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Prevalence and factors linked to renal involvement in prediabetes patients across Europe in the ePREDICE trial

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This sub-analysis of the ePREDICE trial, investigated the prevalence and determinants of renal complications, specifically glomerular hyperfiltration, albuminuria, and reduced kidney function, in individuals with prediabetes (PD). The cohort consisted of 967 participants from diverse backgrounds across seven countries. The kidney function was evaluated using the MDRD-4 equation, and the influence of various clinical and demographic factors on renal involvement was assessed by multivariable regression models. Additionally, insulinogenic and disposition indices were examined. Overall, the prevalence of renal abnormalities in this PD cohort was 9.2% (*n* = 89). Key findings included the detection of hyperfiltration in 20 (2%) individuals, albuminuria in 45 (4.7%), and CKD stage G3a in 29 (3%). Hyperfiltration was inversely correlated with age and height, while albuminuria showed a significant direct association with the disposition index (DI). Age and waist circumference were significantly and directly associated with estimated glomerular filtration rate (eGFR). The ePREDICE study highlights critical factors that affect renal involvement in PD individuals, revealing complex interactions among various parameters. These findings further emphasize the necessity for the search of early kidney abnormalities in people with PD especially in those in older age groups and with a large waist circumference.

Keywords Prediabetes, Chronic kidney disease (CKD), Estimated glomerular filtration rate (eGFR), Albuminuria, Biomarkers

Abbreviations

T2D	Type 2 diabetes
PD	Prediabetes
eGFR	Estimated glomerular filtration rate
DI	Disposition index

Prediabetes (PD), a precursor to type 2 diabetes (T2D), is characterized by higher-than-normal blood glucose levels that are not yet high enough to be classified as diabetes. It encompasses impaired fasting glucose (IFG) with plasma glucose levels of 6.1 to 6.9 mmol/L and impaired glucose tolerance (IGT), defined by 2-hour post-challenge plasma glucose levels of 7.8 to 11.0 mmol/L in the oral glucose tolerance test (OGTT)[1]. The progression from PD to T2D is estimated at 4–6% per year for isolated IFG or IGT, and 6–9% per year for combined IFG and IGT[2,3].

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The escalating prevalence of diabetes and its associated complications poses a significant health challenge for contemporary societies and their healthcare systems (https://www.diabetesatlas.org/en/)[4]. Among the complications that impact morbidity and mortality in individuals with T2D, chronic kidney disease (CKD) is a prominent concern. It accounts for nearly half of all chronic kidney disease (CKD) cases and affects over 4% of the global population[5].

However, not all individuals with PD develop full-fledged diabetes, nor does every person with T2D progress to CKD. Glucose metabolism disturbances in PD are closely linked to microvascular complications, including kidney impairment[6], eye involvement[7], and neuropathy[8]. A meta-analysis of 180,000 individuals found a modest but significant increase in CKD risk among those with PD[9], impacting both morbidity and mortality[10].

A comprehensive study of the prevalence and contributing factors related to renal involvement in individuals with PD is pivotal for early detection, risk stratification, and precisely targeted intervention approaches. In the present study, our primary objective was to investigate the extent of renal dysfunction and delve into the potential factors contributing to the presence of hyperfiltration, albuminuria and the decline of kidney function in a cohort of participants with PD enrolled in the Early Prevention of Diabetes Complications in People with Hyperglycemia (ePREDICE) trial. In pursuit of this objective, we meticulously evaluated a spectrum of anthropometric, physical, metabolic and other biochemical parameters, and lifestyle variables that hold potential implications on renal dysfunction in this population at baseline.

Methods

Study design, population and clinical endpoints in the ePREDICE trial

The ePREDICE trial has been described in detail in a previous article[11] (EUDRA-CT 2013-000418-39; ClinicalTrials.gov NCT03222765 registration 19/07/2017). Briefly, ePREDICE is a multicenter, international, independent, randomized, double-blind, placebo-controlled trial. The participants were randomly assigned with equal probability to one of four parallel study arms: placebo, metformin, linagliptin, or a fixed-dose combination of linagliptin/metformin. All participants also received lifestyle intervention involving dietary and physical activity modifications. Detail un participant flow is provided at Gabriel et al.[11].The active intervention phase was planned to last for 2 years. EUDRA-CT (ID 2013-000418-39) before the first patient was recruited and after in the ClinicalTrials.gov (ID: NCT03222765).

The study recruited men and women aged 45–74 years with the diagnostic of prediabetes from multiple clinical centers in Australia, Austria, Bulgaria, Greece, Kuwait, Poland, Serbia, Spain, and Turkey. The World Health Organization (WHO) criteria for PD were applied, including both IFG and IGT[12]. The inclusion and exclusion criteria can be found in the study description[11].

The primary endpoint of the ePREDICE study is defined as the two-year change in the microvascular index, which is a composite measure consisting of three variables: the retinal "Early Treatment of Diabetic Retinopathy Study" (ETDRS) score, the urinary albumin-to-creatinine ratio (UACR), and the sudomotor index for neuropathy measured using the SUDOSCAN® device. Additional endpoints include the incidence of diabetes, quality of life, cognitive function, depressive symptoms, fatty liver index, insulin sensitivity, beta-cell function, and biomarkers of inflammation and endothelial dysfunction in a subsample of participants.

Ethical issues

The trial protocol was approved by all national Medicine Agencies and local ethic committees of participating centres: Comité Ético de Investigación Clínica del Hospital Universitario La Paz, Madrid, Spain. Approval No. 3850 (01/02/2013); Hellenic Republic Ministry of Health National Ethics Committee, Greece. Approval No. 74/00–01/14 (15/12/2014); The Dean office, Istanbul Medical Faculty Ethical Board for Clinical Trials, Turkey.-pproval No. 2014/495 (10/04/2014); Etickog Odbora. Beograd, Republike Srbije, Serbia. Appoval No. 61/1 (06/04/2013); Ethics Committee of the Faculty of Medicine, University of Belgrade, Serbia. Approval No. 29/III-10(07/03/2013); Komisji Bioetycznej UJ (Uniwersytetu Jagiellonskiego), Poland. Appoval No. BET/185/L/2014(26/06/2014); Executive Officer of Ethics Review Committee (RPAH) & Human Research Ethics Committee (HREC), Australia. Approval No. X13-0046 & HREC/13/RPAH/65 (12/03/2014); комисия по етика "Александровска" ЕАД София, България, Bulgaria. Approval No. КИ-213/18.03.15 (18/03/2015); Die Ethikkommission für das Bundesland Salzburg. "Landeskrankenhaus Salzburg-Universitätsklinikum der PMU, Universitätsklinik für Innere Medizin I", Austria. Approval No. 415-E/1649/10-2014 (08/07/2014).

All study participants gave their written informed consent prior to the participation in the study. The informed consent sheet complied with the applicable regulatory European medical agency requirements, and adheres with the International Good Clinical Practice Guidelines, and the Helsinki Declaration.

Baseline renal function assessment

Albumin and creatinine assays were carried out in morning spot urine samples at the Fundación Jiménez Díaz Diabetes Laboratory in Madrid, Spain. Serum creatinine quantification was performed at each participating clinical center using standardized measurements to calculate the estimated glomerular filtrate (eGFR) using MDRD-4 (Modification of Diet in Renal Disease equation with 4 variables) formula standardized using the isotope dilution mass spectrometry (IDMS)[13]. The MDRD equation is based on four variables (age, sex, ethnicity, and serum creatinine)[14]. According to the eGFR values, people were classified as follows: G1 (> 90 ml/min/1.73 m^2); G2 (89 – 60 ml/min/1.73m^2) and G3a (59 – 45 ml/min/1.73m^2). No participant had eGFR below 45 ml/min/1.73m2. According to the albuminuria/ creatinine ratio (ACR) participants were classified as: A1 (< 30 mg/g); A2 (30–300 mg/g) and A3 (> 300 mg/g), according to the KDIGO (Kidney Disease Improving Global Outcomes) guidelines (see Table 1)[13].

		ALBUMINURIA (ACR)			
CKD-stage	eGFR MDRD-4 (mL/min/1.73m2)	A1 (< 30 mg/g)	A2 (30-300 mg/g)	A3 (>300 mg/g)	Total
G1	>130	18 (1.86%)	2 (0.21%)		20 (2%)
	90-129	330 (34.1%)	18 (1.86%)		348 (36%)
G2	60-89	548 (56.7%)	22 (2.2%)	1 (0.1%)	570 (59%)
G3a	45-59	26 (2.7%)	3 (0.3%)		29 (3%)
G3b	30-44				
G4	15-29				
G5	< 15				
Total		922 (95.35%)	44 (4.55%)	1 (0.1%)	967 (100%)

Table 1. Assessment of kidney function in the study population, according with the KDIGO guidelines for CKD evaluation and management.

The MDRD-4 equation was employed for the GFR estimation, and the percentages for each category are presented. Predominantly, the prediabetic cohort exhibited hyperfiltration/normal renal function (G1 or G2 + A1), highlighted in green. Individuals with diminished eGFR (G3a) or the presence of albumin in urine (A2 or A3), or both concurrently, are depicted in yellow and orange, respectively. We next explored primary determinants that may contribute to renal involvement (hyperfiltration, albuminuria and hypofiltration) (Table 2). For that reason, we compared people with or without renal abnormalities as a whole by sex. Surprisingly, there were no statistically significant differences in BMI and waist circumference between those with and without renal involvement. No marked differences were noted among various components of the glucose metabolism, except in the disposition index (DI). Significant disparities between individuals with or without renal involvement were observed in height ($p = 0.038$) and hepatic gamma-glutamyl transferase (GGT) ($p = 0.005$). A trend for the height discrepancy was discernible among women (158 cm vs. 160 cm, $p = 0.058$), whereas no such variation was noted among men. Conversely, when we compare individuals with renal impairment versus those without renal impairment GGT showed a significant inverse association in women (16 vs. 22, $p < 0.001$), while no association was seen in men (28 vs. 29).

Anthropometric, clinical, biochemical, and metabolic variables at baseline

Several anthropometric variables, including weight, height, waist circumference, and hip circumference, were collected as part of the study. Heart rate and blood pressure values were also recorded. The biochemical profile analysed in all participants included plasma glucose, serum insulin, and C-peptide levels measured at five points (0, 30, 60, 90 and 120 min) during the oral glucose tolerance test (OGTT). Other measures included glycated hemoglobin (HbA1c), serum lipid profile (total cholesterol [T-C], high-density lipoprotein [HDL-C], triglycerides [TG], and estimated low-density lipoprotein [LDL-C]), liver function markers (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transferase [GGT], alkaline phosphatase [ALP], and amylase), and kidney function markers (serum creatinine, albumin, and uric acid). Various formulae were applied to assess insulin resistance and beta-cell function based on glucose, insulin, and C-peptide data, including the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), Quantitative Insulin Sensitivity Check Index (QUICKI), Matsuda Index, Oral Glucose Insulin Sensitivity (OGIS), insulinogenic index, and disposition index. The metabolic syndrome was defined using the National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) criteria[15] and liver involvement was assessed using the fatty liver index (FLI) formula[16].

Statistical analysis

Data were collected and stored in a database developed using the OpenClinica platform (www.openclinica.com). Continuous variables are presented as median and interquartile range (IQR), and comparisons were performed using the Wilcoxon signed-rank test for non-parametric data. Normality of data distribution was assessed using the Shapiro-Wilk or Kolmogorov-Smirnov test, depending on the number of observations. Categorical variables are expressed as percentages and compared using the Pearson chi-squared test. Two-tailed P-values were reported, with $P < 0.05$ considered statistically significant. Multinomial logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs), using normalized z-scores for quantitative variables. All statistical analyses were conducted using R software (v4.0.2) and R Studio (v1.4), employing libraries such as ggplot2, jmv, tidyverse, clinicopath, gtsummary, and finalfit.

Results

Prevalence of renal involvement

In the examination of different features of kidney dysfunction in people with PD three situations were considered: hyperfiltration, albuminuria, and decline in kidney function (Table 1). The presence of renal involvement was considered when at least one of the subsequent conditions was met: (1) an elevation in the eGFR beyond 130 ml/min/1.73 m^2 (98th percentile within our population); (2) an ACR surpassing 30 mg/g; or (3) an eGFR

Variables	Renal involvement (men)	Renal involvement (woman)	No renal involvement (men)	No renal Involvement (woman)	Men p-value	Woman p-value	Total p-value
Physical and antropometric data							
Sex							0.34
Men	33 (100%)		372 (100%)				
Women		56 (100%)		506 (100%)			
Age (yr)	61 (54, 65)	58 (50, 64)	58 (52, 64)	59 (53, 64)	0.24	0.35	0.96
Body mass index	29.5 (27.4, 33.0)	31.4 (27.0, 36.1)	29.5 (27.1, 32.5)	30.5 (27.1, 34.5)	0.85	0.29	0.33
Height (cm)	1.73 (1.69, 1.77)	1.58 (1.54, 1.61)	1.73 (1.69, 1.78)	1.60 (1.55, 1.65)	0.64	0.058	0.038*
Waist circunference (cm)	105 (100, 110)	100 (92, 108)	104 (98, 113)	99 (91, 108)	0.88	0.59	0.72
Systolic blood pressure (mmHg)	142 (124, 151)	131 (123, 144)	133 (123, 143)	131 (120, 142)	0.11	0.56	0.21
Diastolic blood pressure (mmHg)	84 (80, 89)	84 (77, 89)	82 (76, 89)	81 (76, 88)	0.64	0.43	0.38
Antihypertensives (Y)	4 (30%)	30 (50%)	154 (40%)	184 (36%)	0.65	0.04	
Glycemic data							
Fasting glucose (mmol)	6.40 (6.00, 6.70)	6.40 (6.20, 6.62)	6.40 (6.20, 6.73)	6.30 (6.10, 6.70)	0.43	0.67	0.82
Matsuda index	2.38 (1.71, 3.56)	2.51 (1.80, 3.79)	2.56 (1.98, 3.51)	2.69 (1.96, 3.74)	0.72	0.65	0.57
HOMA-IR	3.23 (2.14, 4.60)	3.24 (2.20, 4.60)	3.17 (2.19, 4.39)	3.05 (2.29, 4.25)	0.93	0.74	0.75
Insulinogenic index	0.49 (0.27, 0.70)	0.55 (0.34, 0.86)	0.57 (0.37, 0.90)	0.63 (0.39, 1.00)	0.1	0.28	0.075
Disposition index	1.29 (0.71, 1.68)	1.52 (0.88, 2.09)	1.55 (0.98, 2.21)	1.61 (1.05, 2.45)	0.058	0.28	0.056
HbA1c		5.90 (5.52, 6.03)		5.80 (5.60, 6.10)	0.52	0.74	0.19
Prediabetes criteria	12 (36%)		101 (27%)		0.1	0.31	0.71
IGT	11 (33%)	13 (23%)	149 (40%)	161 (32%)			
IFG	10 (30%)	21 (38%)	122 (33%)	189 (37%)			
IGT + IFG	5.90 (5.60, 6.20)	22 (39%)	5.80 (5.50, 6.00)	156 (31%)			
Lipid profile							
Total cholesterol (mmol)	5.02 (4.68, 5.74)	5.21 (4.50, 6.02)	5.12 (4.53, 5.71)	5.35 (4.66, 6.12)	0.72	0.5	0.8
Triglycerides (mmol)	1.57 (0.99, 2.15)	1.29 (0.96, 1.86)	1.32 (0.95, 1.95)	1.32 (1.01, 1.76)	0.11	0.99	0.31
HDL (mmol)	1.12 (1.05, 1.29)	1.34 (1.19, 1.57)	1.19 (1.03, 1.42)	1.40 (1.20, 1.63)	0.23	0.3	0.18
LDL (mmol)	3.28 (2.74, 3.80)	3.14 (2.54, 3.96)	3.24 (2.69, 3.75)	3.29 (2.68, 3.90)	0.83	0.54	0.73
Hepatic profile							
ALT (SGPT) (UI)	28 (21, 38)	18 (15, 26)	26 (21, 34)	21 (17, 28)	0.31	0.12	0.4
AST (SGOT) (UI)	26 (17, 31)	17 (15, 24)	22 (18, 26)	19 (16, 24)	0.11	0.35	0.97
AST/ALT Ratio	0.84 (0.64, 1.03)	1.00 (0.70, 1.17)	0.82 (0.64, 1.00)	0.94 (0.72, 1.12)	0.7	0.72	0.56
GammaGT (UI)	28 (21, 46)	16 (14, 24)	29 (22, 44)	22 (16, 34)	> 0.99	< 0.001*	0.005*
Fatty liver index	79 (53, 88)	68 (30, 89)	73 (50, 89)	67 (41, 84)	0.45	0.98	0.75
Others							
Urate (mg/dL)	6.80 (5.60, 7.53)	5.06 (4.28, 6.21)	6.20 (5.40, 7.10)	5.00 (4.20, 5.90)	0.12	0.75	0.58
C-reactive protein (ng/mL)	0.27 (0.08, 0.38)	0.32 (0.10, 0.72)	0.17 (0.05, 0.42)	0.26 (0.10, 0.61)	0.37	0.55	0.25

Table 2. Descriptive and comparative statistics in baseline demographic and plasma biochemical parameters in individuals without or with renal involvement defined as the presence of hypofiltration < 60 mL/min/1.73 m^2, hyperfiltration > 130 mL/min/1.73 m^2, and the presence of albuminuria (30 mg albumin per gram of creatinine) Statistics presented are median (interquartile range, IQR) or n (%). Quantitative variables are compared using Wilcoxon rank sum test while for qualitative date Pearson's Chi-squared test are employed. OGTT: oral glucose tolerance test; HbA1c: Hemoglobin A1c; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; HDL: high-density lipoprotein; LDL: low-density lipoprotein; AST (SGPT): Aspartate Aminotransferase, also known as serum glutamic pyruvic transaminase; ALT (SGOT): Alanine Aminotransferase, also known as serum glutamic oxaloacetic transaminase; GGT: Gamma-Glutamyltransferase.

below 60 ml/min/1.73 m^2. Utilizing these criteria, in total 89 individuals (9.2%) were identified as having renal involvement.

Firstly, we executed a separate analysis focusing on individuals with renal hyperfiltration, considering that this condition commonly represents an early and reversible stage of kidney damage preceding the appearance of albuminuria and decline in renal function[17]. Twenty (2%) individuals surpassed this threshold and were defined as having renal hyperfiltration. The presence of albuminuria was detected in 45 (4.65%) participants, and renal failure (CKD stage G3a: 45–59 ml/min/1.73 m^2) in 29 (3%) individuals, while 878 (95%) had normal filtration values ranging between 60 and 129 ml/min/1.73 m^2. Two participants showed anomalous glomerular hyperfiltration (GF) and albuminuria and three hypofiltration and albuminuria concurrently.

When people with renal abnormalities were stratified by the modality of kidney dysfunction (hyperfiltration, albuminuria and hypofiltration) a number of interesting observations appeared.

Association of clinical, biochemical and metabolic variables with hyperfiltration

Defining the threshold for hyperfiltration presents a challenge, and in this study, we established a threshold of > 130 ml/min/1.73 m^2 based on a consensus. This intentionally stringent threshold aimed at having a high specificity, i.e., minimizing false positives at the expense of true positive cases. Employing this criterion, we identified 20 (2%) individuals with hyperfiltration (3 men and 17 women),

The hyperfiltration group comprised 85% women, in contrast to 57% in the normal filtration group ($p = 0.013$). The odds ratio was 4.23 (95% CI: 1.41–18.21, $p = 0.022$), suggesting a significantly higher proportion of women in the hyperfiltration group compared to the normofiltration group.

Furthermore, hyperfiltrating individuals were younger, the mean age was 54 years (SD = 6.6) for the hyperfiltration group and 58.3 years (SD = 7.6) for the normofiltration group, resulting in a Cohen's d of 0.60, indicating a moderate effect size and a meaningful difference in age between the groups ($p = 0.011$), the comparison also exhibit a notable difference in height, primarily attributed to excess of women ($p < 0.001$*) (Table 3).

For glycemic parameters between hyperfiltrating individuals versus those with normal filtration, we observed difference in fasting plasma insulin (7 vs. 11 ; $p = 0.047$) and HOMA-IR (2.94 vs. 3.14; $p = 0.04$), though a statistical significance was not reached for the Matsuda Index (3.32 vs. 2.59; $p = 0.065$).

The hyperfiltration group displayed lower GGT values compared with those with normal filtration (18 vs. 26 UI/L; $p = 0.016$). Also, levels of other hepatic enzymes such as ALT (18 vs. 23 U/L, $p = 0.024$) and AST (17 vs. 20 U/L, $p = 0.064$) were lower in the hyperfiltration group. Another distinguishing factor between the two groups was platelet count (254000 vs. 238000 platelets per microliter of blood, $p = 0.043$).

In terms of renal parameters, people with hyperfiltration had lower serum creatinine and uric acid ($p < 0.001$). Additionally, an association between hyperfiltration and albuminuria was noted (4 vs. 3 mg/g, $p = 0.033$). HsCRP was numerically higher in individuals with hyperfiltration (0.52 GF vs. 0.21 Non-GF; $p = 0.054$).

Multivariable regression analysis indicated significant associations between hyperfiltration and Matsuda index, hepatic AST, and hsCRP (Fig. 1). Sex-specific variations were also evident.

Association of clinical, biochemical and metabolic variables with albuminuria

There were some sex-specific variations in the study parameters. HDL cholesterol ($p = 0.05$) had a significant association with albuminuria, particularly in women. In women, GGT had a significant difference between people with albuminuria vs. non-albuminuria ($p = 0.017$) (Table 4).

The DI showed a significant association with albuminuria; individuals with albuminuria displayed a DI of 1.3, whereas in those without albuminuria it was 1.58 ($p = 0.018$). Of interest, glycemic abnormalities, as well as other related indices such as the Matsuda Index ($p = 0.022$) and HbA1c ($p = 0.034$), were exclusively observed in males.

While the DI stood as the lone statistically significant variable, a comprehensive multivariable analysis was conducted on other variables that approached significance. The aim was to explore whether these variables could influence the disposition index (DI), but it was not the case (Fig. 2).

Association of clinical, biochemical and metabolic variables with hypofiltration (G3a)

To elucidate disparities between individuals with normal eGFR values (60–129 ml/min/1.73 m^2) and those with eGFR < 60 ml/min/1.73 m^2, categorized as stage G3a (hypofiltration) according to KDIGO guidelines, exclusions were applied for individuals with filtration rates exceeding 130 ml/min/1.73 m^2 to facilitate a proper analysis. Among the factors (Table 5) influencing a reduced renal function within our cohort, age emerged as a significant contributor. Those in stage G3awere found to be on average 6 years older than people in stages G1/G2 (58 vs. 64 years, $p = 0.008$). However, this age discrepancy was predominantly influenced by variance among women. Other variables distinguishing the two cohorts included HDL-cholesterol (1.06 vs. 10.09 mmol, $p = 0.014$), LDL-cholesterol (2.9 vs. 3.3 mmol/L, $p = 0.046$), and GGT (21 vs. 26 U/L, $p = 0.014$), all of which were lower in the female G3a group.

An additional discerning factor between the hypofiltrating vs. normo-filtrating individuals was the post-challenge glucose. While FPG the G3a group compared with people with normal filtration (NF) showed a notably greater glucose elevation at 60 min (median 12.09 vs. 11.07 mmol/L, $p = 0.028$). This difference also remained evident at 90 min (10.73 vs. 9.67 mmol/L, $p = 0.021$). While these differences at 30 and 120 min in the OGTT were numerically higher in the G3a group, it was not statistically significant.

No other glycemia-related variables showed significant differences between G3a vs. NF, including HbA1c. A higher proportion of women within the hypofiltration group had combined IGTIFG conditions (58%) compared with those with normal filtration (31%), though this sex-disparity did not achieve statistical significance.

Although there was no overall disparity in the use of various drugs, a greater prevalence of antihypertensive drug use was observed in the hypofiltration cohort (62% vs. 38%, $p = 0.009$), likely attenuating observed blood pressure differences. Figure 3 displays outcomes from the multivariable logistic regression analysis aimed at identifying hypofiltration predictors. This analysis incorporated significant variables from univariate analysis and standardized quantitative data into z-scores for normalization.

Discussion

The ePREDICE study is a comprehensive investigation involving 967 individuals with PD from 7 countries with diverse dietary and lifestyle habits. One of the aims of the study was to assess the presence and degree of renal and other microvascular damage in this population with impaired glucose metabolism. Several studies

Variables	Hyperfiltration (> 130) (Males)	Hyperfiltration (> 130) (Females)	Normofiltration (Males)	Normofiltration (Females)	Males *p*-value	Females *p*-value	Total *p*-value
Physical and antropometric data							
Sex							0.01*
Male	3 (%)		392 (%)				
Female		17 (%)		526 (%)			
Age (yr)	52 (48.7, 57.7)	64 (58, 66)	58 (52, 64)	58 (52, 64)	0.41	0.02*	0.01*
Body mass index (kg/m2)	29.4 (26.1, 38.4)	32.0 (27.9, 33.8)	29.5 (27.3, 32.5)	30.6 (27.1, 34.6)	0.35	0.68	0.89
Height (cm)	1.72 (1.71, 1.74)	1.55 (1.53, 1.58)	1.73 (1.69, 1.78)	1.60 (1.55, 1.65)	0.68	< 0.01*	< 0.01*
Waist circunference (cm)	100 (86, 106)	100 (85.7, 106.3)	104 (98, 113)	99 (91.3, 108)	0.65	0.72	0.33
Systolic blood pressure (mmHg)	128 (124, 135)	128 (124, 132)	133 (124, 144)	131 (120, 142)	0.45	0.51	0.12
Diastolic blood pressure (mmHg)	83 (71, 87)	84 (71, 87)	83 (76, 89)	82 (76, 88)	0.68	0.75	0.56
Antihypertensives (Y)	1 (33%)	7 (41%)	154 (39%)	194 (37%)	0.82	0.72	0.87
Glycemic data							
Fasting glucose (mmol)	6.3 (4.5, 6.5)	6.4 (6.2, 6.6)	6.40 (6.20, 6.73)	6.30 (6.10, 6.70)	0.32	0.74	0.84
OGTT glucose 60 min (mmol)	11.7 (10.5, 16)	11.2 (9.7, 11.8)	11.50 (9.90, 12.80)	10.8 (9.3, 12.3)	0.44	0.82	0.75
OGTT glucose 90 min (mmol)	10 (9.9, 11.5)	9.4 (7.9, 10.5)	9.95 (8.30, 11.50)	9.4 (7.8, 10.97)	0.12	0.62	0.9
Fasting insulin (UI)	6.1 (6.1, 6.1)	7.7 (5.7, 15.5)	11.3 (7.8, 15.3)	11.1 (8.3, 15.1)	0.21	0.42	0.05*
Matsuda index	5 (5, 5.02)	2.2 (1.5, 4.3)	2.55 (1.93, 3.50)	3.1 (2.3, 4.3)	0.17	0.13	0.07
HOMA-IR	1.8 (1.75, 1.8)	2.2 (2.3, 4.3)	3.22 (2.20, 4.48)	3.06 (2.30, 4.27)	0.23	0.07	0.04*
Insulinogenic index	0.1 (0.1, 0.12)	0.6 (0.4, 0.8)	0.56 (0.36, 0.90)	0.63 (0.39, 1.00)	0.13	0.69	0.6
Disposition index	0.59 (0.59, 0.6)	1.6 (1.4, 3.1)	1.50 (0.96, 2.18)	1.61 (1.04, 2.38)	0.18	0.5	0.6
HbA1c	5.8 (5.5, 5.9)	5.8 (5.4, 5.9)	5.8 (5.5, 6.0)	5.8 (5.6, 6.1)	0.77	0.37	0.38
Prediabetes criteria					0.32	0.96	0.93
IGT	1 (30%)	5 (29%)	109 (28%)	165 (31%)			
IFG	0 (0%)	7 (41%)	156 (40%)	199 (38%)			
IGT + IFG	2 (60%)	5 (29%)	127 (32%)	162 (31%)			
Lipid profile							
Total cholesterol (mmol)	5.3 (4.6, 5.55)	5.9 (4.6, 6.6)	5.12 (4.53, 5.72)	5.34 (4.66, 6.13)	0.97	0.31	0.26
Triglycerides (mmol)	1.6 (1.5, 1.67)	1.3 (0.92, 1.64)	1.32 (0.95, 1.98)	1.33 (1.02, 1.77)	0.42	0.6	0.91
HDL (mmol)	1.06 (0.92, 1.3)	1.3 (1.2, 1.5)	1.19 (1.03, 1.41)	1.38 (1.19, 1.62)	0.57	0.86	0.63
LDL (mmol)	3.5(2.79, 3.8)	3.9 (2.7, 4.5)	3.25 (2.70, 3.76)	3.29 (2.68, 3.91)	0.81	0.21	0.18
Hepatic profile							
ALT (SGPT) (U/L)	18 (16.3, 34.7)	17 (14.3, 25)	26 (21, 34)	21 (17, 28)	0.35	0.14	0.02*
AST (SGOT) (U/L)	22 (17.8, 25.5)	16.5 (5.9, 22.8)	22 (18, 26.6)	19 (16, 24)	0.85	0.08	0.06*
AST/ALT Ratio	0.82 (0.64, 1.12)	1.00 (0.2, 1.16)	0.83 (0.63, 1.00)	0.94 (0.72, 1.13)	0.36	0.69	0.75
GammaGT (U/L)	23 (14.7, 37.2)	18 (15.3, 23.7)	29.5 (22, 45)	22 (16, 34)	0.36	0.12	0.02*
Fatty Liver Index	47.4 (36.3, 85)	54.1 (23.1, 92.2)	73.8 (50.5, 89.1)	66.8 (41, 83.9)	0.45	0.7	0.39
Others							
Urate (mg/dL)	4.5 (4.1, 4.6)	4.4 (3.9, 5.2)	6.20 (5.40, 7.12)	5.02 (4.20, 5.90)	0.01*	0.05*	< 0.01*
C-reactive protein (ng/mL)	0.3 (0.3, 0.33)	0.5 (0.08, 1.2)	0.17 (0.06, 0.42)	0.26 (0.10, 0.61)	0.52	0.14	0.05*

Table 3. Descriptive and comparative statistics of subjects with hyperfiltration (> 130 ml/min/1.73m2) using a calibrated serum creatinine MDRD-4 eGFR measurement versus normal (G1 and G2 stages) People with eGFR of less than 60 ml/min/1.73m2 were excluded. Statistics presented as median (IQR) or n (%). Quantitative variables are compared using Wilcoxon rank sum test while for qualitative date Pearson's Chi-squared test are employed. OGTT: oral glucose tolerance test; HbA1c: Hemoglobin A1c; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; HDL: high-density lipoprotein; LDL: low-density lipoprotein; AST (SGPT): Aspartate Aminotransferase, also known as serum glutamic pyruvic transaminase; ALT (SGOT): Alanine Aminotransferase, also known as serum glutamic oxaloacetic transaminase; GGT: Gamma-Glutamyltransferase.

have previously demonstrated that prediabetes, and not only frank diabetes, can cause kidney damage. In other words, there is evidence suggesting an increased risk of renal involvement in prediabetic individuals compared with those with normal glucose metabolism. The prevalence of renal involvement in people with PD can vary depending on the population studied, diagnostic criteria used, and other factors. Individuals with PD have a high burden of cardiovascular risk factors, including renal damage. In an analysis of data from NHANES 2011–2014, adults with PD (defined using ADA-FPG or HbA1C) had a high prevalence of hypertension (36.6%),

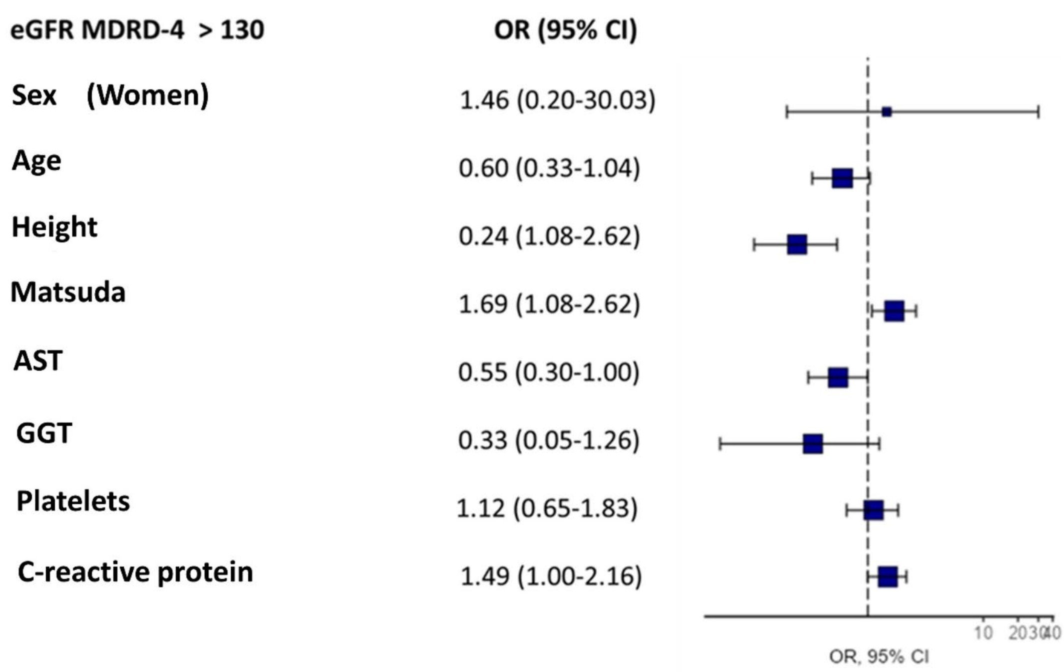

Fig. 1. Odds ratios for statistically significant variables of MDRD-4 G1/G2 vs. hyperfiltating individuals comparison. Expresses as OR (95% CI). Quantitative variables are expressed as z-scores. AST: Aspartate Aminotransferase, GGT: Gamma-Glutamyltransferase.

dyslipidemia (51.2%), albuminuria (7.7%), and a reduced eGFR (4.6%)[18]. These studies indicate that there is a significant prevalence of renal involvement in people with PD, emphasizing the importance of early detection and intervention to prevent progression to overt diabetes and associated complications.

A number of studies on PD and renal involvement have mainly been focused on the presence and development of impaired renal function[19] or glomerular hyperfiltration status[20,21]. Other authors observed than PD was independently linked to proteinuria development (OR 1.233; 95% CI 1.170–1.301), but not to eGFR decline (OR 0.981; 95% CI 0.947–1.017)[22].To better define renal involvement in the PD population, the ePREDICE study categorized kidney damage into three different components: hyperfiltration, albuminuria and decreased eGFR.

At the timing of study entrance (baseline) in the ePREDICE trial the prevalence of renal involvement (1 or 2 out of the 3 components) was 9.2%. Among the participants with renal impairment, 29 individuals had an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73m2, which corresponds to stage G3a CKD (2.99%). Albuminuria, an important marker of kidney damage, was detected in 45 individuals (4.5%). Among these, 44 individuals had urinary albumin excretion between 30 and 300 mg/g (stage A2), while one individual had urinary albumin excretion of 500 mg/g (stage A3). Three participants had both decreased eGFR (G3a) and albuminuria (A2) concurrently. Twenty individuals surpassed presented an elevation in the eGFR beyond 130 ml/min/1.73 m^2 (98th percentile within our population) and were defined as having renal hyperfiltration.

Glomerular hyperfiltration, albuminuria and decreased eGFR probably are the result from different clinical and metabolism, and pathophysiological mechanism. While they often coexist, they are associated with various factors, some of which overlap. Glomerular hyperfiltration is an early renal abnormality mostly occurring as a compensatory response to metabolic changes, such as hyperglycemia, leading to increased shear stress on the glomerular capillary walls causing albuminuria. Over the time hyperfiltration can subsequently elicit structural changes in the glomerulus causing further albuminuria and increasing the risk of progression to chronic kidney disease (CKD)[17,21,23].

Multivariable analysis of the ePREDICE data revealed that two prominent factors influencing eGFR were age and waist circumference. Each year of age increased the odds ratio (OR) for decreased eGFR by 5%. These findings are consistent with previous research by Hallan et al.[16]. Waist circumference showed a strong association with decreased eGFR, with an OR of 3.26.

Glomerular hyperfiltration was inversely associated with age (OR 0.92). It is possible that individuals with factors associated with renal sensitivity to hyperglycemia are more likely to exhibit hyperfiltration at a younger age and progress to hypofiltration at a more advanced age. As a new finding, height was inversely associated with renal function, indicating an increase in hyperfiltrating individuals. It is postulated that this inverse association with height may be due to a bias in the GFR estimation algorithm, which should be further investigated, although height-related increase in post-challenge glucose in the OGTT has also been described[24,25].

Variables	Albuminuria male	Albuminuria female	No Alb male	No Alb female	Male *p*-value	Female *p*-value	Total *p*-value
Physical and antropometric data							
Sex							0.51
Male	21 (100%)		384 (100%)				
Female		24 (100%)		538 (100%)			
Age (yr)	61 (52, 65)	55 (47, 64)	58 (52, 64)	59 (52, 64)	0.44	0.21	0.69
Body mass index (kg/m2)	29.8 (27.9, 33.0)	30.3 (27.0, 35.9)	29.4 (27.0, 32.5)	30.7 (27.1, 34.5)	0.41	0.75	0.57
Waist circumference (cm)	108 (100, 110)	100 (92, 109)	104 (98, 113)	99 (92, 108)	0.71	0.77	0.46
Systolic blood pressure (mmHg)	146 (127, 151)	133 (122, 144)	133 (123, 143)	131 (120, 142)	0.028	0.52	0.055
Diastolic blood pressure (mmHg)	84 (80, 92)	82 (76, 90)	82 (76, 89)	82 (76, 88)	0.38	0.86	0.43
Antihypertensives (Y)	6 (30%)	10 (41.6%)	154 (40%)	204 (38%)	0.35	0.73	0.13
Glycemic data							
Fasting glucose (mmol)	6.30 (6.00, 6.80)	6.40 (6.20, 6.60)	6.40 (6.20, 6.70)	6.30 (6.10, 6.70)	0.35	0.92	0.58
OGTT Glucose 60 min (mmol)	12.30 (10.90, 13.70)	11.20 (9.38, 12.12)	11.50 (9.97, 12.80)	10.85 (9.30, 12.30)	0.13	0.68	0.16
OGTT Glucose 90 min (mmol)	11.40 (7.90, 12.40)	9.55 (7.65, 10.75)	9.90 (8.40, 11.50)	9.40 (7.90, 11.00)	0.1	0.55	0.48
Fasting Insulin (UI)	13 (9, 18)	13 (9, 19)	11 (8, 15)	11 (8, 15)	0.11	0.3	0.062
Matsuda Index	1.98 (1.52, 2.86)	2.54 (1.77, 3.65)	2.59 (1.99, 3.52)	2.65 (1.93, 3.78)	0.022*	0.77	0.074
HOMA-IR	3.83 (2.56, 5.21)	3.71 (2.57, 5.47)	3.16 (2.18, 4.35)	3.05 (2.28, 4.25)	0.13	0.26	0.062
Insulinogenic index	0.52 (0.28, 0.71)	0.58 (0.27, 0.87)	0.56 (0.36, 0.90)	0.63 (0.39, 1.00)	0.32	0.25	0.11
Disposition_Index	1.18 (0.80, 1.46)	1.42 (0.99, 1.91)	1.55 (0.98, 2.20)	1.61 (1.04, 2.46)	0.031*	0.23	0.018*
HbA1c	5.90 (5.80, 6.20)	5.90 (5.42, 6.03)	5.80 (5.50, 6.00)	5.80 (5.60, 6.10)	0.034*	0.83	0.21
Prediabetes criteria					0.56	0.25	0.84
IGT	8 (38%)	4 (17%)	105 (27%)	170 (32%)			
IFG	7 (33%)	12 (50%)	153 (40%)	198 (37%)			
IGT + IFG	6 (29%)	8 (33%)	126 (33%)	170 (32%)			
Lipid profile							
Total cholesterol (mmol)	5.02 (4.73, 5.92)	5.24 (4.62, 6.24)	5.12 (4.53, 5.69)	5.33 (4.63, 6.08)	0.38	0.88	0.69
Triglycerides (mmol)	1.49 (0.96, 2.17)	1.48 (1.12, 1.95)	1.32 (0.96, 1.95)	1.32 (0.98, 1.75)	0.39	0.1	0.074
HDL (mmol)	1.24 (1.09, 1.34)	1.28 (1.00, 1.48)	1.17 (1.03, 1.40)	1.40 (1.20, 1.63)	0.76	0.016*	0.05*
LDL (mmol)	3.28 (2.79, 3.80)	3.28 (2.56, 4.19)	3.24 (2.69, 3.75)	3.29 (2.66, 3.89)	0.71	0.95	0.81
Hepatic profile							
ALT (SGPT) (U/L)	32 (28, 45)	18 (15, 26)	26 (21, 33)	21 (17, 28)	0.018*	0.38	0.33
AST (SGOT) (U/L)	28 (18, 31)	17 (16, 25)	22 (18, 26)	19 (16, 24)	0.058	> 0.99	0.23
AST/ALT Ratio	0.83 (0.58, 0.98)	1.04 (0.83, 1.29)	0.83 (0.64, 1.00)	0.94 (0.72, 1.12)	0.52	0.16	0.64
Gamma-Glutaryltrnasferase (U/L)	33 (23, 84)	16 (14, 24)	29 (22, 43)	22 (16, 34)	0.2	0.017*	0.46
Fatty liver index	79 (72, 88)	70 (40, 89)	73 (49, 89)	67 (40, 84)	0.15	0.83	0.23
Renal profile							
eGFR (MDRD-4 SCr Calib)	86 (75, 95)	87 (83, 101)	88 (76, 99)	84 (73, 94)	0.74	0.16	0.34
Urate (mg/dL)	7.20 (6.20, 7.60)	5.06 (4.18, 5.55)	6.20 (5.37, 7.10)	5.00 (4.20, 5.90)	0.016*	0.98	0.12
Creatinine (mg/dL)	80 (73, 88)	62 (54, 65)	80 (71, 88)	63 (58, 71)	0.74	0.18	0.91
Others							
C-reactive protein (ng/mL)	0.29 (0.10, 0.38)	0.42 (0.16, 0.73)	0.17 (0.05, 0.42)	0.26 (0.10, 0.61)	0.18	0.12	0.061

Table 4. Descriptive and comparative statistics between people with albuminuria versus those without. Statistics presented as median (IQR) or n (%). Quantitative variables are compared using Wilcoxon U test while for qualitative data Pearson test are employed. OGTT: oral glucose tolerance test; HbA1c: Hemoglobin A1c; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; HDL: high-density lipoprotein; LDL: low-density lipoprotein; AST (SGPT): Aspartate Aminotransferase, also known as serum glutamic pyruvic transaminase; ALT (SGOT): Alanine Aminotransferase, also known as serum glutamic oxaloacetic transaminase; GGT: Gamma-Glutamyltransferase.

An inverse association was found between eGFR and GGT, showing a 3% decrease per unit change. Liver dysfunction has been linked to diabetes development in observational studies[26–28]. Elevated liver enzymes, such as ALT[29] and GGT[30], are associated with diabetes incidence and can serve as surrogate predictive biomarkers[31]. Previous studies indicate GGT is not only a marker of liver dysfunction but also a key biomarker in prediabetes and metabolic syndrome. Elevated GGT is associated with oxidative stress, contributing to systemic inflammation, insulin resistance, and the progression to diabetes, as well as cardiovascular and renal risks in prediabetes[32,33].

GGT is also involved in the pathogenesis of metabolic dysfunction-associated steatotic liver disease (MASLD) and related complications, including diabetes-associated chronic vascular conditions[34]. This aligns with our

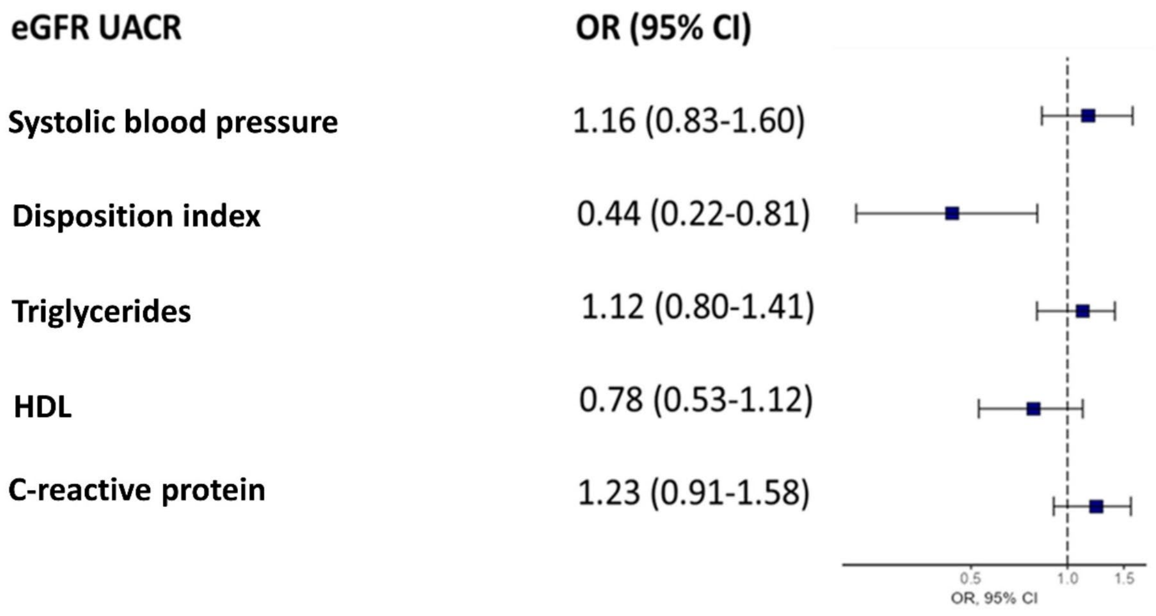

Fig. 2. Odds ratios (95% CI) for major variables between people with albuminuria versus those without. Quantitative variables are expressed as z-scores. HDL: High-Density Lipoprotein.

findings of GGT's association with decreased eGFR, suggesting it may be an early marker of renal involvement in metabolic dysfunction. Research on GGT and CKD presents conflicting results; some studies indicate lower GGT levels in advanced CKD stages, though mechanisms remain unclear. While higher GGT levels are linked to increased CKD risk[35], hemodialysis shows an inverse association[36], and a meta-analysis found no significant link between elevated GGT and CKD risk[37]. The ePREDICE study showed lower GGT levels in stage G3a and hyperfiltrators, but these associations were not statistically significant in multivariable analysis.

Concerning the metabolism abnormalities, glycemic control emerges as a crucial factor in the likelihood of developing kidney disease. This study examined parameters such as the insulinogenic index (IGI) and the DI, which were decreased in prediabetic subjects, but did not reach statistical significance. IGI has been associated with the incidence of type 2 diabetes mellitus (T2DM)[38,39] and assesses early stages of insulin signalling[40]. DI, on the other hand, predicts the development of glucose intolerance, capturing impaired insulin secretion and insulin resistance, which may coexist in individuals with PD[41–43].

Analysing the metabolism abnormalities potentially related to each renal component, our study revealed disparate results. People with renal function impairment (eGFR < 60 ml/min/1.73 m^2) showed alterations in 60 and 90 min OGTT glucose measurements but did not affect parameters of insulin resistance or β-cell function. In subjects with hyperfiltration, variations in insulin resistance measures (such as HOMA-IR or Matsuda Index) were observed. However, albuminuria emerged as the most significant contributor, with a 30% reduction in the odds ratio associated with a decrease in DI.

Limitations of the study: The study has several limitations, including its cross-sectional design, which limits the ability to infer causality. The reliance on eGFR estimates and UACR may not fully capture the complexity of renal function. Additionally, the stringent hyperfiltration threshold may have led to the underestimation of true hyperfiltration cases. Other limitations of this study is the small sample size of the hyperfiltration group, which impacts the statistical power of our analysis. Although significant differences were observed between groups, including a moderate effect size for age (Cohen's d = 0.60) and a high odds ratio for gender (OR = 4.23, $p = 0.022$), the achieved power for gender analysis was 0.74, which is below the recommended threshold of 0.80. This reduced power indicates a higher risk of Type II error, meaning that we may have been less likely to detect true differences, particularly with a small sample size. These limitations suggest that while the observed differences are notable, they must be interpreted with caution.

Also, variability in population characteristics across the seven participating countries could also influence the generalizability of the findings. Further longitudinal studies are needed to validate these results and explore the progression of renal involvement in people with PD.

Conclusions

The ePREDICE study shows that people with PD examined at several centers mainly in Europe depict a notable prevalence (9.2%) of renal disease, indicated by an eGFR outside the normal range (> 130 or < 60 ml/min/1.73 m^2) or the presence of albuminuria. The study identifies impaired insulin signaling as a key determinant of renal

Variables	Hypofiltration (G3a) (Males)	Hypofiltration (G3a) (Females)	Normofiltration (Males)	Normofiltration (Females)	Males *p*-value	Females *p*-value	Total *p*-value
Physical and antropometric data							0.38
Sex							
Male	10 (34%)		392 (43%)				
Female		19 (66%)		526 (57%)			
Age (yr)	62 (57, 66)	64 (58, 66)	58 (52, 64)	58 (52, 64)	0.16	0.021*	0.008*
Body mass index (kg/m2)	29.5 (26.2, 34.7)	32.0 (27.9, 33.8)	29.5 (27.3, 32.5)	30.5 (27.1, 34.6)	0.93	0.54	0.46
Height (cm)	1.75 (1.70, 1.79)	1.60 (1.56, 1.66)	1.73 (1.69, 1.78)	1.60 (1.55, 1.65)	0.39	0.48	0.76
Waist circunference (cm)	105 (101, 111)	100 (94, 109)	104 (98, 113)	99 (92, 108)	0.63	0.32	0.47
Systolic blood pressure (mmHg)	140 (122, 150)	134 (121, 148)	133 (124, 144)	131 (120, 142)	0.63	0.51	0.46
Diastolic blood pressure (mmHg)	85 (77, 87)	85 (76, 90)	83 (76, 89)	82 (76, 88)	0.8	0.68	0.65
Antihypertensives (Y)	6 (30%)	10 (41.6%)	154 (40%)	204 (38%)	0.35	0.73	0.13
Glycemic data							
Fasting glucose (mmol)	6.60 (6.43, 6.77)	6.50 (6.25, 6.70)	6.40 (6.20, 6.73)	6.30 (6.10, 6.70)	0.35	0.34	0.21
OGTT glucose 60 min (mmol)	11.95 (11.12, 12.67)	11.90 (10.80, 13.70)	11.50 (9.90, 12.80)	10.80 (9.30, 12.30)	0.38	0.029*	0.028*
OGTT glucose 90 min (mmol)	9.95 (8.77, 11.78)	11.40 (9.50, 12.45)	9.95 (8.30, 11.50)	9.40 (7.80, 10.97)	0.77	0.007*	0.021*
Fasting insulin (UI)	8 (7, 11)	12 (9, 15)	11 (8, 15)	11 (8, 15)	0.082	0.42	0.69
Matsuda index	3.35 (2.61, 5.48)	2.30 (1.78, 2.85)	2.55 (1.93, 3.50)	2.68 (1.94, 3.68)	0.049*	0.17	0.97
HOMA-IR	2.32 (2.07, 3.18)	3.47 (2.70, 4.06)	3.22 (2.20, 4.48)	3.06 (2.30, 4.27)	0.072	0.36	0.71
Insulinogenic index	0.51 (0.31, 0.58)	0.53 (0.33, 0.92)	0.56 (0.36, 0.90)	0.63 (0.39, 1.00)	0.38	0.42	0.27
Disposition index	1.69 (0.92, 2.07)	1.06 (0.80, 1.96)	1.50 (0.96, 2.18)	1.61 (1.04, 2.38)	0.88	0.077	0.21
HbA1c	5.80 (5.60, 5.97)	6.00 (5.72, 6.10)	5.80 (5.50, 6.00)	5.80 (5.60, 6.10)	0.96	0.088	0.16
Prediabetes criteria					> 0.99	0.044*	0.16
IGT	3 (30%)	4 (21%)	109 (28%)	165 (31%)			
IFG	4 (40%)	4 (21%)	156 (40%)	199 (38%)			
IGT + IFG	3 (30%)	11 (58%)	127 (32%)	162 (31%)			
Lipid profile							
Total cholesterol (mmol)	5.04 (4.40, 5.55)	5.05 (4.14, 5.60)	5.12 (4.53, 5.72)	5.34 (4.66, 6.13)	0.74	0.053	0.09
Triglycerides (mmol)	1.69 (1.25, 2.17)	1.11 (0.92, 1.64)	1.32 (0.95, 1.98)	1.33 (1.02, 1.77)	0.11	0.29	0.88
HDL (mmol)	1.06 (0.92, 1.09)	1.41 (1.25, 1.71)	1.19 (1.03, 1.41)	1.38 (1.19, 1.62)	0.014*	0.27	0.78
LDL (mmol)	3.16 (2.79, 3.41)	2.86 (2.17, 3.43)	3.25 (2.70, 3.76)	3.29 (2.68, 3.91)	0.79	0.019*	0.046*
Hepatic profile							
ALT (SGPT) (U/L)	25 (21, 28)	20 (16, 27)	26 (21, 34)	21 (17, 28)	0.38	0.71	0.39
AST (SGOT) (U/L)	21 (14, 30)	22 (16, 24)	22 (18, 26)	19 (16, 24)	0.82	0.91	0.76
AST/ALT Ratio	0.88 (0.67, 1.12)	1.00 (0.68, 1.16)	0.83 (0.63, 1.00)	0.94 (0.72, 1.13)	0.61	0.67	0.5
GammaGT (U/L)	27 (22, 30)	16 (10, 24)	30 (22, 45)	22 (16, 34)	0.15	0.038*	0.014*
Fatty Liver Index	67 (50, 90)	71 (33, 85)	74 (51, 89)	67 (41, 84)	0.89	0.85	0.83
Others							
Urate (mg/dL)	7.00 (6.03, 8.05)	5.90 (4.72, 6.75)	6.20 (5.40, 7.12)	5.02 (4.20, 5.90)	0.22	0.045*	0.082
C-reactive protein (ng/mL)	0.16 (0.03, 0.36)	0.19 (0.08, 0.36)	0.17 (0.06, 0.42)	0.26 (0.10, 0.61)	0.73	0.23	0.32

Table 5. Descriptive and comparative statistics from G3a vs. G1 and G2 stages using a calibrated serum creatinine MDRD-4 eGFR measurement. Hyperfiltrating subjects (> 130 ml/min/1.73m2) are excluded statistics presented as median (IQR) or n (%). Quantitative variables are compared using Wilcoxon rank sum test while for qualitative date Pearson's Chi-squared test are employed. OGTT: oral glucose tolerance test; HbA1c: Hemoglobin A1c; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; HDL: high-density lipoprotein; LDL: low-density lipoprotein; AST (SGPT): Aspartate Aminotransferase, also known as serum glutamic pyruvic transaminase; ALT (SGOT): Alanine Aminotransferase, also known as serum glutamic oxaloacetic transaminase; GGT: Gamma-Glutamyltransferase.

involvement in the population examined. These findings underscore the importance of targeted screening and early intervention to prevent the progression of CKD. Future research should investigate the mechanisms connecting PD to renal dysfunction and evaluate the effectiveness of therapeutic interventions.

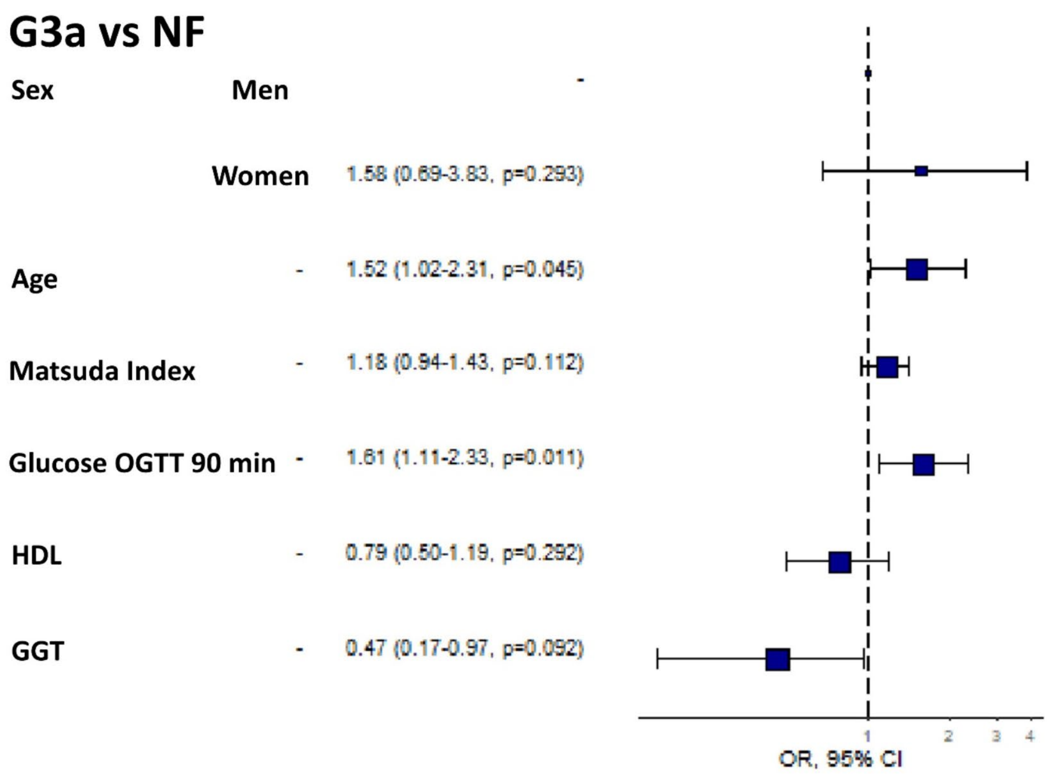

Fig. 3. Odds ratios (95% CI) for major variables between people with hypofiltration versus those without. Quantitative variables are expressed as z-scores. OGTT: Oral Glucose Tolerance Test; HDL: High-Density Lipoprotein; GGT: Gamma-Glutamyltransferase.

Data availability

The data that support the findings of this study are available from ePREDICE Study group but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of ePREDICE Study group (contact person Nisa Boukichou: nisa83_1@hotmail.com).

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Competing interests

The authors declare no competing interests.

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