

Associations between PM_{2.5} exposure and COPD and gastrointestinal conditions: Underlying lung-gut metabolic communication

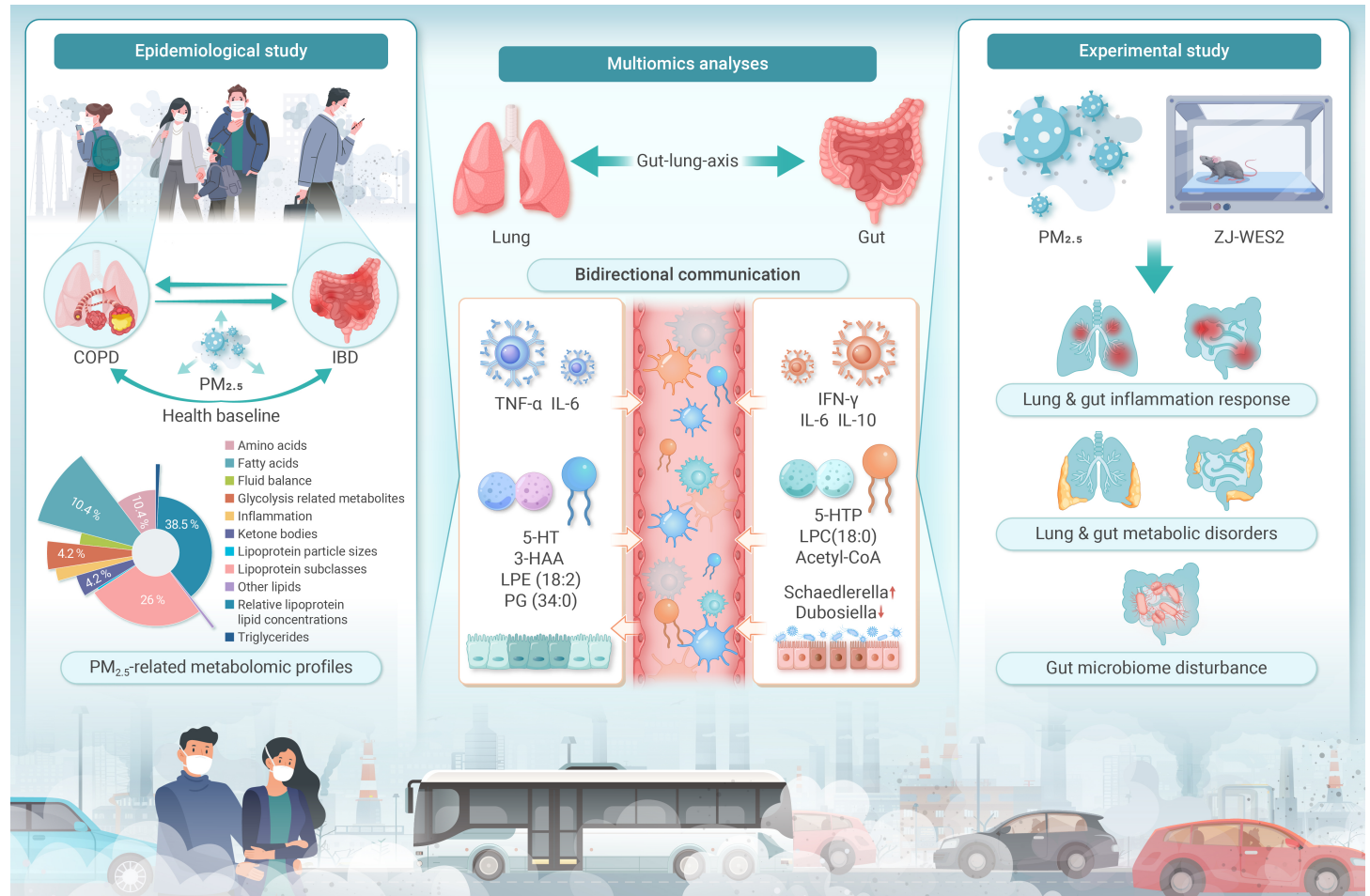
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Received: February 28, 2025; Accepted: November 17, 2025; Published Online: November 19, 2025; <https://doi.org/10.59717/j.xinn-med.2025.100175>

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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Exposure to PM_{2.5} increases the risk of disease transition between COPD and gastrointestinal (GI) diseases.
- PM_{2.5} alters the gut microbiome, affecting lung and gut metabolites and inflammation in both regions.
- Imbalance metabolic communication between the lung and gut under PM_{2.5} exposure.
- Tryptophan and glycerophospholipid metabolism changes are key to lung-gut communication upon PM_{2.5} exposure.

Associations between PM_{2.5} exposure and COPD and gastrointestinal conditions: Underlying lung-gut metabolic communication

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Received: February 28, 2025; Accepted: November 17, 2025; Published Online: November 19, 2025; <https://doi.org/10.59717/j.xinn-med.2025.100175>

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Citation: Shi H., Hou T., Tan L., et al. (2025). Associations between PM_{2.5} exposure and COPD and gastrointestinal conditions: Underlying lung-gut metabolic communication. *The Innovation Medicine* 3:100175.

Background: While the individual effects of PM_{2.5} on the respiratory and gastrointestinal (GI) systems are known, its combined impact on these organs and the underlying mechanisms involved remain unclear. We aimed to investigate the associations between PM_{2.5} exposure and the risk of chronic obstructive pulmonary disease (COPD) and GI diseases and to explore lung-gut metabolic communication. **Methods:** Data from the UK Biobank were analysed. The PM_{2.5}-related metabolic signature was evaluated via elastic net regression analysis. A multistate model was used to assess the dynamic impact of PM_{2.5} on COPD and four GI diseases. Male C57BL/6N mice were exposed to PM_{2.5} or filtered air for 8 weeks. Underlying metabolic mechanisms were elucidated through multiomics analyses. **Results:** Our cohort analysis showed that PM_{2.5} exposure affects the transition from COPD to inflammatory bowel disease (IBD) [HR (95% CI): 1.23 (1.09, 1.49)] and from IBD to COPD [HR (95% CI): 1.09 (1.02, 1.47)]. Similarly, PM_{2.5}-related metabolomic profiles affect COPD and IBD transition. Exposure to PM_{2.5} induced metabolic alterations in lung and gut tissues. Multiomics analysis revealed that tryptophan and glycerophospholipid metabolites were significantly associated with inflammatory markers and the key gut microbiome. Mediation analysis showed that key metabolites mediate the associations between the gut microbiome and inflammatory markers. **Conclusion:** A significant dynamic association was found between PM_{2.5} exposure and the risk of COPD and GI diseases. This association may be attributed to the crucial role of tryptophan and glycerophospholipid metabolism in mediating lung and gut communication under PM_{2.5} exposure, as identified in animal experiments.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and gastrointestinal (GI) diseases are interconnected clinical conditions. Up to 85% of patients with COPD report GI symptoms, and the prevalence of inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) is markedly higher in this population.^{1,2} Furthermore, gastroesophageal reflux disease (GERD) has been identified as a strong risk factor for COPD exacerbation,³ while patients with IBD have a higher incidence of respiratory symptoms than do those without IBD.⁴⁻⁶ The co-occurrence of pulmonary and GI diseases is increasingly recognized and is generally associated with poorer health outcomes.^{7,8}

This interaction is mediated by the gut-lung axis, a bidirectional communication pathway that enables the two systems to influence each other's physiological and pathological processes.^{9,10} Environmental exposure plays a significant role in modulating this axis.¹¹ Cigarette smoking, for example, has been shown to promote IBD and GERD in COPD patients.¹² In recent years, air pollution, especially fine particulate matter with a diameter of 2.5 micrometers or less (PM_{2.5}), has been widely recognized as a significant risk factor for COPD morbidity and mortality,¹³⁻¹⁵ and its association with various intestinal disorders has gradually been revealed.¹⁶⁻¹⁸ Thus, PM_{2.5} is increasingly identified as a potentially important risk factor for gut-lung homeostasis.¹⁹ PM_{2.5} can affect the respiratory and GI systems through different exposure routes: inhaled PM_{2.5} mainly enters circulation through pulmonary blood barrier, while another portion enters the GI tract through swallowing, directly causing mucosal damage or indirectly inducing systemic inflammatory response.²⁰⁻²²

These exposure pathways highlight the common vulnerability of lungs and gut to PM_{2.5}.²³ Despite these findings, the mechanisms by which PM_{2.5} perturbs the gut-lung axis remain poorly understood.

Emerging evidence highlights metabolites and the microbiota as key mediators in this process.^{24,25} Specifically, PM_{2.5} may impair epithelial barrier integrity and promote systemic inflammation through alterations in microbial secretions, metabolites, immune mediators, and lipid metabolism.²⁶⁻²⁹ In addition, metabolites, including sugars, fatty acids, and amino acids, in the lung play crucial roles in modulating immune responses.³⁰ These findings indicate that metabolic biomarkers could offer significant insights into the biological pathways that connect environmental exposure with pulmonary and GI diseases.

Accordingly, this study aimed to integrate evidence from a prospective cohort study with findings from animal toxicology experiments to elucidate the dynamic relationship between PM_{2.5} exposure and the risk of COPD and GI diseases, and to explore the underlying biological mechanisms.

MATERIALS AND METHODS

This research was organized into two parts: a prospective cohort study and a toxicological analysis.

Study design and participants

This epidemiological analysis utilized data from the UK Biobank (UKB), and the detailed methodology has been previously described.³¹ A total of 419,362 participants were initially included to examine the associations between PM_{2.5} exposure and the risk of COPD and GI diseases. After individuals without metabolomics data (n=219,631) were excluded, 199,731 participants remained for analyses of PM_{2.5}-related metabolic profiles and disease associations (Figure 1A).

This study followed the STROBE reporting guidelines. Ethical approval was obtained from the National Research Ethics Service of the National Health Service (11/NW/0382), and this project was conducted under UKB application ID 69550.

Outcome and covariate assessment

The primary outcomes were incident diagnoses of COPD and GI diseases, including IBD, IBS, GERD, and peptic ulcers (PU). The outcomes were ascertained by linkage to UK National Health Service (NHS) electronic health records, which provide longitudinal hospital admission and primary care data. Diagnoses were identified using the 10th Revision of the International Classification of Diseases (ICD-10) codes: COPD (J44), IBD (K50-K51), IBS (K58), GERD (K21), and PU (K25-K27). Follow-up was defined from the baseline assessment until the first recorded diagnosis, loss to follow-up, or December 31, 2022.

Covariates were selected based on prior literature,³² and included age, sex, ethnicity, body mass index (BMI), household income (<£31,000 vs. ≥£31,000), smoking status (never, former, current), alcohol consumption (never, occasional, moderate, heavy), physical activity, dietary score, hypertension, diabetes, hyperlipidemia, and medication use. Physical activity was assessed with the short form of the International Physical Activity Questionnaire (IPAQ).³³ Dietary scores were derived from 24-hour dietary recall question-

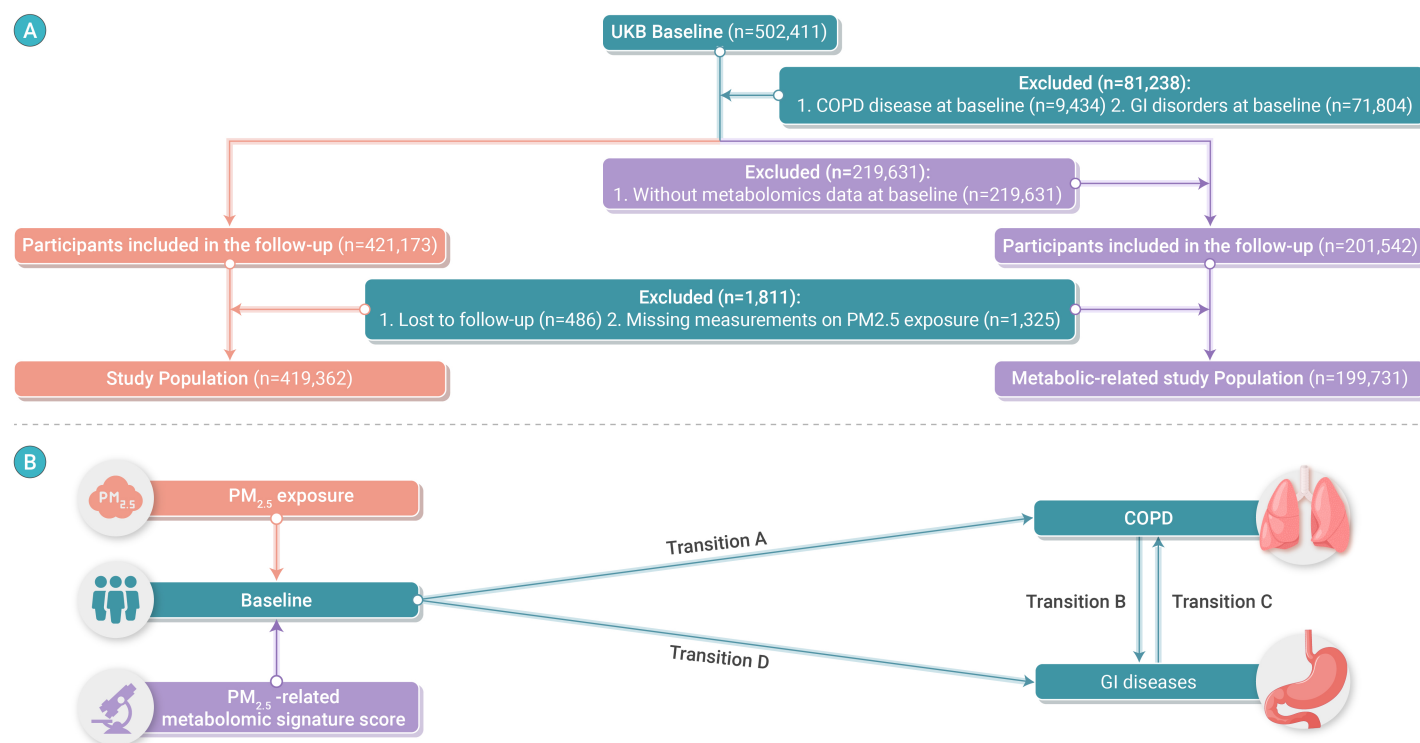


Figure 1. (A) Study participant selection flowchart. (B) Multistate model depicting transitions between health states: participants from baseline to COPD (Transition A); from COPD to GI diseases (Transition B); from GI diseases to COPD (Transition C); and from baseline to GI diseases (Transition D).

naires.³⁴ Hypertension, diabetes, and hyperlipidemia were identified from self-reports and diagnosis codes. Medication data, including the use of non-steroidal anti-inflammatory drugs and aminosalicylates, were collected via touchscreen questionnaires and interviews.⁴ Detailed covariate definitions are provided in the Supplementary Methods.

PM_{2.5} exposure estimates of participants

PM_{2.5} exposure was estimated using high-resolution air pollution data from the UK Department for Environment, Food and Rural Affairs (DEFRA) and annual 1×1 km concentration maps were generated by an air dispersion model.^{35,36} The exposure levels were assigned to geocoded residential addresses by bilinear interpolation from the four nearest grid points.^{37,38} For participants who relocated, exposures were weighted by residential history and duration at each address.³⁹ This approach has been validated in prior studies.^{36,40} To assess long-term exposure more accurately, the estimates included data from the three years preceding enrollment as well as the follow-up endpoints. Details of the exposure model are provided in the Supplementary Methods.

Plasma metabolite profiling of participants

Blood samples (45 ml) were collected from participants at 22 UKB assessment centers between 2007 and 2010, typically under non-fasting conditions. Standardized protocols for sample collection, processing, and storage have been reported previously.⁴¹ Metabolic biomarkers were quantified using a high-throughput NMR platform (Nightingale Health Ltd.), which measures 251 biomarkers spanning lipoprotein lipids, fatty acids, and other low-molecular-weight metabolites.^{42–44} Additional methodological details are available in the Supplementary Methods.

Animals and PM_{2.5} exposure model

Eight-week-old male C57BL/6N mice were obtained from Shanghai Laboratory Animal Co., Ltd. (SLAC) and housed under standard conditions (22–24°C, 55–65% humidity, 12-hour light/dark cycle) with free access to water and food. Mice with abnormal behavior or health issues were excluded before experimentation. All procedures were approved by the Institutional Animal Care and Use Committee of Zhejiang Chinese Medical University (Approval

No. IACUC-20241230-14) and conducted in accordance with ARRIVE guidelines.

After one week of acclimatization, the mice were randomly assigned to the particulate matter (PM) exposure (n=10) or filtered air (FA) exposure (n=10) groups. Exposures were performed using the Zhejiang Whole-body Exposure System 2 (ZJ-WES2), as described previously.^{45,46} Briefly, concentrated PM_{2.5} was generated using serial virtual impactors, dried by diffusion, and delivered to the exposure chamber, whereas FA was generated by passing air through a high-efficiency particulate air (HEPA) filter. The mice in the PM group were exposed to concentrated PM_{2.5} for 12 hours/day for 8 weeks, as described in previous studies.^{46,47} The concentration of PM_{2.5} in the chambers was continuously monitored in real-time utilizing an aerosol monitor.⁴⁸

Sample collection, histology and biochemical analyses

The mice were euthanized by neck dislocation after 8 weeks of exposure, and lung and intestinal (ileum and colon) tissue samples were collected. Sections were stained with hematoxylin and eosin (H&E), alcian blue (AB), and periodic acid-Schiff (PAS). Lung injury scores were calculated as the sum of the inflammatory and mucus exudate scores.^{49,50} Colon pathology was performed according to previous literature.⁵¹ The levels of IL-6, IL-10, TNF-α, and IFN-γ in the lung and gut tissues were quantified by ELISA (Elabscience, Wuhan, China).

Untargeted metabolomics

Lung and gut tissues (30 mg ± 2%) were collected and stored at -80°C. Untargeted metabolomics was performed on a UPLC-Synapt XS system (Waters Corp., Milford, USA). Quality control (QC) samples were prepared by pooling equal aliquots from each sample. Detailed profiling and downstream analyses are provided in the Supplementary Methods.

Metagenomic sequencing

Fresh fecal pellets were collected immediately before euthanasia. DNA extraction and metagenomic sequencing were performed on the BGI DNBSEQ-T7 platform following standardized protocols. The detailed procedures, quality control, and sequencing parameters are described in the Supplementary Methods.

Statistical analyses

Identification of metabolite signatures after PM_{2.5} exposure in participants We applied elastic net regression (ENR) to identify a metabolic signature of PM_{2.5} exposure.^{52,53} Outliers were excluded based on $\pm 1.5 \times$ IQR of log-transformed metabolite values. The optimal penalty parameter was determined by 10-fold cross-validation.⁵⁴ The metabolic signature was calculated as the weighted sum of selected nonzero coefficients, and the z-score was normalized. Path analysis was conducted on the metabolites identified through the ENR using MetaboAnalyst 6.0.⁵⁵ Multiple testing was corrected by the Benjamini–Hochberg false discovery rate (FDR). Details of the ENR parameterization are provided in the Supplementary Methods.

Associations between PM_{2.5}, the metabolic signature and disease in participants. To provide contextual support for our study hypotheses, we first examined associations between COPD and GI diseases using Cox proportional hazards models. We subsequently employed multistate models to analyze the dynamic relationships among PM_{2.5} exposure, the PM_{2.5}-related metabolomic signature, and disease risk (Figure 1B). For each COPD–GI disease pair (IBD, IBS, GERD, and PU), the model included three states: baseline (disease-free), COPD, and GI disease. Transitions captured (A) baseline → COPD, (B) COPD → GI disease, (C) GI disease → COPD, and (D) baseline → GI disease. For participants with concordant COPD and GI diagnosis dates, the COPD diagnosis date was determined by subtracting 0.5 days from the GI diagnosis date. Details of the multistate model are provided in the supplementary Methods.

We further performed mediation analysis to examine whether PM_{2.5}-related metabolic scores mediate the associations between PM_{2.5} exposure and disease outcomes.⁵⁶ A quasi-Bayesian Monte Carlo approach (500 simulations) was used to estimate the average causal mediation effect (ACME), the average direct effect (ADE), and the proportion mediated.

Subgroup and sensitivity analysis. Subgroup analyses were conducted by age (< 65 vs. ≥ 65 years), sex, BMI (< 28 vs. ≥ 28 kg/m²), smoking status (never vs. ever or current), and physical activity (low vs. moderate/high level). Two sensitivity analyses were used to test robustness: (1) applying 1-, 3-, and 5-year intervals for same-day disease transitions; and (2) treating chronic diseases (hypertension, diabetes, and coronary heart disease) as competing risks using Fine–Gray subdistribution hazard models.

All models were adjusted for age, sex, ethnicity, BMI, household income, smoking status, alcohol consumption, dietary score, physical activity, hypertension, diabetes, hyperlipidemia, and medication use. Associations of individual metabolites (log-transformed and z-scored) with disease risk were examined using Cox models. The results are expressed as hazard ratios (HRs) with 95% confidence intervals (CIs) per interquartile range (IQRs) increase in PM_{2.5} exposure.

Statistical analysis of the mouse experiments. The data are expressed as the means ± SDs. Group differences were evaluated by Student's t test. Principal component analysis (PCA) and orthogonal partial least squares discriminant analysis (OPLS-DA) were employed to evaluate alterations in metabolite profiles between groups. OPLS-DA models were validated via a 7-fold cross-validation and 999-fold permutation test.⁵⁷ Differentially abundant metabolites were defined by a VIP value > 1 and an FDR < 0.05. Spearman correlation was used to assess the associations of metabolites within lung and gut tissues (FDR < 0.05). Network Explorer and Debiased Sparse Partial Correlation (DSPC) analyses identified nonlinear interactions and key metabolic nodes, which were visualized using MetaboAnalyst 6.0. Sankey plots illustrating links between metabolic pathways in humans and mice. Finally, integrative multiomics analyses were performed using DIABLO (R package “mixOmics”) to combine metabolomic, gut microbiome, and inflammatory marker data, enabling the identification of biologically relevant features.⁵⁸ Mediation analysis was performed to assess whether metabolites mediate the relationships between gut microbiome and inflammatory markers (FDR < 0.05). Mediation analyses were conducted using the “mediation” package in R (version 4.4.2).

RESULTS

Descriptive analysis of UK Biobank participants

This study included 419,362 participants (Table 1). The mean age was 56.30±8.13 years, 46.0% were male, and the mean BMI was 27.30 kg/m². The

Table 1. Characteristics of 419,362 participants from the baseline.

Variables	Overall (N=419,362)
Demographics	
Age, years	56.30 (8.13)
Male (%)	192,847 (46.0%)
Ethnicity	
White	394,619 (94.1%)
Non-White	24,743 (5.9%)
BMI, kg/m2	27.3(4.74)
Missing	2,555 (0.6%)
Household income (%)	
< £31000	165,477 (39.5%)
≥ £31000	190,864 (45.5%)
Unknown	63,021 (15.0%)
Smoking status (%)	
Never	233,760 (55.7%)
Previous	140,609 (33.5%)
Current	42,602 (10.2%)
Prefer not to answer	2,391 (0.6%)
Alcohol consumption (%)	
Never	31,928 (7.6%)
Occasional	92,783 (22.1%)
Moderate	207,205 (49.4%)
Heavy	86,221 (20.6%)
Missing	1,225 (0.3%)
Physical activity	
Low	62,052 (14.8%)
Moderate	138,175 (32.9%)
High	137,575 (32.8%)
Missing	81,560 (19.4%)
Dietary score	
Missing	84,831 (20.2%)
Clinical characteristics	
Hypertension (%)	177,585 (42.3%)
Diabetes (%)	23,892 (5.7%)
Hyperlipidemia	95,614 (22.8%)
Medication use (%)	18,846 (4.5%)
Ambient pollutants (µg/m³)	
PM _{2.5}	10.5 (2.13)

mean PM_{2.5} concentration was 10.5±2.13 µg/m³. During a median follow-up of 13.93 years, 14,191 (3.38%) participants were diagnosed with COPD, 2,451 (0.58%) with IBD, 8,009 (1.90%) with IBS, 36,812 (8.78%) with GERD, and 7,202 (1.72%) with PU. The baseline characteristics of 199,731 patients with PM_{2.5}-related metabolomic data were similar to those of the overall cohort (Table S1).



Figure 2. Metabolomic signatures and disease associations with $PM_{2.5}$ exposure (A) Metabolites selected by elastic net regression for $PM_{2.5}$ exposure. (B) Heatmap of associations between metabolites and COPD, IBD, IBS, GERD, and PU. (C) Classification of metabolites associated with $PM_{2.5}$ exposure. (D) KEGG pathway analysis of metabolites related to $PM_{2.5}$ exposure. (E) Multistate regression analyses of the associations between $PM_{2.5}$ exposure and the risk of COPD and GI disease. (F) Multistate regression analyses of the associations between the $PM_{2.5}$ -related metabolomic signature score and the risk of COPD and GI disease.

Metabolomic signature of $PM_{2.5}$ exposure

The ENR model has an R^2 of 0.61. The ENR model identified 130 metabolites contributing to the $PM_{2.5}$ -related metabolomic signature (Figure 2A & Table S2), including lipoprotein lipids, fatty acids, amino acids, and ketone bodies (Figure 2C). The mean metabolic signature score was 0.09 ± 14.83

(Figure S1), and was positively correlated with $PM_{2.5}$ exposure (Pearson's $r = 0.70$, $P < 0.001$). Pathway enrichment revealed that $PM_{2.5}$ exposure was significantly associated with the dysregulation of eight metabolic pathways involving amino acid metabolism, lipid metabolism, and glucose metabolism (Figure 2D & Table S3).

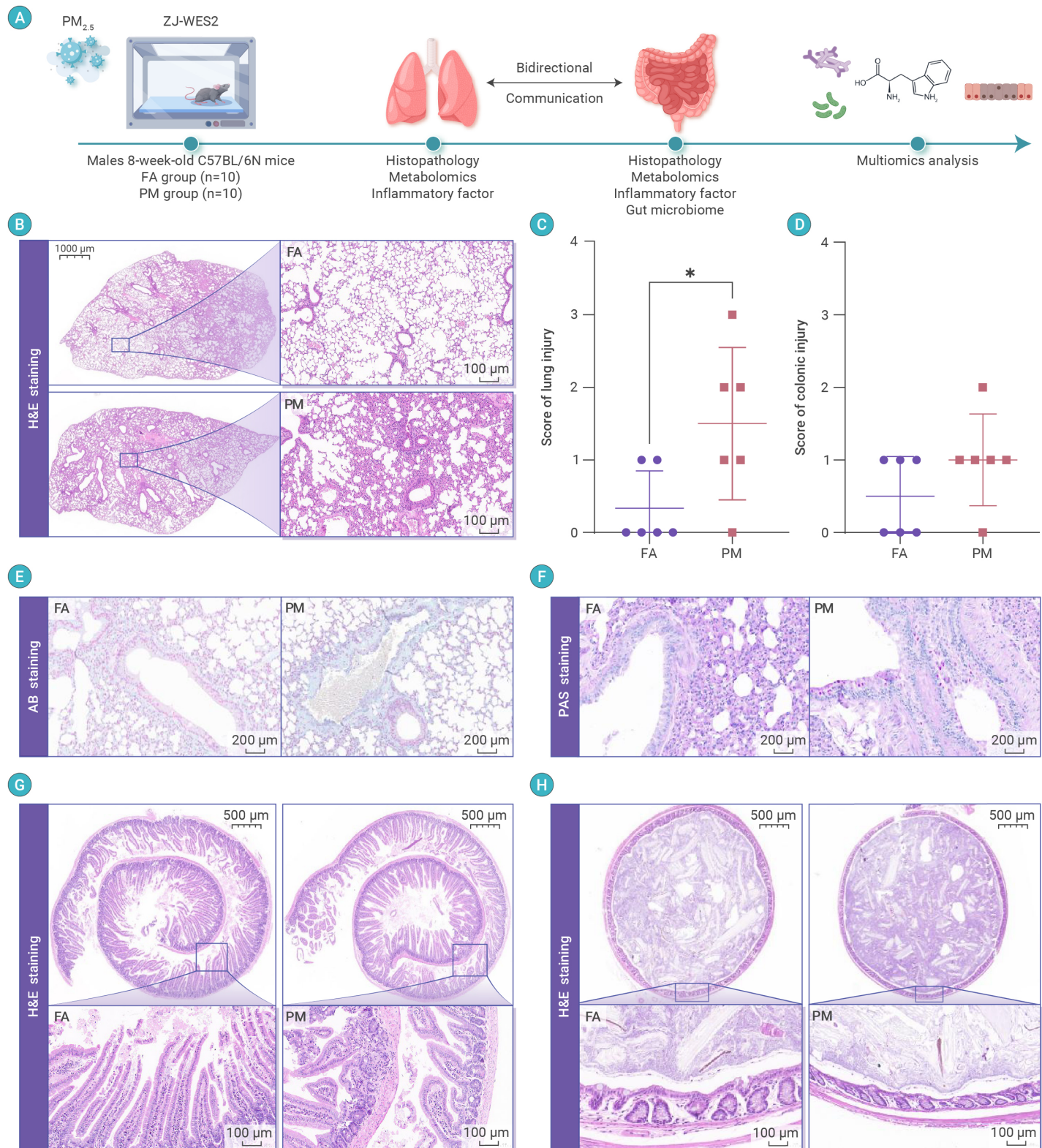


Figure 3. Histopathological assessment of lung and intestinal tissue injury induced by PM_{2.5} exposure in mice (A) Overview of the experimental design. (B) Representative H&E-stained lung tissue images (n=6). (C) Lung injury scores in the PM vs. FA groups (n=6) (D) Colonic injury scores in the PM vs. FA groups (n=6). (E) Representative AB-stained lung tissue images (n=6). (F) Representative PAS-stained lung tissue images (n=6). (G) Representative H&E-stained colon tissue images (n=6). (H) Representative H&E-stained ileum tissue images (n=6). *P < 0.05.

Associations between PM_{2.5}, metabolic profiles, and diseases

Cox models revealed that COPD was associated with higher risks of IBD, IBS, and GERD, while IBD and GERD also increased COPD risk (Tables S4-5). Multivariate regression revealed that PM_{2.5} exposure was significantly asso-

ciated with COPD, IBD, IBS, and GERD (Table S6). Moreover, PM_{2.5} exposure was significantly associated with disease transitions: from COPD to IBD (HR=1.23, 95% CI: 1.09, 1.49), from IBD to COPD (HR=1.09, 95% CI: 1.02, 1.47), from COPD to GERD (HR=1.06, 95% CI: 1.03, 1.21), and from GERD to COPD

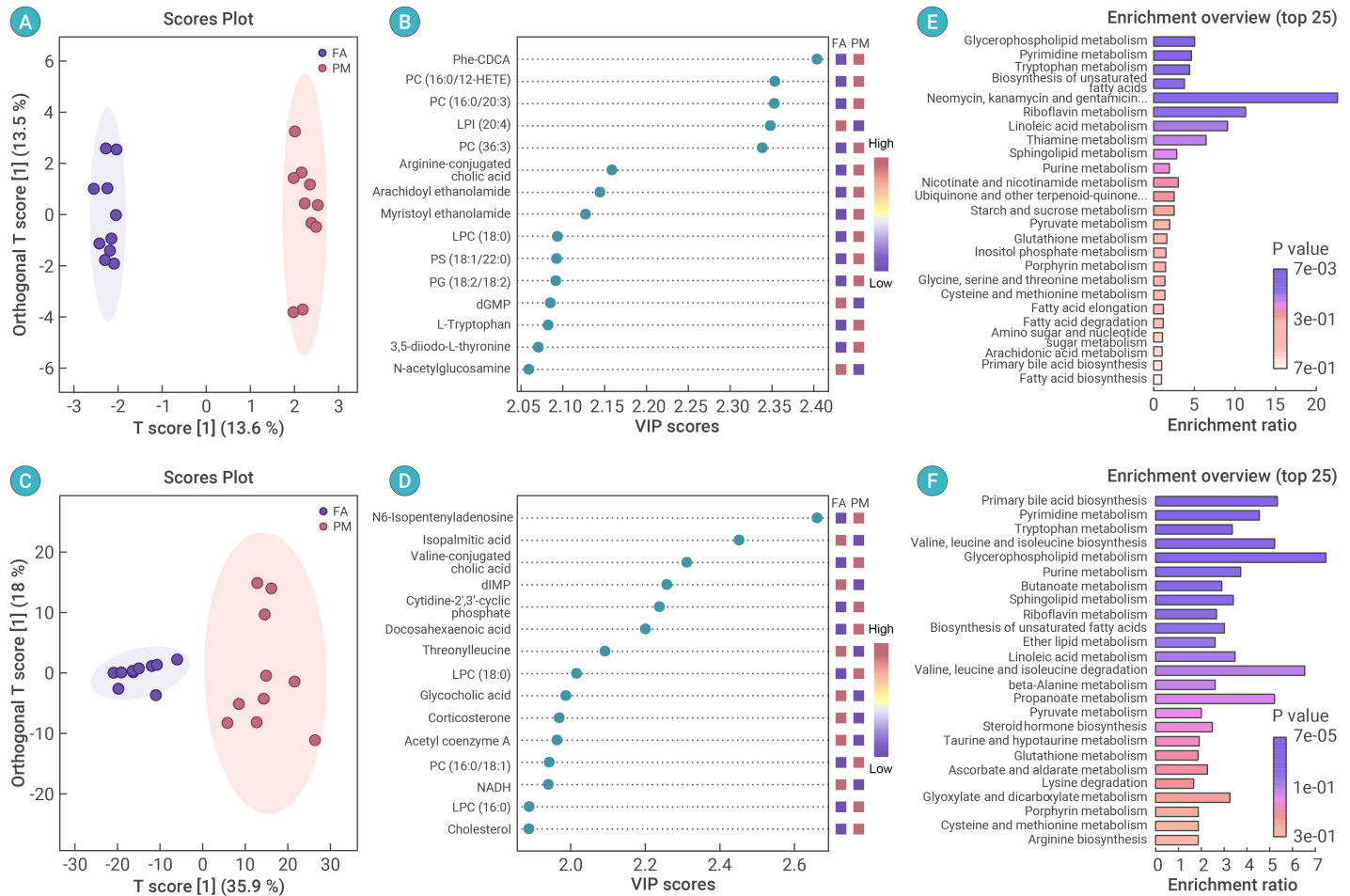


Figure 4. Tissue metabolic profiles and pathway dysregulation induced by PM_{2.5} exposure (A) OPLS-DA score plots of lung metabolism (PM vs. FA group). (B) VIP score of lung metabolites (PM vs. FA group), red: higher abundance in PM; blue: lower abundance in PM. (C) OPLS-DA score plots of gut metabolism (PM vs. FA group). (D) VIP scores of the gut metabolites (PM vs. FA group). (E) KEGG enrichment pathways in lung tissue; (F) KEGG enrichment pathways in gut tissue.

(HR=1.07, 95% CI: 1.04, 1.22) (Figure 2E).

The PM_{2.5}-related metabolomic signature score was also significantly associated with transitions (Table S6): from COPD to IBD (HR=1.21, 95% CI: 1.07, 1.48), from IBD to COPD (HR=1.04, 95% CI: 1.01, 1.08), and from COPD to GERD (HR=1.04, 95% CI: 1.01, 1.16), but not from GERD to COPD (Figure 2F). The associations of individual metabolites with these diseases are shown in Figure 2B. In addition, the PM_{2.5}-related metabolomic signature mediated 5.3%–26.1% of the associations between PM_{2.5} and COPD, IBD, and GERD (Table S7).

Subgroup analyses revealed stronger associations between PM_{2.5} exposure and the risk of IBS or GERD in participants ≥65 years. Among participants ≥65 years, as well as ever/current smokers, PM_{2.5} exposure was associated with a higher risk of transition from COPD to IBD. In physically inactive participants (low levels), PM_{2.5} exposure was associated with the transition from IBD/IBS to COPD (Tables S8–12). In addition, the results were generally robust to sensitivity analyses (Tables S13–14).

Effects of PM_{2.5} exposure on lung and gut injury

During exposure, the mean concentration of PM_{2.5} in the PM chamber was 119.70 ± 18.65 µg/m³. The lung tissues from the PM group exhibited inflammation with alveolar wall thickening and immune cell infiltration (Figure 3B), increased mucin secretion (Figures 3E–F), and higher lung injury scores (Figure 3C). Colon tissues showed mucosal thinning, epithelial disarray, and lymphocytic infiltration, with slightly elevated injury scores in the PM group (P=0.08) (Figures 3D & G–H).

In the PM group, the levels of IL-6 and TNF-α in the lung tissue, as well as the levels of IFN-γ, IL-6, and IL-10 in the intestinal tissue, were significantly higher than those in the FA group (n=10, P<0.05). Correlation analysis

revealed a significant relationship between lung IFN-γ, IL-6, and IL-10, and intestinal IL-10 in both the FA and PM groups (Figure S2). Mantel test analyses suggested that PM_{2.5} may influence lung–gut inflammatory crosstalk, although this finding was not statistically significant (Mantel's $r = 0.76$; $P = 0.08$).

Metabolic alterations under PM_{2.5} exposure

PCA revealed differences in lung tissue metabolic profiles between the FA and PM groups (Figure S3), which OPLS-DA confirmed ($R^2 = 0.82$, $Q^2 = 0.73$) (Figure 4A). In total, 93 differentially abundant metabolites were identified in the lung tissue (Figure 4B & Table S15), including glycerophospholipids (e.g., PC (16:0e/12-HETE), PC (16:0/20:3)), amino acids (e.g., L-tryptophan, kynurenine), bile acids and vitamins. These metabolites were enriched primarily in pathways such as glycerophospholipid metabolism, pyrimidine metabolism, tryptophan metabolism, neomycin, kanamycin, and gentamicin biosynthesis, and the biosynthesis of unsaturated fatty acids (Figure 4E).

Figure S4 presents the PCA of the gut metabolome data, with OPLS-DA confirming significant metabolic differences between groups ($R^2 = 0.61$, $Q^2 = 0.59$; Figure 4C). A total of 216 differentially abundant metabolites were identified (Figure 4D & Table S16), including phospholipids (e.g., LPC (18:0), PC (18:0/18:1(9Z))), fatty acids (e.g., isopalmitic acid, docosahexaenoic acid), amino acids and derivatives (e.g., phenylalanine, 5-hydroxy-L-tryptophan), bile acids, nucleosides and steroids. Pathway enrichment analysis identified six altered metabolic pathways in the gut, including primary bile acid biosynthesis, pyrimidine metabolism, tryptophan metabolism, valine, leucine, and isoleucine biosynthesis, glycerophospholipid metabolism, and purine metabolism (Figure 4F).

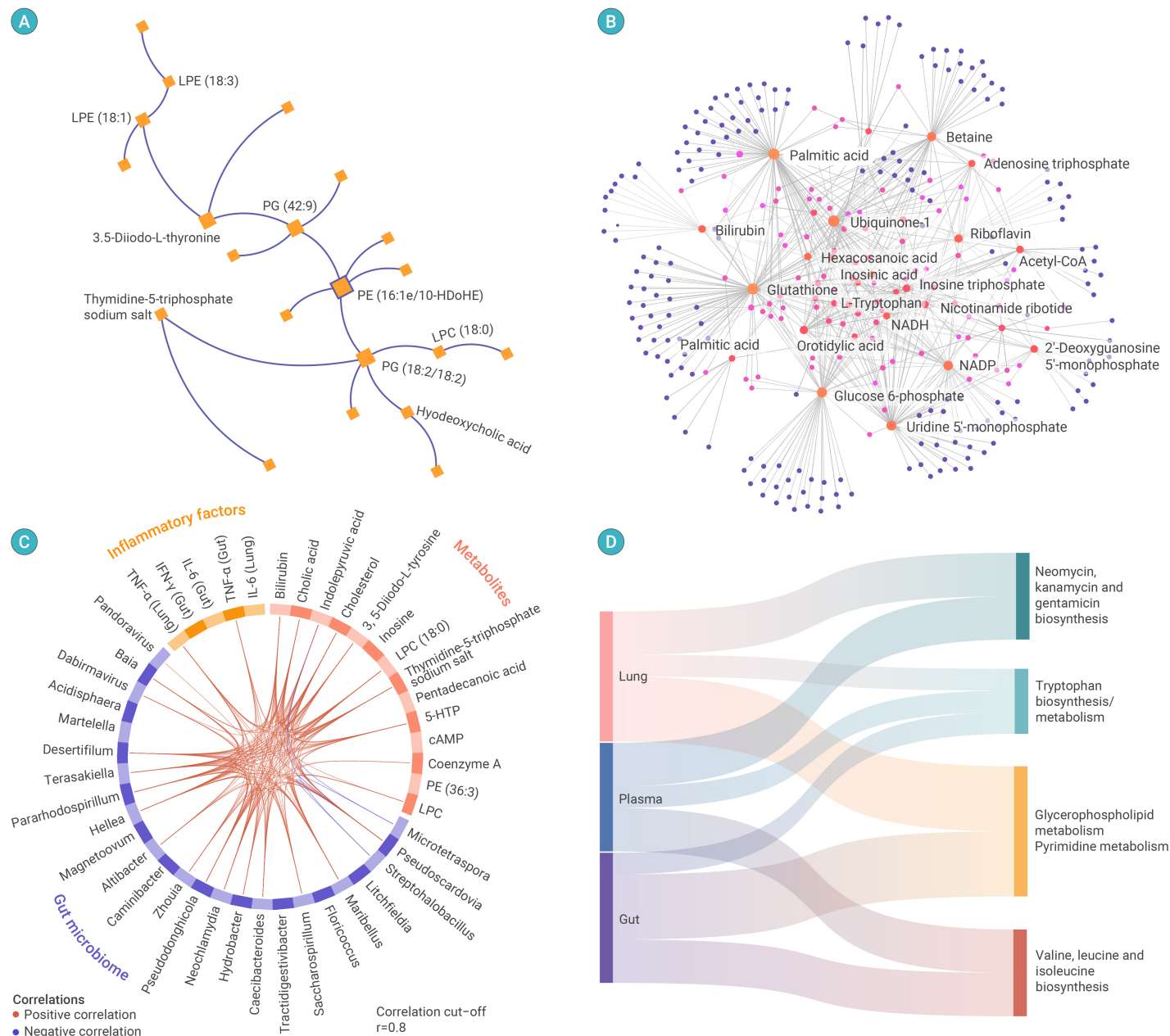


Figure 5. Lung and gut metabolic communication under PM_{2.5} exposure (A) DSPC network of lung and gut metabolites. (B) Network explorer network of lung and gut metabolites. (C) Sankey diagram illustrating metabolic pathways between humans and mice. (D) Multiomics analyses via DIABLO: Circos plot linking metabolites, the gut microbiome, and inflammatory factors.

Effects of PM_{2.5} exposure on the gut microbiome

Compared with that in the FA group, the gut microbiome α diversity in the PM group was significantly lower (ACE index: $P = 0.006$; Chao index: $P = 0.05$) (Figure S5). LEfSe revealed that *Schaedlerella* and *Limosilobacillus reuteri* were significantly enriched in the PM group, whereas *Lachnospiraceae* and *Dubosiella* were more abundant in the FA group (Figure S6).

Metabolic communication between the lung and gut under PM_{2.5} exposure

Approximately 31.6% of the metabolites in the lung and gut tissues were significantly correlated (Table S17), suggesting interorgan metabolic responses. DSPC and network analyses identified PM_{2.5}-induced interorgan interactions involving amino acid and lipid metabolites, highlighting hub metabolites such as NADH, L-tryptophan, glutathione, palmitic acid, and acetyl-CoA (Figures 5A–B). Several gut microbiome-derived metabolites (e.g., phenylacetyl-L-glutamine and taurocholic acid 3-sulfate) were detected in both tissues and were affected by PM_{2.5} exposure, indicating that the gut

microbiome may participate in communication with PM_{2.5}-induced metabolic disturbances between the lung and gut.

Multiomics analysis revealed that simultaneous PM_{2.5} exposure influenced key metabolites (e.g., 5-HTP, LPC, and bilirubin), specific gut microbiomes, and inflammatory mediators (TNF-α, IFN-α, and IL-10) (Figures 5C & S7). Pathway enrichment analysis highlighted consistent PM_{2.5}-induced perturbations in tryptophan metabolism across human plasma and mouse lung and gut tissues. In addition, glycerophospholipid and pyrimidine metabolism were specifically enriched in lung and gut tissues following PM_{2.5} exposure (Figure 5D).

Tryptophan and glycerophospholipid metabolism in lung-gut communication under PM_{2.5} exposure

Further analysis focused on tryptophan and glycerophospholipid metabolism. The levels of the lung tryptophan metabolites 5-HT and 3-HAA were negatively correlated with the gut IL-6 and IFN-γ levels. Several gut tryptophan metabolites (5-HTP, indolepyruvate, crotonyl-CoA and acetyl-

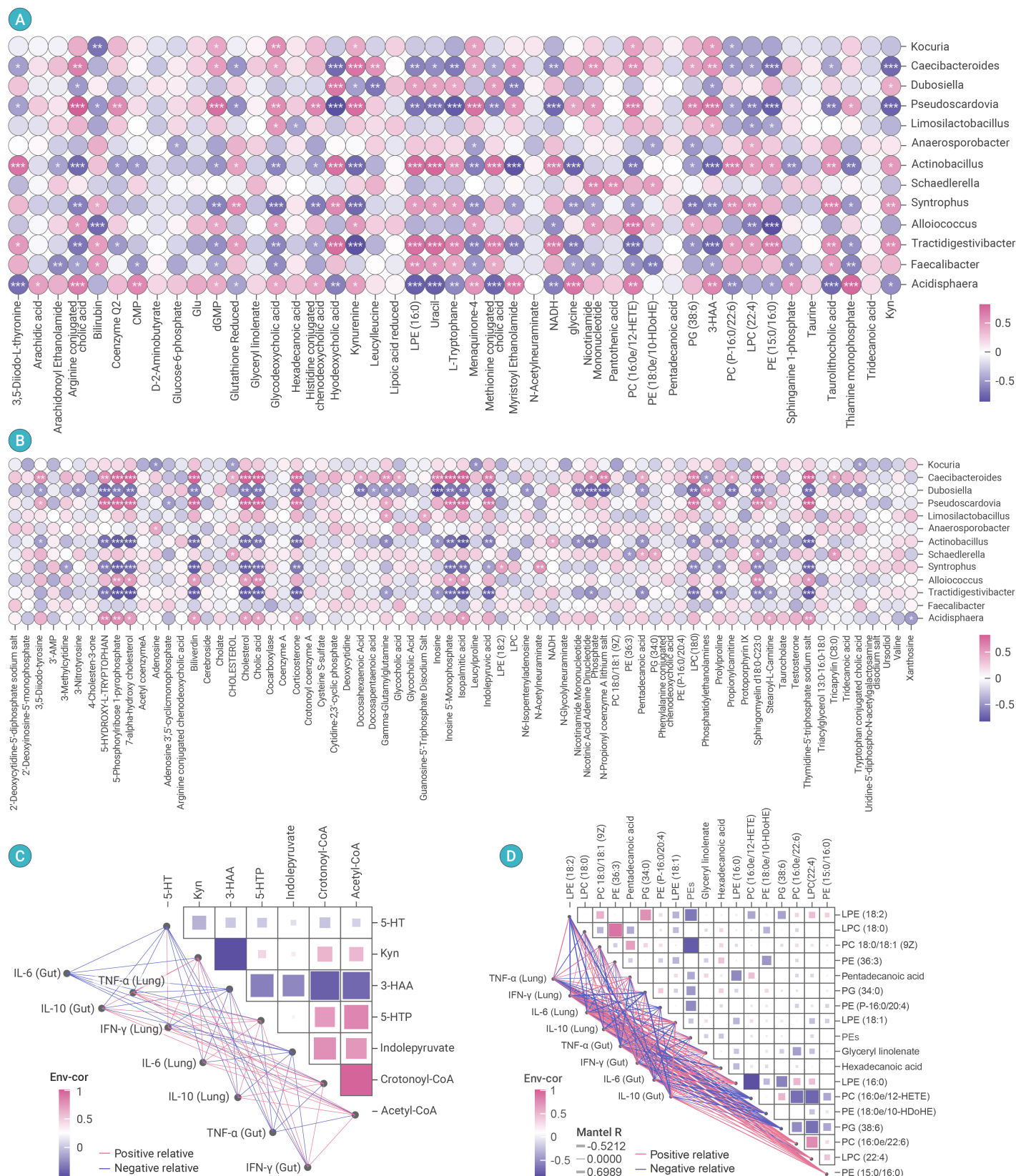


Figure 6. Correlations of tryptophan/glycerophospholipid metabolites with the gut microbiome and inflammatory factors (A) Association between lung tryptophan/glycerophospholipid metabolites in lung tissue and the key gut microbiome. (B) Association with tryptophan/glycerophospholipid metabolites of gut tissue and key gut microbiomes. (C) Association with tryptophan metabolites and inflammatory factors. (D) Association with glycerophospholipid metabolites and inflammatory factors.

CoA) were positively correlated with gut IFN- γ , and acetyl-CoA was positively correlated with lung TNF- α (Figure 6). In glycerophospholipid metabolism, LPE (18:2) was positively correlated with TNF- α , IFN- γ , and IL-6 in the lung

and with IL-10 in the gut; PG (34:0) was positively correlated with IFN- γ , IL-6, and IL-10 in the lung and with IL-10 in the gut; and LPE (18:1) was positively correlated with IL-6 and IL-10 in both organs. Key tryptophan metabolites

were significantly correlated with specific gut microbiomes (e.g., *Caecibacteroides*, *Dubosiella*, *Pseudoscardovia*, *Actinobacillus*, *Syntrophus*, *Tractidigestibacter*, and *Acidisphaera*). Similarly, glycerophospholipid metabolites correlated with *Caecibacteroides*, *Actinobacillus*, *Syntrophus*, *Kocuria*, and *Tractidigestibacter*.

In addition, a mediation analysis was performed to investigate the mediating role of specific metabolites. The findings indicated that four metabolites, L-tryptophan, glucose-6-phosphate, bilirubin, LPC(18:0), and arachidonoyl ethanolamide, serve as mediators of the influence of the gut microbiome on inflammatory markers, specifically gut IL-6 and lung IFN- γ . The proportion of the effects mediated by these metabolites ranged from 13.7% to 83.2%, with statistical significance ($P < 0.05$) (Table S18).

DISCUSSION

This study combined prospective cohort analyses and animal experiments to assess the effects of PM_{2.5} exposure on lung and gut health and metabolic communication. Three main findings emerged: (1) PM_{2.5} exposure was significantly associated with bidirectional disease transitions between COPD and IBD or GERD. (2) PM_{2.5}-related metabolic signature scores are correlated with the bidirectional transition between COPD and IBD and the transition from COPD to GERD. This score partially mediated the associations between PM_{2.5} and COPD, IBD, and GERD (mediating effects 5.3–26.1%). (3) A multi-omic analysis indicated that microbial-mediated modifications in tryptophan and glycerophospholipid metabolism may represent potential mechanisms underlying the communication between the lung and gut induced by PM_{2.5} exposure.

Our analyses confirmed a link between COPD and GI diseases, consistent with previous studies.⁷ Recent research has also identified shared genetic features across various pulmonary and GI conditions.¹¹ There is a correlation and complex interaction between the lungs and the gut, suggesting that the gut-lung axis may play an essential role in elucidating the biological mechanisms underlying the relationships between COPD and various GI diseases.⁵⁹ Furthermore, regression analysis identified PM_{2.5} as an independent risk factor for both COPD and GI disorders. This was substantiated by prior reports.^{60–61} For instance, exposure to high levels of PM_{2.5} was associated with an increased risk of IBD (HR=1.21, 95% CI:1.03, 1.42).⁶⁰ Similarly, an ecological cohort study of Californian residents revealed that each incremental increase in PM_{2.5} exposure was associated with a 3% increase in IBS risk (HR=1.03, 95% CI: 1.02, 1.05).⁶¹

Previous studies have reported associations between PM_{2.5} exposure and individual lung and gut diseases, but studies involving lung-gut communication are limited. Building on this evidence gap, we employed a multistate model to examine the impact of PM_{2.5} on COPD and GI disease progression, finding a significant link between PM_{2.5} exposure and transitions between COPD and IBD or GERD. A significant aspect of COPD pathogenesis involves systemic proinflammatory mediators.⁶² Indeed, circulating levels of IL-6 and CRP in patients with COPD are correlated with an increased risk of developing Crohn's disease (CD) and ulcerative colitis (UC).⁶³ In addition, exposure to PM_{2.5} triggers the activation of alveolar macrophages, which may lead to the release of proinflammatory mediators that facilitate intestinal inflammation via systemic circulation. Collectively, these data indicate that PM_{2.5} affects both the gastrointestinal and respiratory systems, disrupting epithelial barriers and the gut-lung axis, ultimately leading to a shift from homeostasis to inflammation.¹⁰

The gut-lung axis theory highlights the role of metabolites, inflammatory factors, and the gut microbiome in gut-lung interactions, facilitated by the circulatory system and common mucosal immune system.⁶⁴ Previous studies indicate that PM_{2.5} exposure and metabolic risk factors are key contributors to cardiovascular diseases.⁶⁵ Our findings suggest that PM_{2.5}-related metabonomic scores are also associated with an increased risk of COPD and IBD. Exposure to PM_{2.5} alters the levels of 130 human metabolites, significantly impacting metabolism pathways. These pathways play pivotal roles in stress, inflammation, protein synthesis, energy production, and amino acid biosynthesis and degradation.^{66–67} Pathway enrichment analysis indicated that PM_{2.5} exposure may disrupt amino acid metabolism. Notably, tryptophan, phenylalanine, and tyrosine serve as precursors for the synthesis of neurotransmitters, hormones, and other bioactive molecules.⁶⁸ Branched-chain

amino acids such as valine, leucine, and isoleucine not only contribute to protein synthesis but also play key roles in energy metabolism and signal transduction.^{68–69} In patients with COPD and IBD, dysregulation of the tryptophan-kynurenine metabolic pathway may exacerbate disease progression by impeding the differentiation of regulatory T cells.⁷⁰ Our population-based findings indicate that PM_{2.5}-induced metabolic reprogramming may represent a key mechanistic link through which airborne pollutants drive respiratory and gastrointestinal disease evolution via the gut-lung axis.

After 8 weeks of PM_{2.5} exposure, the mice exhibited significant pulmonary inflammation and damage, were more prone to intestinal inflammation, and showed altered metabolic profiles in lung and intestinal tissues, which is consistent with findings from previous studies.⁷¹ In addition, we found that PM_{2.5} exposure significantly reduced the α -diversity of the intestinal microbiota in mice. *Schaedlerella* and *Limosilobacillus reuteri* were significantly enriched in the PM group, whereas *Lachnospiraceae* and *Dubosiella* were enriched in the FA group. *Limosilobacillus reuteri* has been reported to regulate intestinal function, enhance immunity, and promote metabolism.^{72–73} *Dubosiella* was enriched in the FA group, are known producers of butyric acid and other short-chain fatty acids (SCFAs). The reduction in these SCFA-producing taxa in the PM group may have contributed to intestinal barrier impairment due to decreased SCFA levels.^{74–75}

A major finding of this study is that PM_{2.5} exposure significantly alters tryptophan metabolism, a metabolic pathway that may play a key role in mediating communication between the lung and gut. Both network analysis and enrichment analysis suggest that tryptophan metabolic pathway metabolites are significantly enriched in lung and gut tissues, as well as in human plasma under PM_{2.5} exposure. Multiomics analysis showed that disruptions in tryptophan metabolism induced by PM_{2.5} were closely associated with alterations in the composition of the gut microbiome and appeared to coregulate inflammation in both the lung and gut, which is consistent with other research findings.⁷⁶ Toxicological studies have revealed that tryptophan metabolism products are critical mediators of lung and gut communication.⁷⁷ 5-HT has immune-modulating properties, and plays a crucial role in regulating gut motility and inflammation.⁷⁸ In addition, 3-HAA is a significant bioactive molecule within the Trp-kynurenine pathway. It modulates the cytokine balance toward a Th2 response, thereby reducing the levels of IFN- γ .⁷⁹ Moreover, 5-HTP and indole derivatives are key products in the tryptophan metabolic pathway. These metabolites may regulate gut barrier function and immune responses by activating nuclear receptors and modulating gut hormones in the immune system.⁸⁰ Nonetheless, the interrelationships and molecular mechanisms among these pathways require further investigation under PM_{2.5} exposure.

Our findings indicate that PM_{2.5} alters glycerophospholipid metabolism in both lung and gut tissues, which is consistent with previous findings.⁸¹ PM_{2.5} exposure may cause lung and intestinal inflammation, potentially leading to telomere shortening, systemic inflammation, and oxidation.⁸² Disruption of glycerophospholipid metabolism is indicative of systemic oxidative stress and elevated inflammatory markers.⁸³ Moreover, pyrimidine metabolism was enriched in both the lung and gut. Pyrimidines are essential structural components of biomolecules involved in crucial cellular processes, including the synthesis of DNA, RNA, lipids, and carbohydrates.⁸⁴ Modifications in pyrimidine metabolism, encompassing enzymatic processes responsible for the synthesis, salvage, interconversion, degradation, and transport of these molecules, can significantly influence nucleic acid damage and repair mechanisms.⁸⁵

Strengths and limitations

The strengths of this study include high-resolution exposure assessment, the use of multistate models to assess disease transitions, and the integration of human cohort data with animal experiments. Multiomics analyses further provided mechanistic insights into metabolic communication.

However, several limitations should be noted. First, the cohort was restricted to individuals of European ancestry, potentially limiting generalizability. In addition, our findings regarding COPD and four GI diseases should not be generalized to other respiratory and digestive diseases without appropriate validation. Second, the population metabolites were assessed at baseline, which restricts our capacity to evaluate their impact on disease risk

throughout the follow-up period. Future studies should investigate how metabolites mediate dynamic disease transitions in lung-gut communication. Third, some participants were diagnosed with two states at the same time, resulting in the same diagnosis date for both states. We used a 0.5-day interval to calculate the dates of COPD and GI disease, which might lead to inaccuracies. However, testing different intervals did not significantly change the results. Fourth, animal experiments were performed at a single time point, limiting the ability to investigate dynamic changes in metabolic pathways following PM_{2.5} exposure. Fifth, regional variations in PM_{2.5} composition may affect the comparability between epidemiological and experimental findings. Finally, functional validation of key metabolites and targeted interventions were not performed and warrants future investigation. Future research can focus on developing disease models in mice exposed to PM_{2.5}, aiming to elucidate the connections between these models and the clinical phenotypes observed in population studies.

CONCLUSION

In conclusion, this study highlights the dynamic associations among PM_{2.5} exposure, metabolomic signature scores, and the risk of COPD and GI diseases, through the key mechanism of altered lung-gut metabolic communication. This alteration occurs primarily through the disruption of metabolites and pathways linked to tryptophan and glycerophospholipid metabolism, with the gut microbiome and inflammatory markers further implicated in this process.

ABBREVIATIONS

5-HT, 5-hydroxytryptamine; 3-HAA, 3-hydroxyanthranilic acid; AB, alcian blue; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FDR, false discovery rate; GI, gastrointestinal; GERD, gastroesophageal reflux disease; H&E, hematoxylin and eosin; HR, hazard ratio; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IPAQ, International Physical Activity Questionnaire; NMR, nuclear magnetic resonance; OPLS-DA, orthogonal partial least squares discriminant analysis; PCA, Principal component analysis; PM_{2.5}, particulate matter with an aerodynamic diameter of 2.5 µm or less; PAS, periodic acid-Schiff; PUs, peptic ulcers; VIP, variable importance in the projection; ZJ-WES2, Zhejiang Whole-body Exposure System 2.

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FUNDING AND ACKNOWLEDGMENTS

The work was supported by the National Natural Science Foundation of China (grant 82373534 to H.L.L.). The authors appreciate the participants in the UK Biobank for their participation and contribution to the research. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

Conception and design: Hui Shi, Tong Hou, Hualiang Lin; Generation, collection, assembly, analysis and/or interpretation of data: Hui Shi, Lei Tan, Shanshan Ran, Guzhengyue Zheng, Shengtao Wei, Zijun Yang, Jingyi Zhang, Fei Tian, Tong Hou, Jiyang Zhang, Wenjun Fan, Sanduo Li; Drafting or revision of the manuscript: Hui Shi, Zilong Zhang; Approval of the final version of the manuscript: Hualiang Lin.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

This study utilized publicly available, de-identified data, which did not require additional ethical approval or patient consent, and all animal procedures were approved by the Institutional Animal Care and Use Committee of Zhejiang Chinese Medical University (Approval No. IACUC-20241230-14).

DATA AND CODE AVAILABILITY

Data related to this study are available within the text, figures and tables. The date of the experimental study is available from the corresponding author.

SUPPLEMENTAL INFORMATION

It can be found online at <https://doi.org/10.59717/j.xinn-med.2025.100175>