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The global burden and biomarkers of cardiovascular disease attributable to ambient particulate matter pollution

Haoxian Tang[1,2], Jingtao Huang[1,3], Hanyuan Lin[1,4], Xuan Zhang[1,5], Qinglong Yang[1,4], Nan Luo[1,6], Mengyue Lin[1,2], Cuihong Tian[1,2], Shiwan Wu[1,2], Jianan Hong[2], Jiasheng Wen[1,2], Liwen Jiang[1,2], Pan Chen[1,2], Xiaojing Chen[1,7], Junshuang Tang[2], Youti Zhang[8], Kaihong Yi[9*], Xuerui Tan[2,10,11*] and Yequn Chen[2,10,11*]

Abstract

Background Understanding the evolving patterns of cardiovascular disease (CVD) burden attributable to ambient particulate matter pollution (APMP) is essential. Furthermore, research on the underlying mechanisms has mostly been limited to laboratory and animal models, with few large-scale population-based studies.

Methods Using data from the Global Burden of Disease Study (GBD) 2021, we analyzed disability-adjusted life years and mortality for CVD attributable to APMP (measured as particulate matter [PM]$_{2.5}$) from 1990 to 2021. We examined shifts in burden between APMP and household air pollution (HAP), regional disparities by socio-demographic index (SDI), and predicted trends using a Bayesian age-period-cohort model. Additionally, we used UK Biobank (UKB) data (metabolomics: 230,000 + participants; proteomics: 50,000 +) to identify biomarkers mediating the association between $PM_{2.5}$ exposure and CVD outcomes, and further analyzed their biological roles. Metabolic and proteomic signatures were constructed using regression and elastic net models, with predictive performance assessed via time-dependent receiver operating characteristic analysis. Life expectancy was evaluated using flexible parametric survival models. Subgroup analysis was conducted by age, sex, lifestyle, socioeconomic status, and genetic susceptibility.

Results In 2021, the global CVD absolute burden attributable to APMP was more than double that of 1990, with significant regional disparities. The burden shifted from HAP to APMP, with 15% of CVD cases globally attributed to APMP. The CVD burden attributable to APMP increased with age and is projected to rise through 2030. In the UKB, approximately 30 metabolites, including albumin, mediated the association between $PM_{2.5}$ exposure and CVD outcomes, primarily involving lipid and fatty acids metabolism. Over 60 proteins, including growth differentiation factor-15 and trefoil factor 2, mediated the association with CVD outcomes, enriched in cytokine-receptor interaction and leukocyte migration pathways. Metabolic and proteomic signatures outperformed $PM_{2.5}$ alone in predicting 1-, 5-, and 10-year CVD outcomes. Participants in the lowest decile of $PM_{2.5}$ exposure, metabolic, and proteomic signatures had longer life expectancy than those in the highest decile.

*Correspondence:
Kaihong Yi
382091310@qq.com
Xuerui Tan
doctortxr@126.com
Yequn Chen
gdcycyq@163.com
Full list of author information is available at the end of the article

Conclusion The CVD burden attributable to APMP remains a critical public health concern. This study presents a novel approach for identifying and managing susceptible populations through metabolomic and proteomic perspectives.

Keywords Cardiovascular disease, Ambient particulate matter pollution, Metabolites, Proteins, Global burden of disease, UK Biobank

Introduction

Over recent decades, the management of cardiovascular disease (CVD) has primarily focused on traditional risk factors such as hypertension, dyslipidemia, hyperglycemia, and smoking. However, growing evidence indicates that air pollution (AP) also plays a significant role in the development and progression of CVD [1–5]. According to the Global Burden of Disease (GBD) Study, in 2019, nearly 20% of CVD-related mortality was attributed to AP [6]. Moreover, AP ranked as the fourth highest risk factor for mortality, surpassing traditional metabolic factors such as high fasting plasma glucose, high low-density lipoprotein cholesterol, and high body mass index (BMI), as well as lifestyle factors like low physical activity and alcohol use [6].

Among the various components of ambient AP, particulate matter (PM) is the most significant driver of cardiovascular risk and adverse outcomes [7]. Pathophysiological mechanisms, including oxidative stress, inflammation, autonomic imbalance, and the translocation of PM components into the systemic circulation, contribute to this process [6, 8, 9]. However, previous research on these mechanisms has largely been limited to laboratory settings and animal models, with relatively few population-based studies, often involving small sample sizes. Developing a clinical approach to AP and cardiovascular health may offer valuable benefits, such as identifying patients more susceptible to AP, qualitatively and quantitatively assessing exposure risk, and tailoring recommendations and interventions for high-risk groups [10]. In this context, utilizing multi-omics approaches, such as metabolomics and proteomics, to trace the impact of exposure on host biological pathways and develop reliable biomarkers of exposure could hold significant promise [11].

With advancements in research and the emergence of new data and methodologies, the current study aims to examine the epidemiological trends and patterns of the CVD burden attributable to ambient particulate matter pollution (APMA) over the past 30 years (1990–2021), using the latest data from the Global Burden of Disease, Injury, and Risk Factor Study 2021. Additionally, we also use data from the large-scale prospective UK Biobank (UKB) cohort, which includes nuclear magnetic resonance (NMR)-based metabolomics data from over 230,000 participants and high-throughput proteomics data from more than 50,000 participants, to explore potential metabolomic and proteomic biomarkers in this association.

Methods

Data source and data collection

GBD 2021 was coordinated by the Institute for Health Metrics and Evaluation, which encompassed 204 countries and territories from 1990 to 2021. GBD 2021 quantified the levels and trends of 371 diseases and injuries, 288 causes of death, and 88 attributable risk factors contributing to disease burden. The methodological framework and principles of GBD 2021 were extensively detailed in prior publications [12, 13].

In general, the GBD study evaluated risk factors using a hierarchical and standardized Comparative Risk Assessment (CRA) framework, which incorporated extensive data synthesis and robust statistical methods [13]. Risk factors were organized into a four-level hierarchy, with this study focusing on APMA, categorized alongside household air pollution (HAP) under the level 3 risk factor particulate matter pollution (PMP). Relative risk (RRs) for risk-outcome pairs were estimated through meta-regression and systematic reviews, accounting for non-linear relationships and study heterogeneity. Bayesian models were used to estimate exposure levels, while theoretical minimum risk exposure levels (TMRELs) were derived from epidemiological evidence. Population attributable fractions (PAFs) and disability-adjusted life years (DALYs) were calculated to quantify risk-attributable health burdens. Additionally, the burden of proof risk function (BPRF) provided conservative estimates of risk-outcome associations, addressing heterogeneity and potential biases.

Additionally, we calculated the sociodemographic index (SDI), which evaluates social and economic conditions impacting health by computing the geometric mean of lag-distributed income, average years of schooling, and fertility rate. [12]

For the individual-level analysis, we used data from the UKB, a prospective cohort study of over 500,000 participants from England, Scotland, and Wales [14]. Sociodemographic, medical, and lifestyle information was collected through questionnaires, interviews, and health

records, with physical measurements and biological samples obtained using standardized protocols. The study was approved by the North West Multicenter Research Ethics Committee, with all participants providing written informed consent. This research was conducted under UKB application number 205837.

The current study analyzed UKB data across three components: non-omics, metabolomics, and proteomics, with study design and exclusion criteria detailed in Supplementary Fig. 1. In the non-omics analysis, 428,349 participants were included for the analysis of new-onset CVD and 422,503 for CVD mortality after excluding those with baseline CVD or missing $PM_{2.5}$ data. Among the 274,238 participants with metabolomics data, 237,148 were included for new-onset CVD and 233,858 for CVD mortality. Similarly, of the 53,013 participants with proteomics data, 44,849 were included for new-onset CVD and 44,202 for CVD mortality after exclusions.

Exposure of APMA

In GBD 2021, exposure to APMA was defined as the population-weighted annual average mass concentration of particles with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$) in a cubic meter of air. Estimates for ambient AP exposure were derived from multiple sources, including satellite aerosol data, ground monitor measurements, chemical transport model simulations, population estimates, and land-use data. For sites with only PM_{10} measurements, these values were converted to $PM_{2.5}$ using a hierarchy of $PM_{2.5}/PM_{10}$ ratios. HAP evaluated exposure to solid fuels such as wood, coal, charcoal, dung, and agricultural residues. Further methodological details were provided at https://www.healthdata.org/gbd/methods-appendices-2021.

The UKB assessed exposure to $PM_{2.5}$ using a Land Use Regression (LUR) model developed as part of the European Study of Cohorts for Air Pollution Effects (ESCAPE) [15, 16]. This model, which incorporates geographic variables such as traffic data from Geographic Information Systems (GIS), provided estimates of $PM_{2.5}$ concentrations for residential addresses within 400 km of the ESCAPE monitoring area in Greater London. For addresses beyond this range, no estimates were available, and the data were recorded as missing.

Assessment of CVD

The GBD 2021 study evaluated the burden of two major CVD events, ischemic heart disease (IHD) and stroke, attributable to APMA. This included estimates of DALYs and mortality, age-standardized rates (ASR) (relative burden), and PAFs [17, 18]. However, it did not assess the impact of APMA on CVD incidence or prevalence.

In the UKB, we focused on new-onset CVD and CVD mortality. Outcomes were defined using the International Classification of Diseases, 10th Edition (ICD-10): I20–I25 for IHD and I60–I69 for stroke [19]. All participants were followed from the date of their consent to join the UKB study until the earliest occurrence of an outcome event, loss to follow-up, or the end of the follow-up period.

Metabolomics and proteomic profiling

The measurement, processing, and quality control of specific metabolites and proteins are described in detail on the UKB website (https://biobank.ctsu.ox.ac.uk/crystal/cats.cgi), under Categories 220 and 1839. In brief, metabolomic profiling utilized NMR spectroscopy on the Nightingale metabolic biomarker platform, identifying 251 metabolites [20, 21]. These included lipoprotein lipids from 14 subclasses, fatty acids with their compositions, and various low-molecular-weight metabolites, with missing data rates kept below 5%. Proteomic profiling was performed at the Olink Analysis Service (Sweden) using proximity extension assay (PEA) technology, focused on proteins from the cardiometabolic, inflammation, neurology, and oncology panels [22]. Proteins with more than 20% missing data were excluded, resulting in the inclusion of 2910 proteins for analysis. Mean imputation and standardization were applied to all metabolites and proteins prior to analysis [23, 24].

Statistical analysis

In the initial descriptive analysis of GBD, we assessed the number, ASR (per 100,000 population), and their 95% uncertainty interval of DALYs and mortality of CVD attributable to APMP/HAP in 1990 and 2021, across different SDI levels. We also calculated their percent within the total CVD burden, as well as specifically attributable to PMP, to evaluate changes and disparities in burden patterns over the past 30 years. Age-period-cohort (APC) model was used to analyze longitudinal age curves (age-specific rates in the reference cohort, adjusted for period deviations) by sex and SDI levels, to highlight the age-specific concentration of the burden [25].

We further assessed the 2021 rankings of CVD burden attributable to APMP across 204 countries and measured cross-country inequality using the slope and concentration indices [26]. The slope index was based on regressing national DALY rates on a relative position scale defined by the midpoint of the cumulative population ranked by SDI, using weighted regression to account for heteroskedasticity. The concentration index was derived from the Lorenz curve, based on cumulative DALYs and population distribution ranked by SDI. Finally, a Bayesian APC model with integrated nested Laplace approximations

was applied to predict future burdens from 2022 to 2030 [27, 28].

In the descriptive analysis of UKB, baseline characteristics were grouped by CVD outcomes. Continuous variables were reported as means ± standard deviations (SD), and categorical variables as numbers and percentages (%). Missing categorical data were treated as a separate category, while missing continuous data were imputed with the median [23]. Group differences were analyzed using T-tests, Wilcoxon rank sum test and Pearson's Chi-square tests.

To investigate whether specific metabolites and proteins mediated the association between $PM_{2.5}$ exposure and CVD, we conducted a mediation analysis. A two-step approach was used to identify potential mediators [29, 30]. First, multivariable linear regression models were applied to assess the associations between all metabolites/proteins and $PM_{2.5}$, with *P* values corrected using the Bonferroni method. Second, multivariable Cox regression models were used to evaluate the associations between $PM_{2.5}$-related metabolites/proteins and corresponding CVD outcomes. The quasi-Bayesian Monte Carlo method was employed to test the mediation effects and their significance [31]. All models were adjusted for the following covariates: age (continuous), sex (male or female), race (White, Mixed, Asian, Black, or others), educational level (high, intermediate, low, or others) [16], alcohol consumption (never, previous, or current), smoking status (never, previous, or current), physical activity (metabolic equivalent task [MET] minutes per week, continuous) [32], BMI (continuous), history of hypertension (yes or no), and history of diabetes (yes or no). Significant mediating metabolites were categorized; and for significant mediating proteins, Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology biological processes (GO-BP) enrichment analyses were conducted to explore pathways and biological processes related to the target genes. These analyses were performed using the online platform Hiplot (https://hiplot.com.cn/).

To construct metabolomic and proteomic signatures, metabolites and proteins previously identified as significantly associated with $PM_{2.5}$ in multivariable linear regression were further analyzed using Elastic Net model with ten fold cross-validation. This method combines the regularization techniques of Lasso and Ridge regression to select representative metabolomic and proteomic biomarkers. The metabolomic and proteomic signatures were then calculated based on the regression coefficients [23, 24].

We further assessed the predictive performance of $PM_{2.5}$ and metabolomic/proteomic signatures on CVD outcomes at 1, 5, and 10 years by using time-dependent receiver operating characteristic (ROC) analysis. Additionally, we used flexible parametric survival models with age as the time scale to evaluate differences in life expectancy between participants in the lowest and highest deciles of $PM_{2.5}$ exposure, metabolomic signatures, and proteomic signatures for ages 45–100 years. Confidence intervals were calculated using the bootstrap method [23, 33, 34].

Subgroup analyses were conducted to explore the robustness of the associations between $PM_{2.5}$, metabolomic/proteomic signatures, and CVD outcomes across different demographic characteristics, socioeconomic status (SES), genetic susceptibility, and healthy lifestyle factors. Age was categorized into three groups: < 50, 50–59, and ≥ 60 years. SES was measured using the Townsend deprivation index, which integrates information on social class, employment, car availability, and housing [35]. Genetic susceptibility was assessed using a polygenic risk score (PRS); details on genotyping, imputation, quality control in the UKB, and the PRS algorithm have been reported previously [36]. SES and PRS were classified into three groups: bottom 20%, middle 60%, and top 20% of the population [35]. Healthy lifestyle score (0–5) was calculated based on smoking, physical activity, diet, alcohol consumption, and sleep, as described in Supplementary Table 1. Scores were categorized as poor (0–1), intermediate (2–3), or healthy (4–5) [35, 37]. BMI between 18.5 and 24.9 was defined as healthy [37]. Interaction effects were assessed by adding interaction terms to the regression models, and model comparisons were conducted using likelihood ratio tests [38, 39].

All analyses were conducted using R (version 4.4.1), STATA (version 18), and Free Statistics software (version 2.0). Statistical tests were two-sided, with significance set at $P < 0.05$ or more stringent Bonferroni correction thresholds in the respective omics analyses.

Results

Burden pattern of CVD attributable to APMP

The global burden of CVD attributable to APMP and HAP was summarized in Table 1 and Supplementary Table 2. From 1990 to 2021, the burden pattern associated with PMP underwent significant changes. Globally, the absolute burden of CVD attributable to APMP more than doubled over the past 30 years, with DALYs increasing from $3{,}140.93 \times 10^4$ in 1990 to $6{,}329.52 \times 10^4$ in 2021, and mortality rising from 144.44×10^4 to 296.04×10^4 during the same period. In contrast, the ASR of the burden slightly declined, with DALYs decreasing from 829.57 per 100,000 population in 1990 to 740.66 in 2021, and mortality decreasing from 42.98 to 35.64 per 100,000 population. The percent of the total CVD burden attributable to APMP increased significantly from 10.56% in 1990 to 14.78% in 2021. Moreover, within the CVD

Table 1 DALYs and mortality of CVD attributable to APMP from 1990 to 2021

	Global		Low SDI		Low-middle SDI		Middle SDI		High-middle SDI		High SDI	
	1990	2021	1990	2021	1990	2021	1990	2021	1990	2021	1990	2021
Total CVD												
DALYs												
Numbers/10,000	3140.93(2201.45, 4046.10)	6329.52(4518.39, 7874.96)	98.26(64.64, 138.98)	227.57(147.08, 326.24)	350.67(233.29, 493.41)	1290.24(798.37, 1793.59)	731.39(480.58, 1028.24)	2746.12(1854.15, 3433.91)	1176.51(810.19, 1599.07)	1621.07(1244.12, 2029.95)	778.52(516.47, 1065.48)	439.82(326.39, 562.26)
ASDR/100,000	829.57(583.32, 1070.32)	740.66(528.90, 920.32)	436.55(284.81, 621.11)	448.81(290.25, 641.83)	571.25(378.86, 803.92)	887.14(548.05, 1233.45)	729.89(479.36, 1022.95)	1052.54(707.83, 1317.92)	1262.04(870.11, 1718.15)	833.47(639.79, 1043.91)	708.79(470.67, 969.21)	220.03(164.27, 279.91)
Percent of total CVD	10.56(7.41, 13.71)	14.78(10.54, 18.30)	4.69(3.13, 6.69)	6.44(4.14, 9.02)	6.38(4.27, 8.82)	13.06(7.99, 17.90)	8.95(5.86, 12.59)	19.27(12.98, 23.52)	14.79(10.22, 19.92)	16.55(12.96, 20.11)	13.01(8.58, 17.77)	8.24(6.15, 10.51)
Percent of CVD from PMP	39.82(32.73, 44.50)	63.53(55.89, 66.57)	15.02(11.65, 18.09)	19.92(15.34, 24.53)	20.23(15.73, 24.93)	42.47(31.67, 50.58)	28.20(21.80, 34.09)	76.67(65.33, 78.02)	57.57(50.32, 64.12)	92.54(90.76, 92.10)	91.25(86.79, 91.07)	99.52(99.68, 99.07)
Mortality												
Numbers/10,000	144.44(101.68, 186.15)	296.04(211.18, 370.14)	3.70(2.42, 5.28)	8.85(5.73, 12.75)	13.43(8.90, 18.88)	51.77(32.14, 72.17)	29.17(19.11, 40.77)	126.13(84.52, 158.03)	56.81(39.45, 77.27)	85.42(62.96, 106.34)	41.06(26.78, 57.08)	23.63(16.86, 30.70)
ASDR/100,000	42.98(30.21, 55.62)	35.64(25.39, 44.52)	19.81(12.89, 28.43)	21.14(13.65, 30.25)	26.16(17.21, 36.76)	40.16(24.86, 56.01)	35.67(23.36, 49.72)	52.98(35.38, 66.34)	68.59(47.66, 93.21)	44.24(32.70, 55.04)	37.18(24.12, 51.72)	10.15(7.35, 13.04)
Percent of total CVD	11.71(8.26, 15.14)	15.25(10.89, 18.88)	5.38(3.61, 7.59)	7.11(4.58, 9.96)	7.23(4.85, 10.01)	13.54(8.23, 18.55)	9.48(6.21, 13.31)	19.88(13.27, 24.42)	15.68(10.86, 21.23)	16.86(13.08, 20.66)	13.38(8.78, 18.41)	8.11(5.95, 10.48)
Percent of CVD from PMP	43.43(36.11, 48.22)	66.04(59.19, 68.64)	15.09(11.68, 18.61)	19.92(15.28, 24.55)	20.69(15.99, 25.44)	42.20(31.70, 50.64)	28.04(21.63, 33.59)	76.55(65.50, 77.46)	60.42(54.10, 66.66)	92.60(87.98, 90.40)	92.02(87.17, 92.85)	99.47(97.55, 99.01)
IHD												
DALYs												
Numbers/10,000	1807.14(1248.07, 2396.14)	3651.58(2553.95, 4813.06)	44.21(26.78, 65.49)	123.33(77.32, 181.51)	194.28(124.83, 271.86)	827.41(505.55, 1158.96)	354.26(223.13, 492.78)	1516.11(994.48, 1994.82)	673.93(438.64, 935.49)	903.76(635.92, 1181.09)	536.92(328.10, 756.16)	278.00(191.46, 369.87)
ASDR/100,000	479.87(328.35, 640.66)	427.81(299.61, 564.17)	193.76(116.93, 284.59)	240.42(150.86, 354.45)	311.08(200.62, 434.17)	563.56(344.13, 790.84)	353.08(222.21, 489.28)	580.44(381.77, 764.95)	725.45(471.88, 1005.48)	466.53(328.68, 609.05)	489.54(299.11, 688.83)	140.07(96.36, 185.43)
Percent of total IHD	15.17(10.38, 20.15)	19.38(13.59, 25.22)	7.14(4.43, 10.17)	9.65(6.16, 13.93)	9.40(6.10, 13.10)	17.96(11.00, 25.48)	13.35(8.52, 18.31)	24.75(16.55, 31.87)	20.07(13.05, 27.74)	20.28(14.81, 25.98)	16.77(10.17, 23.74)	11.81(8.19, 15.63)
Percent of IHD from PMP	49.42(43.52, 52.65)	66.79(61.32, 71.39)	15.95(12.17, 19.15)	22.09(17.61, 26.50)	22.45(18.31, 25.82)	47.16(36.92, 54.15)	36.16(29.00, 41.00)	79.82(69.79, 83.54)	70.47(62.76, 74.55)	93.01(91.87, 92.96)	93.72(91.16, 95.44)	99.52(99.17, 98.80)
Mortality												
Numbers/10,000	84.98(57.83, 113.11)	172.95(121.25, 228.70)	1.66(1.00, 2.43)	4.81(3.02, 7.08)	7.34(4.75, 10.22)	32.94(20.11, 46.29)	14.13(8.91, 19.53)	69.98(46.46, 92.40)	32.90(21.35, 45.62)	49.56(34.40, 65.18)	28.78(17.53, 40.50)	15.52(10.25, 20.93)
ASDR/100,000	25.55(17.27, 34.24)	20.85(14.63, 27.57)	8.77(5.33, 12.75)	11.39(7.19, 16.76)	14.12(9.19, 19.68)	25.35(15.34, 35.75)	17.61(11.05, 24.70)	29.48(19.55, 39.08)	40.02(25.87, 55.56)	25.78(17.84, 33.84)	26.12(15.90, 36.69)	6.71(4.54, 9.00)
Percent of total IHD	15.83(10.73, 21.21)	19.23(13.57, 25.05)	7.25(4.53, 10.33)	9.74(6.21, 14.07)	9.74(6.29, 13.58)	17.95(10.97, 25.55)	13.60(8.64, 18.75)	24.90(16.49, 32.18)	20.50(13.31, 28.47)	20.22(14.81, 25.83)	16.61(10.02, 23.66)	11.15(7.66, 14.96)
Percent of IHD from PMP	54.12(48.20, 57.52)	69.38(64.96, 73.70)	15.98(12.28, 18.94)	21.93(17.48, 26.37)	23.04(18.92, 26.27)	46.93(36.87, 53.98)	36.50(29.30, 41.29)	79.51(71.38, 83.60)	72.61(65.48, 76.29)	92.89(90.58, 94.40)	94.30(92.52, 95.07)	99.46(98.67, 99.67)

Table 1 (continued)

	Global		Low SDI		Low-middle SDI		Middle SDI		High-middle SDI		High SDI	
	1990	2021	1990	2021	1990	2021	1990	2021	1990	2021	1990	2021
Stroke												
DALYs												
Numbers/10,000	1333.79(921.96, 1846.97)	2677.94(1807.62, 3422.31)	54.05(34.46, 77.82)	104.24(66.00, 153.21)	156.38(101.49, 227.70)	462.83(274.54, 658.78)	377.12(227.54, 573.59)	1230.01(778.16, 1573.90)	502.58(330.44, 707.38)	717.32(509.59, 907.73)	241.61(157.88, 347.03)	161.83(122.04, 207.55)
ASDR/100,000	349.71(241.10, 483.16)	312.85(211.45, 399.79)	242.79(155.20, 350.00)	208.38(132.39, 306.80)	260.17(168.78, 377.52)	323.58(192.02, 459.53)	376.81(226.99, 573.99)	472.10(297.91, 602.67)	536.59(356.23, 750.96)	366.95(260.97, 463.81)	219.24(143.30, 314.22)	79.95(61.36, 101.85)
Percent of total Stroke	10.99(7.68, 15.24)	16.69(11.57, 21.03)	6.26(4.04, 8.84)	7.96(5.12, 11.09)	7.52(4.82, 10.93)	13.73(8.06, 19.12)	9.66(6.04, 14.76)	20.54(13.20, 25.72)	14.27(9.55, 19.97)	18.67(13.98, 23.08)	13.78(9.18, 19.81)	10.64(8.11, 13.65)
Percent of stroke from PMP	31.53(26.68, 36.95)	59.56(51.62, 61.70)	14.34(11.20, 17.38)	17.84(14.15, 22.12)	18.02(14.25, 22.35)	36.06(27.16, 43.20)	23.37(17.20, 29.68)	73.11(62.61, 72.07)	46.22(38.79, 52.50)	91.94(85.91, 89.10)	86.22(80.14, 89.69)	99.53(99.05, 99.67)
Mortality												
Numbers/10,000	59.46(41.07, 81.62)	123.09(83.48, 157.50)	2.04(1.31, 2.94)	4.04(2.60, 5.92)	6.09(3.92, 8.81)	18.83(11.17, 26.93)	15.03(9.05, 22.98)	56.14(35.26, 72.53)	23.91(16.00, 33.37)	35.87(25.51, 46.03)	12.28(8.01, 17.69)	8.12(5.93, 10.70)
ASDR/100,000	17.42(12.14, 23.95)	14.78(10.05, 18.92)	11.04(7.03, 15.96)	9.75(6.22, 14.32)	12.04(7.71, 17.40)	14.81(8.76, 21.12)	18.06(10.87, 27.44)	23.50(14.70, 30.47)	28.57(19.25, 40.18)	18.46(13.17, 23.70)	11.06(7.21, 15.93)	3.44(2.56, 4.49)
Percent of total Stroke	11.81(8.36, 16.05)	16.97(11.84, 21.32)	6.93(4.49, 9.92)	8.50(5.43, 11.85)	8.30(5.40, 12.01)	13.97(8.24, 19.43)	9.97(6.21, 15.18)	20.94(13.35, 26.23)	14.90(10.03, 20.85)	18.46(13.77, 22.89)	13.86(9.26, 20.18)	10.18(7.67, 13.15)
Percent of stroke from PMP	33.88(28.63, 38.97)	61.86(54.54, 63.17)	14.44(11.43, 17.60)	17.96(14.38, 22.20)	18.43(14.54, 22.60)	35.87(27.16, 42.77)	23.02(16.97, 29.04)	73.15(61.97, 71.94)	49.08(42.39, 54.82)	92.20(87.32, 89.85)	87.08(82.58, 90.08)	99.48(98.85, 99.68)

APMP, ambient particulate matter pollution; ASDR, age-standardized rates of disability-adjusted life years; CVD, cardiovascular disease; DALYs, disability-adjusted life years; PMP, particulate matter pollution; IHD, ischemic heart disease

burden attributable to PMP, the share of APMP rose from approximately 40% in 1990 to over 60% in 2021, while the share attributable to HAP decreased correspondingly. This shift highlighted a major transition in the focus of particulate matter pollution over the past three decades.

The burden patterns of PMP demonstrated significant regional disparities. Overall, as the SDI level increased from low to high, the burden shifted from being predominantly attributable to HAP to being primarily driven by APMP. From 1990 to 2021, while the percent of total CVD burden APMP increased globally, it declined in high-SDI regions, dropping from 13.01% in 1990 to 8.24% in 2021, with similar trends observed for IHD and stroke. Additionally, the percent of CVD burden attributable to HAP in high-SDI regions was minimal, accounting for less than 0.1% in 2021. In contrast, in low-SDI regions, although the percent of the CVD burden attributable to HAP slightly declined over the 30 years, it still accounted for approximately one-third of the CVD burden in 2021, while APMP contributed to less than 10%.

APC analysis indicated that the CVD burden attributable to APMP showed an approximate exponential increase with age across different sexes and SDI levels (Supplementary Fig. 2).

As shown in Fig. 1 and Supplementary Tables 3–5, although there were variations among specific CVD conditions, the countries with the largest absolute CVD burden attributable to APMP in 2021 were still the most

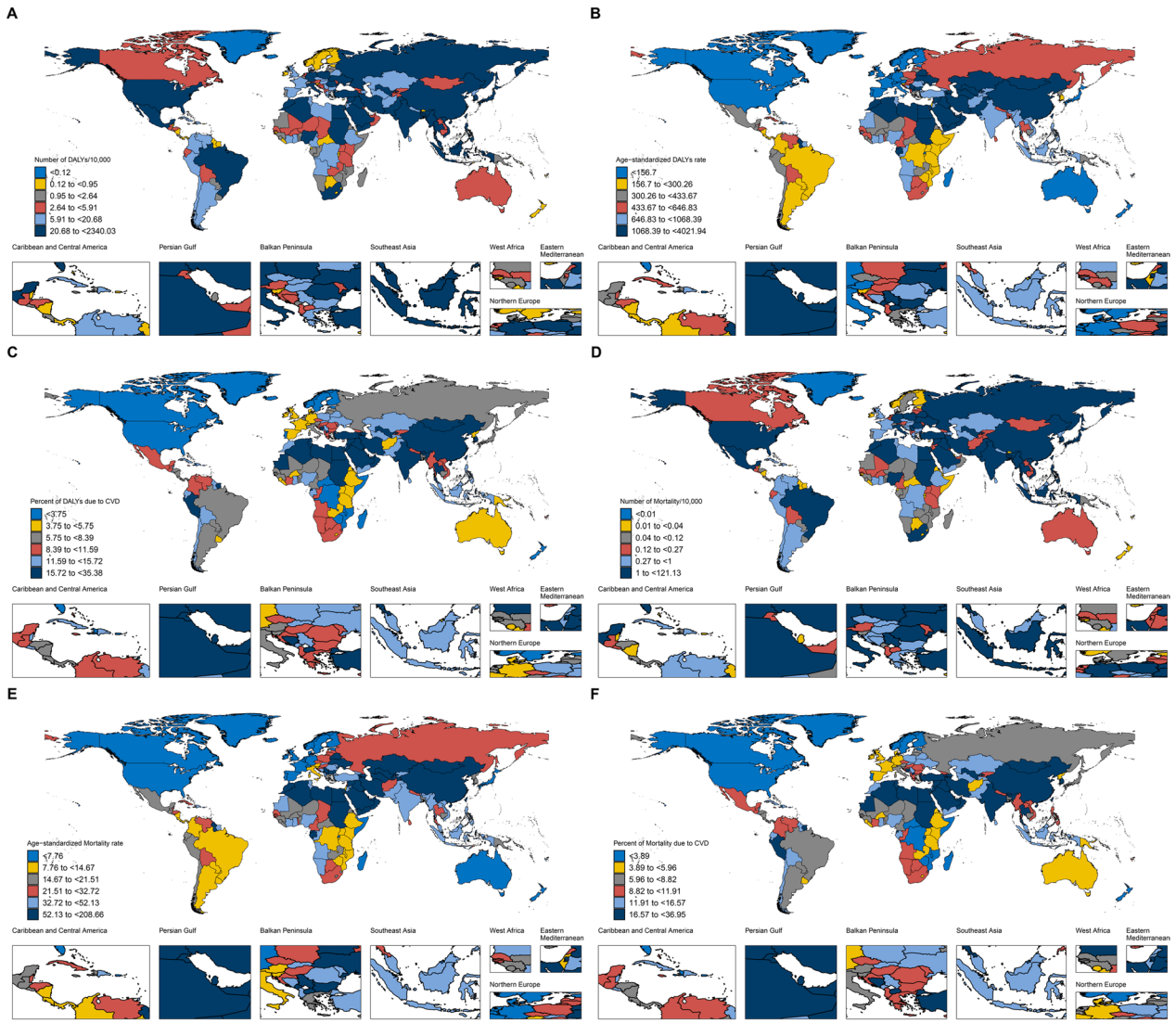

Fig. 1 Global map showing the DALYs (**A–C**) and mortality (**D–F**) of CVD attributable to APMP from in 2021. APMP, ambient particulate matter pollution; CVD, cardiovascular disease; DALYs, disability-adjusted life years

populous ones, such as China and India. In contrast, the highest relative burden was observed in Egypt and Iraq.

Slope index and concentration index analyses revealed a shift in the burden of APMP-related CVD from being primarily concentrated in highly developed countries to increasingly affecting lower-development-level countries (Fig. 2). BAPC analysis further suggested that by 2030, both the absolute and relative CVD burden attributable to APMP are projected to increase (Fig. 2).

Baseline characteristics of participants in the UKB

The baseline characteristics of participants in the non-omics and omics study cohorts were presented in Supplementary Table 6. Over a median follow-up period of approximately 13–14 years, 49,023 of 428,349 participants in the non-omics cohort were identified with new-onset CVD, and 6298 of 422,503 experienced CVD mortality. In the metabolomics cohort, 27,400 of 237,190 participants were identified with new-onset CVD, and 3493 of 233,858 experienced CVD mortality. Similarly, in the proteomics cohort, 5479 of 44,860 participants were identified with new-onset CVD, and 773 of 44,202 experienced CVD mortality. Across all cohorts, individuals who developed CVD outcomes were found to be older, more likely to be male, had lower educational level, were current smokers, had higher BMI, were more likely to have a history of hypertension or diabetes, and were exposed to higher levels of $PM_{2.5}$.

Mediation analysis of metabolites and proteins

Thirty metabolites were identified as mediators of the association between $PM_{2.5}$ exposure and new-onset CVD, with mediating proportions ranging from 0.622% to 4.008%. Similarly, 27 metabolites mediated the association between $PM_{2.5}$ exposure and CVD mortality, with mediating proportions ranging from 0.555% to 4.225% (Fig. 3, Supplementary Table 7). For both CVD outcomes, significant mediators predominantly belonged to three categories: relative lipoprotein lipid concentrations, fatty acids, and lipoprotein subclasses. Additionally, albumin,

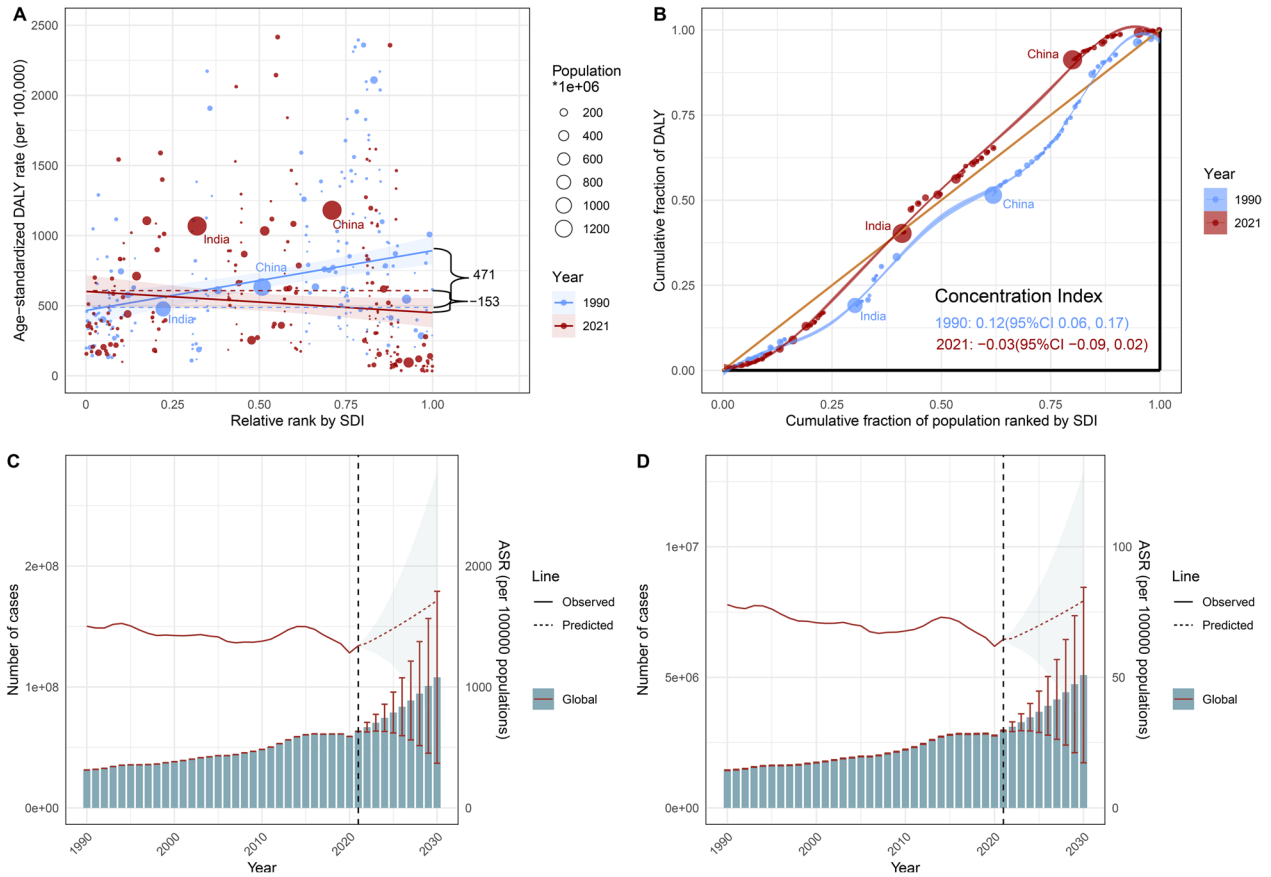

Fig. 2 Cross-country inequality analysis and projections of CVD attributable to APMP. APMP, ambient particulate matter pollution; CVD, cardiovascular disease; DALYs, disability-adjusted life years; SDI, socio-demographic index. **A** and **B** show the slope index and concentration index of CVD attributable to ambient PM pollution in 1990 and 2021, with points representing countries sized by population. **C** and **D** show the predicted case numbers and age-standardized rates of DALYs and mortality through 2030

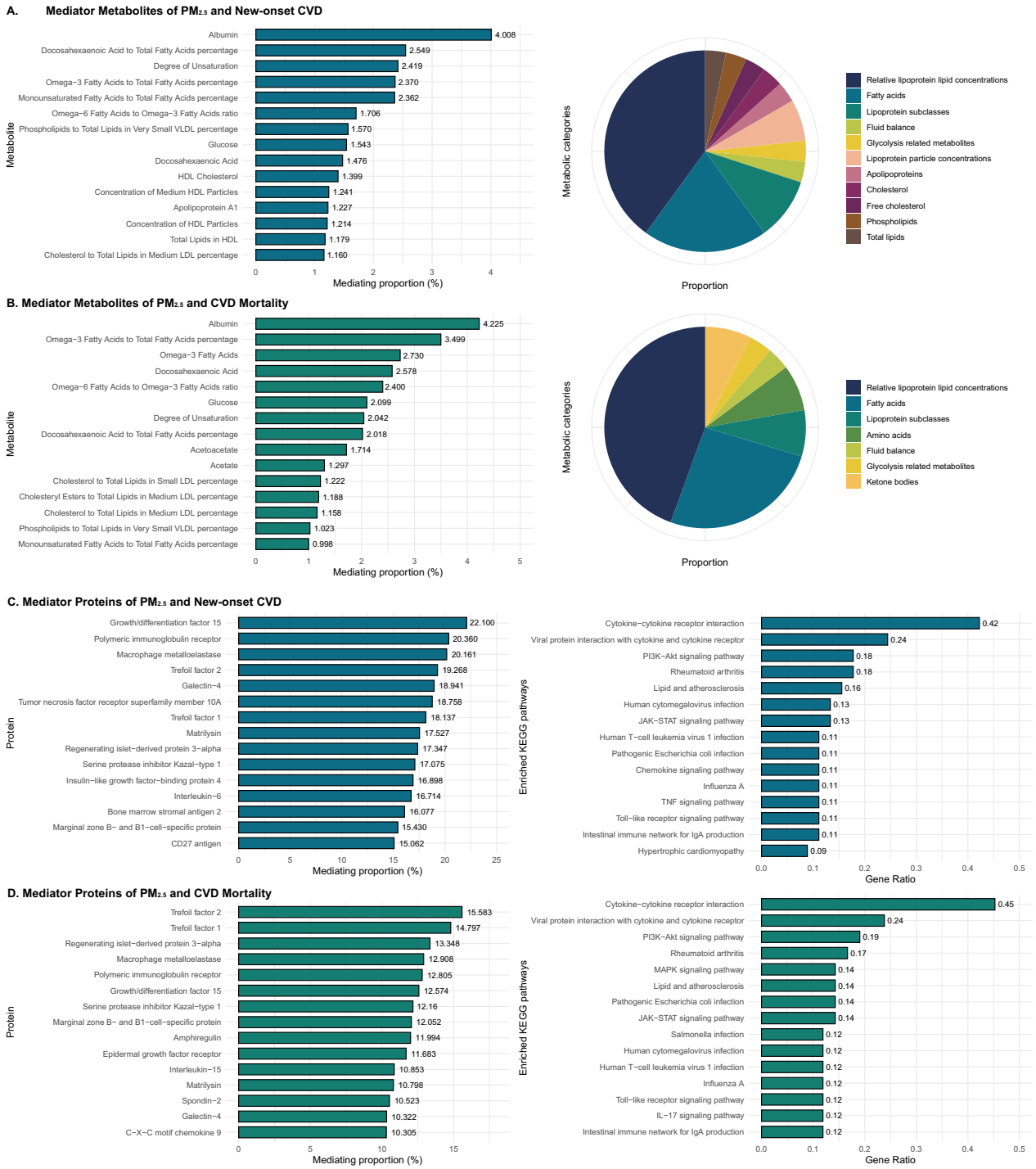

Fig. 3 Metabolic and protein mediators of $PM_{2.5}$ exposure on CVD outcomes in UK Biobank. CVD, cardiovascular disease; PM, particulate matter. **A** and **B** show the top 15 metabolic mediators linking $PM_{2.5}$ exposure to new-onset CVD and CVD mortality, along with the categories of corresponding metabolites. **C** and **D** show the top 15 protein mediators linking $PM_{2.5}$ exposure to new-onset CVD and CVD mortality, along with their enriched KEGG pathways. Analyses were adjusted for age, sex, race, education, smoking status, drinking status, physical activity, body mass index, history of diabetes and hypertensive

classified under fluid balance, was identified as the strongest mediator, accounting for 4.008% and 4.225% of the associations between $PM_{2.5}$ exposure and new-onset CVD and CVD mortality, respectively.

A total of 68 proteins were identified as mediators of the association between $PM_{2.5}$ exposure and new-onset CVD, with mediating proportions ranging from 5.473% to 22.100% (Fig. 3, Supplementary Table 8). The proteins with the highest mediating proportions were growth differentiation factor-15 (GDF-15, 22.100%), polymeric immunoglobulin receptor (PIGR, 20.360%), and macrophage metalloelastase (MMP12, 20.161%). Similarly, 63 proteins were identified as mediators in the association between PM2.5 exposure and CVD mortality, with mediation proportions ranging from 3.713% to 15.583%. The top mediators in this association were trefoil factor 2 (TFF2, 15.583%), trefoil factor 1 (TFF1, 14.797%), and regenerating islet-derived protein 3-alpha (REG3A, 13.348%). For both CVD outcomes, KEGG analysis revealed significant enrichment of these proteins in pathways such as cytokine-cytokine receptor interaction, viral protein interaction with cytokines and cytokine receptors, and the PI3K-Akt signaling pathway (Fig. 3, Supplementary Table 9). GO-BP analysis suggested that these proteins are primarily involved in biological processes including leukocyte migration and cell–cell adhesion.

Associations of $PM_{2.5}$ exposure, metabolic and proteomic signature with CVD outcomes

The construction of metabolic and proteomic signature is detailed in Supplementary Tables 10 and 11. Time-dependent ROC analysis indicated that the predictive performance of the metabolic and proteomic signature for CVD outcomes was significantly higher than that of $PM_{2.5}$ at 1, 5, and 10 years (Fig. 4).

Each 1 $\mu g/m^3$ increase in $PM_{2.5}$ exposure was associated with a 4% higher risk of new-onset CVD and an 8% higher risk of CVD mortality (Table 2). Participants in the lowest decile of $PM_{2.5}$ exposure were expected to live approximately 2.30 years longer at age 45 compared to those in the highest decile (Fig. 5, Supplementary Table 12). Subgroup analyses revealed a significant interaction between SES and $PM_{2.5}$ exposure (P for interaction < 0.05), with the association between $PM_{2.5}$ and new-onset CVD being more significant in individuals with intermediate SES levels (Table 2). Additionally, interactions were observed between $PM_{2.5}$ exposure and genetic susceptibility; however, the association between $PM_{2.5}$ exposure and new-onset CVD remained consistent across subgroups. Moreover, a healthy lifestyle was found to influence the association between $PM_{2.5}$ exposure and CVD mortality (P for interaction < 0.05), where the association was significant for participants with intermediate or poor lifestyle scores but not for those with a healthy lifestyle.

Each one-unit increase in the metabolic signature was associated with a 47% higher risk of new-onset CVD and a 140% higher risk of CVD mortality (Table 2). Similarly, each one-unit increase in the proteomic signature was associated with a 75% higher risk of new-onset CVD and a 191% higher risk of CVD mortality. Participants in the lowest decile of metabolic and proteomic signatures were expected to have a longer life expectancy at age 45, with an estimated 2.62 years longer for the metabolic signature and 8.73 years longer for the proteomic signature compared to those in the highest decile (Fig. 5, Supplementary Table 12). Although potential interactions were observed, the strong positive associations between metabolic/proteomic signature and CVD outcomes remained consistent across different subgroups.

Discussion

The current study found that, over the past 30 years, the global absolute burden of APMP has doubled, while the relative burden had decreased. The distribution of CVD burden attributable to PMP had shifted significantly, with the global burden moving from being primarily driven by HAP to APMP. However, in low SDI regions, HAP remained the dominant source. The CVD burden attributable to APMP increased exponentially with age, and this trend was expected to continue in the future. Approximately 30 metabolites, including albumin, mediated the associations between $PM_{2.5}$ exposure and new-onset CVD or CVD mortality, primarily involving lipoprotein lipids, fatty acids, and their subclasses. Additionally, over 60 proteins were found to mediate the $PM_{2.5}$-CVD relationship, with enrichment in pathways such as cytokine-receptor interactions and biological processes including leukocyte migration. Higher $PM_{2.5}$ exposure, along with metabolic and proteomic signature, was associated with higher risks of CVD outcomes, with individuals in the lowest exposure decile expected to live longer than those in the highest. Interestingly, among individuals maintaining a healthy lifestyle, the association between $PM_{2.5}$ exposure and CVD mortality was no longer significant. Despite potential interactions, the associations of metabolic and proteomic signature with CVD outcomes remained consistent across subgroups.

Building on updated methodologies and data sources, including a refined mediation matrix, the BPRF, and a star-rating system, GBD 2021 enhanced the accuracy of risk modeling and evidence evaluation for risk-outcome pairs [13]. Overall, GBD 2021 estimated a higher burden of CVD attributable to APMP compared to GBD 2019 [40]. Similarly, regional variations in APMP were observed, with our health inequality analysis supporting

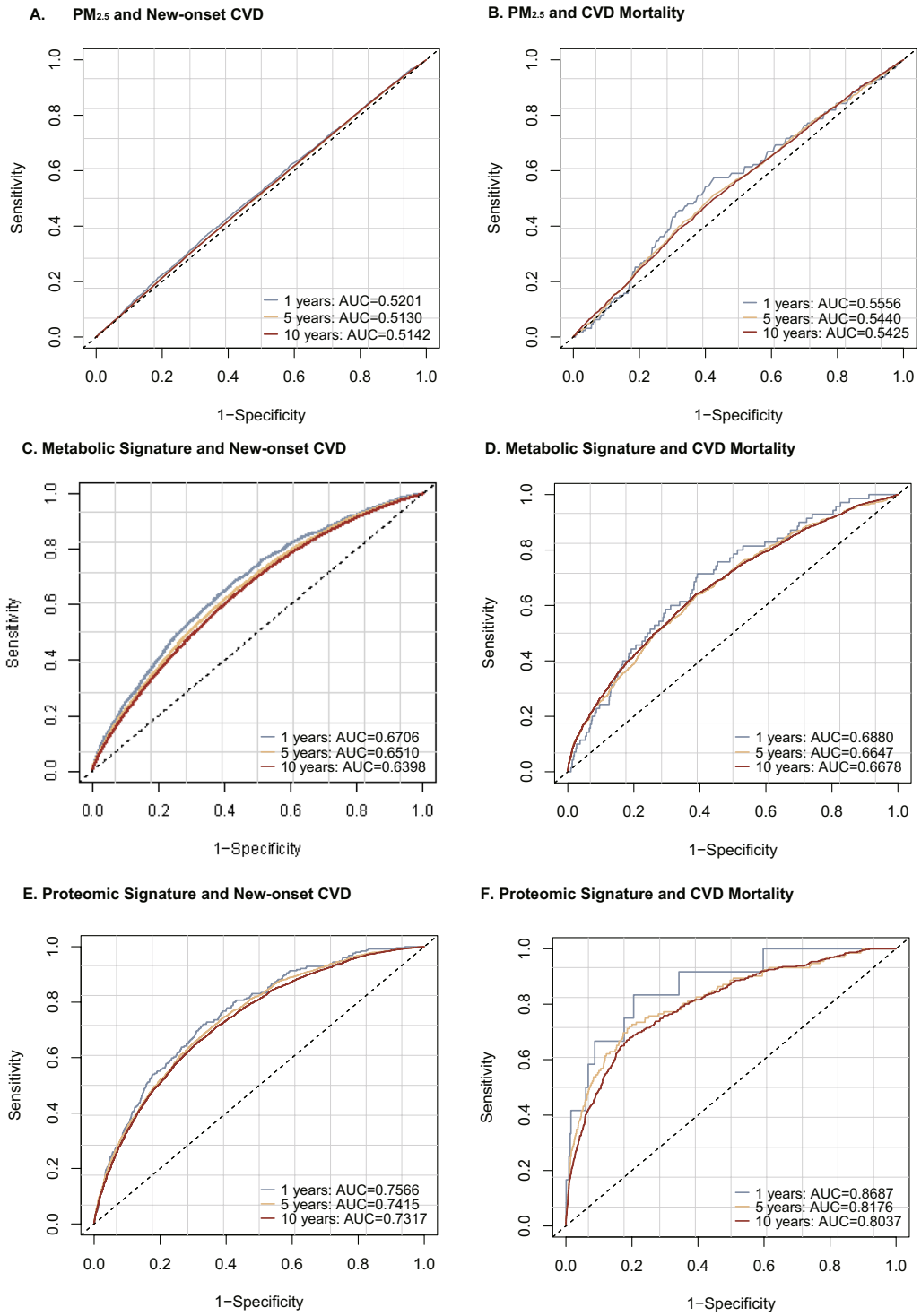

Fig. 4 Time-dependent ROC analysis of $PM_{2.5}$ and metabolomic/proteomic signature at 1, 5, and 10 years. AUC, areas under the curve; CVD, cardiovascular disease; PM, particulate matter; ROC, receiver operating characteristic

the conclusion that the CVD burden associated with APMP shifted from high-SDI to low-SDI region, as a phenomenon consistent with trends in economic development, urbanization, and industrialization [41]. Notably, in low-SDI region, HAP accounted for approximately one-third of the CVD burden in 2021, while

Table 2 Association of PM2.5 exposure, metabolic, and proteomic signature with new-onset CVD and CVD mortality in different subgroup

	New-onset CVD			CVD mortality		
	case/total	**HR(95% CI)**	***P* for interaction**	**case/total**	**HR(95% CI)**	***P* for interaction**
PM2.5						
Total	49023/428349	1.04(1.03, 1.05)		6298/422503	1.08(1.06, 1.11)	
Age						
< 50	4855/105463	1.01(0.99, 1.04)	0.229	369/105044	1.10(1.01, 1.20)	0.253
50–59	13243/145027	1.04(1.03, 1.06)		1310/143533	1.10(1.05, 1.16)	
≥ 60	30925/177859	1.05(1.03, 1.06)		4619/173926	1.07(1.04, 1.10)	
Sex						
Male	28823/189249	1.04(1.03, 1.05)	0.055	4180/186666	1.09(1.06, 1.12)	0.307
Female	20200/239100	1.05(1.04, 1.06)		2118/235837	1.06(1.02, 1.10)	
Healthy lifestyle						
Healthy	8637/89846	1.04(1.02, 1.06)	0.183	962/88880	1.00(0.94, 1.07)	< 0.001
Intermediate	31879/279829	1.06(1.05, 1.07)		3962/276032	1.12(1.08, 1.15)	
Poor	8507/58674	1.05(1.03, 1.07)		1374/57591	1.15(1.09, 1.20)	
BMI						
Healthy	11426/138300	1.04(1.02, 1.05)	0.657	1464/136131	1.05(1.00, 1.10)	0.658
Unhealthy	37171/287591	1.04(1.03, 1.05)		4745/283891	1.08(1.06, 1.11)	
Socioeconomic status						
Least deprived	9083/86296	1.02(0.99, 1.05)	< 0.001	1017/84922	1.02(0.95, 1.10)	0.903
Intermediate	29166/260894	1.04(1.03, 1.05)		3624/257295	1.04(1.00, 1.07)	
Most deprived	10774/81159	1.00(0.98, 1.02)		1657/80286	1.03(0.99, 1.08)	
Genetic risk						
Low	7285/85790	1.06(1.04, 1.08)	0.024	907/84344	1.06(1.00, 1.13)	0.692
Intermediate	29804/263373	1.04(1.03, 1.05)		3830/259642	1.09(1.06, 1.13)	
High	11934/79186	1.03(1.01, 1.05)		1561/78517	1.07(1.02, 1.12)	
Metabolic signature						
Total	27400/237148	1.47(1.43, 1.51)		3493/233858	2.40(2.12, 2.72)	
Age						
< 50	2792/58051	1.95(1.80, 2.12)	< 0.001	216/57802	1.86(1.15, 2.98)	0.003
50–59	7405/80064	1.57(1.50, 1.65)		724/79275	2.77(2.17, 3.55)	
≥ 60	17203/99033	1.36(1.31, 1.41)		2553/96781	2.30(1.97, 2.69)	
Sex						
Male	16145/105751	1.38(1.33, 1.44)	< 0.001	2311/104234	2.05(1.76, 2.40)	< 0.001
Female	11255/131397	1.53(1.47, 1.58)		1182/129624	3.31(2.69, 4.07)	
Healthy lifestyle						
Healthy	4772/49736	1.41(1.30, 1.54)	0.876	527/49193	2.27(1.51, 3.41)	0.012
Intermediate	17895/155040	1.49(1.44, 1.53)		2197/152928	2.72(2.36, 3.14)	
Poor	4733/32372	1.61(1.49, 1.75)		769/31737	2.05(1.56, 2.71)	
BMI						
Healthy	6427/76183	1.54(1.45, 1.63)	< 0.001	829/74981	3.20(2.49, 4.13)	0.024
Unhealthy	20836/160159	1.45(1.41, 1.50)		2639/158063	2.27(1.97, 2.62)	
Socioeconomic status						
Least deprived	5179/49199	1.43(1.32, 1.55)	0.050	558/48428	2.18(1.49, 3.20)	0.72
Intermediate	16282/144263	1.53(1.47, 1.60)		2031/142286	2.30(1.93, 2.75)	
Most deprived	5179/49199	1.43(1.32, 1.55)		904/43144	2.54(2.08, 3.10)	

Table 2 (continued)

	New-onset CVD			CVD mortality		
	case/total	HR(95% CI)	*P* for interaction	case/total	HR(95% CI)	*P* for interaction
Genetic risk						
Low	4158/48611	1.32(1.24, 1.41)	< 0.001	533/47796	2.48(1.88, 3.28)	0.533
Intermediate	16419/143723	1.55(1.48, 1.61)		2079/141678	2.36(1.99, 2.79)	
High	6823/44814	1.55(1.45, 1.65)		881/44384	2.48(1.91, 3.21)	
Proteomic signature						
Total	5479/44849	1.75(1.67, 1.83)		773/44202	2.91(2.60, 3.27)	
Age						
< 50	489/10864	2.03(1.75, 2.36)	< 0.001	40/10817	3.62(2.29, 5.73)	0.004
50–59	1407/14767	1.90(1.73, 2.08)		146/14606	3.86(2.95, 5.04)	
≥ 60	3583/19218	1.68(1.59, 1.78)		587/18779	2.69(2.35, 3.08)	
Sex						
Male	3164/19952	1.74(1.64, 1.85)	0.004	522/19708	2.85(2.49, 3.26)	0.177
Female	2315/24897	1.78(1.66, 1.91)		251/24494	3.18(2.52, 4.00)	
Healthy lifestyle						
Healthy	938/9270	1.63(1.44, 1.84)	0.70	128/9072	3.35(2.50, 4.48)	0.937
Intermediate	3604/29423	1.81(1.71, 1.90)		463/26766	2.93(2.54, 3.38)	
Poor	937/6156	1.98(1.80, 2.17)		182/8364	2.81(2.14, 3.69)	
BMI						
Healthy	1267/14370	1.92(1.74, 2.11)	< 0.001	174/14088	3.19(2.41, 4.22)	0.209
Unhealthy	4174/30282	1.70(1.61, 1.79)		585/29918	2.85(2.49, 3.25)	
Socioeconomic status						
Least deprived	1019/8984	1.57(1.40, 1.76)	0.221	122/8834	3.05(2.22, 4.19)	0.415
Intermediate	3281/27382	1.76(1.66, 1.86)		460/26960	2.66(2.28, 3.12)	
Most deprived	1179/8483	1.78(1.62, 1.96)		191/8408	3.30(2.58, 4.22)	
Genetic risk						
Low	867/9236	1.80(1.61, 2.02)	0.013	105/9134	3.57(2.42, 5.26)	0.619
Intermediate	3296/27186	1.72(1.63, 1.83)		507/29013	3.07(2.70, 3.49)	
High	1316/8427	1.78(1.62, 1.96)		161/6055	3.35(2.66, 4.22)	

Analyses were adjusted for age, sex, race, education, smoking status, drinking status, physical activity, body mass index, history of diabetes and hypertensive, except for the variables used in subgroup analyses. For the analysis of healthy lifestyle, no adjustments were made for smoking status, drinking status, and physical activity

APMP contributed less than 10%, which was similar to the findings of a modeling analysis by Chowdhury et al. [42]. This highlighted the pressing need for some countries to manage and transition away from household solid fuel use by promoting cleaner biomass cookstoves and adopting cleaner energy sources, such as liquefied petroleum gas, ethanol, or electricity, as part of broader efforts to drive energy transitions at both individual and community levels [42, 43]. Additionally, Yin et al. found that individuals aged 60 and above bore more than 59% of the global health-economic burden of $PM_{2.5}$. Similarly, we observed a near-exponential increase in the APMP-related CVD burden with age. These findings underscored the growing concern that, in the context of global aging, the health-economic losses associated with AP would escalate rapidly if pollution levels were not effectively controlled, placing immense pressure on national healthcare systems.

Over the past decade, the Chinese government implemented a series of stringent AP control policies, leading to significant improvements in air quality, which provided valuable insights for global efforts to combat environmental pollution and address climate change [44, 45]. However, this study found that in 2021, approximately 1.21 million CVD mortality in China were attributed to APMP, the highest worldwide and more than twice that of the second-leading country, highlighting the considerable challenges that remained in further improving air quality. China took a firm stance on AP management. As the largest emitter of carbon dioxide, China committed to reaching carbon peak by 2030 and achieving carbon neutrality by 2060. This "dual carbon" goal served as a key driver for improving air quality. Additionally,

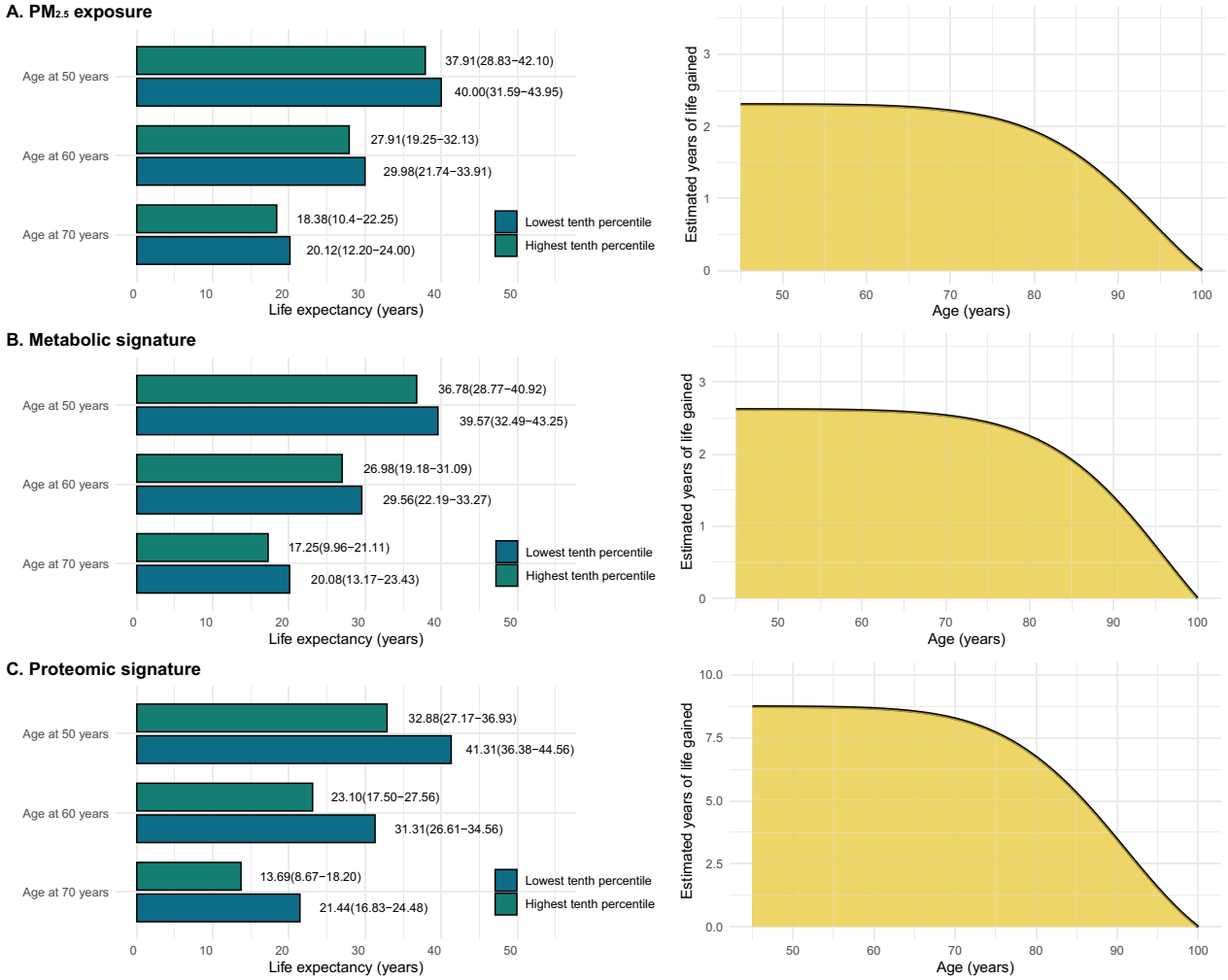

Fig. 5 Estimated years of life expectancy in the highest versus lowest tenth percentiles of $PM_{2.5}$ exposure, metabolic and proteomic signature. Analyses were adjusted for sex, race, education, smoking status, drinking status, physical activity, body mass index, history of diabetes and hypertensive

personalized measures like particulate air purifiers and particle-filtration face masks showed potential benefits [46, 47].

Previous animal models and in vitro studies demonstrated that PM exposure induced pulmonary oxidative stress and inflammation through interactions with lung and immune cells [48]. Ultrafine particles may have disrupted organelle function, while larger particles activated scavenger receptors [48, 49]. The generation of reactive oxygen species (ROS), either directly from particle chemistry or via endogenous pathways (e.g., nicotinamide adenine dinucleotide phosphate oxidase), triggered transcription factors such as nuclear factor-κβ, promoting cytokine release (e.g., interleukin-6, tumor necrosis factor-α) and immune cell activation [50–53]. In this context, PM further induced systemic oxidative stress and inflammation [50]. Recent population-based studies also showed that exposure to PM was associated with elevated levels of circulating CRP, oxidative stress markers (such as malondialdehyde), and markers of coagulation activation (e.g., plasminogen activator inhibitor-1, von Willebrand factor, soluble P-selectin) [54–56]. Furthermore, autonomic nervous system imbalance was implicated as a potential mechanism for PM-induced hemodynamic changes, such as increased blood pressure, arrhythmias, and vasoconstriction [57–60].

Recent advances in high-throughput omics technologies have enabled a better understanding of the molecular mechanisms linking AP to health outcomes [61, 62]. A good example is the study by Jeong et al., which, based on a case–control study of 386 participants, identified that perturbation of the linoleate metabolism pathway could be a critical factor in $PM_{2.5}$-related CVD [63]. Although no mediation by linoleic acid was found in this

study, it supported the notion that $PM_{2.5}$ influences CVD through lipid metabolism. Our research also highlighted the potential role of fatty acids. Yang et al., in a study of 519 pregnant women, found that each interquartile range increase in $PM_{2.5}$ exposure was associated with a 1.72% increase in omega-6 polyunsaturated fatty acids (n-6 PUFA) and a 1.17% decrease in omega-3 polyunsaturated fatty acids (n-3 PUFA) [64]. The current study found that $PM_{2.5}$ exposure may have contributed to CVD outcomes by increasing n-6 PUFAs and decreasing n-3 PUFAs (Supplementary Table 7). The metabolism of n-3 and n-6 PUFAs shared a common pathway, with enzymatic competition between the two [65]. Multiple studies had highlighted the proinflammatory properties of n-6 PUFAs, which serve as precursors to arachidonic acid, subsequently metabolized into thromboxane A2, leukotriene B4, and prostaglandins [65, 66]. Previous research in rats and humans had reported an antagonistic effect between n-3 PUFAs and the damage caused by air pollutants [67–70, 70]. This may be due to the ability of n-3 PUFAs to resist inflammation, reduce ROS, inhibit platelet aggregation, improve endothelial function, and counteract n-6 PUFAs [62, 71, 72]. Interestingly, albumin was identified as the strongest mediator between $PM_{2.5}$ exposure and CVD outcomes. A prospective study and meta-analysis by Ronit et al. showed a strong, independent association between low plasma albumin and CVD, partly due to its role as a negative acute-phase reactant [73]. This association was confirmed by Huang et al. through Mendelian randomization. Although few studies have focused on the impact of air pollution on albumin, Xiao et al. demonstrated that $PM_{2.5}$ exposure could lead to liver injury, which included a reduction in serum albumin levels [74].

In the proteomics analysis of this study, we found that proteins mediating the association between $PM_{2.5}$ exposure and CVD outcomes were primarily enriched in the cytokine-cytokine receptor interaction pathway. Cytokines were soluble extracellular proteins or glycoproteins that played a critical role as intercellular regulators and mobilizers of cells involved in innate and adaptive inflammatory responses, cell growth, differentiation, death, angiogenesis, and tissue repair to restore homeostasis [75]. Several cytokine and chemokine families mediated immune cell recruitment and complex signaling mechanisms that characterize inflammation [75]. Further GO-BP analysis supported these findings, showing that proteins with significant mediating effects were involved in leukocyte and monocyte activation and migration. For example, GDF-15, the strongest mediator between $PM_{2.5}$ exposure and new-onset CVD, was a cytokine released in response to cellular stress and inflammation [76, 77]. A meta-analysis by Kato et al. linked GDF-15 to various CVD events, including myocardial infarction, stroke, heart failure, and CVD mortality [76]. Another potential mediator of the $PM_{2.5}$ and new-onset CVD was the PIGR. A genome-wide interaction study by Caviness et al. found that PIGR was associated with coronary atherosclerosis in individuals chronically exposed to traffic-related air pollution [78]. Similarly, a population-based multicenter study by He et al. reported an association between PIGR, renal function, and CVD. Interestingly, while PIGR was an immune-related protein, it was not expressed in heart cells [79, 80]. In conclusion, although the mechanisms by which $PM_{2.5}$ influences proteins such as TFF1, TFF2 and MMP12 remain unclear, this study provides new insights into potential pathways. Further research was needed to explore these mechanisms in greater detail.

The current study synthesizes globally representative data to assess the current state and future trends of $PM_{2.5}$ pollution, providing insights into its burden and informing mitigation strategies. Leveraging a large prospective cohort, we investigated the biological mechanisms linking $PM_{2.5}$ exposure to CVD outcomes through metabolomic and proteomic analyses. To enhance risk assessment, we developed a signature score that demonstrated significantly greater predictive ability for CVD outcomes than $PM_{2.5}$ alone and remained strongly associated across subgroups. This approach may help identify individuals more susceptible to $PM_{2.5}$-related cardiovascular risks, offering potential clinical and public health applications. The signature score could facilitate early risk stratification, targeted prevention, and intervention monitoring. However, further real-world studies are needed to evaluate its feasibility and cost-effectiveness in clinical and public health settings.

Several limitations needed to be considered. First, due to inherent methodological constraints in the GBD study, data quality varied by country. Data collection practices differed depending on factors such as population size and economic conditions. Low-income countries, in particular, faced challenges with incomplete or low-quality data, which could have led to inaccurate estimates [12, 81]. Second, the GBD study lacks an evaluation of the incidence and prevalence of CVD attributable to APMA. Third, the UKB cohort was predominantly composed of European White participants, and it included individuals who were generally healthier and wealthier, which could introduce selection bias. Therefore, future research should aim to validate the conclusions of this study in more diverse populations. Fourth, although we considered a broad range of CVD risk factors, including demographic characteristics, lifestyle, SES, and genetic susceptibility, there may still be potential unobserved and unmeasured confounders. Additionally, some covariates in the UKB were self-reported, which could have introduced bias. Fifth, there

was a lack of dynamic assessment of $PM_{2.5}$ exposure. Finally, the analysis of the UKB remained observational, and although our mediation analysis assumed causal relationships and temporal precedence between exposure, mediator, and outcome variables, these assumptions could not be verified in this observational study. Therefore, conclusions about causality should be interpreted with caution.

Conclusion

The burden of $PM_{2.5}$-related CVD remains a significant challenge, with notable health inequalities. This study identified potential metabolomic and proteomic biomarkers linking $PM_{2.5}$ exposure to CVD outcomes, offering insights for future research. It is crucial to raise awareness among healthcare professionals and the public about impact of AP on cardiovascular health and to focus on identifying and protecting high-risk populations.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-025-06375-9.

Supplementary Material 1

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Author contributions

Conceptualization: H.T., JT.H., Y.C.; Data Management and Analysis: H.T., JT.H.; Visualization: H.T., H.L., X.Z., JT.H.; Writing-Original Draft Preparation: H.T., JT.H., H.L., X.Z, Q.Y., N.L., M.L., C.T., S.W.; Writing-Review and Editing: C.T., S.W., J.W., JN.H., P.C., L.J.; Provided Critical Revisions to the Manuscript: X.C., J.T., Y.Z., K.Y., X.T., Y.C.; Project Management: X.T., Y.C.

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Availability of data and materials

The Global Burden of Disease data used in the analyses can be accessed at https://ghdx.healthdata.org/gbd-results-tool. The dataset supporting the conclusions of this article is available in the public UK Biobank Resource (www.ukbiobank.ac.uk/).

Declarations

Ethics approval and consent to participate

Ethical approval and informed consent were waived as the GBD data is publicly available and does not include identifiable information. The UKB was approved by the North West Multicenter Research Ethics Committee, with all participants providing written informed consent.

Competing interests

The authors declare no competing interests that pertain to this work.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and accepted responsibility to submit for publication.

Author details

[1]Shantou University Medical College, Shantou, Guangdong, China. [2]Department of Cardiology, The First Affiliated Hospital of Shantou University Medical College, No. 57 Changping Road, Shantou, Guangdong, China. [3]Department of Sports Medicine and Rehabilitation, Peking University Shenzhen Hospital, Shenzhen, Guangdong, China. [4]Department of Urology, The Second Affiliated Hospital of Shantou University Medical College, Shantou, Guangdong, China. [5]Department of Bone & Joint Surgery, Peking University Shenzhen Hospital, Shenzhen, Guangdong, China. [6]Department of Psychiatry, Shantou University Mental Health Center, Shantou, Guangdong, China. [7]Department of Endocrine and Metabolic Diseases, The First Affiliated Hospital of Medical College of Shantou University, Shantou, Guangdong, China. [8]Department of Cardiology, Jiexi People's Hospital, Jieyang, Guangdong, China. [9]Department of Medical Quality Management, The First Affiliated Hospital of Shantou University Medical College, No. 57 Changping Road, Shantou 515000, Guangdong, China. [10]Guangdong Engineering Research Centre of Human Phenome, Chemistry and Chemical Engineering Guangdong Laboratory, Human Phenome Institute of Shantou University Medical College, Shantou 515063, Guangdong, China. [11]Clinical Research Center, The First Affiliated Hospital of Shantou University Medical College, No. 57 Changping Road, Shantou 515000, China.

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