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RESEARCH ARTICLE

Trajectories of renal biomarkers and new-onset heart failure in the general population: Findings from the PREVEND study

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Aims Renal dysfunction is one of the most critical risk factors for developing heart failure (HF). However, the association between repeated measures of renal function and incident HF remains unclear. Therefore, this study investigated the longitudinal trajectories of urinary albumin excretion (UAE) and serum creatinine and their association with new-onset HF and all-cause mortality.

Methods and results Using group-based trajectory analysis, we estimated trajectories of UAE and serum creatinine in 6881 participants from the Prevention of Renal and Vascular End-stage Disease (PREVEND) study and their association with new-onset HF and all-cause death during the 11-years of follow-up. Most participants had stable low UAE or serum creatinine. Participants with persistently higher UAE or serum creatinine were older, more often men, and more often had comorbidities, such as diabetes, a previous myocardial infarction or dyslipidaemia. Participants with persistently high UAE had a higher risk of new-onset HF or all-cause mortality, whereas stable serum creatinine trajectories showed a linear association for new-onset HF and no association with all-cause mortality.

Conclusion Our population-based study identified different but often stable longitudinal patterns of UAE and serum creatinine. Patients with persistently worse renal function, such as higher UAE or serum creatinine, were at a higher risk of HF or mortality.

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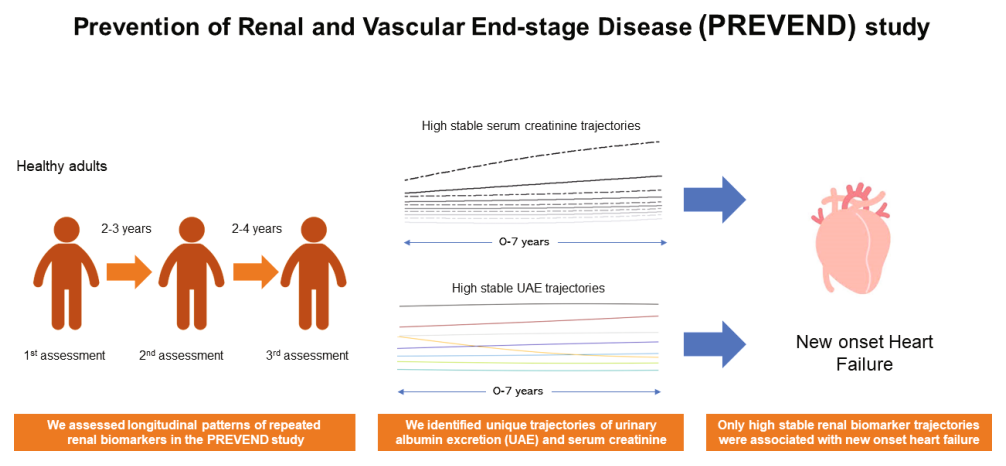
Graphical Abstract



In the PREVEND study, distinct temporal patterns of renal biomarkers among European adults were identified. High urinary albumin excretion (UAE) or creatinine levels, often stable over time, were associated with new-onset heart failure.

Keywords Urinary albumin excretion • Serum creatinine • Longitudinal trajectory of renal biomarkers • New-onset heart failure • Cardio-renal interactions • Microalbuminuria

Introduction

One in five men and women will develop heart failure (HF) during their lifetime.[1–6] While progress has been made in treating HF, prognosis remains poor, with nearly half of patients dying within 5 years.[7] Therefore, primary prevention of HF is critical.

Substantial evidence supports the association between renal dysfunction and major cardiovascular disease,[8] including new-onset HF.[9–11] Previous reports showed the association of biomarkers reflecting renal dysfunction, such as urinary albumin excretion (UAE), serum creatinine and cystatin C, with incident HF.[10,12] However, how longitudinal changes in renal biomarkers are associated with incident HF or mortality remain unclear.[13–15]

The Prevention of Renal and Vascular End-stage Disease (PREVEND) study was designed to assess the prevalence of microalbuminuria and its association with new-onset cardiovascular disease in the population.[16] We hypothesized that longitudinal patterns of UAE and creatinine were associated with new-onset HF or all-cause mortality in the general population. Therefore, this study estimated possible causal trajectories of creatinine and UAE and their association with incident HF.

Methods

Study population

This study was performed using data from the PREVEND study. The PREVEND study recruited the general Dutch population in the North of the Netherlands aged 28–75 years during a baseline visit in 1997–1998.[10,16] For this study; we included 6904 participants from the original 8592 participants based on the availability of either UAE or creatinine at baseline and during at least one follow-up visit. We excluded 23 participants who had HF at baseline. Thus, 6881 individuals were included in recent analyses ($n = 6799$ for UAE, 6841 for serum creatinine, and 6737 for a combination of UAE/serum creatinine). The PREVEND study was approved by the institutional medical Ethics Committee and conducted as per the Declaration of Helsinki. All subjects provided written informed consent.

Definitions

Participants were asked to collect two consecutive 24 h urine samples for baseline, second, and third screenings of UAE, of which we took the mean. Urinary albumin concentration was determined by nephelometry, with a threshold of 2.3 mg/L and intra- and inter-assay coefficients of variation of 2.2% and 2.6%, respectively (BNII, Dade Behring Diagnostics, Marburg, Germany). Serum creatinine was measured by dry chemistry (Eastman Kodak, Rochester, NY, USA), with an intra-assay coefficient of variation of 0.9% and an inter-assay coefficient of variation of 2.9%. We analysed UAE and creatinine measurements at baseline and during two follow-up visits at 3–4 years and 6–7 years after baseline.

Systolic and diastolic blood pressures were calculated as the mean of the last two measurements of the two visits using an automatic Dinamap XL Model 9300 series device. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or self-reported use of antihypertensive medication. Body mass index was calculated as the weight to height squared (kg/m^2) ratio. Dyslipidaemia was defined as total serum

cholesterol ≥6.5 mmol/L (251 mg/dl) or serum cholesterol ≥5.0 mmol/L (193 mg/dl) if a history of myocardial infarction was present or when lipid-lowering medication was used. Statin use was defined by self-report. Type 2 diabetes was defined as fasting plasma glucose ≥7.0 mmol/L (126 mg/dl), non-fasting plasma glucose ≥11.1 mmol/L or use of anti-diabetic drugs. Plasma glucose and serum cholesterol were determined by Kodak Ektachem dry chemistry (Eastman Kodak). High-sensitivity C-reactive protein was determined by nephelometry with a threshold of 0.175 mg/L and an intra- and inter-assay coefficient of less than 4.4% and 5.7%, respectively (BNIIN). N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured with Elecsys™ 2010, with an intra- and inter-assay coefficient of variation of 1.2–1.5% and 4.4–5.0%, respectively (Roche Diagnostics, Mannheim, Germany). High-sensitivivity troponin T (hs-TnT) was measured using modular analytics serum work areas, with a 10% coefficient of variation at the 99th percentile of the reference range (Roche Diagnostics).

Definition for new-onset heart failure and mortality

Briefly, participants were censored at the date they moved to an unknown location or the last follow-up date (1st January 2010), whatever came first. Dates and causes of death for every participant were obtained from national death registries of the Netherlands and coded according to the 10th revision of the International Classification of Diseases.[17]

The definition of new-onset HF was described previously.[10] New-onset HF was identified using criteria following the European Society of Cardiology guidelines.[18,19] Two experts validated each case by reviewing anonymized clinical charts, hospitalization, and physician office records to ascertain the incidence of HF. In case of a difference of opinion about an individual case, the committee made a joint decision.[18,19] The aetiology and the date of onset of HF were derived from clinical charts. The local Ethics Committees of both hospitals granted permission to access hospital records.

Statistical analysis

Latent class growth modelling was used to identify distinct UAE and creatinine trajectories.[20] We used the lowest Bayesian information criterion (BIC) value to select the optimal number of trajectories. The BIC is commonly used to select the correct number of trajectories[21–23] and was found to be as valid as, for example, the likelihood ratio test or the Lo–Mendell–Rubin test.[24] Baseline characteristics were presented to individual patient subgroups based on the latent class growth modelling. Continuous variables were presented as mean (standard deviation), median (interquartile range) or number (percentage), depending on the nature and distribution of the variable. Differences in baseline characteristics between subgroups were tested using the one-way analysis of variance (ANOVA), Kruskal–Wallis test, or Chi-square test, depending on the nature and distribution of the variable. Cause-specific hazards modelling was utilized to determine the associations between UAE and serum creatinine trajectories and subsequent risk of HF or all-cause mortality. We used cause-specific hazard models, which are considered valid in the presence of competing risks.[25] Weighted cause-specific hazard models were used to account for the over-selection of participants with elevated UAE in the PREVEND study as described previously.[10] The exposure variables were modelled as factor (group) variables using the trajectory with the lowest absolute risk (risk nadir) as the reference. Confounders in the model were selected based on clinical relevance and significant differences between trajectories. To estimate outcomes, we used a landmark analysis-based approach. This means that the time to event was estimated using the date of the last known creatinine or UAE measurement as the baseline. We used case-wise deletion for multivariable models leading to a total of 6193 (91%) out of 6799 participants with repeated UAE measurements included and 6148 (95%) out of 6481 participants with repeated creatinine included. Confounders were chosen based on clinical relevance and previous publications.[10] We estimated to variance inflation factor (VIF) to evaluate the possible collinearity of confounders and found that the VIF was <5.0 for all included variables. Due to the low missingness of confounders, we did not consider multiple imputations for our analyses. We tested the possible modifying effect of sex on the association between trajectories and incident HF or all-cause mortality by performing an interaction test. A p-value < 0.05 (two-sided) was defined as statistically significant. All analyses were performed using R 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Longitudinal urinary albumin excretion and creatinine trajectories and baseline characteristics

Online supplementary *Table S1.* shows that the BIC for different latent class growth models was lowest for eight UAE (*Figure 1A*) and ten creatinine trajectories (*Figure 1B*).

Table 1 shows the baseline characteristics according to UAE trajectories, and *Table 2* shows the baseline characteristics according to creatinine trajectories. Participants with increasing or stable high UAE and creatinine trajectories were generally older, more often men had higher systolic and diastolic blood pressure and a higher prevalence of previous myocardial infarction, diabetes, dyslipidaemia, or antihypertensive medication use. Furthermore, those with persistently high UAE or creatinine had higher high-sensitivity C-reactive protein, NT-proBNP and hs-TnT concentrations.

The association between renal biomarker trajectories and outcomes

During a median follow-up of 11.5 years, 278 (4.1%) participants developed HF and 281 (4.1%) participants died.

Table 3 shows the associations between UAE trajectories, incident HF, and UAE trajectories and mortality. The group of patients with the persistently lowest UAE concentrations (Trajectory 1) was used as the reference category since they were at the lowest risk of incident HF or mortality. The hazard ratio (HR) for incident HF ranged from 0.92 (95% confidence interval [CI] 0.77–1.10) for Trajectory 2 to 5.99 (95% CI 3.74–9.61) for Trajectory 7. After adjustments for confounders, persistently elevated UAE (Trajectory 6: HR 1.41, 95% CI 1.00–1.98; and Trajectory 7: HR 1.63, 95% CI 1.01–0.2.64) remained at a higher risk for incident HF than participants with consistently low UAE (Trajectory 1). The association of trajectories with all-cause mortality followed similar patterns. The HR ranged from 1.42 (95% CI 1.22–1.64) for Trajectory 2 to 11.0 (95% CI 7.9–15.4) for Trajectory 7. After correcting

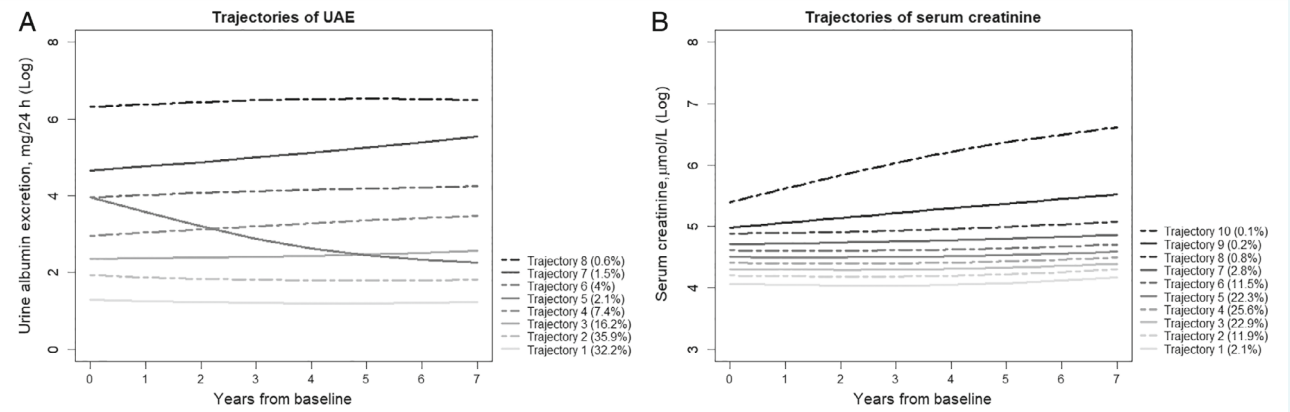


Figure 1 The time-dependent trajectories for urinary albumin excretion (UAE) (*A*) and serum creatinine (*B*). Both UAE and serum creatinine concentrations are shown on a natural logarithmic scale. The percentages reflect the proportion of the population represented by each class trajectory. The lowest Bayesian information criterion value was used to select the optimal number of trajectories.

for confounders, Trajectories 2, 7, and 8 remained at a higher risk for mortality than Trajectory 1.

Table 4 shows the associations between creatinine trajectories, incident HF, and creatinine trajectories and mortality. The HRs for incident HF ranged from 0.93 (95% CI 0.41–2.10) to 12.85 (95% CI 3.44–47.97). After adjustment for confounders, Trajectories 6, 7 and 8 were associated with a higher risk for HF. None of the trajectories were associated with an increased mortality risk compared to Trajectory 1 in the fully adjusted analyses. Sex did not modify the association between any of the trajectories (UAE, creatinine) and all-cause mortality or incident HF ($p_{interaction} \geq 0.2$ for all).

Discussion

This study identified distinct UAE and serum creatinine trajectories in a large, well described population-based cohort. Longitudinal UAE and serum creatinine trajectories largely remained stable for 11-year follow-up. Participants with persistently higher UAE or creatinine trajectories were more likely to develop new-onset HF or die (*Graphical Abstract*).

Previous studies demonstrated a robust association between increased UAE or serum creatinine levels and incident HF or death.[10,12,26,27] However, few studies investigated longitudinal UAE or serum creatinine patterns. Longitudinal UAE and serum creatinine trajectories were stable over time in our study. A study in the Coronary Artery Risk Development in Young Adults (CARDIA) cohort identified five trajectory groups of urinary albumin-to-creatinine ratio (UACR).[28] In this previous study, most participants had low-stable, moderate-stable, or high-stable UACR between the year 10 and year 30 examinations.[28] In CARDIA, those with high-stable UACR were more likely Black and had a history of hypertension.[28] Our results are similar to those in CARDIA, such that most participants had stable UAE or serum creatinine over time and those with worse-stable renal function markers were older and more often used antihypertensive medication. Our results extend on the CARDIA study results by including a relatively older population and a larger sample size.

Participants with persistently high UAE or creatinine had a higher risk of adverse outcomes. Previous studies in PREVEND or the Framingham Heart Study demonstrated the association of cross-sectional UAE or serum creatinine with incident HF and mortality.[10,29] In the previous study from CARDIA, participants with high-stable UACR had a higher left ventricular mass and worse longitudinal strain.[28] Our results extend on these previous studies by demonstrating the association of persistently high worse renal function with incident HF and mortality. These associations were robust after correction for confounders.

The association between a decreasing UAE trajectory (Trajectory 5) and incident HF was not statistically significant. However, these participants constituted only 2.1%. Therefore, the analyses for this trajectory were likely underpowered to show a meaningful difference. The association between UAE trajectories and incident HF or mortality appeared to be linear. The substantial differences between our unadjusted and adjusted analyses, highlighted the significant confounding effects of, among others, age, sex and medical history. There was a less strong stepwise relationship of serum creatinine trajectories with mortality than for UAE in the fully adjusted model. This highlights that UAE is a stronger predictor of mortality than serum creatinine. UAE is a marker of renal dysfunction. Patients with renal dysfunction have high fibroblast growth factor 23 (FGF23) concentrations.[9] Increased concentrations of FGF23 might cause endothelial dysfunction, leading to HF.[9,30] In severe renal dysfunction, the accumulation of toxins through impaired renal clearance might cause direct cardiac muscle inflammation and HF.[9] Blood pressure trajectories might have influenced our results. In the SPRINT trial, estimated glomerular filtration rate and UAE were strong predictors of incident HF but did not modify the effect of intensive blood pressure control in decreasing HF risk.[31] Furthermore, medication initiated during follow-up, for which we could not account, might have influenced the trajectories and their association with incident HF or all-cause mortality.

Together, our results suggest that opportunities for interventions to reduce UAE further exist in this particular subgroup. A

Table 1 Baseline characteristics according to urinary albumin excretion trajectory

	Urinary albumin excretion								*p*-value
	Trajectory 1	Trajectory 2	Trajectory 3	Trajectory 4	Trajectory 5	Trajectory 6	Trajectory 7	Trajectory 8	
No. at risk	2187	2439	1105	503	145	273	104	43	
Age, years	51.3 (11.2)	51.7 (11.8)	54.6 (12.1)	59.6 (11.8)	56.5 (12.8)	60.7 (11.4)	63.3 (11.3)	60.6 (13.5)	<0.001
Male sex, %	36.6	50.9	57.3	66	52.4	72.2	74	72.1	<0.001
BMI, kg/m^2	25.3 (3.8)	25.7 (4.0)	26.7 (4.3)	27.2 (4.1)	26.5 (4.6)	28.1 (4.6)	28.6 (4.1)	29.3 (4.7)	<0.001
Systolic BP, mmHg	121.7 (16.5)	127.3 (18.6)	131.7 (18.9)	136.6 (20.5)	139.2 (25.8)	143.3 (22.0)	144.6 (20.6)	148.3 (25.2)	<0.001
Diastolic BP, mmHg	70.8 (8.3)	73.4 (9.5)	75.5 (9.4)	77.8 (9.5)	79.1 (12.6)	80.2 (9.9)	79.2 (8.8)	81.4 (10.7)	0.07
Myocardial infarction, %	1.3	1.2	3.3	6.6	6.9	5.9	12.5	11.6	<0.001
Diabetes mellitus, %	0.5	0.9	1.4	4.0	3.4	2.2	5.8	9.3	<0.001
Dyslipidaemia or statin use, %	2.7	3.0	5.8	9.4	7.2	8.8	16.0	14.3	<0.001
Antihypertensive medication use, %	11.1	11.5	17.8	27.4	20.2	30.3	45.6	44.4	<0.001
Hs-C-reactive protein, mg/L	1.0 (0.5–2.4)	1.1 (0.5–2.5)	1.4 (0.6–3.2)	1.8 (0.9–4.0)	2.5 (1.0–6.4)	2.2 (0.9–4.0)	2.8 (1.3–6.2)	2.3 (1.2–4.1)	<0.001
NT-proBNP, ng/L	36.4 (17.4–68.1)	33.8 (15.0–65.1)	35.5 (15.2–68.1)	35.5 (15.8–86.1)	58.0 (27.6–109.7)	42.7 (18.6–91.9)	60.4 (26.1–160.8)	69.2 (17.4–171.2)	<0.001
Hs-TnT, ng/L	2.5 (2.5–3.0)	2.5 (2.5–4.0)	3.0 (2.5–5.0)	4.0 (2.5–7.0)	2.5 (2.5–6.0)	5.0 (3.0–8.0)	7.0 (3.0–11.0)	7.0 (2.5–10.0)	<0.001

BMI, body mass index; BP, blood pressure; hs, high-sensitivity; hs-TnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
The lowest Bayesian information criterion value was used to select the optimal number of trajectories.

Table 2 Baseline characteristics according to serum creatinine trajectory

	Serum creatinine									*p*-value
	Trajectory 1	Trajectory 2	Trajectory 3	Trajectory 4	Trajectory 5	Trajectory 6	Trajectory 7	Trajectory 8	Trajectory 9/10	
No. at risk	144	812	1564	1750	1524	787	188	56	16	
Age, years	54.3 (11.6)	53.6 (11.1)	51.4 (11.2)	50.8 (11.8)	52.9 (12.3)	53.9 (12.3)	56.1 (10.6)	64.8 (7.7)	70.5 (11.8)	<0.001
Male sex, %	2.1	5.9	20.1	51.0	78.8	90.9	92.6	92.9	68.8	<0.001
BMI, kg/m^2	26.4 (5.4)	26.2 (4.9)	25.6 (4.4)	25.6 (4.0)	25.9 (3.8)	26.3 (3.2)	26.7 (3.2)	27.4 (3.3)	27.4 (4.5)	0.926
Systolic BP, mmHg	132.5 (20.8)	127 (18.9)	122.3 (18.6)	123.4 (18.6)	127.2 (18.3)	130.9 (19.1)	135.6 (22.3)	145 (22.0)	149.2 (22.6)	<0.001
Diastolic BP, mmHg	74.9 (8.6)	72.0 (8.9)	70.4 (8.9)	71.4 (9.2)	73.4 (9.2)	75.3 (9.8)	77.7 (10.3)	81.5 (11.1)	83.5 (7.3)	<0.001
Myocardial infarction, %	0.0	0.7	0.6	2.2	3.1	4.7	10.1	19.6	25.0	<0.001
Diabetes mellitus, %	2.8	1.6	0.8	1.1	1.4	1.4	2.7	3.6	6.3	<0.001
Dyslipidaemia or statin use, %	5.1	2.4	2.3	4.1	4.9	6.5	13.6	18.9	20.0	<0.001
Antihypertensive medication use, %	16.0	11.3	10.1	12.7	16.6	22.3	42.4	60.8	87.5	<0.001
Hs-C-reactive protein, mg/L	1.8 (0.6–4.9)	1.2 (0.5–3.1)	1.2 (0.5–2.9)	1.1 (0.5–2.7)	1.2 (0.5–2.7)	1.3 (0.6–2.7)	1.9 (0.9–4.2)	2.2 (1.4–3.8)	2.4 (1.1–5.1)	<0.001
NT-proBNP, ng/L	52.9 (25.1–77.3)	44.4 (24.5–80.1)	42.8 (22.8–73.8)	33.9 (15.5–65.0)	27.7 (12.1–60.5)	26.2 (9.8–60.4)	62.3 (23.0–172.5)	121.1 (47.6–299.1)	250.3 (121.6–355.7)	<0.001
Hs-TnT, ng/L	2.5 (2.5–2.5)	2.5 (2.5–2.5)	2.5 (2.5–3.0)	3.0 (2.5–5.0)	4.0 (2.5–6.0)	7.0 (4.0–10.0)	7.0 (4.0–10.0)	11.0 (7.0–16.0)	12.0 (6.0–15.0)	<0.001

BMI, body mass index; BP, blood pressure; hs, high-sensitivity; hs-TnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
The lowest Bayesian information criterion value was used to select the optimal number of trajectories.

Table 3 **Associations between urinary albumin excretion trajectories and outcomes**

	Urinary albumin excretion							
	Trajectory 1	**Trajectory 2**	**Trajectory 3**	**Trajectory 4**	**Trajectory 5**	**Trajectory 6**	**Trajectory 7**	**Trajectory 8**
No. at risk	2187	2440	1105	503	145	273	104	43
Person-years	24 185	27 008	12 186	5477	1610	3031	1062	451
Heart failure								
No. of incident	45	59	62	41	11	36	18	6
Unadjusted HR (95% CI)	Ref	0.92 (0.77–1.10)	1.62 (1.30–2.02)	3.17 (2.39–4.21)	2.32 (1.34–4.01)	5.34 (3.90–7.29)	5.99 (3.74–9.61)	4.13 (1.92–8.92)
Adjusted HR (95% CI)	Ref	0.82 (0.68–0.98)	0.81 (0.63–1.04)	1.35 (1.01–1.81)	0.97 (0.56–1.70)	1.41 (1.00–1.98)	1.63 (1.01–2.64)	1.14 (0.52–2.50)
All-cause mortality								
No. of incident	41	72	58	45	8	22	23	8
Unadjusted HR (95% CI)	Ref	1.42 (1.22–1.64)	2.53 (2.12–3.02)	3.70 (2.91–4.69)	2.01 (1.16–3.48)	3.53 (2.51–4.96)	11.03 (7.90–15.40)	8.85 (5.12–15.31)
Adjusted HR (95% CI)	Ref	1.19 (1.02–1.38)	1.30 (1.07–1.56)	1.22 (0.94–1.57)	0.87 (0.48–1.57)	0.95 (0.66–1.36)	2.58 (1.81–3.68)	2.03 (1.16–3.56)

CI, confidence interval; HR, hazard ratio.
Adjusted HRs were adjusted for age, sex, body mass index, systolic blood pressure, myocardial infarction, diabetes mellitus, hypercholesterolaemia or statin use and antihypertensive medication use.
The lowest Bayesian information criterion value was used to select the optimal number of trajectories.

Table 4 **Associations between serum creatinine trajectories and outcomes**

	Serum creatinine								
	Trajectory 1	**Trajectory 2**	**Trajectory 3**	**Trajectory 4**	**Trajectory 5**	**Trajectory 6**	**Trajectory 7**	**Trajectory 8**	**Trajectory 9/10**
No. at risk	144	812	1564	1750	1524	787	188	56	16
Person-years	1583	8985	17 283	19 410	16 800	8611	2023	584	162
Heart failure									
No. of incident	5	19	38	57	69	48	30	9	3
Unadjusted HR (95% CI)	Ref	0.93 (0.41–2.10)	1.51 (0.69–3.29)	1.66 (0.77–3.61)	2.01 (0.93–4.36)	3.24 (1.15–7.07)	7.06 (3.15–15.82)	12.77 (5.36–30.43)	12.85 (3.44–47.97)
Adjusted HR (95% CI)	Ref	1.06 (0.46–2.45)	2.20 (1.00–4.80)	2.06 (0.94–4.50)	1.97 (0.90–4.50)	2.64 (1.19–5.84)	2.65 (1.15–6.11)	3.29 (1.35–7.97)	2.63 (0.70–9.95)
All-cause mortality									
No. of incident	4	29	36	50	72	48	24	11	4
Unadjusted HR (95% CI)	Ref	0.71 (0.47–1.07)	0.48 (0.32–0.72)	0.48 (0.32–0.72)	0.79 (0.53–1.17)	0.93 (0.62–1.40)	2.15 (1.38–3.35)	3.84 (2.27–6.50)	5.73 (2.45–13.38)
Adjusted HR (95% CI)	Ref	0.98 (0.65–1.50)	0.52 (0.15–1.81)	0.37 (0.10–1.30)	0.39 (0.11–1.44)	0.38 (0.10–1.46)	0.41 (0.10–1.66)	0.46 (0.01–2.21)	0.60 (0.11–3.20)

CI, confidence interval; HR, hazard ratio.
Adjusted HRs were adjusted for age, sex, body mass index, systolic blood pressure, myocardial infarction, diabetes mellitus, hypercholesterolaemia or statin use and antihypertensive medication use.
The lowest Bayesian information criterion value was used to select the optimal number of trajectories.

study in SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53) identified estimated glomerular filtration rate and UACR among the five most important risk factors for incident HF.[28,32] Importantly, participants at a higher risk for HF derived more benefit from treatment with sodium–glucose cotransporter 2 (SGLT2) inhibitors.[32] Therefore, people with higher stable UAE might benefit from SGLT2 inhibitors.

Limitations

The results of our study are best valued in light of several limitations. First, the PREVEND study only included Caucasian participants, preventing extrapolation to other ethnic groups. Furthermore, the observational nature of our study excludes causal estimation. HF was determined by chart review, possibly leading to under-detection of cases. Previously, cystatin C was found to be an important predictor of new-onset HF in PREVEND.[10] Unfortunately, we did not have repeated cystatin C measurements. therefore, we could not estimate cystatin C trajectories. Our analyses did not enable us to identify a clinically meaningful difference for UAE or creatinine. We could not analyse HF subclasses (e.g. HF with reduced or preserved ejection fraction) due to limited statistical power. Unfortunately, we could not account for the type of antihypertensive medication. The current study findings might not generalize to the modern era of guideline-directed medical therapy, including the use of SGLT2 inhibitors and angiotensin receptor–neprilysin inhibitors.

Conclusion

This study identified the population's distinct temporal patterns for UAE and serum creatinine. High levels of UAE or creatinine, which were often stable over time, were associated with greater risk for new-onset HF and all-cause mortality, suggesting that interventions targeted at reducing UAE might benefit these subgroups.

Supplementary Information

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

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Conflict of interest: J.T. has received consulting or speaker fees from Daiichi-Sankyo, Boehringer Ingelheim, Roche Diagnostics and Us2.ai, owns patent US-10702247-B2 unrelated to the present work. All other authors have nothing to disclose.

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