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Association between air pollution exposure and increased chronic kidney disease risk: the modifying effects of genetic susceptibility, transcriptomic, and proteomic signatures

Jian Lu[1†], Shuaigang Sun[1,2†], Xinru Shang[1,3], Zekai Deng[4], Shunwei Wang[5], Shimin Jiang[1*] and Wenge Li[1,2*]

Abstract

Background Air pollution exposure is increasingly recognized as a risk factor for chronic kidney disease (CKD), but the underlying mechanisms, especially the complex gene-environment interactions as reflected in genetic susceptibility, transcriptomic, and proteomic signatures, remain to be elucidated.

Methods We conducted a large-scale prospective cohort study including 330,002 UK Biobank participants with an average follow-up of 13.0 years. Annual average concentrations of $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, NO_2, and NO_X were assessed. Cox proportional hazards models were applied to estimate CKD risk associated with long-term air pollution exposure. We further evaluated non-linear relationships using restricted cubic splines (RCS), potential mediators via mediation analyses, and CKD susceptibility through additive interaction analyses with baseline comorbidities and polygenic risk scores (PRS). Additionally, transcriptome-wide association study (TWAS) and proteome-wide two-step Mendelian randomization (MR) were integrated to explore potential molecular pathways.

Results Higher exposures to $PM_{2.5}$ (HR: 1.36, 95% CI: 1.22–1.51, per 5 μg/m^3), $PM_{2.5-10}$ (HR: 1.25, 95% CI: 1.07–1.46, per 5 μg/m^3), PM_{10} (HR: 1.20, 95% CI: 1.06–1.36, per 10 μg/m^3), and NO_X (HR: 1.04, 95% CI: 1.02–1.07, per 20 μg/m^3) were significantly associated with increased CKD risk, whereas NO_2 showed no significant association (HR: 0.98, 95% CI: 0.95–1.00, per 10 μg/m^3). RCS revealed non-linear relationships for $PM_{2.5-10}$ and PM_{10}. Mediation analyses indicated that incident hypertension and type 2 diabetes mellitus (T2DM) acted as potential mediators in these associations. Crucially, additive interaction analyses revealed that participants with pre-existing hypertension or type 1 diabetes mellitus (T1DM) were significantly more vulnerable to specific pollution-driven CKD. Compared to individuals with low genetic risk and low air pollution exposure, those with both high genetic risk and high exposure exhibited the highest CKD risk, demonstrating a clear gradient effect across categories. TWAS identified shared genes potentially linking air pollutants with CKD, including upregulated transcripts (*STX2*, *PHOSPHO2*, *NECAB3*) and downregulated

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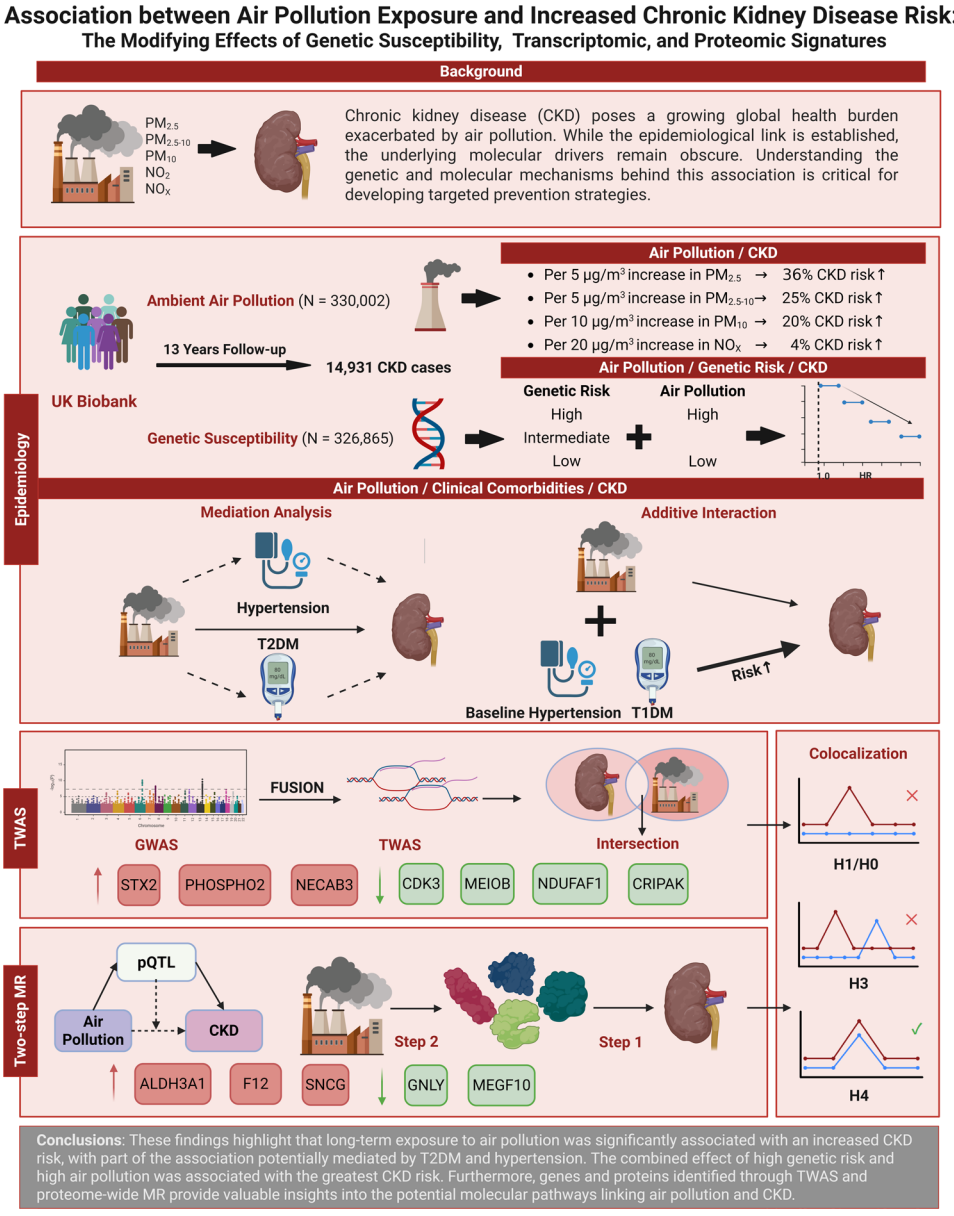
transcripts (*CDK3*, *MEIOB*, *NDUFAF1*, *CRIPAK*). Furthermore, proteome-wide MR analyses identified *ALDH3A1*, *F12*, and *SNCG* as potential risk proteins, and *GNLY* and *MEGF10* as protective proteins.

Conclusions This study provides comprehensive evidence that long-term air pollution exposure is associated with increased CKD risk and offers exploratory insights into the potential molecular pathways underlying this association, advocating the incorporation of renal health considerations into air quality control policies.

Keywords Air pollution, Chronic kidney disease, Polygenic risk score, Transcriptome-wide association study, Proteome-wide Mendelian randomization

Graphical Abstract



Background

Chronic kidney disease (CKD) is a progressive disorder typically characterized by irreversible loss of kidney function and structural renal damage, emerging as a significant global public health challenge [1]. Recent estimates indicate that approximately 359 million people live with CKD, representing a 92% increase over the past three decades [2]. Therefore, exploring the risk factors

and implementing effective prevention strategies for CKD are imperative to curb the rising global burden.

The development and progression of CKD are driven by complex interactions among environmental, behavioral, and genetic factors [3]. In addition to the well-established risk factors such as hypertension, diabetes, obesity, and smoking, environmental exposures—especially air pollution—are increasingly recognized as crucial contributors. While recent investigations have further corroborated the epidemiological link between air pollution and incident CKD [4–7], the majority of existing studies remain confined to establishing phenotypic associations. Crucially, the intermediate clinical pathways—specifically the potential mediating roles of hypertension and diabetes in the air pollution-CKD continuum—have rarely been rigorously quantified in longitudinal settings. More importantly, the potential molecular pathways underlying air pollution-associated renal injury remain largely unexplored, leaving a critical knowledge gap.

Individual vulnerability to environmental insults varies significantly, and genetic variation may substantially modulate susceptibility to air pollutants, thus influencing CKD onset and progression. Polygenic risk scores (PRS) aggregate genetic variants to quantify individual CKD susceptibility [8]. Transcriptome-wide association studies (TWAS) help prioritize candidate genes by identifying associations between genetically predicted gene expression and disease risk [9]. Furthermore, Mendelian randomization (MR) utilizes genetic variants as instrumental variables (IVs) to infer causal effects, minimizing unmeasured confounding and reverse causation biases [10, 11], and based on this framework, proteome-wide two-step MR further offers a novel approach to systematically explore and identify potential molecular pathways linking environmental exposures to clinical diseases.

To address these gaps, we conducted a comprehensive study based on the UK Biobank (UKB) population to investigate the associations between various air pollutants (including $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, NO_2, and NO_X) and incident CKD, and to evaluate the potential mediating roles of clinical comorbidities. Concurrently, we assessed how individual genetic susceptibility modifies these relationships, and prioritized candidate genes and circulating proteins as potential molecular pathways linking air pollution to CKD.

Methods

Study population and data source

The UKB is a large-scale, population-based cohort study that recruited over 500,000 participants aged 40–69 years from 22 assessment centres across England, Scotland, and Wales between 2006 and 2010. Detailed data collection procedures are available in prior studies [12]. The UKB study has been approved by the North West Multi-Centre Research Ethics Committee (MREC), and all participants provided written informed consent prior to data collection.

In this study, 501,946 UKB participants were initially considered (Fig. 1). We first excluded participants with missing values in air pollution data ($n = 42,372$) or baseline covariates ($n = 120,286$). Additionally, those with a prior diagnosis of CKD or an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 at baseline ($n = 9,286$) were further excluded. Consequently, 330,002 participants were included in the main epidemiological analyses. For the downstream genetic analyses, an additional 3,137 individuals lacking genetic data were further excluded.

Genome-wide association study (GWAS) data used in this study were obtained from the Integrative Epidemiology Unit Open GWAS database (IEU OpenGWAS) (**Additional file 1: Table S1**). Data for five air pollutants were derived from the UKB [13], including 423,796 individuals for $PM_{2.5}$, $PM_{2.5-10}$, and PM_{10}, and 456,380 for NO_2 and NO_X. Summary-level GWAS data for CKD were obtained from the FinnGen Consortium, comprising 3,902 cases and 212,841 controls [14].

Assessment of air pollution

Air pollution concentrations ($PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, NO_2, NO_X) were estimated using Land Use Regression (LUR) models and EU-wide air pollution maps. Long-term exposure for each participant was assigned by linking these estimates to their baseline residential addresses. Detailed methodology is provided in **Additional file 2: Supplemental Methods** [15–17].

Assessment of outcome

The primary outcome was the incidence of CKD identified using data from primary care, hospitalization records, or death registry records. Additional self-reported diagnoses were utilized to exclude baseline cases. Detailed disease codes are provided in **Additional file 1: Table S2**. The follow-up period was calculated from baseline to the earliest occurrence of CKD diagnosis, death, loss to follow-up, or the end of follow-up (October 31, 2022). After excluding prevalent kidney disease cases at baseline, several incident kidney disease events that may progress to CKD were defined as supplementary outcomes, including acute kidney injury (AKI), glomerular disease (GD), tubular-interstitial disease (TID), hydronephrosis, kidney stone (KS), and congenital anomalies of kidney (CAK).

Assessment of covariates

Based on prior knowledge and existing literature [18], and guided by a directed acyclic graph (DAG, **Additional file 3: Figure S1**), a comprehensive set of covariates was

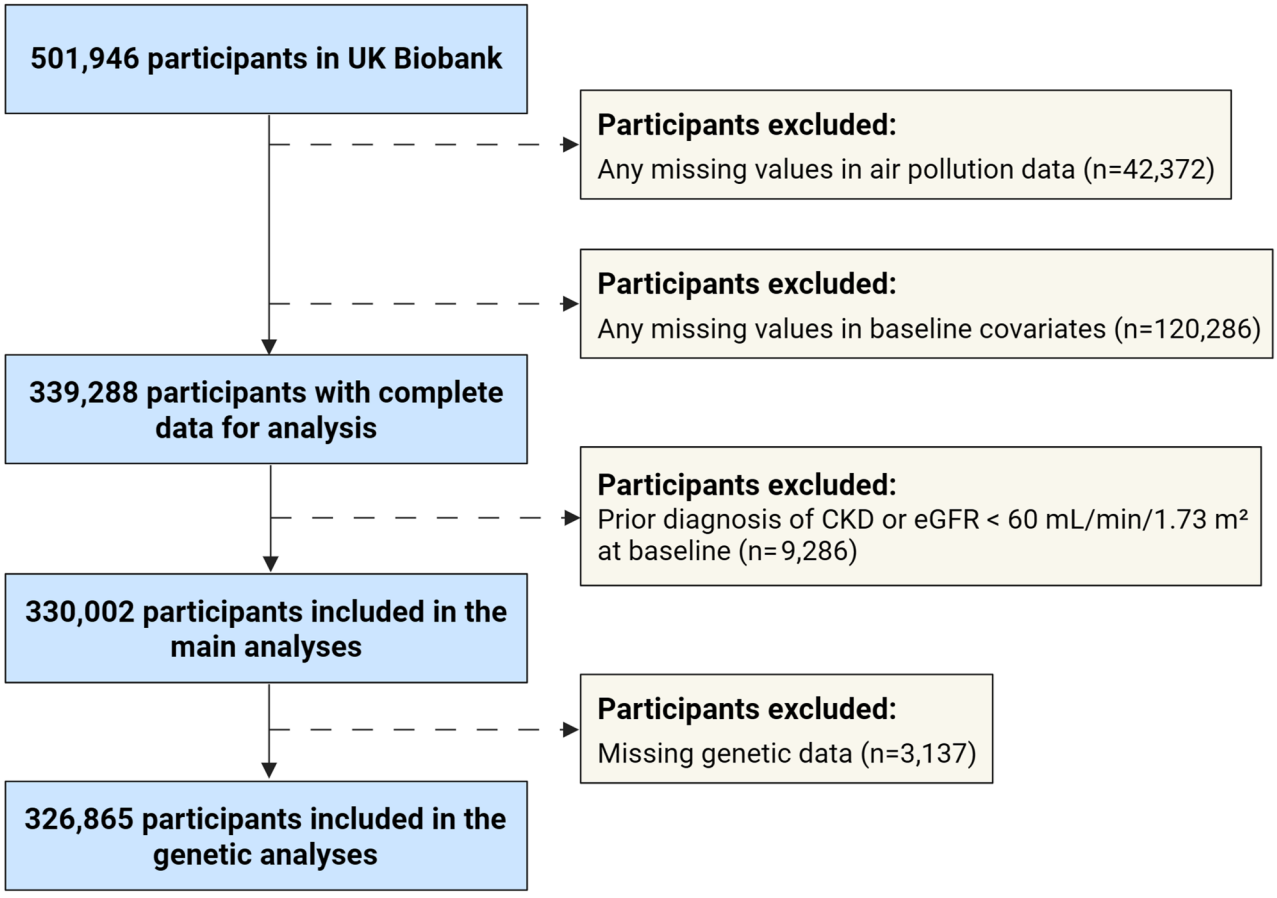


Fig. 1 Flowchart for participant selection

considered to minimize potential confounding. These included socio-demographic and lifestyle factors (including age, sex, body mass index (BMI), ethnicity, education, average total household income, smoking and drinking status), as well as geographic and environmental factors (greenspace percentage within a 300-m buffer, distance to the nearest major road, traffic intensity on the nearest major road, urbanicity, and assessment centre). Furthermore, baseline comorbidities such as hypertension, type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), atherosclerosis, and stroke, along with the use of specific medications were also assessed to account for underlying health vulnerabilities and potential nephrotoxic effects. **Additional file 1: Table S3** presents the UKB Field IDs and missing data statistics for these variables, and further detailed definitions, categorization criteria, and medication lists are provided in **Additional file 2: Supplemental Methods** [19].

PRS calculation

To comprehensively capture the genetic susceptibility to CKD, we constructed a genome-wide PRS using the aforementioned FinnGen GWAS summary data. The posterior single nucleotide polymorphism (SNP) effect sizes (weights) were estimated using PRS-CS, a Bayesian approach that employs a continuous shrinkage prior to account for linkage disequilibrium (LD) patterns based on the 1000 Genomes Project European reference panel [20]. A global shrinkage parameter of $\phi = 10^{-2}$ was applied across all autosomes. These adjusted weights were subsequently applied to the individual-level genotype data in our cohort to generate the continuous PRS. The calculated scores were then standardized (Z-score) for further analysis. Based on the tertiles of the standardized PRS, participants were categorized into three genetic risk groups: low (lowest tertile), intermediate (second tertile), and high (highest tertile) genetic risk.

TWAS analysis

For the TWAS, we employed the FUSION method [21], which uses a linear model based on expression quantitative trait loci (eQTLs) to predict gene expression, utilizing RNA-seq data from European kidney cortex samples in Genotype-Tissue Expression version 8 (GTEx v8) as the reference panel [22]. Independent TWAS analyses were conducted using GWAS summary statistics for each air pollutant and CKD. Overlapping genes significantly

associated with both a specific pollutant and CKD were identified.

Two-step MR analysis

A two-step MR analysis was conducted to explore the genetically proxied associations linking air pollution, circulating plasma proteins, and CKD risk. In the first step, proteome-wide MR was performed using cis protein quantitative trait loci (cis-pQTLs) to identify candidate proteins associated with CKD. In the second step, the genetically predicted effects of air pollutants on these proteins were assessed. Proteins with significant and directionally consistent associations across both steps were prioritized as potential mediators linking air pollution to CKD. **Additional file 2: Supplemental Methods** provides full details regarding the proteomic data source, IV selection criteria, MR assumptions, and all sensitivity analyses performed [23–26].

Colocalization analysis

To explore whether associations of the identified candidate genes and proteins with CKD were attributable to a shared causal genetic variant, we performed a Bayesian colocalization analysis using the coloc R package [27]. All SNPs within 1 Mb around the lead SNPs for the eQTL, pQTL, and CKD GWAS were extracted and calculated the posterior probability for hypothesis 4 (PPH4) under default prior probabilities. Evidence of colocalization was considered strong if PPH4 > 0.8, and moderate if 0.5 < PPH4 ≤ 0.8.

Statistical analysis

Baseline characteristics were reported as mean (standard deviation, SD) for continuous variables and frequencies (percentages) for categorical variables. Pearson correlation coefficients assessed correlations among air pollutants, and variance inflation factors (VIFs) checked multicollinearity among covariates. Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of air pollutants and genetic risk with incident CKD. Four models were considered: Model 0 (unadjusted), Model 1 (adjusted for socio-demographic and lifestyle factors), Model 2 (further adjusted for geographic and environmental factors), and Model 3 (further adjusted for baseline comorbidities and medication use). Restricted cubic spline (RCS) analyses, subgroup and interaction analyses, mediation analyses, assessments of additive interaction between air pollution and PRS, and sensitivity analyses were further conducted to assess robustness. Detailed statistical procedures are described in **Additional file 2: Supplemental Methods** [28, 29]. All analyses were conducted using R software (version 4.3.1).

Results

Baseline characteristics

During an average follow-up of 13.0 years, 14,931 incident cases of CKD were observed. Table 1 summarizes the baseline characteristics of the 330,002 participants, with a mean age of 56.07 ± 8.07 years, and 47.5% were male. Individuals who developed CKD were significantly older and more likely to be male, had higher BMI, lower educational attainment, lower income, and were more likely to have a history of smoking, whereas current drinking was less frequent. They were also more likely to reside in urban and town areas rather than rural, and a significantly higher proportion of them were assessed in Northern England compared to the non-CKD group (all $P < 0.001$). Moreover, they had a significantly higher prevalence of baseline comorbidities, including hypertension, T1DM, T2DM, atherosclerosis, and stroke, and reported greater usage of medications such as NSAIDs, ACEIs, ARBs, and nephrotoxic antibiotics (all $P < 0.001$). Additionally, incident CKD participants were exposed to significantly higher levels of $PM_{2.5}$, $PM_{2.5-10}$, NO_X, and greater traffic intensity on the nearest major road (all $P < 0.001$). However, no significant differences were observed between the two groups regarding PM_{10} ($P = 0.327$), NO_2 ($P = 0.195$), greenspace percentage ($P = 0.863$), or distance to the nearest major road ($P = 0.117$). The distributions of air pollutants and their Pearson correlation coefficients are presented in **Additional file 1: Table S4**.

Air pollutants and CKD

Multicollinearity diagnostics indicated that all VIF values for covariates in the fully adjusted model were below 5 **(Additional file 1: Table S5)**. After adjusting for all covariates in Model 3, long-term exposure to higher levels of air pollution was significantly associated with an increased risk of incident CKD. Specifically, each 5 μg/m³ increase in $PM_{2.5}$ and $PM_{2.5-10}$, each 10 μg/m³ increase in PM_{10}, and each 20 μg/m³ increase in NO_X were associated with HRs of 1.36 (95% CI: 1.22–1.51, $P < 0.001$), 1.25 (95% CI: 1.07–1.46, $P = 0.004$), 1.20 (95% CI: 1.06–1.36, $P = 0.004$), and 1.04 (95% CI: 1.02–1.07, $P = 0.002$), respectively (Table 2). However, no significant association was observed for NO_2 (HR: 0.98, 95% CI: 0.95–1.00, $P = 0.069$).

Similar results were observed when analyzing by IQR increase and quartiles. CKD risk increased significantly for each interquartile range (IQR) increase in $PM_{2.5}$ (HR: 1.06, 95% CI: 1.03–1.09, $P < 0.001$), $PM_{2.5-10}$ (HR: 1.05, 95% CI: 1.02–1.07, $P < 0.001$), PM_{10} (HR: 1.14, 95% CI: 1.10–1.18, $P < 0.001$), and NO_X (HR: 1.03, 95% CI: 1.01–1.05, $P = 0.007$), respectively **(Additional file 1: Table S6)**. Quartile analyses further showed that individuals exposed to higher levels of $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, and

Table 1 Population characteristics of participants included in the study

Characteristics	Overall (*n* = 330,002)	Non-CKD (*n* = 315,071)	CKD (*n* = 14,931)	*P* value
Age, years, mean (SD)	56.07 (8.07)	55.81 (8.05)	61.61 (6.21)	< 0.001
Sex, n (%)				< 0.001
Male	156,719 (47.5)	148,872 (47.3)	7,847 (52.6)	
Female	173,283 (52.5)	166,199 (52.7)	7,084 (47.4)	
BMI, kg/m^2, mean (SD)	27.29 (4.69)	27.20 (4.65)	29.16 (5.16)	< 0.001
Ethnicity, n (%)				0.002
White	313,841 (95.1)	299,606 (95.1)	14,235 (95.3)	
Mixed	1,973 (0.6)	1,907 (0.6)	66 (0.4)	
Asian or Asian British	6,648 (2.0)	6,379 (2.0)	269 (1.8)	
Black or Black British	4,910 (1.5)	4,655 (1.5)	255 (1.7)	
Other	2,630 (0.8)	2,524 (0.8)	106 (0.7)	
Education, n (%)				< 0.001
College/university	115,072 (34.9)	111,701 (35.5)	3371 (22.6)	
Less than college/university	214,930 (65.1)	203,370 (64.5)	11,560 (77.4)	
Average total household income, n (%)				< 0.001
< £18,000	72,536 (22.0)	66,860 (21.2)	5,676 (38.0)	
£18,000–30,999	83,887 (25.4)	79,534 (25.2)	4,353 (29.2)	
£31,000–51,999	86,794 (26.3)	83,767 (26.6)	3,027 (20.3)	
£52,000–100,000	68,373 (20.7)	66,799 (21.2)	1,574 (10.5)	
> £100,000	18,412 (5.6)	18,111 (5.7)	301 (2.0)	
Urbanicity, n (%)				< 0.001
Urban	282,010 (85.5)	269,167 (85.4)	12,843 (86.0)	
Town	23,735 (7.2)	22,575 (7.2)	1,160 (7.8)	
Rural	24,257 (7.4)	23,329 (7.4)	928 (6.2)	
Region of assessment, n (%)				< 0.001
Northern England	155,619 (47.2)	147,792 (46.9)	7,827 (52.4)	
The Midlands	57,702 (17.5)	54,940 (17.4)	2,762 (18.5)	
Southern England	67,100 (20.3)	64,290 (20.4)	2,810 (18.8)	
Greater London	49,581 (15.0)	48,049 (15.3)	1,532 (10.3)	
Greenspace percentage, mean (SD)	35.53 (23.32)	35.52 (23.36)	35.56 (22.55)	0.863
Distance to the nearest major road, n (%)				0.117
≥ 1,000 m	55,294 (16.8)	52,790 (16.8)	2,504 (16.8)	
500–1,000 m	77,137 (23.4)	73,554 (23.3)	3,583 (24.0)	
200–500 m	99,498 (30.2)	94,975 (30.1)	4,523 (30.3)	
< 200 m	98,073 (29.7)	93,752 (29.8)	4,321 (28.9)	
Traffic intensity on the nearest major road, vehicles/day/1,000, median (IQR)	16.99 (12.50, 24.69)	16.99 (12.48, 24.66)	17.12 (12.62, 25.44)	< 0.001
Smoking status, n (%)				< 0.001
Current	33,969 (10.3)	32,344 (10.3)	1,625 (10.9)	
Previous	115,834 (35.1)	109,538 (34.8)	6,296 (42.2)	
Never	180,199 (54.6)	173,189 (55.0)	7,010 (46.9)	
Drinking status, n (%)				< 0.001
Current	306,954 (93.0)	293,604 (93.2)	13,350 (89.4)	
Previous	10,928 (3.3)	10,147 (3.2)	781 (5.2)	
Never	12,120 (3.7)	11,320 (3.6)	800 (5.4)	
Hypertension, n (%)	87,795 (26.6)	80,076 (25.4)	7,719 (51.7)	< 0.001
T1DM, n (%)	1,289 (0.4)	1,103 (0.4)	186 (1.2)	< 0.001
T2DM, n (%)	6,999 (2.1)	5,858 (1.9)	1,141 (7.6)	< 0.001
Atherosclerosis, n (%)	420 (0.1)	350 (0.1)	70 (0.5)	< 0.001
Stroke, n (%)	4,644 (1.4)	4,143 (1.3)	501 (3.4)	< 0.001
NSAIDs, n (%)	88,148 (26.7)	82,254 (26.1)	5,894 (39.5)	< 0.001
ACEIs, n (%)	29,939 (9.1)	26,602 (8.4)	3,337 (22.3)	< 0.001
ARBs, n (%)	12,439 (3.8)	10,863 (3.4)	1,576 (10.6)	< 0.001

Table 1 (continued)

Characteristics	Overall (*n* = 330,002)	Non-CKD (*n* = 315,071)	CKD (*n* = 14,931)	*P* value
Nephrotoxic antibiotics, n (%)	997 (0.3)	905 (0.3)	92 (0.6)	< 0.001
$PM_{2.5}$, μg/m^3, median (IQR)	9.92 (9.28, 10.55)	9.92 (9.27, 10.55)	9.97 (9.33, 10.59)	< 0.001
$PM_{2.5-10}$, μg/m^3, median (IQR)	6.10 (5.84, 6.62)	6.10 (5.84, 6.62)	6.11 (5.85, 6.66)	< 0.001
PM_{10}, μg/m^3, median (IQR)	19.12 (18.04, 20.38)	19.12 (18.04, 20.38)	19.14 (18.11, 20.30)	0.327
NO_2, μg/m^3, median (IQR)	28.10 (22.91, 34.02)	28.10 (22.90, 34.05)	28.10 (23.16, 33.43)	0.195
NO_X, μg/m^3, median (IQR)	42.09 (34.04, 50.69)	42.08 (34.01, 50.68)	42.46 (34.64, 50.89)	< 0.001

Abbreviations: CKD, chronic kidney disease; SD, standard deviation; BMI, body mass index; IQR, interquartile range; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; NSAIDs, nonsteroidal anti-inflammatory drugs; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤ 2.5 μm; $PM_{2.5-10}$, particulate matter with an aerodynamic diameter between 2.5 and 10 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 μm; NO_2, nitrogen dioxide; NO_X, nitrogen oxides

Table 2 The associations between air pollutants and incident CKD risk

Pollutants	Increase	No. cases / *n*	Model 0		Model 1		Model 2		Model 3	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
$PM_{2.5}$	5 μg/m^3	14,931/330,002	1.25 (1.16–1.35)	**< 0.001**	1.22 (1.13–1.32)	**< 0.001**	1.40 (1.25–1.55)	**< 0.001**	1.36 (1.22–1.51)	**< 0.001**
$PM_{2.5-10}$	5 μg/m^3	14,931/330,002	1.18 (1.08–1.28)	**< 0.001**	1.15 (1.05–1.26)	**0.002**	1.25 (1.07–1.46)	**0.005**	1.25 (1.07–1.46)	**0.004**
PM_{10}	10 μg/m^3	14,931/330,002	1.05 (0.97–1.14)	0.258	1.17 (1.07–1.28)	**< 0.001**	1.22 (1.08–1.38)	**0.002**	1.20 (1.06–1.36)	**0.004**
NO_2	10 μg/m^3	14,931/330,002	0.98 (0.97–1.00)	0.055	1.00 (0.98–1.02)	0.848	0.98 (0.96–1.01)	0.211	0.98 (0.95–1.00)	0.069
NO_X	20 μg/m^3	14,931/330,002	1.04 (1.02–1.06)	**< 0.001**	1.03 (1.01–1.05)	**0.002**	1.05 (1.02–1.07)	**< 0.001**	1.04 (1.02–1.07)	**0.002**

Model 0: unadjusted

Model 1: adjusted for age, sex, BMI, ethnicity, education, average total household income, smoking status, and drinking status

Model 2: further adjusted for greenspace percentage, distance to the nearest major road, traffic intensity on the nearest major road, urbanicity, and assessment centre

Model 3: further adjusted for baseline hypertension, baseline T1DM, baseline T2DM, baseline atherosclerosis, baseline stroke, and baseline use of NSAIDs, ACEIs, ARBs, and nephrotoxic antibiotics

Abbreviations: CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤ 2.5 μm; $PM_{2.5-10}$, particulate matter with an aerodynamic diameter between 2.5 and 10 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 μm; NO_2, nitrogen dioxide; NO_X, nitrogen oxides; BMI, body mass index; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; NSAIDs, nonsteroidal anti-inflammatory drugs; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers

NO_X had a significantly higher incident CKD risk compared to those in the lowest quartile, with statistically significant dose-response trends across quartiles (all *P* for trend < 0.01) **(Additional file 1: Table S7)**.

Further stratified analyses adjusted for all covariates indicated that the associations between air pollution and CKD risk were generally consistent across most subgroups **(Additional file 1: Table S8)**. However, significant effect modifications were observed for the region of assessment across multiple pollutants ($PM_{2.5}$, PM_{10}, NO_2, and NO_X). Additionally, baseline T1DM status significantly modified the associations between $PM_{2.5-10}/PM_{10}$ and CKD risk (all *P* for interaction < 0.05). RCS analyses further detected non-linear relationships for $PM_{2.5-10}$ (*P* non-linear = 0.009) and PM_{10} (*P* non-linear = 0.002) (Fig. 2, **Additional file 3: Figure S2**).

Sensitivity analyses

The associations between $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, NO_X levels and CKD risk remained consistent after excluding cases from the first 3 years of follow-up **(Additional file 1: Table S9)**. Besides, restricting the analysis to participants with a fixed residential address for at least 5 years and excluding those with extreme exposure values did not materially alter the results **(Additional file 1: Table S10–S11)**. Throughout these analyses, NO_2 consistently showed no significant association.

Air pollutants, comorbidities, and CKD

We further evaluated the role of incident comorbidities in the air pollution–CKD pathways. Mediation analyses revealed that incident hypertension significantly mediated the effects of $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, and NO_X, yielding natural indirect effect (NIE) HRs of 1.013 (95% CI: 1.009–1.017), 1.010 (95% CI: 1.003–1.017), 1.014 (95% CI: 1.009–1.019), and 1.002 (95% CI: 1.001–1.004), respectively. These pathways accounted for 5.81% (2.22%–9.40%), 3.42% (0.33%–6.51%), 2.95% (1.69%–4.20%), and 5.40% (0.09%–10.70%) of the total effects. Furthermore, incident T2DM also mediated these associations, albeit to a lesser extent, with NIE HRs ranging from 1.001 to 1.002 and mediation proportions between 0.51% and 2.20% (all *P* < 0.05). In contrast, no significant mediation was observed for incident T1DM, atherosclerosis, stroke, or any NO_2-related pathway (Fig. 3, **Additional file 1: Table S12**).

Furthermore, additive interaction analyses revealed that specific baseline comorbidities synergistically

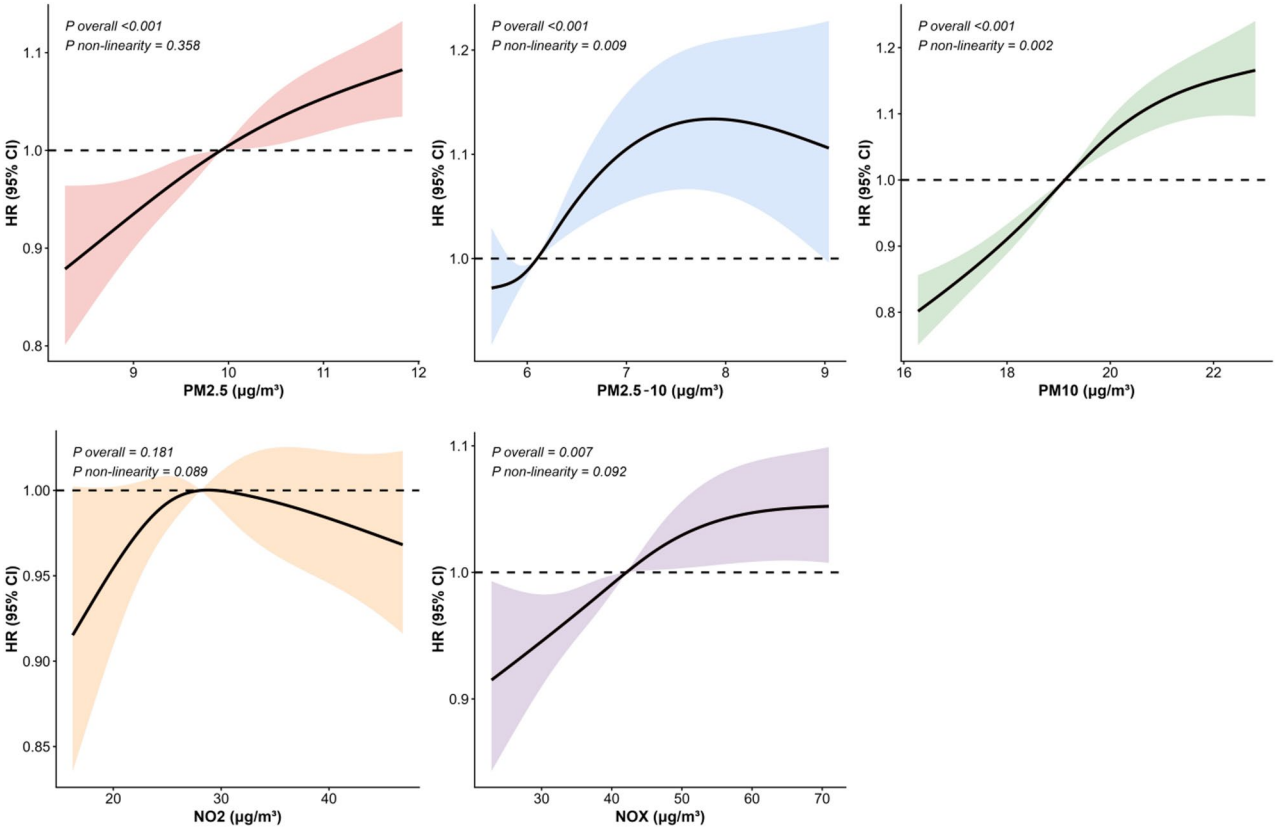


Fig. 2 RCS plots of the associations between air pollutants and incident CKD risk. Abbreviations: RCS, restricted cubic spline; HR, hazard ratio; CI, confidence interval; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤ 2.5 μm; $PM_{2.5-10}$, particulate matter with an aerodynamic diameter between 2.5 and 10 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 μm; NO_2, nitrogen dioxide; NO_X, nitrogen oxides

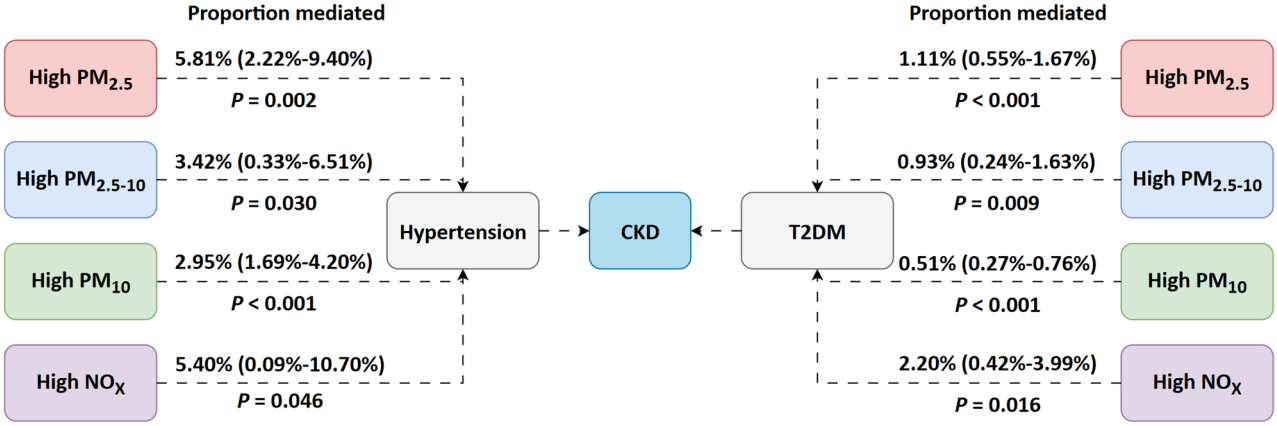


Fig. 3 Mediating effects of hypertension and T2DM in the associations between air pollutants and CKD. Abbreviations: $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤ 2.5 μm; $PM_{2.5-10}$, particulate matter with an aerodynamic diameter between 2.5 and 10 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 μm; NO_X, nitrogen oxides; T2DM, type 2 diabetes mellitus

exacerbated CKD risk (**Additional file 1: Table S13**). Pre-existing hypertension significantly amplified the nephrotoxicity of high PM_{10} (relative excess risk due to interaction [RERI]: 0.112, 95% CI: 0.028–0.196; attributable proportion [AP]: 0.069, 95% CI: 0.018–0.119; synergy index [SI]: 1.213, 95% CI: 1.039–1.416) and high NO_2 (RERI: 0.099, 95% CI: 0.019–0.179; AP: 0.065, 95% CI: 0.013–0.117; SI: 1.234, 95% CI: 1.025–1.486). Baseline T1DM also strongly interacted with high $PM_{2.5-10}$ and PM_{10}, yielding significant interactions for $PM_{2.5-10}$ (RERI: 0.579, 95% CI: 0.099–1.060; AP: 0.291, 95% CI: 0.090–0.492; SI: 2.404, 95% CI: 1.055–5.474) and PM_{10} (RERI: 0.544, 95% CI: 0.050–1.039; AP: 0.266, 95% CI: 0.061–0.470; SI: 2.079, 95% CI: 1.015–4.257).

Air pollutants and kidney diseases

After full adjustment, susceptibility to air pollutants varied across specific kidney diseases **(Additional file 1: Table S14)**. AKI exhibited the broadest susceptibility, with risks significantly increasing by 26% (95% CI: 13%–40%) per 5 μg/m³ increase in $PM_{2.5}$, 69% (95% CI: 46%–94%) per 10 μg/m³ increase in PM_{10}, 10% (95% CI: 7%–13%) per 10 μg/m³ increase in NO_2, and 8% (95% CI: 5%–10%) per 20 μg/m³ increase in NO_X (all $P<0.001$). Furthermore, GD was primarily associated with PM_{10} and NO_2. TID was linked to NO_2 and NO_X, whereas hydronephrosis and KS were significantly associated with NO_2 and $PM_{2.5}$, respectively (all $P<0.05$). No significant associations were observed for CAK.

Air pollutants, genetic risk and CKD

The PRS for CKD was normally distributed **(Additional file 3: Figure S3)**, and higher genetic risk was independently associated with an increased CKD risk **(Additional file 1: Table S15)**. When evaluating joint effects, a clear graded dose–response relationship was observed between air pollutants, genetic risk, and CKD (Fig. 4, **Additional file 1: Table S16)**. Specifically, relative to participants with low genetic risk and low air pollution exposure, CKD risk gradually escalated with increasing exposure categories, and peaked in those with high genetic risk and high pollution exposure [$PM_{2.5}$ (HR: 1.35, 95% CI: 1.27–1.44), $PM_{2.5-10}$ (HR: 1.35, 95% CI: 1.27–1.44), PM_{10} (HR: 1.38, 95% CI: 1.30–1.47), NO_2 (HR: 1.30, 95% CI: 1.22–1.38), and NO_X (HR: 1.32, 95% CI: 1.25–1.41); all $P<0.001$ and P for trend <0.001]. However, no significant additive interactions between genetic risk and air pollution exposure were identified **(Additional file 1: Table S17)**.

Identification of candidate genes commonly expressed in air pollutants and CKD and colocalization analyses of eQTLs

We performed TWAS to identify genes whose genetically predicted expression was associated with both

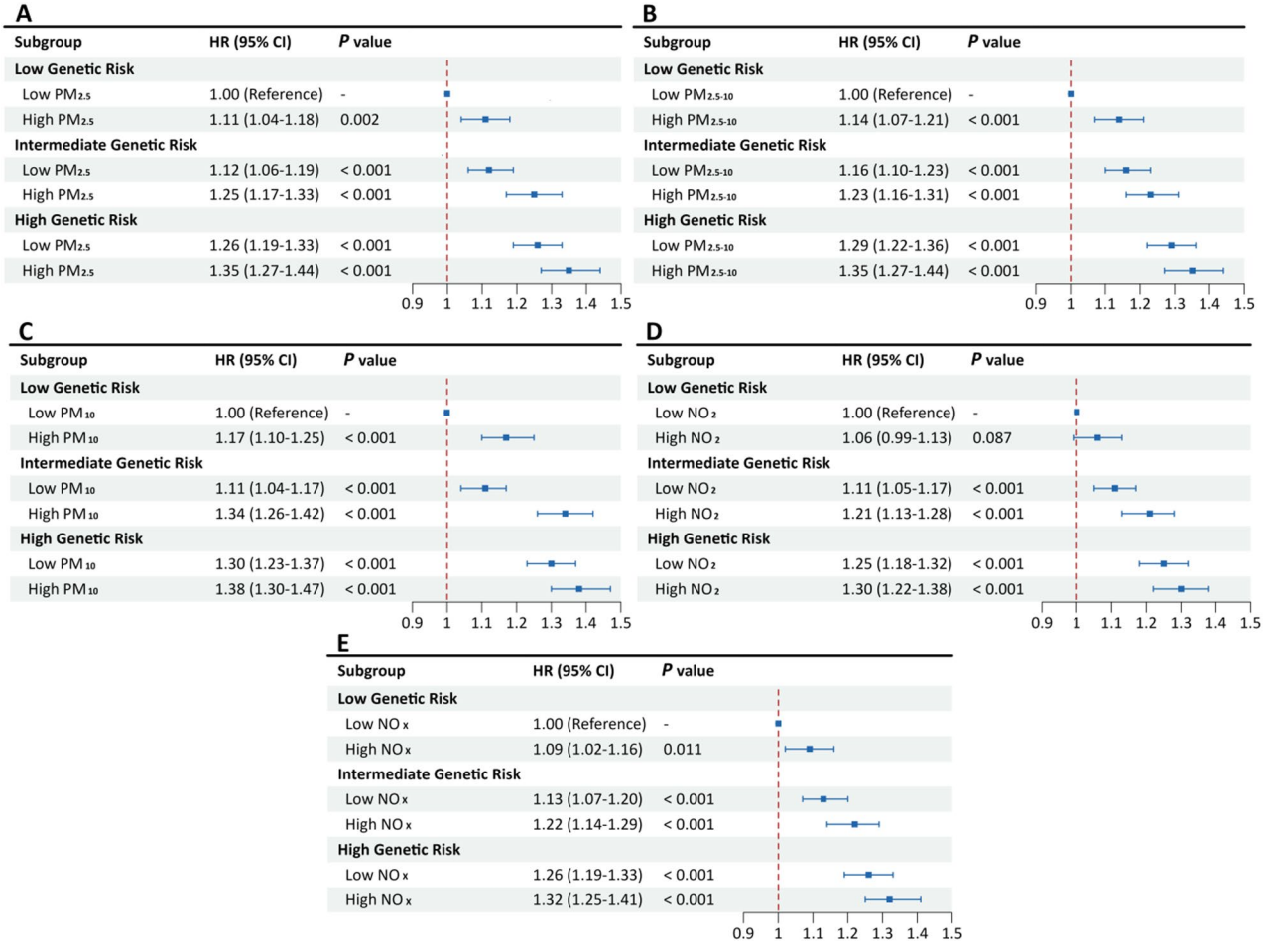


Fig. 4 Risk of incident CKD according to air pollutants and genetic risk categories. Abbreviations: HR, hazard ratio; CI, confidence interval; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤ 2.5 μm; $PM_{2.5-10}$, particulate matter with an aerodynamic diameter between 2.5 and 10 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 μm; NO_2, nitrogen dioxide; NO_X, nitrogen oxides

CKD and the five air pollutants **(Additional file 1: Table S18–S23)**. The top 20 most significant genes from each analysis are presented in Manhattan plots (Fig. 5). After filtering for significance and expression direction, several genes were identified as candidate genes, including *CDK3*, *MEIOB*, *NDUFAF1*, *CRIPAK*, *STX2*, *PHOSPHO2*, and *NECAB3* **(Additional file 1: Table S24)**. However, colocalization analyses using eQTL data did not yield strong evidence of a shared causal variant for these candidate genes **(Additional file 1: Table S25)**.

Identification of candidate proteins linking air pollutants to CKD and colocalization analyses of pQTLs

In the first step of MR, 76 candidate proteins for CKD were identified from 1,812 proteins with suitable genetic instruments ($P < 0.05$, FDR < 0.05, and no pleiotropy) **(Additional file 1: Table S26–S27)**. Among these, genetically predicted higher levels of 34 proteins were associated with increased CKD risk, while 42 with reduced risk (Fig. 6A). In the second step, applying a more lenient nominal $P < 0.05$ and no pleiotropy to filter the results, we identified 5 $PM_{2.5}$, 2 $PM_{2.5-10}$, 1 PM_{10}, 4 NO_2, and 3 NO_X-protein pairs **(Additional file 1: Table S28–S29)**. After further considering the directionality across the two-step MR (Fig. 6B), we ultimately identified 5 potential molecular pathways, including 3 risk proteins (*ALDH3A1*, *F12*, *SNCG*) and 2 protective proteins (*GNLY*, *MEGF10*) **(Additional file 1: Table S30)**. Colocalization analysis revealed strong evidence of colocalization between *ALDH3A1* and CKD at rs887241 (PPH4 = 1), *F12* at rs1801020 (PPH4 = 1), *SNCG* at rs873110 (PPH4 = 0.934), and moderate evidence between *GNLY* and CKD at rs7577293 (PPH4 = 0.524), *MEGF10* at rs112394041 (PPH4 = 0.792) (Fig. 6C, **Additional file 1: Table S31**).

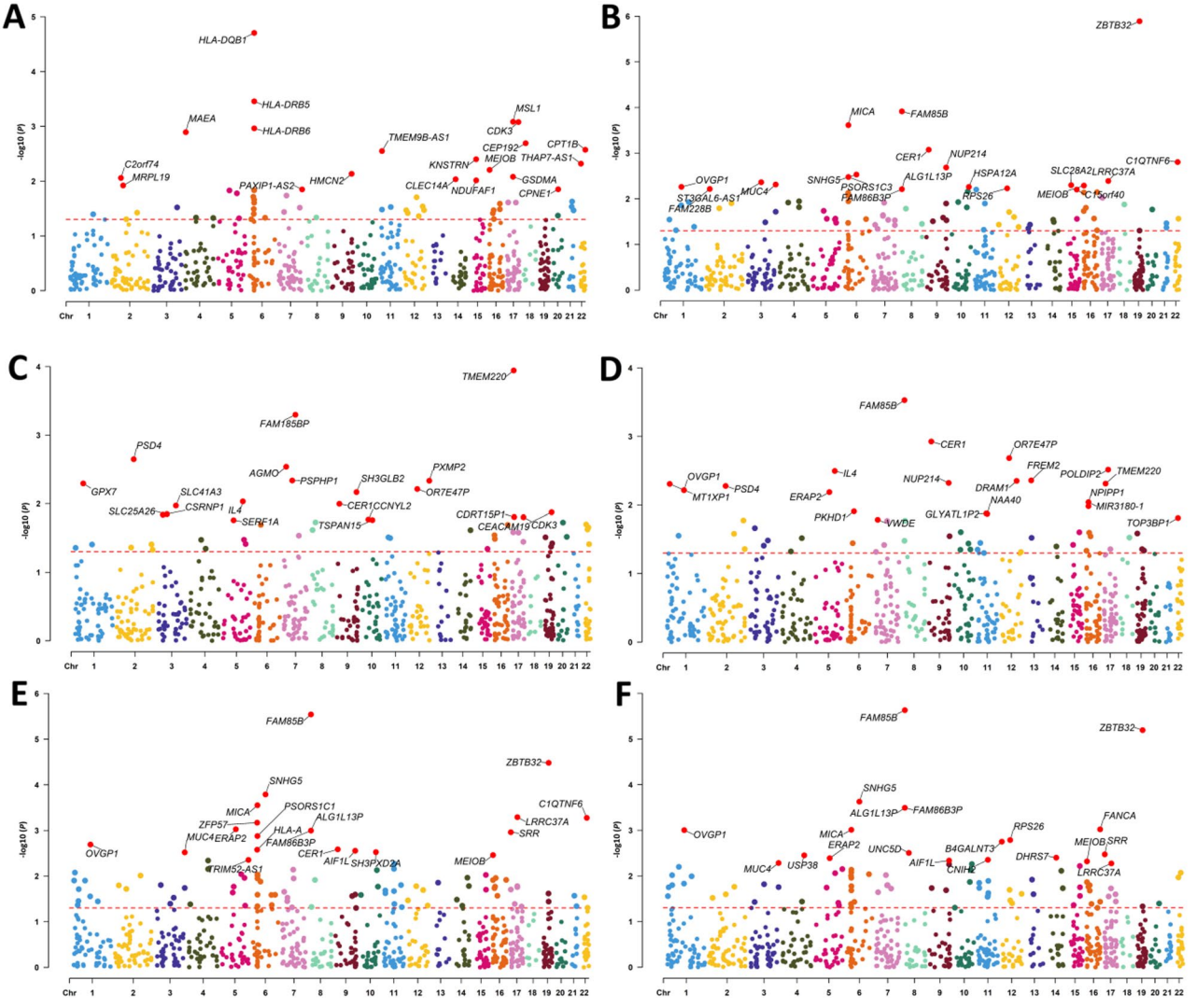


Fig. 5 Manhattan plots of genes associated with CKD and air pollutants. **A** CKD. **B** $PM_{2.5}$. **C** $PM_{2.5-10}$. **D** PM_{10}. **E** NO_2. **F** NO_X. Abbreviations: Chr, chromosome

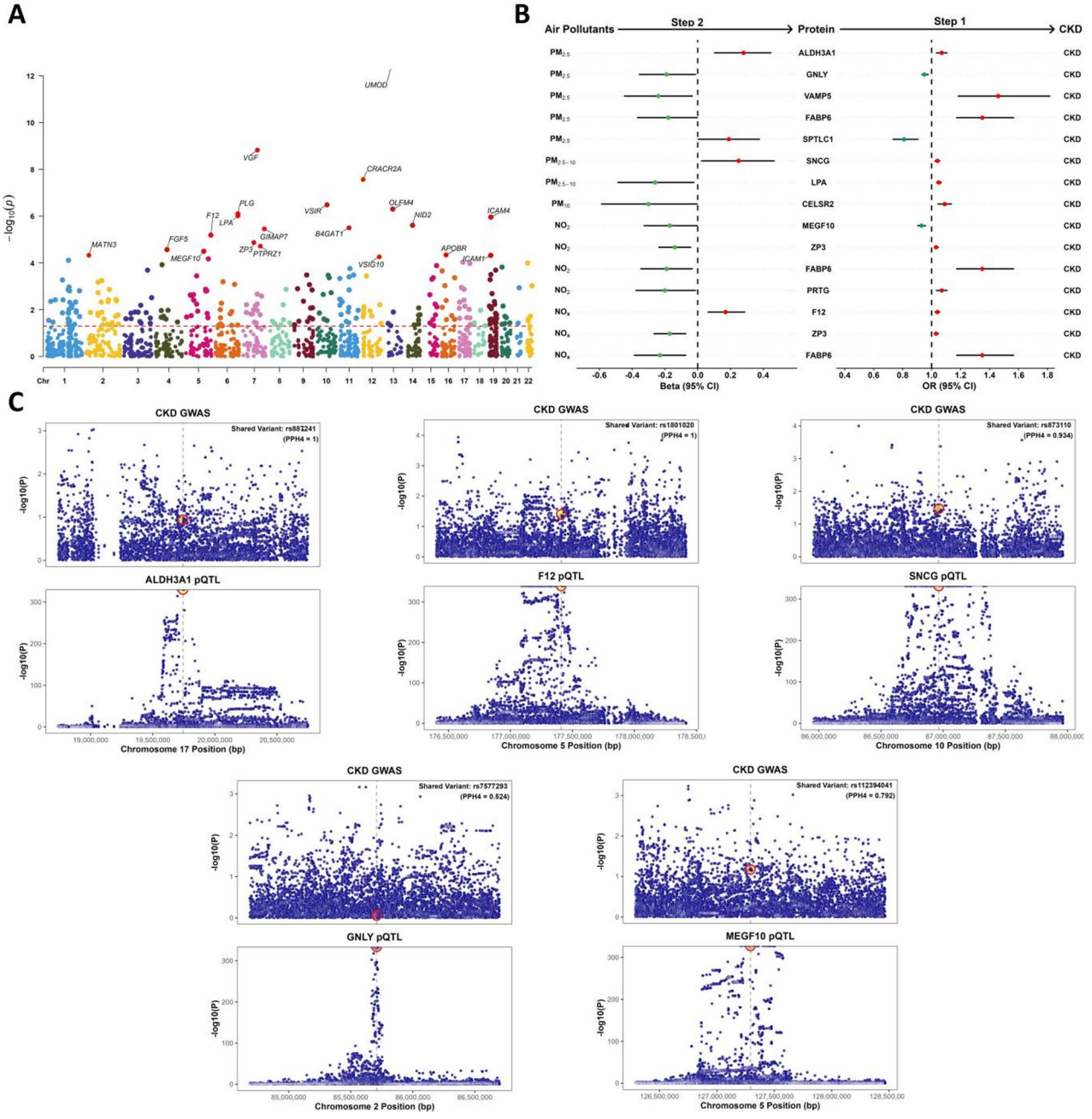


Fig. 6 Two-step MR analysis to identify potential mediating proteins from air pollutants to CKD. **A** Proteome-wide MR identifying proteins associated with the risk of CKD. **B** Effect sizes of the identified air pollutant–protein–CKD pathways. **C** Colocalization of pQTLs and CKD. Abbreviations: $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤ 2.5 μm; $PM_{2.5-10}$, particulate matter with an aerodynamic diameter between 2.5 and 10 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 μm; NO_2, nitrogen dioxide; NO_X, nitrogen oxides; CKD, chronic kidney disease; pQTL, protein quantitative trait locus

Discussion

In this UKB cohort with an average follow-up of 13.0 years, long-term exposure to $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, and NO_X was significantly associated with increased CKD risk, consistent across sensitivity analyses. Notably, several novel aspects of this association were identified: (1) incident hypertension and T2DM served as potential mediators, and participants with baseline hypertension or T1DM appeared more susceptible to the detrimental effects; (2) air pollutants also exhibited potential associations with the incidence of multiple kidney diseases, including AKI, GD, TID, hydronephrosis, and KS; (3) joint analyses revealed a pronounced gradient effect, with the highest CKD risk observed among individuals with both high genetic risk and high pollution exposure; and (4) TWAS and proteome-wide MR further

identified potential molecular pathways underlying these epidemiological links. As the most comprehensive multi-omics study to date examining the relationship between multiple air pollutants and CKD risk, this study provides exploratory insights for formulating targeted prevention strategies.

Current evidence on the air pollution–CKD link remains limited, with inconsistent findings across studies primarily conducted in North America and Asia. For example, while a study of U.S. veterans reported a 27% increase in CKD risk per 10 μg/m³ increase in $PM_{2.5}$ [30], a study in Taipei found no significant association [5]. Furthermore, some studies indicated a 12% increase in CKD risk per 10 μg/m³ increase in NO_2 [31], while evidence from North Carolina suggested an inverse association, linking higher NO_2 exposure to a lower CKD risk [32]. These discrepancies may stem from variations in sample sizes, exposure assessment methods, and geographic pollution profiles. Therefore, these results should be interpreted with caution. After fully adjusting for covariates, our study showed no significant association with NO_2, which aligns with several existing studies from China and Korea [6, 33]. One plausible explanation is that the vast majority of initial emissions from motor vehicle combustion consists of NO, which is gradually oxidized into NO_2 by ozone in the atmosphere over time. Multiple studies indicate that the NO_2/NO_X ratio increases significantly with distance from roadways [34]. Consequently, monitoring station data may overestimate true residential NO_2 exposure, potentially diluting its observed effect on CKD. Furthermore, when adjusting for spatial covariates such as distance to roads and traffic intensity, NO_2 is highly susceptible to over-adjustment. In contrast, NOx integrates both initial NO emissions and secondary NO_2 formation, thereby better capturing the highly localized exposure of populations residing near major emission sources.

Although evidence linking air pollution to CKD risk is increasing, the biological mechanisms remain unclear. The kidneys, being highly perfused, are prone to accumulating harmful particles and toxins from the blood. Ultrafine particles, once inhaled, can easily enter the systemic circulation via the vast surface area of the alveoli. Experimental evidence suggests that approximately 0.2% of inhaled nanoparticles may reach renal tissues [35], and the kidneys have limited capacity to clear particles larger than 6 nm [36]. This may lead to kidney injury through inflammation, oxidative stress, endothelial dysfunction, activation of the renin-angiotensin-aldosterone system, and DNA damage, ultimately resulting in glomerulosclerosis, tubular damage, and interstitial fibrosis [37].

Air pollution may indirectly increase CKD risk by promoting hypertension and diabetes through mechanisms such as insulin resistance, systemic inflammation, and oxidative stress [38]. Consistent with our mediation analyses, the 2019 Global Burden of Disease study estimated that 20% of the global burden of T2DM was attributed to $PM_{2.5}$ exposure [39]. A UKB study found that exposure to air pollutants, including $PM_{2.5}$, PM_{10}, NO_2, and NO_X, was significantly associated with increased incidence and comorbidity risks of hypertension, diabetes, and CKD [40]. Moreover, a U.S. veterans study suggested a potential mediating role of diabetes in the association between $PM_{2.5}$ and CKD/end-stage renal disease (ESRD) [41]. Crucially, beyond this mediating role, our additive interaction analysis revealed a more vulnerable susceptibility to pollution-driven CKD risk among individuals with pre-existing hypertension or T1DM, which aligns with recent evidence that air pollution is more strongly associated with metabolic nephropathies than isolated CKD [42]. Therefore, air pollution may act as a "second hit," superimposing accelerated renal damage upon pre-existing metabolic and hemodynamic vulnerabilities.

We identified several previously unrecognized genes associated with both air pollutants and CKD through TWAS. For example, *PHOSPHO2* (Phosphatase, Orphan 2), involved in osteoblast differentiation and bone mineralization [43], may lead to CKD-related bone mineral disorders and vascular calcification by promoting hyperphosphatemia and abnormal fibroblast growth factor-23 (FGF23), thereby potentially contributing to the onset and progression of CKD [44, 45]. *CRIPAK* (Cysteine-Rich Inhibitor of PAK1), an inhibitor of p21-activated kinase 1 (PAK1) [46], has been reported to reduce the generation of connective tissue growth factor (CTGF), extracellular matrix production, and kidney fibrosis [47]. Under stress conditions, such as ischemia, enhanced PAK1 activity further induces renal epithelial cell death [48]. However, the precise roles of these genes in renal pathophysiology remain unclear.

Our proteome-wide MR analysis provided genetically proxied evidence suggesting a potential pathway where exposure to certain air pollutants might increase CKD risk. Specifically, the upregulation of risk proteins (*ALDH3A1*, *F12*, and *SNCG*) and downregulation of protective proteins (*GNLY* and *MEGF10*) emerged as potential molecular pathways. *ALDH3A1* is a cytosolic aldehyde dehydrogenase scavenging reactive aldehydes [49]. Polycyclic aromatic hydrocarbons enriched $PM_{2.5}$ potently activates the aryl hydrocarbon receptor (AhR), upregulating AhR-responsive detoxifying enzymes like *ALDH3A1* [50, 51]. Crucially, chronic pollution exposure may cause persistent AhR activation, accelerating CKD progression and cardiovascular complications by driving cellular senescence, mitochondrial dysfunction, fibrogenesis, and vascular remodeling [50, 52]. Furthermore, air pollutants can bind and activate coagulation factor XII (*F12*), inducing a chronic low-grade thrombotic

and inflammatory burden via the contact system [53]. Elevated *F12* in CKD correlates with tubular injury, interstitial inflammation, fibrosis, and accelerated renal function decline [54]. Notably, a large-scale East Asian GWAS and recent cell-type-dependent eQTL MR studies have corroborated *F12* genetic variants as determinants of eGFR and promising druggable targets for CKD [55, 56]. Additionally, γ-synuclein (*SNCG*) is a synuclein family member implicated in tumorigenesis and progression. Evidence shows environmental toxins like nicotine upregulate *SNCG*, promoting epithelial-mesenchymal transition (EMT) and cellular invasion [57]. Given that genome-wide studies suggest functional overlap between *SNCG* and its tubular-protective family member α-synuclein (*SNCA*), which is highly expressed in proximal tubular epithelial cells and plays a critical role in maintaining the tubular epithelial phenotype and regulating EMT and fibrotic processes [58], the genetically predicted elevation of *SNCG* may represent a potential maladaptive EMT-related mechanism, warranting further experimental validation.

Conversely, granulysin (*GNLY*) is an effector molecule primarily secreted by NK and cytotoxic T cells to maintain immune homeostasis [59]. Long-term exposure to air pollutants induces severe oxidative stress, inflammation, and immunotoxicity, driving an imbalance in both innate and adaptive immunity, which is notably characterized by T-cell subset dysregulation and the numerical and functional depletion of NK cells [60]. Since persistent chronic inflammation and immune dysregulation drive tubulointerstitial fibrosis and progressive renal function decline [61], the genetically predicted reduction in *GNLY* likely reflects the impairment of host anti-inflammatory and immune defense barriers under chronic exposure. Finally, as a transmembrane scavenger receptor, *MEGF10* regulates apoptotic cell clearance and tissue remodeling [62]. Theoretically, its downregulation could exacerbate apoptotic cell accumulation, inflammation, and fibrogenesis during chronic kidney injury; however, to date, no studies have reported a direct association between *MEGF10* and CKD.

This study has several limitations. First, the predominantly European ancestry of our participants limits the generalizability of our findings. Second, exposure assessment was based on average annual concentrations of ambient pollutants at the residential level for specific years, which may not fully capture individual-level variations in exposure due to indoor pollution, occupational environments, daily mobility, or evolving regional environmental regulations. Third, although our multi-source diagnostic approach maximizes case ascertainment, relying on ICD codes introduces phenotypic heterogeneity, precludes disease severity staging, and risks misclassifying CKD diagnoses recorded in the context of AKI or other conditions. Furthermore, the findings from our multi-omics analyses must be interpreted with restraint. TWAS signals represent statistical associations and do not necessarily imply true biological causality. Similarly, although our two-step MR provides evidence of causal consistency along a hypothesized pathway, it does not formally establish true biological mediation. The observed analytical chains remain sensitive to potential violations of instrument validity and could still be influenced by residual pleiotropy, LD-driven associations, or shared genetic architecture. Additionally, standard single-causal-variant colocalization can be unreliable in regions with multiple independent signals. Moreover, genetic instruments from air pollution GWAS may reflect residential and socioeconomic confounding beyond pure exposure, necessitating cautious interpretation of downstream findings. Finally, the biological functions of those identified genes and proteins remain poorly understood, and further experimental studies are needed for validation.

Conclusions

In summary, long-term exposure to $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, and NO_X is associated with an increased CKD risk, with hypertension and diabetes playing a crucial role in this association. Furthermore, the identified potential molecular pathways linking air pollution to CKD pathogenesis may provide preliminary exploratory evidence for future research.

Abbreviations

CKD	chronic kidney disease
PRS	polygenic risk scores
TWAS	transcriptome-wide association study
MR	Mendelian randomization
IVs	instrumental variables
UKB	UK Biobank
MREC	Multi-Centre Research Ethics Committee
eGFR	estimated glomerular filtration rate
GWAS	genome-wide association study
IEU OpenGWAS	Integrative Epidemiology Unit Open Genome-Wide Association Studies
LUR	land use regression
AKI	acute kidney injury
GD	glomerular disease
TID	tubular-interstitial disease
KS	kidney stone
CAK	congenital anomalies of kidney
DAG	directed acyclic graph
BMI	body mass index
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
SNP	single nucleotide polymorphism
LD	linkage disequilibrium
eQTLs	expression quantitative trait loci
GTEx v8	Genotype-Tissue Expression version 8
cis-pQTLs	cis protein quantitative trait loci
PPH4	posterior probability for hypothesis 4
SD	standard deviation
VIF	variance inflation factor
HR	hazard ratio
CI	confidence interval

RCS	restricted cubic splines
IQR	interquartile range
NIE	natural indirect effect
RERI	relative excess risk due to interaction
AP	attributable proportion
SI	synergy index
ESRD	end-stage renal disease
FGF23	fibroblast growth factor-23
CTGF	connective tissue growth factor
AhR	aryl hydrocarbon receptor
EMT	epithelial-mesenchymal transition

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-026-04909-6.

Supplementary Material 1: Tables S1-S31.

Supplementary Material 2: Supplemental Methods.

Supplementary Material 3: Figures S1-S3

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Author contributions
JL: Conceptualization, Writing - review & editing, Investigation, Data curation. SS: Writing - original draft, Formal analysis, Methodology, Software. XS: Methodology. ZD: Methodology. SW: Methodology. SJ: Funding acquisition, Project administration. WL: Funding acquisition, Supervision. JL and SS contributed equally to this work. All authors read and approved the final manuscript.

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Data availability
Individual-level data from the UKB are not publicly accessible due to institutional policy but can be obtained upon approval of a formal application to the UKB (https://www.ukbiobank.ac.uk/). GWAS summary statistics for air pollutants were obtained from the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/), while CKD summary statistics were sourced from the FinnGen consortium (https://r12.finngen.fi/pheno/N14_CHRONKIDNEYDIS). Kidney cortex eQTL data were obtained from GTEx v8 (https://www.gtexportal.org), and plasma pQTL data were derived from the UKB Pharma Proteomics Project (https://registry.opendata.aws/ukbppp). Analysis scripts are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This research was conducted using data from the UKB (Application No. 896530). The UKB study received ethical approval from the North West Multi-Centre Research Ethics Committee (REC reference: 21/NW/0157). In accordance with the principles outlined in the Helsinki Declaration, written informed consent was obtained from all participants prior to their inclusion in the study.

Consent for publication
Not applicable.

Conflict of interest
The authors declare no competing interests.

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