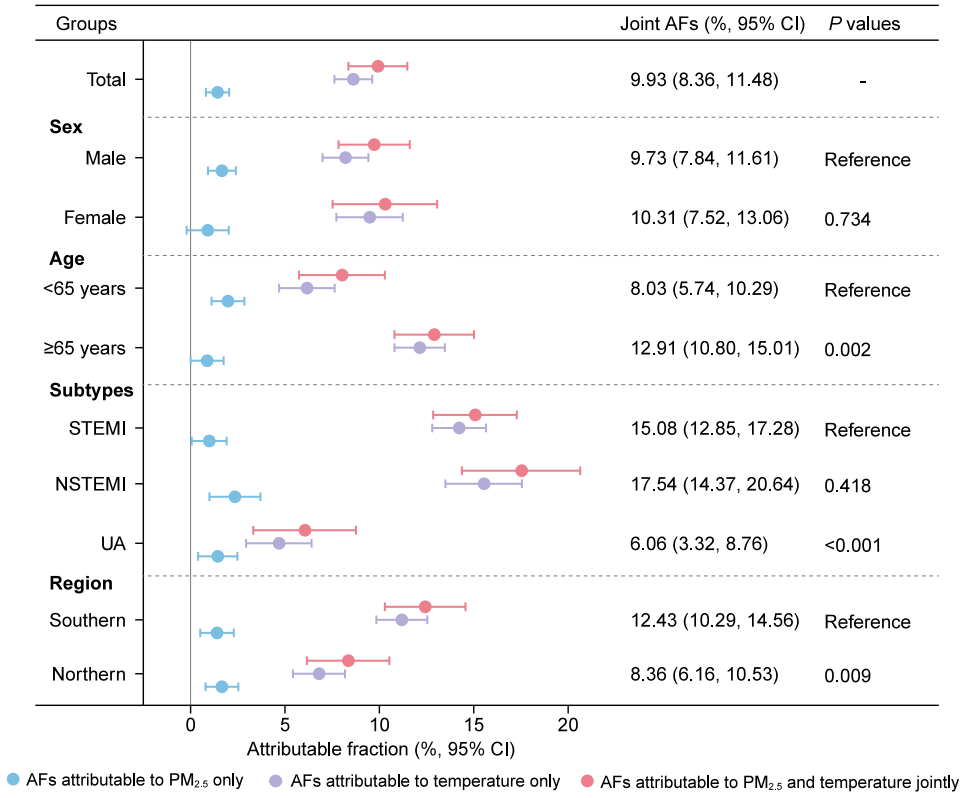

Figure 2. Disease burden of ACS onset attributable to $PM_{2.5}$ and temperature.

$PM_{2.5}$ and TM was 9.93% (95% CI: 8.36%, 11.48%) in all ACS participants. In addition, the joint AFs were larger in females (10.31%, 95% CI: 7.52%, 13.06%), in ACS patients aged 65 years or over (12.91%, 95% CI: 10.80%, 15.01%), in NSTEMI patients (17.54%, 95% CI: 14.37%, 20.64%), and in Southern China (12.43%, 95%CI: 10.29%, 14.56%) (Figure 2, Table S4).

The Interactive Associations among Ambient $PM_{2.5}$ and TM on ACS Onset. We found greater associations of $PM_{2.5}$ with ACS onset in days with lower TM. For example, the ERs for each 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration was 0.75% (95% CI: 0.58%, 0.93%) in days <25% percentile of TM, 0.44% (95% CI: 0.25%, 0.64%) in days 25−75% percentile of TM, and −0.14% (95% CI: −0.47%, 0.19%) in days >75% percentile of TM (Table 2). Results from stratified analyses also showed the highest associations of $PM_{2.5}$ with ACS onset in days lower TM. For example, compared to day with higher TM (>75% percentile), males (0.83%, 95%CI: 0.62%, 1.04%, $P < 0.001$), people aged less than 65 years (0.87%, 95%CI: 0.62%, 1.12%, $P = 0.024$), patients with STEMI (0.82%, 95%CI: 0.56%, 1.09%, $P < 0.001$), and people lived in Norther China (0.79%, 95%CI: 0.57%, 1.01%, $P = 0.002$) had greater associations of exposure to $PM_{2.5}$ with ACS in days with lower TM (<25% percentile). In addition, an additive interaction between $PM_{2.5}$ and TM was also observed. For example, in all ACS populations, we estimated the AP of 0.013 (95% CI: 0.003, 0.023), indicating the synergistic interactions among higher $PM_{2.5}$ and lower TM on the onset of ACS (Table S5).

Sensitivity Analyses. Results from sensitivity analyses showed the robustness of our findings (Table S6). Changing the exposure windows of $PM_{2.5}$ (3-, 4- or 5-days moving average) and TM (15- or 22-days moving average) did not substantially change the joint AF of $PM_{2.5}$ and TM with ACS onset. For example, the joint AFs attributable to $PM_{2.5}$ and TM in the longest (lag0−4 days for $PM_{2.5}$ and lag0−21 days for TM) and shortest (lag0−2 days for $PM_{2.5}$ and lag0−14 days for TM) exposure windows were 9.68% (95% CI: 8.08%, 11.27%) and 10.97% (95% CI: 9.56%, 12.37%), respectively. Two-pollutants models controlling for MDA8 O_3 or SO_2 showed similar results to that from the main models. However, we observed a lower joint AF from the two-pollutant model adjusting for NO_2, which may be due to the relatively high correlation between NO_2 and $PM_{2.5}$ ($r = 0.62$, Figure S4). Finally, regression model without adjustment for RH also showed similar results with that from the main models.

DISCUSSION

In this national case-crossover study across China, ambient $PM_{2.5}$ and TM exhibited great short-term associations with ACS onset and could jointly increase the risk of ACS conditions substantially. The joint burden of disease attributable to ambient $PM_{2.5}$ and TM was greater among older patients, NSTEMI patients, and those in Southern China. The associations of $PM_{2.5}$ and ACS onset were greater in days with low TM. To our knowledge, this is the first and largest case-crossover study to investigate the joint and interactive associations of $PM_{2.5}$ and TM with ACS onset with individual-level information. Our findings provided clear evidence that ACS and its subtypes could be triggered by joint exposure to higher levels of ambient pollutant and cold temperatures.

Previous studies have also investigated the associations between ambient air pollutants with the onset of ACS.[29,34−38] For example, Kuźma et al. found higher $PM_{2.5}$ and NO_2 concentrations increased risk of NSTEMI in Poland.[38] Li et

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Table 2. Excess Risk in ACS Onset Associated with a 10μg/m^3 Increase in $PM_{2.5}$ Stratified by Temperature

Strata by temperature	Excess risk (%, 95% CI)	[a]P for difference
Total		
<25% TM	0.75 (0.58 to 0.93)	ref.
25−75% TM	0.44 (0.25 to 0.64)	0.048
>75% TM	−0.14 (−0.47 to 0.19)	<0.001
Sex		
Male		
<25% TM	0.83 (0.62 to 1.04)	ref.
25−75% TM	0.44 (0.21 to 0.67)	0.028
>75% TM	0.02 (−0.38 to 0.42)	<0.001
Female		
<25% TM	0.59 (0.28 to 0.89)	ref.
25−75% TM	0.45 (0.11 to 0.79)	1.000
>75% TM	−0.51 (−1.10 to 0.08)	0.004
Age (years)		
<65		
<25% TM	0.87 (0.62 to 1.12)	ref.
25−75% TM	0.56 (0.29 to 0.83)	0.196
>75% TM	0.20 (−0.26 to 0.66)	0.024
≥65		
<25% TM	0.63 (0.39 to 0.88)	ref.
25−75% TM	0.32 (0.05 to 0.59)	0.196
>75% TM	−0.50 (−0.97 to −0.03)	<0.001
Type		
STEMI		
<25% TM	0.82 (0.56 to 1.09)	ref.
25−75% TM	0.16 (−0.13 to 0.45)	0.004
>75% TM	−0.62 (−1.12 to −0.12)	<0.001
NSTEMI		
<25% TM	0.99 (0.59 to 1.38)	ref.
25−75% TM	0.77 (0.34 to 1.21)	0.924
>75% TM	0.33 (−0.41 to 1.09)	0.260
UA		
<25% TM	0.54 (0.25 to 0.83)	ref.
25−75% TM	0.58 (0.27 to 0.90)	1.000
>75% TM	0.16 (−0.38 to 0.71)	0.460
Region		
Southern		
<25% TM	0.75 (0.45 to 1.05)	ref.
25−75% TM	0.44 (0.11 to 0.76)	0.332
>75% TM	−0.26 (−0.77 to 0.26)	0.002
Northern		
<25% TM	0.79 (0.57 to 1.01)	ref.
25−75% TM	0.49 (0.25 to 0.73)	0.140
>75% TM	0.00 (−0.43 to 0.43)	0.004

[a]P values were adjusted by Bonferroni correction. Adjustment for relative humidity in all models.

al. found that ambient $PM_{2.5}$ was positively associated with STEMI hospitalizations in China.[35] However, there are still few studies that have comprehensively estimated the associations between air pollution and the three subtypes of ACS. And some studies have failed to find the statistical relationship between air pollution and ACS.[34,39] For example, Pope et al. found that higher ambient $PM_{2.5}$ concentration was positively associated with STEMI, but they did not observe statistical associations of $PM_{2.5}$ and NSTEMI onset.[34] In our results, we found short-term exposure to $PM_{2.5}$ increased risks of STEMI, NSTEMI, and UA. The inconsistencies in the findings may be due to the difference of study locations; on the other hand, our study had a large sample size with higher statistical power, which helped us to detect the true exposure-response relationship.

We also found increased risks of ACS onset in moderate cold temperatures, whereas the risks associated with extremely low temperatures were comparatively diminished, which is consistent with several previous studies.[29,40,41] For example, Jiang et al. estimated the associations of ambient temperatures and risk of acute myocardial infarction (AMI) onset, and found that the risks increased when ambient temperatures decreased from over 30 to 0 °C. However, the risks of AMI onset largely decreased in days with extremely low temperatures (<−10 °C).[29] The decreasing phenomenon at extremely cold temperatures may be largely related to adaptation measures in the heating regions. People in Northern China usually use central heating in the winter seasons,[31] which could substantially protect their health from the extremely low temperatures.[42] In addition, we found decreasing risks of ACS onset with lower temperatures in Southern China, although the reduction was not as pronounced. Possible reasons could be that, although rare, some cities in Southern China have also developed distributed heating systems in recent years;[43] and people living in Southern China may use air conditioning for heating during extremely cold conditions.[44] Furthermore, the harvesting effect may be related to the decreased risks of ACS onset during lower temperatures. Those sensitive individuals may already experience morbidity when exposed to moderately low temperature, and thus, the impacts of extreme cold on ACS risks would be underestimated.

As a major strength of this study, we examined the interactive associations among ambient $PM_{2.5}$ and TM with the risk of ACS onset, and found stronger associations of $PM_{2.5}$ with ACS onset in lower temperature stratums. Several previous studies have also reported enhanced effects of air pollutants on cardiovascular health by low temperatures.[14,45] Several mechanisms have been proposed to explain the modifications of low temperature on the cardiovascular effect of air pollution. In cold days, the low temperature may reduce the beat frequency of nose and trachea cilia, and hence reduce the clearance rate of inhaled air pollutants.[14] Second, exposure to cold temperature can increase red cell counts, plasma cholesterol, and fibrinogen concentrations, which could subsequently increase the risk of thrombosis.[46] In addition, cold temperature can stimulate cold receptors in the skin, constrict the blood vessels near the skin to reduce heat loss, and increase the catecholamine levels, which would largely increase blood pressure.[45,47] These marked changes could make people more susceptible to adverse cardiovascular outcomes caused by air pollutants. Furthermore, previous researches have demonstrated that ambient $PM_{2.5}$ concentrations were generally the highest in winter across China,[48] which could exacerbate the harmful effects of $PM_{2.5}$ on human under cold conditions. Therefore, more rigorous prevention and intervention measures should be implemented to protect people from ACS onset during days with low temperatures and severe air pollution. For example, encouraging people to wear masks when going outdoors in cold weather could help reduce the inhalation of PM to some extent, thereby mitigating the adverse effects of air pollution under extremely cold conditions.

Results from stratified analyses further verified the synergistic interactions among higher $PM_{2.5}$ and lower TM on the onset of ACS in a specific population. For example, we

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found that males and females had a similar trend in the greater associations between $PM_{2.5}$ and ACS onset with lower temperature exposures. Although previous studies have indicated sex differences in the effects of extreme cold on cardiovascular events,[29] our findings highlighted the widespread amplification of harmful effects from air pollution under extreme cold conditions and underscored the importance of addressing the complex interactions among environmental factors. Additionally, under high-temperature conditions, $PM_{2.5}$ exposure had null associations with NSTEMI and UA onset but was negatively associated with STEMI onset. The potential reason for this inconsistent phenomenon is that STEMI patients are generally more affected by high temperatures compared to those with NSTEMI.[49] The blood viscosity of STEMI patients tends to be more sensitive to seasonal variations.[50] Therefore, during hot weather, individuals at a high risk of STEMI are more likely to stay indoors to avoid direct exposure to high temperatures, which also reduces their exposure to outdoor air pollution.

Considering that both air pollution and nonoptimal temperatures are risk factors for ACS onset, we calculated the joint associations of $PM_{2.5}$ and TM with ACS conditions. We found that a total of 9.93% of ACS onsets were jointly attributed to exposures to $PM_{2.5}$ and TM across China. In addition, nonoptimal TM (AF = 8.62%) dominated in the joint burden of disease. To the best of our knowledge, this is the first study to quantify the burden of ACS onset attributable to both air pollutant and temperatures. Although few studies have estimated the burden of CVD morbidity attributable to individual air pollutant or temperature,[29,51,52] none of them has estimated the joint associations of air pollutants and temperature, the mixed conditions we are usually exposed to. It was projected that the morbidity and mortality burden of ACS conditions in China will continue to increase in the future, under the impacts of population aging, environmental changes, urbanization, etc.[53] Therefore, more research work is urgently needed to estimate the joint effects of multiple environmental exposures on ACS conditions, which could provide valuable information for preventing ACS onset. Our results also suggested that exposure to nonoptimal TM contributed more to the disease burden of ACS, and highlighted the adaptive measures for climate change should be considered to prevent the ACS risks from environmental risk exposures.

Subgroup analyses could identify a sensitive population and better target preventive measures under adverse environmental conditions. Results from stratified analyses showed substantially different joint AFs among the subgroups. Greater joint associations of $PM_{2.5}$ and TM with ACS onset were observed in the elderly people than in younger people, which was consistent with previous studies.[29,54] Older people usually suffer from several kinds of diseases and have worse thermoregulatory system than younger people, therefore older people are more vulnerable to climate change and more likely to develop other CVDs when exposed to nonoptimal TM.[55] Meanwhile, the elderly are usually more susceptible to adverse environmental conditions due to their worse metabolic and physiological processes. Therefore, simultaneous exposure to high level air pollution and nonoptimal temperature would greatly impose health burdens on older people. We also found that joint exposure to $PM_{2.5}$ and TM brought greater burden of ACS to Southern China than to Northern China. In China, the cities with central heating are mainly concentrated in north of China.[42] Therefore, central heating may mitigate the effects of low TM on people living in Northern China, resulting in regional variations in the disease burden of TM on ACS.[29] Additionally, we found greater joint burden of diseases attributable to $PM_{2.5}$ and TM in AMI (including STEMI and NSTEMI) than in UA. Although the associations of air pollution with ACS had been widely confirmed,[28] there are still few studies on the exploring the association of TM and UA. Abrignani et al. argued that the effects of seasonal variation may differ between angina and AMI. They found that admissions for AMI rose during the winter, but not for UA.[56] Another study from Germany found hospitalizations for both AMI and UA increased at lower TM.[57]

The findings of this study have important implications for the prevention of ACS. First, our findings provide the joint effects of both major air pollutant and nonoptimal TM on risk of ACS onset, which is very useful for developing a comprehensive early warning system integrating both air pollution and meteorological exposures. Second, we provided the interactive associations between $PM_{2.5}$ and temperature, which could help to identify the days with the highest risk of ACS and make targeted prevention and intervention measurements. Finally, special attention should be given to those vulnerable groups, and targeted prevention measures are particularly required.

This study has several strengths. First, this study was based on a standardized and nationally representative registry database of ACS patients across China. The large sample size (1.29 million) provided us adequate statistical power to identify the potential associations of environmental exposures on CVD health and to examine the vulnerable groups and regions. Second, we quantitatively calculated the joint and interactive associations of air pollution and temperature with ACS onset, which could help the public and policy makers to comprehensively understand the health impacts of multiple environmental factors. Third, the individual level time-stratified case-crossover study design combined with the detailed information on the time of ACS onset could substantially reduce the temporal mismatch of exposure and ACS onset. Fourth, this is a comprehensive study not only focusing on the associations of environmental exposures with the risk ACS onset but also estimates the morbidity burden as measured by AF.

There are also several limitations. First, we did not obtain the residential address of each patient due to the privacy concerns and alternatively matched the environmental exposures at the county/district level, which may lead to misclassification bias of exposure assessment. However, patients with ACS onset are usually sent to the nearest hospital within a short time in China, which would limit the spatial mismatch between residential and hospital addresses. For example, a study across 21 provinces in China reported that the median time from onset of AMI symptom to the hospital arrival was 4 h (interquartile range 2−7.5 h).[58] In addition, Sheppard et al.' study suggested that the measurement error will not affect the exposure response relationship in the linear model,[59] and Bergen S et al. also suggested that this measurement error may lead to underestimating the risk of the impact of pollutants on health.[60] Second, some confounders, such as individuals' lifestyle behaviors, were not adequately considered due to unavailable data. Although the time-stratified case-crossover design could perfectly control for those slowly varying individual-level risk factors, some

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confounders that vary transiently may not be sufficiently adjusted for such factors as physical activity, smoking, and alcohol drinking. Previous studies have demonstrated the adverse effects of these risk factors on ACS onset risk.[1,8] Third, we did not measure indoor air pollution and temperature, which may also potentially confound the associations of ambient air pollution and temperature with ACS onset or lead to misclassification bias. Because people usually spend about 80%−90% of their time indoors, and the indoor environmental quality are closely associated with human health.[61] Fourth, only ACS patients admitted to hospitals were included in this study. Those who died before hospital admission were excluded, but they may be more susceptible to environmental exposures. Fifth, we were not able to identify who were recurrent ACS patients due to the deidentification nature of the present study, which limited us to conduct stratified analysis. It was suggested that recurring CVD were more sensitive to environmental changes.[62] Sixth, in the sensitivity analyses, we used data of other air pollutants (MDA8 O_3, SO_2, and NO_2) to conducted two-pollutants model, but these data had different spatial resolutions with $PM_{2.5}$ data, which may affect the accuracy of the results. Finally, this large case-crossover study is still an ecological study and has limitations such as impacts of autocorrelation. Therefore, the associations between environmental factors and the ACS should be cautiously interpreted.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.4c07508.

Methodology (SI Method 1.1−1.3); characteristics of study population across subtypes of ACS (Table S1); statistical description of environmental exposures (Table S2); detailed values of ERs, AFs, and APs (Table S3−S5); results of sensitivity analyses (Table S6); flowchart of samples inclusion and exclusion (Figure S1); study sites (Figure S2); validations of ERA-5 data set (Figure S3); correlations between environmental exposures (Figure S4); exposure-response curves of TM (Figure S5) (PDF)

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