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REVIEW ARTICLE

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Renal hyperfiltration defined by high estimated glomerular filtration rate: A risk factor for cardiovascular disease and mortality

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Abstract

Renal hyperfiltration, defined as an increased glomerular filtration rate above normal values, is associated with early phases of kidney disease in the setting of various conditions such as obesity and diabetes. Although it is recognized that glomerular hyperfiltration, that is, increased filtration per nephron unit (usually studied at low glomerular filtration levels and often referred to as single nephron hyperfiltration), is a risk factor for the progression of chronic kidney disease, the implications of having renal hyperfiltration for cardiovascular disease and mortality risk are incompletely understood. Recent evidence from diverse populations, including healthy individuals and patients with diabetes or established cardiovascular disease, suggests that renal hyperfiltration is associated with a higher risk of cardiovascular disease and all-cause mortality. In this review, we critically summarize the existing studies, discuss possible mechanisms, and describe the remaining gaps in our knowledge regarding the association of renal hyperfiltration with cardiovascular disease and mortality risk.

KEYWORDS
cardiovascular disease, cardiovascular mortality, diabetes, glomerular hyperfiltration, renal hyperfiltration

1 | INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality globally,[1] accounting for >30% of global deaths.[2] An important risk factor for cardiovascular (CV) mortality is chronic kidney disease (CKD). In particular, a low glomerular filtration rate (GFR) has been associated with high CV risk. In patients with stage 3 CKD, CV mortality is approximately twice as probable and the risks of developing heart failure, stroke, peripheral artery disease, coronary heart disease (CHD) and atrial fibrillation are significantly increased compared with individuals with normal kidney function, independently of age,[3] gender[4] and ethnicity.[3-9]

However, beyond this relationship solely with impaired kidney function, CV risk is not only increased with low GFR, but also with higher than normal GFR. Patients in this elevated GFR group have been defined as hyperfilterers based on "whole kidney" renal hyperfiltration (RHF), a condition that should be differentiated from glomerular hyperfiltration (GHF) or "single-nephron" hyperfiltration, which occurs in subjects with decreased total GFR or decreased renal mass (as discussed below). RHF is defined as estimated GFR (eGFR) of more than two standard deviations above the mean GFR of healthy individuals[10] by the kidney disease outcomes quality initiative (K/DOQI) guidelines. The clinical description of RHF is "an 'unexpectedly high eGFR' above a certain threshold, varying between 130 and 140 ml/min per 1.73 m^2".[11] The strict definition of this threshold is complicated by the fact that GFR also varies among individuals of different sex, ethnicity and nephron number at birth. Furthermore, there is considerable GFR variability over time, including age-related GFR decline, and inaccuracy in GFR measurements, as virtually all studies estimate GFR through plasma creatinine measurements. Nevertheless, RHF is a frequently observed, albeit disregarded phenomenon, observed in both physiologic and pathologic states, including pregnancy, high protein diets, early diabetes and obesity.[2,11-20] The importance of RHF was proposed by Mogensen et al., who showed that an early phase of renal involvement in patients with type 1 diabetes frequently involves a period of elevated GFR levels, which leads to a slow decline in kidney function over time, ultimately leading to end-stage kidney disease in a proportion of those afflicted with this condition.[21]

GHF, on the other hand, is a condition that occurs in patients with impaired kidney function and/or reduced nephron numbers, reflecting increased filtration per single nephron, which has been classically considered the culprit of subsequent renal injury in various kidney diseases,[22] and is characterized by increased glomerular pressure.[23,24] In humans, the filtration fraction (GFR/renal plasma flow) is used as a surrogate for glomerular pressure, but is impractical for utilization in large populations given the elaborate techniques required to measure GFR and renal plasma flow. This, in part, explains why the prognostic importance of increased glomerular pressure with respect to renal and CV outcome is unknown in humans.

RHF has long been recognized as associated with certain diseases. However, it has only been recently suggested that RHF has an independent predictive value for clinical outcomes, such as increased CV and overall mortality,[25,26] as well as for eGFR decline.[26,27] RHF is also related to an increased incidence of coronary artery calcification[25,28] and left ventricular hypertrophy.[25,29] Some meta-analyses examining the relationship between CKD and mortality have also reported an increased mortality risk in patients with high GFR values.[3,4,30,31]

However, whether this concerns a cause-and-effect relationship, and which underlying mechanisms are involved, is not well-defined. Considering these uncertainties, we critically summarized the studies exploring the association between high GFR and CVD and overall mortality in a systematic review.

2 | METHODS

2.1 | Data sources and literature search

The electronic databases of Ovid-MEDLINE, PubMed/MEDLINE, Web of Science, EMBASE (Elsevier), CINAHL (EBSCO), Cochrane Central Register of Controlled Trials (Wiley), and the clinicaltrials.gov website were searched (up to September 7, 2018) using the terms "GFR", "hyperfiltration", "mortality", "cardiovascular events", "all-cause mortality" and "cardiovascular mortality". The search was limited to peer-reviewed journals and congress abstracts (American Society of Nephrology, International Society of Nephrology, European Renal Association, American Heart Association, European Society of Cardiology) that were published in English from January 1988 to September 2018. Unpublished data were not included in the study (Figure 1). Three authors (L. A. E., E. O. and M. K.) independently screened the titles and abstracts, and the full text if needed, of the search results, to determine which studies fulfilled the inclusion criteria. A manual search of reference lists from relevant articles was also conducted.

2.2 | Study selection

Eligibility criteria for inclusion in this review were: (i) prospective (randomized or non-randomized), cross-sectional or retrospective design; (ii) estimation or measurement of GFR through serum creatinine-based equations or other means; and (iii) reports of all-cause mortality, CV risk indicators, CV events (CVEs) and/or mortality. Exclusion criteria included (i) the absence of an adequate description of results despite requesting missing data from the corresponding author of the article, and (ii) articles not classified as original articles (e.g. reviews and meta-analyses).

Quality assessment of the included studies was conducted using the Newcastle Ottawa Scale.[32] This scale takes into account three dimensions of a study to determine its relative quality: selection of study groups, comparability of the groups, and assessment of outcome. Stars were given for each quality item to serve as a quick visual assessment; studies of the highest quality were awarded nine stars (Table S1).

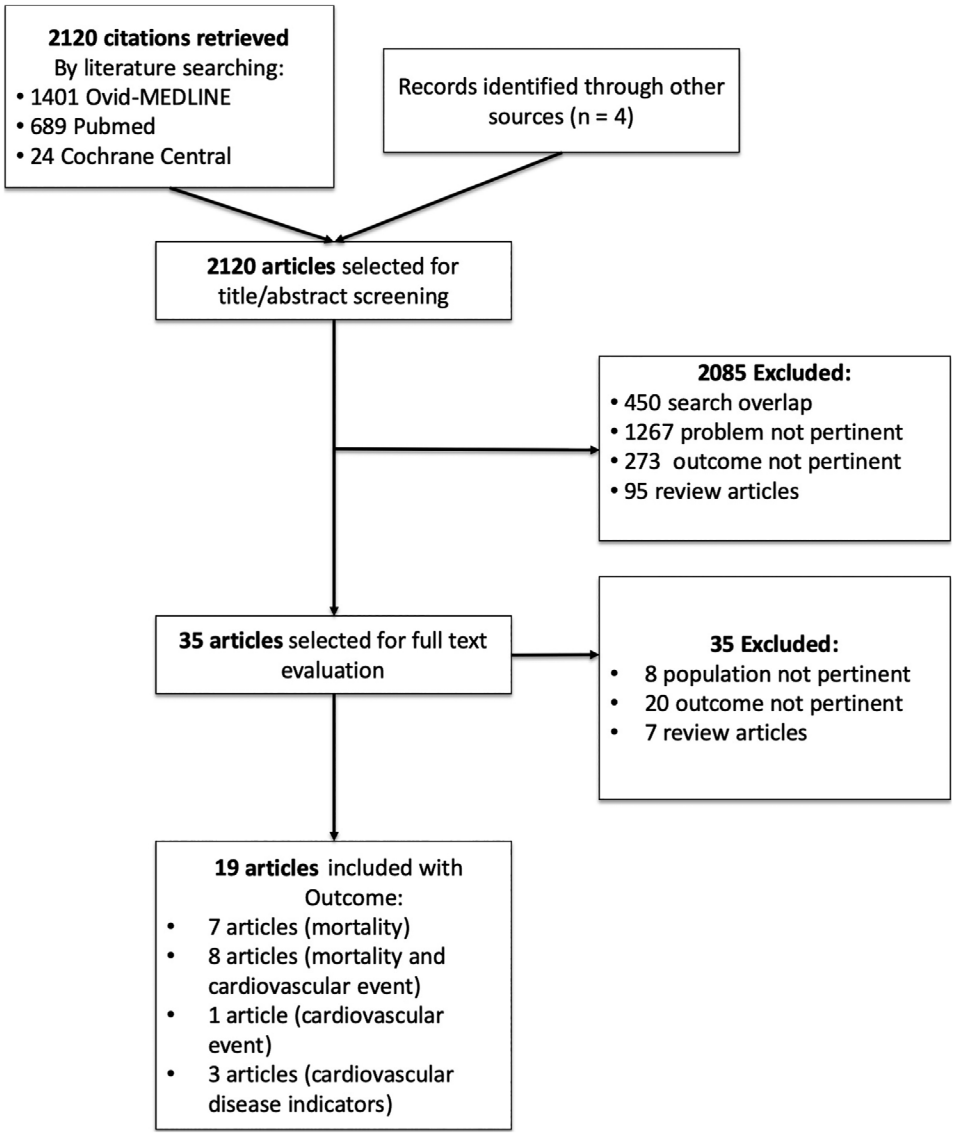

FIGURE 1 Flow diagram of the study selection process

2.3 | Outcome measures

We assessed the association between RHF/high GFR with all-cause mortality, CVEs, CVD indicators and CV mortality.

3 | RESULTS

Nineteen studies, three cross-sectional, five prospective and 11 retrospective, fulfilled the entry criteria for investigating the relationship between RHF/high renal function and all-cause mortality, CVEs or CVD indicators. All reviewed studies involving all-cause and CV mortality, and CVE/CVD indicators, are summarized in Table 1. The majority of these studies were performed in general cohorts, while three included patients with type 2 diabetes,[33-35] five included patients with prior CVD,[27,35-38] and one included patients without diabetes and prior CVD.[39] The assessments used to study GFR were heterogeneous: one used eGFR/kidney length and kidney volume,[26] one used measured GFR (mGFR) by iohexol clearance,[25] one used GFR measured by creatinine clearance,[29] while the others used eGFR calculated with either Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[26-28,34,35,40-44] and/or Modification of Diet in Renal Disease (MDRD) Equations.[27,33,36-39,43,45,46]

Some of the studies abstained from using the terminology "hyperfiltration", considering that high eGFR values may not be an accurate indication of true RHF, and used instead the terminology "high/-highest GFR quartiles/groups".[35,36,39,40,43,45,46] Several authors never used the "hyperfiltration" term in their studies and discarded their findings of high GFR merely as a "false overestimation of GFR by creatinine-based equations".[38-40,45] In fact, only a few studies defined the high-GFR group as "hyperfiltering patients"[27,34,42,44] or indicated that these represented 'hyperfiltration'.[26,37]

3.1 | RHF and all-cause mortality

Fourteen studies examined the relationship between RHF and all-cause mortality; the odds ratios that were provided in those studies

TABLE 1 Characteristics of the included trials for renal hyperfiltration

Trials (year)	Type	RHF definition/ highest eGFR category threshold	Patient group and number (n)	Age[a] (years)	Sex (% males)	GFR measurement method	GFR (ml/min per 1.73 m^2)	Follow-up (years)[a]	Outcome measure	CV/overall death/CVE	Effect of RHF
Park et al. (2015)[44]	Retrospective cohort	eGFR >95th percentile after adjustments[b]	43 503 (GFR ≥60)	49.2 ± 10.4	51.2	CKD-EPI	Overall 80.36 ± 11.5	Median 12.4	Mortality	1743 deaths 330 CV deaths	HR of all-cause mortality for RHF was 1.37 (95% CI, 1.11 to 1.70)
Altay et al. (2014)[27]	Prospective cohort	eGFR >110	469 with no CHD 320 with CHD total 789	55.6 ± 8.2	35 with no CHD 69 with CHD	CKD-EPI and MDRD	Highest eGFR group 117.3 ± 6.8	Median 1.8	Volunteers free of CKD: CVD and death	25 all-cause death 75 CV/ pulmonary events	RR 6 for combined death, CV and pulmonary events for RHF
Choi et al. (2015)[28]	Cross-sectional	Highest eGFR category defined as eGFR >105	6986	48.1 (range 46.5–50.5)	100	CKD-EPI	Overall 89.3 (79.9–100.6) highest eGFR group 107.1 (106.2–107.8)	NA	Coronary artery calcium scores and e-GFR in healthy volunteers	321 CAC	High GFR is associated with CAC in middle-aged Korean men without CKD
Eriksen et al. (2013)[25]	Cross-sectional	Highest GFR (measured by iohexol clearance) category defined as GFR ≥101.2	1521	Range 50–62	49.3	Single-sample plasma clearance of iohexol	Highest eGFR group 107.6 (103.9–113.7)	NA	Evaluation of the carotid USG and ECHO for carotid plaque area and LVH in healthy volunteers	NA	Both greater than normal carotid plaque area and LVH were associated with increased GFR (OR 1.56, 95% CI 1.02–2.39 for carotid plaque and OR 1.62, 95% CI 1.10–2.38 for LVH)
Reboldi et al. (2018)[41]	Retrospective cohort	eGFR >95th percentile (adjusted for age and sex)	8794 (7805 with hypertension)	52.3 ± 15.7	55	CKD-EPI	Highest eGFR group 111.2 (99.1–126.7)	Mean 6.2	CVE	722 CVE	High GFR associated with an increased risk of CVE [HR 1.5 (95% confidence

(Continues)

TABLE 1 (Continued)

Trials (year)	Type	RHF definition/ highest eGFR category threshold	Patient group and number (n)	Age[a] (years)	Sex (% males)	GFR measurement method	GFR (ml/min per 1.73 m^2)	Follow-up (years)[a]	Outcome measure	CV/overall death/CVE	Effect of RHF
											interval 1.2–2.1)]
Tonelli et al. (2011)[43]	Prospective cohort	Highest eGFR category defined as eGFR >105	1526 437	Range 21–88.6	44.2	Non-isotope/ isotope dilution mass spectrometry traceable MDRD study equation	NA	Median 3 range 0–4.9	CVE and overall mortality	27 959 deaths 5772 MI 4692 stroke/ TIA	High GFR was associated with an increased risk for overall mortality (HR of death 3.7 for eGFR >105) compared with the reference group
Schmieder et al. (1990)[29]	Cross-sectional	eGFR >130	111	47 ± 9	90.1	Creatinine clearance	Highest eGFR category 142 ± 14	NA	The left ventricular cross-sectional area and mass measured in patients with essential hypertension for the relationship between RHF and LVH	NA	HTN patients with LVH disclosed a higher GFR and filtration fraction than those without LVH
van der Sande et al. (2017)[26]	Retrospective cohort	Highest eGFR/ cm^3 category >0.6 highest eGFR/ cm^3 > 7.8	6926	Range 46–73	73.8	CKD-EPI	Highest eGFR/ cm^3 category 87 ± 13	Median 7	Patients with pre-existing arterial disease were biannually questioned about CVE, CV mortality and all-cause mortality. The correlation	1117 CVE 1235 deaths	High e-GFR/ volume and e-GFR/length, which might indicate RHF, are related to kidney function decline. High e-GFR/length confers an

(Continues)

TABLE 1 (Continued)

Trials (year)	Type	RHF definition/ highest eGFR category threshold	Patient group and number (n)	Age[a] (years)	Sex (% males)	GFR measurement method	GFR (ml/min per 1.73 m^2)	Follow-up (years)[a]	Outcome measure	CV/overall death/CVE	Effect of RHF
									between the variables mentioned above and e-GFR/kidney volume was analyzed using Cox regression		increased risk for all-cause mortality in patients with clinically manifest vascular disease
Cox et al. (2008)[46]	Retrospective cohort	Highest eGFR category eGFR >120	33 386	Median 68 (range 60–76)	NA	MDRD	NA	6	The data of patients since 2000 and mortality ratios in 2006 were collected	6367 deaths	Mortality among RHF patients was higher than reference GFR. HR 1.29 (1.19–1.41) for GFR 90–119; HR 2.63 (2.16–3.21) for GFR 120–150. As a marker of mortality, both low and high eGFRs are equally predictive of increased mortality
Yoo et al. (2017)[42]	Retrospective cohort	eGFR >95th percentile (adjusted for age and sex)	114 966	Median 54.4	53.4	CKD-EPI	Overall 92.7 ± 10	6.25	Correlation between RHF and mortality	2559 deaths	Significant association between mortality and hyperfiltration only in men
Inrig et al. (2007)[36]	Retrospective cohort	Highest eGFR category eGFR >125	8941 with atherosclerotic vascular disease	62.2 ± 11.1	70.7	MDRD	NA	Median 1	Correlation between the composite end point of	750 composite endpoint (death, MI,	An elevated risk of CV outcomes among

(Continues)

TABLE 1 (Continued)

Trials (year)	Type	RHF definition/ highest eGFR category threshold	Patient group and number (n)	Age[a] (years)	Sex (% males)	GFR measurement method	GFR (ml/min per 1.73 m^2)	Follow-up (years)[a]	Outcome measure	CV/overall death/CVE	Effect of RHF
									death/ CVE and eGFR (calculated with MDRD formula)	CHF and stroke)	patients with atherosclerotic CVD who had an eGFR ≥125. The relationship between eGFR and CV outcomes was parabolic with increased risk with both reduced and elevated eGFRs
Putaala et al. (2011)[36]	Retrospective cohort	eGFR >120	958 young patients with first ever ischaemic stroke	41.2 ± 7.7 range 15–49	62.9	MDRD	Overall mean 93 (80–107)	Mean 8.9 ± 3.8	To assess the association between eGFR and all-cause mortality and CVE in young poststroke patients	199 composite vascular endpoint	Low and high GFR predicted long-term mortality after ischaemic stroke
Luo et al. (2014)[35]	Retrospective cohort	Highest eGFR category eGFR >120	4836 with cerebrovascular events and type 2 diabetes	Range 41–82	57.6	CKD-EPI equation with adjusted coefficient of 1.1 for the Asian population	Overall median 92.6 highest eGFR category 126.9 (123.0–136.5)	1 year after stroke onset	Patients with type 2 diabetes were followed for 1 year after the incidence of acute stroke and data were correlated with eGFR values (calculated with CKD-EPI)	1422 deaths 2024 stroke recurrence	Low and high eGFR were independent predictors of all-cause mortality after ischaemic stroke. High eGFR associated with an increased risk of adverse outcomes in all stroke subtypes

(Continues)

TABLE 1 (Continued)

Trials (year)	Type	RHF definition/ highest eGFR category threshold	Patient group and number (n)	Age[a] (years)	Sex (% males)	GFR measurement method	GFR (ml/min per 1.73 m^2)	Follow-up (years)[a]	Outcome measure	CV/overall death/CVE	Effect of RHF
Davis et al. (2016)[34]	Retrospective cohort	eGFR ≥120 mL	1296 with type 2 diabetes	Mean 64 ± 11.3	48.6	CKD-EPI	NA	12.6 ± 6.1	Association between eGFR and all-cause mortality in community-based patients with type 2 diabetes	738 deaths	High eGFR was associated with increased risk of all-cause mortality (HR 2.01 above GFR > 90)
Mostofsky et al. (2009)[38]	Retrospective cohort	Highest eGFR category >125	1175 patients hospitalized with acute ischaemic stroke	Range 42.6–90	45.4	MDRD	Overall mean eGFR 72	Median 3.3	Association between eGFR and mortality risk among patients hospitalized for acute ischaemic stroke	508 deaths	The association between high eGFR and all-cause mortality did not reach statistical significance
Di Angelantonio et al. (2010)[45]	Prospective cohort	Highest eGFR category >90	16 958 without manifest vascular disease	Mean 53 (range 33–81)	49	MDRD	Overall mean 78.7 (14.4)	Median 24	Association of CKD stages with CVD and non-vascular mortality	4010 CHD outcomes 559 deaths from stroke 662 deaths from other vascular causes 3875 deaths from non-vascular cause	eGFR >90 was associated with CHD and non-vascular mortality
Donfrancesco et al. (2013)[40]	Retrospective cohort	Highest eGFR category ≥109	2924	Mean 53	50	CKD-EPI	Highest eGFR category 114 ± 4	Median 10.3	Association of eGFR and all-cause mortality and CVD	246 deaths 146 CVE	High eGFR associated with increased all-cause mortality and incident CVD
Groop et al. (2009)[33]	Prospective cohort	Highest eGFR category >120	4201 with type 1 diabetes	Range 24–52	45	MDRD	NA	Median 7	Premature mortality in type 1 diabetes	291 deaths	High eGFR associated with increased mortality

(Continues)

TABLE 1 (Continued)

Trials (year)	Type	RHF definition/ highest eGFR category threshold	Patient group and number (n)	Age[a] (years)	Sex (% males)	GFR measurement method	GFR (ml/min per 1.73 m^2)	Follow-up (years)[a]	Outcome measure	CV/overall death/CVE	Effect of RHF
											independent of the presence of albuminuria
Van Biesen et al. (2007)[39]	Prospective cohort	Highest quartile of eGFR (eGFR >104.3 mL/ min/1.73m^2)	8913 without diabetes and CVD	Mean 48.2	52	MDRD	Overall mean eGFR 92.0 ± 26.5 mL/ min/1.73m^2	Median 10	Level of GFR below which CV mortality starts to increase	783 deaths	High eGFR was associated with decreased risk of CV mortality

Abbreviations: BP, blood pressure; CAC, coronary artery disease; CHD, coronary heart disease; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; CVD, cardiovascular disease; CVE, cardiovascular events; ECHO, electrocardiogram; eGFR, estimated glomerular filtration rate (in ml/min/1.73 m^2); GFR, glomerular filtration rate; HTN, hypertension; LVH, left ventricular hypertrophy; MDRD, the Modification of Diet in Renal Disease; MI, myocardial infarction; NA, not available; RR, relative risk; RHF, renal hyperfiltration; TIA, transient ischaemic attack; USG, ultrasonography.

[a]mean ± SD, median or range.

[b]adjusted for age, sex, muscle mass, and history of diabetes and/or hypertension medication.

are given in Figure 2.[26,27,33-38,40,42-46] Eleven of these defined hyperfiltration/high GFR according to different thresholds of eGFR,[27,33-38,40,43,45,46] while one study assessed quartiles of eGFR/kidney length and eGFR/kidney volume,[26] and the remaining two used adjusted eGFR percentiles (for gender and age in both studies; and for muscle mass, history of diabetes/hypertension medication in one study).[42,44] Except for one study,[38] all of these studies found a significant association between mortality and hyperfiltration.

Tonelli et al. observed that hyperfiltration (eGFR >105 mL/min per 1.73 m^2) was associated with an increased risk of death after adjustment for age and exclusion of patients with diagnosed diabetes.[43] Similar findings were reported by Park et al., who found increased mortality in the hyperfiltrating group [adjusted for possible confounding factors; the significance of the association did not change according to body mass index (BMI)].[44] Another study observed that the risk of mortality increased as the eGFR increased when compared with a reference eGFR of 60–89 mL/min per 1.73 m^2.[44] In a study including only patients with clinical CVD, van der Sande et al. showed increased risk of all-cause mortality in the highest quartile of eGFR/kidney length ratio, which was presumed to represent hyperfiltration.[26] Altay et al. analyzed a "combined outcome" of mortality plus CVE and found a significantly increased risk for the highest eGFR quartile in patients with and without CVD.[27] Yoo et al. found a significant association between mortality and hyperfiltration only in men (multivariate analysis)[42]; this association was not affected by diabetes or hypertension.[42] Davis et al. studied the relationship between eGFR and all-cause mortality in patients with type 2 diabetes, showing that the strongest association for all-cause mortality was present for eGFR >90 mL/min/1.73 m^2 (compared with stage 3 CKD – eGFR 45–59 mL/min/1.73 m^2 – as a reference).[34]

Among patients with baseline atherosclerotic CVD, Inrig et al. showed an increased risk of all-cause mortality and CV outcomes in the eGFR ≥125 mL/min/1.73 m^2 group. Above an eGFR ≥100 mL/min/1.73 m^2 threshold, each 10 mL/min/1.73 m^2 increase in eGFR was associated with a 9% increase in the risk for the combined outcome.[36] Putaala et al. reported that a high eGFR (≥120 mL/min/1.73 m^2) was significantly related to higher risk of all-cause mortality after first ever ischaemic stroke in young patients (aged 15–49 years); importantly, the association remained significant after adjustment for age, gender, traditional risk factors, stroke severity and stroke subtype.[37] Similar findings were observed in another study: a significant association between high eGFR (≥120 mL/min/1.73 m^2) and increased risk of all-cause mortality in patients with type 2 diabetes followed a first stroke.[35] A study including more than 4000 patients with type 1 diabetes showed that high eGFR correlated to increased mortality risk.[33] Among elderly people, Donfrancesco et al. found that eGFR ≥109 mL/min/1.73 m^2 was associated with a 4-fold risk of mortality when compared with an eGFR range of 90–108 mL/min/1.73 m^2, while the same association was not observed for the 35 to 59-year-old group.[40]

Some studies included in this systematic review also reported on the relationship between low eGFR (as a definition of CKD) and

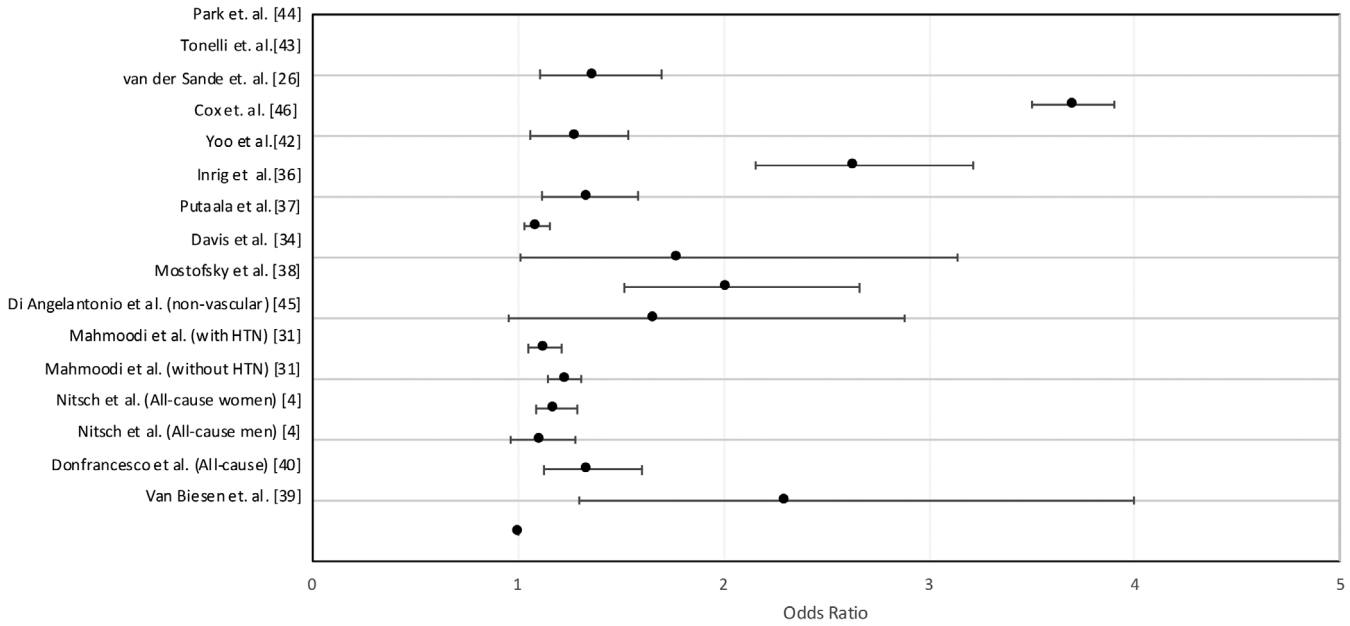

FIGURE 2 The effects of odds ratios of renal hyperfiltration versus normal renal function on development of all-cause mortality. Only the odds ratios that were provided in the studies are given. HTN, hypertension

mortality. In one study performed in patients hospitalized for acute ischaemic stroke, Mostofsky et al. found a U-shaped link between eGFR and all-cause mortality, but the curve increased sharply at eGFR values above 110 mL/min/1.73 m^2. The all-cause mortality rate was 66% higher among patients with eGFR >125 mL/min/1.73 m^2 compared with patients with eGFR 75–125 mL/min/1.73 m^2.[38] Finally, in a cohort study with approximately 17 000 participants followed for a mean of 24 years, Di Angelantonio et al. showed that an eGFR ≥90 mL/min/1.73 m^2 was associated with an increased risk of non-vascular mortality, with borderline significance after full adjustments.[45]

3.2 | RHF and development of CVEs and death

The relationship between hyperfiltration and CVEs was assessed in eight studies; the odds ratios that were provided in the studies are given in Figure 3.[26,27,39-41,43-45] Most of these studies also assessed all-cause mortality, as described above. Six of the studies revealed significant associations between RHF and CVEs,[27,40,41,43-45] and three reported associations between RHF and CV mortality[4,30,31]; only two reported no significant associations between these outcomes and RHF.[26,39]

Park et al. reported a higher risk of developing hypertension and CVD in subjects with hyperfiltration after adjusting for confounding factors.[44] Similarly, another study showed that hyperfiltration was a predictor of CVEs, independent of BMI and albuminuria.[41] After excluding patients with diabetes from the analysis, the relationship remained significant. Tonelli et al. reported a borderline significant increase in stroke/transient ischaemic attack risk in the high eGFR quartile, while acute myocardial infarction (MI) risk was lower in the same quartile.[43] One of the highest hazard ratios was reported by Donfrancesco et al., as incident CVD risk increased in the eGFR ≥109 mL/min/1.73 m^2 category by 7.0 (2.2–22.9) among the elderly.[40] Besides all-cause mortality, a study showed that eGFR ≥90 mL/min/1.73 m^2 was modestly associated with CHD.[45] Finally, although they reported a significant relationship with mortality, van der Sande et al. did not find a relationship between CVEs and eGFR/kidney length or eGFR/kidney volume in patients with clinically manifest CVD.[26] Similarly, a population-based study that included subjects without diabetes and CVD found the lowest mortality in subjects in the higher eGFR group.[39]

3.3 | RHF and CVD indicators

Three studies assessed the relationship between various CVD indicators and GFR.[25,28,29] Eriksen et al. studied total carotid plaque area and left ventricular hypertrophy as indicators of atherosclerotic disease.[25] This study is especially relevant as GFR was measured by iohexol clearance, thus precluding any impact of reduced muscle mass (a feature that lowers serum creatinine values) on the results. The high mGFR quartile was associated with higher total carotid plaque area and left ventricular hypertrophy compared with the lowest mGFR quartile group, even after adjustment for CV risk factors, urinary albumin excretion and fasting serum glucose.[25] Similarly, a recent study showed that high eGFR was associated with coronary artery calcification in middle-aged Korean men in a fully adjusted model.[28] Another study evaluated echocardiographic left ventricular hypertrophy in patients with mild to moderate essential hypertension and showed a significant correlation between left ventricular mass and high eGFR. Also, the cardiac index was significantly higher in the group with the highest eGFR (eGFR >130 mL/min/1.73 m^2).[29]

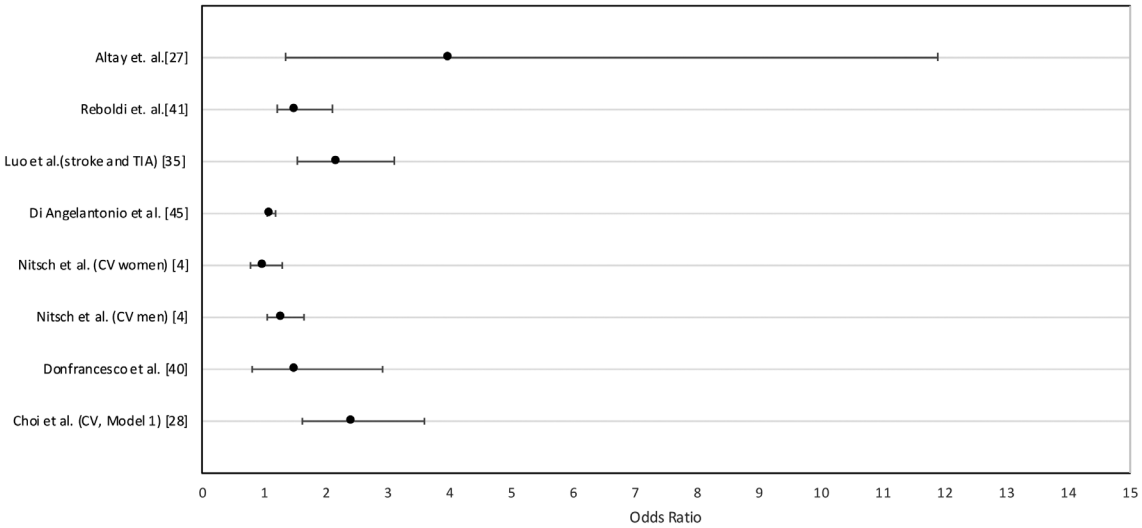

FIGURE 3 The effects of odds ratios of renal hyperfiltration versus normal renal filtration on development of cardiovascular event or disease. Only the odds ratios that were provided in the studies are given. CV, cardiovascular; TIA, transient ischaemic attack

4 | DISCUSSION

The findings collected in this review suggest that RHF is independently associated with CV and all-cause mortality, as well as with clinical and subclinical CVD.

Although the pathophysiology of RHF and its consequences for kidney disease are well known, the potential systemic consequences are not well established. The evaluation of studies describing the association between RHF and mortality strongly suggests RHF to be a powerful predictor of mortality and CVD, with 13 out of 15 studies reporting a significant correlation with mortality.[26,27,33-40,42-46] In addition, seven studies reported that RHF is a predictor of CVD.[26,27,40,41,43-45] From our literature search, three studies found RHF to be significantly associated with surrogate CVD endpoints: total carotid plaque area,[25] coronary artery calcification[28] and left ventricular hypertrophy,[25,29] which are all considered as subclinical CVD indicators.

Approximately 20–50% of patients with diabetes have been reported as having RHF early in the course of the disease, and constitute a high-risk population for RHF. Given that diabetes is a risk factor for RHF development and also for increased risk of CVD and mortality, it is crucial to show whether the association between RHF and mortality/CVD is dependent on the presence of diabetes. Of the 15 studies that did not solely include patients with diabetes, the risk was adjusted for a history of diabetes in nine studies.[26,28,37,38,40-43,45] In three studies, excluding patients with diabetes in sensitivity analyses did not change the results.[41,43,44] Furthermore, one study revealed an association between RHF and mortality in patients with and without diabetes.[42] Putaala et al. also found that RHF was associated independently with both type 2 diabetes and increased risk of death.[37] Interestingly, Van Biesen et al. included subjects without diabetes and CVD and found the lowest CV mortality in subjects in the higher eGFR group.[39] Current findings suggest that the association between RHF and mortality and CVD is seen in both diabetic and non-diabetic populations, although patients with diabetes have a higher risk of developing RHF.

4.1 | Potential mechanisms

Beyond describing the relationship between RHF and CVD, it is also important to consider potential mechanisms responsible for this phenomenon, as illustrated in Figure 4. First, RHF may be a simple marker for the presence and severity of the primary pathology causing RHF itself, such as diabetes, hypertension and obesity. Increased severity of those conditions could also lead to increased risk of mortality. Indeed, factors associated with these conditions, such as renin angiotensin aldosterone system (RAAS) activation and increased sympathetic nervous system activity may lead to the development of RHF[47,48] and premature mortality.[13,49,50] Interestingly, Reboldi et al. found an increased 24-hour pulse pressure in patients with RHF, suggesting increased large-artery stiffness and peripheral vascular alterations. Such alterations, in turn, may lead to increased risk of CVEs.[41] The same study also showed that hyperfiltering individuals had an attenuated nocturnal decrease in blood pressure, possibly as a result of sympathetic overactivity and RAAS activation.[41] In addition, other vascular processes that drive hyperfiltration, including endothelial dysfunction, increased arterial stiffness, higher blood pressure and low-grade inflammation, may similarly drive large-vessel disease leading to CVEs.[51-55] However, there are arguments against the hypothesis that RHF is merely a disease marker, such as the lack of any difference in the association between RHF and mortality in patients with or without diabetes or in any subgroup analysis of several studies, as discussed above.

Another explanation may be the direct harmful effect of RHF on the kidney because of disturbed glomerular haemodynamics, as already established in diabetes and obesity.[56-58] However, in such a

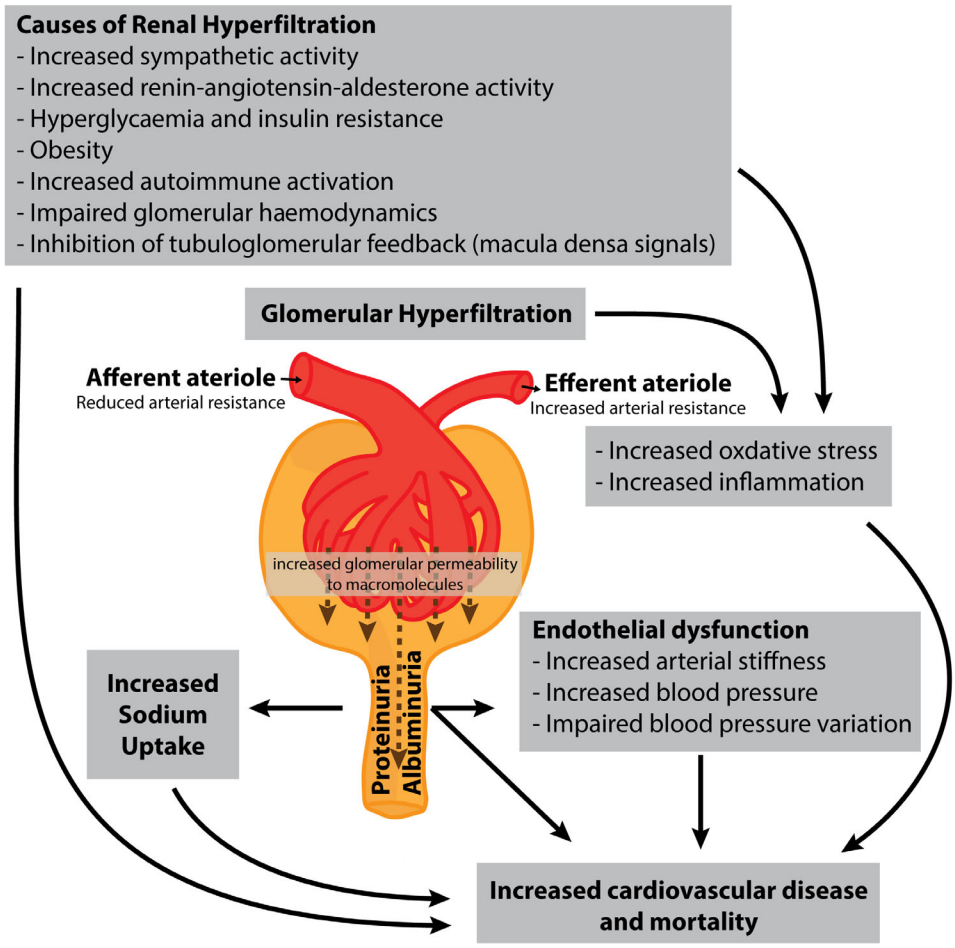

FIGURE 4 Postulated mechanisms for association between glomerular hyperfiltration and cardiovascular disease

scenario, it would be expected for high eGFR to have a stronger correlation with CKD progression than with mortality, which was not observed in two studies.[43,58] Hence, it is probable that a systemic pathophysiology underlies the increased risk of mortality rather than a predominantly renal pathology. It is also not plausible to attribute the increased mortality risk to the detrimental effects of albuminuria, as the studies have shown the association to be independent of albuminuria, as discussed above.

It has been proposed that high eGFR values may not reflect a true hyperfiltration but rather decreased serum creatinine caused by low muscle mass and inflammation. If this hypothesis was correct, then no association between mGFR and CV outcomes should have been reported. All the reviewed studies here, except for Eriksen et al.,[25] used serum creatinine-based eGFR, not mGFR, making assessments vulnerable to bias from non-GFR factors that regulate serum creatinine values. Although most of the reviewed studies included BMI in their adjustments, BMI alone is insufficient to assess muscle mass.

Given that sarcopenia is predictive of mortality[59] and all-cause mortality includes death because of malignancy and chronic diseases associated with cachexia, which are common in the elderly, muscle mass could be a confounding factor for the relationship between all-cause mortality and serum creatinine levels. However, such studies were adjusted for surrogates of muscle mass. For example, in a cohort of young apparently healthy men with a mean age of 18.4 years, RHF was associated with high metabolic risk, in terms of blood pressure, glucose, HDL-cholesterol, triglycerides and BMI.[60] Importantly, the analysis was adjusted for fat-free mass, completely excluding the possibility of a low muscle mass bias.[60] Nevertheless, some studies have attributed the association between RHF and mortality to the low muscle mass among the elderly and females rather than to any underlying disease-related cachexia.[61] Most of the studies examining the association of RHF and outcomes found significant associations even after adjusting for age and gender, suggesting that the increased risk of mortality is not completely explained by the lower creatinine levels in the elderly and in females.[46] In this regard, a cohort consisting of only young (aged 15–49 years) patients with ischaemic stroke also showed significantly increased risk of mortality in RHF patients.[37]

Inflammation associated with elevated cardiorenal metabolic risk has also been proposed to explain the higher risk of CVEs and mortality in patients with RHF[62-64] by mechanisms beyond reduced muscle mass.[27,65] Low-grade systemic inflammation is associated with oxidative stress, which could cause oxidative damage to circulating creatinine, favouring its aggregation to components such as apoA-I and adiponectin,[66] leading to low serum creatinine levels. The strongest argument against the role of a decreased muscle mass or interference with serum creatinine assessment comes from the study by Eriksen et al.[25] of more than 1500 subjects, which reported a significant

association between subclinical CVD and high mGFR by iohexol clearance, showing a relationship between RHF and CVD for the first time using true GFR. However, additional studies using mGFR that address its relationship with hard outcomes are needed to clarify the association of RHF with outcomes.

An additional potential mechanism that has not been adequately explored is proximal tubular cell overload by molecules filtered in excess by hyperfiltrating glomeruli that have to be reabsorbed, which is referred to as the tubular hypothesis. While the mechanism for the CV protection afforded by sodium-glucose co-transporter-2 (SGLT-2) inhibitors is still being debated,[67] the key mechanism of action is to decrease glucose reabsorption in proximal tubules, that is, decreasing the proximal tubular overload of excessively filtered molecules (in the case of diabetes, glucose overload). Some of these molecules are reabsorbed together with sodium (e.g. phosphate, glucose), facilitating sodium overload, while others, such as albumin, directly decrease the expression of nephroprotective and antiageing factors such as klotho by tubular cells.[68-70] Increased proximal tubular reabsorption of excessively filtered albumin secondary to RHF may prevent albumin from leaking into urine in the form of pathological albuminuria. The increased sodium reuptake, probably secondary to tubular hyperglycaemia and SGLT-2 upregulation, which inhibits tubuloglomerular feedback, drives hyperfiltration (by lowering afferent arteriolar pressure) and is believed to contribute to CV disease.

4.2 | Potential confounders

Several confounders may limit the validity of the current conclusions. Next to the lack of accuracy of the GFR measurements discussed above, the included studies also show variations in co-morbidities for the high-eGFR group. Well-known risk factors for CVD and mortality, such as hypertension, body weight and albuminuria, could also have distorted the correlations found between renal hyperperfusion and outcome. Unfortunately, no study has been designed to evaluate the effect of BMI on the association of RHF with mortality or CVD. Low muscle mass may lead to low BMI and interfere with the accuracy of creatinine-based assessment of eGFR. BMI is one of the most important covariants in RHF studies. Most of the studies included BMI in their adjusted analysis,[25-28,34-36,40,44,45] while one was adjusted for obesity,[37] and another excluded patients with BMI < 18.5 kg/m^2,[44] with no significant change in the results.

It is well known that albuminuria is a strong predictor of mortality,[6] and such a relationship has been also shown in some studies discussed here,[41,43] raising concern that the association between RHF and adverse outcomes may be linked to the detrimental effects of albuminuria. Indeed, severe albuminuria will increase GFR by lowering oncotic pressure in the intracapillary compartment and by increasing it in the urinary compartment of the Bowman's capsule. However, all of the studies that used models adjusted for albuminuria found the association of RHF with all-cause mortality and CVD to be independent of urinary protein excretion.[25,26,34,42,44]

4.3 | Discrepant findings

Most of the reviewed studies have similar findings, although some discrepant results should be noted. Tonelli et al. found a trend towards a lower risk of acute MI in the high-eGFR group.[43] In the absence of statistical significance, these results are difficult to interpret. Van der Sande et al. did not find a significant association between CVEs and eGFR/kidney length or eGFR/kidney volume in patients with clinically manifest vascular disease.[26] However, the interpretation that high eGFR/kidney length or volume represents RHF has yet to be confirmed, as differences in kidney size are not particularly characteristic of type 2 diabetes or patients without diabetes, but have been reported in type 1 diabetes. Also notable was the discrepancy between women and men in terms of RHF associations in two studies: Yoo et al.[42] observed that RHF had a significant correlation with mortality only in men; however, women have both a lower CV risk[71] and all-cause mortality risk than men.[4]

Donfrancesco et al. observed age group differences in RHF associations. RHF was related to increased risk of mortality only in elderly patients but not in people younger than 60 years old.[40] Again, in the general population, the risk of death is higher in older individuals. There have been contradictory data in studies on younger populations.[28,37]

On the other hand, glomerular hyperfiltration without RHF usually occurs in preterm infants. An interesting study showed that five children born with extremely low birthweight (23–25 weeks of gestation, birthweight ranging from 532–732 g) all had proteinuria when they were aged 6–15 years. Renal biopsy showed a diffuse increase in glomerular size, consistent with glomerular hypertrophy. The authors speculated that there was compensatory glomerular hyperfiltration, hypertrophy and hypertension in children born with extremely low birthweight when they developed proteinuria.[72] Observational studies have also revealed high rates of CKD in survivors of neonatal acute kidney injury. Proposed mechanisms include nephron loss and hyperfiltration for the progression of CKD following acute kidney injury.[73]

In a recent article, Oliver-Williams et al. explored the association between parity and subsequent CVD in women based on the atherosclerosis risk in communities (ARIC) study.[74] Data were from 8583 white and African American women aged 45–64 years. The authors showed that women with 5+ births had a greater risk of CHD (1.29, 1.10–1.52) and hospitalized MI (1.38, 1.13–1.69) after adjustment for baseline characteristics and breastfeeding.[74] Based on the above findings, one can speculate that RHF for extended periods (over many years) may contribute to this negative outcome. However, there was no mention of RHF in that study. Also, we did not find any specific data regarding RHF, multiple pregnancies and CV outcome. In contrast to the above findings, Piccoli et al. showed that in pregnant stage 1 CKD patients, hyperfiltration (defined as CKD-EPI-calculated eGFR >120 mL/min) was not associated with maternal-foetal outcomes.[75]

4.4 | Limitations and future study areas

One of the biggest caveats is the ambiguity of the definition of RHF and the lack of a consensus regarding its definition when used in

studies. The GFR thresholds used to define RHF differed enormously among studies. A literature review on RHF definitions in 405 studies showed that the thresholds to define RHF ranged from 90.7 to 175 mL/min/1.73m^2.[76] Among the studies included in our review, the range of RHF/high eGFR group thresholds varied from 90 to 130 mL/min/1.73m^2[2,29,34] with some studies defining RHF as GFR > 95th percentile[41,42,44] and others having a multitude of diverse definitions.[26] Another limitation, as discussed, is the fact that eGFR equations are typically used in the daily setting, and were used in all of the studies reviewed here except for one, because of feasibility and cost-effectiveness. This in turn results in discussion as to whether or not high eGFR values are a consequence of true RHF or false positive results affected by other confounding factors, including low muscle mass.

Although an elevated eGFR often reflects RHF, studies showed that the performance of the MDRD and CKD-EPI formulas decreased in obese subjects and in people with decreased muscular mass.[77] Thus, studies measuring GFR with more reliable methods will be of value. Indeed, more reliable studies are needed with direct measures of GFR. This issue is especially important when serum creatinine levels are low (cirrhosis, malnutrition), which result in falsely elevated GFR. In these patients, 24-hour urine collection or scintigraphic methods may be more valid to measure GFR.

Another important issue could be the role of salt intake. Excessive salt intake has been associated with poorer CV outcomes. Both blood pressure-dependent and independent effects of salt play a role in these adverse outcomes. Although the kidney has the ability to maintain blood flow and keep GFR stable (renal autoregulation) despite changes in systemic blood pressure, this autoregulation has some limits (within about 80–180 mmHg). Santos et al., in a cross-sectional, population-based study of 1211 Brazilians, showed that eGFR was independently and positively correlated with sodium excretion.[78] Thus, considering sodium intake in future studies by urine sodium excretion may give more valid information regarding RHF and CV outcomes.

An important confounder in the context of RHF is the use of RAAS inhibitors. These drugs are both nephroprotective and cardioprotective and their main action is to lower glomerular hyperfiltration independent of systemic blood pressure-lowering effects. Thus, it can be speculated that RHF is associated with the (absence of) intake of these drugs, which could affect the relation between hyperfiltration and cardiorenal outcomes.

Apart from composite CV deaths, patients with RHF may also have increased non-vascular mortality. Indeed, Di Angelantonio et al. studied 16 958 people aged 33–81 years without manifest vascular disease and with information regarding stage of CKD (defined by both eGFR and urinary protein).[45] During a median follow-up of 24 years, 4010 CHD outcomes, 559 deaths from stroke, and 3875 deaths from non-vascular causes, were recorded. While the authors did not suggest any potential explanations for this observation, one can speculate that this indicates the presence of unmeasured confounders for mortality unrelated to CVD.[45]

In conclusion, we suggest that RHF may be independently associated with CVD and all-cause mortality in patients with and without diabetes and hypertension. To confirm this, studies are needed using mGFR instead of eGFR, and a uniform definition of RHF in different studies. While the mechanisms responsible for this association are not yet known, a better understanding of the relationship between RHF and CVD is important in order to better understand the cogent use of medications that reduce RHF and CVD, such as RAAS inhibitors and SGLT-2 inhibitors. For example, if the detrimental effects of RHF become a point of no question, we could follow these patients more closely for timely interventions, such as strict blood pressure and blood glucose regulation. Additionally, we could start GFR-reducing therapy (GFR hypofiltrators) such as RAAS inhibitors and SGLT-2 inhibitors at an earlier stage. Indeed, apart from traditional GFR-lowering RAAS blockers, SGLT-2 inhibitors have recently been shown to be protective with respect to renal and CV outcomes.[79] Accordingly, more research is warranted to fully clarify the role of RHF as a potential biomarker and eventual treatment target.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

MK, LAE, BA, EO, ZSK have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; MK, AO, AC, MK, MK, DHR, DZIC, DZ were involved in drafting the manuscript or revising it critically for important intellectual content; MK, LAE, BA, EO, ZSK, AO, AC, MK, DZIC, DHR, DZ gave final approval of the version to be published. MK, BA, DZI, DHR, DZ agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPORTING INFORMATION

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

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