Supplementary material

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Figure S22: Observed rate of healthcare utilisation in hospital setting

Figure S1: Study population diagram

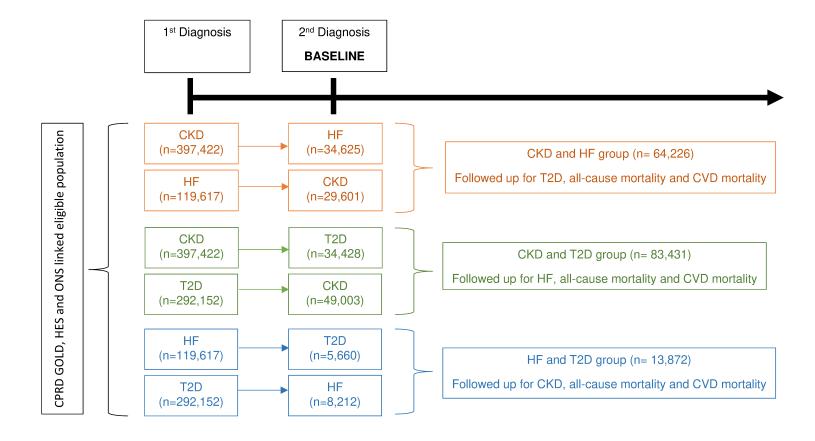


Table S1: Codelists for defining our chronic kidney disease, heart failure and type 2 diabetes cohorts

	Read code	ICD-10	Clinical
	(Primary care)	(Hospital	biomarkers
		admissions)	(primary care)
Chronic	1Z12.00, 1Z13.00, 1Z14.00, 1Z15.00, 1Z16.00,	N18.3, N18.4,	eGFR
kidney disease	1Z1B.00, 1Z1C.00, 1Z1D.00, 1Z1E.00, 1Z1F.00,	N18.5, T82.4,	COPK
kidney disease	1Z1G.00, 1Z1H.00, 1Z1J.00, 1Z1K.00, 1Z1L.00,	T86.1, Y60.2,	
	7B06300, 8L50.00, K0100, K010.00, K011.00,	Y61.2, Y62.2,	
	K012.00, K013.00, K013.11, K013.12, K014.00,	Y84.1, Z49.0,	
	K015.00, K016.00, K017.00, K018.00, K019.00,	Z49.1, Z49.2,	
	K01A.00, K01B.00, K01w.00, K01w000, K01x000,	Z94.0, Z99.2,	
	K01x100, K01x111, K01x200, K01x300, K01x400,	N18.6, I77.0,	
	K01x411, K01y.00, K01z.00, K0200, K0211,	N16.5	
	K0212, K020.00, K021.00, K022.00, K023.00,		
	K02y.00, K02y000, K02y200, K02y300, K02yz00,		
	K02z.00, K0500, K0511, K0512, K050.00,		
	K0D00, K100.00, K100000, K100100, K100200,		
	K100300, K100400, K100500, K100600, K100z00,		
	SP08300, TB00100, TB00111, ZV42000		
Heart failure	14A6.00, 14AM.00, 1O100, 388D.00, 661M500,	I11.0, I13.0,	
	662T.00, 662W.00, 662f.00, 662g.00, 662h.00, 662i.00,	I13.2, I50	
	662p.00, 679W100, 679X.00, 8B29.00, 8CL3.00,		
	8CMK.00, 8CMW800, 8CeC.00, 8H2S.00, 8HBE.00,		
	8HHz.00, 8Hk0.00, 9N2p.00, 9N6T.00, 9On00,		
	9On0.00, 9On1.00, 9On2.00, 9On3.00, 9On4.00,		
	9Or00, 9Or0.00, 9Or1.00, 9Or2.00, 9Or3.00, 9Or4.00,		
	9Or5.00, 9h100, 9h11.00, 9h12.00, 9hH00, 9hH0.00,		
	9hH1.00, G1yz100, G210100, G211100, G21z100,		
	G232.00, G234.00, G400.00, G41z.11, G554000,		
	G554011, G5800, G5811, G580.00, G580.11,		
	G580.12, G580.13, G580.14, G580000, G580100,		
	G580200, G580300, G580400, G581.00, G581.11,		
	G581.13, G581000, G582.00, G584.00, G58z.00,		
	G58z.12, G5yy900, G5yyA00, ZRad.00	710	
Type 2	C108A11, C109.13, C109011, C109012, C109111,	E10	
diabetes	C109112, C109211, C109212, C109411, C109412,		
	C109511, C109512, C109611, C109612, C109711,		
	C109712, C109A11, C109B11, C109C11, C109C12,		
	C109D11, C109D12, C109E11, C109E12, C109F11,		
	C109F12, C109G11, C109G12, C109H11, C109H12, C109J00, C109J12, C10EA11, C10F.11, C10F000,		
	C10F011, C10F100, C10F200, C10F211, C10F300,		
	C10F311, C10F400, C10F411, C10F500, C10F600,		
	C10FQ00, C10FR00		
	C10F611, C10F700, C10F711, C10F900, C10F911, C10FA00, C10FA11, C10FB00, C10FB11, C10FC00, C10FD00, C10FD11, C10FE00, C10FE11, C10FF00, C10FG00, C10FH00, C10FJ00, C10FJ11, C10FL00, C10FL11, C10FM00, C10FM11, C10FN00, C10FP00, C10FQ00, C10FR00		

Table S2: Baseline characteristics of the cohort stratified by the order of CKD, HF or T2D disease diagnoses

	CKI	D and HF	CKE	and T2D	HF	and T2D
N	CKD then HF 34,625	HF then CKD 29,601	CKD then T2D 34,428	T2D then CKD 49,003	HF then T2D 5,660	T2D then HF 8,212
Demographics and behaviours	34,023	25,001	34,420	45,003	3,000	OJEIL
Age (years), Mean (SD)	81.5 (9.32)	78.2 (10.30)	73.8 (10.05)	71.5 (9.99)	69.5 (11.40)	71.2 (11.26)
Age (years), Mean (SD) Age (years), range	18.4. 109	18.7. 107	24.7, 109	18.6, 109	25.4. 105	20.2. 100
Women	,	,			,	,
	18878 (54.5)	14154 (47.8)	19765 (57.4)	24281 (49.6)	1871 (33.1)	2752 (33.5)
Ethnicity				()	()	
White	22514 (65)	16607 (56.1)	22133 (64.3)	29352 (59.9)	2991 (52.8)	4226 (51.5)
Black	175 (0.5)	114 (0.4)	339 (1)	577 (1.2)	37 (0.7)	65 (0.8)
South Asian	302 (0.9)	233 (0.8)	604 (1.8)	1210 (2.5)	62 (1.1)	151 (1.8)
Other	141 (0.4)	112 (0.4)	242 (0.7)	415 (0.8)	31 (0.5)	58 (0.7)
Unknown	11493 (33.2)	12535 (42.3)	11110 (32.3)	17449 (35.6)	2539 (44.9)	3712 (45.2)
Smoking status						
Non-Smoker	6736 (19.5)	5830 (19.7)	7132 (20.7)	10390 (21.2)	812 (14.3)	1162 (14.2)
Smoker	3399 (9.8)	3510 (11.9)	4195 (12.2)	6648 (13.6)	1005 (17.8)	1563 (19)
Ex-Smoker	24047 (69.4)	19312 (65.2)	22732 (66)	31224 (63.7)	3686 (65.1)	5385 (65.6)
Missing %	1.3	3.2	1.1	1.5	2.8	1.2
Excess alcohol consumption	12185 (35.2)	9552 (32.3)	11924 (34.6)	16811 (34.3)	2110 (37.3)	3446 (42)
Multimorbidity characteristics						
Time between diagnoses (years), Median (IQR)	4.08 (1.49, 7.49)	2.44 (0.76, 5.20)	3.36 (1.15, 6.49)	4.21 (1.67, 7.84)	3.05 (1.06, 5.96)	4.91 (1.94, 8.67)
Medical history	·	·		·	·	
Myocardial infarction	8838 (25.5)	8856 (29.9)	3432 (10)	4259 (8.7)	1798 (31.8)	2328 (28.3)
Unstable angina	3208 (9.3)	3014 (10.2)	1217 (3.5)	1497 (3.1)	601 (10.6)	778 (9.5)
Stable angina	10773 (31.1)	10479 (35.4)	6458 (18.8)	7939 (16.2)	2194 (38.8)	2569 (31.3)
Percutaneous coronary intervention	2407 (7)	2185 (7.4)	1424 (4.1)	1782 (3.6)	684 (12.1)	852 (10.4)
Coronary artery bypass graft	2721 (7.9)	2965 (10)	1251 (3.6)	1788 (3.6)	647 (11.4)	722 (8.8)
Unspecified coronary heart disease	12360 (35.7)	12516 (42.3)	6566 (19.1)	7916 (16.2)	2703 (47.8)	2906 (35.4)
					195 (3.4)	
Peripheral arterial disease	1746 (5)	1144 (3.9)	662 (1.9)	886 (1.8)		331 (4)
Ischaemic stroke	1697 (4.9)	1053 (3.6)	765 (2.2)	1004 (2)	178 (3.1)	306 (3.7)
Hypertension	25136 (72.6)	17392 (58.8)	24998 (72.6)	34409 (70.2)	3134 (55.4)	5448 (66.3)
Atrial fibrillation	15098 (43.6)	12964 (43.8)	4264 (12.4)	4621 (9.4)	2232 (39.4)	2834 (34.5)
Chronic obstructive pulmonary disease	5972 (17.2)	5256 (17.8)	3435 (10)	4129 (8.4)	1122 (19.8)	1631 (19.9)
Cancer	9266 (26.8)	6160 (20.8)	6384 (18.5)	8424 (17.2)	896 (15.8)	1582 (19.3)
Clinical Biomarkers						
Body mass index, Mean (SD)	28.0 (6.18)	28.2 (6.21)	31.2 (6.26)	31.0 (6.35)	32.8 (7.16)	32.0 (7.12)
Missing %	46.8	45.5	33.1	16.8	33.5	19.6
Systolic blood pressure (mmHg), Mean (SD)	133 (20.1)	129 (19.9)	138 (16.8)	135 (17.3)	131 (18.3)	133 (18.7)
Missing %	6.1	8	5.7	5.4	8.4	5.5
Diastolic blood pressure (mmHg), Mean (SD)	73.8 (11.6)	72.3 (11.2)	76.8 (10.1)	74.9 (10.0)	75.6 (10.8)	75.5 (11.3)
Missing %	6.1	8	5.7	5.4	8.4	5.5
HbA1c, Median (IQR)	45 (39.9, 55.2)	48 (41.0, 60.7)	52 (48.6, 61.0)	52 (46.0, 61.7)	54 (49.0, 65.0)	53 (46.0, 63.0)
Missing %	75.9	78.8	39	7.2	42.3	12.9
HDL (mg/dL), Median (IQR)	1.30 (1.10, 1.61)	1.26 (1.00, 1.53)	1.20 (1.00, 1.44)	1.20 (1.00, 1.41)	1.10 (0.90, 1.30)	1.15 (0.96, 1.40)
Missing %	48.4	45.6	27.6	19.2	32.5	25.5
LDL (mg/dL), Median (IQR)	2.20 (1.70, 2.88)	2.20 (1.70, 2.84)	2.50 (1.90, 3.20)	2.10 (1.60, 2.70)	2.22 (1.70, 2.90)	2.00 (1.56, 2.61)
Missing %	60.7	58.2	43.3	38.5	47.5	43.8
=	1.20 (0.90, 1.70)	1.33 (1.00, 1.90)	1.80 (1.30, 2.51)	1.70 (1.20, 2.34)	1.83 (1.30, 2.60)	
Triglycerides (mg/dL), Median (IQR)						1.50 (1.06, 2.10)
Missing %	54.9	50.8	33.7	27.9	38.8	35.7
Creatinine, Median (IQR)	112 (93, 138)	118 (103, 137)	101 (87, 119)	112 (96, 124)	85 (74, 99)	81 (69, 95)
Missing %	9.8	3.5	5.5	0.7	12.8	9
Prescribed medication						
Ace Inhibitors	22296 (64.4)	23318 (78.8)	19676 (57.2)	33774 (68.9)	4481 (79.2)	5839 (71.1)
Beta blockers	17385 (50.2)	16723 (56.5)	13211 (38.4)	17029 (34.8)	3528 (62.3)	4111 (50.1)
Antiplatelets	18953 (54.7)	17122 (57.8)	14408 (41.8)	23272 (47.5)	3062 (54.1)	4490 (54.7)
Statins	19118 (55.2)	17325 (58.5)	21091 (61.3)	36097 (73.7)	3888 (68.7)	6093 (74.2)
Diuretics	25506 (73.7)	25035 (84.6)	17689 (51.4)	23316 (47.6)	4090 (72.3)	5068 (61.7)
Metformin	2154 (6.2)	2010 (6.8)	6971 (20.2)	29252 (59.7)	1239 (21.9)	5076 (61.8)
Insulin	1784 (5.2)	1586 (5.4)	511 (1.5)	4203 (8.6)	144 (2.5)	872 (10.6)
Non-steroidal anti-inflammatory drugs	7470 (21.6)	5399 (18.2)	8451 (24.5)	12306 (25.1)	1047 (18.5)	1764 (21.5)

Figure S3: Kaplan-Meier analysis of the risks of development of third condition, all-cause mortality and cardiovascular mortality in disease pairs, stratified by order of first two conditions

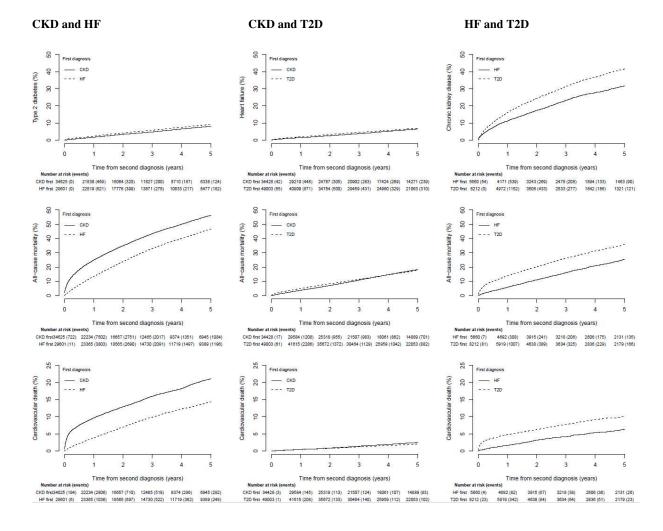
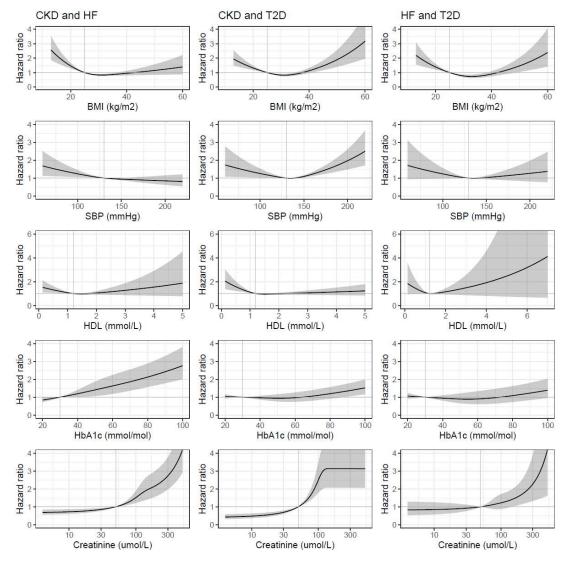


Figure S4: Risk of cardiovascular death in disease pairs of heart failure, chronic kidney disease and type 2 diabetes, using multivariable Cox regression models on multiply imputed data.

Risk factors	CKD and HF	HR (95% CI)	CKD and T2D	HR (95% CI)	HF and T2D	HR (95% CI)
	N (events) = 64,226 (9,159)		N (events) = 83,431 (2,1	131)	N (events) = 13,872 (1,0	62)
Age (per 10 years)	-	1.79 (1.66, 1.94)		2.63 (2.43, 2.85)		1.83 (1.65, 2.02)
Women: Men	+	0.95 (0.83, 1.08)	+	1.06 (0.92, 1.22)	+	0.94 (0.78, 1.14)
Smoker: Non-Smoker		1.26 (1.00, 1.58)		1.42 (1.15, 1.75)		1.48 (1.10, 1.99)
Ex-Smoker: Non-Smoker	-=-	1.25 (1.06, 1.48)	-	1.17 (1.00, 1.37)		1.13 (0.88, 1.45)
Excess alcohol consumption	-	1.32 (1.19, 1.48)	-=-	1.26 (1.12, 1.41)	-=-	1.25 (1.07, 1.47)
First diagnosis*	-	1.46 (1.30, 1.63)	•	0.79 (0.71, 0.89)	-	1.54 (1.29, 1.82)
Myocardial infarction		1.20 (1.06, 1.36)	-	1.07 (0.91, 1.27)	*	1.10 (0.91, 1.32)
Atrial fibrillation		1.36 (1.22, 1.51)	-	1.70 (1.48, 1.95)		1.28 (1.09, 1.50)
Hypertension		1.25 (1.10, 1.42)	+	1.06 (0.92, 1.21)	-	0.88 (0.75, 1.04)
Peripheral arterial disease		2.43 (2.07, 2.85)	_	3.62 (2.93, 4.48)		2.80 (2.17, 3.62)
Stable angina	-	0.84 (0.74, 0.95)	+	0.97 (0.83, 1.14)	+	1.00 (0.82, 1.20)
Unstable angina		1.55 (1.34, 1.80)		1.56 (1.25, 1.94)		1.31 (1.03, 1.66)
Ischaemic stroke		1.71 (1.38, 2.11)		3.13 (2.50, 3.93)		2.33 (1.74, 3.13)
CHD (unspecified)	-=-	1.51 (1.33, 1.72)		1.30 (1.11, 1.52)		1.54 (1.28, 1.87)
COPD		1.38 (1.21, 1.57)		1.86 (1.59, 2.18)		1.50 (1.25, 1.80)
Cancer	-8-	1.19 (1.05, 1.35)	-=-	1.29 (1.14, 1.47)	-=-	1.25 (1.03, 1.50)
Beta blockers	•	0.75 (0.67, 0.84)	+	0.94 (0.84, 1.06)	+	0.71 (0.60, 0.84)
Diuretics	 -	1.13 (0.98, 1.31)	+	1.24 (1.10, 1.39)	+	1.03 (0.87, 1.23)
NSAIDs	-	0.81 (0.71, 0.93)	-	0.87 (0.77, 0.99)	-	0.83 (0.68, 1.01)
Statins	+	0.97 (0.85, 1.11)	-	0.84 (0.74, 0.95)	-	0.79 (0.66, 0.95)
	0 0.5 1 1.5 2 2.5 3 3.5	4	0 0.5 1 1.5 2 2.5 3	3.5 4	0 0.5 1 1.5 2 2.5 3	3.5 4
	Hazard ratio		Hazard ratio		Hazard ratio	

^{*}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% confidence intervals. These models were also adjusted for the continuous variables modelled using restricted cubic splines displayed in figure S5.

Figure S5: Restricted cubic splines to model continuous biomarkers in the multivariable Cox regression models on multiple imputed data: Risk of cardiovascular death in disease pairs of heart failure, chronic kidney disease and type 2 diabetes



Note: The reference value for each risk factor was BMI: 25kg/m², SBP: 130mmHg, HDL: .1.2mmol/L, HbA1c: 30 mmol/mol and creatinine: 50µmol/L. The shaded area in each panel is the 95% confidence interval. All estimates are from the fully adjusted model including the risk factors displayed in figure S4.

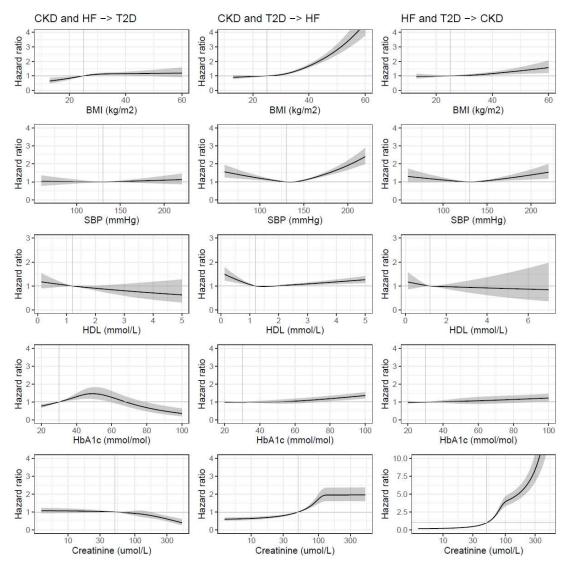
Figure S6: Risk factors for developing third condition in disease pairs of heart failure, chronic kidney disease and type 2 diabetes, using multivariable Cox regression models on multiply imputed data, in the subgroup of the study population aged >60 years at baseline

Risk factors	CKD and HF -> T2D N (events) = 61,807 (3,426)	HR (95% CI)	CKD and T2D -> HF N (events) = 74,128 (5,984)	HR (95% CI)	HF and T2D -> CKD N (events) = 11,375 (3,471)	HR (95% CI)
Age (per 10 years)	-	1.06 (1.01, 1.12)	-	1.87 (1.80, 1.95)	+	1.37 (1.30, 1.44)
Women: Men	•	0.93 (0.85, 1.02)	+	1.07 (1.00, 1.15)	•	0.64 (0.58, 0.69)
Smoker: Non-Smoker		1.10 (0.97, 1.25)	-	1.42 (1.29, 1.57)	-	0.98 (0.86, 1.11)
Ex-Smoker: Non-Smoker	-= 	0.93 (0.84, 1.02)		1.13 (1.05, 1.21)	-=-	0.90 (0.82, 0.99)
Excess alcohol consumption	+	0.95 (0.89, 1.03)	+	1.00 (0.94, 1.05)	-	0.93 (0.87, 1.00)
First diagnosis*	•	0.83 (0.78, 0.90)	•	0.67 (0.64, 0.71)	+	0.96 (0.90, 1.04)
Myocardial infarction	+	1.00 (0.91, 1.09)		1.57 (1.45, 1.69)	-	1.12 (1.03, 1.22)
Atrial fibrillation	-	1.16 (1.08, 1.25)		2.03 (1.90, 2.17)	+	1.03 (0.95, 1.10)
Hypertension	-	0.80 (0.74, 0.87)	-	0.95 (0.89, 1.01)	+	1.03 (0.95, 1.11)
Peripheral arterial disease		0.85 (0.71, 1.02)	——	1.67 (1.45, 1.93)		1.31 (1.10, 1.55)
Stable angina		0.93 (0.85, 1.01)	-=-	1.10 (1.02, 1.19)	-	0.88 (0.81, 0.96)
Unstable angina		1.07 (0.95, 1.20)		1.31 (1.18, 1.47)	+	0.99 (0.87, 1.12)
Ischaemic stroke	- -	1.10 (0.91, 1.32)	_ -	1.71 (1.48, 1.98)	_ 	1.29 (1.08, 1.54)
CHD (unspecified)	+	1.01 (0.93, 1.10)	-	1.24 (1.16, 1.34)	+	1.02 (0.94, 1.11)
COPD		1.20 (1.10, 1.31)		1.60 (1.48, 1.73)	-	1.05 (0.96, 1.15)
Cancer	-	1.12 (1.02, 1.22)	-	1.09 (1.02, 1.16)	+	0.95 (0.87, 1.04)
Beta blockers	-	1.08 (1.00, 1.16)	•	1.11 (1.05, 1.18)	•	0.89 (0.83, 0.96)
Diuretics	+	0.98 (0.89, 1.07)	-	1.41 (1.33, 1.50)	-	1.04 (0.96, 1.13)
NSAIDs	=-	1.05 (0.97, 1.14)	•	0.92 (0.87, 0.98)	+	0.97 (0.89, 1.05)
Statins	•	0.64 (0.59, 0.70)	•	0.75 (0.71, 0.80)	+	0.92 (0.85, 1.00)
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	0 0.5 1 1.5 2	2.5	0 0.5 1 1.5 2	2.5	0 0.5 1 1.5 2	2.5
	Hazard ratio		Hazard ratio		Hazard ratio	

^{*}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.

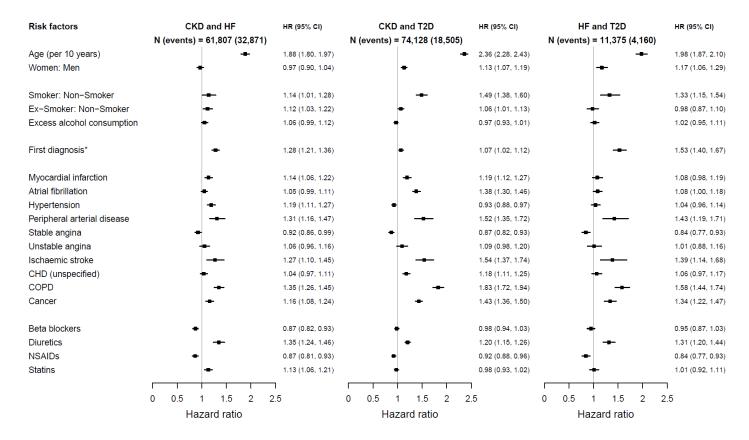
Note: The upper and lower limits for each point are the 95% confidence intervals. These models were also adjusted for the continuous variables modelled using restricted cubic splines displayed in figure S7.

Figure S7: Restricted cubic splines to model continuous biomarkers in the multivariable Cox regression models on multiple imputed data: Risk factors for developing a third condition in disease pairs of heart failure, chronic kidney disease and type 2 diabetes, in the subgroup of the study population aged >60 years at baseline



Note: The reference value for each risk factor was BMI: 25kg/m², SBP: 130mmHg, HDL: .1.2mmol/L, HbA1c: 30 mmol/mol and creatinine: 50µmol/L. The shaded area in each panel is the 95% confidence interval. All estimates are from the fully adjusted model including the risk factors displayed in figure S6

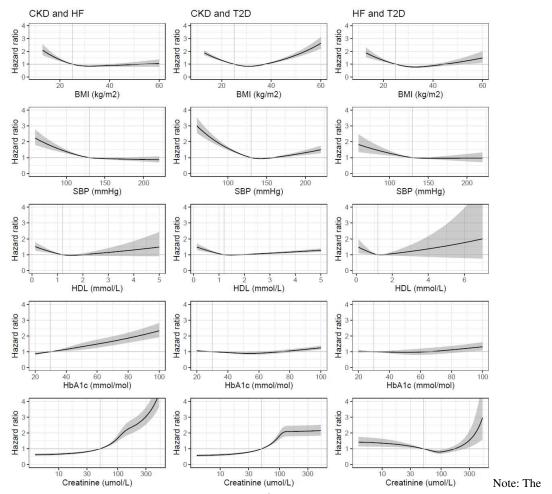
Figure S8: Risk factors for all-cause mortality in disease pairs of heart failure, chronic kidney disease and type 2 diabetes, using multivariable Cox regression models on multiply imputed data, in the subgroup of the study population aged >60 years at baseline



^{*}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.

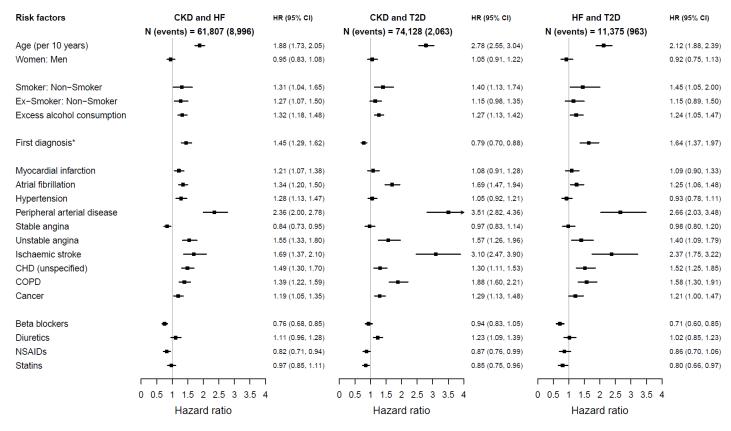
Note: The upper and lower limits for each point are the 95% confidence intervals. These models were also adjusted for the continuous variables modelled using restricted cubic splines displayed in figure S9.

Figure S9: Restricted cubic splines to model continuous biomarkers in the multivariable Cox regression models on multiple imputed data: Risk of all-cause mortality in disease pairs of heart failure, chronic kidney disease and type 2 diabetes, in the subgroup of the study population aged >60 years at baseline



reference value for each risk factor was BMI: $25 kg/m^2$, SBP: 130 mmHg, HDL: .1.2 mmol/L, HbA1c: 30 mmol/mol and creatinine: $50 \mu mol/L$. The shaded area in each panel is the 95% confidence interval. All estimates are from the fully adjusted model including the risk factors displayed in figure S8

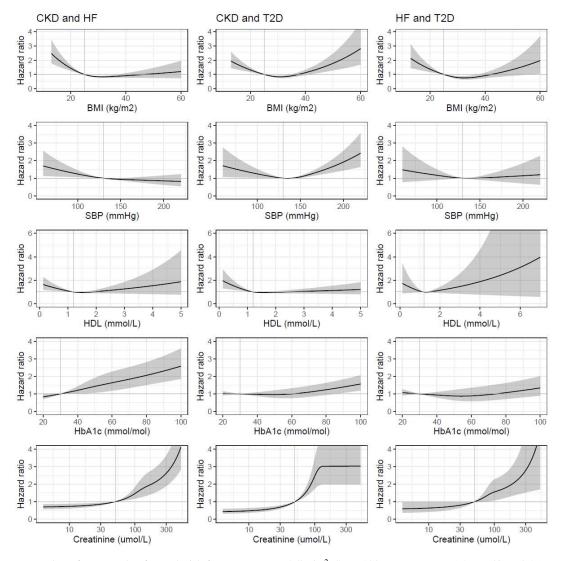
Figure S10: Risk factors for cardiovascular death in disease pairs of heart failure, chronic kidney disease and type 2 diabetes, using multivariable Cox regression models on multiply imputed data, in the subgroup of the study population aged >60 years at baseline



^{*}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.

Note: The upper and lower limits for each point are the 95% confidence intervals. These models were also adjusted for the continuous variables modelled using restricted cubic splines displayed in figure S11.

Figure S11: Restricted cubic splines to model continuous biomarkers in the multivariable Cox regression models on multiple imputed data: Risk of cardiovascular death in disease pairs of heart failure, chronic kidney disease and type 2 diabetes, in the subgroup of the study population aged >60 years at baseline



Note: The reference value for each risk factor was BMI: 25kg/m², SBP: 130mmHg, HDL: .1.2mmol/L, HbA1c: 30 mmol/mol and creatinine: 50µmol/L. The shaded area in each panel is the 95% confidence interval. All estimates are from the fully adjusted model including the risk factors displayed in figure S11

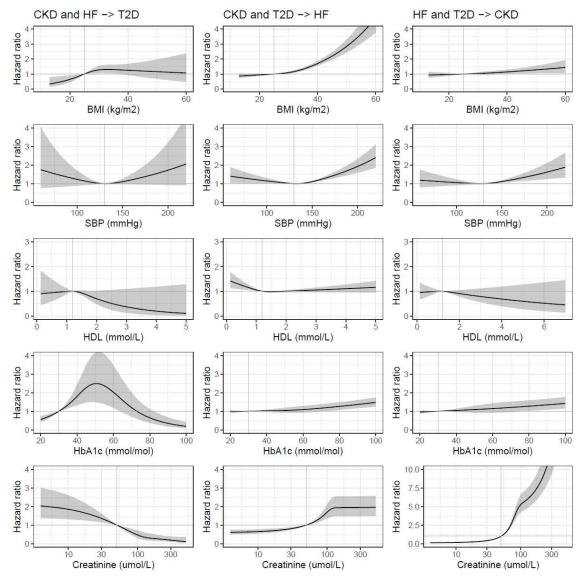
Figure S12: Risk factors for developing third condition in disease pairs of heart failure, chronic kidney disease and type 2 diabetes, using multivariable Cox regression models on complete case data.

Risk factors	CKD and HF -> T2D	HR (95% CI)	CKD and T2D -> HF	HR (95% CI)	HF and T2D -> CKD	HR (95% CI)
	N (events) = 7,706 (305)		N (events) = 43,785 (3,281)		N (events) = 6,884 (1,880)	
Age (per 10 years)		0.75 (0.65, 0.86)	-	1.71 (1.63, 1.80)	-	1.29 (1.23, 1.37)
Women: Men		1.25 (0.94, 1.66)	-	1.09 (1.00, 1.20)	•	0.60 (0.53, 0.67)
Smoker: Non-Smoker		1.27 (0.85, 1.91)		1.50 (1.31, 1.71)		1.12 (0.94, 1.34)
Ex-Smoker: Non-Smoker		0.77 (0.56, 1.06)	-=-	1.24 (1.12, 1.37)	-	1.05 (0.91, 1.21)
Excess alcohol consumption	-	1.00 (0.79, 1.27)	-	1.07 (1.00, 1.16)	+	0.97 (0.88, 1.07)
First diagnosis*		0.88 (0.69, 1.12)	-=-	1.25 (1.15, 1.36)		1.63 (1.46, 1.83)
Myocardial infarction		0.90 (0.69, 1.19)		1.63 (1.47, 1.81)	-	1.06 (0.95, 1.19)
Atrial fibrillation	 	1.13 (0.89, 1.43)		2.06 (1.88, 2.25)	†	0.98 (0.89, 1.08)
Hypertension		0.93 (0.71, 1.21)	 -	1.05 (0.96, 1.15)		1.19 (1.07, 1.32)
Peripheral arterial disease		0.70 (0.40, 1.24)		1.82 (1.51, 2.20)	-	1.19 (0.93, 1.52)
Stable angina		0.82 (0.62, 1.08)	-	1.12 (1.01, 1.24)	-	0.85 (0.75, 0.96)
Unstable angina		1.09 (0.76, 1.55)		1.43 (1.24, 1.65)	+	1.02 (0.87, 1.20)
Ischaemic stroke		0.83 (0.43, 1.62)		1.58 (1.28, 1.94)		1.13 (0.87, 1.46)
CHD (unspecified)		1.39 (1.05, 1.83)		1.31 (1.18, 1.45)	-	1.10 (0.98, 1.24)
COPD		1.21 (0.90, 1.62)		1.71 (1.54, 1.90)	-	1.07 (0.95, 1.21)
Cancer		1.15 (0.86, 1.53)	-=-	1.12 (1.03, 1.23)	+	0.96 (0.84, 1.08)
Beta blockers	+=-	1.16 (0.90, 1.49)	-	1.11 (1.03, 1.20)	-	0.87 (0.78, 0.95)
Diuretics		0.92 (0.68, 1.25)		1.45 (1.34, 1.56)		1.16 (1.05, 1.30)
NSAIDs	 -	1.13 (0.86, 1.47)	-	0.88 (0.81, 0.96)	-	1.05 (0.94, 1.17)
Statins		0.81 (0.61, 1.07)	+	0.88 (0.81, 0.96)	-=-	1.23 (1.09, 1.39)
		\neg		٦		\neg
	0 0.5 1 1.5 2	2.5	0 0.5 1 1.5 2	2.5	0 0.5 1 1.5 2	2.5
	Hazard ratio		Hazard ratio		Hazard ratio	

^{*}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.

Note: The upper and lower limits for each point are the 95% confidence intervals. These models were also adjusted for the continuous variables modelled using restricted cubic splines displayed in figure S13.

Figure S13: Restricted cubic splines to model continuous biomarkers in the multivariable Cox regression models on complete case data: Risk factors for developing a third condition in disease pairs of heart failure, chronic kidney disease and type 2 diabetes



Note: The reference value for each risk factor was BMI: 25kg/m², SBP: 130mmHg, HDL: .1.2mmol/L, HbA1c: 30 mmol/mol and creatinine: 50µmol/L. The shaded area in each panel is the 95% confidence interval. All estimates are from the fully adjusted model including the risk factors displayed in figure S12

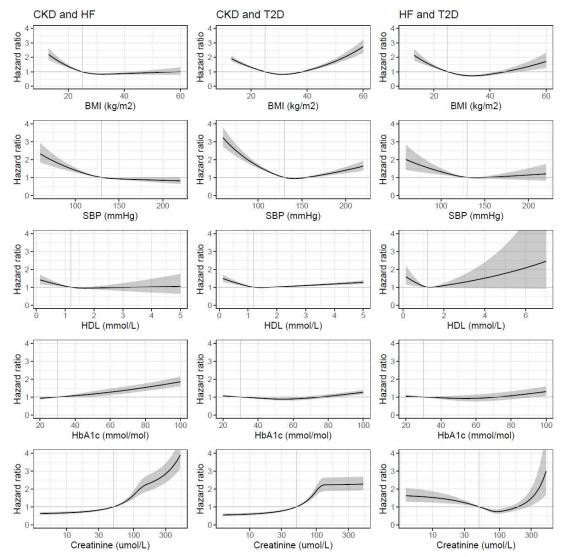
Figure S14: Risk of all-cause mortality in disease pairs of heart failure, chronic kidney disease and type 2 diabetes, using multivariable Cox regression models on complete case data

Risk factors	CKD and HF	HR (95% CI)	CKD and T2D	HR (95% CI)	HF and T2D	HR (95% CI)
	N (events) = 7,706 (3,848)		N (events) = 43,785 (8,943))	N (events) = 6,884 (2,019)	
Age (per 10 years)	+	1.59 (1.52, 1.66)	-	2.14 (2.08, 2.21)		1.77 (1.67, 1.87)
Women: Men	-	0.93 (0.86, 1.00)	•	1.13 (1.07, 1.19)		1.20 (1.07, 1.34)
Smoker: Non-Smoker		1.24 (1.08, 1.43)		1.64 (1.52, 1.77)		1.41 (1.19, 1.68)
Ex-Smoker: Non-Smoker	-	1.13 (1.02, 1.24)	•	1.08 (1.02, 1.14)	+	1.00 (0.87, 1.16)
Excess alcohol consumption	+	1.00 (0.93, 1.07)	+	0.96 (0.92, 1.01)	+	0.99 (0.91, 1.09)
First diagnosis*	-	1.28 (1.20, 1.37)	•	1.12 (1.06, 1.18)		1.54 (1.37, 1.72)
Myocardial infarction	-	1.15 (1.07, 1.24)	-	1.24 (1.15, 1.33)	-	1.08 (0.97, 1.21)
Atrial fibrillation	-	1.05 (0.99, 1.13)	-	1.38 (1.30, 1.47)	 -	1.06 (0.97, 1.17)
Hypertension	-	1.10 (1.02, 1.19)	•	0.92 (0.88, 0.97)	+	0.98 (0.89, 1.08)
Peripheral arterial disease		1.26 (1.11, 1.42)		1.61 (1.42, 1.84)	-	1.40 (1.14, 1.72)
Stable angina	-	0.87 (0.80, 0.94)	•	0.88 (0.83, 0.94)	-	0.88 (0.79, 0.99)
Unstable angina		1.08 (0.98, 1.20)	-	1.08 (0.96, 1.20)	-	0.97 (0.83, 1.14)
Ischaemic stroke	_ -	1.33 (1.14, 1.55)		1.49 (1.30, 1.70)		1.40 (1.11, 1.75)
CHD (unspecified)	-	1.05 (0.98, 1.14)	-	1.15 (1.08, 1.23)	-	1.06 (0.95, 1.19)
COPD		1.25 (1.15, 1.36)	-	1.78 (1.67, 1.90)		1.51 (1.36, 1.68)
Cancer		1.15 (1.07, 1.25)	-	1.51 (1.44, 1.59)		1.42 (1.28, 1.57)
Beta blockers	-	0.85 (0.80, 0.91)	+	0.99 (0.95, 1.04)		0.91 (0.83, 1.01)
Diuretics		1.27 (1.16, 1.40)	•	1.19 (1.14, 1.25)		1.36 (1.23, 1.51)
NSAIDs	-	0.86 (0.79, 0.93)	-	0.93 (0.88, 0.97)	-	0.86 (0.77, 0.97)
Statins	+	0.98 (0.90, 1.06)	+	0.97 (0.92, 1.01)	+	0.96 (0.86, 1.07)
		\neg				\neg
	0 0.5 1 1.5 2	2.5	0 0.5 1 1.5 2	2.5	0 0.5 1 1.5 2	2.5
	Hazard ratio		Hazard ratio		Hazard ratio	

^{*}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.

Note: The upper and lower limits for each point are the 95% confidence intervals. These models were also adjusted for the continuous variables modelled using restricted cubic splines displayed in figure S15.

Figure S15: Restricted cubic splines to model continuous biomarkers in the multivariable Cox regression models on complete case data: Risk of all-cause mortality in disease pairs of heart failure, chronic kidney disease and type 2 diabetes



Note: The reference value for each risk factor was BMI: 25kg/m^2 , SBP: 130 mmHg, HDL: .1.2 mmol/L, HbA1c: 30 mmol/mol and creatinine: $50 \mu \text{mol/L}$. The shaded area in each panel is the 95% confidence interval. All estimates are from the fully adjusted model including the risk factors displayed in figure S14.

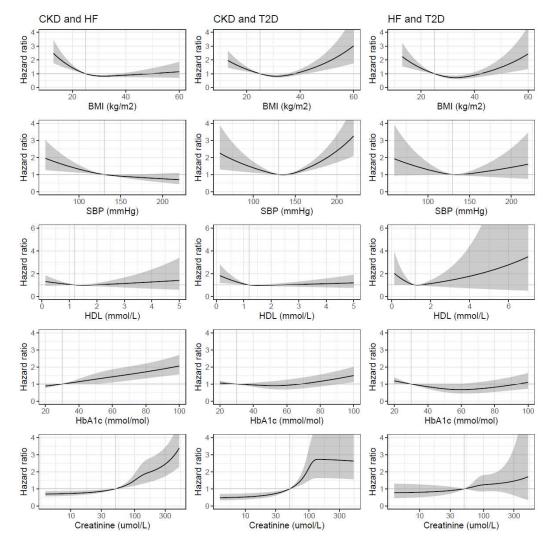
Figure S16: Risk of cardiovascular death in disease pairs of heart failure, chronic kidney disease and type 2 diabetes, using multivariable Cox regression models on complete case data

N (events) = 7,706 (1,133) Age (per 10 years) Women: Men 1.59 (146, 1.73)
Women: Men 0.87 (0.76, 1.01) 1.11 (0.93, 1.32) 0.94 (0.74, 1.19) Smoker: Non-Smoker 1.33 (1.02, 1.73) 1.47 (1.14, 1.90) 1.36 (0.94, 1.96) Ex-Smoker: Non-Smoker 1.29 (1.06, 1.56) 1.21 (1.00, 1.46) 1.01 (0.74, 1.38) Excess alcohol consumption 1.22 (1.08, 1.38) 1.32 (1.16, 1.51) 1.27 (1.05, 1.54) First diagnosis* 1.55 (1.37, 1.76) 0.98 (0.85, 1.14) 1.70 (1.34, 2.16) Myocardial infarction 1.24 (1.08, 1.41) 1.08 (0.87, 1.33) 1.25 (1.01, 1.56) Atrial fibrillation 1.38 (1.22, 1.56) 1.61 (1.35, 1.91) 1.33 (1.10, 1.61) Hypertension 1.16 (1.00, 1.34) 1.23 (1.04, 1.45) 0.89 (0.73, 1.09) Peripheral arterial disease 2.17 (1.82, 2.58) 4.27 (3.35, 5.45) 2.77 (2.06, 3.73) Stable angina 0.82 (0.71, 0.94) 1.02 (0.84, 1.24) 0.92 (0.73, 1.16) Unstable angina 1.57 (1.34, 1.84) 1.55 (1.9, 2.03) 1.20 (0.91, 1.59) Ischaemic stroke 1.77 (1.41, 2.23) 2.95 (222, 3.91) 2.18 (1.25, 3.14) COPD 1.26 (1.08, 1.45) 1.26 (1.08, 1.45) 1.27 (1.04, 1.54) 1.50 (1.21, 1.85)
Smoker: Non-Smoker 1.33 (1.02, 1.73) 1.47 (1.14, 1.90) 1.36 (0.94, 1.96) Ex-Smoker: Non-Smoker 1.29 (1.06, 1.56) 1.21 (1.00, 1.46) 1.01 (0.74, 1.38) Excess alcohol consumption 1.22 (1.08, 1.38) 1.32 (1.16, 1.51) 1.27 (1.05, 1.54) First diagnosis* 1.55 (1.37, 1.76) 0.98 (0.85, 1.14) 1.70 (1.34, 2.16) Myocardial infarction 1.38 (1.22, 1.56) 1.61 (1.35, 1.91) 1.33 (1.10, 1.61) Atrial fibrillation 1.38 (1.22, 1.56) 1.61 (1.35, 1.91) 1.33 (1.10, 1.61) Hypertension 1.16 (1.00, 1.34) 1.23 (1.04, 1.45) 0.89 (0.73, 1.09) Peripheral arterial disease 2.17 (1.82, 2.58) 427 (3.35, 5.45) 2.77 (2.06, 3.73) Stable angina 1.02 (0.71, 0.94) 1.02 (0.84, 1.24) 0.92 (0.73, 1.16) Unstable angina 1.57 (1.34, 1.84) 1.55 (1.19, 2.03) 1.20 (0.91, 1.59) Ischaemic stroke 1.77 (1.41, 2.23) 2.95 (2.22, 3.91) 2.18 (1.52, 3.14) COPD 1.25 (1.08, 1.45) 1.89 (1.56, 2.28) 1.50 (1.21, 1.85)
Ex-Smoker: Non-Smoker Excess alcohol consumption 1.29 (1.06, 1.56) 1.22 (1.08, 1.38) 1.22 (1.08, 1.38) 1.22 (1.08, 1.38) 1.22 (1.08, 1.38) 1.22 (1.08, 1.38) 1.22 (1.08, 1.51) 1.27 (1.05, 1.54) 1.27 (1.05, 1.54) 1.27 (1.05, 1.54) 1.27 (1.05, 1.54) 1.27 (1.05, 1.54) 1.27 (1.05, 1.54) 1.27 (1.05, 1.54) 1.27 (1.05, 1.54) 1.27 (1.05, 1.54) 1.27 (1.05, 1.54) 1.27 (1.05, 1.54) 1.27 (1.05, 1.54) 1.28 (1.01, 1.56) 1.29 (1.08, 1.31) 1.20 (1.08, 1.31) 1.21 (1.00, 1.34) 1.22 (1.08, 1.38) 1.23 (1.16, 1.51) 1.24 (1.08, 1.41) 1.25 (1.01, 1.56) 1.25 (1.01, 1.56) 1.26 (1.01, 1.56) 1.27 (1.04, 1.45) 1.28 (1.04, 1.45) 1.29 (0.24, 1.24) 1.20 (0.24, 1.
Ex-Smoker: Non-Smoker Excess alcohol consumption 1.29 (1.06, 1.56) 1.22 (1.08, 1.38) 1.22 (1.08, 1.38) 1.22 (1.08, 1.38) 1.22 (1.08, 1.38) 1.22 (1.08, 1.4) 1.27 (1.05, 1.54) Myocardial infarction Atrial fibrillation 1.24 (1.08, 1.41) 1.25 (1.01, 1.56) 1.24 (1.08, 1.41) 1.25 (1.01, 1.56) 1.26 (1.01, 1.56) 1.27 (1.04, 1.45) 1.28 (1.04, 1.45) 1.29 (1.04, 1.45) 1.20 (0.84, 1.24) 1.20 (0.91, 1.59) 1.20 (0.91, 1.59) 1.20 (0.91, 1.59) 1.20 (0.91, 1.59) 1.21 (1.00, 1.46) 1.22 (1.08, 1.38) 1.23 (1.10, 1.46) 1.24 (1.08, 1.41) 1.25 (1.01, 1.56) 1.26 (1.01, 1.56) 1.27 (1.04, 1.45) 1.28 (1.02, 1.38) 1.29 (1.04, 1.45) 1.20 (0.91, 1.59) 1.20 (0.91, 1.59) 1.20 (0.91, 1.59) 1.21 (1.04, 1.54) 1.21 (1.00, 1.46) 1.22 (1.08, 1.48) 1.23 (1.04, 1.46) 1.24 (1.08, 1.41) 1.25 (1.01, 1.56) 1.26 (1.01, 1.56) 1.27 (1.04, 1.54) 1.28 (1.52, 3.14) 1.29 (1.20, 1.54) 1.20 (0.91, 1.59) 1.20 (0.91, 1.59) 1.21 (1.03, 1.45) 1.22 (1.04, 1.54) 1.23 (1.04, 1.54) 1.24 (1.05, 1.54) 1.25 (1.04, 1.54) 1.27 (1.04, 1.54) 1.28 (1.52, 3.14) 1.29 (1.21, 1.85)
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First diagnosis* 1.55 (1.37, 1.76) Myocardial infarction 1.24 (1.08, 1.41) 1.08 (0.87, 1.33) 1.25 (1.01, 1.56) Atrial fibrillation 1.38 (1.22, 1.56) 1.61 (1.35, 1.91) 1.33 (1.10, 1.61) Hypertension Peripheral arterial disease 2.17 (1.82, 2.58) Stable angina 0.82 (0.71, 0.94) Unstable angina 1.57 (1.34, 1.84) 1.56 (1.19, 2.03) Ischaemic stroke 1.56 (1.35, 1.80) 1.56 (1.35, 1.80) 1.59 (1.04, 1.54) 1.50 (1.21, 1.85) 1.50 (1.21, 1.85) 1.50 (1.21, 1.85)
Myocardial infarction - 1.24 (1.08, 1.41) - 1.08 (0.87, 1.33) - 1.25 (1.01, 1.56) Atrial fibrillation - 1.38 (1.22, 1.56) - 1.61 (1.35, 1.91) - 1.33 (1.10, 1.61) Hypertension - 1.16 (1.00, 1.34) - 1.23 (1.04, 1.45) - 0.89 (0.73, 1.09) Peripheral arterial disease 2.17 (1.82, 2.58) - 4.27 (3.35, 5.45) - 2.77 (2.06, 3.73) Stable angina - 0.82 (0.71, 0.94) - 1.02 (0.84, 1.24) - 0.92 (0.73, 1.16) Unstable angina - 1.57 (1.34, 1.84) - 1.55 (1.19, 2.03) - 1.20 (0.91, 1.59) Ischaemic stroke - 1.77 (1.41, 2.23) - 2.95 (2.22, 3.91) - 2.18 (1.52, 3.14) CHD (unspecified) - 1.56 (1.35, 1.80) - 1.27 (1.04, 1.54) - 1.50 (1.21, 1.85)
Myocardial infarction - 1.24 (1.08, 1.41) - 1.08 (0.87, 1.33) - 1.25 (1.01, 1.56) Atrial fibrillation - 1.38 (1.22, 1.56) - 1.61 (1.35, 1.91) - 1.33 (1.10, 1.61) Hypertension - 1.16 (1.00, 1.34) - 1.23 (1.04, 1.45) - 0.89 (0.73, 1.09) Peripheral arterial disease 2.17 (1.82, 2.58) - 4.27 (3.35, 5.45) - 2.77 (2.06, 3.73) Stable angina - 0.82 (0.71, 0.94) - 1.02 (0.84, 1.24) - 0.92 (0.73, 1.16) Unstable angina - 1.57 (1.34, 1.84) - 1.55 (1.19, 2.03) - 1.20 (0.91, 1.59) Ischaemic stroke - 1.77 (1.41, 2.23) - 2.95 (2.22, 3.91) - 2.18 (1.52, 3.14) CHD (unspecified) - 1.56 (1.35, 1.80) - 1.27 (1.04, 1.54) - 1.50 (1.21, 1.85)
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Atrial fibrillation
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Peripheral arterial disease 2.17 (1.82, 2.58) Stable angina
Stable angina - 0.82 (0.71, 0.94) - 1.02 (0.84, 1.24) - 0.92 (0.73, 1.16) Unstable angina - 1.57 (1.34, 1.84) - 1.55 (1.19, 2.03) - 1.20 (0.91, 1.59) Ischaemic stroke - 1.77 (1.41, 2.23) - 2.95 (2.22, 3.91) - 2.18 (1.52, 3.14) CHD (unspecified) - 1.56 (1.35, 1.80) - 1.27 (1.04, 1.54) - 1.71 (1.35, 2.15) COPD - 1.25 (1.08, 1.45) - 1.89 (1.56, 2.28) - 1.50 (1.21, 1.85)
Unstable angina
Ischaemic stroke 1.77 (1.41, 2.23) 2.95 (2.22, 3.91) 2.18 (1.52, 3.14) CHD (unspecified) 1.56 (1.35, 1.80) 1.27 (1.04, 1.54) 1.71 (1.35, 2.15) COPD 1.25 (1.08, 1.45) 1.89 (1.56, 2.28) 1.50 (1.21, 1.85)
CHD (unspecified) 1.56 (1.35, 1.80) 1.27 (1.04, 1.54) 1.71 (1.35, 2.15) COPD 1.25 (1.08, 1.45) 1.89 (1.56, 2.28) 1.50 (1.21, 1.85)
COPD 1.25 (1.08, 1.45) - 1.89 (1.56, 2.28) - 1.50 (1.21, 1.85)
Cancer = 1.20 (1.04, 1.38) = 1.34 (1.15, 1.57) = 1.26 (1.02, 1.57)
Beta blockers • 0.73 (0.64, 0.82) • 1.00 (0.87, 1.15) • 0.65 (0.53, 0.79)
Diuretics - 1.01 (0.87, 1.19) - 1.17 (1.02, 1.35) - 1.05 (0.85, 1.30)
NSAIDs - 0.84 (0.72, 0.97) - 0.86 (0.74, 1.00) - 0.90 (0.71, 1.14)
Statins - 0.90 (0.78, 1.05) - 0.95 (0.81, 1.10) - 0.77 (0.62, 0.97)
0 0.5 1 1.5 2 2.5 3 3.5 4 0 0.5 1 1.5 2 2.5 3 3.5 4 0 0.5 1 1.5 2 2.5 3 3.5 4
Hazard ratio Hazard ratio Hazard ratio

^{*}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.

Note: The upper and lower limits for each point are the 95% confidence intervals. These models were also adjusted for the continuous variables modelled using restricted cubic splines displayed in figure S17.

Figure S17: Restricted cubic splines to model continuous biomarkers in the multivariable Cox regression models on complete case data: Risk of cardiovascular death in disease pairs of heart failure, chronic kidney disease and type 2 diabetes



Note: The reference value for each risk factor was BMI: 25kg/m^2 , SBP: 130 mmHg, HDL: .1.2 mmol/L, HbA1c: 30 mmol/mol and creatinine: $50 \mu \text{mol/L}$. The shaded area in each panel is the 95% confidence interval. All estimates are from the fully adjusted model including the risk factors displayed in figure S16.

Figure S18: Cumulative incidence functions estimating the probability of patients being diagnosed with a third condition in the presence of the competing risk of all-cause mortality

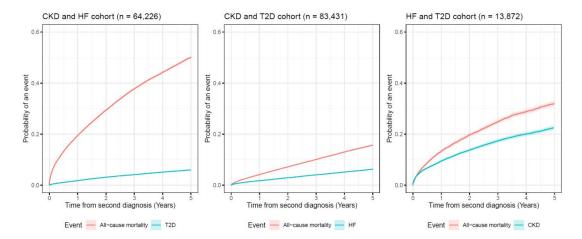
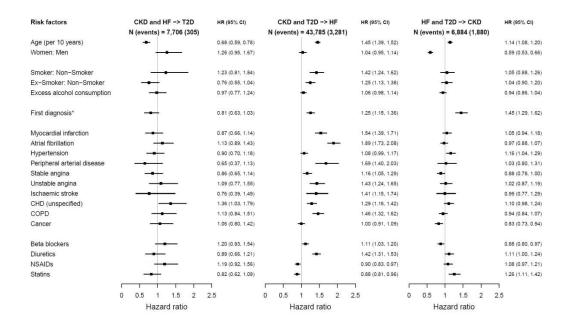


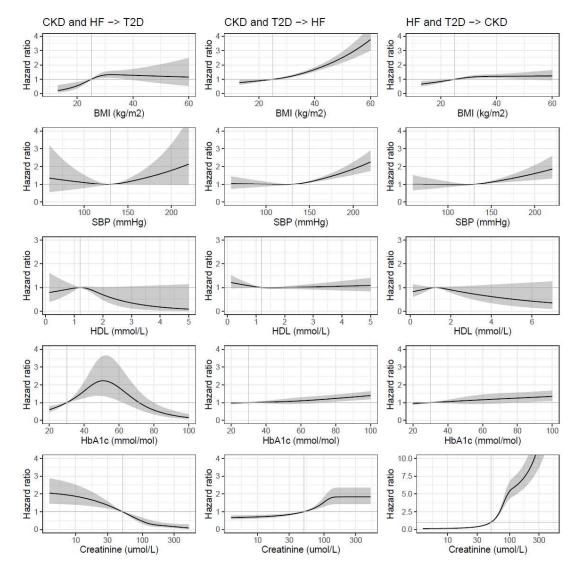
Figure S19: Risk factors for developing third condition in disease pairs of heart failure, chronic kidney disease and type 2 diabetes, using multivariable Fine and Grey regression models on complete case data.



*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.

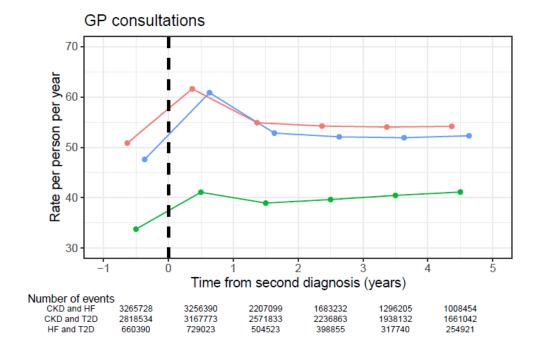
Note: The upper and lower limits for each point are the 95% confidence intervals. These models were also adjusted for the continuous variables modelled using restricted cubic splines displayed in figure S20.

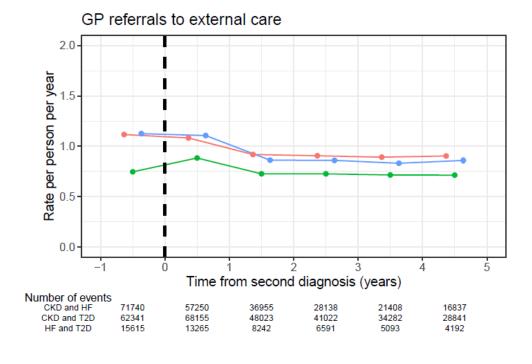
Figure S20: Restricted cubic splines to model continuous biomarkers in the multivariable Fine and Grey models on complete case data: Risk factors for developing a third condition in disease pairs of heart failure, chronic kidney disease and type 2 diabetes



Note: The reference value for each risk factor was BMI: 25kg/m², SBP: 130mmHg, HDL: .1.2mmol/L, HbA1c: 30 mmol/mol and creatinine: 50µmol/L. The shaded area in each panel is the 95% confidence interval. All estimates are from the fully adjusted models including the risk factors displayed in figure S19.

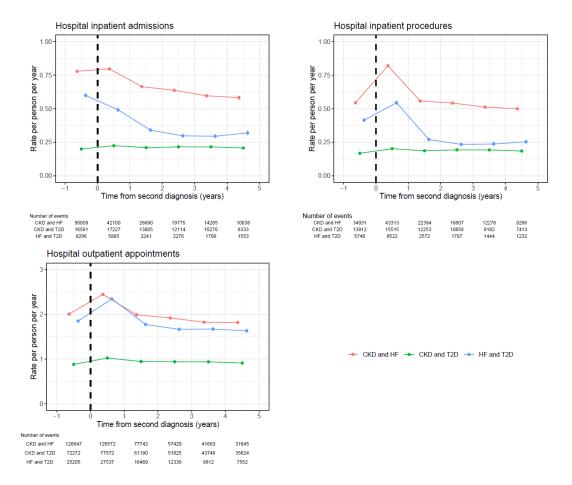
Figure S21: Observed rate of healthcare utilisation in primary care setting





→ CKD and HF → CKD and T2D → HF and T2D

Figure S22: Observed rate of healthcare utilisation in hospital setting



Note: Outpatient data limited to individuals who entered the cohort from 2003 onwards.