Chronic Kidney Disease and Heart Failure: A Burden of Proof Meta-analysis

Tristan Andrew Casady

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Dr. Stephen Hawes

Dr. Gregory Roth

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Abstract

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Tristan Andrew Casady

Chair of the Supervisory Committee:

Dr. Stephen Hawes

Department of Epidemiology

Chronic kidney disease (CKD), defined by prolonged reduction in estimated glomerular filtration rate (eGFR), is an established risk factor for cardiovascular disease; however, the quantified magnitude of risk of reduced renal function on incident heart failure (HF) remains poorly characterized across the full exposure range of CKD severity. This study applies the Institute for Health Metrics and Evaluation's (IHME) Burden of Proof (BoP) meta-analytic methodology to quantify the conservative excess risk of incident HF across the continuum of eGFR. A systematic review was conducted in PubMed (January 1980 - August 2025) following PRISMA 2020 guidelines, yielding 12 prospective cohort studies for inclusion in the primary meta-analytic pipeline from 733 records identified. Dose-response meta-analysis was performed using the BoP pipeline, which employs a Bayesian regularized spline approach to estimate a non-linear risk function. The meta-regression yielded an inverse, non-linear risk relationship between eGFR and

incident HF, with the greatest change in risk occurring at low levels of eGFR and attenuation toward the null at higher levels. The exposure-averaged Burden of Proof Risk Function (BPRF) was 1.11, reflecting an average of 11% excess risk of incident HF under the most conservative interpretation of the evidence, yielding a Risk-Outcome Score of approximately 0.10 and a two-star rating. This is the first application of the BoP methodology to the CKD–incident HF risk-outcome pair, with results indicating a consistent, modest association between reduced eGFR and increased risk of incident HF, with the greatest risk elevation occurring below the clinical CKD threshold of eGFR 60. These findings suggest that HF screening efforts may benefit from consideration of renal function decline prior to formal CKD diagnosis, and further large-scale cohort studies across diverse populations are needed to refine the dose-response relationship and its implications for clinical risk stratification.

Introduction

Specific Aims

The aims of this systematic review and meta-analytic study include:

1. To explore the relationship between the severity of prolonged reduced renal function - known as chronic kidney disease (CKD) - and incident heart failure (HF) using previously published literature, including the identification of appropriate classification and measurement of both.

2. Quantify the risk relationship between CKD severity and incident HF using the Burden of Proof (BOP) methodology to produce a rating reflecting the magnitude of risk for this relationship and to contribute to the BOP body of literature.

Background and Significance

Heart failure (HF) is an important contributor to the burden of cardiovascular disease globally. It is universally defined as a clinical syndrome with symptoms or signs caused by a structural or functional cardiac abnormality, corroborated by natriuretic peptide levels and/or objective evidence of pulmonary congestion.[1] This is clinically diagnosed via two primary subtypes: HF with reduced Ejection Fraction (HFrEF) where left ventricular ejection fraction is less than 40% and HF with preserved Ejection Fraction (HFpEF) where left ventricular ejection fraction is greater than 50%. Though specific definitions of HF may vary depending on clinical or research setting, it is universally understood as progressing in stages: at risk for HF (Stage A), Pre-HF (Stage B), Symptomatic HF (Stage C) and Advanced HF (Stage D).[1] At risk population

characteristics include biological factors such as older age and genetic predisposition, as well as lifestyle factors including diabetes mellitus, obesity, hypertension, chronic kidney disease, and other factors like cancer comorbidities and race.[2] All of these factors lead to increased risk of incident HF and persistence or progression – making it an important public health focus. While the global prevalence of overall HF is roughly 3% to 4%, it continues to increase with aging populations.[3] Screening and timely diagnosis of incident HF is primarily reserved for populations with known comorbidities of HF. A quantitative framework of HF risk factors for a general, diverse population is needed to identify opportune screening timelines for these comorbidities. This is especially important given the prognosis of HF in the general population, as the five-year survival rate is roughly 50% for persistent HF.[4]

One important pathway is the role of reduced renal function in predicting incident HF, regardless of HF subtype. Prolonged reduced renal function, CKD, represents a large burden of global disease, affecting greater than 10% of the population as prevalence continues to increase.[5] While the body of literature exploring the relationship between CKD and general cardiovascular disease (CVD) strongly suggests increased risk and mortality, it is if far less robust for CKD and incident HF.[6,7] The magnitude of risk that CKD presents for incident HF can be quantified using analyses of existing cohorts. As treatment options that prevent CKD progress become increasingly available, a greater understanding of the risk of incident HF across the full exposure range of CKD severity may improve prevention efforts for HF.

Methods

Study design

This research utilized a systematic review and meta-analytic approach to understand the magnitude of association between CKD and incident heart failure. The systematic review component of this project followed PRISMA guidelines to identify, review, and extract measures of association. Measures included relative risks, hazard ratios, and odds ratios from observational studies. Additionally, all study-level population characteristics and covariates of interest were extracted.

Estimated glomerular filtration rate (eGFR), a measure of renal function, is used to clinically assess CKD severity when measured over a three-month period. Gold standard analyses utilized the Chronic Kidney Disease Epidemiology Collaboration equation, the most clinically accepted iteration of the universal eGFR measurement.[8] Both creatinine and cystatin C-based eGFR measurements - as well as composite eGFR measures using both biomarkers - were included when collected at baseline, with a preference for the 2012 or 2021 combined creatinine and cystatin C formula when available. eGFR, which was extracted as categorical or per-unit increases, was modeled on a continuous scale. Other known indicators of renal function such as urine albumin-to-creatinine ratio (uACR) and B-type natriuretic peptide (BNP) levels were included in the initial search but were not preferred indicators of renal function in this analysis. Incident heart failure in gold standard analyses was classified as a binary outcome based on physician validated diagnosis or study adjudication. Due to the nature of heart failure development and progression, true incident heart failure was not expected to be commonly diagnosed in study or clinical settings due to early stages of HF being largely asymptomatic. This

analysis utilized both incident HF diagnosis based on cohort criteria and first hospitalization due to HF (ICD code assignment or clinical diagnosis when those with prior HF were believed to be removed at baseline) as measures of incident stage C heart failure for the analysis. Though cohort definitions of HF varied slightly depending on diagnostic testing availability, they were considered clinically homogenous diagnoses in this analysis. Acute decompensated heart failure (the sudden worsening of existing heart failure) was not a desired outcome of interest in this analysis but was reviewed on a case-by-case basis for inclusion. Sub-populations were considered for inclusion during the screening process. All bias covariates of interest that were sufficiently supported by the data were considered for model inclusion.

Search String and Study Selection

The search string for this new systematic review was conducted entirely using PubMed. A combination of MeSH terms and title/abstract keywords across four conceptual domains: chronic kidney disease and renal function; heart failure and left ventricular dysfunction; incidence; and relevant biomarkers and renal function measures including creatinine, cystatin C, NT-proBNP, and albuminuria. The search was restricted to records published between January 1, 1980 and August 12, 2025, with no restrictions on language or geographic region. Publication type exclusions (case reports, editorials, letters, systematic reviews, meta-analyses, and clinical trial reports) and a human-only filter were applied. One additional record was identified via hand search during an exploratory literature review, yielding 733 total records for screening.

Title and abstract screening was conducted by hand using PRISMA-concordant IHME screening templates. A second title/abstract review was completed by a lead research scientist on a random

subset (n=50) to harmonize screening decisions. Non-English language records were eligible for inclusion at this stage; however, no non-English language studies were selected during title and abstract screening. Studies advancing past initial screening underwent full-text review to assess extraction viability. Inclusion required that studies report an empirical association between eGFR as the primary exposure and incident heart failure as the outcome, with an extractable effect size (hazard ratio, odds ratio, or relative risk) and accompanying variance estimate. Studies were eligible regardless of geographic region or participant age at the search and title/abstract screening stages. Pediatric populations and studies reporting results exclusively in dialysis-dependent populations were excluded during full-text review, as these populations were considered to represent distinct physiological contexts not generalizable to the broader CKD population of interest. Studies were additionally excluded for the following reasons: exposure not eGFR (n=23), outcome not incident heart failure (n=20), no relevant effect size reported (n=19), non-representative cohort (n=5), cohort overlap (n=4), model incompatibility with the meta-analytic pipeline (n=3), or results limited to an unsuitable sub-population (n=2). This yielded 12 studies for inclusion in the primary meta-analytic pipeline. Excluded studies with cohort overlap, model incompatibility, or sub-population concerns may be considered for sensitivity analyses where viable. A detailed 2020 PRISMA-compliant flow diagram is presented in Figure 1 (appendix).

Statistical Analysis

Following the extraction of effect size information and relevant cohort metadata, each extraction was cleaned in preparation for the meta-analysis. All remaining open exposure bounds – where upper and lower values of eGFR were not provided in the literature – were imputed from the

mean (SD) under the assumption of normal distributions of eGFR in the study population. Additionally, all per-unit change in eGFR effect sizes were transformed into the reference and alternative risk group measures to reflect the categorical risk measure extractions. Finally, all unique risk measures were standardized into relative risks and standard errors on the log scale. Demographic measures such as age and study duration were standardized to the same unit.

The Burden of Proof (BoP) pipeline, a Bayesian meta-regression model developed by IHME, was then utilized to generate a burden of proof risk function for the mean risk relationship between CKD and incident HF.[9] The model utilized a Bayesian regularized spline approach for fitting the standardized risk measures extracted during the systematic review process, allowing for a non-linear risk curve. Several model configurations were modified to fit the expected risk relationship between increasing eGFR and relative risk of heart failure: enforcement of a right linear tail where data is sparse at high levels of eGFR, a frequency approach to knot placement, and the normalization of the risk curve to the minimum risk exposure level to accommodate the expected reduction of HF risk with increasing eGFR, such that the lowest eGFR levels correspond to the greatest heart failure risk. Exposure status, defined by alternative eGFR risk quantiles compared to a reference risk quantile, was treated as a true exposure range for each group to accommodate differences in exposure classification across studies. To address potential influence of observations most unaligned with the majority of the observed data, 10% of points were automatically trimmed using a least trimmed squares (LTS) approach to avoid subjective researcher-based exclusion. Between-study heterogeneity was estimated via maximum likelihood and adjusted using the Fisher Information Matrix (FIM) quantile to address potential underestimation in settings with limited studies. In addition to study-level adjustments, retained

bias covariates (where data is sufficient) were statistically evaluated for influence on the BoP effect size as compared to the gold standard measure using a Lasso-penalized meta-regression framework. Potential publication or reporting bias was assessed using Egger's regression, testing for a significant association between model residuals and their standard errors after accounting for the signal and bias covariates, with a p-value below 0.05 used as the threshold for flagging potential small-study bias.

Finally, the burden of proof risk function was defined as the 5^{th} percentile risk curve – as compared to the cumulative mean risk curve – and assigned a risk score according to the percentile of average excess risk across the defined exposure range of eGFR. The final output included a star rating reflective of risk score, allowing for simple quantification of the magnitude of risk for CKD and incident HF. Relative risks and confidence intervals were additionally estimated at clinically relevant thresholds of eGFR (30, 45, 60 and 90 mL/min/1.73m^2) to reflect stages of CKD (stage 4, 3, 2, and 1 or no CKD, respectively).[10] The risk curve was generated in both the linear and log space and was supplemented with a funnel plot for a visual diagnostic of publication bias. As opposed to a single effect measure per included study, the risk curves included unique relative risk observations for each defined alternative risk category per study to allow for a non-linear dose-response relationship.

Results

The systematic review included 21 observational study cohorts. During the meta-analytic phase overlapping cohorts, non-general population representative cohorts, and cohorts missing data

needed for the BoP model were identified as outliers in the primary analysis. This left 12 cohorts in the final analytical cohort. These cohorts are presented in Table 1 with demographic summary statistics and relevant study metadata. All included studies were prospective cohort studies reporting hazard ratios or relative risk ratios, with eight reporting eGFR as a categorical variable and four reporting per-unit changes in eGFR. The CKD-EPI collaborative eGFR equations derived from baseline laboratory serum collection were used in all extracted measures, though serum availability and equation year varied between cohorts. Table 2 lists the covariates adjusted for each observational study. At minimum, all cohorts adjusted for age and sex at the study level. Other cardio-metabolic risk factors and measures (i.e. urine albumin) were commonly adjusted for across cohorts, while none included adjustments for covariates equivalent to the exposure or outcome (i.e. other eGFR formulas or NT-proBNP).

Table 1

Table 1. Cohort characteristics of studies included in the CKD-HF systematic review

Study	Cohort location	% Male	Mean age	Duration (years)	Cohort size (n)	eGFR formula*
Bibbins-Domingo 2006	USA	0.49	73.6	5.7	2,800	eGFR(cys)
Buckley 2023	USA	0.43	76.0	7.1	5,170	eGFR(cr-cys)
Chen 2023	United Kingdom	0.47	53.1	11.0	7,738	eGFR(cys)
Chen 2024	USA	0.46	65.0	12.1	24,348	eGFR(cys)
Fu 2024	Sweden	0.45	73.0	3.7	82,154	eGFR(cr-cys)
He 2017	USA	0.55	57.9	6.3	3,557	eGFR(cys)
Rehm 2022	Western Europe	0.49	51.4	8.0	48,518	eGFR(cr-cys)
Sarnak 2005	USA	0.41	75.0	8.3	4,384	eGFR(cr)
Shara 2013	USA	0.40	56.0	15.0	4,081	eGFR(cr)
Shetty 2024	USA	0.45	62.3	10.0	15,512	eGFR(cr-cys)

Svensson-Farbom 2013	Sweden	0.40	57.5	13.9	4,650	eGFR(cr-cys)
Werner 2018	Sweden	0.44	73.0	11.0	2,059	eGFR(cr-cys)

All included studies were prospective cohort designs reporting hazard ratios or relative risk effect measures.

*All cohorts used the CKD-EPI collaboration eGFR formula for serum creatinine (2009, 2021), cystatin C (2012), or combined (2012, 2021).

The primary meta-regression results suggest an inverse risk relationship between increasing eGFR and heart failure, meaning reduced levels of eGFR – the clinical indicator of CKD – correspond with increased risk of heart failure. The risk curve was non-linear, with the greatest change in risk occurring at low levels of eGFR until flattening at a relative risk of one at higher levels of eGFR. An eGFR of 30 – indicating severely reduced renal function – was associated with a mean relative risk of 1.76 (95% CI: 1.34, 2.30). Moderately reduced renal function at an eGFR of 45 corresponded with a relative risk of 1.47 (95% CI: 1.23, 1.77) and was 1.21 (95% UI: 1.11, 1.33) at an eGFR of 60, which represents the clinical threshold of CKD. The estimated relative risk at an eGFR of 93.7 (normal kidney function) was 1.

Table 2

Table 2. Confounder adjustment by included study

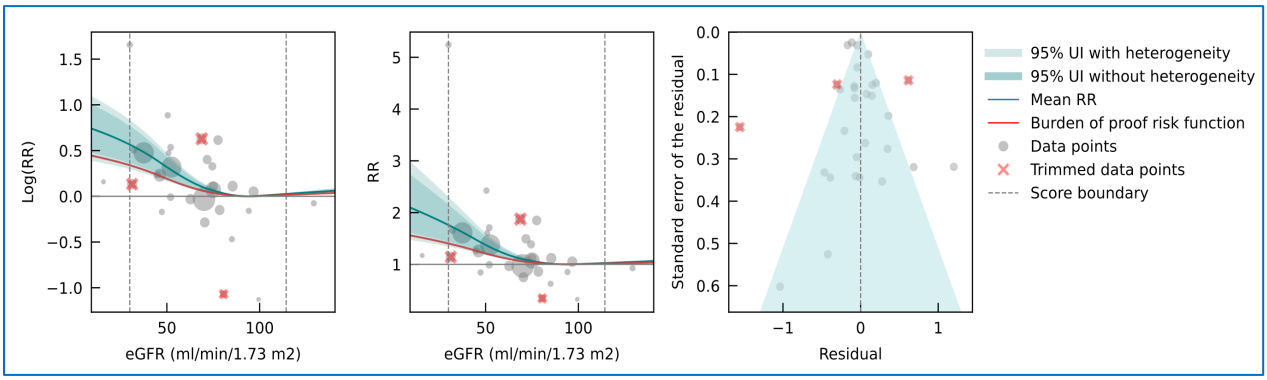
Study	Covariates adjusted for in extracted model
Bibbins-Domingo 2006	age, sex, site, coronary disease, cerebrovascular disease, left ventricular hypertrophy, current smoking, levels of fasting glucose and albumin; systolic blood pressure and other diuretics
Buckley 2023	age, sex, race, bmi, diabetes mellitus, coronary heart disease, hypertension, AF, pulse pressure, UACR
Chen 2023	age, sex, ethnicity, type 2 diabetes; hypertension; systolic blood pressure; tobacco smoking; family history of ASCVD; urine albumin-to-creatinine ratio; body mass index; waist circumference; low-density lipoprotein; high-density lipoprotein; hemoglobin A1c; lipoprotein (a); and use of aspirin, statin, angiotensin converting enzyme inhibitor or angiotensin receptor blocker, or βblocker, adiposity and metabolism
Chen 2024	age, sex, race, income, diabetes, hypertension, hyperlipidemia, peripheral artery disease, smoking, aspirin use, low-density lipoprotein, high-density lipoprotein, C-reactive protein, UAC ratio

Fu 2024	age, sex, hypertension, diabetes, cardiovascular disease, logarithm of UACR, antihypertensive medication use, total and HDL cholesterol
He 2017	age, sex, race, and urine albumin
Rehm 2022	age, sex, and cohort, BMI, smoking, diabetes, and systolic blood pressure, log-transformed concentrations of hs-CRP and hs-cTnI
Sarnak 2005	age, sex, body mass index, diabetes, hypertension, high-density lipoprotein cholesterol, ankle arm index, common carotid intima–media wall thickness, internal carotid intima–media thickness, atrial fibrillation on electrocardiography, C-reactive protein level, albumin level, factor VII level, presence of coronary heart disease, and left ventricular hypertrophy on electrocardiography
Shara 2013	age, sex, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, hypertension (yes vs. no), diabetes (yes vs. no), and smoking (never, past, or current), albuminuria
Shetty 2024	age, sex, diabetes mellitus, anti-hypertensive medication use, smoking history, statin use, BMI, SBP, total cholesterol
Svensson-Farbom 2013	age, gender, use of antihypertensive treatment, systolic blood pressure, diastolic blood pressure, diabetes, body mass index, waist circumference, P-HDL, P-LDL, and smoking
Werner 2018	age, sex, smoking, diabetes, and treated hypertension

AF, atrial fibrillation; BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; hs-cTnI, high-Sensitivity Cardiac Troponin I; uACR, Urine Albumin-to-Creatinine Ratio

As shown in the plots within Figure 2, the unique alternative risk observations from each of the 12 included studies were plotted for a total of 30 relative risk points. Three outlier observations were trimmed during the 10% automatic trimming process. The funnel plot showed adequate symmetrical distribution of residuals in the majority of extracted risk measures. Supplemented by an Egger's regression p-value of 0.13, there was insufficient evidence of publication bias in this analysis based on an alpha level of 0.05. Bias covariates were included for per-unit extraction measures and for studies reporting first hospitalization of heart failure based on ICD codes (compared to incident diagnosis). The Fisher Information Matrix-adjusted gamma estimate measuring per-study variance was 0.0058.

Figure 2. Burden of Proof Risk Curve and Funnel plot



The exposure-averaged Burden of Proof Risk Function (BPRF) was 1.11, meaning the most conservative interpretation of the risk relationship across the range of modeled eGFR was an average of 11% excess risk of heart failure due to reduced eGFR. The risk-outcome score from modeled data was roughly 0.1 (a two-star rating). The model output summary is presented in Table 3.

Table 3

Table 3. Strength of the evidence for the relationship between chronic kidney disease and hf.

Outcome	RR at eGFR 30	RR at eGFR 45	RR at eGFR 60	RR at eGFR 93.7	Exposure-averaged BPRF	Conservative interpretation of average risk increase/decrease	ROS	Star rating
hf	1.76 (1.34, 2.3)	1.47 (1.23, 1.77)	1.21 (1.11, 1.33)	1	1.11	11%	0.1	★★

RR = relative risk; BPRF = Burden of Proof Risk Function; ROS = risk-outcome score.

Discussion

The burden of proof risk score indicates that reduced eGFR is associated with increased risk of heart failure among the general study population. Though a two-star risk score reflects modest excess risk, the association is consistent across the bounds of eGFR included in the model. These results confirm previous study-level findings that identify CKD and/or reduced renal function as an important risk factor for incident heart failure.[5,6,11] When the risk curve is assessed at clinically relevant eGFR levels corresponding to CKD stages, excess risk is in accordance with previous literature. Compared to other spline-based risk curves, the BPRF curve ceases to show a true protective effect (RR < 1) when approaching the upper bound of eGFR.[12,18] Instead, the curve shows attenuation towards the null when approaching high levels of eGFR. However, the model still shows a modest amount of risk at an eGFR of 60, meaning clinically normal levels of eGFR may already be associated with risk of HF prior to clinical diagnosis of CKD.

This is the first application of the BoP pipeline to CKD and HF. Specifically, is the first usage of the BPRF to estimate the conservative average excess risk across the range of eGFR. The inclusion of prospective cohort studies with significant follow-up periods and exclusion of HF at baseline reduces the potential for bias by reverse causation. The CKD-EPI collaborative eGFR equations was used in all 12 included studies with lab-collected serum creatinine and cystatin C, indicating consistent exposure reporting across the entire analytic cohort. Although eGFR measurement differed depending on year and serum availability, different iterations of the eGFR formula reflect changes in calibration but not fundamental differences in renal function measurement. Because the BoP approach estimates the risk relationship using the relative distribution of eGFR, calibration-based differences in eGFR measurement between studies is

unlikely to affect the overall BPRF risk estimate – though future sensitivity analyses are needed to confirm this assumption. Consistent adjustment for age and sex/gender across the included cohorts improves the comparability and generalizability of the model output for the general population. There was no statistical evidence of publication bias in the model output, though it cannot be ruled out in this meta-analysis due to the relatively small number (n=12) of included studies and potential for selective reporting of statistically significant effect sizes. For studies reporting per-unit effect sizes and non-gold standard outcome measurement, the inclusion of bias covariates helps reduce the potential effects of exposure and outcome misclassification bias on the BPRF estimates introduced by these studies.

There were several limitations in this systematic review and meta-analysis. The causal pathway of CKD and HF is known to be bidirectional – where kidney dysfunction can promote heart failure through volume overload, adverse myocardial remodeling, and impaired cardiac function, while heart failure can worsen kidney function through reduced renal perfusion, creating a cycle of reduced cardiorenal function.[13] The issue of bidirectionality was mitigated by selecting cohorts that exclude prevalent HF at baseline and exhibit sufficient follow-up time; however, it is impossible to completely rule out potential effects of bidirectionality. For cohorts without CKD as an eligibility criterion, reduced eGFR measures at baseline (with no follow up measurements) may misclassify CKD as acute kidney damage in some cases. Additionally, some iterations of the eGFR formula prior to 2021 incorporate a race coefficient for creatinine-based equations which may overestimate CKD risk for black populations.[23] Pre-2021 creatinine-based eGFR was assessed for inclusion as a bias covariate but was omitted due to a lack of study sample size. Due to the nature of HF progression – where individuals are often undiagnosed until clinically

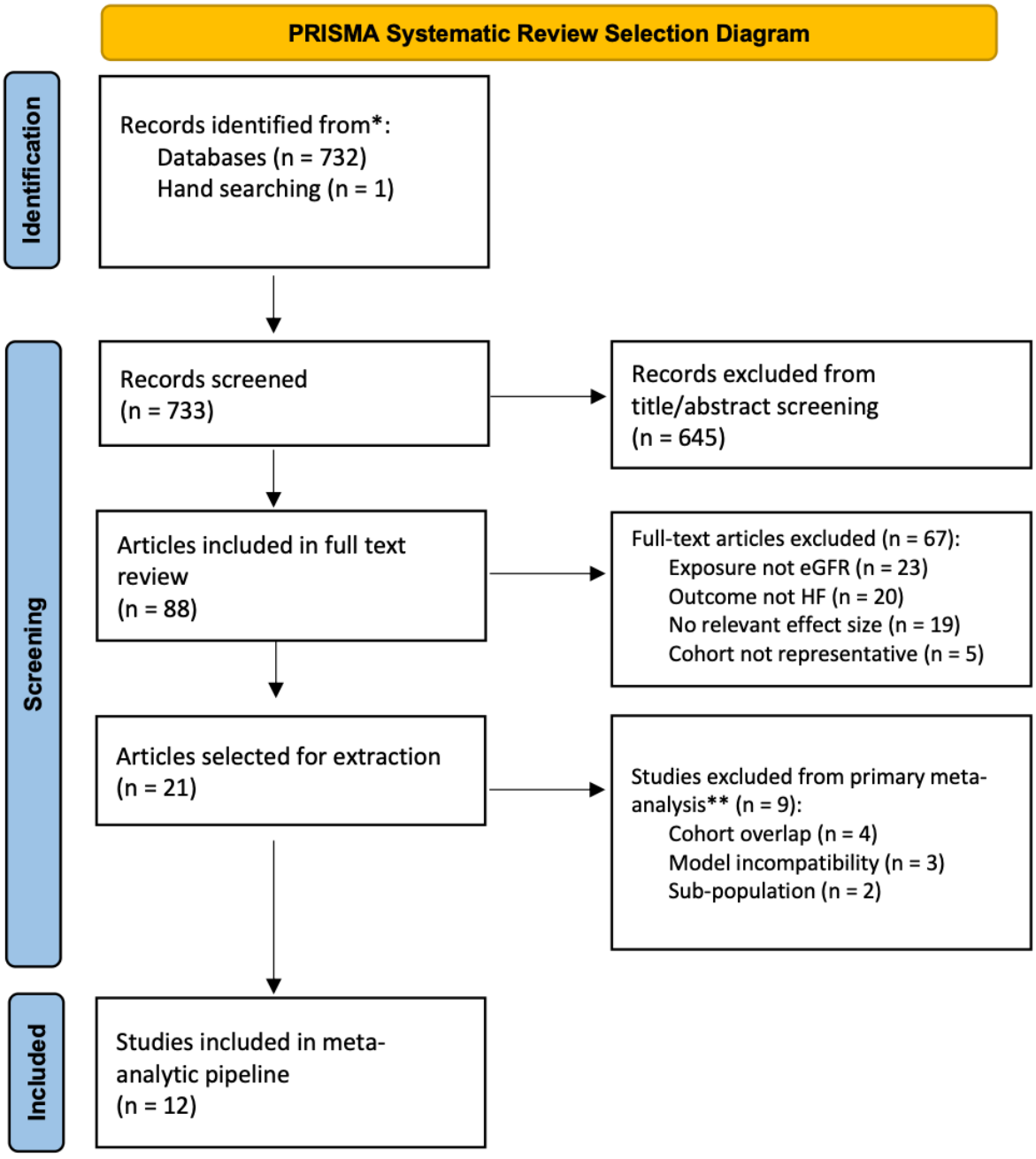
presenting Stage C symptoms, first hospitalizations for HF are used as a measure for incident HF in many cohorts, which may represent sudden progression of disease (ADHF) instead of true incidence. While the BoP model is robust in its handling of study-level bias and inter-study heterogeneity, other forms of bias which are not captured in the data may be unaccounted for. All included studies adjusted for multiple clinically relevant confounders, though the inability to randomize exposure within cohorts means that residual and unmeasured confounding cannot be completely ruled out. This meta-analysis does not account for different subtypes of HF (HFrEF and HFpEF) which may differ in their relationship to eGFR. The analytic cohort included cohorts exclusively from Western Europe, Sweden, and the U.S., limiting interpretation to these populations. Finally, there is potential for systematic omission of relevant articles due to the search string being confined to PubMed, which may not index all globally published CKD or HF literature.

In summary, this systematic review and application of the BoP pipeline to quantify the excess risk of heart failure by reduced eGFR is a novel approach for this risk-outcome pair. Further cohort studies are needed to improve the robustness of the model results and better understand the non-linear risk relationship between eGFR and incident HF. In terms of clinical diagnosis and intervention for early-stage HF, the level at which eGFR increases HF risk may lead to improved clinical definitions of at-risk populations. The prioritization of HF screening at eGFR levels corresponding to significant increases in the magnitude of HF risk, beyond the clinical definition of CKD at an eGFR of 60, may improve health outcomes for at-risk populations. HF screening methods and guidance may improve with the continuous improvement of renal function measures. Further investigations into the relationship between renal function and heart

failure subtypes (HFpEF/HFrEF) are needed to better inform individual-level clinical care. The broadening of research to cohorts in Asia and the Global South would improve the global generalizability of these findings. Additionally, the use of cohorts with diverse cardio-renal risk profiles such as T2D and CVD-based study populations would broaden the understanding of renal function and risk of heart failure.

Appendix

Figure 1. PRISMA Flow Diagram



* Search string conducted exclusively in PubMed; hand search conducted during exploratory literature review.

**Excluded studies may be considered for inclusion sensitivity analyses if viable.

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