Long-Term Exposure to Fine Particulate Matter and Cardiovascular Disease in China

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ABSTRACT

BACKGROUND Evidence of the effects of long-term fine particulate matter (PM2.5) exposure on cardiovascular diseases (CVDs) is rare for populations exposed to high levels of PM2.5 in China and in other countries with similarly high levels.

OBJECTIVES The aim of this study was to assess the CVD risks associated with long-term exposure to PM2.5 in China.

METHODS A nationwide cohort study, China-PAR (Prediction for Atherosclerotic Cardiovascular Disease Risk in China), was used, with 116,972 adults without CVD in 2000 being included. Participants were followed until 2015. Satellite-based PM2.5 concentrations at 1-km spatial resolution during the study period were used for exposure assessment. A Cox proportional hazards model with time-varying exposures was used to estimate the CVD risks associated with PM2.5 exposure, adjusting for individual risk factors.

RESULTS Annual mean concentrations of PM2.5 at the China-PAR sites ranged from 25.5 to 114.0 μg/m³. For each 10 μg/m³ increase in PM2.5 exposures, the multivariate-adjusted hazard ratio was 1.251 (95% confidence interval: 1.220 to 1.283) for CVD incidence and 1.164 (95% confidence interval: 1.117 to 1.213) for CVD mortality. The slopes of concentration-response functions of PM2.5 exposure and CVD risks were steeper at high PM2.5 levels. In addition, older residents, rural residents, and never smokers were more prone to adverse effects of PM2.5 exposure.

CONCLUSIONS This study provides evidence that elevated long-term PM2.5 exposures lead to increased CVD risk in China. The effects are more pronounced at higher PM2.5 levels. These findings expand the current knowledge on adverse health effects of severe air pollution and highlight the potential cardiovascular benefits of air quality improvement in China and other low- and middle-income countries. (J Am Coll Cardiol 2020;75:707–17) © 2020 by the American College of Cardiology Foundation.
As the leading cause of mortality, cardiovascular diseases (CVDs) were responsible for 17.6 million deaths in 2016, which was estimated to account for 32.3% all-cause global deaths (1). CVD mortality increased by 58.5% from 1990 to 2016 in China, and this rapid increase imposes a heavy disease burden (2). Therefore, research focusing on risk factors of CVD is necessary to combat this widespread disease.

Fine particulate matter (PM$_{2.5}$) consists of airborne particles with an aerodynamic diameter of ≤2.5 µm. Exposure to ambient PM$_{2.5}$ is currently ranked fifth among all risk factors contributing to global deaths in 2015 (3). With increasing energy consumption over the past few decades, high exposure of PM$_{2.5}$ pollution has become a serious concern in China because of its implications for public health. Associations between long-term exposure to PM$_{2.5}$ and CVD risk have been investigated in both Europe and the United States (4,5), with concentration-response (C-R) functions proposed (6,7). However, little is known with respect to highly polluted countries such as China. Although Burnett et al. (8) developed a model of relationships between long-term PM$_{2.5}$ exposure and mortality that covered the global range of PM$_{2.5}$ exposure, some uncertainties still exist, because limited evidence from regions with severe air pollution was available.

A major challenge to longitudinal studies on the health effects of PM$_{2.5}$ in China is the absence of PM$_{2.5}$ measurements before the establishment of the ground monitoring network in 2013. To support such studies, spatial statistical models driven by satellite-retrieved aerosol optical depth (AOD) have been proposed to provide long-term estimates of PM$_{2.5}$, mainly since 2000, as well as filling spatial gaps between ground monitors (9,10). Most previous epidemiological studies in China adopted exposure data at relatively coarse spatial resolutions (e.g., 10 km) (11,12), which is likely to reduce exposure sensitivity and accuracy, thereby increasing the likelihood of misclassification in exposure assessment (13).

Incorporating high-quality PM$_{2.5}$ estimates at 1-km resolution with a well-established prospective cohort (14), we conducted a national scale study over a 16-year period to assess the long-term effects of PM$_{2.5}$ exposure on CVD incidence and mortality across the adult population in China.

**METHODS**

**STUDY POPULATION.** The China-PAR (Prediction for Atherosclerotic Cardiovascular Disease Risk in China) project was initiated to investigate the CVD epidemic and identify risk factors in the general Chinese population. A detailed study design has been published elsewhere (14,15) and is summarized in the Online Appendix. Briefly, the China-PAR project involves 4 subcohorts and covers 15 provinces across China (Figure 1). A total of 127,840 Chinese adults (≥18 years of age) were initially enrolled between 1992 and 2008. The most recent follow-up visits commenced between 2012 and 2015. Research protocols were systematically embedded, and standardized questionnaires were implemented across all subcohorts.

Of the original study population, 6.6% (n = 8,452) who were lost to follow-up were excluded. Because the collection of exposure data began in 2000, deaths and those diagnosed with CVD (n = 2,316) occurring prior to 2000 or their baseline dates were also excluded. We excluded an additional 100 participants without detailed residential address information. The remaining number of eligible participants was 116,972. See Online Table 1 for baseline characteristics of both the included and excluded participants.

This study was approved by the Institutional Review Board and ethics committee at Fuwai Hospital of Chinese Academy of Medical Sciences in Beijing and all participating institutions. Written informed consents were obtained from all participants prior to commencing physical examinations and interviews.

**HEALTH DATA.** Demographic characteristics, lifestyle information, and medical history related to CVDs were extracted from standardized questionnaires at the baseline and each subsequent follow-up visit. All participants were invited to undergo a physical examination, which included measurements of height, weight, and blood pressure. Blood pressure was measured 3 times for each participant after a 5-min rest, and the average was used as the final measurement. Blood samples after an overnight fast...
of at least 10 h were drawn from participants to measure serum glucose and total cholesterol levels under unified quality control criteria.

CVD histories during the follow-up period were recorded, including hospital records, residential and health insurance records, and verified death certificates. To ascertain disease status, a studywide endpoint assessment committee was established to review all medical records (including medical histories, physical examination findings, laboratory test results, and procedure reports) or death certificates. Each endpoint was assessed by 2 committee members independently and then discussed by additional members when discrepancies emerged. All committee members were blinded to baseline characteristics of cohort participants to reduce potential bias.

CVD events in the present study included nonfatal acute coronary syndrome (including acute myocardial infarction and unstable angina), nonfatal stroke and heart failure, and death from any CVD causes (16). CVD incidence was defined as the first ever CVD event, while CVD death was defined as any death from CVD during the pre-defined follow-up period. The International Classification of Diseases-10th Revision codes for CVD death were I00 to I99 and those for ischemic heart disease, acute myocardial infarction, and stroke were I20 to I25, I21, and I60 to I69, respectively. Event date was ascertained from either the initial point of diagnosis or a death certificate.

**EXPOSURE ASSESSMENT.** Long-term exposure levels of PM$_{2.5}$ for each participant were assessed using satellite-based PM$_{2.5}$ concentrations at 1-km spatial resolution. Monthly mean PM$_{2.5}$ concentrations across China were estimated from 2000 to 2015 using machine-learning approaches. The modeling methodology was adopted from a previous study (10). A complete description is available in the Online Appendix. Briefly, the Multi-Angle Implementation of Atmospheric Correction AOD product made available by NASA was used to enhance the spatial resolution of PM$_{2.5}$ estimates to 1 km (17). Compared with the standard algorithms, Multi-Angle Implementation of Atmospheric Correction AOD has demonstrated excellent agreement with ground measurements over diverse land cover types (18). A multiple imputation model was adopted to fill missing AOD due to cloud cover and calculate accurate monthly mean AOD values (10). The gap-filled AOD was then combined with meteorologic variables, land-use type, road information, elevation, and emissions, which were used to train models separately using random forest and extreme gradient boosting approaches. To improve prediction accuracy, predicted PM$_{2.5}$ concentrations calculated using these 2 machine-learning models were averaged to represent the monthly mean PM$_{2.5}$ exposure levels in each 1-km$^2$ grid cell. Random 10-fold cross-validation R$^2$ values of 0.93 at the monthly level and 0.95 at the annual level were obtained. For the period without national ground measurements (i.e., prior to 2013), prediction accuracy was assessed by comparing estimates with observations in Hong Kong and Taiwan and via the U.S. embassy, with a prediction R$^2$ value of 0.80 and a root mean squared error of 8.90 µg/m$^3$ at the annual level.

To assess individual long-term exposure levels of PM$_{2.5}$, residential addresses collected at baseline and each follow-up visit were geocoded for each participant over the entire study period. Annual mean PM$_{2.5}$ concentrations were assigned to the participants who were at risk for CVD events during that year, on the basis of the grid cells in which they resided. For those who changed their residential addresses during the follow-up period, the most recent address before the year being analyzed was used.

**STATISTICAL ANALYSIS.** A Cox proportional hazards model was implemented with time-varying exposures (19) on a 1-year (annual) time scale, accounting for
TABLE 1 Summary Statistics and Baseline Characteristics of the Study Subjects

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Quartile 1*</th>
<th>Quartile 2*</th>
<th>Quartile 3*</th>
<th>Quartile 4*</th>
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<tbody>
<tr>
<td>PM$_{2.5}$, µg/m$^3$</td>
<td>25.5–114.0</td>
<td>25.5–42.8</td>
<td>42.9–59.3</td>
<td>59.4–75.5</td>
<td>75.6–114.0</td>
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<td>Population</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Subject counts</td>
<td>116,792</td>
<td>15,970</td>
<td>31,387</td>
<td>37,456</td>
<td>32,159</td>
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<td>Counts of incident CVD</td>
<td>5,760</td>
<td>755</td>
<td>1,614</td>
<td>1,558</td>
<td>1,833</td>
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<tr>
<td>Counts of fatal CVD</td>
<td>2,359</td>
<td>366</td>
<td>683</td>
<td>611</td>
<td>699</td>
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<td>Individual factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>52.1 ± 11.7</td>
<td>50.2 ± 8.4</td>
<td>52.0 ± 10.9</td>
<td>50.7 ± 12.7</td>
<td>51.5 ± 12.5</td>
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<td>Male, %</td>
<td>41.0</td>
<td>48.3</td>
<td>40.0</td>
<td>40.3</td>
<td>39.1</td>
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<td>BMI, %</td>
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<tr>
<td>&lt;25 kg/m$^2$</td>
<td>67.8</td>
<td>81.4</td>
<td>71.0</td>
<td>67.5</td>
<td>58.2</td>
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<td>25–30 kg/m$^2$</td>
<td>27.4</td>
<td>16.5</td>
<td>25.2</td>
<td>27.9</td>
<td>34.5</td>
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<td>≥30 kg/m$^2$</td>
<td>4.8</td>
<td>2.1</td>
<td>3.8</td>
<td>4.6</td>
<td>7.3</td>
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<td>Smokers, %</td>
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<td>Never smokers</td>
<td>72.5</td>
<td>64.6</td>
<td>71.6</td>
<td>70.4</td>
<td>89.8</td>
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<td>Former smokers</td>
<td>3.7</td>
<td>4.7</td>
<td>3.9</td>
<td>4.0</td>
<td>2.6</td>
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<tr>
<td>Current smokers</td>
<td>23.8</td>
<td>30.7</td>
<td>24.5</td>
<td>25.6</td>
<td>17.6</td>
</tr>
<tr>
<td>Alcohol consumption, %</td>
<td>19.5</td>
<td>27.2</td>
<td>23.0</td>
<td>18.9</td>
<td>13.1</td>
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<tr>
<td>Educational level, %</td>
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<td>Illiteracy</td>
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<td>12.6</td>
<td>23.6</td>
<td>21.0</td>
<td>18.9</td>
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<tr>
<td>Primary to middle school</td>
<td>65.7</td>
<td>65.4</td>
<td>58.2</td>
<td>66.8</td>
<td>71.8</td>
</tr>
<tr>
<td>High school or above</td>
<td>14.3</td>
<td>22.0</td>
<td>18.2</td>
<td>12.2</td>
<td>9.3</td>
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<td>Work-related physical activity level, %</td>
<td>55.5</td>
<td>49.5</td>
<td>61.6</td>
<td>46.9</td>
<td>62.5</td>
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<td>Rigorous or moderate level</td>
<td>28.1</td>
<td>37.8</td>
<td>25.9</td>
<td>36.1</td>
<td>16.1</td>
</tr>
<tr>
<td>Light or sedentary level</td>
<td>16.4</td>
<td>12.7</td>
<td>12.5</td>
<td>17.0</td>
<td>21.4</td>
</tr>
<tr>
<td>No job or retirement</td>
<td>31.8</td>
<td>19.5</td>
<td>23.7</td>
<td>32.3</td>
<td>45.3</td>
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<tr>
<td>Hypertension, %</td>
<td>5.2</td>
<td>3.1</td>
<td>4.0</td>
<td>5.3</td>
<td>7.3</td>
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<tr>
<td>Diabetes, %</td>
<td>175.3 ± 188.3</td>
<td>173.2 ± 169.3</td>
<td>177.8 ± 134.2</td>
<td>173.2 ± 119.3</td>
<td>175.8 ± 32.4</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl†</td>
<td>17.5 ± 35.5</td>
<td>37.8</td>
<td>35.9</td>
<td>33.6</td>
<td>34.2</td>
</tr>
<tr>
<td>Urban, %</td>
<td>12.3</td>
<td>39.9</td>
<td>14.7</td>
<td>8.5</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Values are range, % mean ± SD, or percentage. *Quartiles were classified using annual mean PM$_{2.5}$ concentrations across study sites during 2000 and 2015. †To convert total cholesterol to millimoles per liter, multiply by 0.0259. BMI = body mass index; CVD = cardiovascular disease; PM$_{2.5}$ = fine particulate matter.

spatiotemporal variations of PM$_{2.5}$, CVD risk factors, and the related health effects. The proportional hazards assumption in each Cox model was verified by evaluating the weighted Schoenfeld residuals (20), and we detected no violations, with all p values >0.05. Person-years of follow-up were calculated as the interval from the dates of baseline interviews or January 2000 (if one’s baseline date was earlier than 2000) to the dates of the final follow-up interviews, death, or the occurrence of a CVD event. For each annual scale within the time-varying model, all risk factors acquired from the most recent interviews were used. Covariates used within the multivariate-adjusted models included individual age grouping, sex, educational and work-related physical activity level, smoking status, alcohol consumption, body mass index (BMI) grouping, total cholesterol level, hypertension status, diabetes status, geographic region, and urbanicity. Cohort source was used as a stratum in the model to address potential effect variation among different cohorts. Covariate definitions are provided in the Online Appendix. Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) associated with each 10 µg/m$^3$ increase in annual mean PM$_{2.5}$ concentrations were investigated, and the effects of quartile exposures were also estimated using the first exposure quartile as a reference.

To estimate the C-R functions of PM$_{2.5}$ exposure and CVD incidence and mortality, PM$_{2.5}$ exposure was fitted as a smooth term using restricted cubic splines with 3 knots in the multivariate-adjusted model. The number of knots was selected by comparing Akaike information criterion and Bayesian information criterion values (21,22). Then functions between PM$_{2.5}$ exposures and HRs of CVD events were reported by fitting restricted cubic splines. Subgroup analyses were conducted to examine potential effect modifiers, stratified by age, sex, urbanicity, BMI, smoking status, alcohol consumption, hypertension, diabetes, and total cholesterol level, separately. Because of the limited sample size of former smokers (3.7%), both former smokers and current smokers were defined as smokers to ensure sufficient statistical power in the subgroup analyses. Statistical significance between subgroup-specific effects was assessed using a 2-sample z-test (23). The significance threshold was defined as 0.05 between the 2 samples and 0.025 for triple-group comparisons (e.g., BMI <25 kg/m$^2$ vs. 25 to 30 kg/m$^2$ and BMI <25 kg/m$^2$ vs. ≥30 kg/m$^2$).

Fitted models with time-varying exposures on scales of 3 years were developed for sensitivity analyses. Time-weighted average PM$_{2.5}$ exposure between 2000 and 2015 was used as an alternative exposure measurement to assess the effects on CVD events. Finally, because baseline characteristics were collected several years prior to 2000 for the ChinaMUCA (China Multi-Center Collaborative Study of Cardiovascular Epidemiology; 1992 to 1994) cohort, we reran the main analysis after excluding this subcohort.

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina) and R version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In total, 5,760 CVD incidents were observed during the 891,914 person-years of follow-up. For fatal CVD events, there were 2,359 CVD deaths with a follow-up duration of 903,412 person-years. Study participants were on average 51.2 ± 11.7 years of age, and 41.0% were men. Annual mean PM$_{2.5}$ concentrations across
study sites ranged from 25.5 to 114.0 μg/m³, with 3 quartile cutoff points of 42.8, 59.3, and 75.5 μg/m³. The averaged exposure level of annual mean PM$_{2.5}$ concentrations during the follow-up period was calculated for each participant, with a mean exposure concentration during the follow-up period was 67.4 ± 15.1 μg/m³ (5th to 95th percentile range: 42.6 to 90.1 μg/m³) and 67.5 ± 15.1 μg/m³ (5th to 95th percentile range: 42.6 to 89.7 μg/m³) for CVD incidence and mortality analyses, respectively. Summary statistics and baseline characteristics of the study population are provided in Table 1, and those for each subcohort are presented in Online Table 2.

HRs and 95% CIs of CVD incidence and mortality, as well as cause-specific events in association with PM$_{2.5}$ exposures, are presented in Table 2. For an increase of 10 μg/m³ in annual mean PM$_{2.5}$ concentrations, the estimated HR was 1.251 (95% CI: 1.220 to 1.283) for CVD incidence and 1.110 (95% CI: 1.047 to 1.177) for stroke events, respectively. For all 4 models with different adjusted covariates, PM$_{2.5}$ concentrations were positively and significantly associated with CVD events (Online Table 3).

Fitted C-R functions of CVD incidence and mortality had similar upward trends, although the HR of CVD incidence was slightly larger than those of CVD mortality (Figure 2). Associations between long-term PM$_{2.5}$ exposure and CVD events were nonlinear throughout the entire exposure range, with p values of the likelihood ratio test <0.001. Both C-R functions created steeper slopes at higher PM$_{2.5}$ exposure levels (i.e., higher than ~60 μg/m³). Functions of fitted C-R curves are presented in Online Table 4.

HRs for CVD incidence and mortality across different subgroups are provided in Figure 3. Overall, the long-term health effects of PM$_{2.5}$ exposure on both CVD incidence and mortality were statistically significant among the separate subgroups. The estimated effect on CVD incidence was significantly larger among older adults (~65 years of age), rural participants, and never smokers compared with their reference counterparts (i.e., younger subjects, urban residents, and smokers, respectively). No statistically significant effect modification was identified for CVD mortality.

Estimated HRs changed little after extending the time window of time-varying exposures from 1 to 3 years in sensitivity analyses (Online Table 5). In addition, when using average PM$_{2.5}$ levels during the entire study period as exposure, no substantial changes were observed from the main analysis. Associations between 16-year average PM$_{2.5}$ on CVD incidence and mortality were 1.259 (95% CI: 1.225 to 1.294) and 1.171 (95% CI: 1.121 to 1.224), respectively.

**Table 2 Multivariate-Adjusted HRs and 95% CIs of CVD Incidence and Mortality Associated With Long-Term PM$_{2.5}$ Exposure**

<table>
<thead>
<tr>
<th>CVD incidence†</th>
<th>Number of Events</th>
<th>Per 10 μg/m² Increase</th>
<th>Quartile 2*</th>
<th>Quartile 3*</th>
<th>Quartile 4*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>5,760</td>
<td>1.251 1.220-1.283</td>
<td>0.999 0.859-1.161</td>
<td>1.081 0.925-1.263</td>
<td>1.913 1.622-2.257</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>1,398</td>
<td>1.383 1.312-1.458</td>
<td>1.246 0.915-1.697</td>
<td>1.075 0.779-1.483</td>
<td>2.813 2.011-3.935</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>879</td>
<td>1.222 1.141-1.309</td>
<td>1.096 0.750-1.600</td>
<td>1.073 0.720-1.599</td>
<td>1.770 1.163-2.692</td>
</tr>
<tr>
<td>Stroke</td>
<td>3,540</td>
<td>1.132 1.096-1.169</td>
<td>0.953 0.785-1.156</td>
<td>1.181 0.967-1.443</td>
<td>1.447 1.170-1.791</td>
</tr>
</tbody>
</table>

CVD mortality

| Cardiovascular disease | 2,359 | 1.164 1.117-1.213 | 1.168 0.916-1.488 | 1.225 0.952-1.578 | 1.803 1.379-2.358 |
| Ischemic heart disease | 609 | 1.391 1.276-1.517 | 1.285 0.709-2.328 | 1.422 0.772-2.619 | 2.998 1.594-6.539 |
| Acute myocardial infarction | 399 | 1.515 1.360-1.687 | 1.647 0.825-3.291 | 1.737 0.840-3.589 | 4.599 2.169-9.749 |
| Stroke | 1,162 | 1.110 1.047-1.177 | 1.298 0.907-1.859 | 1.384 0.953-2.009 | 1.770 1.195-2.623 |

Covariates used within the multivariate-adjusted models included individual age grouping, sex, educational and work-related physical activity level, smoking status, alcohol consumption, body mass index grouping, total cholesterol level, hypertension status, diabetes status, geographic region, urbanicity, and stratum of subcohort. *Quartile 1 was used as the reference. **CVD incidence refers to the first ever CVD event (other nonfatal or fatal).
for each increase of 10 µg/m³ in long-term PM₂.₅ concentrations. Estimated HRs for CVD risk were slightly larger in the analysis without the China MUCA (1992 to 1994) subcohort, which were 1.313 (95% CI: 1.278 to 1.349) for CVD incidence and 1.198 (95% CI: 1.146 to 1.251) for CVD mortality.

DISCUSSION

This was a prospective study from highly polluted regions to comprehensively investigate associations between long-term PM₂.₅ exposure and CVD incidence and mortality, involving 116,972 participants over a 16-year period. Increased risk for CVD events was associated with elevated PM₂.₅ concentrations, and risk was larger among cohort participants with higher ambient PM₂.₅ exposure compared with areas with lower concentrations (Central Illustration).

Several biological mechanisms have been proposed to explain the linkage between PM₂.₅ exposure and CVD events, including increased systemic inflammation and oxidative stress, accelerated atherosclerosis, and alteration of cardiac autonomic function (24–27). Systemic inflammation is a vital component of atherogenesis (28), which may mediate the effects of PM₂.₅ on CVD events. Endothelial dysfunction, vasoconstriction induced by PM₂.₅ exposure may also increase blood pressure and trigger atherosclerotic plaque instability by which myocardial infarction and stroke could occur (29). The effects of long-term exposure to PM₂.₅ on accelerating coronary artery calcification or increasing vulnerability to plaque rupture have also been reported (25,30).

Early large-scale cohort studies reported the effects of long-term exposure to air pollution on CVD events in Europe and the United States, where ambient PM₂.₅ exposure levels were generally <35 µg/m³ (5,31–33). The adverse effects of long-term PM₂.₅ exposure have been reported, but our findings are distinct from those conducted in relatively developed countries. Variations in PM₂.₅ composition, exposure assessment strategy, and model adjustments may contribute to the discrepancies among studies (34). Differences within study populations may also provide an interesting contrast, although more important, air pollution levels substantially differ. In China, PM₂.₅ concentrations have been much higher than those in the developed countries. As reported by the Global Burden of Diseases Study, the effect estimates of CVD at high levels of PM₂.₅ were simulated from studies with exposures of secondhand or active smoking (8). Previous research conducted in comparatively clean regions of the world suggested that the C-R functions relating to PM₂.₅ exposure and mortality were nearly linear or supralinear with flattening slopes at high PM₂.₅ levels (6,8). However, there was no evidence of dramatic flattening of C-R functions on CVD risk in this study, and actually the effects became even more pronounced when PM₂.₅ exposure was extended to higher levels (Figure 2, Table 2). This suggests that a greater reduction in excess CVD incidence or mortality in highly polluted regions would be obtained compared with regions with low to moderate levels of air pollution, for a given reduction in PM₂.₅ concentrations. Considering population size and density,
baseline and variations in CVD incidence and mortality rates, incremental improvements in air quality in China will have a greater impact on public health than they might in less densely inhabited regions of the world with low levels of PM$_{2.5}$ pollution (35).

To the best of our knowledge, effects of long-term exposure to PM$_{2.5}$ on CVD incidence have not been reported in mainland China. A previous study reported an association between PM$_{2.5}$ exposure and cardiovascular mortality in Chinese men using PM$_{2.5}$ at 10-km spatial resolution for exposure assessment, with an HR of 1.09 per 10$^{\mu g/m^3}$ increase (95% CI: 1.08 to 1.10) (12). However, their data were derived from a male cohort initially designed to study the health effects of smoking, which did not involve some other critical risk factors, such as lipids, blood pressure, and glucose levels, that may have affected estimation of the effects of PM$_{2.5}$ on CVD mortality. By using a prospective cohort specifically designed for CVDs and an advanced exposure model at a finer spatial resolution, we were able to obtain more precise HRs for CVD risks across both the entire study population and various subgroups, including the male subgroup (Table 2, Figure 3). And our results on CVD incidence, CVD mortality, and cause-specific events contribute a more comprehensive understanding of the impact of PM$_{2.5}$ exposures in different disease processes. In addition, the range of PM$_{2.5}$ exposure in the Yin et al. (12) study was relatively narrow (up to 84$^{\mu g/m^3}$). This study extended the PM$_{2.5}$ range to a maximum annual exposure level of 114$^{\mu g/m^3}$.

Several studies indicated that the effects of long-term PM$_{2.5}$ exposure vary across disease types. The effect of PM$_{2.5}$ exposure on CVD mortality was smaller than that on lower respiratory infections but similar to the causes of lung cancer and chronic obstructive pulmonary disease (6,12). As the leading cause of death, CVD contributed the largest proportion of disease burden caused by ambient PM$_{2.5}$ exposure worldwide and in China (36,37), although the
estimated exposure-response association between PM$_{2.5}$ and CVD was unremarkable. Therefore, substantial health benefits may be attained by improving air quality consistently. We estimated that each 10 μg/m$^3$ decrease in PM$_{2.5}$ concentrations would result in approximately 1,557,000 avoidable CVD incidents and 433,000 CVD-related deaths annually among adults in mainland China (see Online Table 6 for further
reported stronger associations between PM 2.5 and subclinical atherosclerosis among never smokers compared with smokers (42). It has been hypothesized that smoking and air pollution may increase the risk for CVD by the same pathways of oxidative stress and inflammation (42). Among smokers, smoking dominated the main effect on CVD events, and therefore additional exposure to PM2.5 does not further enhance the effects through these pathways as much as among never smokers (42).

The extended follow-up duration, wide exposure range, and nationwide study participations with high-quality outcome collection made our estimated associations of PM2.5 and CVD events representative in China. Our high-quality exposure model allowed us to assign exposure levels accurately during the entire study period, with spatial and temporal variations of PM2.5 exposure considered. High-resolution PM2.5 estimates helped us capture fine-scale PM2.5 variations, especially for subjects who resided near emission sources such as major highways and industrial facilities (43), avoid oversmoothed exposures, and retain more accurate exposure gradients within each sampling population cluster. As a result, greater statistical precision and power could be obtained (44). Although exposures at 1-km resolution were previously applied in an epidemiological study in China (22), our estimates showed better agreement with existing ground measurements (cross-validation $R^2 = 0.93$ vs. 0.81).

**STUDY LIMITATIONS.** First, information on indoor combustion of solid fuels and time spent indoors was not collected. Lack of indoor-related characteristics of participants would likely result in miscategorization of exposures and/or bias the health effect estimation. Indoor sources of air pollution and individual time-activity patterns are being collected in our ongoing follow-up visit, and their potential confounding effects will be investigated in future work.

Second, gaseous pollutants, such as ozone and sulfur dioxide, temperature, noise, and the mixture of air pollutants were not considered in this study, because high-quality exposure estimates were not available at the time of this study.

Third, despite our effort to use the best available satellite data, our ambient exposures were not able to resolve the near-roadway PM2.5 gradients within each 1-km$^2$ grid cell. Our future work will continue to update health data records relating to CVD risks from the ongoing follow-up, further improve the accuracy of exposure assessment by integrating indoor sources, and investigate the effects of PM2.5 on cause-specific CVD events in detail.

**CONCLUSIONS**

This study provides important evidence that long-term PM2.5 exposure is a strong risk factor for CVD incidence and mortality in China. The findings substantially expand current knowledge on the chronic health effects of air pollution in moderate- to high-pollution environments, which is crucial for policy making on air quality improvement and combating the CVD epidemic in China and other highly polluted countries in the world.

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COMPETENCY IN MEDICAL KNOWLEDGE: Elevated long-term exposure to PM$_{2.5}$ is associated with a higher risk for CVD incidence and mortality in China.

TRANSLATIONAL OUTLOOK: Future studies are needed to clarify the effects on health of indoor and personal exposures to air pollution and its specific particulate components.

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KEY WORDS cardiovascular diseases, cohort study, incidence and mortality, long-term exposure, satellite-based PM2.5 estimation

APPENDIX For supplemental methods and tables, please see the online version of this paper.