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Risk factors, outcomes and healthcare utilisation in individuals with multimorbidity including heart failure, chronic kidney disease and type 2 diabetes mellitus: a national electronic health record study

Laura Pasea,[1] Ashkan Dashtban,[1] Mehrdad Mizani,[1] Anish Bhuva ,[2,3] Tamsin Morris,[4] Jil Billy Mamza,[4] Amitava Banerjee [1,2]

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[1]Institute of Health Informatics, University College London, London, UK
[2]Department of Cardiology, Barts Heart Centre, London, UK
[3]Institute of Cardiovascular Sciences, University College London, London, UK
[4]Real World Evidence, AstraZeneca, London, UK

Correspondence to
Dr Amitava Banerjee; ami.banerjee@ucl.ac.uk

ABSTRACT

Background Heart failure (HF), type 2 diabetes (T2D) and chronic kidney disease (CKD) commonly coexist. We studied characteristics, prognosis and healthcare utilisation of individuals with two of these conditions.

Methods We performed a retrospective, population-based linked electronic health records study from 1998 to 2020 in England to identify individuals diagnosed with two of: HF, T2D or CKD. We described cohort characteristics at time of second diagnosis and estimated risk of developing the third condition and mortality using Kaplan-Meier and Cox regression models. We also estimated rates of healthcare utilisation in primary care and hospital settings in follow-up.

Findings We identified cohorts of 64 226 with CKD and HF, 82 431 with CKD and T2D, and 13 872 with HF and T2D. Compared with CKD and T2D, those with CKD and HF and HF and T2D had more severe risk factor profile. At 5 years, incidence of the third condition and all-cause mortality occurred in 37% (95% CI: 35.9%, 38.1%%) and 31.3% (30.4%, 32.3%) in HF+T2D, 8.7% (8.4%, 9.0%) and 51.6% (51.1%, 52.1%) in HF+CKD, and 6.8% (6.6%, 7.0%) and 17.9% (17.6%, 18.2%) in CKD+T2D, respectively. In each of the three multimorbid groups, the order of the first two diagnoses was also associated with prognosis. In multivariable analyses, we identified risk factors for developing the third condition and mortality, such as age, sex, medical history and the order of disease diagnosis. Inpatient and outpatient healthcare utilisation rates were highest in CKD and HF, and lowest in CKD and T2D.

Interpretation HF, CKD and T2D carry significant mortality and healthcare burden in combination. Compared with other disease pairs, individuals with CKD and HF had the most severe risk factor profile, prognosis and healthcare utilisation. Service planning, policy and prevention must take into account and monitor data across conditions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Heart failure (HF), chronic kidney disease (CKD) and type 2 diabetes (T2D) are major causes of morbidity and mortality worldwide (Vos *et al*, *Lancet* 2016) and throughout the life course (Zhang *et al*, *BMC Medicine* 2022), and commonly coexist (Triposkiadis *et al*, *European Journal of Heart Failure* 2016; Birkeland *et al, Diabetes, Obes and Metab* 2020). In a study of nearly 500 000 individuals with T2D, among those free from cardiovascular and renal disease, lifetime risks of CKD and HF were 54% and 29%. Individually and together, HF, CKD and T2D have high impact on individuals, populations, healthcare utilisation and economies (Norhammar *et al*, *Diabetes Obes and Metab* 2022).

WHAT THIS STUDY ADDS

⇒ Among those with HF and T2D, 37% went on to also be diagnosed with CKD. Diagnosis of the third condition was less common in the other two groups. The observed 5-year risk of mortality among those with HF and CKD, HF and T2D, and CKD and T2D was 51.6%, 31.3% and 17.9%, respectively. We also identified risk factors associated with developing the third condition and mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ HF, CKD and T2D carry significant mortality and healthcare burden in combination. Compared with other disease pairs, individuals with CKD and HF had the most severe risk factor profile, prognosis and healthcare utilisation. Service planning, policy and prevention must take into account and monitor data across conditions.

INTRODUCTION

Multimorbidity, defined as co-occurrence of two or more long-term conditions, affects over a quarter of adults in the UK[1] and is

projected to affect over two-thirds of individuals over the age of 65 years.[2] With growing multimorbidity globally,[3] single-disease approaches are increasingly inadequate whether in real-world clinical practice, in evidence-based management guidelines or in research.[4] Diseases need to be studied together so prevention, treatment and healthcare delivery can be planned and implemented in holistic, patient-centred and effective ways.

Heart failure (HF), chronic kidney disease (CKD) and type 2 diabetes (T2D) are major causes of morbidity and mortality worldwide[5] and throughout the life course,[6] and commonly coexist.[7] In a study of nearly 500 000 individuals with T2D, among those free from cardiovascular and renal disease, lifetime risks of CKD and HF were 54% and 29%, respectively. Individually and together, HF, CKD and T2D have high impact on individuals, populations, healthcare utilisation and economies.[8] These diseases (increasingly referred to as 'CaReMe' diseases—'Cardiovascular–Renal–Metabolic') are important not only as a component of multimorbidity,[9] but also in development of integrated models of care.[10 11] Earlier, effective prevention strategies require better knowledge of risk factors in individuals with overlapping HF, CKD and T2D, but such epidemiological studies are currently lacking.

The burden of adverse cardiovascular and renal events could be reduced by 'ideal cardiovascular health', by attaining target levels of blood pressure, cholesterol, glucose, smoking, physical activity, diet and body mass index (BMI) (ie, modifiable risk factors). For example, in individuals with T2D, achieving ideal cardiovascular health could reduce adverse cardiovascular and renal events by 42%, 24% and 17% for those with one or more, less than three, and three or more modifiable health behaviours, respectively.[6] As well as behaviour modification, there are effective, evidence-based therapies to improve clinical outcomes for HF, CKD and T2D, with similarities in approaches across the individual diseases, whether statins, renin–angiotensin system inhibitors or sodium-glucose cotransporter-2 inhibitors.[12] Behavioural and drug recommendations could be informed and optimised by better characterisation of risk factor profile, trajectory and prognosis of overlapping conditions, with benefits and synergies across diseases. Moreover, such research will provide individualised information to patients and health professionals, facilitating shared decision-making.

The major healthcare resource implications of HF, CKD and T2D, particularly in individuals with multimorbidity, are likely to be predictable, and may, in some instances, be preventable. For example, in individuals with T2D, cardiovascular disease (CVD) events and admissions over a 4-year period were lower in those who received annual CVD screening tests.[13] Better knowledge of the overlap between HF, CKD and T2D and their outcomes could identify missed opportunities for guideline-recommended care and inform clinical and policy prioritisation for treatment and prevention. However, different combinations of HF, T2D and CKD have neither been fully studied (eg, trajectory of disease after second and third diagnoses) nor compared in terms of epidemiology and healthcare utilisation.

Therefore, in a UK electronic health record (EHR) study, our objectives were to investigate:

1. Baseline characteristics of individuals with coexisting HF, T2D or CKD.
2. Prognosis by diagnosis of a third condition and mortality.
3. Healthcare utilisation in these multimorbid populations.

METHODS

Study design and data sources

We conducted a retrospective cohort study using EHRs, primary care data (Clinical Practice Research Datalink (CPRD)) linked with hospital admissions episode data and cause of death registry data (Office for National Statistics) in England from 1998 to 2020. CPRD has been shown to be representative of the English population by age, sex and ethnicity and validated for research.[14] This study was carried out as part of the CALIBER resource which provides validated EHR phenotyping algorithms and tools for national structured data sources.[15] The disease phenotypes and codelists used in this study are from the HDR UK phenotype library (https://phenotypes.healthdatagateway.org/).

Study population

We included patients aged 18 years and above, diagnosed with two of CKD (stage 3 or above), T2D or HF between January 1998 and April 2020, resulting in three groups: CKD and HF, CKD and T2D and HF and T2D. The baseline data for each individual were the date of their second diagnosis, that is, the date that they had overlapping conditions. Individuals were required to have at least 1 year of data in CPRD prior to their baseline date and were followed up until they had an outcome, transferred out of their general practitioner (GP) practice, died or until the administrative censoring date for data collection.

Baseline covariate definitions

Baseline covariates included demographics (age, sex and ethnicity), behaviours (smoking and excess alcohol consumption), medical history, clinical biomarkers (BMI, systolic blood pressure (SBP), diastolic blood pressure, haemoglobin, glycated haemoglobin (HbA1c), high-density lipoproteins (HDLs), low-density lipoproteins, triglycerides and creatinine) and prescribed medication. Medical histories were defined as any record in primary or secondary care prior to the baseline date. Behaviours and clinical biomarkers were captured in primary care data and were taken as the most recent record within a year prior to baseline. Prescribed medications were defined as any record of a prescription in primary care prior to the baseline date.

Study endpoints

Individuals were followed up for the diagnosis of a third condition among CKD, T2D and HF, that is, individuals with CKD and T2D at baseline were followed up for HF and so on. We also followed up for CVD mortality and all-cause mortality. Healthcare utilisation in primary care (GP consultations and GP referrals to external care) and hospital (inpatient admissions, inpatient procedures and outpatient appointments) settings was also observed.

Statistical analysis

Patient characteristics at baseline were summarised by overlap group (CKD and HF, CKD and T2D, or HF and T2D) using mean and SD or median and IQR, as appropriate, for continuous variables, and frequency and percentage for categorical variables. We tested for differences in baseline characteristics between the three groups using X^2, F-tests and Kruskal-Wallis tests as appropriate. Kaplan-Meier analyses were used to estimate the observed risks of each outcome stratified by overlap groups and log-rank tests were used to assess if the risks of each outcome were different between the groups. Cumulative incidence functions were also used to estimate the incidence of the diagnosis of a third condition in the disease pair groups, in the presence of the competing risk of all-cause mortality.[16]

For each overlap group, we fit multivariable Cox regression models to estimate HRs and 95% CIs for the associations between baseline risk factors and each of the outcomes: developing the third condition, all-cause mortality and cardiovascular mortality. We considered all baseline variables for inclusion in the models, and choice of variables included in the final models was based on a combination of clinical knowledge and minimising the potential for collinearity. The final variables included in the models were age, sex, smoking status, first diagnosis, history of myocardial infarction, atrial fibrillation, hypertension, peripheral arterial disease, stable angina, unstable angina, ischaemic stroke, unspecified coronary heart disease, chronic obstructive pulmonary disease, cancer, prescriptions for beta-blockers, diuretics, non-steroidal anti-inflammatory drugs and statins and BMI, SBP, HDL, HbA1c and creatinine. Continuous variables were fitted using restricted cubic splines with three knots. The proportional hazards assumption was checked using log (−log) and Schoenfeld residual plots.

We reported observed rates per person per year and estimated 95% CIs for each measure of healthcare utilisation for each year of follow-up from baseline.

Missing data

Missing covariate data at baseline were imputed by multiple imputation using chained equations. We imputed 10 datasets using models with all covariates and outcomes included to estimate missing values. Predictive mean matching was used to impute continuous variables and multinomial regression was used to impute categorical variables.

Sensitivity analyses

Given the wide age range of the cohort, we also carried out our primary analyses on the subgroup of individuals aged older than 60 years at baseline (the time of the second diagnosis). We performed a complete case analysis, fitting the multivariable models on the subset of the cohort with complete baseline data. Furthermore, on the complete case population, we fit Fine and Gray competing risk models[16] considering the presence of the competing risk of all-cause mortality on the event of being diagnosed with a third condition. Analyses were completed using R V.4.1.2.

RESULTS

Study population and characteristics

Our study population included 160 529 individuals diagnosed with two of CKD, HF or T2D: 64 226 with CKD and HF, 82 431 with CKD and T2D, and 13 872 with HF and T2D (online supplemental figure 1). The cohort was followed up for a median of 3.3 (IQR: 1.3–6.6) years. The characteristics of the baseline cohort and the time of the second diagnosis are presented in table 1. Individuals with CKD and HF were on average older than those with CKD and T2D or HF and T2D (80.0 (9.9) vs 72.7 (10.1) and 70.5 (11.4) years, respectively). The majority of individuals were women in the CKD and HF (51.4%) and CKD and T2D (52.8%) groups, compared with only 33.3% in the HF and T2D groups.

Individuals with HF and T2D had the longest median time between their diagnosis, 4.0 years (IQR: 1.5–7.6), while those with CKD and HF had the shortest median time, 3.2 years (IQR: 1.1–6.5). History of other comorbidities was most prevalent in the groups with HF (CKD and HF and HF and T2D) with the exception of hypertension. Individuals with CKD and T2D or HF and T2D had a higher mean BMI than those with CKD and HF. The mean SBP was lower among those with HF. The median creatinine was higher among those with CKD.

We further stratified the groups by the order of diagnoses (online supplemental table 2). Within the disease pairs, characteristics of patients were generally similar despite differing disease progression. Some noted differences were that within the CKD and HF group, those who were diagnosed CKD followed by HF were mostly women (54.5%) but not those who had HF followed by CKD (47.8%). In the CKD and T2D group, those who were diagnosed CKD followed by T2D were mostly women (57.4%), whereas there was a more even split between those with T2D followed by CKD (49.6%).

Observed outcomes

Among those with HF and T2D, 37.0% (95% CI: 35.9%, 38.1%) developed CKD over 5 years. Diagnosis of third condition was less common in the other two groups: T2D in 8.7% (95% CI: 8.4%, 9.0%) of those with HF and CKD, and HF in 6.8% (95% CI: 6.6%, 7.0%) of those with CKD and T2D (figure 1). All-cause mortality at 5 years was

Table 1 Characteristics at time of second diagnosis in individuals with two or more of heart failure (HF), chronic kidney disease (CKD) and type 2 diabetes (T2D)

	CKD and HF	CKD and T2D	HF and T2D	
	N=64 226	N=83 431	N=13 872	P value
Demographics and behaviours				
Age (years), mean (SD)	80.0 (9.92)	72.5 (10.08)	70.5 (11.35)	<0.0001
Age (years), range	18.4–109	18.6–109	20.2–105	
Women	33 032 (51.4)	44 046 (52.8)	4623 (33.3)	<0.0001
Ethnicity				<0.0001
White	39 121 (60.9)	51 485 (61.7)	7217 (52)	
Black	289 (0.4)	916 (1.1)	102 (0.7)	
South Asian	535 (0.8)	1814 (2.2)	213 (1.5)	
Other	253 (0.4)	657 (0.8)	89 (0.6)	
Unknown	24 028 (37.4)	28 559 (34.2)	6251 (45.1)	
Smoking status				<0.0001
Non-smoker	12 566 (19.6)	17 522 (21)	1974 (14.2)	
Smoker	6909 (10.8)	10 843 (13)	2568 (18.5)	
Ex-smoker	43 359 (67.5)	53 956 (64.7)	9071 (65.4)	
Missing %	2.2	1.3	1.9	
Excess alcohol consumption	21 737 (33.8)	28 735 (34.4)	5556 (40.1)	<0.0001
Multimorbidity characteristics				
First diagnosis				
CKD	34 625 (53.9)	34 428 (41.3)	0 (0)	
HF	29 601 (46.1)	0 (0)	5660 (40.8)	
T2D	0 (0)	49 003 (58.7)	8212 (59.2)	
Time between diagnoses (years), median (IQR)	3.24 (1.06–6.47)	3.85 (1.42–7.26)	4.04 (1.48–7.58)	
Medical history				
Myocardial infarction	17 694 (27.5)	7691 (9.2)	4126 (29.7)	<0.0001
Unstable angina	6222 (9.7)	2714 (3.3)	1379 (9.9)	<0.0001
Stable angina	21 252 (33.1)	14 397 (17.3)	4763 (34.3)	<0.0001
Percutaneous coronary intervention	4592 (7.1)	3206 (3.8)	1536 (11.1)	<0.0001
Coronary artery bypass graft	5686 (8.9)	3039 (3.6)	1369 (9.9)	<0.0001
Unspecified coronary heart disease	24 876 (38.7)	14 482 (17.4)	5609 (40.4)	<0.0001
Peripheral arterial disease	2890 (4.5)	1548 (1.9)	526 (3.8)	<0.0001
Ischaemic stroke	2750 (4.3)	1769 (2.1)	484 (3.5)	<0.0001
Hypertension	42 528 (66.2)	59 407 (71.2)	8582 (61.9)	<0.0001
Atrial fibrillation	28 062 (43.7)	8885 (10.6)	5066 (36.5)	<0.0001
Chronic obstructive pulmonary disease	11 228 (17.5)	7564 (9.1)	2753 (19.8)	<0.0001
Cancer	15 426 (24)	14 808 (17.7)	2478 (17.9)	<0.0001
Clinical biomarkers				
Body mass index, mean (SD)	28.1 (6.20)	31.0 (6.32)	32.3 (7.14)	<0.0001
Missing %	46.2	23.5	25.3	
Systolic blood pressure (mm Hg), mean (SD)	131 (20.1)	136 (17.1)	132 (18.6)	<0.0001
Missing %	7	5.5	6.7	
Diastolic blood pressure (mm Hg), mean (SD)	73.1 (11.4)	75.7 (10.1)	75.6 (11.1)	<0.0001
Missing %	7	5.5	6.7	
HbA1c, median (IQR)	46 (40–58.0)	52 (47–61.7)	53 (48–63.9)	<0.0001

Continued

Table 1 Continued

	CKD and HF	CKD and T2D	HF and T2D	
	N=64 226	N=83 431	N=13 872	P value
Missing %	77.3	20.3	24.9	
HDL (mg/dL), median (IQR)	1.3 (1.05–1.60)	1.2 (1.00–1.42)	1.1 (0.92–1.38)	<0.0001
Missing %	47.1	22.6	28.3	
LDL (mg/dL), median (IQR)	2.2 (1.7–2.86)	2.2 (1.7–2.90)	2.1 (1.6–2.75)	<0.0001
Missing %	59.5	40.5	45.3	
Triglycerides (mg/dL), median (IQR)	1.30 (0.94–1.8)	1.71 (1.28–2.4)	1.60 (1.12–2.3)	<0.0001
Missing %	53	30.3	37	
Creatinine, median (IQR)	115 (97–137)	108 (93–122)	83 (71–96)	<0.0001
Missing %	6.9	2.7	10.5	
Prescribed medication				
ACE inhibitors	45 614 (71)	53 450 (64.1)	10 320 (74.4)	<0.0001
Beta-blockers	34 108 (53.1)	30 240 (36.2)	7639 (55.1)	<0.0001
Antiplatelets	36 075 (56.2)	37 680 (45.2)	7552 (54.4)	<0.0001
Statins	36 443 (56.7)	57 188 (68.5)	9981 (72)	<0.0001
Diuretics	50 541 (78.7)	41 005 (49.1)	9158 (66)	<0.0001
Metformin	4164 (6.5)	36 223 (43.4)	6315 (45.5)	<0.0001
Insulin	3370 (5.2)	4714 (5.7)	1016 (7.3)	<0.0001
Non-steroidal anti-inflammatory drugs	12 869 (20)	20 757 (24.9)	2811 (20.3)	<0.0001

Categorical data are summarised using frequency (%).
P values are testing the hypothesis of difference between groups, using the X^2 test for categorical variables, and F-tests (ANOVA) or the Kruskal-Wallis test for continuous variables, as appropriate.
ANOVA, analysis of variance; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

highest among the HF and CKD group (51.6%, 95% CI: 51.1%, 52.1%), followed by the HF and T2D group (31.3%, 95% CI: 30.4%, 32.3%), and then CKD and T2D group (17.9%, 95% CI: 17.6%, 18.2%). A similar trend was observed for cardiovascular mortality (figure 2).

Order of the first two diagnoses

When stratifying by the order of the first two diagnoses, the 5-year risk of developing T2D among those with CKD and HF was similar whether CKD or HF was first diagnosed (8.1% (95% CI: 7.6%, 8.5%) and 9.3% (95% CI: 8.8%, 9.7%), respectively) and the risk of developing HF was similar among those with CKD and T2D whether CKD or T2D was the first diagnosis (6.6%, 95% CI 6.3%, 6.9%; and 7.0%, 95% CI: 6.7%, 7.3%, respectively) (online supplemental figure 3). However, in the HF and T2D group, the 5-year CKD risk was higher in those who were diagnosed T2D first than those who had HF first (41.5% (95% CI: 40.0%, 43.0%) and 31.6% (95% CI: 30.1%, 33.1%), respectively) (online supplemental figure 3). Within the CKD and HF group, we observed higher 5-year risks of all-cause and cardiovascular mortality in those diagnosed with CKD followed by HF, than those diagnosed with HF followed by CKD. Similarly, within the HF and T2D group, we observed higher mortality risks in those diagnosed with T2D followed by HF, than those diagnosed with HF followed by T2D. Within the CKD and T2D group, there were minimal differences in all-cause and cardiovascular mortality between groups stratified by order of diagnosis (online supplemental figure 3).

Risk factors for clinical outcomes

Developing the third overlapping condition

Figures 3 and 4 illustrate HRs for risk factors for developing the third condition for each patient group, using multivariable Cox regression models. In the CKD and HF group, history of atrial fibrillation (HR: 1.17, 95% CI: 1.09, 1.25) and chronic obstructive pulmonary disease (HR: 1.2 95% CI: 1.1, 1.31) were associated with increased risk of developing T2D, while hypertension was associated with reduced risk (HR: 0.80, 95% CI: 0.74, 0.86). Individuals whose first diagnosis was CKD had lower risk of developing T2D than those whose first diagnosis was HF (HR: 0.84, 95% CI: 0.79, 0.90). Those prescribed statins also had markedly reduced risk of developing T2D (HR: 0.64, 95% CI: 0.59, 0.69) compared with those who were not (figure 3).

In the CKD and T2D group, increased risk of developing HF was associated with increasing age, sex (women had increased risk compared with men), smoking status (smokers and ex-smokers had increased risk compared with non-smokers), history of CVDs and other comorbidities. Those who were diagnosed with T2D first had lower risk of developing HF compared with those who were diagnosed with CKD first (figure 3). Additionally, we observed increasing risk

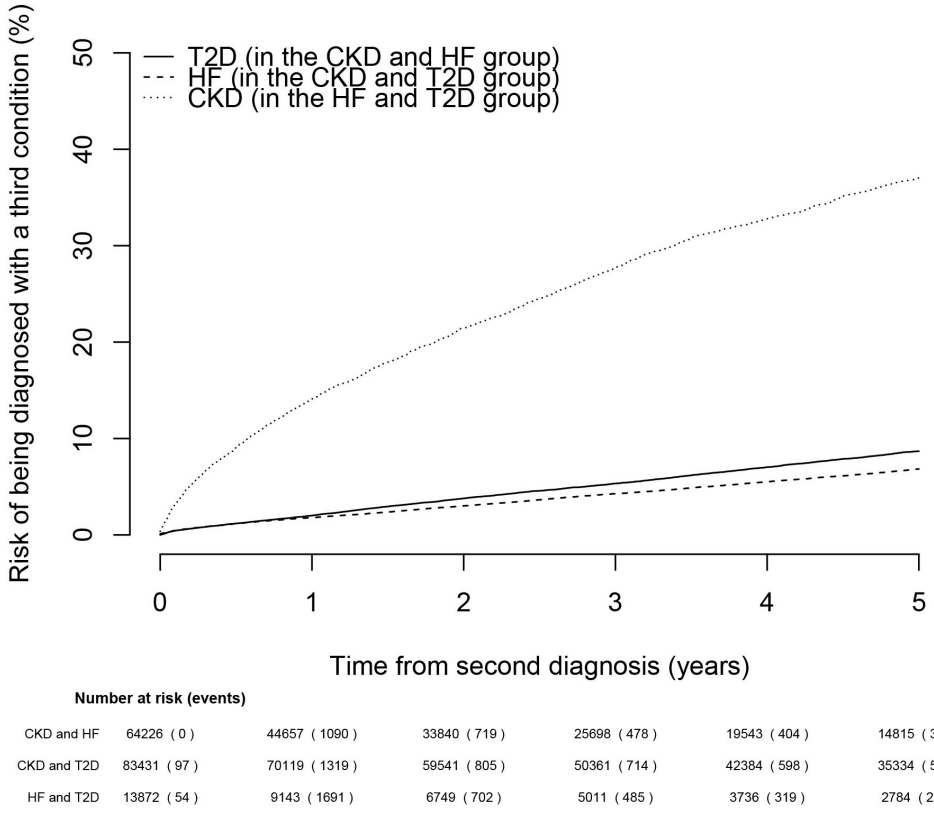

Figure 1 Risk of development of third condition in individuals with two of heart failure (HF), chronic kidney disease (CKD) and type 2 diabetes (T2D).

of T2D with increasing BMI and HbA1c. J-shaped relationships were observed for SBP and HDL (figure 4).

In the HF and T2D group, increased risk of developing CKD was driven by increased age, sex (men had higher risk than women), history of peripheral arterial disease, ischaemic stroke, increased SBP, increased HbA1c and increased creatinine levels. Those with a history of stable angina had lower risk of CKD than those without. There was no significant difference in risk of developing T2D associated with the order of HF and CKD diagnoses (figure 3).

All-cause mortality

Figures 5 and 6 illustrate the risk factors for all-cause mortality among the three overlap groups using

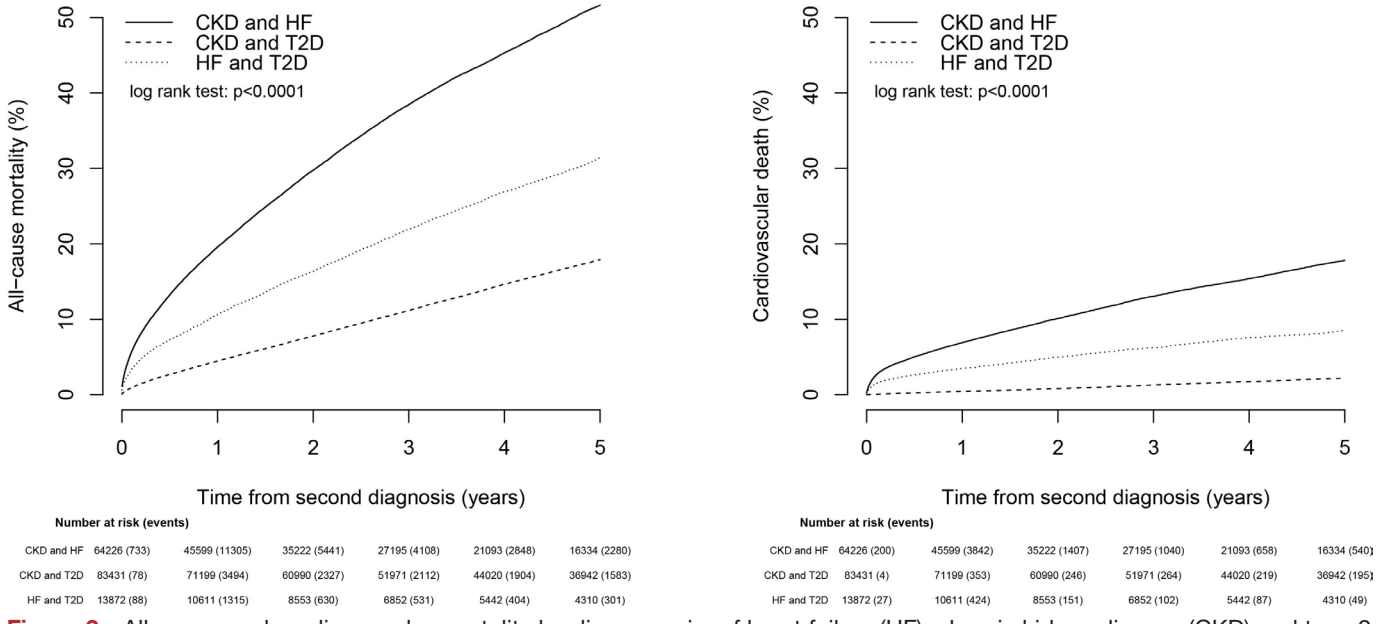

Figure 2 All-cause and cardiovascular mortality by disease pairs of heart failure (HF), chronic kidney disease (CKD) and type 2 diabetes (T2D).

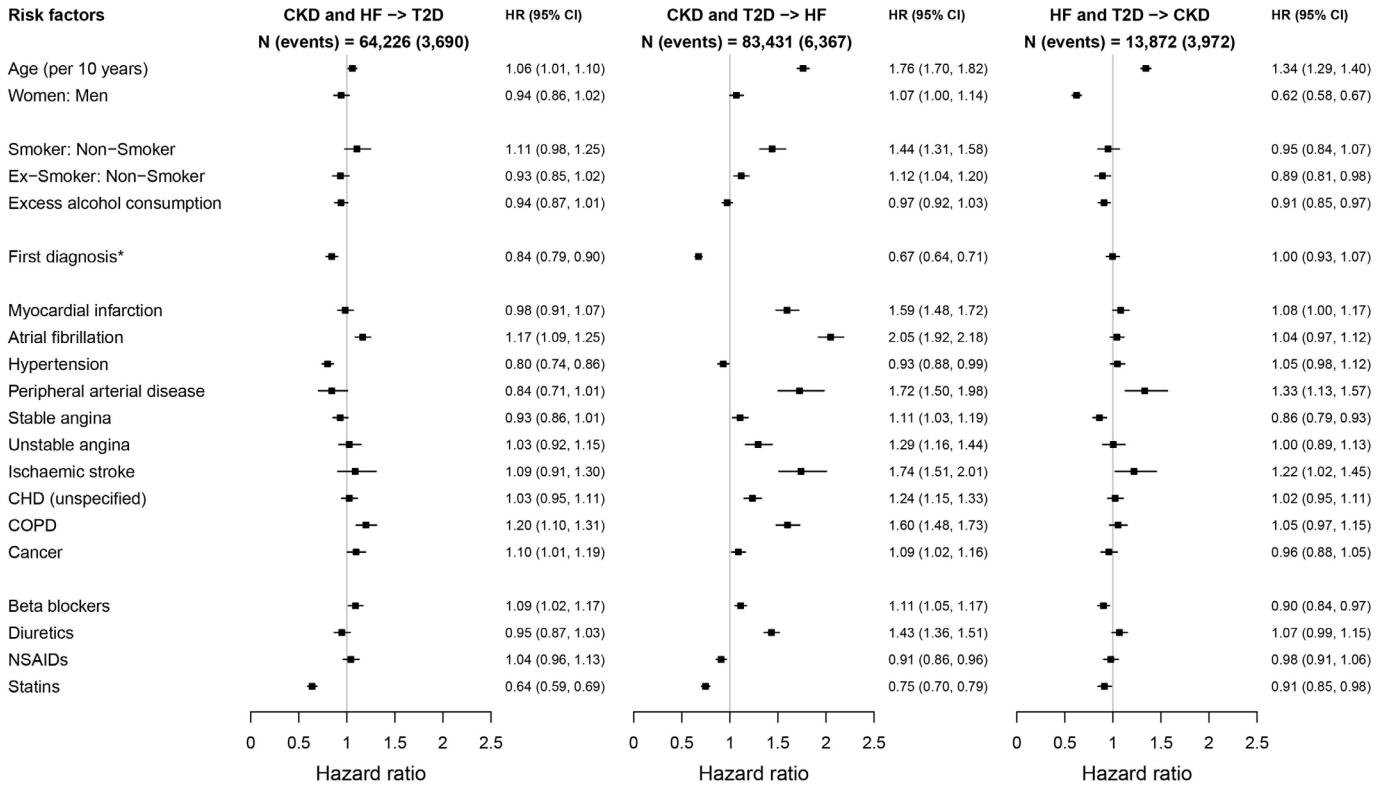

Figure 3 Risk of developing third condition in disease pairs of heart failure (HF), chronic kidney disease (CKD) and type 2 diabetes (T2D), using multivariable Cox regression models. *For first diagnosis, HF is the reference group for CKD and HF, CKD is the reference group for CKD and T2D, and HF is the reference group for HF and T2D. The upper and lower limits for each point are the 95% CIs. All estimates are from fully adjusted models including the continuous risk factors displayed in figure 4. CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; NSAIDs, non-steroidal anti-inflammatory drugs.

multivariable Cox regression models. Risk factors for all-cause mortality were similar for the three groups. Increased age, smokers compared with non-smokers, history of cardiovascular conditions, chronic obstructive pulmonary disease and cancer were associated with increased risk of all-cause mortality for all three groups. We observed increased risks of all-cause mortality within the CKD and HF group among those diagnosed with CKD prior to HF, within the CKD and T2D group among those who were diagnosed with T2D prior to CKD, and within the HF and T2D group among those who were diagnosed with T2D prior to HF.

Cardiovascular mortality

Online supplemental figures 4 and 5 show risk factors for cardiovascular mortality among three overlap groups using multivariable Cox regression models. In all three groups, age and history of peripheral arterial disease and ischaemic stroke were most strongly associated with increased risk of cardiovascular death.

Age subgroup analysis

In the subgroup of individuals aged above 60 years at baseline (N=61 807 with CKD+HF, N=74 128 with CKD+T2D, N=11 375 with HF+T2D), our analysis showed largely similar results to those seen in the full cohort (online supplemental figures 6–11).

Complete case analysis

In the complete case analyses, fitting the multivariable Cox models to the subgroup of the cohort with no missing data (N=7706 with CKD and HF, N=43 785 with CKD and T2D, N=6884 with HF and T2D), we observed generally similar results to the analysis of imputed data (online supplemental figures 11–17). One difference is the change in direction of the association between first diagnosis and subsequent development of HF in the CKD and T2D group. In our imputed analysis, those diagnosed with T2D first had lower risk (HR: 0.67 (95% CI: 0.64, 0.71)) (figure 3), whereas in the complete case analysis, the same group had increased risk (HR: 1.25 (95% CI: 1.15, 1.36)) (online supplemental figure 12).

Competing risk analysis

Cumulative incidence functions (online supplemental figure 18) demonstrated that when we consider the competing risk of all-cause mortality, the estimated risk of being diagnosed with a third condition is slightly lower than estimated with the Kaplan-Meier curves. We estimated at 5 years that the probability of patients with CKD and HF being diagnosed with T2D was 5.96% (95% CI: 5.75%, 6.17%), patients with CKD and T2D being diagnosed with HF was 6.28% (95% CI: 6.09%, 6.47%) and patients with HF and T2D being diagnosed with CKD was 32.0% (95% CI: 31.1%, 32.9%). Similarly, Fine and Gray

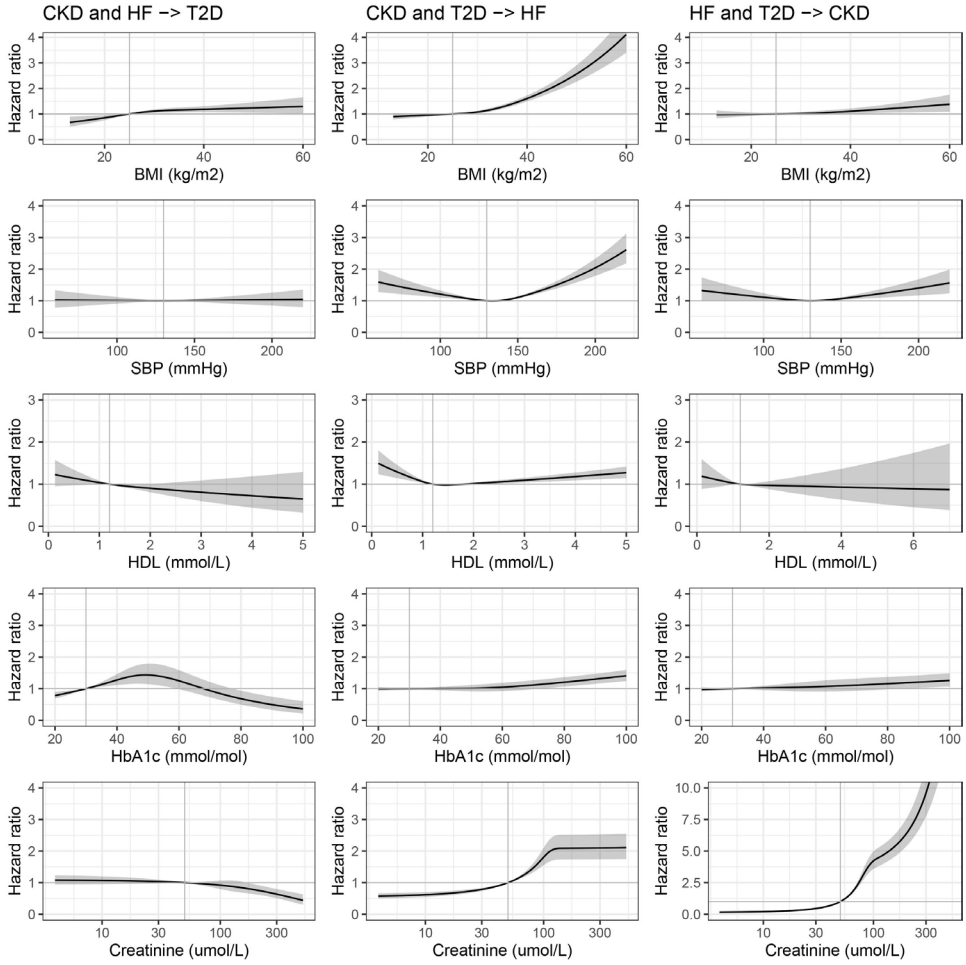

Figure 4 Risk factors for developing third condition in disease pairs of heart failure (HF), chronic kidney disease (CKD) and type 2 diabetes (T2D), using restricted cubic splines for continuous biomarkers in the multivariable Cox regression models. The reference value for each risk factor was BMI: 25 kg/m^2, SBP: 130 mm Hg, HDL: 1.2 mmol/L, HbA1c: 30 mmol/mol and creatinine: 50 µmol/L. The shaded area in each panel is the 95% CI. All estimates are from fully adjusted models including the risk factors displayed in figure 3. BMI, body mass index; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; SBP, systolic blood pressure.

multivariable regression models fitted to the complete case cohort subset (online supplemental figures 19 and 20) estimated effects of the risk factors that were attenuated but similar in terms of effect size and direction compared with the estimates from the complete case Cox regression models (online supplemental figures 12 and 13).

Healthcare utilisation

Over the duration of follow-up from the second disease diagnosis, the HF and CKD and HF and T2D groups had highest rates of GP consultations and referrals to external care and the CKD and T2D group had lowest rates (online supplemental figure 21). For example, in the first year of follow-up, we observed per-person per-year GP consultation rates of 61.6 (95% CI: 61.5, 61.7), 60.8 (95% CI: 60.7, 61.0) and 41.1 (95% CI: 41.0, 41.1) and in the fifth year, we observed rates of 54.2 (95% CI: 54.1, 54.3), 52.3 (95% CI: 51.1, 52.5) and 41.1 (95% CI: 41.1, 41.2) for CKD and HF, HF and T2D and CKD and T2D, respectively. Besides a spike in the first year of follow-up, the rates of healthcare utilisation in the primary care setting remained fairly constant over time for all groups.

In the hospital setting (online supplemental figure 22), the HF and CKD group had highest rates of inpatient admissions and procedures, followed by the HF and T2D group and the CKD and T2D group. For example, in the first year of follow-up, we observed per-person per-year inpatient admissions rates of 0.80 (95% CI: 0.79, 0.80), 0.49 (95% CI: 0.48, 0.50) and 0.22 (0.22, 0.23) and in the fifth year, we observed rates of 0.58 (95% CI: 0.57, 0.59), 0.32 (95% CI: 0.30, 0.34) and 0.21 (95% CI: 0.20, 0.21) for CKD and HF, HF and T2D and CKD and T2D, respectively. There appeared to be a decreasing rate of inpatient admissions and procedures over time for the CKD and HF group. The rates of healthcare utilisation appeared to be generally constant in all settings for the CKD and T2D group.

DISCUSSION

In the largest real-world study to date to consider the detailed impact of combinations of HF, CKD and T2D on

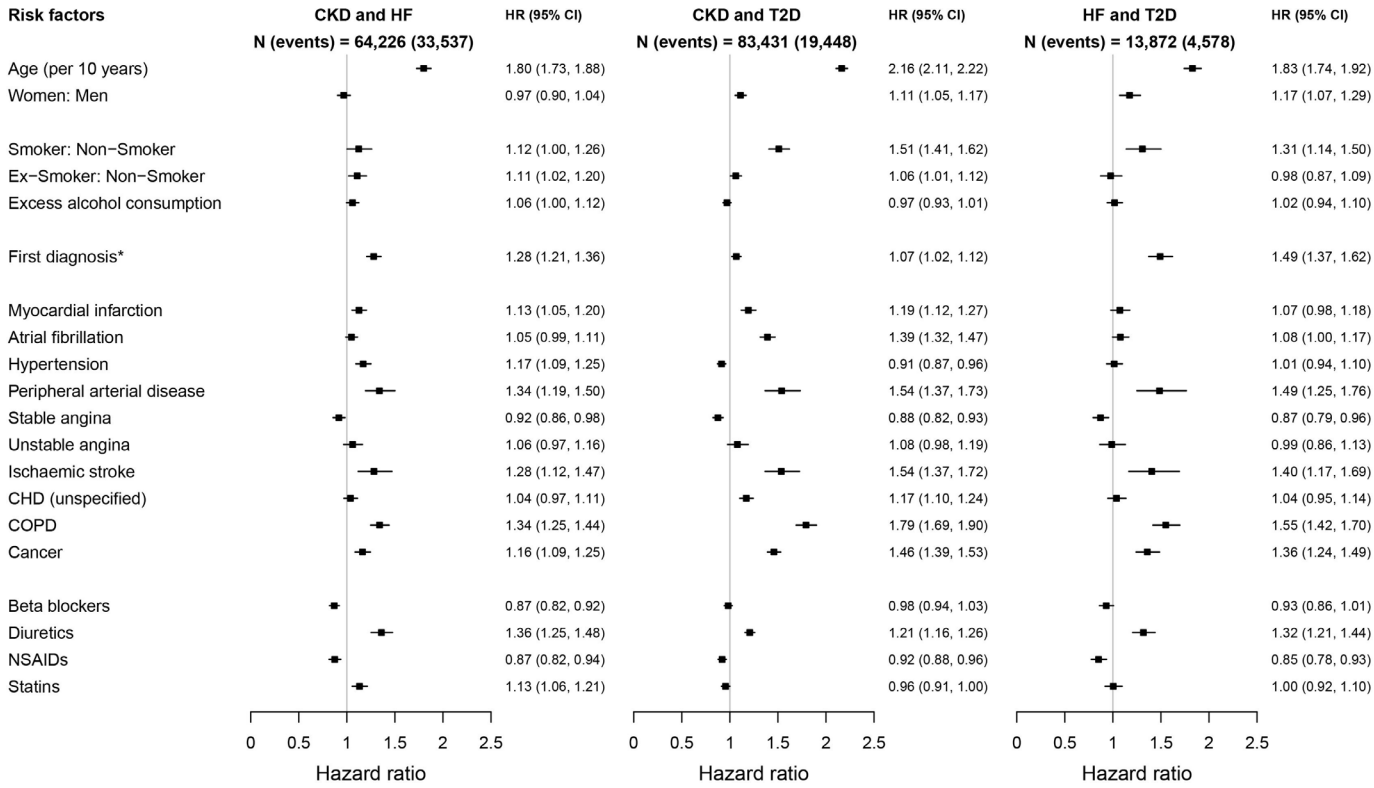

Figure 5 Risk of all-cause mortality in disease pairs of heart failure (HF), chronic kidney disease (CKD) and type 2 diabetes (T2D), using multivariable Cox regression models. *For first diagnosis, HF is the reference group for CKD and HF, CKD is the reference group for CKD and T2D, and HF is the reference group for HF and T2D. The upper and lower limits for each point are the 95% CIs. All estimates are from fully adjusted models including the continuous risk factors displayed in figure 6. CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; NSAIDs, non-steroidal anti-inflammatory drugs.

baseline characteristics, outcomes and healthcare utilisation, we have four main findings. First, HF, CKD and T2D carry significant mortality and healthcare burden in combination and across different disease trajectories. Second, CKD and HF is the combination with the worst prognosis in terms of all-cause mortality and cardiovascular mortality, and the highest rate of healthcare utilisation. Third, use of established, evidence-based therapies such as beta-blockers and ACE inhibitors at baseline was low across disease combinations, including those individuals with HF and CKD. Fourth, there are opportunities to prevent development of CKD in HF and T2D.

Lifetime risk of CVD and CKD is known to be high in those with T2D.[6] In our representative population-based cohort, CKD and T2D was the most common two-disease combination at baseline, followed by CKD and HF, then HF and T2D. Individually, these diseases are common, carrying significant morbidity, mortality and healthcare utilisation.[5] We confirm that development of the third condition is also common. For example, among those with HF and T2D, 37.0% developed CKD in the next 5 years of follow-up (compared with 8.7% diagnosed with T2D in those with HF and CKD and 6.8% diagnosed with HF in those with CKD and T2D). Evidence already supports treatment and prevention of T2D, HF and CKD individually and together.[6–8] Our findings support prevention of the third diagnosis when individuals already have two conditions, and highlight need for integrated care across diseases from screening and diagnosis to management and prevention.[17 18]

HF and CKD emerged as the disease combination with most impact on patients in terms of risk factors, prognosis and healthcare utilisation, which is supported by prior studies[8 9 19] and suggests that prevention and monitoring of T2D should be further prioritised in those with HF and CKD. In atherosclerotic CVD, comparative epidemiology has led to knowledge about progression, severity and service planning, for example, in recognising the relatively worse prognosis with peripheral arterial disease compared with coronary artery disease.[20] Similar comparisons need to occur across individual diseases and across disease combinations in order to better understand cross-disease pathophysiology, personalised clinical decision-making and public health strategies. For example, risk prediction and health economic models are increasingly looking at disease combinations rather than single diseases.[21 22]

In recent years, there have been several therapeutic advances for individual diseases (eg, angiotensin receptor-neprilysin inhibitors in HF[23]) and across diseases (eg, sodium-glucose cotransporter-2 inhibitors in HF, T2D and CKD[24–26]). However, in our study, there was room for improvement in the prescription of even well-established, guideline-based drugs. For example,

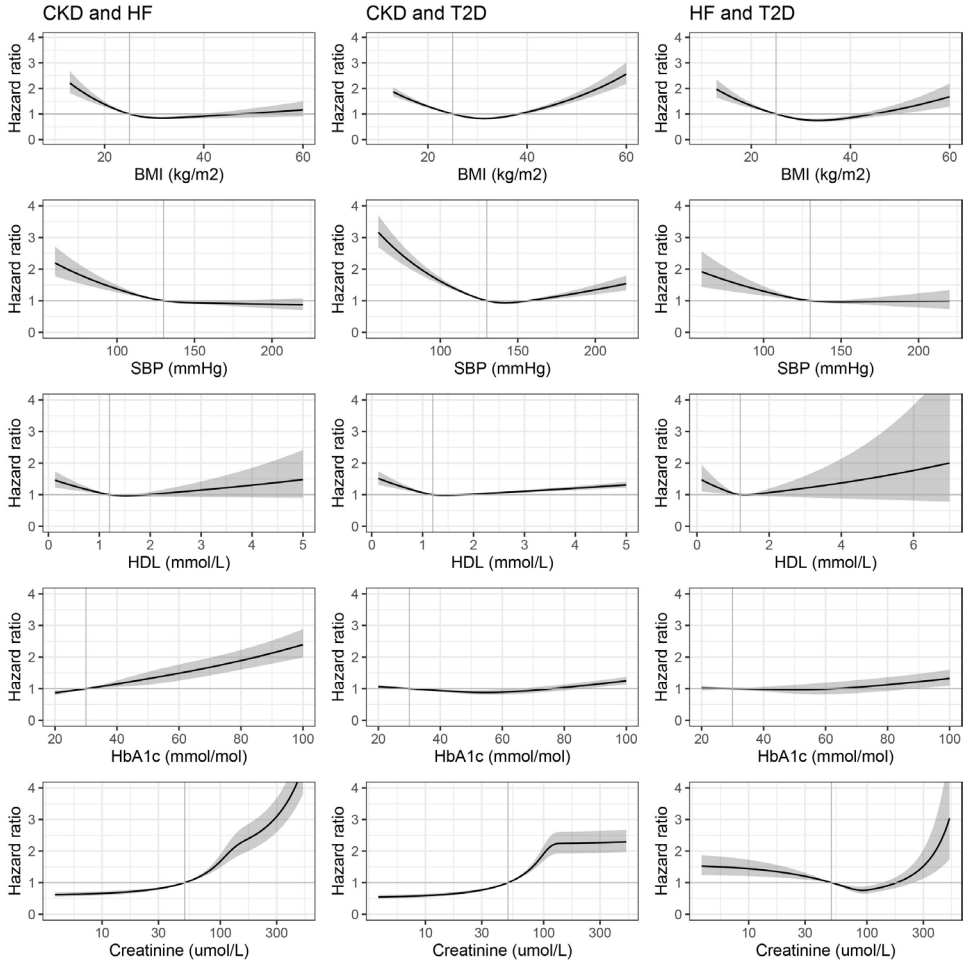

Figure 6 Risk of all-cause mortality in disease pairs of heart failure (HF), chronic kidney disease (CKD) and type 2 diabetes (T2D), using restricted cubic splines for continuous variables in the multivariable Cox regression models. The reference value for each risk factor was BMI: 25 kg/m^2, SBP: 130 mm Hg, HDL: 1.2 mmol/L, HbA1c: 30 mmol/mol and creatinine: 50 µmol/L. The shaded area in each panel is the 95% CI. All estimates are from fully adjusted models including the risk factors displayed in figure 5. BMI, body mass index; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; SBP, systolic blood pressure.

only half of individuals with HF were prescribed beta-blockers and ~70% were on ACE inhibitors, based on prescriptions at the time of the second diagnosis. Adherence is likely to be suboptimal and so this reflects an overestimate of actual use. Moreover, we observed that inpatient and outpatient healthcare utilisation was highest for the HF+CKD combination and that this was greatest in the first year after diagnosis, which could suggest that the diagnosis of the third condition (T2D in this case) occurs during admissions or outpatient attendance for other conditions and complications. This healthcare utilisation decreases over time, possibly as routine monitoring and follow-up of the three conditions together (HF, CKD and T2D) occur, suggesting that early prevention of the third condition or its progression will lead to less healthcare burden. These types of analyses need to be conducted across disease combinations and by order of diagnosis. Therefore, there are important gaps which need to be bridged in order to improve morbidity, mortality and healthcare efficiency across these diseases. If we consider multimorbidity more broadly, polypharmacy and associated low rates of prescription and adherence need to be investigated and tackled.

In this study, we have concentrated on incident second and third diagnoses in people with pre-existing CKD, HF or T2D. There are opportunities and proven strategies to prevent onset of these diseases (eg, antihypertensive treatment to prevent CKD,[27] post-myocardial infarction therapy to prevent HF[28] and management of obesity to prevent T2D[29]), but coordinated approaches across the patient pathway are required. Moreover, risk factors are rarely investigated comprehensively either in observational or interventional studies for primary prevention. For example, in a large UK-based EHR study, we showed that among new HF cases, 28.5% had no risk factors supported by evidence for HF primary prevention, 38.6% had no risk factors with evidence for CVD primary prevention, and 15.6% had either no risk factors or only risk factors without any trial evidence for HF or CVD prevention.[30]

Strengths and limitations

The strengths of our study design are the nationally representative, linked EHR data, the inclusive and validated definitions of diseases and the detailed analysis plan. There are several limitations. First, due to the nature of the EHR data, we only considered certain comorbidities and risk factors of medications and sources of healthcare utilisation and could not include a comprehensive list. Second, we did not have measures of disease severity such as HF stage or ejection fraction and we did not use CKD stage in the analyses other than restricting the CKD cohort to those diagnoses with stage 3 and above. Third, we concentrated on pairs of diseases and only looked at incidence of second and third diseases. Fourth, we had significant missing data for some of the risk factors analysed. We used multiple imputation in order to be able to include these variables in our analysis under the assumption that the data were missing at random. The results of our complete case analysis found minimal deviations between the analysis on imputed and complete case data. Fifth, our analysis used only patient characteristics and risk factors measured at baseline and did not consider changing risk factor profiles of the cohort over time, for example, additions or modifications to medications were not reflected after diagnosis of the second condition. Sixth, we did not account for changes and updates to clinical guidelines for medications during the study period from 1998 and did not have data for indication for prescription of medications. We do not compare the study population with controls, whether healthy or those who develop a first condition. Seventh, for T2D, our EHR phenotype excluded codes with unclear or conflicting type of diabetes, which may have led to underascertainment,[31] perhaps explaining the relatively low T2D event rates in those with HF and CKD (8.7%). Finally, we performed Fine and Gray regression competing risk analyses taking into account the competing risk of all-cause mortality on the event of being diagnosed with a third condition on only the complete case subset of the cohort, due to computational limitations.

CONCLUSIONS

In a large observational study in national EHRs, we showed the importance of detailed epidemiological studies in the context of multimorbidity to inform targeted individual and population-level healthcare. CKD, HF and T2D frequently co-occur leading to major morbidity and mortality in combination. There are multiple opportunities to fill evidence and practice gaps to improve knowledge and outcomes, and future research in multimorbidity must take this into account.

Twitter Anish Bhuva @mrimypacemaker and Amitava Banerjee @amibanerjee1

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Contributors JBM, LP and A Banerjee contributed to the conception of the study and study design. LP and A Banerjee led the development of the statistical analysis plan, review of results and drafted and revised the final manuscript. JBM obtained the data. LP, MM and AD prepared the data for analysis and LP analysed all data. MM, AD, A Bhuva, TM and JBM critically reviewed and edited the manuscript. A Banerjee is the guarantor of the study.

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ORCID iDs
Anish Bhuva http://orcid.org/0000-0001-7532-7815
Amitava Banerjee http://orcid.org/0000-0001-8741-3411

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