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Baseline and 4-year associations between prediabetes and kidney impairment: Insights from the ILERVAS cohort

Aitziber Izarra BSc[1,2] | Marcelino Bermúdez-López PhD[3,4,5] | José M. Valdivielso PhD[3,4] | Reinald Pamplona PhD[5] | Gerard Torres PhD[6,7,8] | Dídac Mauricio PhD[9,10] | Eva Castro-Boqué RN[3,4] | Elvira Fernández PhD[3,4] | Rafael Simó PhD[10,11,12] | Cristina Hernández PhD[10,11,12] | Albert Lecube PhD[10,11,12] | on behalf of the ILERVAS project collaborators

[1]University of Lleida, Lleida, Spain

[2]Medical Department, AstraZeneca, Madrid, Spain

[3]Vascular and Renal Translational Research Group, Institute for Research in Biomedicine of Lleida (IRBLleida), Lleida, Spain

[4]Renal Research Network (RICORS2040, ISCIII), Lleida, Spain

[5]Department of Experimental Medicine, Lleida, Spain

[6]Translational Research in Respiratory Medicine, Arnau de Vilanova and Santa Maria University Hospitals, Lleida, Spain

[7]Institute for Research in Biomedicine of Lleida (IRBLleida), Lleida, Spain

[8]CIBER of Respiratory Diseases (CIBERES), Institute of Health Carlos III, Lleida, Spain

[9]Department of Endocrinology and Nutrition, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[10]CIBER of Diabetes and Metabolic Diseases (CIBERDEM), Institute of Health Carlos III, Barcelona, Spain

[11]Department of Endocrinology and Nutrition, University Hospital Vall d'Hebron, Barcelona, Spain

[12]Diabetes and Metabolism Research Group, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain

Correspondence
Cristina Hernández and Albert Lecube, Department of Endocrinology and Nutrition, Vall d'Hebron University Hospital, Passeig Vall d'Hebron 119, 08035 Barcelona, Spain.
Email: albert.lecube@vallhebron.cat and cristina.hernandez@vhir.org

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Abstract

Aims: Prediabetes is a prevalent condition associated with increased cardiovascular and renal risk. However, the long-term impact of haemoglobin A1c (HbA1c) within the range defined as prediabetes on kidney function remains unclear. This study aimed to evaluate the association between prediabetes and renal function (estimated glomerular filtration rate [eGFR] and albuminuria) through cross-sectional and prospective analyses over 4 years in a cohort of individuals with no diagnosis of diabetes or established cardiovascular disease.

Materials and Methods: Analysis using data from 8153 participants in the ILERVAS cohort, a prospective cross-sectional study. Prediabetes was defined as HbA1c 5.7%–6.4% (ADA criteria). Kidney impairment was defined as eGFR <60 mL/min/1.73 m^2 and/or urinary albumin-to-creatinine ratio (ACR) ≥30 mg/g at a single time point. A prospective study was conducted in 3222 participants, who were reassessed after

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4 years. Associations were explored using multivariable regression models adjusted for confounders.

Results: At baseline, prediabetes was associated with higher kidney impairment prevalence (17.8% vs. 13.7%; $p < 0.001$), lower eGFR and increased ACR. Each 1% increase in HbA1c was linked to a 4.6 mL/min/1.73 m^2 decrease in eGFR. Prediabetes remained independently associated with kidney impairment (OR 1.17; 95% CI: 1.03–1.34; $p = 0.020$) and lower eGFR ($\beta = -0.76$; 95% CI: -1.40 to -0.13; $p = 0.019$). At follow-up, prediabetes predicted further eGFR decline, and HbA1c increase was independently associated with eGFR decline.

Conclusions: HbA1c-defined prediabetes is independently associated with early renal impairment and accelerated kidney function decline. These findings support incorporating renal risk assessment in prediabetes and suggest HbA1c as a marker for chronic kidney disease prevention strategies.

KEYWORDS
cohort study, diabetic nephropathy, glycaemic control, observational study, real-world evidence, type 2 diabetes

1 | INTRODUCTION

Prediabetes is a metabolic state that constitutes an intermediate stage between normoglycaemia and type 2 diabetes (T2D). Its diagnosis is based on alterations in glycaemic markers, including fasting plasma glucose (FPG), 2-hour plasma glucose after an oral glucose tolerance test (OGTT), or haemoglobin A1c (HbA1c), according to criteria defined by the American Diabetes Association (ADA),[1] the World Health Organization (WHO), or the International Expert Committee (IEC). However, these definitions differ significantly in cut-off points and emphasis, leading to substantial heterogeneity in reported prevalence and complicating comparisons across populations.[2] For example, applying an HbA1c range of 5.7%–6.4% (ADA) versus 6.0%–6.4% (IEC), or using different FPG thresholds (100 vs. 110 mg/dL), results in different prediabetic populations, each potentially with different risk profiles.[3]

Globally, the prevalence of prediabetes varies widely, from 3.4% to over 37.3%, depending on the population studied and the diagnostic criteria applied.[3,4] Individuals with prediabetes have a higher risk of progressing to type 2 diabetes (T2D) but are also at increased risk for cardiovascular (CV) disease, microvascular complications and possibly chronic kidney disease (CKD).[1,5,6] In fact, several studies have reported associations between prediabetes and early renal abnormalities such as glomerular hyperfiltration and albuminuria.[7–9] Nevertheless, the strength and consistency of this association remain controversial, likely due to differences in study design, population characteristics, duration of follow-up, and, particularly, the diagnostic criteria used for defining both prediabetes and CKD.[10,11]

Moreover, most available evidence is cross-sectional or short-term investigations. Only a few large, prospective cohort studies have specifically evaluated the long-term impact of prediabetes (particularly as defined by HbA1c) on renal outcomes. For example, in a 9-year prospective cohort study, participants with prediabetes had a higher risk of incident CKD compared with those with normoglycaemia (hazard ratio [HR] 1.39, 95% confidence interval [CI] 1.21–1.60, $p < 0.001$).[12] In addition, in a subcohort of the Chinese REACTION study including individuals with prediabetes, 6.4% developed CKD over 3.6 years of follow-up, and a urinary albumin-to-creatinine ratio (ACR) threshold of 7.54 mg/g was proposed as an effective tool to identify individuals al risk.[13] By contrast, the Chronic Renal Insufficiency Cohort (CRIC) study found no significant association between prediabetes and composite renal endpoints, although an increased risk of proteinuria progression was reported.[14] These inconsistencies underscore the need for well-designed, longitudinal studies using harmonized definitions and studying diverse, well-characterized populations.

It is also important to note that CKD and CV disease are closely associated, with CKD being both a risk factor for and a frequent outcome of CV disease.[15,16] Thus, most guidelines consider CKD an independent risk factor for CV events and mortality, and conversely, individuals with CV disease frequently present with impaired renal function.[17] Given this strong interplay, it is crucial to account for CV risk factors when studying the association between prediabetes and CKD to avoid confounding.

In this context, the aim of this study was to bridge these gaps by evaluating the association between prediabetes (as defined by ADA HbA1c criteria) and renal function, using both cross-sectional and prospective analyses over 4 years, in a large European cohort of over 8000 individuals aged 45–70 years with no diabetes and/or established CV disease. Unlike most previous studies, this analysis provides a detailed assessment of early renal alterations (albuminuria and estimated glomerular filtration rate, eGFR) and their longitudinal evolution. By comprehensively characterizing these outcomes over an extended follow-up period, the findings provide new evidence that helps clarify the long-term kidney-related consequences of prediabetes in real-world populations, and may inform risk stratification and preventive strategies.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This is an exploratory analysis based on data from the ILERVAS project (ClinTrials.gov Identifier: NCT03228459), a prospective, multicentre, longitudinal study conducted in primary care centres across the province of Lleida (Catalonia, Spain) between 2015 and 2017. The primary aim of the ILERVAS project was to determine the prevalence of subclinical atheromatous disease and hidden CKD among a population at low to moderate CV risk.[18] For this study, we retrospectively analysed baseline data from 8153 participants (cross-sectional study). After completion of the initial recruitment, a representative subsample of participants was invited to undergo a second evaluation approximately 4 years later. For this longitudinal component, entry time was defined as the date of the baseline ILERVAS visit and exit time as the date of the 4-year follow-up visit, when eGFR and ACR were reassessed. Consequently, 3222 participants with both baseline and follow-up data were included in the prospective observational study.

The study protocol was approved by the Ethics Committee of Arnau de Vilanova University Hospital (First visit: CEIC-1410, 19/12/2014; Follow-up: CEIC-2015, 20/12/2018), and all participants provided informed consent. The study complied with the Declaration of Helsinki, International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices, Good Clinical Practice guidelines and all applicable local regulations.

Inclusion criteria were: (i) aged 45–70 years; (ii) no history of CV disease; and (iii) presence of at least one CV risk factor (dyslipidaemia, hypertension, obesity, current smoking, or first-degree relative with premature CV disease [<55 years in men or <65 in women]). Exclusion criteria comprised: (i) known diabetes mellitus; (ii) known CKD; (iii) active cancer; (iv) life expectancy <18 months; and (v) pregnancy. Information on both inclusion and exclusion criteria was obtained during the recruitment period from electronic health records using International Classification of Diseases, 10th Revision (ICD-10) codes, complemented by clinical records and/or patient report (Table S1). Clinical data on prior diagnoses were obtained from the *Information System for the Development of Research in Primary Care* (SIDIAP), which contains anonymized, longitudinal data from the *Catalan Health Institute* coded according to ICD-10. Microalbuminuria detected at baseline screening was not an exclusion criterion.

2.2 | Outcomes

Information regarding demographic characteristics, comorbidities, and current smoking habits was collected from patients' electronic medical records. Renal function was assessed using fasting spot urine samples and dried blood spot capillary samples. Albuminuria was measured using Clinitek Microalbumin 2 Reagent Strips and the Siemens Clinitek Status® analyser. Serum creatinine (mg/dL) was determined via dried blood testing, and albumin-to-creatinine ratio (ACR, mg/g) was calculated. Participants were categorized by ACR into three groups: <30 mg/g, 30–300 mg/g and >300 mg/g.[19] In addition, eGFR was estimated using the creatinine-based CKD-EPI 2009 equation, which accounts for age, sex and race.[20] Kidney function was categorized according to KDIGO thresholds for eGFR and albuminuria (eGFR <60 mL/min/1.73 m^2 and/or ACR ≥30 mg/g).[19] However, because eGFR and ACR were measured only once at each visit, we could not confirm persistence of these abnormalities for ≥3 months as required for a formal CKD diagnosis. Therefore, in the cross-sectional analyses we use the term 'kidney impairment' to refer to eGFR <60 mL/min/1.73 m^2 and/or ACR ≥30 mg/g at a single time point, rather than clinically confirmed CKD.

2.3 | Exposure

The main exposure was glycaemic status assessed by HbA1c. Glycaemic status was defined according to American Diabetes Association criteria as normoglycaemia (HbA1c <5.7% [<39 mmol/mol]) or prediabetes (HbA1c 5.7%–6.4% [39–47 mmol/mol]).[21] HbA1c was also analysed as a continuous variable within the range observed in our study population to explore dose–response associations with renal outcomes.

2.4 | Anthropometric data

Participants were measured barefoot and wearing minimal clothing. Weight and height were recorded using calibrated instruments (precision: 0.5 kg and 1.0 cm). Measurements were performed by trained nurses following standardized procedures; intrarater relative technical error was <1%. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2), and obesity was defined as BMI ≥30 kg/m^2.[22] In addition, total body fat percentage was estimated using the Clínica Universidad de Navarra Body Adiposity Estimator (CUN-BAE) formula.[23]

2.5 | Endpoints

The primary objective was to evaluate whether prediabetes was independently associated with increased ACR, decreased eGFR and/or presence of CKD. Secondary objectives were: (i) to evaluate the association between HbA1c levels and renal function parameters (eGFR and ACR), including CKD prognosis categories; and (ii) to examine the association between baseline HbA1c levels and kidney function at the 4-year follow-up.

2.6 | Statistical methods

Descriptive statistics are used to summarize demographic and clinical variables. Categorical variables are presented as absolute frequencies and percentages, while continuous variables are presented as means ± standard deviation (SD) or medians (interquartile range, IQR). Participants with missing eGFR or ACR data, or with previously undiagnosed diabetes, were excluded from the analysis (the participant selection flowchart is shown in Figure S1). A complete-case analysis without multiple imputation was performed. In the cross-sectional analyses, key variables (prediabetes, HbA1c, ACR and eGFR) had no missing data, and all other baseline covariates had ≤0.1% of missing values; given this negligible proportion of missing data, multiple imputation was not considered necessary.

Comparisons between groups were conducted using the Chi-square test for categorical variables. The Shapiro–Wilk test assessed normality of continuous variables. Depending on distribution and group number, the Student's *t* test or ANOVA were used for normally distributed data, and the Mann–Whitney *U* or Kruskal–Wallis test for non-normally distributed data.

Associations between glycaemic status and renal function and damage were evaluated using Pearson's correlation coefficients and univariate linear regression. To further explore independent associations, binary outcomes (kidney impairment [yes/no]; urinary ACR ≥30 mg/g [yes/no]) were analysed using logistic regression, while eGFR and 4-year change in eGFR were modelled using linear regression. The initial set of candidate predictors includes age, sex, hypertension, dyslipidaemia, current smoking, prediabetes, obesity, CUN-BAE and the use of statins and renin–angiotensin–aldosterone system (RAAS) inhibitors. In addition, baseline urinary ACR and eGFR were included as covariates in the corresponding models when indicated. In an exploratory analysis, we also evaluated the association of baseline HbA1c and 4-year changes in HbA1c with changes in eGFR during the follow-up period. Collinearity among covariates was assessed using the variance inflation factor (VIF), with VIF >5 considered indicative of problematic collinearity (Table S2).

In addition to the prespecified adjusted models (Model 1, fully adjusted, conventional regression) (Table S3) we applied the Least Absolute Shrinkage and Selection Operator (LASSO) method to the full candidate set of predictors for each outcome. This approach shrinks regression coefficients and performs variable selection, thereby reducing the potential impact of multicollinearity and overfitting and allowing us to assess the robustness of the associations observed in the conventional models. The optimal penalization parameter (lambda.min) was selected via a 10-fold cross-validation approach in all LASSO models. Variables retained by LASSO (non-zero coefficients) were then refitted into conventional linear or logistic regression models, as appropriate, to estimate effect sizes (regression coefficients or odds ratios [OR] with their 95% confidence intervals [CI]) and *p*-values (Model 2, fully adjusted, LASSO-based). Graphical representations of the LASSO coefficient trajectories for each outcome are provided in Figure S2.

All tests were two-sided; *p*-values <0.05 were considered statistically significant. Analyses were conducted using R version 4.4.1 (R Core Team, 2024), with the 'glmnet' package used for LASSO regression modelling.

3 | RESULTS

3.1 | Baseline clinical characteristics of participants

The study cohorts included 8153 participants in the cross-sectional study, of whom 1228 (15.1%) met the criteria for kidney impairment (eGFR <60 mL/min/1.73 m^2 and/or ACR ≥30 mg/g). Table 1 summarizes the main clinical and metabolic characteristics of the participants, stratified by the presence or absence of kidney impairment. Individuals with kidney impairment were predominantly women and presented a more adverse CV risk profile, including older age and higher prevalence of hypertension and obesity, compared to those without kidney impairment. Moreover, participants with kidney impairment had significantly higher BMI and total body fat percentage. Furthermore, the prevalence of kidney impairment was also greater in participants with prediabetes than in those with normoglycaemia (17.8% vs. 13.7%, $p < 0.001$).

3.2 | Association between glycaemic status and renal outcomes

An inverse correlation was found between eGFR and HbA1c levels ($r = -0.109$; $p < 0.001$). Specifically, each 1 percentage-point increase in HbA1c was associated with a 4.637 mL/min/1.73 m^2 decrease in eGFR (Figure 1A). Conversely, a positive association was observed between HbA1c levels and ACR categories, with the highest HbA1c observed in the group with ACR >300 mg/g ($p = 0.009$). In line with these findings, HbA1c levels increased slightly but progressively across KDIGO risk categories, with individuals in the high or very high-risk categories showing the highest median HbA1c values compared to those in the low and moderately increased risk groups. On average, HbA1c levels increased by 0.04% (95% CI: 0.02–0.06) with each successive CKD risk category (Figure 1B).

3.3 | Analysis of potential predictors of kidney impairment, albuminuria and eGFR decline

Prediabetes was independently associated with lower eGFR (estimate = −0.76; 95% CI −1.40 to −0.13, $p = 0.019$), together with older age, obesity, and RAAS inhibitors use. In contrast, current smoking was independently associated with higher eGFR (Table 2).

TABLE 1 Main clinical and metabolic data of the ILERVAS cohort according to the presence of kidney impairment.

	No kidney impairment (*n* = 6925)	Kidney impairment (*n* = 1228)	*p*-value
Women, *n* (%)	3416 (49.3)	721 (58.7)	<0.001
Age (years old)	57.0 [52.0–62.0]	59.0 [53.0–64.0]	<0.001
Current smoking habit, *n* (%)	2048 (29.6)	357 (29.1)	0.748
High blood pressure, *n* (%)	2629 (38.0)	619 (50.4)	<0.001
Pulse pressure (mmHg)	47.0 [41.0–56.0]	50.0 [42.0–60.0]	<0.001
Dyslipidaemia, *n* (%)	3569 (51.5)	632 (51.5)	0.988
Total cholesterol (mg/dL)	204 [180–229]	204 [179–231]	0.920
Obesity, *n* (%)	2480 (35.8)	516 (42.1)	<0.001
Body mass index (kg/m^2)	28.3 [25.5–31.6]	29.0 [25.8–32.4]	<0.001
CUN-BAE (%)	35.6 [29.8–42.1]	38.0 [32.1–43.7]	<0.001
HbA1c (%)	5.50 [5.30–5.70]	5.50 [5.30–5.80]	<0.001
Prediabetes, *n* (%)	2238 (32.3)	484 (39.4)	<0.001
Statin use, *n* (%)	1097 (15.8)	240 (19.5)	0.001
RAAS inhibitors use, *n* (%)	1644 (23.7)	387 (31.5)	<0.001

Note: Numerical variables summarized with median [Q1–Q3]. *p*-values from the Mann–Whitney test. *p*-values of categorical variables from the Chi-square test. Impaired kidney is defined as GFR <60 mL/min/1.73 m^2 and/or ACR ≥30 mg/g at a single time point.
Abbreviations: CUN-BAE, Clínica Universidad de Navarra Body Adiposity Estimator; RAAS, renin–angiotensin–aldosterone system.

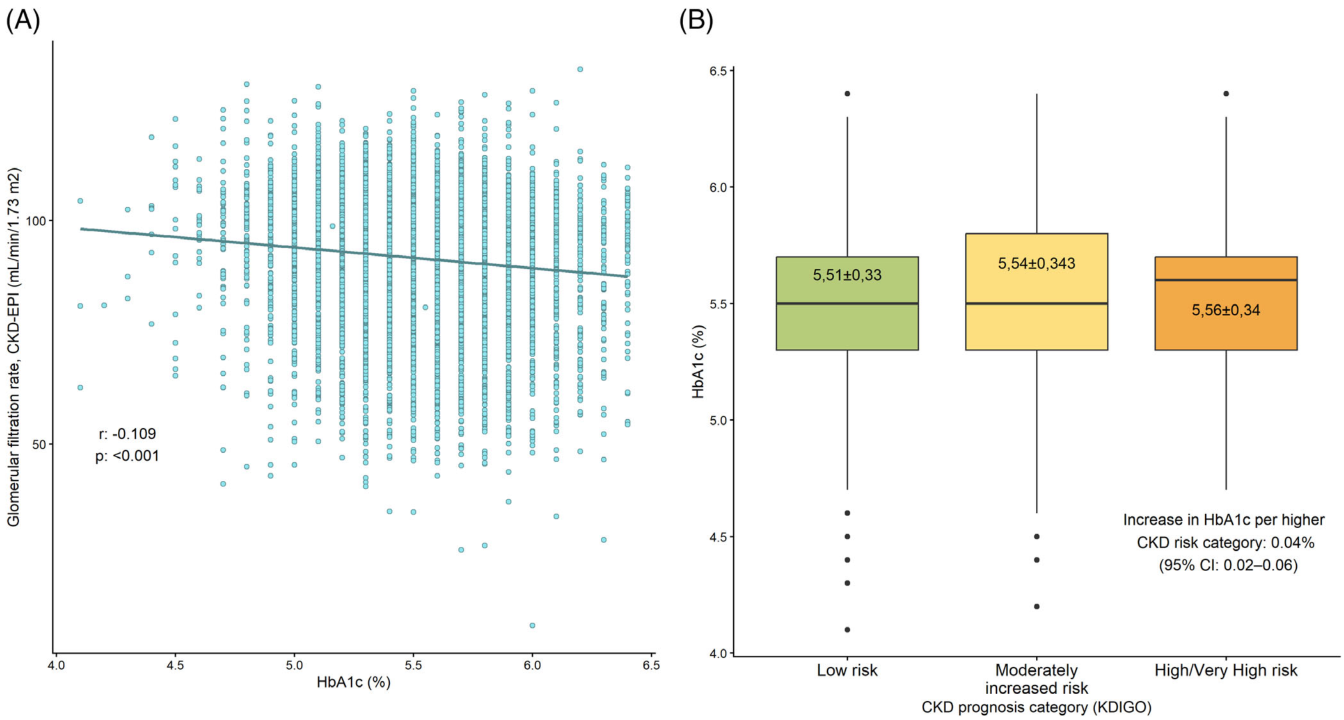

FIGURE 1 Association between HbA1c levels and eGFR and KDIGO risk categories. (A) Scatter plots showing the association between HbA1c (%) levels and eGFR. Pearson correlation coefficients (*r*) and *p* values are indicated. The lines represent fitted univariate linear regressions. (B) Box plot showing the distribution of HbA1c (%) levels in the three different CKD prognosis categories (low risk, moderately increased risk and high/very high risk). The box plot shows the median and Q1–Q3, and the whiskers denote lowest and highest values. Outliers are shown as individual points. Risk categorization is based on single eGFR and/or urinary albumin-to-creatinine ratio measurements.

TABLE 2 Multivariable regression models (fully adjusted–LASSO penalized) for estimated glomerular filtration rate (A), impaired kidney function (B) and elevated urinary albumin-to-creatinine ratio (C).

	Regression coefficient	CI lower	CI upper	*p*-value
(A) eGFR				
Age (years)	−0.68	−0.74	−0.63	<0.001
Sex (female)	−0.11	−0.74	0.53	0.742
Hypertension	−0.81	−1.60	0.03	0.058
Dyslipidaemia	−0.53	−1.20	0.11	0.104
Current smoking	1.30	0.60	2.00	<0.001
Prediabetes	−0.76	−1.40	−0.13	0.019
Obesity	−0.89	−1.50	−0.27	0.005
Statin use	−0.08	−0.94	0.78	0.858
RAAS inhibitors use	−1.30	−2.20	−0.40	0.005
Urinary ACR ≥30 mg/g	−0.54	−1.40	0.34	0.231
	Odds ratio	**CI lower**	**CI upper**	***p*-value**
(B) Impaired kidney function				
Sex (female)	1.32	1.16	1.50	<0.001
Hypertension	1.44	1.26	1.64	<0.001
Dyslipidaemia	0.95	0.83	1.09	0.490
Current smoking	1.32	1.14	1.53	<0.001
Prediabetes	1.17	1.03	1.34	0.020
Obesity	1.15	1.01	1.31	0.038
Statin use	1.18	0.99	1.41	0.067
eGFR (mL/min/1.73 m^2)	0.97	0.96	0.97	<0.001
	Regression coefficient	**CI lower**	**CI upper**	***p*-value**
(C) Urinary ACR ≥30 mg/g				
Age (years)	1.00	0.99	1.02	0.447
Sex (female)	1.33	1.15	1.53	<0.001
Hypertension	1.56	1.35	1.79	<0.001
Dyslipidaemia	0.93	0.81	1.08	0.370
Current smoking	1.31	1.12	1.52	<0.001
Prediabetes	1.14	0.99	1.31	0.068
Obesity	1.13	0.98	1.29	0.090
Statin use	1.31	1.09	1.57	0.004
eGFR (mL/min/1.73 m^2)	1.00	0.99	1.00	0.254

Note: Linear regression for eGFR (A). Logistic regression for kidney impairment (B) and urinary ACR≥30 mg/g (C). Impaired kidney function is defined as eGFR <60 mL/min/1.73 m^2 and/or ACR ≥30 mg/g obtained by a single measurement; therefore, these analyses cannot establish the ≥3-month persistence required by KDIGO for CKD diagnosis. For impaired kidney function, age, RAAS inhibitor use, and urinary ACR were not retained in the LASSO-based variable selection and were therefore not included in the final model; for urinary ACR ≥30 mg/g, RAAS inhibitor use was not retained and was therefore not included in the final model.
Abbreviations: ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; RAAS, renin–angiotensin–aldosterone system.

In addition, prediabetes was independently associated with increased risk of kidney impairment (OR = 1.17; 95% CI 1.03–1.34, $p = 0.020$), together with female sex, hypertension, current smoking habit and obesity (Table 2).

Sex (female), hypertension, current smoking habit and statin use were independently associated with ACR, whereas prediabetes showed only a marginal association (OR = 1.14; 95% CI 0.99–1.31, $p = 0.068$) (Table 2).

3.4 | Four-year longitudinal analysis of glycaemic status and renal function

Participants who completed and those who did not complete the 4-year reassessment had broadly similar baseline characteristics (Table S4). Prediabetes status at baseline was associated with significantly lower eGFR at the 4-year follow-up (Figure 2A). In line with this, baseline HbA1c levels were negatively correlated with eGFR at follow-up ($r = -0.083$; $p < 0.001$; Figure 2B), and the change in HbA1c over time was negatively correlated with the change in eGFR ($r = -0.100$; $p < 0.001$; Figure 2C). Specifically, a 1 percentage-point increase in baseline HbA1c was associated with a 3.80 mL/min/1.73 m^2 decrease in eGFR at the 4-year follow up (95% CI −5.38 to −2.22). Similarly, a 1 percentage-point increase in HbA1c over time was associated with a 4.12 mL/min/1.73 m^2 reduction in the change in eGFR over the follow-up period. Importantly, the change in HbA1c over time was independently associated with the change in eGFR (estimate = −4.0; 95% CI: −5.5 to −2.6; $p < 0.001$), together with female sex and urinary ACR (Table 3).

4 | DISCUSSION

In this large population-based study, we show that prediabetes is independently associated with reduced eGFR and increased risk of kidney impairment, even after adjusting for major CV and metabolic risk factors. This cohort included a rigorously phenotyped, European population aged 45–70 years, mainly free from known kidney and CV disease, which reinforces the importance of identifying early renal impairment. Although the association between overt diabetes and

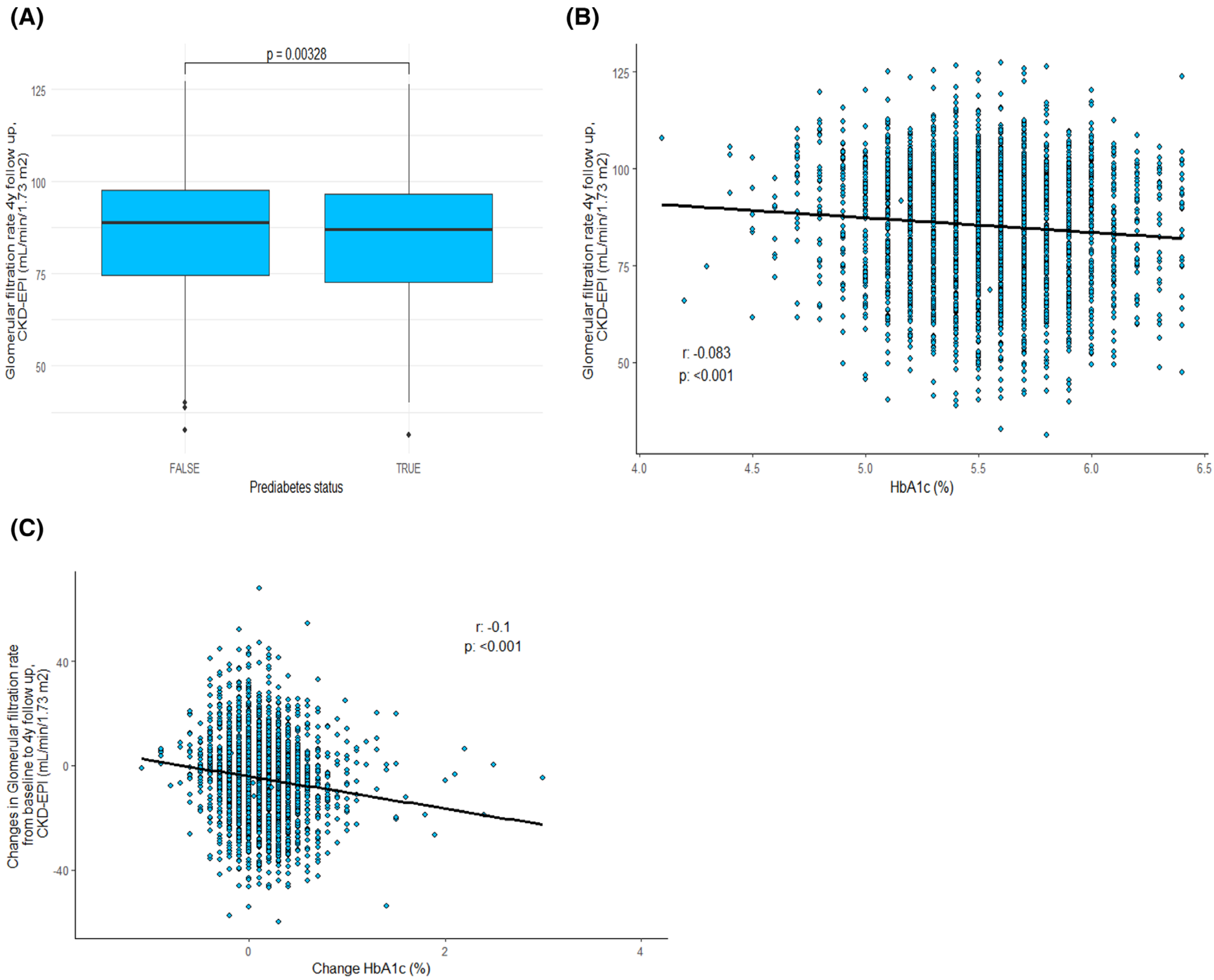

FIGURE 2 Association between baseline prediabetes and HbA1c levels and eGFR at the 4-year follow-up. (A) Box plot showing the eGFR distribution in participants with and without prediabetes. The box plot shows the median and Q1–Q3, and the whiskers denote the lowest and highest values. Outliers are shown as individual points. (B) Scatter plots showing the association between baseline HbA1c (%) levels and eGFR at the 4-year follow-up and (C) the association between change in HbA1c (%) levels and change in eGFR. Pearson correlation coefficients and *p* values are indicated. The lines represent fitted univariate linear regressions.

TABLE 3 Multivariable linear regression model for the change in glomerular filtration rate during the 4-year follow-up.

	Odds ratio	CI lower	CI upper	*p*-value
Age (years)	−0.08	−0.17	0.01	0.071
Sex (female)	−1.90	−3.00	−0.85	<0.001
Dyslipidaemia	−0.33	−1.40	0.76	0.551
Prediabetes	0.63	−0.46	1.70	0.257
Obesity	1.30	0.25	2.30	0.015
Statin use	−1.30	−2.70	0.11	0.070
RAAS inhibitors use	−1.10	−2.30	0.10	0.071
Urinary ACR ≥30 mg/g	−1.50	−3.00	−0.03	0.046
Change in HbA1c (%)	−4.00	−5.50	−2.60	<0.001

Note: Hypertension, current smoking and baseline eGFR were not retained in the LASSO-based variable selection and were therefore not included in the final model.

Abbreviations: ACR, albumin-to-creatinine ratio; RAAS, renin–angiotensin–aldosterone system.

kidney disease is well established, the present study supports a progressive increase in HbA1c across CKD risk strata, highlighting that even early dysglycaemia can have a detrimental impact on renal function. This underscores the importance of identifying and monitoring individuals with prediabetes.

CKD is an increasingly prevalent condition that affects more than 10% of the general population worldwide.[24] This progressive decline in renal function is associated with multiple comorbidities and reduces patients' quality of life and life expectancy.[25–27] Although there is robust evidence supporting the impact of T2D on the course and progression of CKD, the role of prediabetes in this condition is less well understood.[10] The present study finds a prevalence of kidney impairment in prediabetes of 17.8%, nearly 4 points higher than in non-prediabetic participants, supporting the independent contribution of this early stage of dysglycaemia to established risk factors such as older age, female sex, hypertension and smoking habit.[24] These findings are consistent with US data from the National Health and Nutrition Examination Survey (1999–2006, $n = 8188$), showing a CKD prevalence of 17.7% in prediabetes, as well as with a recent Iranian cohort study (2016–2022, $n = 3642$), which found a CKD prevalence among prediabetic individuals of 16.5%.[28,29]

However, the strength and consistency of this association remain controversial, likely due to differences in study design, population characteristics, duration of follow-up, and, particularly, the diagnostic criteria used for defining both prediabetes and CKD.[7,10,11] It is important to note that the use of HbA1c as a standalone criterion for prediabetes, as applied in the present study, may capture individuals with more prolonged or higher chronic glycaemic exposure, and thus potentially at higher renal risk, an aspect previously highlighted.[12,21] For example, the present study shows that, at baseline, prediabetes has a negative effect on eGFR values, which appear lower and may exceed the 'hyperfiltration' stage. In contrast, a recent study in an Indian working-age population ($n = 1031$, 59.4% men, 30–70 years) recruited from occupational health check-ups reported a higher prevalence of glomerular hyperfiltration among individuals with prediabetes and diabetes versus normoglycaemic individuals, with no significant differences between the prediabetic and diabetic groups; albuminuria, however, was only elevated in diabetes.[30] Similarly, in 5003 people aged 35–69 who participated in the Shizuoka part of the Japan Multi-Institutional Collaborative Cohort (J-MICC), the prevalence of hyperfiltration increased in subjects with FPG >100 mg/dL as well as HbA1c >5.7% compared to controls, suggesting that both glycaemic markers play a role in the development of hyperfiltration, observed at all stages of CKD.[31] These discrepancies may stem from the heterogeneous definition of prediabetes across studies, particularly regarding HbA1c versus FPG or the OGTT as diagnostic tools, each of which may identify subpopulations with different risk profiles for renal impairment.[21,32]

Regarding the impact of the prediabetes stage on future renal decline, a systematic review and meta-analysis of nine cohort studies ($n = 185\,452$, mostly Asian and white participants, 835 146 person-years in total) found that prediabetes, when defined by FPG, was only modestly associated with increased CKD risk (relative risk 1.12, 95% CI 1.02–1.21).[11] The present study adds new prospective data: an increase in HbA1c over the 4-year follow-up period was independently associated with a decline in eGFR. Notably, in multivariable models, each 1% increase in HbA1c over time was associated with a 4.14 mL/min/1.73 m^2 reduction in eGFR, independent of baseline risk factors. In addition, participants who completed the 4-year reassessment were broadly similar at baseline to those who did not, with only a modest overrepresentation of current smokers and a slightly lower prevalence of dyslipidaemia, suggesting that selection bias in these longitudinal estimates is likely to be limited. In patients with T2D, higher baseline HbA1c resulted in greater annual eGFR decline in a retrospective cohort ($n = 1699$, over 4 years): −1.89, −1.29 and −0.68 mL/min/1.73 m^2/year for baseline HbA1C >9, 7 to ≤9 and ≤7%, respectively.[33] As in the baseline studies, the diagnostic approach to the prediabetes stage, definition of kidney dysfunction, and population characteristics all influence the strength of the observed association. In a Norwegian cohort ($n = 1261$, aged 50–62) which used measured GFR (mGFR) rather than estimated GFR, prediabetes was independently associated with glomerular hyperfiltration (mGFR >90th percentile; OR 1.95, 95% CI 1.20–3.17) and high-normal ACR (>10 mg/g; 1.83, 95% CI 1.04–3.22) after a median 5.6-year follow-up period.[34] Similarly, a prospective cohort of 7728 Korean adults free from CKD and diabetes at baseline found that only HbA1c- or impaired glucose tolerance (IGT)-defined prediabetes, but not impaired fasting glucose, predicted incident CKD (eGFR < 60 mL/min/1.73m^2) over 8.7 years, after adjusting for risk factors (HbA1c HR = 1.391, 95% CI 1.213–1.595, $p < 0.001$; IGT HR = 1.135, 95% CI 1.182–1.310, $p = 0.043$, compared with the non-prediabetic group).[12]

Insulin resistance and β-cell dysfunction are major mechanisms underlying the adverse impact of early dysglycaemia on kidney function.[35] Insulin resistance impairs renal vasculature, podocyte viability, and tubular function, and activates the RAAS, contributing to renal damage through glomerular hypertension, inflammation and fibrosis.[36–38] Hyperglycaemia additionally promotes metabolic pathways, such as activation of the polyol pathway, increased generation of reactive oxygen species and inflammation, which damage critical renal cells and the glomerular filtration barrier.[38–40] The accumulation of advanced glycation end-products further thickens the glomerular basement membrane and increases matrix deposition.[41–44] This sequence of haemodynamic and structural alterations may help to explain the dissociation observed in the present study, where prediabetes was associated with reduced eGFR but not with significant albuminuria, suggesting that modest functional decline can precede overt albuminuria in some individuals. Similar findings have been reported by others, reinforcing the concept that mechanisms primarily linked to insulin resistance (e.g., proinflammatory cytokines, oxidative stress, RAAS activation) may have an earlier and stronger impact on glomerular filtration than on overt structural damage to the glomerular barrier, which appears to depend more on sustained hyperglycaemia and its downstream metabolic pathways.[30,34] Together, these mechanisms interact to promote an early, and in some cases predominantly non-albuminuric, phenotype of kidney impairment, even at prediabetic stages.[45,46] In addition, in our cohort the overall burden of albuminuria was relatively low and ACR was assessed from a single spot urine sample at each visit, which may have reduced the power to detect modest associations with ACR compared with eGFR.

Interestingly, current smoking was independently associated with a higher eGFR, while at the same time conferring an increased risk of elevated ACR and kidney CKD. This apparently paradoxical pattern is compatible with smoking-induced glomerular hyperfiltration in the early stages of kidney damage, as previously reported in cohorts without baseline renal disease, where current smokers showed a higher incidence of hyperfiltration, proteinuria, and higher eGFR than nonsmokers.[47,48] In our cohort, current smoking was associated with a 1.3 mL/min/1.73 m^2 higher eGFR, which should not be interpreted as a renal benefit of smoking but rather as an early hemodynamic change that may precede and contribute to subsequent albuminuria and CKD. Consistently, current smoking was also associated with higher ACR and a higher prevalence of kidney impairment, supporting an overall adverse renal profile related to smoking in this population.

This study has limitations that must be considered, some shared with prior studies. First, the duration of prediabetes prior to inclusion, as well as the potential presence of concomitant renal damage, was unknown, which could affect the magnitude of the observed associations. In addition, prediabetes was defined solely on the basis of the ADA HbA1c criteria, measured with a point-of-care device in the mobile examination unit, which may limit extrapolation to other prediabetes definitions and could lead to under- or over-diagnosis of prediabetes in some ethnic or haematological subgroups.[1] As a result, we could not perform sensitivity analyses using FPG- or IGT-based criteria. Future studies specifically designed to collect these glycaemic measurements are needed to directly compare different prediabetes definitions in relation to early kidney impairment and CKD. Second, information on non-steroidal anti-inflammatory drug (NSAID) use or inflammatory markers was not available, so residual confounding by nephrotoxic medications or inflammation-related effects cannot be excluded. Third, the association between changes in HbA1c and 4-year eGFR decline was modelled assuming linearity. Although visual inspection of the data did not suggest major deviations from a linear pattern, we cannot exclude more complex dose–response relationships that might be captured by spline-based or generalized additive models. Fourth, participants typically presented one or more cardiometabolic risk factors, so findings may not be generalized to healthy prediabetic populations. Moreover, total body fat was estimated using the CUN-BAE equation rather than direct measurement methods such as dual-energy x-ray absorptiometry or bioelectrical impedance analysis, which may have introduced some degree of misclassification.[22] Finally, kidney dysfunction was identified by a single eGFR and ACR measurement, with no confirmatory follow-up, which may lead to an overestimation of CKD prevalence at a single time point. Therefore, our cross-sectional estimates should be interpreted as kidney impairment at a single time point rather than clinically confirmed CKD. Nonetheless, the study has notable strengths: the large cohort size enhances statistical power and robustness; strict selection criteria minimized bias by excluding participants with known diabetes, CKD, or advanced CV disease; and detailed adjustment for key CKD risk factors improves the internal validity and supports the interpretation of associations as relevant for primary prevention.

In conclusion, the findings indicate that prediabetes is independently associated with both cross-sectional and longitudinal declines in renal function, as well as higher CKD risk, and that elevated HbA1c has a quantifiable impact on renal decline over 4 years. Therefore, early detection of HbA1c-defined prediabetes may be fundamental for CKD prevention, and HbA1c itself could serve as a marker of renal risk, beyond its established role in diabetes risk stratification. Future studies are warranted to determine whether early intervention in this population can effectively halt CKD progression.

AUTHOR CONTRIBUTIONS

Design: Aitziber Izarra, Marcelino Bermúdez-López, José M. Valdivielso, Rafael Simó, Cristina Hernández, Albert Lecube; *Conduct/data collection*: Aitziber Izarra, Marcelino Bermúdez-López, José M. Valdivielso, Reinald Pamplona, Gerard Torres, Dídac Mauricio, Eva Castro-Boqué, Elvira Fernández, Albert Lecube; *Analysis*: Aitziber Izarra, Rafael Simó, Cristina Hernández, Albert Lecube; *Writing manuscript*: Aitziber Izarra, Rafael Simó, Cristina Hernández, Albert Lecube.

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CONFLICT OF INTEREST STATEMENT

Aitziber Izarra is an employee of AstraZeneca and holds stocks in the company. Aitziber Izarra is a PhD student, and this work is included in her overall research.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70560.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Dídac Mauricio https://orcid.org/0000-0002-2868-0250
Rafael Simó https://orcid.org/0000-0003-0475-3096
Albert Lecube https://orcid.org/0000-0001-9684-0183

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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