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Associations Between $PM_{2.5}$ Components and Cardiovascular Diseases

A Cohort Study of 0.5 Million Chinese Adults

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ABSTRACT

BACKGROUND Evidence linking components of particulate matter with diameters ≤2.5 μm ($PM_{2.5}$) to the incidence of cardiovascular disease (CVD) remains scarce and inconsistent.

OBJECTIVES The aim of this study was to investigate the associations of long-term exposure to $PM_{2.5}$ components with incident CVD risk, considering both absolute concentrations and relative proportions.

METHODS This study included 487,037 participants from the China Kadoorie Biobank who were free of CVD or cancer at baseline. Three-year moving average concentrations of $PM_{2.5}$ and its components (black carbon [BC], organic matter, chloride [Cl^-], nitrate [NO_3^-], sulfate [SO_4^{2-}], and ammonium [NH_4^+]) were geocoded to participants at 1 × 1 km resolution according to their community recruitment clinic locations. Time-varying Cox proportional hazards models were used to evaluate the associations between $PM_{2.5}$ components and incident CVD risk. Substitution models were used to estimate the effects of reallocating $PM_{2.5}$ component proportions while keeping total $PM_{2.5}$ mass constant, thereby evaluating changes in CVD risk associated with shifts in component composition.

RESULTS Over a median 15.1-year follow-up, a total of 196,224 CVD cases, including 72,747 of ischemic heart disease, 74,594 of ischemic stroke, 17,553 of hemorrhagic stroke, and 54,306 of other cerebrovascular diseases, were documented. Long-term exposure to $PM_{2.5}$ components was associated with increased risk for CVD and its major subtypes. For total CVD, the HRs per IQR increase were 1.15 (95% CI: 1.13-1.17) for BC, 1.17 (95% CI: 1.15-1.18) for organic matter, 1.28 (95% CI: 1.25-1.32) for Cl^-, 1.29 (95% CI: 1.24-1.33) for NO_3^-, and 1.23 (95% CI: 1.20-1.25) for SO_4^{2-}. Higher proportions of Cl^-, SO_4^{2-}, and BC were associated with an increased risk for ischemic stroke, and the aforementioned inorganic ions were also positively associated with ischemic heart disease. Substituting 1% of any other $PM_{2.5}$ component with Cl^- was associated with a 3% to 8% higher risk for total CVD, whereas substitutions with BC were associated with a 1% to 8% higher risk for ischemic stroke, and substitution with SO_4^{2-} was associated with a 2% to 5% higher risk for ischemic heart disease.

CONCLUSIONS Long-term exposure to $PM_{2.5}$ chemical components was positively associated with CVD risk. Critically, CVD risk was influence by compositional shifts, with a particularly hazardous profile characterized by higher proportions of Cl^-, BC, or SO_4^{2-}. These findings underscore the importance of implementing targeted, health-oriented control strategies that prioritize specific $PM_{2.5}$ components. (JACC. 2026;■:■-■) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

BC = black carbon

BMI = body mass index

CHAP = ChinaHighAirPollutants

CKB = China Kadoorie Biobank

CVD = cardiovascular disease

OM = organic matter

$PM_{2.5}$ = particulate matter with diameters ≤2.5 μm

WC = waist circumference

Particulate matter pollution remains a leading contributor to the global disease burden, accounting for 4.48 million deaths of cardiovascular disease (CVD) worldwide in 2021.[1,2] Despite substantial reductions in concentrations of particulate matter with diameters ≤2.5 μm ($PM_{2.5}$)[3] and related premature deaths[4] achieved through comprehensive clean air actions in China, control measures that focus solely on mass concentration are becoming less effective[3] and cannot proportionately mitigate health risks.[5]

The health effects of $PM_{2.5}$ are determined not only by mass concentrations but also by its sources and chemical compositions. Toxicologic studies have demonstrated that the oxidative stress and cytotoxicity induced by source-specific $PM_{2.5}$ could vary by up to 2 orders of magnitude, largely because of differences in chemical components.[6,7] A growing body of cohort evidence, predominantly from Western countries such as the United States, Sweden, and Germany, indicates that $PM_{2.5}$ from traffic[8-10] and coal combustion[8] is associated with stronger adverse effects, with black carbon (BC), nitrate (NO_3^-), sulfate (SO_4^{2-}), and ammonium (NH_4^+) showing positive associations with CVD mortality.[8,9,11-13] However, the findings of studies relying on mortality endpoints may be influenced by certain unmeasured factors during disease progression, such as reduced physical activity, that may alter exposure levels and medical interventions received.[14] Furthermore, such studies are limited in their ability to inform earlier public health interventions.[15] To date, population-based cohort studies examining the associations between long-term exposure to $PM_{2.5}$ components and incident CVD in Chinese populations remain limited and inconclusive.[16-19] Evidence regarding major CVD subtypes is also inconsistent, with the same $PM_{2.5}$ component showing heterogeneous associations for stroke vs ischemic heart disease,[16,20] as well as mixed positive[16] and null[18] associations for the same subtype across regions.

Furthermore, $PM_{2.5}$ compositional profiles, defined by the relative proportions of components rather than their absolute levels, serve as crucial source fingerprints that influence mass-normalized oxidative potential[21] and modify the overall health effects of total $PM_{2.5}$ mass.[22] Despite the value of these complementary insights, epidemiologic evidence from a compositional perspective remains scarce. A primary methodological barrier is that $PM_{2.5}$ component proportions constitute compositional data subject to a constant-sum constraint. This inherent property induces perfect multicollinearity, precluding their simultaneous inclusion in conventional regression models.[23] The isometric log-ratio transformation addresses this closure problem,[23,24] enabling statistical modeling within a substitution analysis framework. Unlike conventional regression that estimates risks per unit increase in component concentrations, this framework theoretically quantifies the health effects of reallocating proportions among components while holding total mass constant, a novel application in this specific field.[25] Consequently, it provides a vital public health perspective by evaluating the impacts of compositional shifts, which is particularly relevant when further reductions in total mass are challenging but source contributions remain modifiable.

To address the aforementioned evidence gap, in this study we used data from the China Kadoorie Biobank (CKB) to investigate the associations between long-term exposure to $PM_{2.5}$ components and the incident risk for CVD and its major subtypes, considering both absolute concentrations and relative proportions.

METHODS

STUDY DESIGN AND PARTICIPANTS. Details regarding the CKB have been previously described.[26,27] Briefly, the CKB cohort recruited 512,724 participants aged 30 to 79 years in 10 areas across China from 2004 to 2008 and completed the baseline study. Participants were invited from administrative units (villages for rural areas and street committees for urban areas), and a survey clinic was established in a central location within about 1 km of the residences. Trained staff members collected baseline information using laptop-based questionnaires with built-in quality control procedures and logical error detection functions, as well as physical assessments and blood draws. We excluded participants who had heart disease (n = 15,472), stroke (n = 8,884), or cancer (n = 2,578) at baseline,

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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as well as those with missing data for body mass index (BMI) (n = 2) or $PM_{2.5}$ concentration (n = 177), leaving 487,037 participants eligible for analysis (Supplemental Figure 1). All participants provided written informed consent. The Ethical Review Committee of the Chinese Center for Disease Control and Prevention, the Peking University Institutional Review Board, and the Oxford Tropical Research Ethics Committee, University of Oxford, approved the study.

AIR POLLUTION ESTIMATES. The daily mean concentrations of $PM_{2.5}$ and its 5 key chemical components (BC, chloride [Cl^-], NO_3^-, SO_4^{2-}, and NH_4^+) at 1 × 1 km spatial resolution from 2001 to 2021 were obtained from the ChinaHighAirPollutants (CHAP) data sets. More detailed information about CHAP can be found elsewhere.[28-31] Briefly, the predicted concentrations of these pollutants were derived using artificial intelligence by integrating ground-based measurements, satellite remote sensing products, atmospheric reanalysis, and model simulations. The CHAP $PM_{2.5}$ chemical composition data set exhibits high quality, with sample-based cross-validation coefficients of determination of 0.82, 0.66, 0.75, 0.74, and 0.71 and root-mean-square errors of 1.64, 2.30, 6.61, 5.99, and 4.29 $\mu g/m^3$ for BC, Cl^-, NO_3^-, SO_4^{2-}, and NH_4^+, respectively, on a daily basis. Organic matter (OM) was approximately estimated as the difference between total $PM_{2.5}$ and the sum of the 5 main components. Annual concentrations of $PM_{2.5}$ and its 6 components were assigned to each participant by linking the geocodes of the study clinics where they were recruited using 1 × 1 km grid cells. In the primary analyses, we used moving 3-year average concentrations as time-varying variables, which were calculated as the mean concentrations over the 3 preceding years relative to the index year, to account for the long-term variation over the study period.

OUTCOME ASCERTAINMENT. All participants were followed immediately after completing the baseline survey. Disease, death, and hospitalization events were ascertained via electronic links to local disease and death registry systems, the national health insurance database, and the first-page information database of inpatient medical records, supplemented by active follow-up with annual checks. Individuals who moved out of their baseline cities were considered lost to follow-up, with a proportion of <1%. All events were coded using the International Classification of Diseases-10th Revision. The prespecified primary outcome was total CVD (codes I00-I99), defined as the occurrence of the first CVD event. To investigate subtype-specific associations, we designated several secondary outcomes, including ischemic heart disease (codes I20-I25), ischemic stroke (code I63), hemorrhagic stroke (codes I60-I62), and other cerebrovascular diseases excluding the aforementioned major stroke subtypes (codes I64-I69).

COVARIATE ASSESSMENT. The moving 3-year average ambient temperature and relative humidity for study clinics were derived from the CHAP[32] and HiMIC-Monthly[33] data sets, respectively, and incorporated as time-varying variables to account for potential confounding by meteorological factors. Participants were interviewed to complete baseline questionnaires that collected information on sociodemographic characteristics (sex, age, highest level of education, household income, and occupation), lifestyle factors (tobacco smoking, alcohol consumption, dietary habits of red meat, fresh vegetables, and fresh fruits, physical activity, and leisure sedentary time), exposure to passive smoking (weekly hours of secondhand smoke exposure and years of living with a smoker), indoor air pollution (solid fuel use for cooking and heating and cookstove ventilation in the past 3 residences), self-rated health status, and personal and family medical histories. The Supplemental Methods provide a detailed description of the assessment of covariates. Anthropometric measurements, including height (meters), weight (kilograms), and waist circumference (WC; centimeters) were taken on site by trained staff members following standardized protocols and using calibrated instruments. BMI (kg/m^2) was calculated by dividing weight by the square of standing height.

STATISTICAL ANALYSIS. We divided the participants into high- and low-exposure groups according to the rounded median of average concentrations of $PM_{2.5}$ from 2004 to 2021. Baseline characteristics are expressed as mean ± SD (continuous variables) or percentages (categorical variables), adjusted for sex, age, and study areas. Spearman's rank tests were used to test the pairwise correlations among components.

Person-years of follow-up were calculated from the date of recruitment until the date of specific CVD outcomes, death, loss to follow-up, or December 31, 2022 (whichever came first). In single-component analyses, time-varying Cox proportional hazards models were used to estimate the marginal associations of long-term exposure to $PM_{2.5}$ and its components with incident CVD risk, without adjustment for other correlated components or total $PM_{2.5}$ mass. HRs and 95% CIs were estimated per IQR increase in $PM_{2.5}$ and its components for total CVD, ischemic heart disease, ischemic stroke, hemorrhagic stroke, and

other cerebrovascular diseases. The proportional hazards assumption was tested using Schoenfeld residuals, and no violation was found. The models were stratified by 5-year age groups and 10 study areas, with age as the underlying timescale, and adjusted for potential confounders, including age; sex; education; household income; occupation; tobacco smoking; alcohol consumption; dietary habits of red meat, fresh vegetables, and fresh fruits; total physical activity levels; leisure sedentary time; fuel types for cooking and heating; cookstove ventilation at baseline residence; hours of secondhand smoke exposure per week; years living with a smoker; prevalent diabetes and hypertension; self-rated health status; family history of CVD; BMI; WC; and time-varying ambient temperature and relative humidity. The concentration-response relationships of $PM_{2.5}$ components with total CVD and specific CVD outcomes were plotted using restricted cubic splines with 3 knots at the 5th, 50th, and 95th centiles.

To test the robustness of the associations, sensitivity analyses were conducted by: 1) excluding participants who experienced CVD events within the first 2 years of follow-up; 2) changing the exposure time window and using the 1-year (lag 1), 2-year (lag 2), and 3-year (lag 3) averages prior to each calendar year as time-varying variables in the model to assess the lagged effects of exposure; 3) further adjusting for 3-year moving concentrations of NO_2 and O_3, derived from CHAP data sets[34-37]; and 4) further adjusting for the residuals of each component after regressing out total $PM_{2.5}$ mass. We also conducted subgroup analyses stratified by baseline characteristics, including sex, age, urban or rural residence, smoking categories, indoor heating pollution, cooking fuel type with ventilation, prevalent hypertension, general obesity defined by BMI, and central fatness defined by WC. Region-specific analyses were additionally performed across the 10 study areas. The heterogeneity of associations between subgroups was tested using Cochrane's *Q* test. Details regarding the residual model and region-stratified analyses are provided in the Supplemental Methods.

For component-proportion analyses, we replaced the absolute concentration of each $PM_{2.5}$ component with its respective proportion relative to the total $PM_{2.5}$ mass. We then adjusted for total $PM_{2.5}$ concentration to evaluate the associations between component proportions and the risk for CVD outcomes, conditional on a fixed total $PM_{2.5}$ mass.

Given that the proportions of the 6 components within $PM_{2.5}$ sum to 1, an increase in any one proportion necessarily entails a reduction in others. To address this compositional constraint, we applied isometric log-ratio transformation,[24] thereby facilitating subsequent substitution analysis. Substitution analyses were performed using Cox proportional hazards models to evaluate changes in CVD risk associated with hypothetically reallocating proportions among $PM_{2.5}$ components, while keeping total $PM_{2.5}$ mass constant. The primary analysis used a one-to-one substitution strategy, estimating the effect of substituting one component with an equal proportion of another. The results are reported as HRs (95% CIs) for a 1% proportional exchange. We also complemented a one-to-others substitution analysis to assess the effect of increasing a single component by 1%, offset by a decrease in all other components weighted by their relative proportions in the geometric mean composition. Detailed methods are provided in the Supplemental Appendix.

Given the inherent coupling of NH_4^+ with SO_4^{2-} and NO_3^-, governed by atmospheric ionization equilibrium and charge neutrality, their associations based on ion equivalents were comparable in our supplementary analyses. To avoid potential misinterpretation, NH_4^+ was excluded from the single-component analyses; in the substitution analyses, its proportion was held constant, while reallocations were performed among the remaining components.

Statistical significance for the primary outcome was set at $P < 0.05$ using a 2-sided test, with the Benjamini-Hochberg false discovery rate correction applied for CVD subtypes in main analyses. All statistical analyses were performed using R version 4.2.3 (R Foundation for Statistical Computing).

RESULTS

BASELINE CHARACTERISTICS OF PARTICIPANTS. The mean $PM_{2.5}$ concentration across 10 study areas between 2001 and 2021 was 54.4 ± 13.2 $\mu g/m^3$, ranging from 23.9 ± 4.6 $\mu g/m^3$ in Haikou to 81.7 ± 15.8 $\mu g/m^3$ in Henan (Supplemental Figure 2). Annual concentrations of $PM_{2.5}$ and its components have shown a declining trend since 2013 (Supplemental Figure 3). Moderate to high correlations were observed between $PM_{2.5}$ and its components, with pairwise Spearman correlation coefficients ranging from 0.48 to 0.91 (Supplemental Figure 4). The mean proportions of the 6 components in total $PM_{2.5}$, ranked in descending order, were 38.8% for OM, 19.8% for SO_4^{2-}, 17.6% for NO_3^-, 12.0% for NH_4^+, 7.9% for BC, and 3.9% for Cl^-, with the proportion of OM decreasing by year in most study areas (Supplemental Figure 5). The study participants

TABLE 1 Baseline Characteristics of Cohort Participants by Median $PM_{2.5}$ Concentration

	All Participants (N = 487,037)	Average $PM_{2.5}$ From 2004 to 2021	
		<54 μg/m³ (n = 273,373)	≥54 μg/m³ (n = 213,664)
Age, y	51.5 ± 10.5	51.7 ± 10.6	51.3 ± 10.4
Female	59.1	58.9	59.3
Urban areas	43.1	44.2	41.7
High school or higher	20.7	19.1	23.3
Household income >20,000 RMB/y	42.8	44.1	40.8
Current smokers or quitters because of illness	29.4	29.4	29.3
Heavy alcohol consumers[a]	6.9	7.2	6.7
Daily consumers of			
Fresh fruits	18.3	17.4	19.4
Fresh vegetables	94.7	94.3	96.4
Red meat	29.0	28.0	30.5
Total physical activity, MET-h/d	21.6 ± 13.9	22.5 ± 13.7	20.4 ± 14.1
Leisure sedentary time, h/wk	21.0 ± 10.8	20.5 ± 10.0	21.7 ± 11.5
BMI, kg/m²	23.6 ± 3.4	23.5 ± 3.3	23.7 ± 3.3
WC, cm	80.0 ± 9.7	79.7 ± 9.7	80.6 ± 9.6
Heating with solid fuels at baseline residence	36.6	40.6	30.3
Cooking with solid fuels at baseline residence	34.8	38.3	30.8
Years living with smokers	22.7 ± 18.5	23.1 ± 18.3	22.3 ± 18.4
Secondhand smoke exposure, h/wk	6.8 ± 9.7	6.8 ± 8.3	6.8 ± 11.1
Self-rated good health	47.1	47.2	47.0
Prevalence of diabetes	5.4	5.0	5.9
Prevalence of hypertension	33.7	34.7	32.5
Family history of cardiovascular diseases	20.0	19.7	20.3
Average concentrations of $PM_{2.5}$ components from 2004 to 2021, μg/m			
BC	4.3 ± 1.5	4.0 ± 0.7	4.8 ± 1.3
OM	21.2 ± 6.1	20.5 ± 4.7	22.0 ± 5.6
Cl^-	2.1 ± 0.8	2.0 ± 0.5	2.2 ± 0.7
NO_3^-	9.6 ± 3.3	9.4 ± 2.8	9.8 ± 2.8
SO_4^{2-}	10.8 ± 2.7	10.7 ± 1.7	11.0 ± 3.2
NH_4^+	6.5 ± 1.8	6.4 ± 1.2	6.6 ± 1.9
Average temperature from 2004 to 2021, °C	15.8 ± 4.5	15.6 ± 4.4	16.1 ± 4.1
Average relative humidity from 2004 to 2020, %	71.4 ± 6.8	72.3 ± 5.5	70.2 ± 7.6

Values are mean ± SD or %. All means and percentages in the two groups were adjusted for age, sex, and 10 study areas, with the exception of these 3 variables. SDs are unadjusted values. All *P* values for between-group comparisons were <0.05, except for smoking category ($P = 0.357$), secondhand smoke exposure ($P = 0.838$), and self-rated health ($P = 0.682$). [a]Heavy alcohol consumption was defined as daily intake of ≥30 g pure alcohol or being a former weekly drinker.

BC = black carbon; BMI = body mass index; Cl^- = chloride; MET = metabolic equivalent of task; NH_4^+ = ammonium; NO_3^- = nitrate; OM = organic matter; $PM_{2.5}$ = particulate matter with diameters <2.5 μm; SO_4^{2-} = sulfate; WC = waist circumference.

(n = 487,037) had a mean age of 51.5 ± 10.5 years, with 59.1% being women. Those exposed to median or higher levels of $PM_{2.5}$ were more likely to live in rural areas (Table 1).

ASSOCIATIONS BETWEEN $PM_{2.5}$ COMPONENTS AND CVD RISK. During a median follow-up period of 15.1 years (6,260,716 person-years), a total of 196,224 incident CVD cases were identified, including 72,747 cases of ischemic heart disease, 74,594 cases of ischemic stroke, 17,553 cases of hemorrhagic stroke, and 54,306 cases of other cerebrovascular diseases (Supplemental Table 1).

In single-component analyses, long-term exposure to $PM_{2.5}$ and its components was consistently associated with an increased risk for overall CVD, ischemic heart disease, ischemic stroke, and other cerebrovascular diseases. For total CVD, the HRs per IQR increase were 1.15 (95% CI: 1.13-1.17) for BC, 1.17 (95% CI: 1.15-1.18) for OM, 1.28 (95% CI: 1.25-1.32) for Cl^-, 1.29 (95% CI: 1.24-1.33) for NO_3^-, and 1.23 (95% CI: 1.20-1.25) for SO_4^{2-}, respectively (Table 2). In the primary analysis, no statistically significant associations were observed between $PM_{2.5}$ or OM and hemorrhagic stroke. However, positive associations of $PM_{2.5}$ and all components with cause-specific CVD

TABLE 2 Associations Between a Per IQR Increase in $PM_{2.5}$ and Its Components and the Incidence of Cardiovascular Disease, Ischemic Heart Disease, Ischemic Stroke, Hemorrhagic Stroke, and Other Cerebrovascular Diseases

		Cardiovascular Disease (n = 196,224)		Ischemic Heart Disease (n = 72,747)		Ischemic Stroke (n = 74,594)		Hemorrhagic Stroke (n = 17,553)		Other Cerebrovascular Diseases (n = 54,306)	
	IQR, μg/m³	HR (95% CI)	*P* Value	HR (95% CI)	P_{FDR}	HR (95% CI)	P_{FDR}	HR (95% CI)	P_{FDR}	HR (95% CI)	P_{FDR}
$PM_{2.5}$	19.7	1.20 (1.18-1.21)	<0.001	1.17 (1.14-1.20)	<0.001	1.12 (1.09-1.15)	<0.001	1.04 (0.99-1.10)	0.126	1.29 (1.25-1.33)	<0.001
BC	2.2	1.15 (1.13-1.17)	<0.001	1.12 (1.09-1.15)	<0.001	1.17 (1.13-1.20)	<0.001	1.08 (1.02-1.15)	0.006	1.21 (1.17-1.24)	<0.001
OM	10.7	1.17 (1.15-1.18)	<0.001	1.14 (1.11-1.16)	<0.001	1.09 (1.07-1.12)	<0.001	1.01 (0.96-1.06)	0.784	1.27 (1.24-1.30)	<0.001
Cl^-	1.2	1.28 (1.25-1.32)	<0.001	1.30 (1.25-1.35)	<0.001	1.27 (1.22-1.32)	<0.001	1.12 (1.02-1.22)	0.014	1.45 (1.38-1.52)	<0.001
NO_3^-	6.0	1.29 (1.24-1.33)	<0.001	1.30 (1.23-1.38)	<0.001	1.12 (1.06-1.19)	<0.001	1.14 (1.02-1.28)	0.023	1.43 (1.34-1.52)	<0.001
SO_4^{2-}	4.1	1.23 (1.20-1.25)	<0.001	1.21 (1.17-1.25)	<0.001	1.13 (1.09-1.17)	<0.001	1.10 (1.02-1.18)	0.009	1.24 (1.20-1.29)	<0.001

Moving 3-year average concentrations of each $PM_{2.5}$ component were included as time-dependent variables in Cox proportional hazards models stratified by 5-year age groups and 10 study areas. The models were adjusted for age (years); sex (male or female); education (no formal school, primary school, middle school, high school, technical school or college, or university); household income (<2,500, 2,500-4,999, 5,000-9,999, 10,000-19,999, 20,000-34,999, or ≥35,000 RMB/y); occupation (agriculture and related workers, factory workers, administrators or managers, professional or technical workers, sales and service workers, retired, self-employed, house wife or husband, unemployed, or others); tobacco smoking (never smokers, smoking quitters for reasons other than illness, quitters because of illness, or current smokers [1-9, 10-19, or ≥20 cigarettes or equivalent per day]); alcohol consumption (nonregular or nonweekly drinkers, former weekly drinkers, weekly but not daily drinkers, and daily drinkers [<30, 30-59, or ≥60 of pure alcohol per day]); consumption of red meat, fresh fruits, and fresh vegetables (days per week; assigning according to the midpoint of each frequency category); total physical activity level (MET-h/d); leisure sedentary time (h/d); fuel types for cooking (clean fuels, solid fuels, other fuels, or no monthly cooking) and fuel types for heating (clean fuels, solid fuels, other fuels or no heating in the winter) at the baseline residence; cookstove ventilation at the baseline residence (yes or no); secondhand smoke exposure (h/d); years living with a smoker; body mass index (kg/m²); waist circumference (centimeters); prevalent diabetes (yes or no); prevalent hypertension (yes or no); family medical history of cardiovascular diseases (yes or no); self-rated health status (excellent, good, fair, or poor); and moving 3-year average temperature (degrees Celsius) and relative humidity (percentage).

P_{FDR} = *P* value adjusted by false discovery rate correction; other abbreviations as in Table 1.

events were detected when incident cases occurring within the first 2 years of follow-up were excluded (Supplemental Tables 1 and 2). Other sensitivity analyses did not substantially alter the primary results (Supplemental Tables 3 to 6). Subgroup analyses revealed that women, urban residents, and noncurrent smokers had a higher risk for incident CVD associated with $PM_{2.5}$ components than their counterparts (Supplemental Figures 6 and 7). We observed regional heterogeneity in $PM_{2.5}$-CVD associations across study areas (Supplemental Table 7). The I^2 value decreased from 94.9% to 71.6% after including component concentrations as meta-predictors and further declined to 64.5% after adding component proportions ($P < 0.001$ for both) (Supplemental Table 8).

The incidence of total CVD and ischemic stroke increased in an approximately linear manner with exposure to BC and OM. In contrast, the concentration-response relationships between inorganic ions and CVD were nonlinear, showing a linear rise at lower concentrations and attenuated growth around the median level (**Figure 1**). All $PM_{2.5}$ chemical components exhibited generally monotonic positive associations with the incidence of ischemic heart disease, although the risk associated with SO_4^{2-} plateaued at higher exposure levels. Apart from OM, other $PM_{2.5}$ components showed nearly linear relationships with the incidence of hemorrhagic stroke.

ASSOCIATIONS BETWEEN $PM_{2.5}$ COMPONENT PROPORTIONS AND CVD RISK. In component-proportion models conditional on fixed total $PM_{2.5}$ mass, higher relative proportions of BC, Cl^-, and SO_4^{2-} were each positively associated with the risk for ischemic stroke, with HRs per IQR increase in proportion of 1.04 (95% CI: 1.01-1.06), 1.07 (95% CI: 1.04-1.11), and 1.11 (95% CI: 1.07-1.15), respectively (**Table 3**). The latter inorganic ions were also associated with an increased risk for ischemic heart disease, with effect sizes similar to those observed for stroke.

SUBSTITUTION ANALYSES. Substituting 1% of any other $PM_{2.5}$ component with Cl^- was associated with an increased risk for incident CVD. The strongest associations were observed when NO_3^- was replaced, with corresponding HRs of 1.08 (95% CI: 1.05-1.10) for CVD, 1.07 (95% CI: 1.03-1.11) for ischemic heart disease, and 1.15 (95% CI: 1.11-1.19) for ischemic stroke (**Figure 2**). In terms of other major anions, substituting NO_3^- with SO_4^{2-} also was associated with an elevated risk for multiple CVD outcomes. Substituting BC for any component other than Cl^- was associated with an increased risk for ischemic stroke, with HRs of 1.01 (95% CI: 1.00-1.02), 1.08 (95% CI: 1.06-1.09), and 1.02 (95% CI: 1.00-1.04) for replacing 1% of OM, NO_3^-, and SO_4^{2-}, respectively. In contrast, associations for hemorrhagic stroke were observed only for substitutions involving SO_4^{2-}. Supplemental Figure 8 illustrates a clear positive exposure-response relationship, wherein increasing the substitution proportion of Cl^- or BC corresponded to progressively higher risk for specific CVD outcomes. For Cl^- and BC, an increase in relative proportion, offset by a proportional reduction in other components, was consistently associated with an elevated risk for incident CVD (Supplemental Table 9).

DISCUSSION

This large cohort study of Chinese adults revealed that long-term exposure to $PM_{2.5}$ components was associated with an increased risk for CVD and its major subtypes. The magnitude of this risk varied according to compositional shifts; specifically, higher proportions of Cl^-, SO_4^{2-}, and BC were linked to elevated risk for specific CVD outcomes.

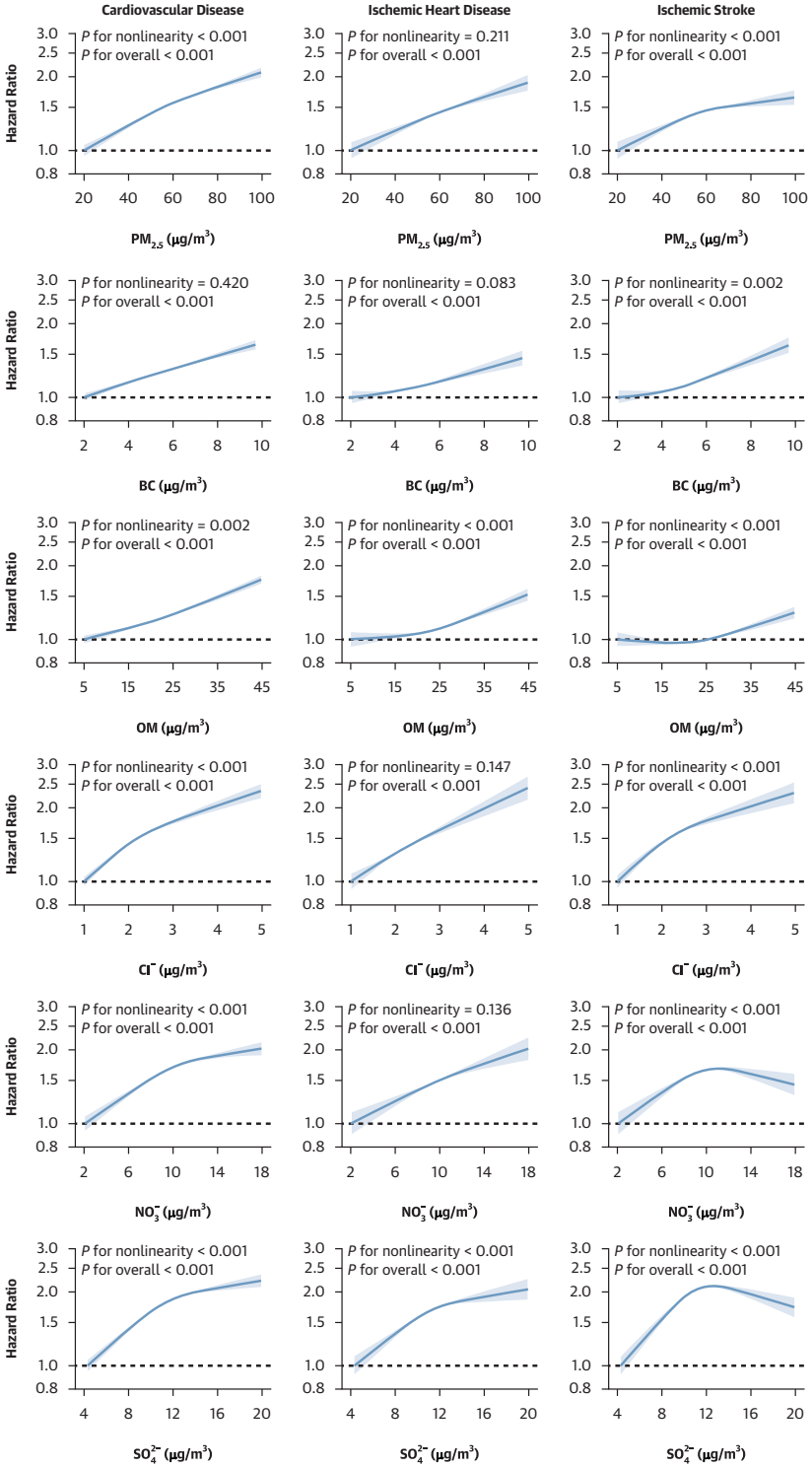
A previous study conducted in the highly polluted Beijing-Tianjin-Hebei region of China (mean $PM_{2.5}$ 71.7 ± 15.0 μg/m^3) followed 26,851 adults over a mean period of 2.1 years and documented 629 self-reported CVD hospitalizations.[17] Carbonaceous components (ie, BC and OM), but not inorganic ions (ie, NO_3^-, SO_4^{2-}, and NH_4^+), were associated with an increased risk for CVD. Conversely, the China Family Panel Study involved 14,331 participants across 25 provinces in 2010 and recorded 1,575 CVD and 342 stroke incidents via standard questionnaires during 3 biennial follow-up surveys.[18] This study reported positive associations between county-level $PM_{2.5}$ inorganic ions and BC, apart from OM, and self-reported total CVD. In terms of CVD major subtypes, none of the constituents was associated with incident stroke in the aforementioned study.[18] Another subcohort from the China Multi-Ethnic Cohort (2018) included 14,427 participants from Sichuan Province (mean $PM_{2.5}$ 55.2 ± 5.2 μg/m^3).[16] By 2021, a total of 1,837 incident CVD cases had been identified through hospital-based surveillance systems. BC, Cl^-, and NO_3^- were each positively associated with risk for both ischemic heart disease and cerebrovascular diseases. In contrast, OM and SO_4^{2-} showed positive associations with cerebrovascular diseases but no associations with ischemic heart disease. The inconsistent results may be attributed to the regional heterogeneity, which implies variations in pollution composition and underlying emission sources. Specifically, particulate matter in the heavily industrialized Beijing-Tianjin-Hebei region originates primarily from industry, followed by the residential sector.[38] In contrast, in the Sichuan Basin, residential sources are the dominant anthropogenic contributor to local $PM_{2.5}$, with industrial sources being secondary and other sources remaining minor.[39] Furthermore, the generalizability of the aforementioned findings may be constrained by the inability of short follow-up to assess long-term risk and the potential for recall bias from self-reported outcomes. The aforementioned cohort studies did not examine the association between Cl^- and incident CVD risk. However, a 22-year cohort study conducted in 4 northern Chinese cities revealed a positive association between Cl^- and cardiovascular mortality.[40]

The present study, based on a median follow-up period of 15 years, identified a substantial number of incident CVD cases. The results demonstrated consistent positive associations between long-term exposure to all $PM_{2.5}$ components and both total CVD and its 2 major subtypes among Chinese adults. Additionally, the study revealed an approximately linear concentration-response relationship for carbonaceous components with respect to CVD incidence, whereas inorganic ions exhibited a nonlinear association characterized by a linear rise at lower concentrations and attenuated growth around the median level. These distinct exposure-response patterns align with the exposure-response functions for $PM_{2.5}$ and mortality summarized in the World Health Organization air quality guideline[41] and the GBD (Global Burden of Disease) study.[42] Extending previous findings, we conducted an exploratory 2-stage meta-analysis across the 10 CKB study areas, which not only revealed substantial regional heterogeneity but also helped disentangle its underlying sources. Our results indicate that although absolute concentrations and meteorological factors contribute to heterogeneity for individual components, the relative proportions of $PM_{2.5}$ components are the predominant factor explaining geographic differences in health effects of total $PM_{2.5}$.

Despite their public health significance, the health effects of $PM_{2.5}$ component proportions remained underexplored. In the UK Biobank, higher baseline proportions of BC and SO_4^{2-} were each associated with an increased risk for incident myocardial infarction; however, these analyses did not adjust for total $PM_{2.5}$ mass or other components.[43] A meta-analysis of 210 cities across 16 countries in North America, Europe, and Asia confirmed the short-term association of 2-day average $PM_{2.5}$ with mortality, while demonstrating divergent risk trends according to composition: mortality risk increased with higher SO_4^{2-} proportion, decreased with higher NO_3^- proportion, and remained flat for carbonaceous components (BC and organic carbon) regardless of their relative proportions.[22] We extend these findings by revealing that, conditional on a fixed total $PM_{2.5}$ mass, higher proportions of Cl^-, SO_4^{2-}, and BC were associated with an increased risk for ischemic stroke, while inorganic ions were specifically linked to ischemic heart disease.

Furthermore, our study innovatively applied substitution analysis to examine the health effects of relative proportions of $PM_{2.5}$ components. This

FIGURE 1 Concentration-Response Relationships of $PM_{2.5}$ and Its Components With the Incidence of Cardiovascular Disease, Ischemic Heart Disease, Ischemic Stroke, Hemorrhagic Stroke, and Other Cerebrovascular Diseases



Moving 3-year average concentrations of particulate matter with diameters ≤2.5 μm ($PM_{2.5}$) and its components were included as time-dependent variables in Cox proportional hazards models stratified by 5-year age groups and 10 study areas, respectively. The models were adjusted for the same covariates as those in Table 2. The solid line represents the HR, and the gray ribbon represents the 95% CI. BC = black carbon; Cl^- = chloride; NO_3^- = nitrate; OM = organic matter; SO_4^{2-} = sulfate.

Continued on the next page

FIGURE 1 Continued

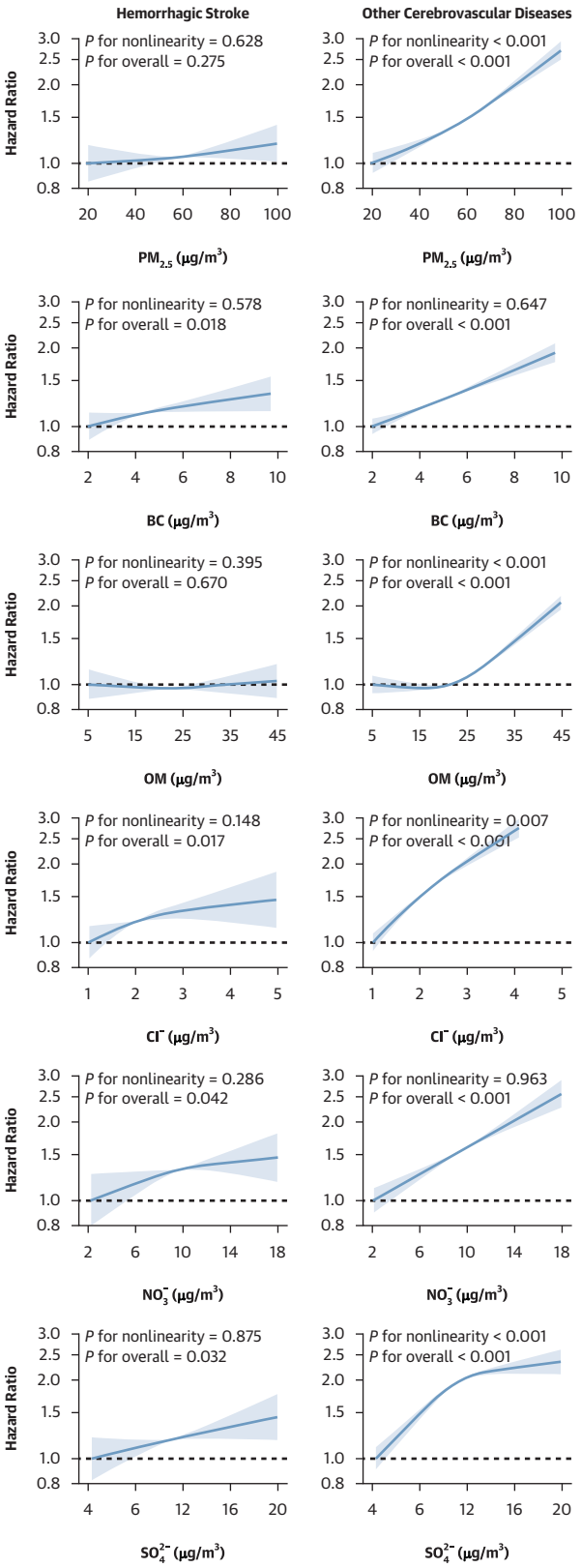


TABLE 3 Associations Between a Per IQR Increase in $PM_{2.5}$ Component Proportions and the Incidence of Cardiovascular Disease, Ischemic Heart Disease, Ischemic Stroke, Hemorrhagic Stroke, and Other Cerebrovascular Diseases

		Cardiovascular Disease (n = 196,224)		Ischemic Heart Disease (n = 72,747)		Ischemic Stroke (n = 74,594)		Hemorrhagic Stroke (n = 17,553)		Other Cerebrovascular Diseases (n = 54,306)	
	IQR (%)	HR (95% CI)	*P* Value	HR (95% CI)	P_{FDR}	HR (95% CI)	P_{FDR}	HR (95% CI)	P_{FDR}	HR (95% CI)	P_{FDR}
BC	2.8	1.00 (0.99-1.02)	0.714	0.99 (0.97-1.02)	0.657	1.04 (1.01-1.06)	0.002	1.05 (1.00-1.10)	0.057	0.99 (0.96-1.02)	0.460
OM	7.8	0.98 (0.97-1.00)	0.045	0.93 (0.90-0.95)	<0.001	0.93 (0.90-0.95)	<0.001	0.91 (0.86-0.96)	0.002	0.94 (0.92-0.97)	<0.001
Cl^-	1.2	1.03 (1.01-1.05)	0.013	1.06 (1.03-1.10)	0.001	1.07 (1.04-1.11)	<0.001	1.11 (1.03-1.20)	0.007	1.09 (1.05-1.14)	<0.001
NO_3^-	6.7	0.94 (0.90-0.97)	0.001	1.07 (1.01-1.14)	0.029	0.96 (0.91-1.01)	0.136	1.10 (0.96-1.25)	0.161	1.02 (0.96-1.09)	0.489
SO_4^{2-}	3.9	1.01 (0.99-1.04)	0.330	1.14 (1.09-1.19)	<0.001	1.11 (1.07-1.15)	<0.001	1.15 (1.05-1.25)	0.002	1.04 (0.99-1.09)	0.126

The respective proportions of $PM_{2.5}$ components in the overall $PM_{2.5}$ concentrations were included as time-dependent variables in Cox proportional hazards models stratified by 5-year age groups and 10 study areas. The models were adjusted for the same covariates as those in Table 2 and further adjusted for moving 3-year average concentrations of $PM_{2.5}$ (time-varying variables).

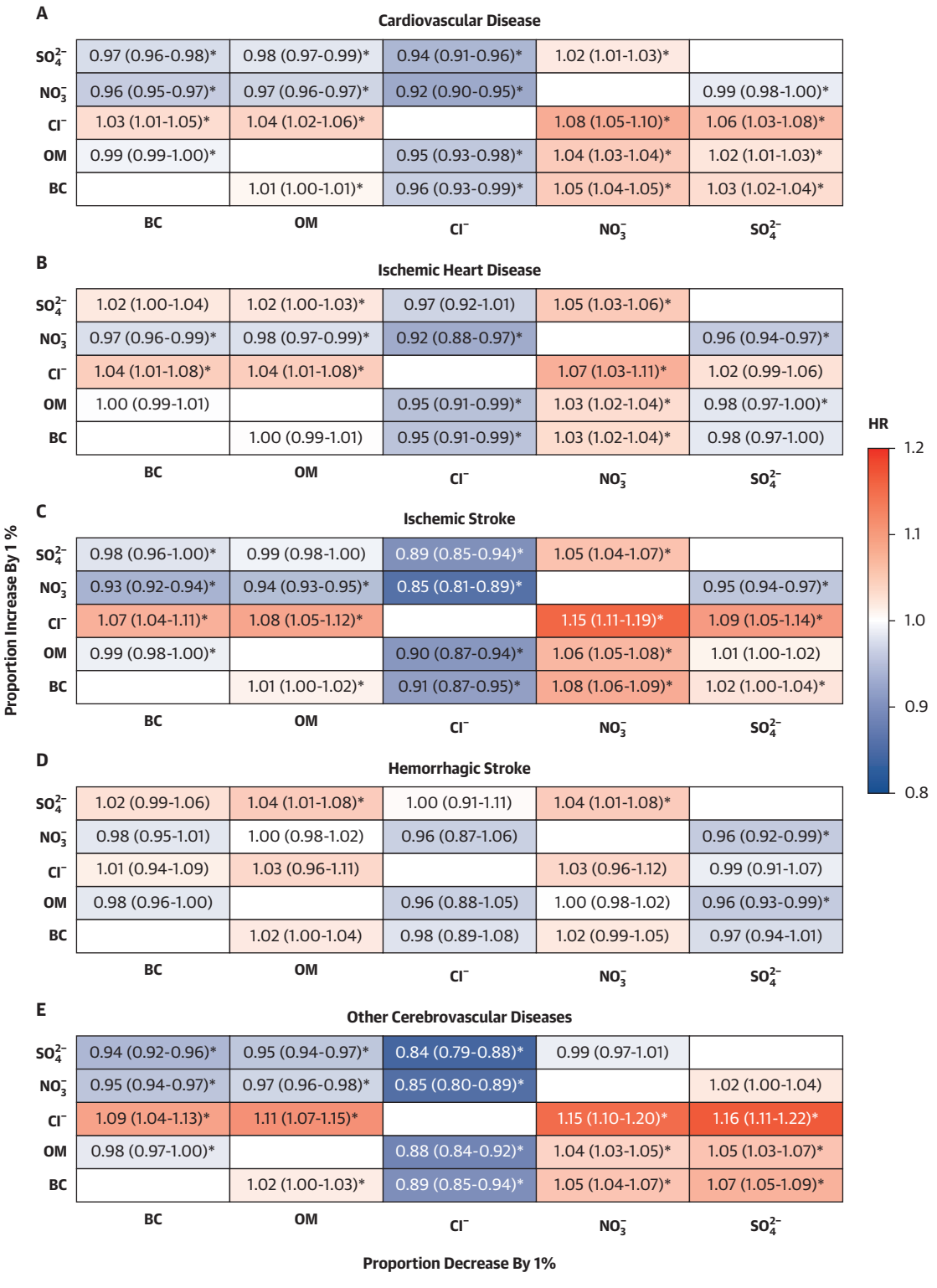
Abbreviations as in Tables 1 and 2.

approach uses isometric log-ratio transformation to address the closure effect inherent in compositional data, thereby simulating health risks associated with pairwise component substitutions under a constant total $PM_{2.5}$ mass. We found that increasing the relative proportions of Cl^-, BC, and SO_4^{2-} was associated with higher risk for various CVD subtypes. In contrast, higher proportions of NO_3^- and OM were associated with a reduced risk for ischemic heart disease and stroke. These findings provide population-based evidence on component-specific CVD risks, challenging the "equitoxicity" assumption, which may lead to over- or underestimation of disease burden attributable to specific emission sources, depending on the relative toxicity profiles of emitted components.[44] Although the substitution analysis uses a simplified statistical framework rather than directly simulating actual air quality intervention scenarios, the resulting theoretical risk estimates offer valuable public health insight. Specifically, our findings indicate that compositional shifts, which mirror real-world modifications in emission sources, can yield cardiovascular benefits independent of reductions in total $PM_{2.5}$ levels. This perspective is highly pertinent for regions such as China, where achieving further declines in total mass is increasingly difficult, and public health objectives need to be carefully weighed against economic realities.[3] Our study provide actionable insights for health-oriented air quality policies by identifying a hazardous compositional profile enriched with Cl^-, BC, or SO_4^{2-}. Because this profile is characteristic of fossil fuel-heavy industrial regions, targeted interventions such as structural transition and clean coal use may be effective.

Consistent with the China-PAR study,[45] our study observed stronger associations between $PM_{2.5}$ components and CVD among non-current smokers. A plausible explanation lies in the shared pathogenic pathways (eg, oxidative stress, inflammation) between smoking and $PM_{2.5}$ exposure. Smoking exerts a more dominant influence on CVD risk compared with air pollutants.[46] In current smokers, the overriding role of smoking may diminish the additional effect of $PM_{2.5}$ and its components.[45]

Several biological mechanisms have been proposed to explain the adverse effects of $PM_{2.5}$ on cardiovascular homeostasis, including systemic inflammation, oxidative stress, and epigenetic changes, which collectively contribute to endothelial dysfunction, thrombosis, atherosclerosis, and cardiovascular injury.[47-49] Specifically, BC can induce cardiac inflammation and metabolic gene dysregulation,[50] disturb cardiac autonomic function and heart rate variability in mice,[51] and cause mitochondrial or autophagic damage in human endothelial cells in vitro,[52] indicating both structural and functional pathways. Hydrophobic organic compounds are characterized by environmental persistence, bioaccumulation, and lipid solubility, properties that may enable them to act as endocrine disruptors and lead to cardiac dysfunction.[53] Polycyclic aromatic hydrocarbons, the most ubiquitous organic contaminants in $PM_{2.5}$, have been shown to induce inflammatory cell infiltration, fibrosis, and cardiomyocyte hypertrophy in mice[54] and to increase macrophage content in atherosclerotic plaques.[55] Unlike in most regions, where Cl^- is predominantly marine derived, Cl^- in China is primarily anthropogenic, originating mainly from coal and biomass combustion and industrial processes.[56,57] Cl^- participates in atmospheric chemical reactions,[58] enhances the oxidative potential of particulate matter,[59] and increases circulating inflammatory biomarkers.[60] Secondary inorganic aerosols (ie, NO_3^-, SO_4^{2-}, and NH_4^+), which are commonly present in particulate matter as ammonium sulfate and ammonium nitrate, have been shown to increase messenger RNA expression of

FIGURE 2 Association Between Substituting 1% of One $PM_{2.5}$ Component With Another and the Incidence of Cardiovascular Disease, Ischemic Heart Disease, Ischemic Stroke, Hemorrhagic Stroke, and Other Cerebrovascular Diseases



Substitution Cox regression models were stratified by 5-year age groups and 10 study areas and adjusted for the same covariates as those in Table 3. The values in the table represent HRs and 95% CIs for cardiovascular disease outcomes, derived from substitution models that estimated the effect of replacing 1% of one $PM_{2.5}$ component with an equal amount of another, while keeping total $PM_{2.5}$ concentrations constant. *P value (adjusted by false discovery rate correction) < 0.05. Abbreviations as in Figure 1.

proinflammatory cytokines in the heart[61] and to aggravate myocardial cell apoptosis in murine models.[62] SO_4^{2-} is a key driver of oxidative potential by promoting the formation of highly acidic aerosols that facilitate the dissolution of soluble metals,[63] whereas NH_4^+ itself is not considered directly toxic, exhibiting no significant respiratory effects in mice.[64] Given the coexistence and high correlations among $PM_{2.5}$ components, further research is warranted to elucidate the mechanisms underlying cardiovascular damage induced by specific particulate constituents.

STUDY STRENGTHS. The extended follow-up period, combined with multisource outcome ascertainment, facilitated the identification of a large number of incident cases and provided sufficient statistical power to detect associations across the general population, major CVD subtypes, and crucial subgroups. Individual-level exposure concentrations were estimated using high spatiotemporal resolution models, effectively capturing long-term exposure variations in $PM_{2.5}$ exposure. To our knowledge, our study represents the first application of substitution analysis in the context of $PM_{2.5}$ composition research. This method, originally developed for modeling reallocations in physical activity time[65] and dietary patterns,[66] allowed us to quantify how hypothetical adjustments in $PM_{2.5}$ component proportions alter CVD risk. Consequently, it offers an intuitive way to interpret the health implications of varied $PM_{2.5}$ compositions.

STUDY LIMITATIONS. First, OM was estimated indirectly by subtracting the concentrations of 5 major components from the total $PM_{2.5}$, rather than through direct measurement or the commonly adopted organic carbon-to-OM conversion approach. This residual-based calculation may inadvertently include unaccounted constituents, such as trace metals or additional inorganic species, potentially leading to an overestimation of OM.

Second, because of limited availability of ground-based measurement data, certain CVD-related constituents, such as heavy metals,[11] were not incorporated in our analyses. However, a nationwide study across 50 Chinese cities (2014-2021) reported that Fe exhibited the highest concentration among detected metals, with its proportion in $PM_{2.5}$ increasing from 0.19% to 1.40%, while the proportions of other metals (ie, Pb, As, Mn, Ni, Cr, Cd, Zn, and Cu) consistently decreased over the same period.[67] These findings suggest that heavy metals collectively constitute a minimal fraction of total $PM_{2.5}$[68] and are therefore unlikely to have a substantial influence on our results.

Third, $PM_{2.5}$ component concentrations were assigned to participants according to their nearest clinic locations, which may have introduced nondifferential misclassification. Furthermore, unaccounted residential address migration may also introduce exposure misclassification. However, this impact is likely minimal: approximately 1% of participants had intra-area mobility,[69] while fewer than 1% relocated outside their baseline cities and were classified as lost to follow-up.

Fourth, to balance model complexity and interpretability, our analyses do not account for potential synergistic or antagonistic effects among $PM_{2.5}$ components, despite their shared sources and plausible interactive pathways. Future studies integrating source apportionment with advanced statistical methods are warranted to better characterize interactions within compositional data.

Finally, the observed associations may inherently involve cohort-period interactions and temporal shifts in disease spectrum or health care access and should therefore be interpreted as average period effects rather than invariant effects.

CONCLUSIONS

This large prospective cohort study among Chinese adults demonstrates that long-term exposure to $PM_{2.5}$ components was positively associated with risk for CVD and its major subtypes, with this risk varying by compositional shifts. Our findings highlight the necessity of targeted pollution control strategies that prioritize specific, high hazardous $PM_{2.5}$ components, namely, Cl^-, BC, and SO_4^{2-}. This evidence advocates for a paradigm shift in air quality management, advancing a dual approach that integrates "mass concentration control" with "toxicity risk control." Future studies quantifying the health effects of source-specific $PM_{2.5}$ components will be essential to further guide prioritized regulatory interventions.

DATA SHARING The CKB is a global resource for the investigation of lifestyle, environmental, blood biochemical, and genetic factors as determinants of common diseases. The CKB study group is committed to making the cohort data available to the scientific community in China, the United Kingdom, and worldwide to advance knowledge about the causes, prevention and treatment of disease. For detailed information on what data are currently available to open access users and how to apply for

it, visit https://www.ckbiobank.org/data-access. Researchers who are interested in obtaining the raw data from the CKB study that underlie this paper should contact pdc@kscdc.net. A research proposal will be requested to ensure that any analysis is performed by bona fide researchers and, where data are not currently available to open access researchers, is restricted to the topic covered in this paper.

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KEY WORDS **cardiovascular diseases, cohort study, $PM_{2.5}$ components, substitution models**

APPENDIX **For a list of the members of the steering committee and collaborative group, supplemental methods, supplemental results, supplemental figures, supplemental tables, and supplemental references, please see the online version of this paper.**