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Association of mild kidney dysfunction with diastolic dysfunction and heart failure with preserved ejection fraction

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Abstract

Aims   We aim to investigate the association between kidney dysfunction and left ventricular diastolic dysfunction parameters and heart failure with preserved ejection fraction (HFpEF) and whether this is sex-specific.

Methods and results   We included participants from the HELPFul observational study. Outpatient clinical care data, including echocardiography, and an expert panel judgement on HFpEF was collected. Estimated glomerular filtration rate (eGFR) was calculated by creatinine and cystatin C without race. The association between eGFR with E/e', left ventricular mass index, relative wall thickness, and stage C/D heart failure was tested by multivariable adjusted regression models, stratified by sex, reporting odds ratios and 95% confidence intervals (95% confidence interval). We analysed 880 participants, mean age 62.9 (standard deviation: 9.3) years, 69% female. Four hundred six participants had mild (37.6%) kidney dysfunction (eGFR: 60–89 mL/min/1.73 m^2) or moderate (8.5%) kidney dysfunction (eGFR: 30–59 mL/min/1.73 m^2). HFpEF was significantly more prevalent in participants with mild and moderate kidney dysfunction (10.3% and 16.0%, respectively) than participants with normal kidney function (3.4%). A lower kidney function was associated with higher E/e' and higher relative wall thickness values. Participants with moderate kidney dysfunction had a higher likelihood of American College of Cardiology/American Heart Association stage C/D HF (odds ratio: 2.07, 95% confidence interval: 1.23, 3.49) than participants with normal kidney functions.

Conclusions   Both mild and moderate kidney dysfunction are independently associated with left ventricular diastolic dysfunction parameters and HFpEF. This association is independent of sex and strongest for moderate kidney dysfunction. Considering mild-to-moderate kidney dysfunction as risk factor for HFpEF may help identify high-risk groups benefiting most from early intervention.

Introduction

Around 50% of the patients with heart failure (HF) have HF with preserved ejection fraction (HFpEF),[1,2] and all types of

HF, including HFpEF, are associated with an increased mortality risk.[3–5] Kidney dysfunction is seen in 30–60% of the patients with all-type HF,[6,7] whereas, *vice versa*, in patients with chronic kidney disease (CKD) the prevalence

of newly detected HF is estimated to be between 17% and 44%.[8,9] Both CKD and HFpEF are more prevalent in females compared with males,[10,11] while, on the other hand, more males have heart failure with reduced ejection fraction (HFrEF). The relation between CKD and HFrEF is well established, and the main direction seems to be that HFrEF causes CKD, while in HFpEF, it could well be the other way around; kidney dysfunction increases the risk of HFpEF.[12–20] Additionally, concurrent CKD is a strong risk factor for increased mortality in established HFpEF.[21] Finally, HFpEF and CKD co-exist due to common underlying co-morbidities related to systemic low-grade inflammation, systemic microvascular dysfunction, neurohormonal activation, oxidative stress, and chronic left ventricular pressure overload.[22,23]

HFpEF concerns symptoms suggestive of HF plus (echocardiographic) evidence of left ventricular diastolic dysfunction (LVDD). Thus, LVDD may be considered as the underlying pathophysiological process of HFpEF; however, not everybody with LVDD develops HFpEF because LVDD without symptoms of HF may be reversible or develop into LV systolic dysfunction and thus finally HFrEF.[24,25] Interestingly, LVDD is equally prevalent in both sexes, while HFpEF is more prevalent in females, and HFrEF is more prevalent in males.[26,27] This suggests that there are different 'preferred pathways' among sexes from LVDD to heart failure.

Importantly, approximately one third of all patients with CKD also have LVDD.[28–30] Few longitudinal studies found that kidney dysfunction is associated with the progression of asymptomatic LVDD to all-type HF, also independent of other cardiovascular risk factors.[31] A previous screening study showed that natriuretic peptide-based screening of high-risk patients, for example, hypertension, type 2 diabetes mellitus, prior myocardial infarction, in combination with intensified collaborative care in those with marginally increased B-type natriuretic peptide (BNP) levels (>50 pg/mL), resulted in reduced HF incidence and reduced major adverse cardiac and cerebrovascular events.[32] Importantly, this effect was mainly driven by intensified renin-angiotensin system (RAS) inhibition treatment. From more recent studies, we know that also sodium-glucose cotransporter 2 (SGLT2) inhibitors and mineral corticosteroid antagonists may have beneficial potential in patients with HFpEF, with SGLT2 inhibitors also a beneficial effect on kidney function.[33–35]

Even though an association between kidney and cardiac dysfunction is apparent, there is a gap in knowledge on whether already mild kidney dysfunction relates with a higher prevalence of LVDD and HFpEF and whether this is sex-specific. Therefore, we investigated the association of kidney dysfunction with (i) echocardiographic diastolic dysfunction parameters of LVDD and (ii) a panel diagnosis of HFpEF in out-patient males and females referred for cardiovascular evaluation, with no prior cardiac interventions or congenital heart disease.

Methods

Study participants

For this cross-sectional study, we included consecutive participants from the HEart failure with Preserved ejection Fraction in patients at risk for cardiovascular disease (HELPFul) study, for which the design has been described in detail elsewhere.[36] A random sample of patients, enriched with participants with an early filling (E) to early diastolic mitral annular velocity (e') ratio (E/e' ratio) ≥ 8, measured with echocardiography, were included. All were referred by their general practitioner to an outpatient cardiology clinic (Cardiology Centres of the Netherlands, location Galgenwaard, Utrecht), because of cardiovascular disease suspicion. Participants had to be aged 45 years or older, and without prior cardiac intervention (e.g. percutaneous coronary intervention or coronary artery bypass graft) or congenital heart disease.

Written informed consent was obtained from all participants and this study was approved by the Medical Ethics committee of the UMC Utrecht (number 16-290/M) and was conducted according to the principles of the Declaration of Helsinki (version 2013) and the Medical Research Involving Human Subjects Act (WMO).

Data collection

Standard care measurements, including blood pressure measurement in sitting position, physical examination, electrocardiography, bicycle exercise testing, echocardiography, and basic laboratory testing (haemoglobin, haematocrit, random glucose, potassium, lipid spectrum, and creatinine levels), were collected from all participants. Additionally, venous blood was collected for storage at the UMC Utrecht biobank. In every participant, BNP and high sensitivity troponin were measured. Creatinine, cystatin C, 25-hyrdoxy vitamin D, aspartate transaminase, and C-reactive protein were measured in the first 72% of participants, with the appropriate assay (ARCHITECT i2000 analyser, Abbott Park, Chicago, Illinois, USA). We calculated the estimated glomerular filtration rate (eGFR) with the new CKD-EPI 2021 equation for creatinine and cystatin C in combination without race.[37]

Expert panel diagnosis

An expert panel, consisting of three qualified cardiologists and one general practitioner specialized in heart failure care (R. M., M. C., A. T., and F. R.), was responsible for diagnosing HF and LVDD based on all available diagnostic information, including BNP levels and echocardiography. Classification of the participants was undertaken by the panel that was not aware of the kidney function at the moment of assessment,

with a majority of votes or at least after discussion by two panel members. In 10%, diagnoses were re-evaluated in a blinded fashion. The echocardiographic measurements that were used consisted of left atrial diameter, left atrial volume index (LAVI), interventricular diameter at end-diastole, left ventricle (LV) dimension at end-diastole, thickness of the LV posterior wall at end-diastole, LV dimension at end-systole, LV ejection fraction, early (E) and late filling (A), blood flow ratio (E/A ratio), E wave deceleration time, peak mitral annual velocity e', E/e', LV mass index (LVMI), and relative wall thickness (RWT).[38] The panel diagnosis of LVDD was based on echocardiography parameters,[39] and for the diagnosis of HF, symptoms suggestive of heart failure had to be present. The panel used both the HFA-PEFF and HF2-PEF scores[40,41] to determine HFpEF diagnosis. Then, all participants were further categorized according to the American College of Cardiology (ACC)/American Heart Association (AHA) staging system in Stage A (no structural cardiac abnormalities), Stage B [structural abnormalities (LVDD), without signs or symptoms of HF], and Stage C/D [signs and symptoms of HF accompanied with structural echocardiographic abnormalities (e.g. HFpEF, HFmrEF, or HFrEF)].[40] Because we wanted to study the association of kidney function with early HFpEF, participants with possible or probable symptoms of heart failure were classified as ACC/AHA stage C/D.

Data analysis

Normally distributed variables are reported as mean ± standard deviation, non-normally distributed variables as median and interquartile range, and categorical data as count and percentages. Analyses regarding kidney function were stratified by normal kidney function (GFR $\geq$ 90 mL/min/ 1.73 m^2), mild kidney dysfunction (eGFR 60–89 mL/min/ 1.73 m^2), and moderate to severe kidney dysfunction (eGFR $<$60 mL/min/1.73 m^2). The association between kidney function and echocardiography results and the diagnosis of ACC/AHA stage C/D was assessed with linear regression models reporting the betas, and logistic regression models reporting the odds ratio [OR, both with the respective 95% confidence interval (95% CI)], respectively. The relationship between continuous variables and outcomes was explored by restricted cubic splines. For the non-linear variables, log-transformations were applied. The thresholds for the logistic regression models were based on the third quartile of the distribution, that is, E/e' $>$ 10, LAVI $>$30 mL/m^2, LVMI for males $>$90 g/m^2 and females $>$80 g/m^2, and RWT $>$ 0.48. The results of multivariable regression analyses were adjusted for cardiovascular risk factors and lifestyle factors based on the literature and previous studies on LV dysfunction,[42–45] including body mass index, diabetes mellitus, hypertension, hypercholesterolaemia, cardiovascular history, alcohol consumption, smoking status, and education level.

Age and sex were not included as confounder given that they are part of the dependent variable (i.e. eGFR). We also reported descriptive statistics and regression analyses sex-stratified. Missing data were imputed by multiple imputation (iteration = 10) using the 'mice' R statistical package and the missing values for all variables are reported in *Table S1*. Two-tailed tests were applied and a *P* value of $<$0.05 was considered statistically significant. All statistical analyses were performed using the R v. 3.5.1. software.

Sensitivity analyses

We performed sensitivity analyses excluding all participants with HF (defined as ACC/AHA stage C/D) to see whether the association between kidney dysfunction and echocardiographic parameters was not driven by individuals already affected with HF. Finally, sensitivity analyses have been performed to rule out that our results would depend on cystatin C levels. Therefore, we used creatinine dependent eGFR calculations, that is, the Cockcroft–Gault and the CKD-EPI equations.[46,47] Given that the large majority ($>$90%) of the included participants was Caucasian, although this was not collected in a standardized manner, for the CKD-EPI equation, the ethnicity of our sample was assumed to be Caucasian.

Results

Baseline characteristics

In total, 880 participants were included in the main analyses, with a mean age 62.9 [standard deviation (SD): 9.3] years, of whom 69% were female, and the mean body mass index was 27.2 (SD: 4.5) kg/m^2 (*Table 1*). The mean eGFR of all included participants was 96.9 (SD: 31.7) mL/min/1.73 m^2. Approximately half of the participants (*n* = 474) had normal kidney function (eGFR of $\geq$90 mL/min/1.73 m^2). In total, 331 (37.6%) had mild kidney dysfunction (eGFR of 60–89 mL/ min/1.73 m^2), and 75 (8.5%) moderate kidney dysfunction (eGFR $<$59 mL/min/1.73 m^2). Females had a similar eGFR compared with males. Participants with mild kidney dysfunction and moderate kidney dysfunction were on average older, had higher systolic blood pressure, and higher BNP levels compared with participants with normal kidney function.

Heart failure

HFpEF was more often diagnosed in participants with moderate kidney dysfunction (*n* = 12, 16%) and mild kidney dysfunction (*n* = 34, 10%) compared with participants with normal kidney function (*n* = 16, 3%) (*Table 2*). ACC/AHA stage C/D HF was diagnosed in 41 (55%), 128 (38%), and 153 (32%)

Table 1 Baseline characteristics of the included patients stratified by kidney function

Mean variable (SD)	eGFR (≤59 mL/min/ 1.73 m² ; n = 75)	eGFR (60–89 mL/min/ 1.73 m² ; n = 331)	GFR (≥90 mL/min/ 1.73 m² ; n = 474)	P-value
Age in years	71.2 (8.8)	65.2 (8.8)	59.9 (8.4)	<0.001
Women (%)	52 (69.3)	222 (67.1)	330 (69.6)	0.738
BMI in kg/m²	28.2 (5.4)	27.5 (4.3)	26.7 (4.4)	0.006
Education level: ≥ first year of university	20 (26.7)	152 (45.9)	195 (41.1)	0.009
Smokers (%)				0.771
Never	33 (44.0)	125 (37.8)	187 (39.5)	
Current	5 (6.7)	34 (10.3)	41 (8.6)	
Former	37 (49.3)	172 (52.0)	246 (51.9)	
Alcohol consumption (%)				0.898
Never	8 (10.7)	48 (14.5)	61 (12.9)	
Current	63 (84.0)	263 (79.5)	386 (81.4)	
Former	4 (5.3)	20 (6.0)	27 (5.7)	
Systolic blood pressure (mmHg)	151.2 (19.3)	149.0 (19.7)	144.0 (19.3)	<0.001
Diastolic blood pressure (mmHg)	86.4 (11.3)	87.0 (10.6)	86.8 (10.7)	0.84
Hypertension (%)	55 (77.3)	200 (60.4)	249 (52.5)	0.001
Diabetes (%)	10 (13.3)	31 (9.4)	28 (5.9)	0.036
Cardiovascular history (%)	46 (61.3)	221 (66.8)	260 (54.9)	0.003
Haemoglobin (mmol/L)	9.6 (0.9)	9.5 (1.1)	9.4 (1.0)	0.13
Potassium (mmol/L)	4.2 (0.4)	4.1 (0.4)	4.2 (0.4)	0.44
Total cholesterol (mmol/L)	5.3 (1.3)	5.5 (1.2)	5.2 (1.1)	<0.001
Dyslipidaemia (%)	31 (41.3)	147 (44.4)	184 (38.8)	0.284
B-type natriuretic peptide (pg/mL)*	45.0 (21.4–80.3)	29.1 (17.3–49.3)	21.9 (12.9–42.2)	<0.001
High-sensitivity Troponin I (pg/mL)*	3.9 (2.7–6.9)	2.9 (2.1–4.8)	2.3 (1.6–3.7)	<0.001
25-hydroxy vitamin D (ng/mL)	28.55 (9.1)	24.7 (9.8)	24.7 (10.3)	0.007
Aspartate transaminase (IU/L)*	26.0 (20.5–33.7)	25.0 (21.0–30.0)	22.0 (18.3–26.0)	<0.001
C-reactive protein (mg/L)*	3.5 (1.6–6.6)	1.7 (0.7–6.2)	1.2 (0.5–3.3)	<0.001
Cystatin C (mg/L)	1.4 (0.2)	1.1 (0.1)	0.8 (0.1)	<0.001
Albumin (g/L)	43.1 (3.7)	43.7 (3.6)	41.0 (3.9)	<0.001
Creatinine (μmol/L)	93.7 (16.3)	73.9 (10.7)	63.1 (9.3)	<0.001

Renal function was estimated using the CKD-EPI 2021 equation for creatinine and cystatin C in combination without race.
BMI, body mass index; eGFR, estimated glomerular filtration rate; SD, standard deviation.
*Median and interquartile range.

participants with moderate kidney dysfunction, mild kidney dysfunction, and normal kidney function, respectively. More females (n = 47, 8% of females) than males (n = 15, 5% of males) were diagnosed with HFpEF, and also more females (n = 252, 42% of females) than males (n = 70, 25% of males) were diagnosed with ACC/AHA stage C/D HF (*Table S2A* and *Table S2B*). Participants with moderate kidney dysfunction were at increased risk, after adjustment for other cardiovascular risk factors, of being diagnosed with ACC/AHA stage C/D HF compared with participants with a normal kidney function (adjusted OR: 2.07, 95% CI: 1.23, 3.49) (*Table 3*). This was not statistically significant for patients with mild kidney dysfunction (adjusted OR: 1.16, 95% CI: 0.85, 1.58). Additionally, only in males, moderate kidney dysfunction was associated with ACC/AHA stage C/D HF (adjusted OR: 3.52, 95% CI: 1.34, 9.26) (*Table S3A* and *Table S3B*).

Echocardiography parameters

The echocardiography parameters stratified by categories of kidney dysfunction are presented in *Table 2*. The mean E/e' ratio and LVMI was higher, while the LV dimension at end-diastole, LV dimension at end-systole, and E/A ratio was lower for participants with kidney dysfunction compared with participants with normal kidney function (*Table 2*). There were no important differences in echocardiography findings when stratifying for sex (*Table S1A* and *Table S1B*), except for LVMI, that was expectedly higher in men. Both participants with mild as well as participants with moderate kidney dysfunction had more often an E/e' > 10 (adjusted OR: 1.55 [95% CI: 1.10, 2.08] and adjusted OR: 1.80 [95% CI: 1.07, 3.02], respectively) compared with participants with normal kidney function (*Table 3*). Participants with moderate kidney dysfunction had a higher risk of increased LVMI (adjusted OR: 1.70 [95% CI: 1.00, 2.86]) compared with participants with normal kidney function. Also, a higher risk was found for both participants with mild and moderate kidney dysfunction for a RWT > 0.48 (respectively, adjusted OR 1.75 [95% CI: 1.25, 2.45] and adjusted OR 2.15 [1.24–3.68]) compared with participants with normal kidney function. There was no relevant association between kidney dysfunction and LAVI. Sex-stratified analysis resulted in non-significant findings for most associations. After excluding participants in HF class C/D, there was still a significant association of moderate and severe kidney function with E/e' ratio; however, for LVMI and RWT, no

Table 2 Echocardiography values and panel diagnoses regarding heart failure and left ventricular diastolic dysfunction stratified by stages of kidney dysfunction

Mean variable (SD)	eGFR ($\leq$59 mL/min/ 1.73 m^2; n = 75)	eGFR (60–89 mL/min/ 1.73 m^2; n = 331)	GFR ($\geq$90 mL/min/ 1.73 m^2; n = 474)	P-value
Echocardiography values				
Interventricular diameter at end-diastole (mm)	10.2 (1.9)	9.9 (1.9)	9.4 (1.7)	<0.001
Left ventricle dimension at end-diastole (mm)	43.8 (5.8)	44.2 (5.4)	44.9 (5.0)	0.056
Thickness of the left ventricular posterior wall at end-diastole	9.7 (1.5)	9.7 (1.7)	9.3 (1.5)	<0.001
Left ventricle dimension at end-systole (mm)	28.4 (5.7)	27.7 (4.4)	27.9 (4.2)	0.687
Left ventricular ejection fraction (%)	66.0 (9.2)	67.2 (8.1)	67.6 (7.8)	0.273
E/A ratio	0.85 (0.30)	0.92 (0.40)	1.00 (0.30)	<0.001
E wave deceleration time (ms)	204.7 (55.6)	204.0 (52.4)	204.3 (49.9)	0.994
E velocity (cm/s)	70.6 (19.8)	68.5 (16.6)	70.6 (16.2)	0.222
E/e' ratio	10.4 (3.2)	9.5 (2.9)	8.9 (2.2)	<0.001
LVMI (g/m^2)				
Men	87.8 (29.4)	82.1 (22.7)	80.7 (20.7)	0.559
Women	77.7 (22.0)	72.7 (17.1)	70.2 (14.9)	0.023
Relative wall thickness	0.45 (0.09)	0.44 (0.10)	0.42 (0.08)	<0.001
LA volume index (mL/m^2)	27.7 (17.7)	24.9 (8.9)	25.3 (8.6)	0.071
Panel diagnoses				
Heart failure				<0.001
No HF	34 (45.3)	203 (61.3)	321 (67.7)	
'Intermediate' HFpEF	26 (34.7)	91 (27.5)	135 (28.5)	
HFpEF	12 (16.0)	34 (10.3)	16 (3.4)	
HFrEF/HFmrEF	3 (4.0)	3 (0.9)	2 (0.4)	
ACC/AHA HF class				0.002
Stage A	14 (18.7)	104 (31.4)	178 (37.6)	
Stage B	20 (26.7)	99 (29.9)	143 (30.2)	
Stage C/D	41 (54.7)	128 (38.7)	153 (32.3)	

Renal function was estimated using the CKD-EPI 2021 equation for creatinine and cystatin C in combination without race.
ACC/AHA, American College of Cardiology/American Heart Association; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVMI, left ventricular mass index; SD, standard deviation.

significant association was observed (*Tables S4* and *S5*). The baseline characteristics of the patients without HF class C/D at baseline are described in *Tables S6* and *S7*.

For the continuous measures of eGFR, in the adjusted analyses, a statistically significant association with E/e' [β: −0.01 (95% CI: −0.01, −0.003), P = 0.002] and RWT [β: −0.0003 (95% CI: −0.0005, −0.0001), P = 0.004] was also found, but again, there was no association of eGFR with LAVI (*Figure 1* and *Table 4*). The association of eGFR with E/e' ratio was also present when repeating the analysis sex-stratified (*Table S8*). For the other associations, except for RWT in females, there were no significant findings. After excluding participants with HF class C/D, eGFR was only significantly associated with RWT (P = 0.02, and not with E/e', LVMI, or LAVI; *Table S4*). No apparent different findings were identified in the sensitivity analyses based on different kidney function equations (*Tables S9* and *S10*).

Discussion

In our cross-sectional study, we found an association between moderate and mild kidney dysfunction, and diastolic dysfunc-

tion and HFpEF, independent of other risk factors (*Figure 2*). This association was already present for mild kidney dysfunction, and stronger for moderate kidney dysfunction. There was a significant association between kidney dysfunction and single echocardiographic parameters of LVDD, notably E/e' ratio, even after excluding participants with HF. Although the prevalence of HFpEF was higher in females in this study, there was no stronger association of eGFR with worse diastolic function or HFpEF. Hence, our results indicate that the association between reduced kidney function and elevated filling pressures may be evident prior to the development of symptomatic HF and CKD, independent of other cardiovascular risk factors and sex.

Previous studies found differing results between the association of kidney dysfunction and diastolic dysfunction.[23,42,43,45,48–50] Comparing previous studies with ours is hampered by heterogeneity in patient characteristics across the studies; the majority of earlier studies evaluated patients with a baseline mean eGFR of approximately 60 mL/min/1.73 m^2 or lower.[13,23,42–44,50] Also, other studies were limited to patients with diagnosed CKD at baseline,[47,48] established HF at baseline,[21] or were limited to individuals with hypertension or diabetes.[5,50–52] Other studies included

Table 3 Univariable and multivariable logistic regression for the association between stages of renal dysfunction and echocardiographic measures

	E/e' > 10		LAVI > 30 mL/m²		LVMI > 90 g/m² (male)LVMI > 80 g/m² (female)		RWT > 0.48		ACC/AHA Stage C/D	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Model 1: Crude										
eGFR categories										
eGFR ≥90 mL/min/1.73 m²	Ref.	-	Ref.	-	Ref.	-	Ref.	-	ref.	-
eGFR 60–89 mL/min/1.73 m²	1.62 (1.20, 2.18)	0.002	0.97 (0.70, 1.33)	0.84	1.19 (0.87, 1.62)	0.28	1.85 (1.33, 2.57)	<0.001	1.32 (0.99, 1.77)	0.06
eGFR <60 mL/min/1.73 m²	2.01 (1.22, 3.31)	0.006	1.11 (0.64, 1.88)	0.70	2.10 (1.27, 3.46)	0.004	2.43 (1.43, 4.09)	<0.001	2.53 (1.55, 4.16)	<0.001
Model 2: Adjusted										
eGFR categories										
eGFR ≥90 mL/min/1.73 m²	Ref.	-	Ref.	-	Ref.	-	Ref.	-	Ref.	-
eGFR 60–89 mL/min/1.73 m²	1.55 (1.14, 2.11)	0.005	0.92 (0.67, 1.27)	0.61	1.07 (0.77, 1.58)	0.69	1.75 (1.25, 2.45)	0.001	1.16 (0.86, 1.57)	0.35
eGFR <60 mL/min/1.73 m²	1.80 (1.07, 2.98)	0.02	1.06 (0.61, 1.81)	0.83	1.72 (1.02, 2.88)	0.04	2.09 (1.21, 3.55)	0.007	2.09 (1.25, 3.51)	0.005
Model 3: Adjusted										
eGFR categories										
eGFR ≥90 mL/min/1.73 m²	Ref.	-	Ref.	-	Ref.	-	Ref.	-	Ref.	-
eGFR 60–89 mL/min/1.73 m²	1.55 (1.10, 2.08)	0.005	0.92 (0.67, 1.27)	0.62	1.07 (0.77, 1.47)	0.69	1.75 (1.25, 2.45)	0.001	1.16 (0.85, 1.58)	0.35
eGFR <60 mL/min/1.73 m²	1.80 (1.07, 3.02)	0.03	1.03 (0.58, 1.76)	0.93	1.70 (1.00, 2.86)	0.047	2.15 (1.24, 3.68)	0.005	2.07 (1.23, 3.49)	0.006

Model 1: Crude. Model 2: Adjusted for BMI, diabetes mellitus, hypertension, hypercholesterolaemia, and history of cardiovascular disease. Model 3: Adjusted for model 2 + alcohol of >2 units/day, current smoking, and education level. Renal function was estimated using the CKD-EPI 2021 equation for creatinine and cystatin C in combination without race. ACC/AHA, American College of Cardiology/American Heart Association; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; LAVI, left atrial volume index; LVMI, left ventricular mass index; OR, odds ratio; RWT, relative wall thickness.

Figure 1 Scatter plot of kidney function against E/e' (A), against LAVI (B), LVMI (C), and RWT (D).
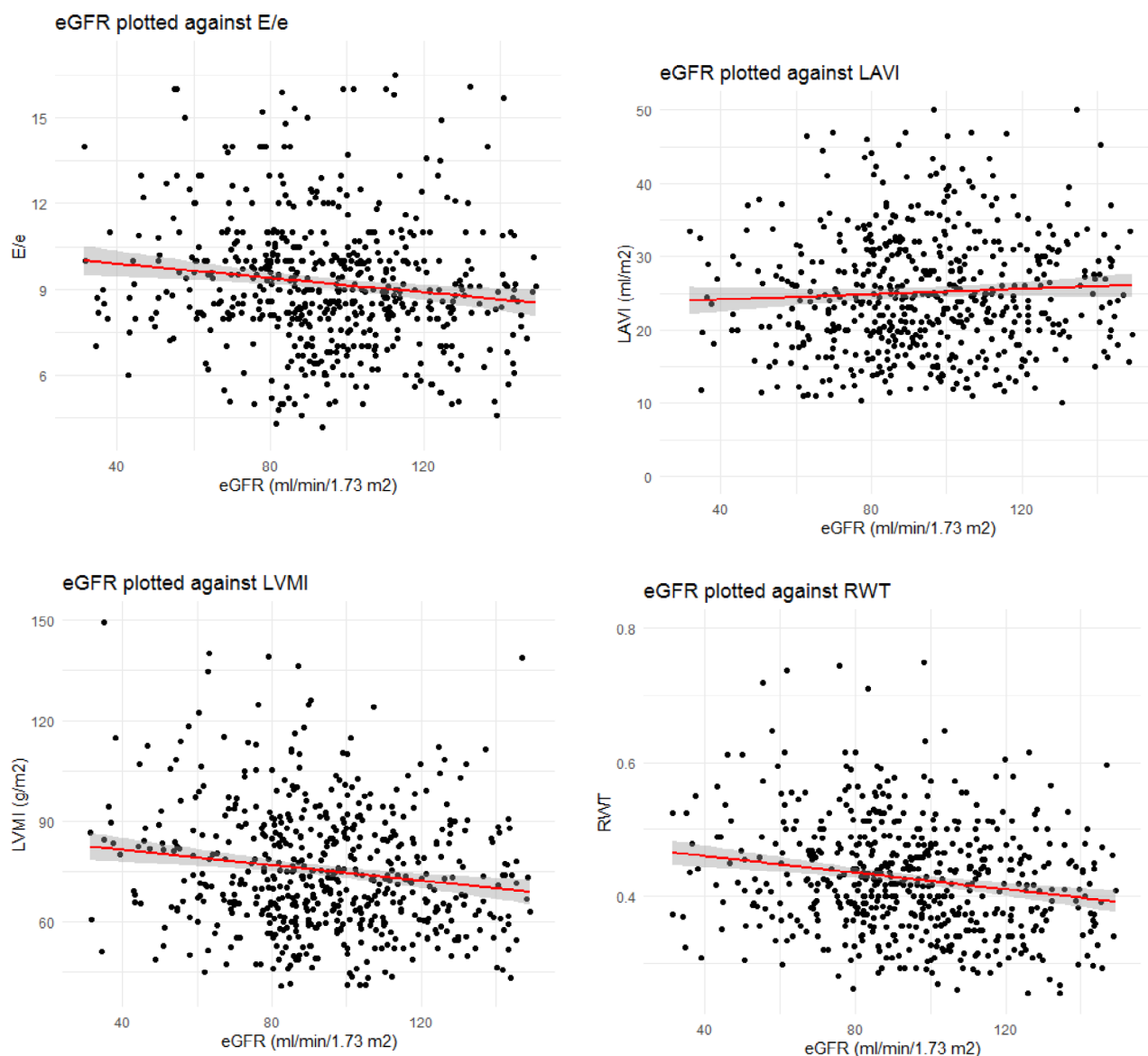
only outcomes from echocardiography without either the diagnosis of HFpEF or LVDD.[42,43] Our study shows a cardiorenal connection in a unique large cohort of patients with largely normal renal function or mild renal dysfunction, that was well-phenotyped with respect to both kidney function (i.e. creatinine and cystatin C measurement) and cardiac function (i.e. diastolic function and HFpEF diagnosis). Our study adds new information on participants with milder renal function, for example, with a mean eGFR between 60 and 90 mL/min/1.73 m^2, and we have phenotyped our patients more extensively on cardiac function, including a panel diagnosis of HF. Additionally, our study provides sex-specific data on the prevalence of kidney dysfunction, diastolic function

abnormalities, and HFpEF. This is important as risk factor associations may differ by sex, especially for HFpEF, but these differences are often not assessed.[53]

Our findings show that kidney dysfunction is independently associated with E/e' ratio, which is considered a parameter of elevated filling pressures. This association remained after we excluded individuals that had already symptoms suggestive of HF (Supporting Information). However, when these individuals were excluded, the association of kidney function with structural abnormalities (LVMI and RWT) disappeared. Although we should be cautious to over-interpret cross-sectional data, it could be speculated that elevated filling pressures are the first consequence of kidney dysfunction,

Table 4 Univariable and multivariable linear regression for the association between stages of renal dysfunction and echocardiographic measures

	E/e'		LAVI (mL/m²)		LVMI (g/m²)		RWT	
	Beta (95% CI)	P	Beta (95% CI)	P	Beta (95% CI)	P	Beta (95% CI)	P
Model 1: Crude								
eGFR (mL/min/1.73 m²)	−0.01 (−0.02, −0.005)	<0.001	−0.006 (−0.03, 0.01)	0.58	−0.06 (−0.10, −0.02)	0.005	−0.0003 (−0.0005, −0.0001)	<0.001
Model 2: Adjusted								
eGFR (mL/min/1.73 m²)	−0.01 (−0.01, −0.003)	0.001	−0.003 (−0.02, 0.01)	0.77	−0.03 (−0.07, 0.005)	0.09	−0.0003 (−0.0005, −0.0001)	0.004
Model 3: Adjusted								
eGFR (mL/min/1.73 m²)	−0.01 (−0.01, −0.003)	0.002	−0.003 (−0.02, 0.02)	0.77	−0.03 (−0.07, 0.006)	0.10	−0.0003 (−0.0005, −0.0001)	0.004

Model 1: Crude. Model 2: Adjusted for BMI, diabetes mellitus, hypertension, hypercholesterolaemia, and history of cardiovascular disease. Model 3: Adjusted for model 2 + alcohol of >2 units/day, current smoking, and education level. Renal function was estimated using the CKD-EPI 2021 equation for creatinine and cystatin C in combination without race. BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; LAVI, left atrial volume index; LVMI, left ventricular mass index; RWT, relative wall thickness.

while overt changes in left ventricular mass and geometry occur later in the disease trajectory. Another study in individuals with hypertension did not find any association of eGFR with functional or structural parameters relating to LVDD but did observe that individuals with albuminuria had higher RWT and E/e' ratio.[52]

We observed that mild renal dysfunction is linked to elevated filling pressures and structural remodelling and HFpEF. These structural echocardiographic abnormalities, representative of diastolic dysfunction can deteriorate to HFpEF. Our data suggest that high-risk individuals would benefit from early intervention, targeting, for example, pressure overload, volume overload or systemic inflammation, to prevent deterioration towards HF.[32] Drugs that could prove beneficial and need further investigation are, for example, renin-angiotensin-aldosterone system (RAAS) inhibitors, SGLT2 inhibitors, statins, or colchicine.[33–35,54,55] Further investigations are needed to analyse whether these therapeutic options also would lead to (a better) prevention of HF in a population with mild renal dysfunction.

Adequate measurement of both cardiac function and renal function is important to draw reliable conclusions on their association. In our study, we assessed kidney function using a new equation of cystatin C and creatinine, without race, with diastolic function parameters and HF.[37] Previous studies on the cardiorenal connection mostly used an assessment of renal function based on creatinine, such as the Modification in Renal Disease formula,[5,42,51,56,57] and Cockroft–Gault,[50] or cystatin C as marker of kidney function.[42–44] The added value of race in eGFR arguments has recently been under debate, as this offers only modest benefits to precision.[58,59] Using the new formula, omitting information on race, has recently been reported to be more accurate and lead to smaller differences between Caucasian participants and non-Caucasian participants than other equations.[37] Similarly, different strategies to classify diastolic function and heart failure have been reported, including an invasive exercise right heart catheterization or non-invasive stress echocardiography to measure elevated LV filling pressures and increased pulmonary artery pressure[60] when there is uncertainty on findings during rest. Using an expert panel in our study allowed us to provide the best possible final diagnosis, by adding clinical expertise to all available findings including established HF scores in every participant.[61]

A limitation is that cross-sectional data analysis precludes us from drawing conclusions about causality. Another limitation is that we classified participants as having kidney dysfunction based on a single measurement. Consequently, the strict definition of CKD, including two measurements in 3 months, could not be applied in this population. Also, we were not able to validate our kidney function measurement in our study with other type of kidney damage markers (e.g. urinary samples of albumin or protein). Thus, our approach might have led to incorrect classification of some due to temporary alterations in kidney function. For our main analyses, we have used the

Figure 2 Summary of our results.

Funding
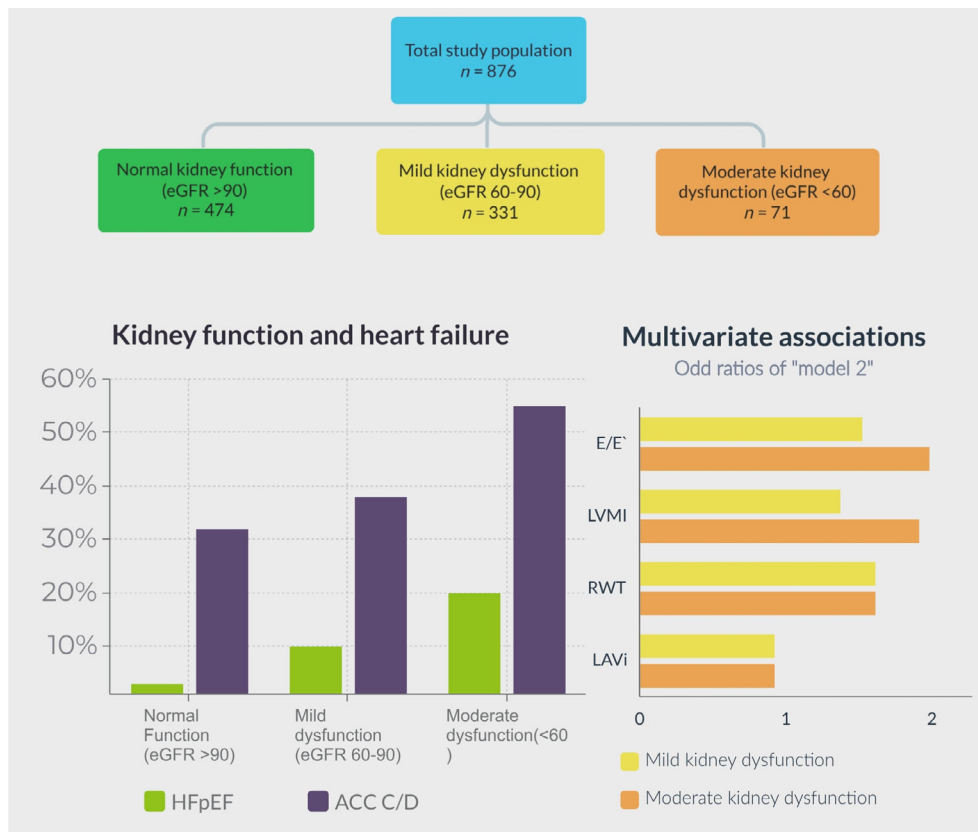
most recent eGFR equation without race, which provides the most accurate GFR estimates.[37] Finally, a low number of participants with moderate to severe renal dysfunction (eGFR < 60 mL/min/1.73 m^2) were present in our study, limiting the precision to explore the association between moderate CKD and HFpEF in specific subgroups. At the same time, some of our analyses have limited power (e.g. HF diagnosis).

Conclusions

Both mild and moderate kidney dysfunction are independently associated with LVDD parameters and HFpEF. This association is independent of sex and strongest for moderate kidney dysfunction. Considering mild-to-moderate kidney dysfunction as risk factor for HFpEF may help identify high-risk groups benefiting most from early intervention.

Conflict of interest

None declared.

Supporting information

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

Table S1. Missing values for baseline characteristics and echocardiography values and panel diagnoses.
Table S2A. Echocardiography values and panel diagnoses regarding heart failure and left ventricular diastolic dysfunction stratified by stages of kidney dysfunction for men.
Table S2B. Echocardiography values and panel diagnoses regarding heart failure and left ventricular diastolic dysfunction stratified by stages of kidney dysfunction for women.

Table S3A. Univariable and multivariable logistic regression for the association between stages of renal dysfunction and echocardiographic measures for men.

Table S3B. Univariable and multivariable logistic regression for the association between stages of renal dysfunction and echocardiographic measures for women.

Table S4. Univariable and multivariable logistic regression for the association between stages of renal dysfunction and echocardiographic measures excluding the patients with heart failure at baseline.

Table S5. Univariable and multivariable linear regression for the association between stages of renal dysfunction and echocardiographic measures excluding the patients with heart failure at baseline.

Table S6. Baseline characteristics of the included patients stratified by renal function excluding the patients with heart failure at baseline.

Table S7. Echocardiography values and panel diagnoses regarding heart failure and left ventricular diastolic dysfunction stratified by stages of kidney dysfunction excluding the patients with heart failure at baseline.

Table S8A. Univariable and multivariable linear regression for the association between stages of renal dysfunction and echocardiographic measures for men.

Table S8B. Univariable and multivariable linear regression for the association between stages of renal dysfunction and echocardiographic measures for women.

Table S9. Univariable and multivariable logistic regression for the association between stages of renal dysfunction and echocardiographic measures.

Table S10. Univariable and multivariable linear regression for the association between stages of renal dysfunction and echocardiographic measures.

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