Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Proteomics mediates the effects of preserved ratio impaired spirometry on chronic kidney disease progression: a UK Biobank study

Xu Hu
The First Affiliated Hospital of Nanchang University
Hanbin Yang
The First Affiliated Hospital of Nanchang University
Weiwen Ye
The First Affiliated Hospital of Nanchang University
Yue Wang
The First Affiliated Hospital of Nanchang University
Yuyang Yuan
The First Affiliated Hospital of Nanchang University
Lizhi Zhou
The First Affiliated Hospital of Nanchang University
Wei Liu
nfyfy04414@ncu.edu.cn
The First Affiliated Hospital of Nanchang University

Article

Keywords: preserved ratio impaired spirometry, proteomics, chronic kidney disease, mediation analysis, UK Biobank

Posted Date: April 23rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9239065/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: No competing interests reported.

Abstract

Impaired lung function is increasingly recognized as a contributor to multi-organ failure, yet the mechanisms linking preserved ratio impaired spirometry (PRISm) to chronic kidney disease (CKD) remain unelucidated. To address this knowledge gap, we aimed to uncover the underlying proteomic mediators driving the progression from PRISm to CKD.Using UK Biobank data (N = 38,800), PRISm was defined as an FEV1/FVC ≥ 0.70 and FEV1 < 80% predicted. Multivariable Cox proportional hazards modeling assessed the longitudinal relationship between baseline PRISm and incident CKD, while the mediation effects of 2,911 plasma proteins were analyzed via LASSO-penalized Cox regression and causal mediation analysis.Over a 13.6-year median follow-up, 1,540 participants developed CKD. Compared to those with normal pulmonary function, individuals with PRISm (n = 5,655) exhibited a 43% higher risk of incident CKD (HR: 1.43; 95% CI: 1.26–1.63). Proteomic analysis identified 847 significant mediators (FDR < 0.05),from which 12 core proteins emerged. Notably, GDF15, RNASE1, and WFDC2 exhibited the highest mediation proportions (28.3%, 24.2%, and 19.5%, respectively). Collectively, these 12 biomarkers accounted for 41.6% (95% CI: 32.6%–61.0%) of the total pathogenic effect.Our study revealed the association of PRISm with new-onset CKD and highlighted the potential roles of specific circulating proteins in mediating this biological pathway.

1 Introduction

Chronic kidney disease (CKD) has become one of the leading causes of death and disability globally, affecting more than 10% of the adult population worldwide[1, 2]. With the aging population, the prevalence of metabolic diseases, and its irreversible pathological process, the economic burden of CKD is expected to increase exponentially in the next few decades[3, 4]. Consequently, identifying novel, modifiable risk factors or therapeutic targets for CKD is critically important.

In recent years, impaired lung function has emerged as a potential contributor to multi-organ failure, and preserved ratio impaired spirometry (PRISm) has drawn particular attention[5–7]. PRISm is defined as a forced expiratory volume in one second to forced vital capacity (FEV1/FVC) ratio of ≥ 0.70 and FEV1 < 80% of the predicted value[8]. This spirometric pattern is relatively common in the general population and is strongly associated with elevated risks of cardiovascular disease and all-cause mortality[9, 10]. Recent large-scale prospective cohort studies have indicated that PRISm can significantly increase the risk of chronic kidney disease (CKD) independently of traditional metabolic or cardiovascular risk factors[11]. However, the mediating factors behind the association between PRISm and CKD have not been elucidated yet.

With the rapid development of high-throughput detection technologies (such as the Olink platform), circulating proteomics has demonstrated great potential in discovering key effector molecules in the body[12–14]. For example, 395 plasma proteins act as intermediary molecules in more than 1400 pathways during the progression from underlying diseases such as diabetes to secondary target organ damage including renal diseases[15], and 9 plasma proteins have been proven to mediate the pathways from biological aging to Cardio-renal-metabolic (CRM) comorbidity[16]. In addition, abnormal lung function (such as PRISm) often triggers secondary systemic inflammatory responses, impaired endothelial function, and oxidative stress, and these pathological changes are highly consistent with renal microvascular remodeling[17–19]. We therefore hypothesize that circulating proteins measured by high-throughput proteomics may mediate the pathway from PRISm to incident CKD.

If this hypothesis is verified, early identification and targeted regulation of these core intermediary proteins in the PRISm population will provide a novel intervention strategy for the prevention of new-onset CKD. In this work, we investigated the prospective association between PRISm and CKD in the population with plasma protein data. Then, we first identified and quantified the role of protein markers mediating PRISm and incident CKD as potential mediators.

2 Results

2.1 Baseline characteristics of study participants

A total of 38,800 baseline participants were ultimately included in this study. Among them, 5,655 participants (14.6%) were assessed as having PRISm at baseline. According to the baseline characteristics shown in Table 1, compared with those with

normal pulmonary function tests (n = 33,145), patients with PRISm at baseline were more likely to be smokers (12.0% vs 8.2%). They were less likely to be white (79.1% vs 96.1%) and had a higher Townsend deprivation index (-0.38 vs -1.47). In addition, they had a higher proportion of obesity (37.1% vs 22.0%) and a higher prevalence of clinical comorbidities, including hypertension (11.2% vs 6.0%), diabetes (3.9% vs 1.3%), and cardiovascular diseases (8.6% vs 4.1%) (all $P < 0.001$). There were no significant differences between the two groups in terms of age ($P = 0.626$), gender ($P = 0.073$), and baseline estimated glomerular filtration rate (eGFR) ($P = 0.127$).

Table 1
Baseline characteristics of the study population

Age (years)	**Total**	**Normal Spirometry**	**PRISm**	***P* value**
	(N = 38,800)	**(n = 33,145)**	**(n = 5,655)**	
	55.95 (8.19)	**55.96 (8.17)**	**55.90 (8.31)**	**0.626**
Gender				0.073
Female	21,766 (56.1%)	18,656 (56.3%)	3,110 (55.0%)	
Male	17,034 (43.9%)	14,489 (43.7%)	2,545 (45.0%)	
Body mass index				< 0.001
Less than 18.5	168 (0.4%)	141 (0.4%)	27 (0.5%)	
18.5 to 25	12,503 (32.2%)	11,215 (33.8%)	1,288 (22.8%)	
25 to 30	16,741 (43.1%)	14,497 (43.7%)	2,244 (39.7%)	
Greater than 30	9,388 (24.2%)	7,292 (22.0%)	2,096 (37.1%)	
Townsend deprivation index	-1.31 (3.12)	-1.47 (3.01)	-0.38 (3.56)	< 0.001
Education				< 0.001
College degree	13,163 (33.9%)	11,495 (34.7%)	1,668 (29.5%)	
Other levels	19,407 (50.0%)	16,631 (50.2%)	2,776 (49.1%)	
Unknown	6,230 (16.1%)	5,019 (15.1%)	1,211 (21.4%)	
Smoking				< 0.001
Never	22,355 (57.6%)	19,194 (57.9%)	3,161 (55.9%)	
Previous	13,063 (33.7%)	11,245 (33.9%)	1,818 (32.1%)	
Current	3,382 (8.7%)	2,706 (8.2%)	676 (12.0%)	
Drinking				< 0.001
Never	1,735 (4.5%)	1,192 (3.6%)	543 (9.6%)	
Previous	1,351 (3.5%)	1,090 (3.3%)	261 (4.6%)	
Current	35,714 (92.0%)	30,863 (93.1%)	4,851 (85.8%)	
Ethnicity				< 0.001
White	36,333 (93.6%)	31,859 (96.1%)	4,474 (79.1%)	
Others	2,467 (6.4%)	1,286 (3.9%)	1,181 (20.9%)	
Clinical Comorbidities				
Hypertension	2,616 (6.7%)	1,983 (6.0%)	633 (11.2%)	< 0.001
Diabetes	650 (1.7%)	427 (1.3%)	223 (3.9%)	< 0.001
Cardiovascular disease	1,843 (4.8%)	1,355 (4.1%)	488 (8.6%)	< 0.001
Renal Function				

Data are presented as mean (standard deviation) for continuous variables and n (%) for categorical variables. Abbreviations: BMI, body mass index;FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PRISm, preserved ratio impaired spirometry; eGFR, estimated glomerular filtration rate

Age (years)	Total (N = 38,800)	Normal Spirometry (n = 33,145)	PRISm (n = 5,655)	*P* value
	55.95 (8.19)	**55.96 (8.17)**	**55.90 (8.31)**	**0.626**
eGFR (mL/min/1.73 m²)	91.71 (12.03)	91.67 (11.92)	91.93 (12.65)	0.127
Lung Function				
FVC (L)	3.73 (0.99)	3.89 (0.94)	2.82 (0.73)	< 0.001
FEV1 (L)	2.91 (0.77)	3.04 (0.73)	2.16 (0.54)	< 0.001
FEV1/FVC	0.78 (0.04)	0.78 (0.04)	0.77 (0.05)	< 0.001

Data are presented as mean (standard deviation) for continuous variables and n (%) for categorical variables. Abbreviations: BMI, body mass index;FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PRISm, preserved ratio impaired spirometry; eGFR, estimated glomerular filtration rate

2.2 Association between PRISm and incident CKD

During a median follow-up of 13.6 years, 1,540 (3.97%) participants developed CKD. After multivariable stepwise adjustment, we observed a significant prospective association between baseline pulmonary dysfunction with PRISm and the risk of incident CKD. Compared with individuals with normal pulmonary function, participants with PRISm at baseline had a significantly higher risk of CKD (fully adjusted hazard ratio [HR], 1.43; 95% confidence interval [CI], 1.26–1.63; P < 0.001) (Table 2). Multiple sensitivity analyses supported the robustness of this finding: the results after excluding cases that occurred in the first two years (HR 1.43, 95% CI 1.26–1.62) and considering the competing risk of death (subdistribution hazard ratio [SHR] 1.37, 95% CI 1.20–1.56) were consistent with the main analysis (all P < 0.001) (Table S2). Stratified analysis confirmed the universality of this association. No significant heterogeneity was observed among subgroups such as gender, BMI, and baseline comorbidities, and the risk effect was more significant in those under 60 years old (P for interaction = 0.002) (Figure S1).

Table 2
Association of baseline PRISm with the risk of incident CKD

Spirometry Status	N	Cases	Person-Years	Incidence Rate (per 1000 person-years)	Model 1 HR (95% CI)	P value	Model 2 HR (95% CI)	P value	Model 3 HR (95% CI)	*P* value
Normal	33145	1178	438916.7	2.68	Reference		Reference		Reference	
PRISm	5655	362	72522.2	4.99	1.89 (1.68–2.13)	< 0.001	1.86 (1.65–2.11)	< 0.001	1.43 (1.26–1.63)	< 0.001

Model 1: Adjusted for Age ,Gender. Model 2: Adjusted for model 1 plus TDI, Education, Smoking status, Drinking status, Ethnicity. Model 3: Adjusted for model 2 plus CVD, Hypertension, Diabetes, BMI, eGFR.

Abbreviations: BMI, body mass index; PRISm, preserved ratio impaired spirometry; eGFR, estimated glomerular filtration rate, CVD: Cardiovascular disease; TDI: Townsend deprivation index; CKD: Chronic kidney disease.

2.3 Preliminary protein mediation analysis

In the proteomic screening phase, we first comprehensively analyzed the mediating roles of a total of 2,911 plasma proteins in the association between PRISm and incident CKD. Through preliminary mediation analysis, we found that a total of 847 plasma proteins exhibited significant mediating effects (proportion of mediating effect > 0 and false discovery rate [FDR] < 0.05) (Fig. 2a). Enrichment analysis (GO/KEGG) showed that these mediating proteins were mainly enriched in the extracellular space and secretory vesicles, and were involved in biological processes such as regulation of inflammatory response, regulation of cell proliferation, and extracellular matrix organization (Fig. 2b). Their molecular functions were mainly receptor ligand activity,

cytokine activity, and growth factor binding activity. These GO molecular functions corresponded to the significantly enriched cytokine-cytokine receptor interaction and extracellular matrix-receptor interaction pathways in KEGG.

2.4 Identify core proteins and construction of protein scores

Preliminary mediation analysis identified 847 candidate proteins with significant mediation effects. The LASSO-Cox regression was applied to optimize the proteins associated with the risk of incident CKD. In this study, lambda.1se (0.015) was selected as the final tuning parameter (Figure S2a). Ultimately, 12 core proteins (GDF15, RNASE1, WFDC2, VSIG4, IGFBP4, FSTL3, HAVCR1, YAP1, COLEC12, EDA2R, SCARB2, SHISA5) were identified (Fig. 2c). We used the Four-way decomposition method to quantify the mediation effects of these 12 proteins (Supplementary Table S4). All 12 core proteins were significantly associated with the mediation pathway of incident CKD ($P < 0.001$). Among them, GDF15 had the highest mediation proportion (28.3%), followed by RNASE1 (mediation proportion 24.2%) and WFDC2 (mediation proportion 19.5%). We constructed a protein risk score from the 12 LASSO-Cox selected proteins. The protein risk score constructed in the full-variable model (HR per standard deviation increment was 2.01, 95% confidence interval: 1.91–2.11, $P < 0.001$) was significantly positively associated with the risk of CKD (Supplementary Table S5). Kaplan-Meier survival analysis showed that during the 15-year follow-up period, compared with participants with a high protein risk score, the cumulative probability of remaining CKD-free was significantly lower in participants with a low protein risk score ($P < 0.0001$) (Supplementary Figure S3). Causal effect decomposition showed that among the total effect of PRISm on new-onset CKD (HR = 1.48, 95% CI: 1.30–1.69), these 12 core proteins mediated 41.6% of the total pathogenic effect of PRISm (95% CI: 32.6% − 61.0%, $P < 0.001$) (Fig. 3).

These findings highlight the protein mediators of PRISm and CKD, and provide mechanistic insights into the prevention or treatment of chronic kidney disease associated with impaired lung function.

3 Discussion

In the subgroup with plasma protein data and an average follow-up time of 13.6 years, baseline PRISm was an independent risk factor for new-onset CKD, increasing the disease risk by 43%. Through systematic proteomic mediation analysis, among 2911 plasma proteins, we observed that 847 proteins contributed to the pathway from PRISm to chronic kidney disease, which were enriched in key pathways such as inflammatory response and extracellular matrix organization. Twelve core mediator proteins (e.g., GDF15, RNASE1, etc.) were screened out by LASSO-Cox, which together mediated 41.6% of the total effect of PRISm on CKD. These findings suggest that individuals with a PRISm pattern in baseline pulmonary function tests have an increased risk of CKD, which is probably due to alterations in specific metabolic pathways associated with this pulmonary function phenotype.

Numerous epidemiological studies have shown that, compared with individuals with normal lung function, patients with pulmonary function impairment with preserved ratio not only face a higher risk of progression of respiratory diseases but also have a significantly increased risk of developing comorbidities in other systems such as cardiovascular and metabolic systems[7, 22, 23]. Previous studies have observed an association between decreased lung function and adverse renal outcomes[24–26]. The results of this study are generally consistent with the findings of previous prospective studies on the association between PRISm and CKD. However, most of the existing studies are limited to describing epidemiological associations, and the molecular mediation mechanisms involved are almost unknown, which prompts us to search for potential intermediate variables that may mediate this association[11].

Our study initially evaluated 2,911 plasma proteins and found that 847 of them had a significant mediating effect on the progression from PRISm to CKD. Eventually, 12 core molecular markers were precisely identified through a dimensionality reduction algorithm. Among these core proteins, the comprehensive mediating ratio of growth differentiation factor 15 (GDF15) was as high as 28.3%. As a classic marker of cellular stress and systemic inflammation, the level of GDF15 was significantly elevated in PRISm patients, which was highly consistent with the hypothesis that impaired ventilation function triggers persistent hypoxic stress and systemic chronic inflammation[27, 28]. The study showed that the large-scale release of proinflammatory factors triggered by the lungs may, in turn, induce the deterioration of the target organ microenvironment and abnormal infiltration of macrophages[29, 30]. GDF15 is involved in the regulation of cellular stress, mitochondrial dysfunction, and macrophage activation[31, 32]. Prior studies show that excessive activation of GDF15-mediated stress responses causes

glomerular podocyte dysfunction and apoptosis, leading to proteinuria and progressive renal function loss[33]. Therefore, our results indicate that the abnormal inflammatory response associated with PRISm may promote the occurrence of chronic kidney disease in this context, which is also consistent with the conclusions of multiple previous studies confirming the association between GDF15 and the transformation of acute kidney injury to CKD and the rapid progression of CKD.

Multiple different target proteins also exhibited extremely high mediation ratios (e.g., RNASE1: 24.2%), suggesting that early monitoring and preservation of vascular endothelial function in PRISm patients could slow CKD progression. RNASE1 has been widely reported to have a significant impact on vascular endothelial barrier homeostasis and microcirculatory hemodynamics[34, 35]. Firstly, systemic inflammation caused by abnormal pulmonary respiratory physiology can directly damage the systemic microvascular endothelial barrier[36]. For example, there is a strong positive feedback loop between persistent hypoxia and cytokine stimulation and RNASE1-mediated endothelial dysfunction[37]. Secondly, abnormal RNASE1 levels are a direct manifestation of microcirculatory hemodynamic disorders, as the damaged endothelial system directly increases the permeability of glomerular capillaries, accelerating renal hyperfiltration and hyperperfusion injury[34]. Notably, four-way decomposition analysis revealed that RNASE1 has a significant mediating interaction effect. This interactivity suggests that future intervention strategies should not only focus on simply reducing the concentration of this protein but also emphasize blocking its amplified endothelial toxicity in the PRISm state.

In addition, pro-fibrotic proteins such as WFDC2 also play a significant mediating role (19.5%) in explaining the association between PRISm and CKD. WFDC2 has been previously confirmed to be highly correlated with tubulointerstitial fibrosis and abnormal extracellular matrix (ECM) deposition in multiple population-based and in vitro studies[38]. Abnormal accumulation of WFDC2 can excessively activate the ECM receptor interaction pathway, leading to a large amount of abnormal deposition of collagen and other matrix components in the renal parenchyma, ultimately resulting in irreversible tubulointerstitial fibrosis and loss of nephrons[39]. Moreover, these core mediators may continuously amplify the vicious cycle of oxidative stress and local tissue ischemia during the long-term chronic pathological process[40].

This study presents a significant advantage by introducing high-throughput proteomics and the CMAverse four-way decomposition model to systematically assess the potential mediating effects of circulating proteins, such as GDF15, RNASE1, and WFDC2, on the relationship between PRISm and chronic kidney disease for the first time. Other advantages of our study also include professional and standardized pulmonary function measurement, a long follow-up duration, and the adjustment of models for multiple potential confounders. However, this study also has certain limitations that need to be considered. First, although we strictly adjusted for baseline confounding factors, as an observational study, it is still impossible to completely exclude the residual interference of unmeasured confounding factors. The exact molecular pathogenic mechanism still needs to be experimentally verified by future animal disease models or Mendelian randomization (MR) studies. Second, proteomic characteristics were only measured once at the baseline, which limits our ability to capture the dynamic evolution of proteins throughout the progression from PRISm to CKD. Finally, the current protein score and mediating targets were mainly constructed based on participants of European white ancestry. Therefore, external validation using diverse population cohorts with varying genetic backgrounds is imperative to assess their generalizability.

In conclusion, this prospective study demonstrates an association between PRISm and incident CKD, and this association may be mediated by several key circulating proteins. These findings suggest a reasonable biological pathway between PRISm and CKD and provide novel insights into potential molecular targets. Our results may contribute to understanding and alleviating the clinical burden of renal complications caused by PRISm.

4 Methods

4.1 Research design and participants

The UK Biobank is a large-scale prospective cohort that enrolled approximately 500,000 residents of the United Kingdom, aged between 37 and 73 years, from 2006 to 2010[20]. The present study is a secondary analysis of data from the UK Biobank (Application Number: 532564). The UK Biobank study obtained overarching ethical approval from the North West Multi-Centre

Research Ethics Committee (REC reference: 21/NW/0157); and all participants provided written informed consent. All methods were performed in accordance with the relevant guidelines and regulations. At baseline, participants completed touchscreen questionnaires and nurse-administered interviews to document lifestyle, dietary, environmental, and reproductive factors, and they underwent physical measurements and biological sample collection. Participant incidence and mortality are tracked via electronic linkage to hospitalization records and death registries. For the present analysis focusing on preserved ratio impaired spirometry (PRISm), we applied the following exclusion criteria: (a) No proteomics data. (b) Having chronic kidney disease at baseline. (c) A missing rate of covariates greater than 20%. (d) No pulmonary function test measurement data at baseline. (e) Being diagnosed with obstructive pulmonary function at baseline pulmonary function test. A total of 38,800 participants were finally included in this study (Fig. 1).

4.2 Assessment of Spirometry

Baseline pre-bronchodilator spirometry was performed by trained healthcare professionals within the UK Biobank using Vitalograph Pneumotrac 6800 spirometers. The protocol required participants to perform two to three forced expiratory maneuvers over six minutes, with the instrument calibrated prior to each session. A computer algorithm assessed the reproducibility of the first two maneuvers; if the difference between them was less than 5%, a third maneuver was not required. The highest recorded measurement was used for subsequent analysis. We only used the available pre-bronchodilator pulmonary function test data from the UK Biobank. Pulmonary function tests were classified into three groups based on baseline pulmonary function: PRISm was defined as an FEV1/FVC ratio ≥ 0.70 and FEV1 < 80% predicted; normal pulmonary function test was defined as an FEV1/FVC ratio ≥ 0.70 and FEV1 ≥ 80% predicted; obstructive pulmonary function test was described as an FEV1/FVC ratio < 0.70 [21].

4.3 Plasma proteomic measurement

A large-scale plasma proteomic investigation was conducted as part of the UK Biobank Pharmacoproteomics Project (UKB-PPP). Using the Olink™ Explore 3072 Near Extended Assay, the UKB-PPP analyzed plasma samples from 52,995 participants. This platform comprises eight panels, including cardiometabolism, inflammation, neurology, oncology, cardiometabolism II, inflammation II, neurology II, and oncology II, covering 2,923 different proteins. The measurements are expressed as standardized protein expression values (log2-transformed). After excluding proteins with > 20% missing values, a total of 2,911 proteins were included in the proteomic analysis. All protein levels were standardized in the analysis, and missing values were multiply imputed using K-nearest neighbors (KNN).

4.4 Outcome

The chronic kidney disease outcome in this study was defined by integrating hospital inpatient records, self-reported medical conditions, and baseline biochemical indicators of estimated glomerular filtration rate (eGFR < 60 ml/min/1.73m^2) (Table S1). The calculation started from the baseline enrollment date. For participants who developed CKD, follow-up ended on the date of the first diagnosis; for those who did not, follow-up was censored at death, loss to follow-up, or the most recent database update. Baseline health records were available through October 31, 2022.

4.5 Covariate

To adjust for potential confounding factors, this study included covariates covering demographics, socioeconomic status, lifestyle, and clinical characteristics. The basic characteristics included age, gender (male or female), and ethnicity (White or others). Socioeconomic status was evaluated using the Townsend Deprivation Index (TDI), and educational level was classified according to the participants' highest educational level. Smoking status (never, previous and current) and drinking status (never, previous and current) were obtained through the baseline questionnaire. Body mass index (BMI) was calculated based on the height and weight measured at baseline. Baseline renal function was represented by estimated glomerular filtration rate (eGFR), computed from serum creatinine using the CKD-EPI formula. Clinical comorbidities were obtained from ICD-10 inpatient diagnosis records: hypertension (ICD-10: I10), diabetes (ICD-10: E10, E11), and cardiovascular disease (CVD) was defined as angina, myocardial infarction, atrial fibrillation, heart failure, stroke, and peripheral vascular disease (ICD-10: I20 - I25, I48, I50, I60 - I64, I70, I73) (Table S1). Cases with more than 20% missing data were deleted; remaining missing values were imputed

using Multiple Imputation by Chained Equations (MICE). Continuous baseline variables are reported as median (SD), and categorical variables as number (percentage).

4.6 Statistical analysis

Multivariable Cox proportional hazards regression models were used to evaluate the association between PRISm and incident CKD, and the hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. In the fully adjusted multivariable model (Model 3), we adjusted for age, gender, ethnicity, BMI, TDI, educational level, smoking status, drinking status, baseline comorbidities (hypertension, diabetes, CVD), and baseline eGFR. We conducted stratified analyses to examine whether the association between PRISm and the risk of CKD was stable across subgroups with different characteristics. Stratification factors included age (< 60 years, ≥ 60 years), gender (male, female), smoking status, BMI (< 25, 25–30, ≥ 30), and the presence of hypertension or diabetes. Multiplicative interaction terms between exposure variables and stratification variables were used to evaluate the potential modulating effects of these factors on the outcome risk. We used the Fine - Gray subdistribution hazard model to correct for the competing risk of death and calculated the subdistribution hazard ratios (SHRs) and 95% CIs. Considering the reverse effect of undiagnosed potential severe conditions on pulmonary function at baseline, we excluded individuals who developed CKD within the first 2 years of follow-up and then reran the fully adjusted variable model.

To explore the potential mediating role of plasma proteins in the association between PRISm and incident chronic kidney disease, we conducted a mediation analysis on 2,911 measured plasma proteins. A generalized linear model was used to evaluate the effect of PRISm (independent variable) on the levels of each protein (mediator variable). A parametric survival regression model with a Weibull distribution was employed to assess the combined effects of PRISm and protein levels on CKD (dependent variable). All the above models were adjusted for full confounding variables (including age, gender, education level, smoking, drinking, ethnicity, BMI, TDI, hypertension, diabetes, CVD and eGFR). The significance of the proportion mediated and the average causal mediation effect (ACME) was estimated using a bootstrap method based on 1000 resamples. Proteins were advanced for further analysis if the mediation proportion was > 0 and the false discovery rate (FDR) was < 0.05. Additionally, we performed KEGG and GO enrichment analyses on the obtained proteins to elucidate the relevant pathways and biological processes. The species was set as Homo sapiens in the KEGG database for analyzing related genes. The GO analysis covered biological processes (BP), cellular components (CC), and molecular functions (MF).

We built a LASSO-penalized Cox proportional hazards model using the glmnet package in R. The candidate protein expression matrix identified in the initial screening was entered into the penalized model for 10-fold cross-validation to determine the optimal tuning parameters. We used the non-zero regression coefficients output by the LASSO-Cox model as weights to perform a linear weighted sum of the screened core proteins to obtain the protein risk score:

$$Protein\ Score = \sum_{i=1}^{n} (\beta_i \times X_i)$$

n represents the total number of representative core proteins with non-zero coefficients selected by LASSO regression; β_i is the partial regression coefficient assigned to the core protein by the LASSO-Cox model; X_i is the relative expression level of the core protein in participants' baseline blood samples. After standardizing this score, we applied the CMAverse package with the bootstrap method (1,000 resamples) to perform a mediation analysis under the full confounder model for the protein score in order to assess the mediating role of the composite protein system between PRISm and CKD.

Declarations

Acknowledgments The data used in this study were obtained from the UK Biobank(Application Number: 532564). The UK Biobank data were accessedand analyzed in accordance with the terms of the UK Biobank's Accessand Use Agreement.

Author contributions XH ,WY and HY participated in study design and drafting the manuscript. HX and WL contributed to the collection and analysis of data. YW ,WL ,LZ and WY contributed to the discussion and revision of the manuscript. All authors read and approved the submitted version

Ethics Approval Statement The UK Biobank study obtained ethical approval from the North West Multi-Centre Research Ethics Committee (REC reference: 21/NW/0157)

Funding National Natural Science Foundation of China (No. 82400848) and the Medical Interdisciplinary Innovation Fund of Nanchang University (No. NCUJCCX-2024-03)

Data availability Data used in this project are available from the UK Biobank by submitting a data request proposal (www.ukbiobank.ac.uk)

Code availability The custom R code used for statistical analysis in this study is available from the corresponding author upon reasonable request.

Competing interests The authors declare that they have no conflict of interest

References

1. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl. 2022.
2. Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management: A Review. JAMA. 2019;322(13):1294–1304.
3. Chesnaye NC, Ortiz A, Zoccali C, Stel VS, Jager KJ. The impact of population ageing on the burden of chronic kidney disease. Nat Rev Nephrol. 2024;20(9):569–585.
4. Rao N, Brotons-Munto F, Moura AF, et al. Holistic Impact of CKD: A Clinical, Economic, and Environmental Analysis by IMPACT CKD. Kidney Int Rep. 2025.
5. Li D, Ruan Z, Xie S, Xuan S, Zhao H, Wu B. The relationship between preserved ratio impaired spirometry and mortality in the myocardial infarction survivors: a population-based cohort study. BMC Cardiovasc Disord. 2023;23(1).
6. Phillips DB, James MD, Vincent SG, et al. Physiological Characterization of Preserved Ratio Impaired Spirometry in the CanCOLD Study: Implications for Exertional Dyspnea and Exercise Intolerance. Am J Respir Crit Care Med. 2024;209(11):1314–1327.
7. Wang H, Yang R, Liu D, Li W. Prevalence, Risk Factors, Lung Function, and Associated Comorbidities of Adult Preserved Ratio Impaired Spirometry: A Meta-Analysis. MedComm. 2025;6(6):e70235.
8. Wijnant SRA, de Roos E, Kavousi M, et al. Trajectory and mortality of preserved ratio impaired spirometry: the Rotterdam Study. Eur Respir J. 2020;55(1).
9. Huang J, Li W, Tao H. Preserved Ratio Impaired Spirometry (PRISm): A Global Epidemiological Overview, Radiographic Characteristics, Comorbid Associations, and Differentiation from Chronic Obstructive Pulmonary Disease. Int J Chron Obstruct Pulmon Dis. 2024.
10. The Prognostic Performance of Lung Diffusing Capacity in Preserved Ratio Impaired Spirometry: An Observational Cohort Study. Int J Chron Obstruct Pulmon Dis. 2022.
11. He D, Yan M, Zhou Y, et al. Preserved Ratio Impaired Spirometry and COPD Accelerate Frailty Progression: Evidence From a Prospective Cohort Study. Chest. 2024.
12. Cui M, Cheng C, Zhang L. High-throughput proteomics: a methodological mini-review. Lab Invest. 2022.
13. Petrera A, Toerne VC, Hauck SM. Multiplatform Approach for Plasma Proteomics: Complementarity of Olink Proximity Extension Assay Technology to Mass Spectrometry-Based Protein Profiling. J Proteome Res. 2021.
14. Petricoin EF, Paweletz CP, Liotta LA. Clinical Applications of Proteomics: Proteomic Pattern Diagnostics. J Mammary Gland Biol Neoplasia. 2002;7(4):433–440.
15. Beydoun MA, Beydoun HA, Hooten NN, et al. Plasma proteomic biomarkers as mediators or moderators for the association between poor cardiovascular health and white matter microstructural integrity: The UK Biobank study. Alzheimers Dement. 2025;21(2):e14507.

16. Lin Z, Wang C, Lin Z, Lin K, Guo Y. Proteomics mediates the effects of biological aging on the progression of cardio-renal-metabolic comorbidity: a UK biobank cohort study. Cardiovasc Diabetol. 2025;25(1):8..
17. Husain-Syed F, Slutsky AS, Ronco C. Lung-Kidney Cross-Talk in the Critically Ill Patient. Am J Respir Crit Care Med. 2016;194(4):402–414.
18. Campanholle G, Landgraf RG, Goncalves GM, et al. Lung inflammation is induced by renal ischemia and reperfusion injury as part of the systemic inflammatory syndrome. Inflamm Res. 2010;59(10):861–869.
19. Ravarotto V, Bertoldi G, Innico G, Gobbi L, Calo LA. The Pivotal Role of Oxidative Stress in the Pathophysiology of Cardiovascular-Renal Remodeling in Kidney Disease. Antioxidants. 2021;10(7).
20. Conroy MC, Lacey B, Besevic J, et al. UK Biobank: a globally important resource for cancer research. Br J Cancer. 2022;128(4):519–527.
21. Ding Q, Mi BB, Wei X, et al. Small Airway Dysfunction in Chronic Bronchitis with Preserved Pulmonary Function. Can Respir J. 2022.
22. Ramalho SHR, Shah AM. Lung function and cardiovascular disease: A link. Trends Cardiovasc Med. 2021.
23. Win K, Tsai MK, Gao W. Impaired lung function and lung cancer risk in 461 183 healthy individuals: a cohort study. BMJ Open Respir Res. 2024.
24. Hussain J, Grubic N, Akbari A, et al. Associations between modest reductions in kidney function and adverse outcomes in young adults: retrospective, population based cohort study. BMJ. 2023;381:e075062.
25. Sumida K, Kwak L, Grams ME, et al. Lung Function and Incident Kidney Disease: The Atherosclerosis Risk in Communities (ARIC) Study. Am J Kidney Dis. 2017.
26. Navaneethan SD, Mandayam S, Arrigain S, et al. Obstructive and Restrictive Lung Function Measures and CKD: National Health and Nutrition Examination Survey (NHANES) 2007–2012. Am J Kidney Dis. 2016.
27. Morris A. Advances in GDF15 research. Nat Rev Endocrinol. 2020;16(3):129.
28. Sigvardsen CM, Richter MM, Engelbeen S, Kleinert M, Richter EA. GDF15 is still a mystery hormone. Trends Endocrinol Metab. 2025.
29. Laskin D, Sunil V, Laumbach R, Kipen H. Inflammatory Cytokines and Lung Toxicity. Brain Sci. 2007.
30. Hoyer FF, Naxerova K, Nahrendorf M. Tissue-Specific Macrophage Responses to Remote Injury Impact the Outcome of Subsequent Local Immune Challenge. Immunity. 2019.
31. Starling S. GDF15 signals nutritional stress. Nat Rev Endocrinol. 2019;15(3):130.
32. Jena J, Garcia-Pena LM, Pereira RO. The roles of FGF21 and GDF15 in mediating the mitochondrial integrated stress response. Front Endocrinol. 2023;14.
33. Liu J, Kumar S, Heinzel A, et al. Renoprotective and Immunomodulatory Effects of GDF15 following AKI Invoked by Ischemia-Reperfusion Injury. J Am Soc Nephrol. 2020;31(4):701–715.
34. Bedenbender K, Schmeck BT. Endothelial Ribonuclease 1 in Cardiovascular and Systemic Inflammation. Front Cell Dev Biol. 2020;8.
35. Bedenbender K, Scheller N, Vollmeister E. Inflammation-mediated deacetylation of the ribonuclease 1 promoter via histone deacetylase 2 in endothelial cells. FASEB J. 2019.
36. Visovatti S, Ohtsuka T, Pinsky D. Interactions of Leukocytes and Coagulation Factors with the Vessel Wall. Circulation. 2011.
37. Wang B, Yan B, Liu SF. Chronic intermittent hypoxia down-regulates endothelial nitric oxide synthase expression by an NF-κB-dependent mechanism. Sleep Med. 2013.
38. LeBleu VS, Teng Y, O'Connell JT, et al. Identification of human epididymis protein-4 as a fibroblast-derived mediator of fibrosis. Nat Med. 2013;19(2):227–231.
39. Zhang L, Liu L, Bai M, et al. Hypoxia-induced HE4 in tubular epithelial cells promotes extracellular matrix accumulation and renal fibrosis via NF-κB. FASEB J. 2020;34(7):9504–9517.
40. Li L, Fu H, Liu Y. The fibrogenic niche in kidney fibrosis: components and mechanisms. Nat Rev Nephrol. 2022;18(9):545–557.

Figures

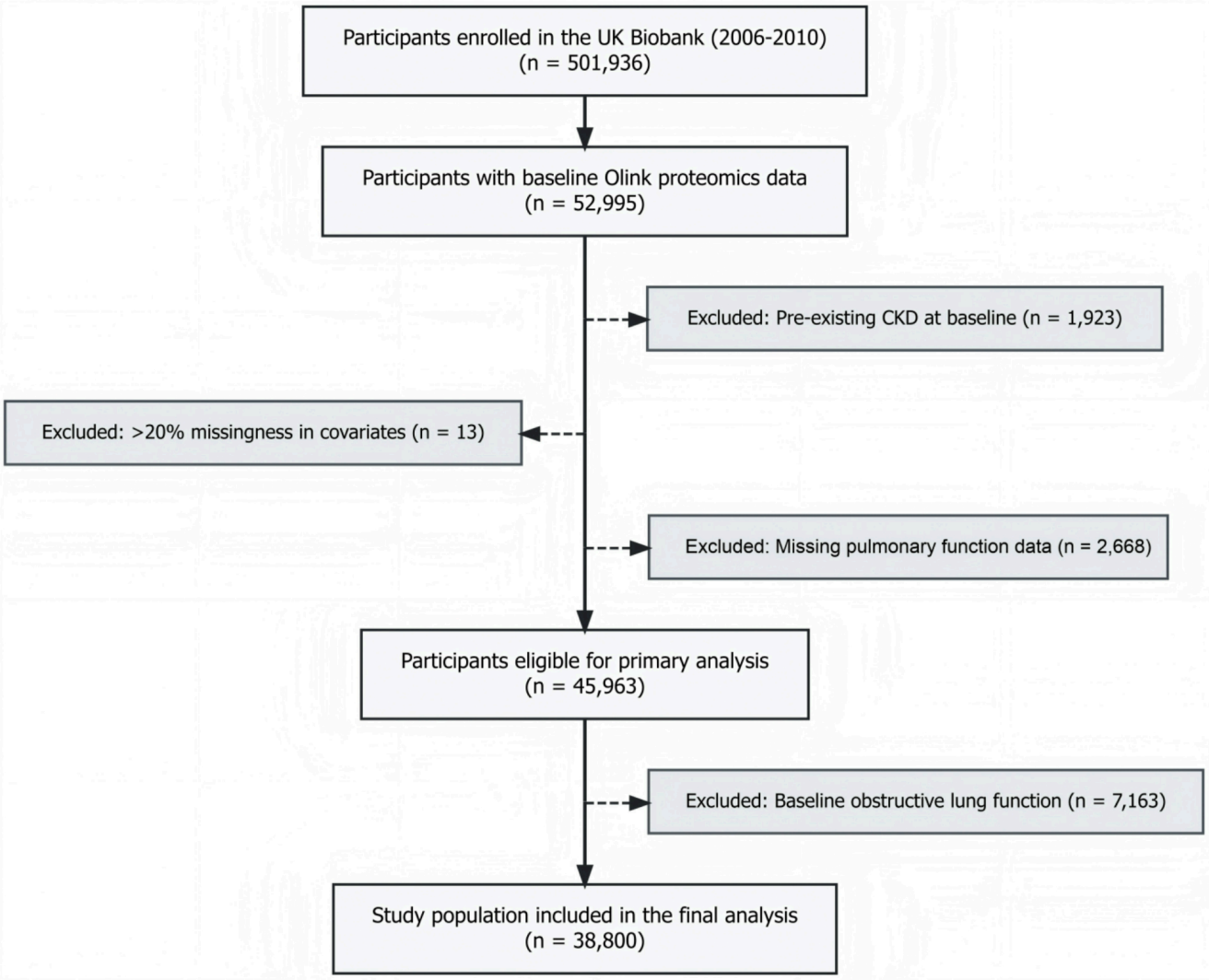


Figure 1

Flowchart of the selection of study participants from the UK Biobank.

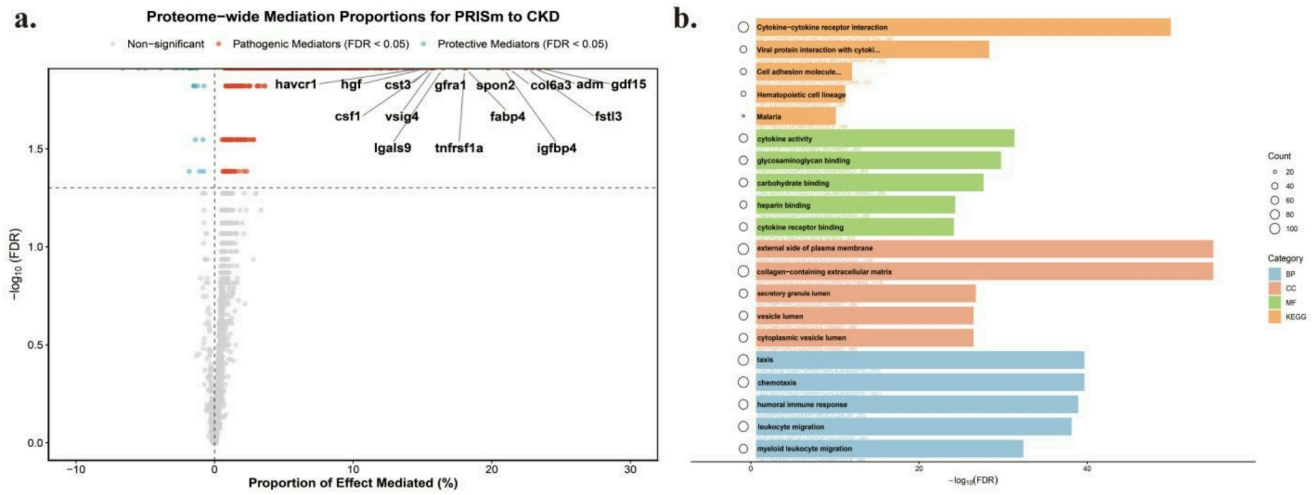


Figure 2

Proteome-wide Mediation Analysis and Pathway Enrichment from PRISm to CKD.**(a)** Scatter plot of mediation proportions: Depicts the proportion of effect mediated by proteins in the progression from PRISm to CKD (x-axis) against their statistical significance (y-axis, $-\log_{10}$(FDR)). The horizontal dashed line represents the significance threshold. Grey dots indicate non-significant proteins; red dots represent significant pathogenic mediators (FDR < 0.05); blue dots denote significant protective mediators (FDR < 0.05). **(b)** Pathway enrichment analysis of significant mediators: Displays the enriched pathways across GO and KEGG databases. Colors distinguish functional categories: Biological Process (BP), Cellular Component (CC), Molecular Function (MF), and KEGG pathways. The x-axis indicates the significance level $-\log_{10}$(FDR), and the bubble size (Count) on the right reflects the number of proteins involved in each pathway.

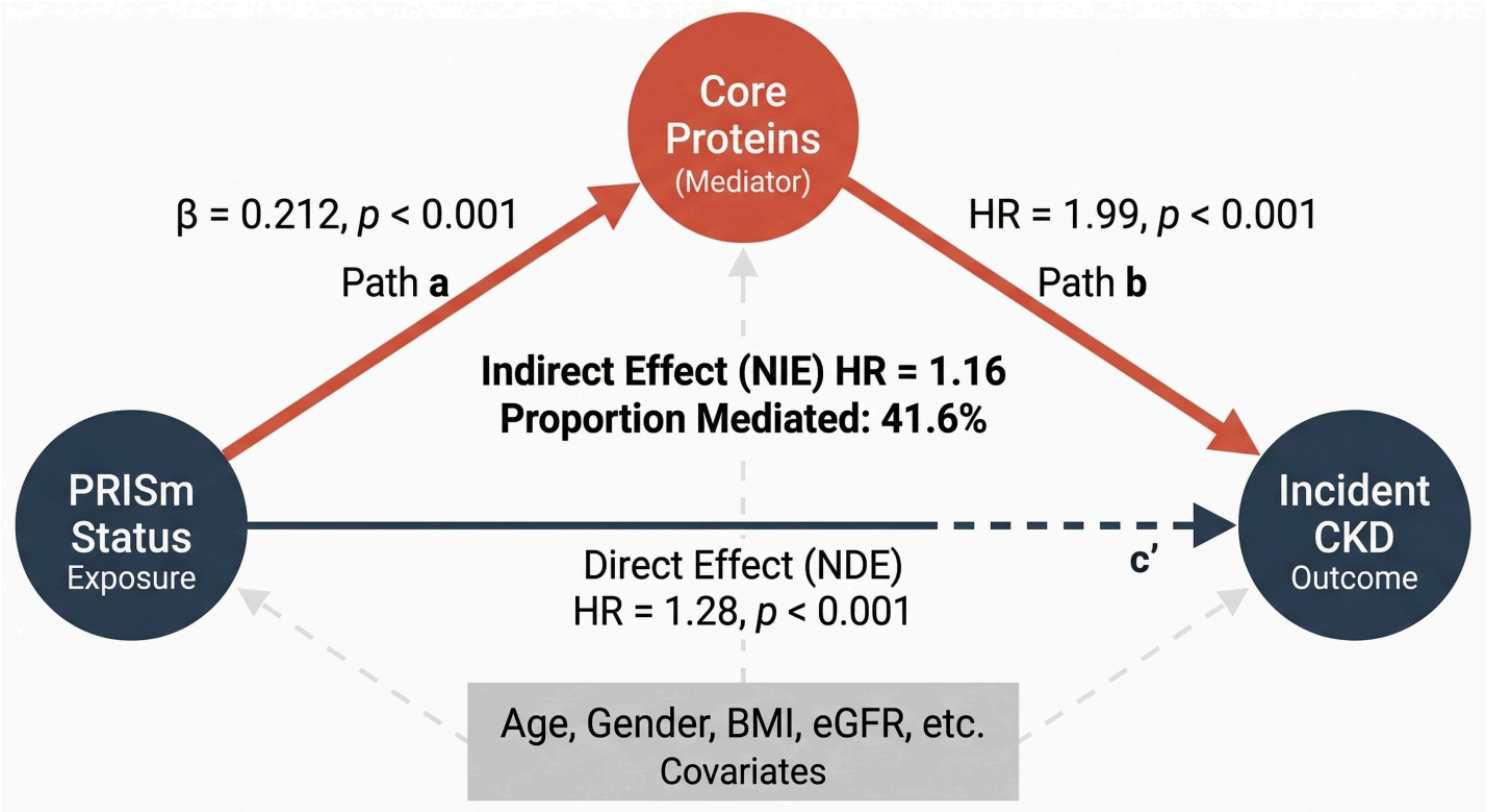


Figure 3

Mediation analysis of core proteins in the association between PRISm and incident CKD.Path a represents the estimated effect of PRISm status on core proteins (β= 0.212, p < 0.001), and Path b represents the effect of core proteins on the risk of incident CKD (HR = 1.99, p < 0.001). The natural direct effect (NDE) of PRISm on incident CKD is significant (HR = 1.28, p < 0.001), while the natural indirect effect (NIE) mediated through core proteins shows an HR of 1.16. The proportion of the total effect mediated by these core proteins is 41.6%. The models were adjusted for age, gender, TDI, education, smoking, drinking, ethnicity, hypertension, diabetes, CVD, BMI, eGFR.

Abbreviations: PRISm, Preserved Ratio Impaired Spirometry; CKD, Chronic Kidney Disease; HR, Hazard Ratio; NIE, Natural Indirect Effect; NDE, Natural Direct Effect; BMI, Body Mass Index; eGFR, estimated Glomerular Filtration Rate; TDI:Townsend deprivation index; CVD: Cardiovascular disease.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FigureS1.pdf
- FigureS2.jpg
- FigureS3.pdf
- TableS1.xlsx
- TableS2.xlsx
- TableS3.xlsx
- TableS4.xlsx
- TableS5.xlsx