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Association between kidney function and Parkinson's disease risk: a prospective study from the UK Biobank

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Abstract

Background Parkinson's disease (PD) is a neurodegenerative influenced by various clinical factors. The potential relationship between renal function and the risk of PD remains poorly understood. This study aims to explore the association between kidney function and the risk of developing PD.

Methods A population-based cohort study was conducted using data from 400,571 UK Biobank participants. Renal function was assessed using the estimated glomerular filtration rate (eGFR), calculated from serum creatinine and cystatin C levels. The association between eGFR levels and PD risk was evaluated using univariate and multivariate Cox regression analyses, Restricted Cubic Spline (RCS) analysis, and Kaplan-Meier analysis. Additionally, a clinical prediction model was developed and its diagnostic accuracy was evaluated using ROC analysis. A heatmap was also constructed to examine the relationship between clinical factors and gray matter volume in various brain regions.

Results Over a median observation period of 13.8 years, 2740 PD events were recorded. Cox regression and Kaplan-Meier analyses revealed a significant association between decreased eGFR and increased PD risk, particularly in participants with eGFR < 30 ml/min/1.73 m^2. This association was confirmed across three adjusted models. RCS analysis demonstrated a nonlinear relationship between decreasing eGFR and increasing PD risk. Furthermore, changes in eGFR were correlated with alterations in subcortical gray matter volume in regions such as the frontal cortex, striatum, and cerebellum. The clinical prediction model showed high diagnostic accuracy with AUC values of 0.776, 0.780, and 0.824 for 4-, 8-, and 16-year predictions, respectively.

Conclusion Renal insufficiency is significantly associated with an increased risk of PD, highlighting the importance of maintaining good kidney function as a potential preventive measure against PD.

Keywords Parkinson's disease, Kidney function, Estimated glomerular filtration rate, Chronic kidney disease, UK Biobank

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease, with its incidence increasing with age, affecting 1-2% individuals aged 60 years and above [1]. The progressive nature and incurability of PD present significant challenges for patients, families, and society [2]. PD is characterized by the degeneration of dopaminergic neurons in the substantia nigra and striatum, leading to hallmark clinical manifestations such as bradykinesia, resting tremor, rigidity, and postural instability [3, 4]. Despite extensive research, the precise etiology of PD remains elusive, with the disease believed to result from a complex interplay of genetic, environmental, and lifestyle factor [5]. Therefore, active PD screening and a more comprehensive understanding of its etiology, disease-related risks, and protective factors are of great significance for the diagnosis and prevention of PD.

Recent studies have highlighted the potential role of chronic diseases, including renal dysfunction, in the development of PD [6]. A study based on the National Health Interview Survey (NHIS) database indicated that chronic kidney disease (CKD) might be an independent risk factor for PD in individuals aged 65 and older [7]. Clinical observations have noted that patients with uremia exhibit motor symptoms similar to those seen in PD, such as bradykinesia, resting tremor, rigidity, and postural instability [8]. Additionally, research by Deckers et al. [9]. has shown that PD patients with renal insufficiency experience more severe cognitive impairment, psychological disorders, orthostatic hypotension, fatigue, and hallucinations, suggesting that renal damage may exacerbate the non-motor symptoms of PD.

Despite these findings, the relationship between renal dysfunction and PD remains inadequately explored, particularly in longitudinal studies. Most existing studies are cross-sectional, limiting the ability to infer causality. There is a critical need for prospective studies to better understand this potential relationship and its implications for PD prevention and management.

In this study, we utilized data from a large-scale, prospective cohort of 400,571 participants from the UK Biobank (UKB) to investigate the longitudinal association between chronic renal insufficiency and the risk of PD. To assess renal function, we used estimated glomerular filtration rate (eGFR) values derived from serum creatinine and cystatin C levels. By employing advanced statistical methods, including Cox regression analyses, Restricted Cubic Spline (RCS) analysis, and Kaplan-Meier analysis, we aimed to provide robust clinical evidence on the potential link between renal function and PD risk. Furthermore, we explored the association between renal function and brain gray matter volumes to gain insights into the neurological impact of renal insufficiency. This study seeks to emphasize the importance of renal health management in reducing the risk of PD and to offer new directions for future clinical intervention strategies.

Materials and methods

Study population

Participants were sourced from the UK Biobank (https://www.ukbiobank.ac.uk), a prospective cohort study that included approximately 501,314 participants aged 39–72 years, whose baseline data was collected between 2006 and 2010 [10]. Participants provided detailed personal, lifestyle, sociodemographic, and health information, underwent comprehensive physical evaluations, and provided blood, urine, and saliva samples for analysis. Ethical approval was obtained from the Northwest Multi-Center Research Ethics Committee, and all participants provided written informed consent. This study was conducted under UK Biobank application number 104,811.

Participant selection

Initially, 501,434 participants were considered for this study. Individuals with incomplete baseline data were first excluded (n=99,151), as well as those with a recorded history of renal replacement interventions, including kidney transplantation, hemodialysis, or peritoneal dialysis (n=415), and cases of participants who lost during the study period (n=1,297). And ensure that there are no PD patients at baseline. Finally, a total of 400,571 participants were included in the final analysis.

Kidney function exposures

The eGFR was computed utilizing the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, incorporating serum creatinine (Scr) and serum cystatin C (Scys). The CKD-EPI creatinine-cystatin C equation, expressed as a single equation [11], is:

$$\begin{aligned} &135 \times \ min\left(Scr/\kappa\ ,\ 1\right)\alpha\ \times\ max\left(Scr/\kappa\ ,\ 1\right) - 0.601 \\ &\times\ min(Scys/0.8,\ 1) - 0.375 \times\ max(Scys/0.8,\ 1) - 0.711 \\ &\times\ 0.995Age\left[\times\ 0.969\ if\ female\right]\left[\times\ 1.08\ if\ black\right] \end{aligned}$$

(Where Scr is serum creatinine, Scys is serum cystatin C, κ is 0.7 for women and 0.9 for men, α is -0.248 for women and −0.207 for men, min indicates the minimum of Scr/κ or 1, and max means the maximum of Scr/κ or 1).

The calculation yielded eGFR values, which were then categorized into five distinct groups: ≥105 (reference group), 90–104, 60–89, 30–59, and <30 ml/min/1.73 m² in this study [12, 13]. This stratification enabled a comprehensive assessment of renal function across varying degrees of impairment, facilitating the exploration of its association with PD risk.

Covariates

The study incorporated a comprehensive array of covariates, including age, gender, educational attainment, ethnic background, body mass index (BMI), polygenic risk score (PRS), smoking status, alcohol intake, Townsend deprivation index (TDI), hypertension, and diabetes.

Age was computed by juxtaposing the birth date with the date of the baseline assessment. Gender (Male/Female) is chosen by the subjects. Ethnic categorizations were streamlined into "White" and "Non-White" with the latter encompassing groups such as Asian or Asian British, Black or Black British, Chinese, Mixed Race, and other specified ethnicities. Educational qualifications were classified as "College" and "Non-College". BMI, expressed in kg/m^2, was calculated as the quotient of weight (in kilograms) and square of height (in meters). The Townsend Deprivation Index serves as a reflection indicator of socioeconomic standing [14]. PRS represents an individual's susceptibility to disease (here: PD), which has been calculated previously in UKB from genome-wide genotyping data and categorized into "High Risk", "Medium Risk" and "Low Risk" [15]. Smoking practices were divided into never-smokers, previous smokers, and current smokers. Alcohol intake was derived from touchscreen on digital interfaces that solicited information on the volume of each alcohol variety consumed weekly and automatically converts scores in the system. Further covariate considerations included incidence metrics such as hypertension and diabetes, which were captured via standardized touchscreen questionnaires and rendered as binary choices (yes or no). The urinary creatinine and urinary phosphate levels as covariates for evaluation in laboratory indicators.

Model adjustment

A multifactorial Cox regression model was used to determine the relationship between eGFR and PD, with three adjustment models. Model 1 adjusted for age, gender, ethnicity, and education. Subsequently, Model 2 further adjusted for BMI, PRS, smoking status, and alcohol intake. Finally, all variables were included in Model 3, including age, gender, ethnicity, educational attainment, BMI, PRS, smoking status, alcohol intake, hypertension and diabetes.

Neuroimaging

Cranial imaging data were obtained using a standard Siemens 3T MRI scanner. The scanned image has undergone preliminary processing and analysis, detailed information about the MRI processing can be found in the UK Biobank Protocol (https://biobank.ndph.ox.ac.uk/showcase/field.cgi). Gray matter volumes (T1-weighted MRI) from 24 brain regions were analyzed separately for the left and right hemispheres. Linear regression analysis was performed to assess the association between eGFR values and brain volume changes, with a correlation heatmap generated using the "ComplexHeatmap" package in R software.

Statistical analysis

Missing data rows were eliminated using R software (version 4.3.0). Continuous variables in the baseline characteristics are presented as mean ± standard deviation, and categorical variables were expressed as percentages. Comparisons across eGFR categories were performed using one-way ANOVA (perform Bonferroni correction) for continuous variables and the chi-square test for categorical variables.

Cox regression analyses were used to explore the association between various predictors and the PD incidence, with results presented as hazard ratios (HR) and 95% confidence intervals (95% CI). The Kaplan-Meier method depicted cumulative PD incidence, with log-rank tests assessing differences across eGFR categories. Restricted Cubic Spline (RCS) models analyzed the nonlinear relationship between eGFR and PD risk using the "rms" package in R. A nomogram model was created to predict survival rates (the 5-, 10-, and 15-year) using "nomogramEx" package in R, with ROC analysis evaluating model accuracy using "pROC" package in R. And area Under Curve (AUC) is used to measure the performance of the ROC model. All statistical analyses were performed using R (version 4.3.0), and $P<.05$ was considered statistically significant.

Results

Sample characteristics

Among the 501,434 participants between 2006 and 2010, 99,151 with missing data, 415 with a history of renal intervention treatment, and 1,297 with losing follow-up data were excluded, resulting in a final sample of 400,571 participants. Figure 1 shows the selection of participants and the analysis process of this study. Table 1 presents the baseline characteristics of 400,571 patients stratified by eGFRcr-cys levels. In this large cohort study within the age range of 39 to 72 years old, over a median observation period of 13.8 years, 2,740 incidents of PD were documented. Participants with lower eGFR (30–59 and <30 ml/min/1.73 m^2) were generally older, predominantly female, had lower educational attainment, higher BMI, and a higher prevalence of PD, diabetes, and hypertension. Adjustment in the p-value was done for multiple comparisons (Supplementary Table 1). Furthermore, significant variations were observed in ethnicity, smoking status, alcohol intake, TDI, hypertension, diabetes, urine creatinine, Scys, Scr, phosphate levels, and observation time across different eGFR categories.

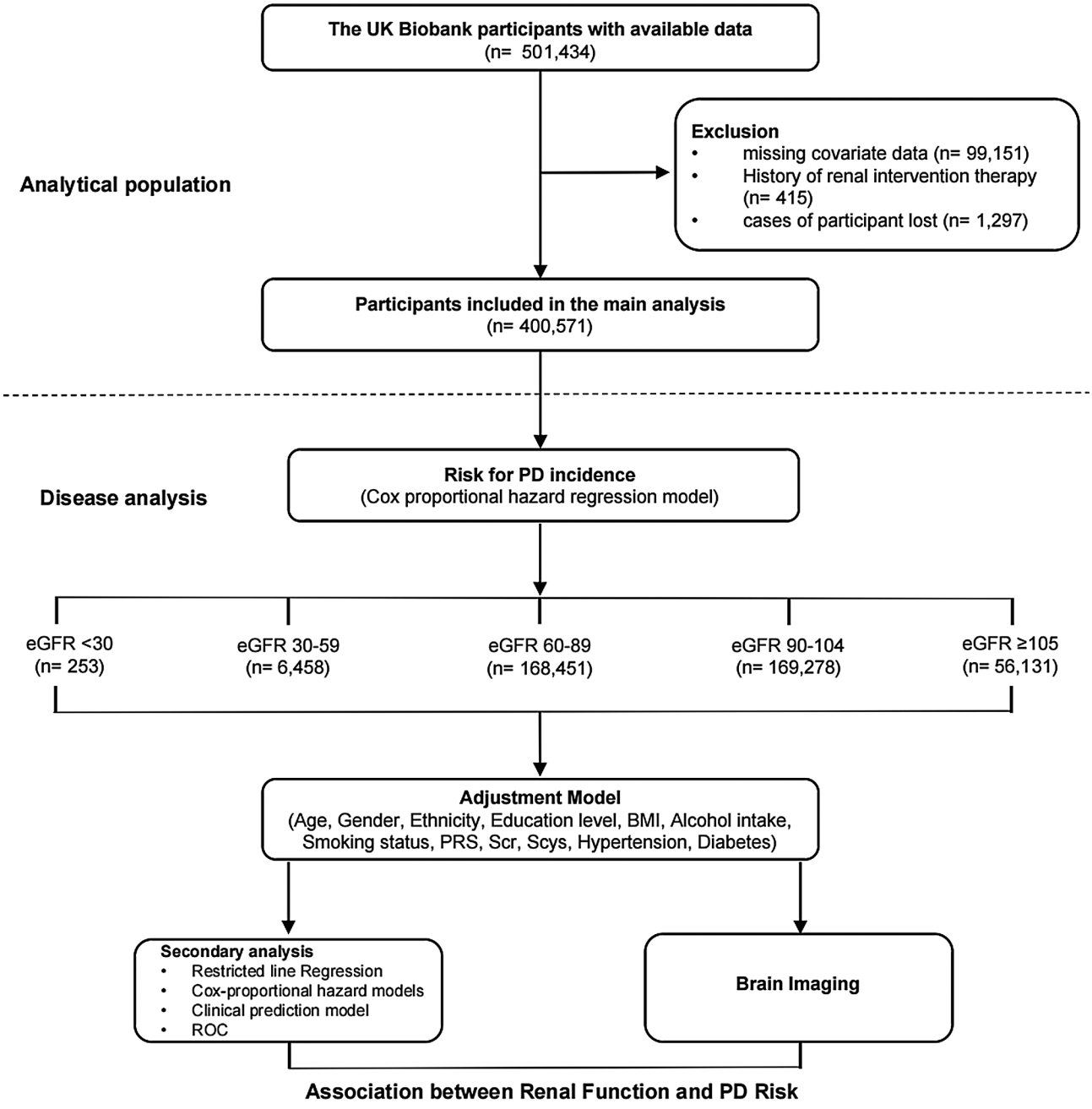

Fig. 1 Flowchart. Flowchart depicting the study design and participant selection process

Cox proportional hazard model analysis

Univariate cox analysis (non-adjusted analyses) identified hypertension (HR=1.34, 95% CI: 1.32–1.37, $P<.0001$) and diabetes (HR=1.40, 95% CI: 1.36–1.44, $P<.0001$) as independent risk factors for PD (Fig. 2). Stratified analysis indicated that female gender (HR=2.03, 95% CI: 1.88–2.19, $P<.0001$), non-white ethnicity (HR=1.48, 95% CI: 1.20–1.82, $P<.0001$), lower education (HR=1.24, 95% CI: 1.14–1.35, $P<.0001$), higher BMI and previous smoking status were positively associated with PD risk. Additionally, lower eGFR showed a significant association with PD risk (Fig. 2).

Table 2 presents the results of Cox proportional-hazards models investigating the association between eGFRcr-cys and PD. In the crude model, eGFR categories were associated with varying HRs for PD incidence. Compared to the reference group (eGFR≥105), the HRs (95% CI) for PD in the eGFR 90–104, 60–89, 30–59, and <30 categories were 0.92 (0.64–1.92), 1.46 (0.72–1.79), 1.49 (1.12–2.01), and 1.59 (1.12–2.07), respectively. After adjusting for covariates in three models, the associations

Table 1 Baseline characteristics of 400,571 participants by eGFRcr-cys status

Baseline characteristics of 400,571 patients by eGFRcr-cys categories								
		eGFRcr-cys category (mL/min per 1.73 m^2)						
Variables	Levels	< 30 (*N* = 253)	30–59 (*N* = 6,458)	60–89 (*N* = 168,451)	90–104 (*N* = 169,278)	≥ 105 (*N* = 56,131)	Ovalall (*N* = 400,571)	*P*_Value
Age (year)	Mean ± SD	60.9 ± 7.1	63.3 ± 5.4	60.6 ± 6.4	54.9 ± 7.5	48.4 ± 6.3	57.4 ± 7.4	< 0.001
Gender	Female	167 (66%)	4,978 (77.1%)	95,282 (56.6%)	83,396 (49.3%)	31,547 (56.2%)		< 0.001
	Male	86 (34%)	1,480 (22.9%)	73,169 (43.4%)	85,882 (50.7%)	24,584 (43.8%)		
Education	College	42 (16.6%)	1,114 (17.2%)	46,447 (27.6%)	60,678 (35.8%)	23,089 (41.1%)		< 0.001
	Non-College	211 (83.4%)	5,344 (82.8%)	122,004 (72.4%)	108,600 (64.2%)	33,042 (58.9%)		
BMI (kg/m^2)	< 18.5	8 (3.2%)	27 (0.4%)	560 (0.3%)	905 (0.5%)	538 (1%)		< 0.001
	18.5–24.9	55 (21.7%)	1,027 (15.9%)	40,730 (24.2%)	59,453 (35.1%)	25,225 (44.9%)		
	25-29.9	84 (33.2%)	2,259 (35%)	74,803 (44.4%)	73,777 (43.6%)	21,802 (38.8%)		
	≥ 30	106 (41.9%)	3,145 (48.7%)	52,358 (31.1%)	35,143 (20.8%)	8,566 (15.3%)		
Ethnicity	Non-white	25 (9.9%)	315 (4.9%)	6,981 (4.1%)	8,282 (4.9%)	4,359 (7.8%)		< 0.001
	White	228 (90.1%)	6,143 (95.1%)	161,470 (95.9%)	160,996 (95.1%)	51,772 (92.2%)		
Smoking.status	Current	24 (9.5%)	728 (11.3%)	18,201 (10.8%)	17,182 (10.2%)	5,851 (10.4%)		< 0.001
	Never	123 (48.6%)	3,166 (49%)	87,486 (51.9%)	94,913 (56.1%)	33,347 (59.4%)		
	Previous	106 (41.9%)	2,564 (39.7%)	62,764 (37.3%)	57,183 (33.8%)	16,933 (30.2%)		
Alcohol.intake	0	110 (43.5%)	2,582 (40%)	37,766 (22.4%)	26,723 (15.8%)	9,058 (16.1%)		< 0.001
	1	34 (13.4%)	838 (13%)	19,648 (11.7%)	17,781 (10.5%)	6,197 (11%)		
	2	60 (23.7%)	1,446 (22.4%)	42,732 (25.4%)	44,247 (26.1%)	15,215 (27.1%)		
	3	29 (11.5%)	833 (12.9%)	35,443 (21%)	42,868 (25.3%)	14,428 (25.7%)		
	4	20 (7.9%)	759 (11.8%)	32,862 (19.5%)	37,659 (22.2%)	11,233 (20%)		
Townsend. deprivation. index	Mean ± SD	-0.4 ± 3.2	-0.7 ± 3.3	-1.4 ± 3.1	-1.4 ± 3.0	-1.1 ± 3.1	-1.4 ± 2.9	< 0.001
PRS	High Risk	49 (19.4%)	1,589 (24.6%)	41,857 (24.8%)	42,428 (25.1%)	14,126 (25.2%)		0.078
	Low Risk	68 (26.9%)	1,667 (25.8%)	42,502 (25.2%)	42,127 (24.9%)	13,935 (24.8%)		
	Medium Risk	136 (53.8%)	3,202 (49.6%)	84,092 (49.9%)	84,723 (50%)	28,070 (50%)		
Hypertension	un_Hypertension	234 (92.5%)	4,567 (70.7%)	68,560 (40.7%)	43,331 (25.6%)	9,035 (16.1%)		< 0.001
	Hypertension	19 (7.5%)	1,891 (29.3%)	99,891 (59.3%)	125,947 (74.4%)	47,096 (83.9%)		
Diabetes	un_Diabetes	92 (36.4%)	1,646 (25.5%)	18,579 (11%)	11,688 (6.9%)	3,229 (5.8%)		< 0.001
	Diabetes	161 (63.6%)	4,812 (74.5%)	149,872 (89%)	157,590 (93.1%)	52,902 (94.2%)		
urine.creatinine (umol/L)	Mean ± SD	7,777.5 ± 5,304.1	9,778.8 ± 6,626.4	9,314.4 ± 5,971.4	8,762.3 ± 5,744.3	7,946.7 ± 5,387.1	9,072.7 ± 5,643.2	< 0.001
Scys (umol/L)	Mean ± SD	3.0 ± 1.0	1.4 ± 0.3	1.0 ± 0.1	0.8 ± 0.1	0.7 ± 0.1	0.9 ± 0.3	< 0.001
Scr (umol/L)	Mean ± SD	3.3 ± 2.1	1.2 ± 0.4	0.9 ± 0.2	0.8 ± 0.1	0.7 ± 0.1		< 0.001
Phosphate (umol/L)	Mean ± SD	1.3 ± 0.3	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.1 ± 0.2	1.2 ± 0.2	< 0.001
time (year)	Mean ± SD	10.5 ± 4.5	12.7 ± 3.5	13.7 ± 2.5	14.0 ± 1.9	14.2 ± 1.7	13.8 ± 2.1	< 0.001
PD	un_Parkinson's	250 (98.8%)	6,383 (98.8%)	166,894 (99.1%)	168,300 (99.4%)	56,004 (99.8%)		< 0.001
	Parkinson's	3 (1.2%)	75 (1.2%)	1,557 (0.9%)	978 (0.6%)	127 (0.2%)		

remained significant only for the < 30 ml/min/1.73 m^2 group (Model 1, HR = 1.79, 95% CI: 1.56–5.65, *P* = .031; Model 2, HR = 1.66, 95% CI: 1.52–5.24, *P* = .038; Model 3, HR = 1.90, 95% CI: 1.43–5.39, *P* = .031), indicating a positive association between decreased eGFR and PD risk.

Independent association between kidney function and PD

Using the Kaplan-Meier method, the cumulative disease probability of PD between the five eGFR groups was plotted, and differences were tested using the log-rank test (Fig. 3, *P* < .001). Throughout the 16-year follow-up period, the eGFR < 30 ml/min/1.73m^2 group exhibited the highest cumulative disease risk of PD. Furthermore, the result of RCS analysis demonstrated the nonlinear relationship between PD risk and eGFR value (Fig. 4). A smooth spline plot displayed an increase in the risk of incident PD as eGFR values decreased (Fig. 4A; Overall *P* < .0001, Nonlinear *P* < .0001), with consistent findings observed in all three adjusted models (Fig. 4B-D).

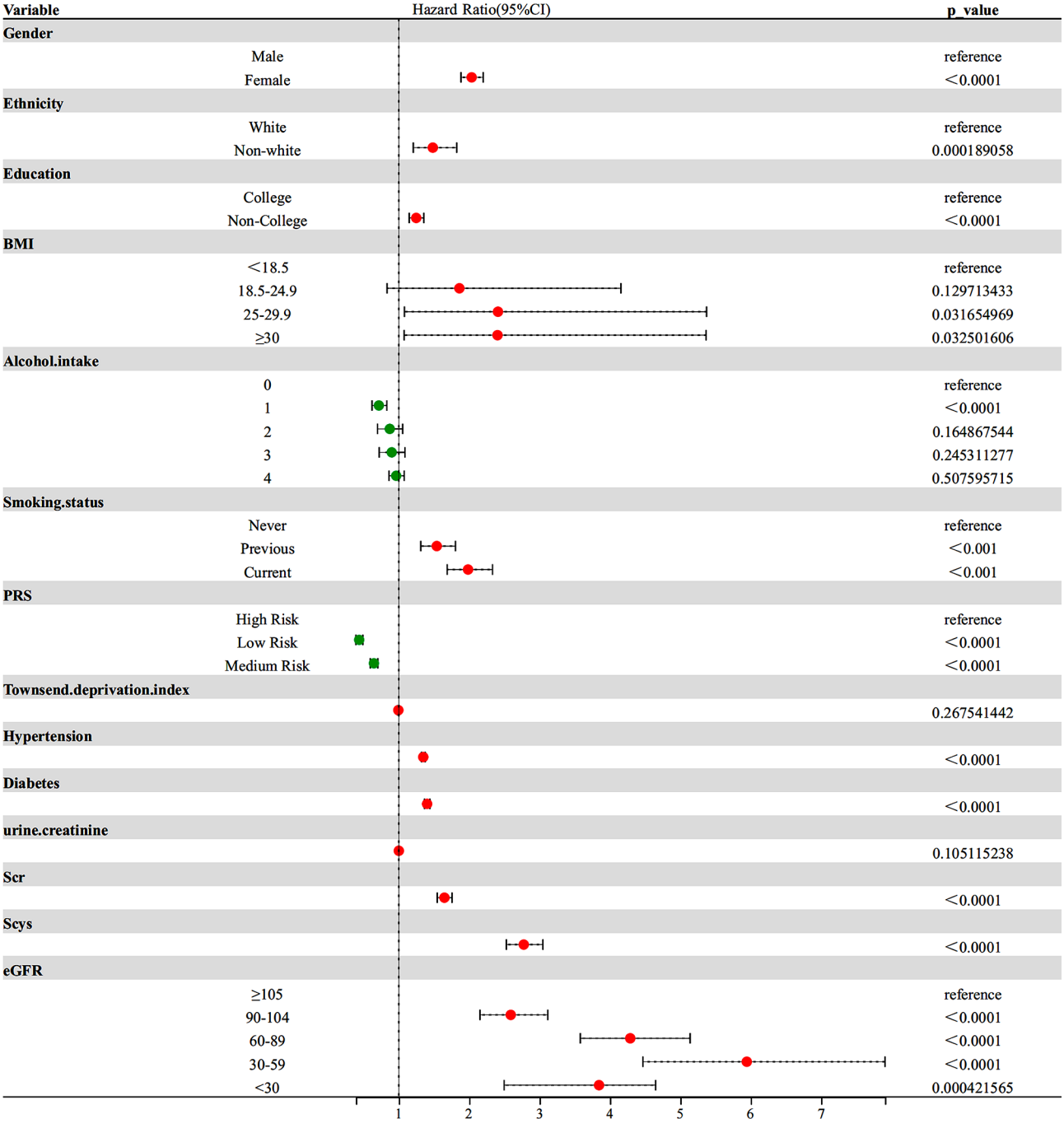

Fig. 2 Association between risk factors and PD Risk in Cox proportional hazard model. Graph illustrating the hazard ratios of various risk factors, including renal function, for Parkinson's disease in the Cox proportional hazard model

Establishment and validation of a nomogram

A nomogram model was constructed incorporating factors such as age, gender, ethnicity, education, BMI, PRS, Townsend deprivation index, smoking status, alcohol intake, hypertension, diabetes, and eGFR (Supplementary Fig. 1). The model predicted 4-, 8-, and 16-year survival rates with high accuracy, as indicated by AUC values of 0.776, 0.780, and 0.824, respectively (All AUC>0.7, Supplementary Fig. 2).

Associations between eGFR and brain volumes

To delve deeper into the connection between renal insufficiency and PD, we conducted a association analysis between cortical volumes in brain subregions and PD risk factors. The results revealed a potential association

Table 2 Cox regression analysis of renal function biomarkers and PD

eGFR	Crude Model		Model 1		Model 2		Model 3	
mL/min per 1.73 m^2	HR (95% CI)	*P*_Value	HR (95% CI)	*P*_Value	HR (95%CI)	*P*_Value	HR (95%CI)	*P*_Value
eGFR_class ≥ 105	reference		reference		reference		reference	
eGFR_class 90–104	0.92 (0.64–1.92)	0.328	0.99(0.82–1.20)	0.093	0.98 (0.82–1.20)	0.088	0.97 (0.80–1.18)	0.086
eGFR_class 60–89	1.46 (0.72–1.79)	0.261	0.93(0.76–1.13)	0.048	0.92 (0.71–1.15)	0.034	0.93 (0.82–1.31)	0.043
eGFR_class 30–59	1.49 (1.12–2.01)	0.032	2.18(1.87–2.59)	0.027	1.10 (0.81–1.48)	0.053	1.06 (1.01–1.60)	0.070
eGFR_class < 30	1.59 (1.12–2.07)	**0.033**	1.79(1.56–5.65)	**0.031**	1.66 (1.52–5.24)	**0.038**	1.90 (1.43–5.39)	**0.031**

Model 1, adjusted for age, gender, ethnicity, and educational attainment

Model 2, adjusted for age, gender, ethnicity, educational attainment, BMI, PRS, smoking status, and alcohol intake

Model 3, adjusted for age, gender, ethnicity, educational attainment, BMI, PRS, smoking status, alcohol intake, hypertension and diabetes

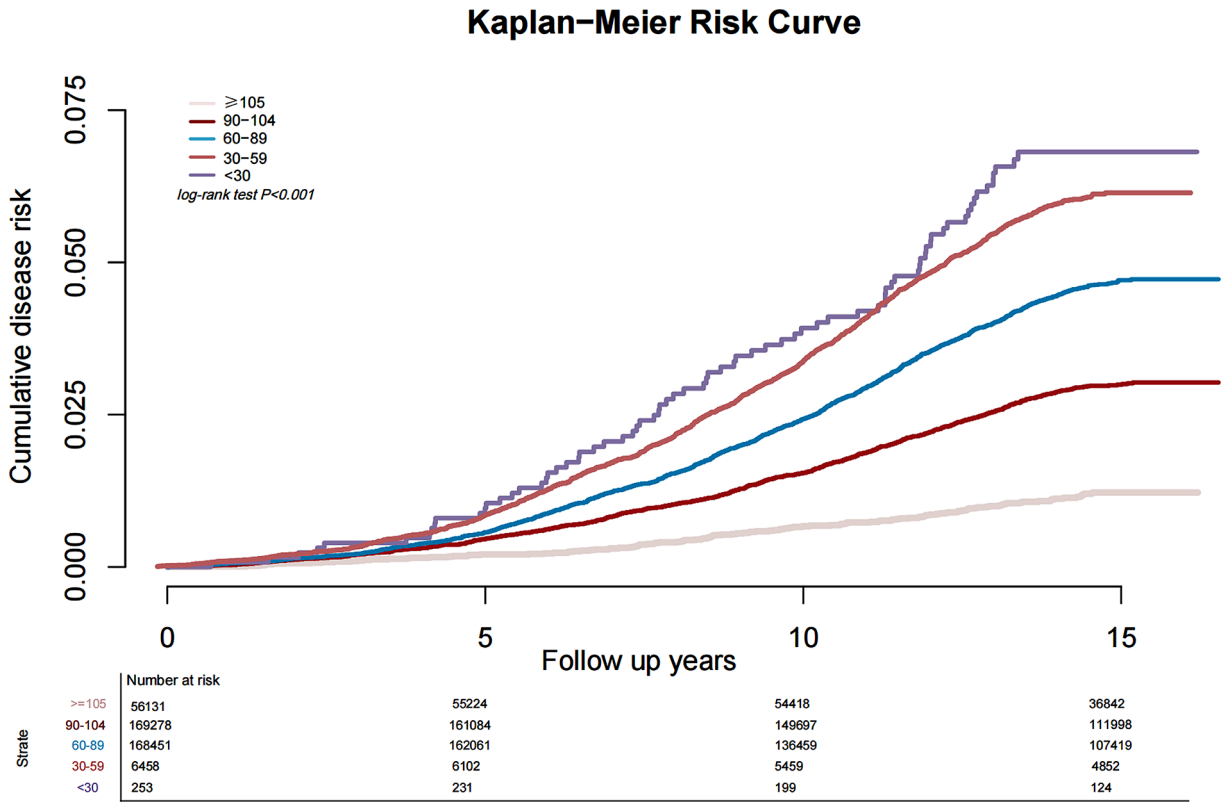

Fig. 3 Kaplan-Meier analysis of cumulative PD risk by eGFR levels. Kaplan Meier curves showing the cumulative incidence of Parkinson's disease over a 16-year follow-up period stratified by different eGFR levels

between eGFR and changes in gray matter volumes across multiple subcortical brain regions (Fig. 5). In the eGFR < 30 ml/min/1.73m^2 group, subcortical brain volumes, including Angular Gyrus (right hemisphere, $P<.01$), Frontal Operculum Cortex (left hemisphere, $P<.01$), Superior Frontal Gyrus (left hemisphere, $P<.05$), Supramarginal Gyrus anterior division (left hemisphere, $P<.05$), Temporal Fusiform Cortex posterior division(right hemisphere, $P<.05$), VIIIa Cerebellum (left hemisphere, $P<.001$), Ventral Striatum (left hemisphere, $P<.05$; right hemisphere, $P<.01$), and X Cerebellum vermis (right hemisphere, $P<.05$), may exhibit a potential positive correlation with eGFR levels. These findings provide compelling evidence supporting the association between renal function and PD from an alternative perspective, shedding light on the potential role of renal insufficiency in influencing brain structure and function, thus contributing to our understanding of PD pathogenesis.

Discussion

The findings of this prospective cohort study from the UK Biobank shed light on the intricate association between renal function and the risk of PD. Our results reveal a significant and independent association between decreased eGFR and elevated PD risk, even after comprehensive adjustment for various confounding factors. These findings align with prior research indicating a potential link

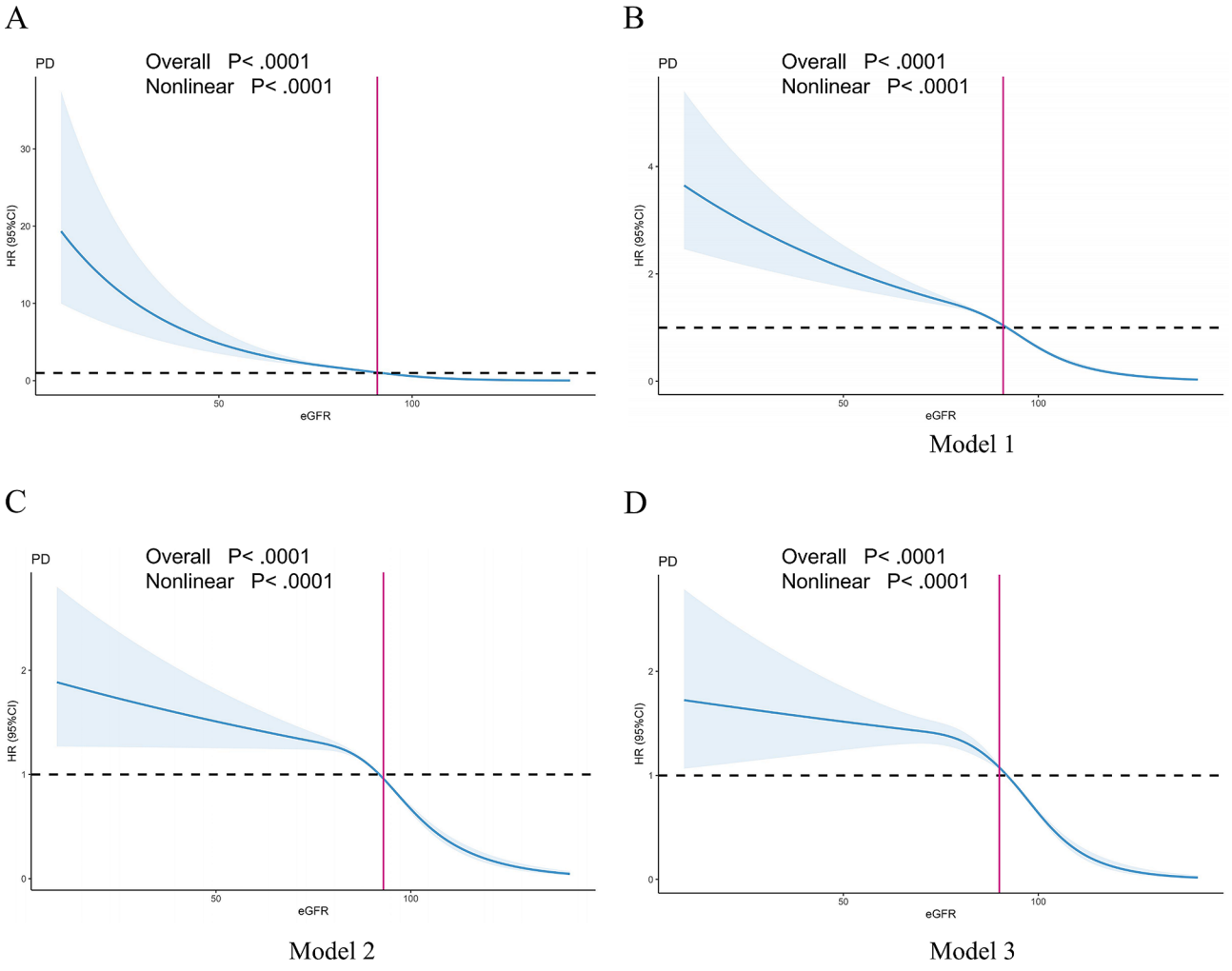

Fig. 4 Restricted cubic spline analysis of eGFR and PD risk. Nonlinear relationship between eGFR and Parkinson's disease risk analyzed using restricted cubic spline models. (**A**) Unadjusted analysis, (**B**) Analysis based on Model 1, (**C** Model 3

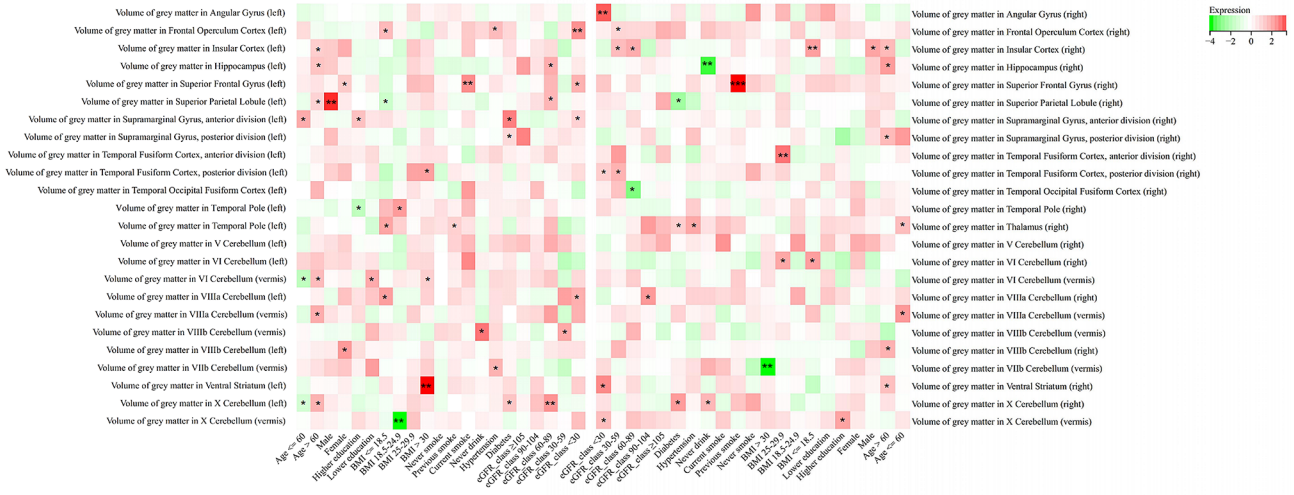

Fig. 5 Association between eGFR and brain structure volumes. Heatmap indicating the association between eGFR levels and brain volume changes in various regions. Red denotes a positive correlation with increasing eGFR, while green denotes a negative correlation. P-values indicate the statistical significance of these correlations

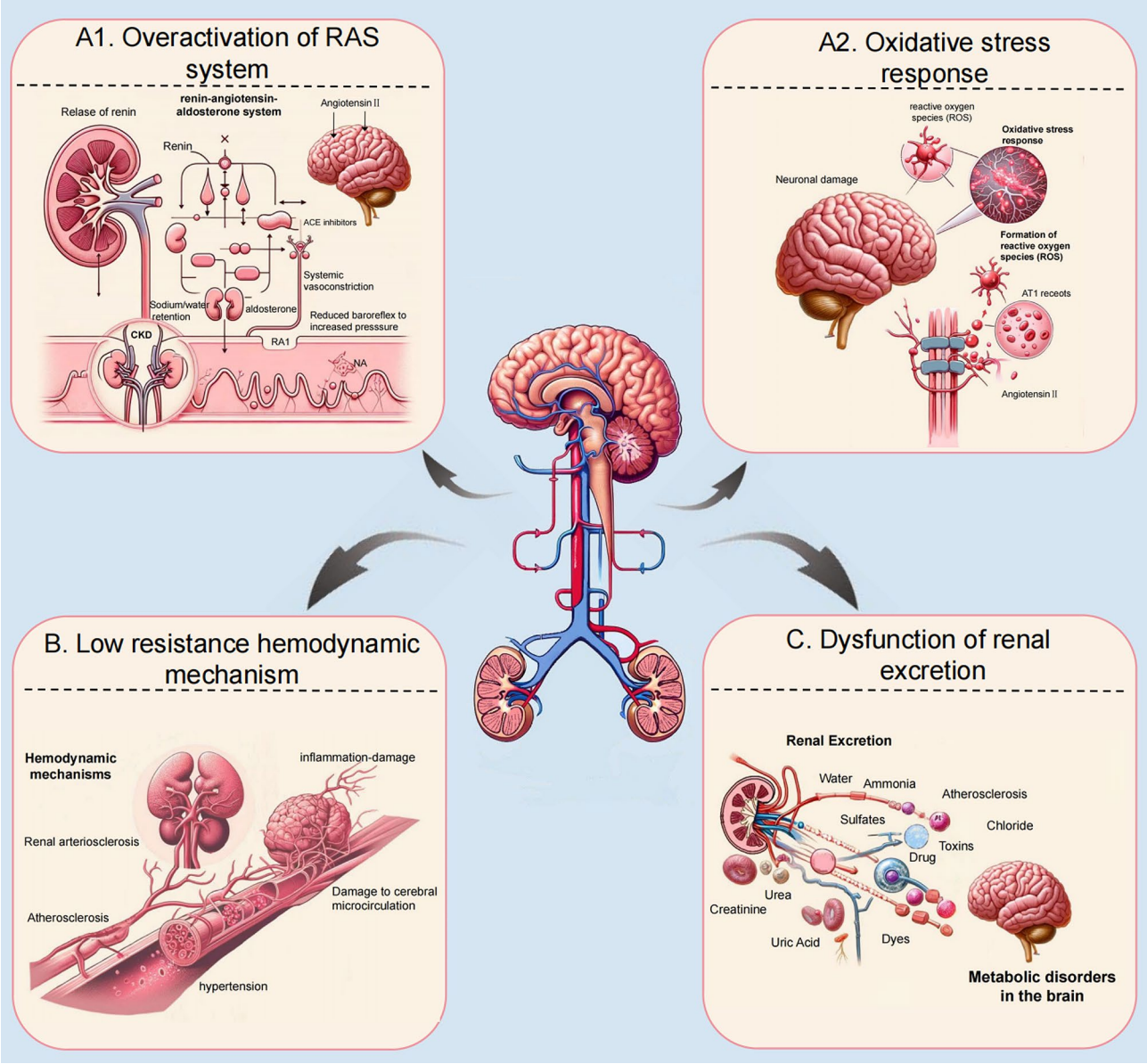

Fig. 6 Kidney-brain axis diagram. Diagram illustrating the proposed association between kidney and brain health, created using Procreate and Adobe Illustrator

between renal dysfunction and neurodegenerative diseases, including PD [16–18].

Consistent with previous literature, our study underscores the importance of longitudinal assessments in elucidating the relationship between renal insufficiency and PD [19]. While cross-sectional studies have hinted at this association [20], their limitations in establishing causality necessitated a more rigorous investigation, which our study aimed to address. By leveraging data from a large-scale, population-based cohort with extensive follow-up, we provide robust evidence supporting the notion that renal health plays a crucial role in PD pathogenesis.

Our study contributes to the existing body of literature by employing advanced statistical techniques, including Cox regression analyses, RCS analysis, and Kaplan-Meier analysis, to delineate the complex relationship between eGFR levels and PD risk. Through these methodologies, we not only confirmed the linear association between decreased eGFR and increased PD risk but also unveiled a nonlinear pattern, highlighting the nuanced nature of this relationship. These findings underscore the importance of considering renal function as a continuum rather than a dichotomous variable when assessing its impact on PD risk.

Furthermore, our study extends beyond traditional epidemiological analyses by exploring the potential neurological mechanisms underlying the association between renal dysfunction and PD. Previous studies have suggested that CKD can lead to systemic inflammation and oxidative stress, both of which are known contributors to neurodegenerative processes [21, 22]. Both the brain and kidneys are low-resistance terminal organs with similar hemodynamic mechanisms, making them susceptible to blood pressure fluctuations [23]. In CKD patients, increased arteriosclerosis and microvascular damage can exacerbate cerebral microcirculation damage [24]. This hypothesis is further supported by CKD animal models, which show extensive damage to both large blood vessels and micro vessels [25, 26]. Vascular injury, impaired cerebral hemodynamics, and changes in the extracellular environment are critical mechanisms in the development of neurodegenerative diseases including PD [27]. Moreover, damage to cerebral vascular endothelium and inflammation can lead to the abnormal accumulation of toxic substances in the brain [28, 29]. The nephrotoxic effects associated with CKD can also cause metabolic disorders, leading to disruption of the blood-brain barrier, neurotransmitter imbalances, and the onset of PD and cognitive decline [30, 31] (Fig. 6). Through neuroimaging analysis, we observed association between eGFR levels and alterations in subcortical gray matter volumes, particularly in regions such as the frontal cortex, striatum, and cerebellum, which are implicated in PD pathology. These findings provide novel insights into the interplay between renal function and brain structure, suggesting that renal insufficiency may contribute to PD pathogenesis through neurodegenerative processes.

In comparison to existing literature, our study offers several advancements. While prior studies [32] have hinted at the association between renal dysfunction and PD, our study provides robust evidence from a large, prospective cohort with extensive follow-up, enabling more definitive conclusions regarding causality. Moreover, our study employs a comprehensive approach by adjusting for a wide array of demographic, genetic, and socioeconomic factors, thereby minimizing confounding effects and enhancing the validity of our findings.

Despite these strengths, our study has certain limitations that warrant consideration. Firstly, the reliance on observational data precludes definitive causal inference, and residual confounding may influence our results. Additionally, the generalizability of our findings may be limited to the UK Biobank cohort and may not extend to other populations. Previous studies have noted variations in the prevalence and progression of CKD and PD across different populations [6, 32, 33], which suggests that replication of our findings in diverse cohorts is necessary to confirm their generalizability. Future research should aim to replicate our findings in diverse cohorts and explore potential biological mechanisms underlying the observed association.

Conclusion

In this large-scale prospective cohort study utilizing UK Biobank data, we found that reduced eGFR is significantly associated with an increased risk of PD. Our findings suggest that renal dysfunction is an important risk factor for PD. Neuroimaging analysis revealed the association between lower eGFR levels and brain volume atrophy in regions implicated in PD, providing further neuropathological support for this association. These results underscore the need to consider renal health in PD risk assessments and highlight the potential of maintaining kidney function as a preventive measure against PD. Future research should incorporate chronic renal insufficiency in studies of PD high-risk populations to develop effective prevention strategies.

Abbreviations

BMI	Body Mass Index
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology
eGFR	Estimated Glomerular filtration rate
eGFRcr	Estimated Glomerular filtration rate-creatinine
eGFRcys	Estimated Glomerular filtration rate-cystatin C
eGFRcr-cys	Estimated Glomerular filtration rate creatinine-cystatin
HR	Hazard ratios
MRI	Magnetic resonance imaging
NHIS	National Health Interview Survey
PD	Parkinson's disease
PRS	Polygenic risk score
ROS	Reactive oxygen species
RAS	Reticular activating system
RCS	Restricted Cubic Spline
Scr	Serum creatinine
Scys	Serum cystatin C
SD	Standard deviation
SOD	Superoxide dismutase

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Author contributions

X.Li and H.Peng, conceived the article; H.Peng, prepared the manuscript; L.Wu and Q.Chen, Processed relevant data; S.Chen, S.Wu and X.Shi, searched for relevant studies; J.Ma, H.Yang and X.Li, revised the manuscript. All authors reviewed the manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The current analysis is based on publicly available summary data (UK biobank, https://www.ukbiobank.ac.uk). The original data from the UK biobank have been approved by ethic committees and written informed consent was obtained from study participants or caregivers.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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