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Long-term exposure to $PM_{2.5}$, aging hallmarks, and age-related diseases: a nationwide prospective cohort study

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HIGHLIGHTS

- Long-term exposure to $PM_{2.5}$ was associated with increased risks of 12 age-related diseases and 6 aging hallmarks.
- Counterfactual estimates show that reducing $PM_{2.5}$ to $\leq$10 μg/m^3 would cut 10-year risks for most ARDs and all aging hallmarks.
- 35 circulating proteins collectively explained 59%-83% of the $PM_{2.5}$-aging hallmark associations.
- The identified proteins were enriched in vascular, epithelial, immune, and environmental response pathways.

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ABSTRACT

Long-term exposure to fine particulate matter ($PM_{2.5}$) has been linked to increased risks of morbidity and mortality, yet its association with age-related diseases (ARDs) and the underlying molecular mechanisms remains unclear. Leveraging data from 502,128 participants (mean age 56.5 years) in the UK Biobank, we systematically estimated the associations between exposure to 3-year moving-average $PM_{2.5}$ and 83 ARDs and 9 recognized aging hallmarks. We additionally integrated large-scale plasma proteomics to explore potential biological pathways. Long-term exposure to $PM_{2.5}$ was associated with increased risks of 12 ARDs and 6 aging hallmarks. Hazard Ratios (HRs) per 10 μg/m^3 increase in $PM_{2.5}$ ranged from 1.12 to 2.38 across the 12 ARDs, with the most pronounced associations observed for primary thrombocytopaenia and plasma cell cancer. Among aging hallmarks, long-term exposure to $PM_{2.5}$ was linked to increased risks of loss of proteostasis (HR: 1.07, 95% CI: 1.03, 1.10), stem cell exhaustion (HR: 1.06, 95% CI: 1.03, 1.09), telomere attrition (HR: 1.06, 95% CI: 1.02, 1.09), deregulated nutrient-sensing (HR: 1.05, 95% CI: 1.02, 1.09), mitochondrial dysfunction (HR: 1.05, 95% CI: 1.02, 1.08), and cellular senescence (HR: 1.04, 95% CI: 1.01, 1.07). Compared with no intervention, a hypothetical $PM_{2.5}$ reduction to the annual standards of 10 μg/m^3 could substantially lower 10-year risks for most of the 12 ARDs, particularly for hypertension and cataract, and significantly attenuate all aging hallmarks. Proteomic profiling of 2923 circulating proteins identified 35 aging-related proteins that were jointly associated with both chronological age and $PM_{2.5}$ exposure. These proteins were enriched in pathways involving immune regulation, epithelial integrity, vascular biology, extracellular matrix organization, and environmental responses. Mediation

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analyses showed that these 35 proteins collectively explained 59%-83% of the $PM_{2.5}$-aging hallmark associations, with key contributors including WFDC2, TFF1, and CXCL17. Collectively, these findings provide large-scale population evidence linking long-term exposure to $PM_{2.5}$ to multiple age-related diseases and aging hallmarks, and highlight candidate circulating proteins that may partially explain these associations.

1. Introduction

Aging is an intricate biological process characterized by the progressive accumulation of irreversible cellular damage and functional deficits, resulting in compromised physiological integrity, increased disease susceptibility, and elevated mortality (Ferrucci et al., 2018, 2019). According to the Global Burden of Disease study, approximately 31.4% of all diseases are aging-related, with age-related diseases (ARDs) contributing to 47.6%-55.9% of the total disease burden (Chang et al., 2019). Therefore, identifying modifiable factors that accelerate or decelerate aging has emerged as a critical priority in global public health.

Human aging is influenced by a complex interplay of genetics, lifestyle, and environmental determinants (Chen et al., 2025; Jiang et al., 2025; Kivimäki et al., 2025). Established lifestyle risk factors, including cigarette smoking, unhealthy dietary patterns, physical inactivity, obesity, and chronic psychosocial stress, have been associated with accelerated biological aging (Kivimäki et al., 2024; Lorenzo et al., 2022). However, these factors do not fully explain interindividual variation in aging trajectories, highlighting the potential contribution of environmental exposures. Among these, ambient fine particulate matter ($PM_{2.5}$) is one of the most prevalent and hazardous air pollutants globally. Long-term $PM_{2.5}$ exposure has been linked to increased morbidity and mortality across cardiovascular, respiratory, neurological, and metabolic systems (Grande et al., 2020; Hussain et al., 2023; Lin et al., 2022; Schwarz et al., 2024). Despite this well-documented burden, its specific role in biological aging remains insufficiently understood.

Emerging evidence suggests that $PM_{2.5}$ may influence biological processes implicated in aging (Peters et al., 2021; Ward-Caviness et al., 2016), including systemic inflammation (Tripathy et al., 2021), epigenetic alterations (Koenigsberg et al., 2023; Wang et al., 2024), telomere attrition (Ferrucci and Fabbri, 2018; Kennedy et al., 2014; López-Otín et al., 2023; Martens et al., 2017; Pieters et al., 2016), and metabolic dysregulation (Zhao et al., 2022). Biological aging can be conceptualized through nine established hallmarks: genomic instability (GI), telomere attrition (TA), epigenetic alterations (EA), loss of proteostasis (LOP), deregulated nutrient sensing (DNS), mitochondrial dysfunction (MD), cellular senescence (CS), altered intercellular communication (AIC), and stem cell exhaustion (SCE) (López-Otín et al., 2013, 2023). This framework provides a systematic approach to assess whether environmental exposures affect the fundamental biological processes driving aging. However, previous studies investigating $PM_{2.5}$ and aging have largely employed individual measures of biological aging, such as telomere length, frailty indices, epigenetic clocks, and multi-omics-based aging signatures (Ferrucci and Fabbri, 2018; Kennedy et al., 2014; López-Otín et al., 2023; Martens et al., 2017; Pieters et al., 2016), each of which captures only a limited facet of the aging process. Consequently, it remains unknown whether long-term exposure to $PM_{2.5}$ is associated with multiple aging hallmarks and a broad spectrum of ARDs. Moreover, the molecular pathways linking $PM_{2.5}$ exposure to these aging processes remain poorly characterized.

To address these knowledge gaps, we leveraged the large-scale prospective cohort from the UK Biobank to systematically investigate the associations of long-term exposure to $PM_{2.5}$ with 83 ARDs and 9 aging hallmarks. We further integrated plasma proteomics to identify circulating proteins that may mediate the link between $PM_{2.5}$ exposure and aging hallmarks. Finally, we estimated the potential reduction in disease risk under a hypothetical intervention that lowers ambient $PM_{2.5}$ concentrations to the annual average standards of 10 $\mu g/m^3$ or less. This integrated population-to-molecular framework advances our understanding of the potential biological pathways through which long-term $PM_{2.5}$ exposure may contribute to biological aging and ARDs.

2. Materials and methods

2.1. Study design and population

This study utilized data from the UK Biobank, a large-scale prospective cohort that recruited 502,536 adults aged 37-73 years between 2006 and 2010 (Sudlow et al., 2015). At baseline, participants completed standardized questionnaires, underwent physical examinations, and provided biological samples. Longitudinal follow-up for health outcomes was conducted through linkage to national electronic health records, with data available until October 31, 2022. The UK Biobank study received approval from the North West Multi-Centre Research Ethics Committee, and all participants provided written informed consent.

Our analyses were conducted under UK Biobank Application Number 104745. Of the 502,356 participants, we excluded those with missing residential addresses ($n = 13$) or incomplete mortality information ($n = 215$), resulting in a final analytical cohort of 502,128. To minimize reverse causality, we further excluded participants with ARDs diagnosed at or before baseline and those with ARDs onset within 365 days after enrollment. The overall study design is illustrated in Fig. 1.

2.2. Assessment of particulate matter exposure

$PM_{2.5}$ and PM_{10} concentration data for 2002-2022 were retrieved from the UK Department for Environment, Food & Rural Affairs (DEFRA), which administers a high-spatial-resolution data platform for near-surface atmospheric pollutants. DEFRA's annual mean concentrations of major air pollutants are generated using the Atmospheric Dispersion Modeling System (ADMS), which integrates emissions data from the National Atmospheric Emission Inventory (NAEI), meteorological data, and calibrated oxidant distribution simulations to estimate $PM_{2.5}$ and PM_{10} concentrations on a 1×1 km horizontal resolution (Yang et al., 2025). These estimated concentrations are further calibrated using measurements from background monitoring sites within DEFRA's Automatic Urban and Rural Network.

Annual $PM_{2.5}$ and PM_{10} concentrations were assigned to each participant based on their residential address via geospatial matching to the corresponding 1×1 km grid cell. Annual concentrations were estimated for each participant through follow-up (Wu et al., 2022). To evaluate long-term exposure to $PM_{2.5}$, we selected the 3-year moving average (lag 0-2) as the primary exposure metric (Vanoli et al., 2024). For each follow-up year, moving-average exposures were recalculated using a rolling exposure framework. Specifically, the lag 0-2 exposure for a given year was derived from $PM_{2.5}$ concentrations in that year and the two preceding years. The 1-year (lag 0) and 5-year (lag 0-4) averages were additionally examined in sensitivity analyses.

2.3. Outcome ascertainment

Longitudinal health data were obtained through linkage to the electronic health records system of the United Kingdom's National Health Service (NHS), enabling continuous ascertainment of incident ARD cases. Primary disease diagnoses were ascertained from hospital inpatient records, while mortality information, including date and

underlying cause of death, was obtained from the NHS Central Registry.

A total of 83 ARDs were included in the final analysis, identified using International Classification of Diseases, Tenth Revision (ICD-10) codes from hospital inpatient and mortality records (Kivimäki et al., 2024). The selection of these diseases was based on previously established aging frameworks and validated disease-based definitions from prior studies (Fraser et al., 2022; Kivimäki et al., 2025), which define ARDs as conditions with incidence that increases monotonically with advancing age.

To evaluate aging hallmarks, we mapped the 83 ARDs to 9 established biological hallmarks of aging according to previously validated classification schemes (Fraser et al., 2022; Kivimäki et al., 2025). These schemes link individual ARDs to specific hallmarks based on shared pathophysiological mechanisms, with some diseases assigned exclusively to a single hallmark and others contributing to multiple hallmarks. For each participant, we considered a given hallmark to be present if they had at least one ARD mapped to that hallmark. A complete list of the 83 ARDs, their ICD-10 codes, and their corresponding hallmark assignments is provided in Table S1.

2.4. Measurement of plasma proteins and quality control

Plasma samples were collected at baseline from UK Biobank participants and stored at −80 °C before proteomic analysis. Protein measurements were generated as part of the UK Biobank centralized proteomics initiative using the Olink Explore 3072 platform (Olink Proteomics AB, Uppsala, Sweden), which applies proximity extension assay technology coupled with next-generation sequencing to quantify 2923 circulating proteins across eight specialized panels. Comprehensive details on sample handling and proteomic measurement protocols have been previously described (Sun et al., 2023).

Proteomic assessments were carried out blindly within the UK Biobank proteomics workflow. Protein abundance was expressed as normalized protein expression (NPX) values following standard quality control and normalization processes. Proteins with missing data in ≥50% of samples were excluded from subsequent analyses. Further information on quality control and standardization procedures can be found in the previous literature (Sun et al., 2023).

2.5. Covariates

Covariates were selected a priori based on established epidemiological evidence and theoretical frameworks. These included: demographic characteristics (age, sex, ethnicity), anthropometric measures (body mass index [BMI], calculated as weight in kilograms divided by height in metres squared), socioeconomic indicators (educational attainment, employment status, household income, Townsend deprivation index), and lifestyle/behavioral factors (smoking status, alcohol consumption, physical activity, urbanicity, sleep duration, and living alone). Detailed descriptions of all covariates are provided in Table 1. Unless otherwise specified, these variables were included in all statistical models.

2.6. Statistical analysis

The overall analytical framework is illustrated in Supplementary Fig. S1. We used time-varying Cox proportional hazards models to estimate the association between long-term exposure to $PM_{2.5}$ and the risk of incident ARDs and aging hallmarks. Follow-up time was used as the underlying time scale, calculated as the date of recruitment to the date of disease of interest, death, or the administrative censoring date (October 31, 2022), whichever occurred first. In the models, we adjusted for age, sex, ethnicity, BMI, educational attainment, employment status, household income, Townsend deprivation index, smoking status, alcohol consumption, physical activity, urbanicity, sleep duration, and living alone. Results were reported as hazard ratios (HRs) with 95%

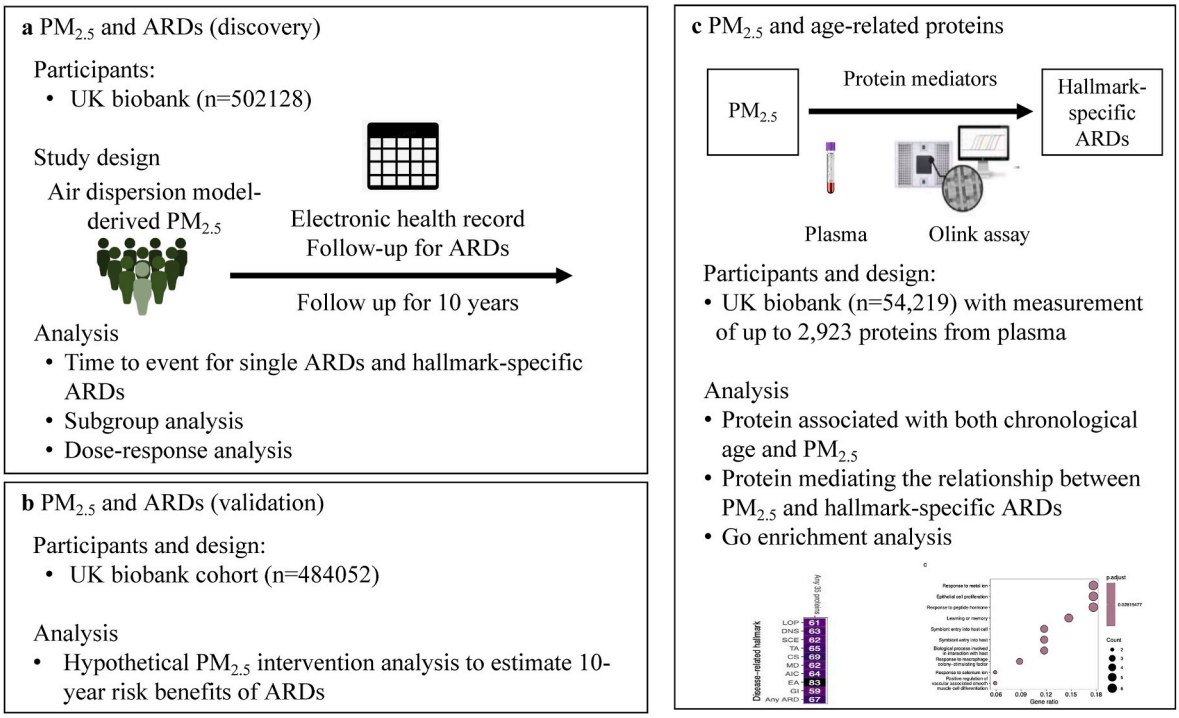

Fig. 1. Overview of the study design. **a.** Summary of discovery study characteristics and analysis in the UK Biobank. Annual mean $PM_{2.5}$ concentration at participants' residential addresses were obtained from the UK Department for Environment Food & Rural Affairs. ARDs were derived from UK national electronic health records, including dates and International Classification of Diseases diagnostic codes for hospitalizations and deaths of all participants. **b.** Schematic of the counterfactual intervention analysis. Hypothetical interventions were defined as threshold-based scenario in which individual-level ambient $PM_{2.5}$ exposures were reduced to 10 μg/m^3, consistent with England's 2040; Scotland's 2020 $PM_{2.5}$ control targets.

Table 1
Basic characteristics of participants.

Characteristics	n or %
Number of participants	502128
Age (years), mean (SD)	56.5 (8.1)
Sex	
Men	228973 (45.60%)
Female	273155 (54.40%)
Ethnicity	
British	442291 (88.08%)
Asian	11400 (2.27%)
Mixed	2971 (0.59%)
Others	45466 (9.05%)
BMI (kg/m^2), mean (SD)	27.4 (4.8)
Physical activity (MET, min/week)	
<500	59381 (11.83%)
500-1000	58228 (11.60%)
1000-1500	50021 (9.96%)
1500	217369 (43.29%)
Unknown	117129 (23.33%)
Education level	
High	161001 (32.06%)
Intermediate	160398 (31.94%)
Low	180729 (35.99%)
Smoking status	
Current	52937 (10.54%)
Never	273323 (54.43%)
Previous	172920 (34.44%)
Unknown	2948 (0.59%)
Alcohol consumption	
Current	460033 (91.62%)
Never	22359 (4.45%)
Previous	18084 (3.60%)
Unknown	1652 (0.33%)
Townsend deprivation index	
Tertile 1 (≤−3.14)	166965 (33.25%)
Tertile 2 (−3.14 to −0.59)	166987 (33.26%)
Tertile 3 (≥−0.59)	167552 (33.37%)
Missing	624 (0.12%)
Sleeping duration per night (hours)	
<7	132387 (36.36%)
7-9	365530 (72.80%)
>9	3324 (0.66%)
Household income (£)	
Less than 18,000	97144 (19.35%)
18,000–30,999	108099 (21.53%)
31,000–51,999	110690 (22.04%)
52,000–100,000	86201 (17.17%)
>100,000	22914 (4.56%)
Missing	71072 (14.15%)
Living alone	
Yes	92824 (18.49%)
No	404763 (80.61%)
Missing	4541 (0.90%)
Urbanization	
Village	23076 (4.59%)
Town	33843 (6.74%)
Urban	428453 (85.33%)
Missing	16756 (3.34%)
Employment	
Employed	286885 (57.13%)
Retired	166919 (33.24%)
Others	46250 (9.21%)
Missing	2074 (0.41%)

Continuous data was expressed as mean (SD), while categorical data was presented as number (%). Abbreviations: BMI, body mass index; SD, standard deviation.

confidence intervals (CIs) per 10 $\mu g/m^3$ increase in $PM_{2.5}$. To account for multiple comparisons across the large number of outcomes evaluated, we used Bonferroni correction, with statistical significance defined as $P < 0.05/83$ for analyses of the 83 ARDs and $P < 0.05/9$ for analyses of the 9 aging hallmarks.

To identify susceptible populations, we assessed effect modification by stratifying the analyses by age group (<65 years vs. ≥ 65 years) and sex (male vs. female). We used the two-sample *Z*-test to assess subgroup differences.

To characterize exposure-response relationships between long-term $PM_{2.5}$ exposure and the risk of any ARDs and the 9 hallmarks, we used restricted cubic spline (RCS) regression models with three knots for $PM_{2.5}$. The number of knots was determined based on the minimum of the Akaike Information Criterion (AIC) or Bayesian Information Criterion (BIC) (Yang et al., 2025), as detailed in Table S2. We used a likelihood ratio test to assess potential nonlinearity, comparing models with smooth $PM_{2.5}$ terms against those with linear terms (Yang et al., 2025).

To evaluate the potential public health impact of hypothetical ambient $PM_{2.5}$ intervention, we applied the parametric g-formula to estimate 10-year risks of ARDs and aging hallmarks under a counterfactual scenario in which $PM_{2.5}$ exposure was limited to ≤ 10 $\mu g/m^3$. For outcomes with statistically significant associations in the primary Cox models, we estimated the risk difference between the intervention scenario and the natural course, treating death as a competing event. Analyses were conducted under the assumptions of no unmeasured confounding, positivity, and consistency. Results were presented as the risk difference per 1000 population estimated using Monte Carlo simulation with 1000 iterations. Detailed methods are provided in **supplementary materials 1 (Method S1)**.

To explore the molecular mechanisms linking $PM_{2.5}$ exposure to aging hallmarks, we conducted a multi-stage proteomic analysis. First, we estimated the associations of 2923 circulating plasma proteins with long-term $PM_{2.5}$ exposure and chronological age using multiple linear regression models adjusted for sex, ethnicity, and assessment center. Effect estimates were presented as β coefficients with 95% CIs. To address multiple testing, we applied Bonferroni correction, with significance defined as adjusted $P < 0.05/2923$. Proteins showing significant associations with both $PM_{2.5}$ exposure and age were identified as candidates for downstream mediation analysis.

Second, we performed causal mediation analysis to quantify the pathways linking $PM_{2.5}$ exposure to aging hallmarks via the candidate proteins. Using inverse odds ratio weighting, we decomposed the total effect of $PM_{2.5}$ exposure into the natural direct effect (the effect independent of the protein-mediated pathway) and the natural indirect effect (the effect mediated through the protein network) (Shi et al., 2021). Mediation proportions were first determined for individual proteins within each hallmark, and subsequently aggregated across all significant mediators to estimate their collective contribution. Missing values were handled using multiple imputation, and 1000 bootstrap samples were used to calculate 95% CIs.

Third, we conducted functional annotation and pathway enrichment analyses of these candidate proteins using the Enrich platform, focusing on Gene Ontology (GO) terms in the Biological Process, Molecular Function, and Cellular Component categories. *P*-values were adjusted for multiple comparisons using the Benjamini–Hochberg method, with statistical significance defined as a false discovery rate (FDR) < 0.05.

To evaluate the robustness of our findings, we performed several sensitivity analyses. First, we considered alternative exposure windows using the 1-year (lag 0) and 5-year (lag 0-4) average. Second, to further mitigate potential reverse causality, we excluded participants diagnosed with any specific ARD within two years before baseline and repeated the main analyses. Third, we additionally adjusted for time-varying PMcoarse concentrations (lag 0-2), calculated as PM_{10} minus $PM_{2.5}$, to assess the robustness to adjustment for the coarse particulate fraction.

All statistical analyses were performed using R software (version 4.4.1). Two-tailed *P* values < 0.05 were considered statistically significant, and Bonferroni correction was applied when appropriate.

3. Results

3.1. Baseline characteristics

Of the 502,536 participants in the UK Biobank, 502,128 (99.9%) had complete data on residential address and mortality and were included in

the analytical cohort (Fig. 1). The mean age was 56.5 years [standard deviation (SD): 8.1], and the mean BMI was 27.4 kg/m^2 (SD: 4.8). The cohort comprised 273,155 (54.40%) women. Most participants were of British ethnicity (88.1%) and resided in urban areas (85.3%). Over half were never smokers (54.4%), reported current alcohol consumption (91.6%), achieved at least 1500 MET-minutes of physical activity per week (43.3%), and slept 7-9 h per night (72.8%) (Table 1).

From 2006 to 2022, $PM_{2.5}$ concentrations exhibited a consistent downward trend across all recruitment regions (Fig. S2). The overall mean $PM_{2.5}$ concentration over the study period was 9.38 μg/m^3 (SD: 1.74).

3.2. Association between $PM_{2.5}$ exposure and risk of ARDs and aging hallmarks

After Bonferroni correction, each 10 μg/m^3 increase in $PM_{2.5}$ was associated with higher risks of 12 ARDs, with HRs ranging from 1.12 to 2.38 (Fig. 2a and b; Fig. S3; Table S3). The strongest associations were observed for hematologic and lymphatic disorders, with primary thrombocytopaenia showing the greatest risk (HR: 2.38, 95% CI: 1.01, 5.58), followed by plasma cell cancer (HR: 2.06, 95% CI: 1.17, 3.62). The affected disease spectrum spanned hematologic and lymphatic disorders, metabolic diseases, kidney diseases, circulatory disorders, respiratory conditions, infections, and ophthalmologic degenerative

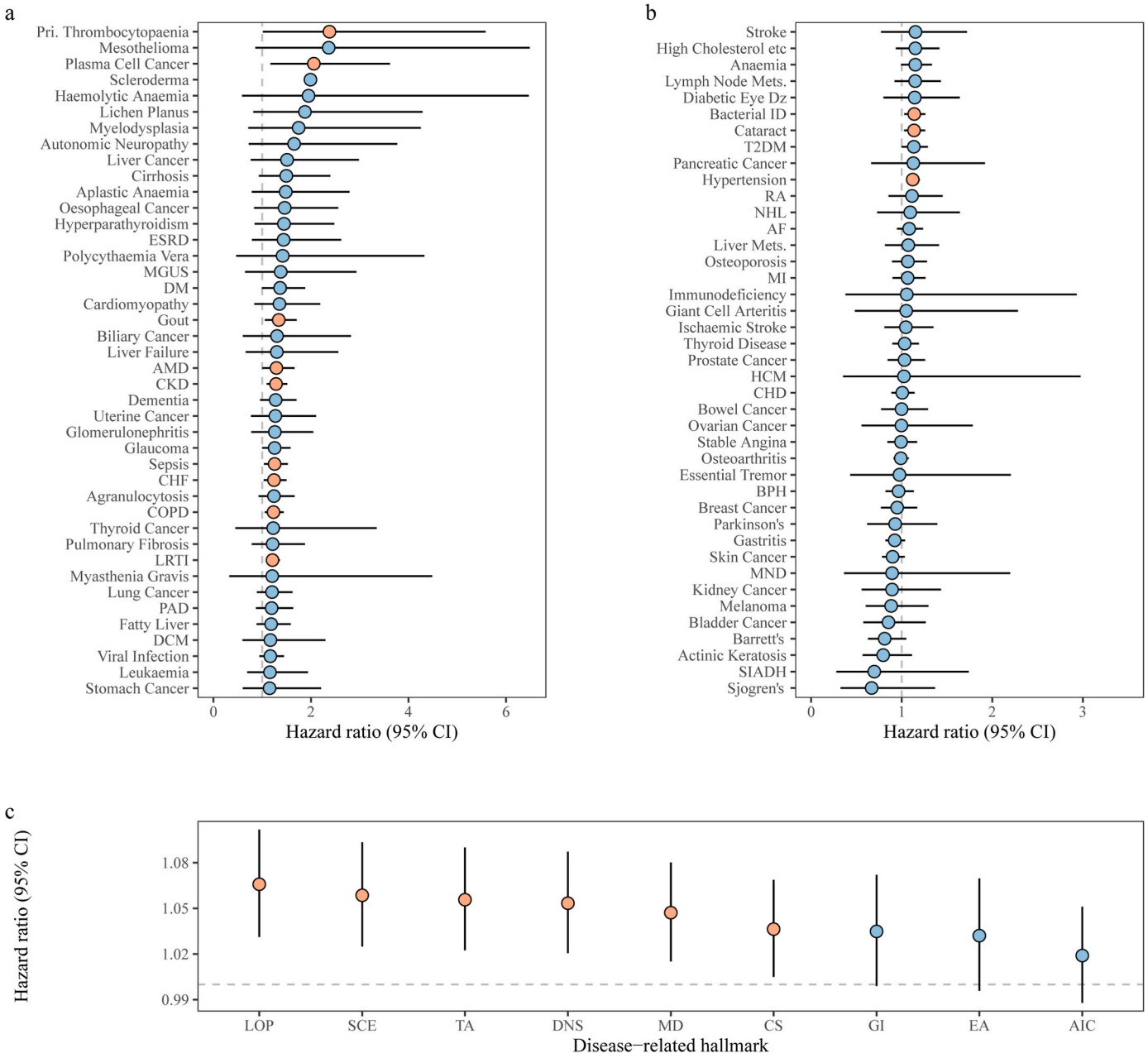

Fig. 2. Associations between 3-year average $PM_{2.5}$ exposure and hallmark-specific diseases and aging-related hallmarks. Forest plots showing hazard ratios (HRs) from Cox proportional hazards models for the association between long-term exposure to $PM_{2.5}$ (3-year moving average) and (**a** and **b**) 83 age-related diseases (ARDs) and (**c**) 9 aging-related hallmarks among participants free of the specific disease at baseline. Points represent HRs per 10 μg/m^3 increase in $PM_{2.5}$, with orange indicating statistical significance after Bonferroni correction ($P < 0.05/83$ for ARDs; $P < 0.05/9$ for hallmarks) and blue indicating non-significant associations. Error bars denote 95% confidence intervals. Abbreviations: AIC, altered intercellular communication; CI, confidence interval; CS, cellular senescence; DNS, deregulated nutrient sensing; EA, epigenetic alterations; GI, genomic instability; LOP, loss of proteostasis; MD, mitochondrial dysfunction; SCE, stem cell exhaustion; TA, telomere attrition. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

diseases.

Of the 9 aging hallmarks examined, exposure to $PM_{2.5}$ was associated with 6 after Bonferroni correction (Fig. 2c; Table S4), including LOP (HR: 1.07, 95% CI: 1.03, 1.10), SCE (HR: 1.06, 95% CI: 1.03, 1.09), TA (HR: 1.06, 95% CI: 1.02, 1.09), DNS (HR: 1.05, 95% CI: 1.02, 1.09), MD (HR: 1.05, 95% CI: 1.02, 1.08), and CS (HR: 1.04, 95% CI: 1.01, 1.07).

In restricted cubic spline analyses, LOP, EA, TA, and MD showed monotonic linear associations with increasing $PM_{2.5}$ concentrations. In contrast, GI, AIC, SCE, DNS, and CS displayed nonlinear relationships (nonlinear $P < 0.05$) (Fig. 3).

3.3. Subgroup analysis

The associations between long-term exposure to $PM_{2.5}$ and ARDs and aging hallmarks differed by sex and age (Table S5–S8). For example, males exhibited stronger associations with thyroid disease (HR: 1.56, 95% CI: 1.04, 2.35), diabetic eye disease (HR: 1.42, 95% CI: 1.03, 1.97), and glaucoma (HR: 1.11, 95% CI: 1.01, 1.22), whereas females showed higher risks for infections (e.g., sepsis, and lower respiratory tract infections) and cardiovascular disorders (e.g., hypertension, and congestive heart failure) (Table S5). In terms of aging hallmarks, exposure to $PM_{2.5}$ was associated with increased risks of TA, LOP, DNS, and SCE for females, while GI and MD for males (Fig. S4; Table S6).

Stratified analyses by age demonstrated that the associations were more pronounced among participants aged < 65 years than in those aged ≥ 65 years (Table S7–S8). Younger participants showed higher risks for bacterial infections, mesothelioma, primary thrombocytopaenia, cataract, COPD, and gout. Notably, significant associations between $PM_{2.5}$ and the hallmarks TA, LOP, DNS, MD, SCE, EA, and CS were observed exclusively in the younger age group, with no significant associations detected in older participants.

3.4. Hypothetical $PM_{2.5}$ reduction on the risk of ARDs and aging hallmarks

Compared with no intervention, the hypothetical intervention was estimated to reduce10-y risks for most ARDs, with the largest decreases observed for hypertension (10.20 per 1000 population; 95% CI: 6.28, 14.13) and cataract (8.22 per 1000 population; 95% CI: 7.77, 8.67). Substantial risk reductions were also observed across 9 aging hallmarks, with decreases ranging from 10.62 (95% CI: 6.47, 14.78) to 15.70 (95% CI: 10.81, 20.59) per 1000 population, particularly for LOP and DNS (Fig. 4).

3.5. Circulating proteins associated with $PM_{2.5}$ and aging

We identified 35 circulating proteins significantly associated with both chronological age and long-term $PM_{2.5}$ exposure (Fig. 5a and b). Exposure to $PM_{2.5}$ was associated with reduced levels of 15 proteins, with WFDC2, TFF1, and CXCL17 exhibiting the most pronounced

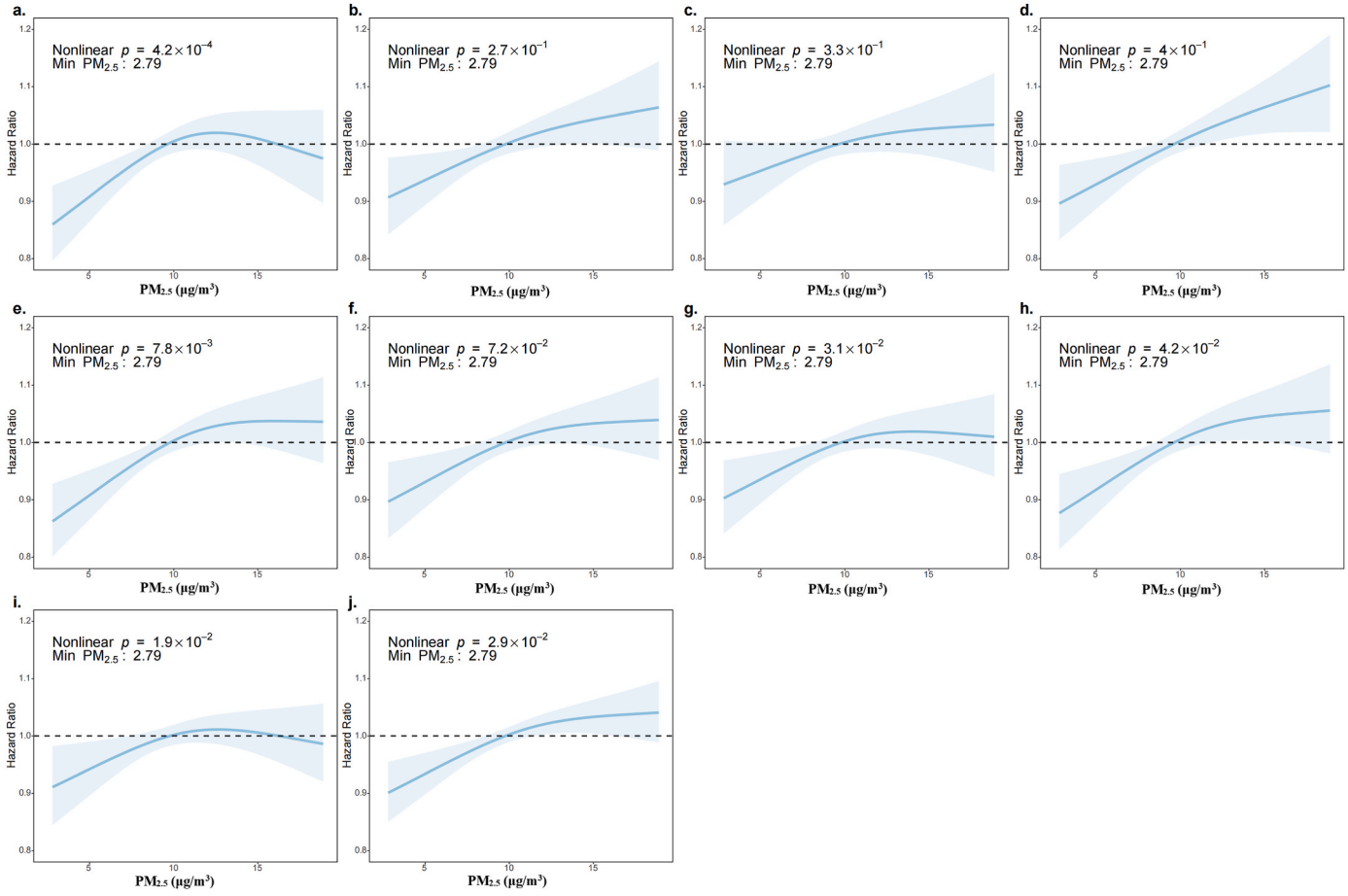

Fig. 3. Exposure-response relationships between long-term $PM_{2.5}$ exposure and aging-related hallmarks. Restricted cubic splines (RCS) models with three knots were used to evaluate the associations between long-term $PM_{2.5}$ exposure and the risks of aging hallmarks. The solid blue lines represent adjusted hazard ratios (HRs), and the shaded areas indicate 95% confidence intervals. *P* values for nonlinearity were derived from Wald χ^2 tests comparing models with smooth $PM_{2.5}$ terms against those with linear terms. **a.** Genomic instability; **b.** Telomere attrition; **c.** Epigenetic alterations; **d.** Loss of proteostasis; **e.** Deregulated nutrient sensing; **f.** Mitochondrial dysfunction; **g.** Cellular senescence; **h.** Stem cell exhaustion; **i.** Altered intercellular communication. **j.** Any hallmarks. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

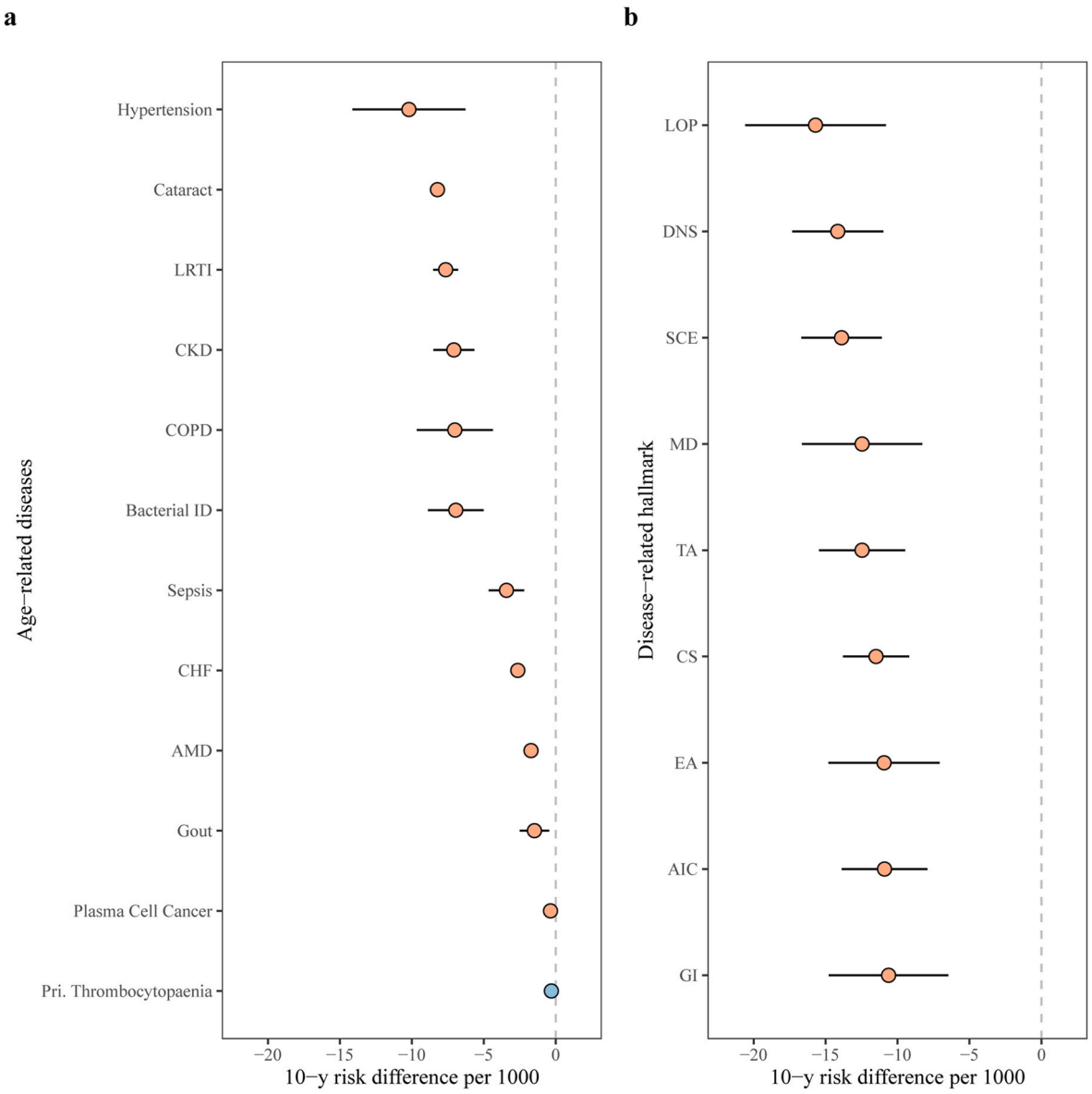

Fig. 4. Effects of hypothetical $PM_{2.5}$ intervention on aging-related hallmarks and hallmark-specific diseases. Forest plots showing estimated 10-year risk differences (per 1000 population) between the intervention scenario (reducing $PM_{2.5}$ to 10 μg/m^3 or less) and the natural course exposure for: (left panel) 9 aging-related hallmarks and (right panel) 12 hallmark-specific diseases. Orange points represented statistically significant associations after Bonferroni correction; blue points indicated non-significant results. Abbreviations: AIC, altered intercellular communication; CS, cellular senescence; DNS, deregulated nutrient sensing; EA, epigenetic alterations; GI, genomic instability; LOP, loss of proteostasis; MD, mitochondrial dysfunction; SCE, stem cell exhaustion; TA, telomere attrition. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

downregulation. The association between age and CXCL17 was exceptionally pronounced ($\beta > 2$) (Fig. 5d).

Collectively, these 35 proteins mediated 59-83% of the $PM_{2.5}$-aging hallmark associations, with the highest proportion for EA (83%) and the lowest for GI (59%). While most individual proteins contributed less than 10% of the total mediated effect, WFDC2, TFF1, and CXCL17 contributed 21%, 18%, and 14%, respectively (Fig. 5e).

3.6. GO enrichment analysis

Enrichment analysis of 35 $PM_{2.5}$-sensitive proteins revealed significant enrichment in aging-related mechanisms, environmental responses (e.g., response to metal ion, selenium ion, and peptide hormone), immune regulation, epithelial functions, host-symbiont interactions, and neural plasticity (gene ratios: 0.06-0.18; Fig. 5c). At the Molecular Function level, proteins were enriched in transmembrane receptor activities, including tyrosine phosphatases, tyrosine kinases, and serine-type endopeptidases. At the Cellular Component level, enrichment was observed in the endoplasmic reticulum lumen, collagen-containing extracellular matrix, and focal adhesion (Fig. S7).

3.7. Sensitivity analysis

We performed a series of sensitivity analyses to assess the robustness of our findings. Results remained consistent when using alternative $PM_{2.5}$ exposure windows (lag 0 and lag 0-4; Fig. S3–S4), after excluding participants with hallmark-related diseases diagnosed within two years before baseline (Table S9–S14), and following additional adjustment for time-varying PMcoarse (lag 0-2; Table S15–S16).

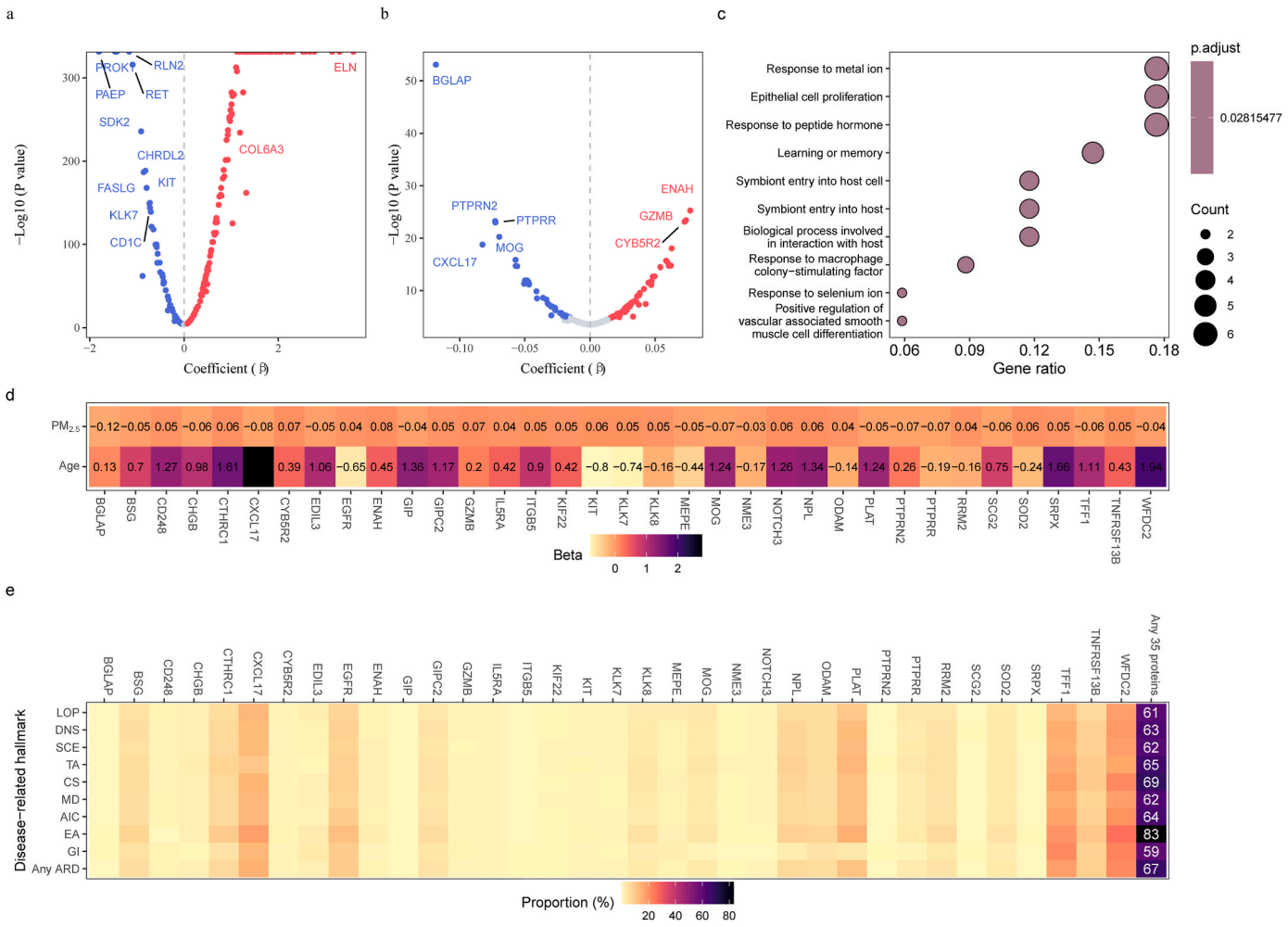

Fig. 5. Plasma protein biomarkers linking $PM_{2.5}$ exposure to aging-related hallmarks. Volcano plots (**a.** and **b.**) showing proteins associated with (**a.**) chronological age and (**b.**) $PM_{2.5}$ exposure from linear regression models. Red points indicate positive associations; blue points indicate negative associations; gray points indicate non-significant associations. **c.** Gene Ontology (GO) enrichment analysis identified 35 $PM_{2.5}$-sensitive proteins, with dot size representing the number of proteins enriched in each term, and the x-axis showing enrichment proportion. **d.** Heatmap displaying linear regression coefficients for $PM_{2.5}$ exposure (top) and age (bottom) associations with candidate mediator proteins. **e.** Mediation analysis showing the proportion of $PM_{2.5}$-hallmark associations mediated by the 35 proteins. The color gradient (yellow to purple) represents the direction and magnitude of the mediation proportion; black indicates strong positive mediation. Abbreviations: AIC, altered intercellular communication; ARDs, age-related diseases; CS, cellular senescence; DNS, deregulated nutrient sensing; EA, epigenetic alterations; GI, genomic instability; LOP, loss of proteostasis; MD, mitochondrial dysfunction; SCE, stem cell exhaustion; TA, telomere attrition. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

4. Discussion

In this large prospective cohort study of 502,128 UK Biobank participants, we found that long-term exposure to $PM_{2.5}$ was associated with increased risks of multiple age-related diseases and several hallmarks of aging. Counterfactual analyses estimated substantial 10-year risk reductions for both ARDs and aging hallmarks under a hypothetical scenario in which $PM_{2.5}$ concentrations were reduced to $\leq$10 μg/m^3. Proteomic profiling further identified 35 circulating proteins that collectively mediated a substantial proportion of the observed $PM_{2.5}$–aging hallmark associations, with WFDC2, TFF1, and CXCL17 emerging as key contributors. Collectively, our findings extend current understanding of $PM_{2.5}$-related health risks by integrating disease outcomes, aging biology, and molecular correlates within a unified analytical framework.

Our findings align with and extend previous epidemiological studies linking $PM_{2.5}$ exposure to increased risks of specific ARDs. Prior analyses within the UK Biobank and other large cohorts have reported associations between long-term $PM_{2.5}$ exposure and immune thrombocytopenic purpura, heart failure, gout, and ocular diseases, including glaucoma and cataracts (Abdolalizadeh and Falavarjani, 2023; Cui et al., 2024; Hu and Lin, 2020; Wang et al., 2021). Additional studies have shown that $PM_{2.5}$ exposure contributes to respiratory morbidity, particularly asthma and COPD, and accelerates vascular aging, thereby increasing cardiovascular disease risk (Chen et al., 2024; Renzi et al., 2022). However, most existing studies have focused on individual diseases or organ systems. In contrast, our study adopts a comprehensive, system-wide analytical framework encompassing 83 ARDs across multiple organ systems, allowing us to delineate which disease clusters are most strongly linked to $PM_{2.5}$. By demonstrating that $PM_{2.5}$-related risks span hematologic, metabolic, renal, cardiovascular, respiratory, infectious, and degenerative ocular diseases, our results suggest that air pollution contributes to a generalized acceleration of age-related disease burden rather than selective pathogenic effects.

A key novel contribution of this study is the explicit integration of ARD spectra with conserved hallmarks of aging. We observed consistent associations between long-term $PM_{2.5}$ exposure and six aging hallmarks—LOP, SCE, TA, DNS, MD, and CS, whereas associations with AIC, EA, and GI-related immune changes were relatively modest. This pattern provides a biologically coherent explanation for the multisystem

disease associations observed. The biological plausibility of these findings is supported by substantial experimental and epidemiological evidence. $PM_{2.5}$ exposure has been shown to induce oxidative stress and protein misfolding, impairing proteasomal and autophagic pathways and thereby exacerbating proteostasis imbalance (Levine and Kroemer, 2019; Rajagopalan et al., 2024). Experimental and epidemiological evidence further indicates that $PM_{2.5}$ disrupts hematopoietic stem cell function through inflammation- and NRF2-dependent mechanisms, contributing to stem cell exhaustion (Wang et al., 2023). Telomere shortening and telomerase inhibition following $PM_{2.5}$ exposure have been consistently reported (Gomes et al., 2025; Martens et al., 2017), while DNA double-strand breaks and compromised DNA repair efficiency underpin genomic instability (Ren et al., 2017). Additionally, $PM_{2.5}$ inhibition of mitochondrial respiratory chain complexes I and III leads to mitochondrial membrane depolarization and mtDNA leakage, reinforcing mitochondrial dysfunction and inflammatory signaling (Cui et al., 2024). Together, these findings from previous studies support the biological plausibility of pathways linking $PM_{2.5}$ exposure to aging-related processes.

Our mediation analyses identified 35 circulating proteins that collectively explained 59% to 83% of the observed associations between $PM_{2.5}$ exposure and aging hallmarks. While most individual proteins contributed modestly, their collective contribution suggests that multiple interconnected biological pathways may be involved, consistent with the multifactorial nature of biological aging. Among these proteins, WFDC2, TFF1, and CXCL17 emerged as prominent mediators. WFDC2, one of the most strongly age-upregulated proteins, plays critical roles in inflammation, epithelial homeostasis, and tumorigenesis. Dysregulation of WFDC2 may disrupt the balance between cell proliferation and apoptosis, promoting senescent cell accumulation and functional tissue decline—hallmark features of aging (Chen et al., 2012; Xu et al., 2024). The observed negative association between $PM_{2.5}$ exposure and TFF1 suggests impaired mucosal barrier integrity, which may facilitate pollutant penetration, chronic inflammation, and cumulative tissue damage (Aihara et al., 2017; Soutto et al., 2019). CXCL17, a chemokine involved in immune regulation and inflammatory recruitment, may amplify $PM_{2.5}$-induced inflammatory cascades, contributing to persistent low-grade inflammation, a recognized driver of aging processes (Franceschi et al., 2018; Ocón et al., 2024). Nevertheless, these mediation findings should be interpreted cautiously, as observational mediation analyses rely on assumptions that cannot be fully verified, including the absence of unmeasured confounding between exposure, mediators, and outcomes. Therefore, the estimated mediation proportions should not be interpreted as definitive evidence of causal biological pathways; instead, these findings highlight candidate proteins that warrant further mechanistic investigation.

Our counterfactual analyses indicate that reducing $PM_{2.5}$ concentrations below 10 $\mu g/m^3$ would yield the largest absolute risk reductions for hypertension and cataracts, alongside consistent reductions across all aging hallmarks, particularly LOP and DNS. These findings are biologically plausible, as oxidative stress and protein damage are shared mechanisms underlying both vascular dysfunction and lens opacity (Li et al., 2023; Zhang et al., 2018). Importantly, the estimated reductions were observed not only for individual diseases but also across multiple aging hallmarks, suggesting that aging-related processes may contribute to the broad health burden associated with long-term $PM_{2.5}$ exposure. From a population health perspective, these findings provide additional support for efforts to reduce ambient air pollution and achieve WHO-recommended air quality standards. Because these estimates were derived from a counterfactual framework applied to observational data, they should be interpreted as estimated risk reductions under specified model assumptions rather than direct evidence of intervention effects.

This study has several limitations. First, the UKB cohort primarily consists of white participants recruited through voluntary enrollment rather than random sampling, which may introduce healthy volunteer bias. Caution is warranted when generalizing the findings to populations with different racial/ethnic, geographic, or socioeconomic backgrounds. Second, long-term $PM_{2.5}$ exposure was estimated using residential geocoding, which may have resulted in some degree of exposure misclassification because individual-level exposure variability related to indoor air pollution sources, occupational environments, commuting patterns, residential mobility, and time spent away from home was not captured. Third, the aging hallmarks examined in this study were inferred through disease-based classifications rather than direct biological measurements. As a result, they may not fully capture the complexity and interconnected nature of aging biology. Therefore, the observed associations should be interpreted as associations with aging hallmark–related disease phenotypes rather than direct evidence of dysregulation of specific aging mechanisms. Fourth, although we adjusted for a comprehensive set of covariates, the observational study design cannot entirely rule out unmeasured confounders such as genetic background, early-life environmental exposures or other socioeconomic factors that may influence both air pollution exposure and aging.

In conclusion, long-term exposure to $PM_{2.5}$ was associated with increased risks of multiple ARDs and several recognized aging hallmarks. By integrating disease outcomes, aging hallmarks, and proteomic correlates, our study provides epidemiological evidence linking air pollution exposure to aging-related processes across multiple biological systems. From a public health perspective, our findings suggest that reducing long-term $PM_{2.5}$ exposure and achieving WHO-recommended air quality standards may help lessen the burden of ARDs and promote healthy aging at the population level.

CRediT authorship contribution statement

Furong Wang: Formal analysis, Methodology, Visualization, Writing – original draft. **Jingsong Luo:** Conceptualization, Formal analysis, Investigation, Methodology. **Yangchang Zhang:** Data curation. **Niya Zhou:** Funding acquisition, Writing – review & editing. **Wangnan Cao:** Supervision, Writing – review & editing. **Shengzhi Sun:** Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atmosenv.2026.122313.

Data availability

This research was conducted with the UK Biobank Resource, under application number 104745. The data employed in this research are obtainable from UK Biobank, subject to applicable access restrictions. Individuals may request access to UK Biobank data by following the standard application process (https://www.ukbiobank.ac.uk/register-apply/). $PM_{2.5}$ exposure concentration data for this study were provided by DEFRA and can be accessed at the link: https://uk-air.defra.gov.uk/data/pcm-data.

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