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Figure S1: Study population diagram

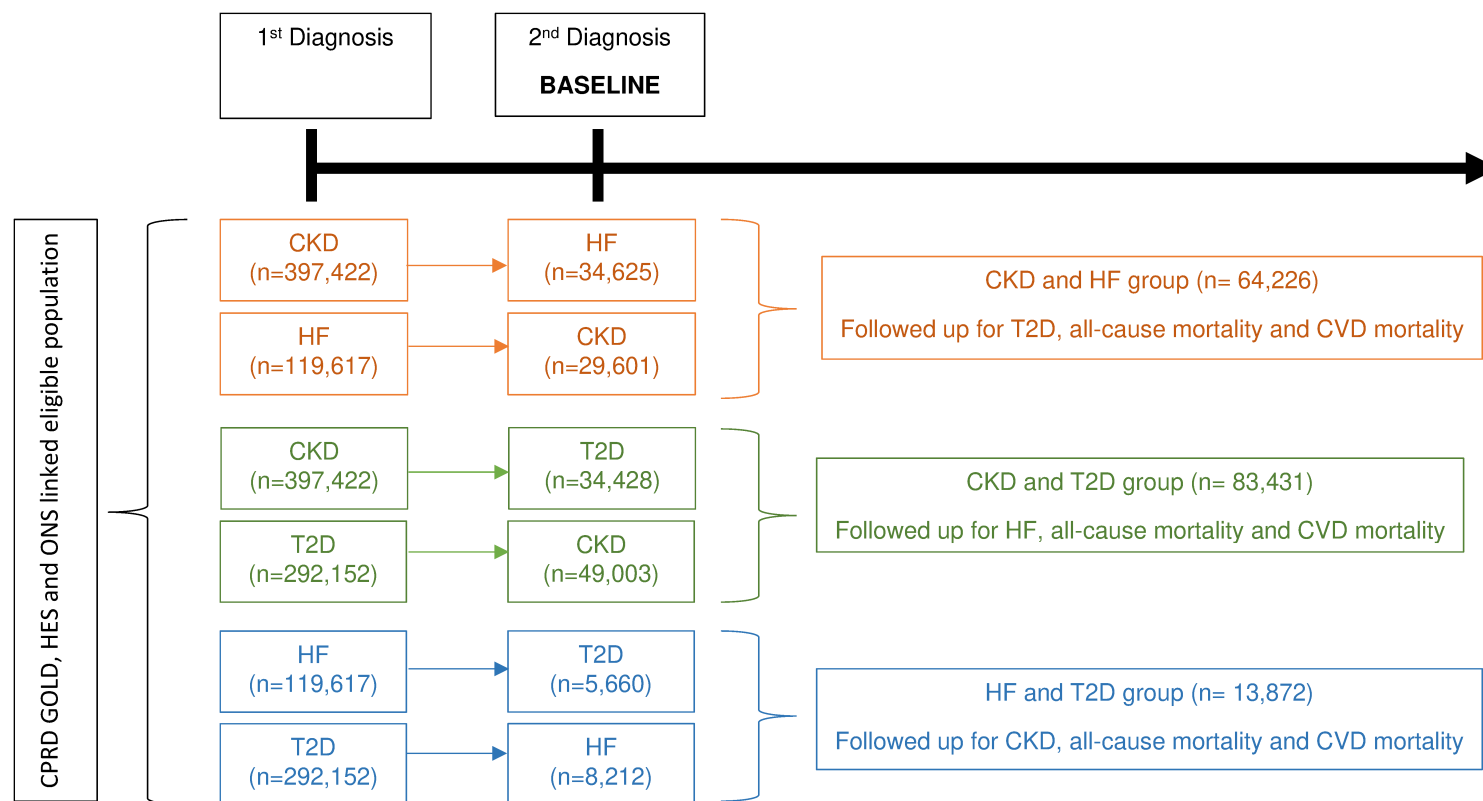


Table S1: Codelists for defining our chronic kidney disease, heart failure and type 2 diabetes cohorts

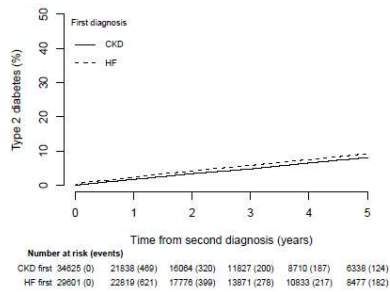
	Read code (Primary care)	ICD-10 (Hospital admissions)	Clinical biomarkers (primary care)
<b>Chronic kidney disease</b>	1Z12.00, 1Z13.00, 1Z14.00, 1Z15.00, 1Z16.00, 1Z1B.00, 1Z1C.00, 1Z1D.00, 1Z1E.00, 1Z1F.00, 1Z1G.00, 1Z1H.00, 1Z1J.00, 1Z1K.00, 1Z1L.00, 7B06300, 8L50.00, K01.00, K010.00, K011.00, K012.00, K013.00, K013.11, K013.12, K014.00, K015.00, K016.00, K017.00, K018.00, K019.00, K01A.00, K01B.00, K01w.00, K01w000, K01x000, K01x100, K01x111, K01x200, K01x300, K01x400, K01x411, K01y.00, K01z.00, K02.00, K02.11, K02.12, K020.00, K021.00, K022.00, K023.00, K02y.00, K02y000, K02y200, K02y300, K02yz00, K02z.00, K05.00, K05.11, K05.12, K050.00, K0D.00, K100.00, K100000, K100100, K100200, K100300, K100400, K100500, K100600, K100z00, SP08300, TB00100, TB00111, ZV42000	N18.3, N18.4, N18.5, T82.4, T86.1, Y60.2, Y61.2, Y62.2, Y84.1, Z49.0, Z49.1, Z49.2, Z94.0, Z99.2, N18.6, I77.0, N16.5	eGFR
<b>Heart failure</b>	14A6.00, 14AM.00, 1O1.00, 388D.00, 661M500, 662T.00, 662W.00, 662f.00, 662g.00, 662h.00, 662i.00, 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, 9On.00, 9On0.00, 9On1.00, 9On2.00, 9On3.00, 9On4.00, 9Or.00, 9Or0.00, 9Or1.00, 9Or2.00, 9Or3.00, 9Or4.00, 9Or5.00, 9h1.00, 9h11.00, 9h12.00, 9hH.00, 9hH0.00, 9hH1.00, G1yz100, G210100, G211100, G21z100, G232.00, G234.00, G400.00, G41z.11, G554000, G554011, G58.00, G58.11, 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	I11.0, I13.0, I13.2, I50	
<b>Type 2 diabetes</b>	C108A11, C109.13, C109011, C109012, C109111, 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, 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	E10	

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

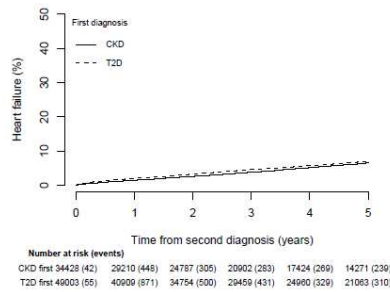
N	CKD and HF		CKD and T2D		HF and T2D	
	CKD then HF 34,625	HF then CKD 29,601	CKD then T2D 34,428	T2D then CKD 49,003	HF then T2D 5,660	T2D then HF 8,212
<b>Demographics and behaviours</b>						
Age (years), Mean (SD)	81.5 (9.32)	78.2 (10.30)	73.8 (10.05)	71.5 (9.99)	69.5 (11.40)	71.2 (11.26)
Age (years), 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)
<b>Multimorbidity characteristics</b>						
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)
<b>Medical history</b>						
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)
Peripheral arterial disease	1746 (5)	1144 (3.9)	662 (1.9)	886 (1.8)	195 (3.4)	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)
<b>Clinical Biomarkers</b>						
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
Triglycerides (mg/dL), Median (IQR)	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)	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
<b>Prescribed medication</b>						
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**

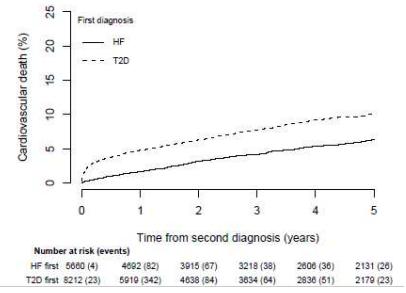
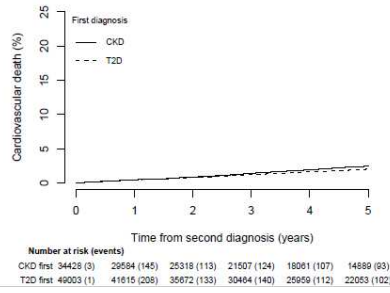
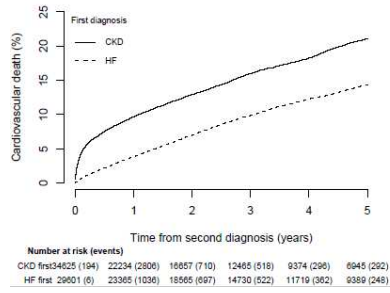
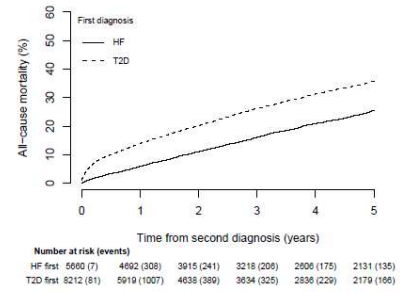
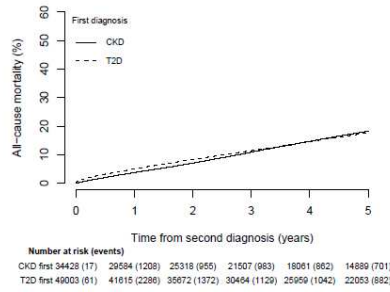
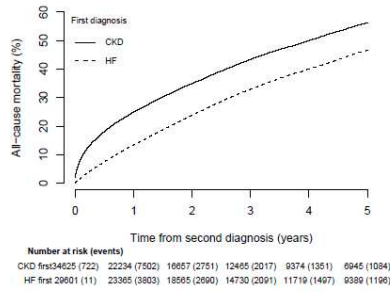
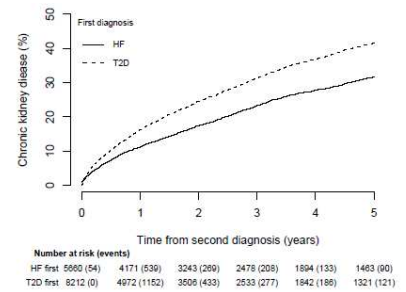
**CKD and HF**



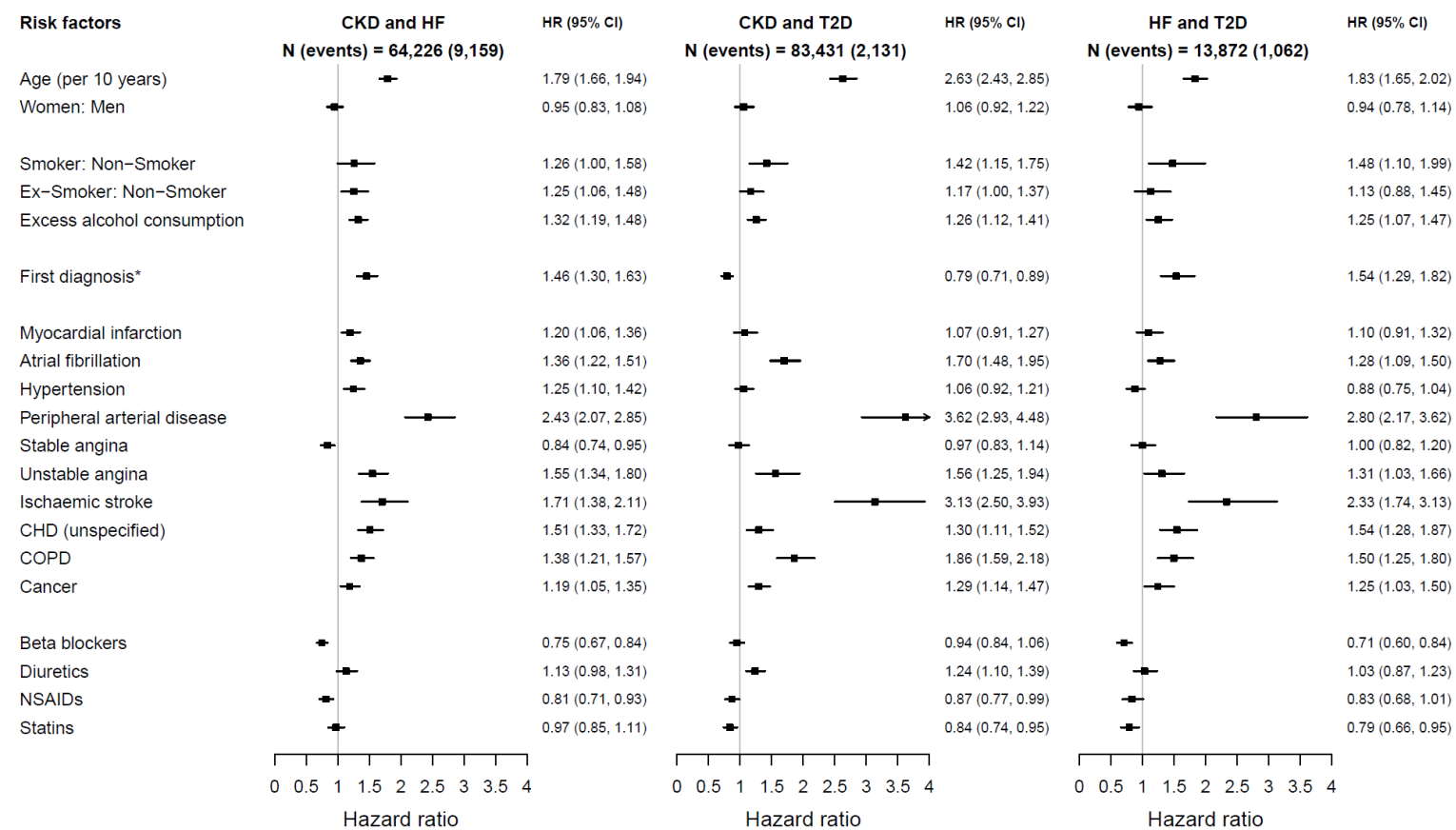
**CKD and T2D**



**HF and T2D**

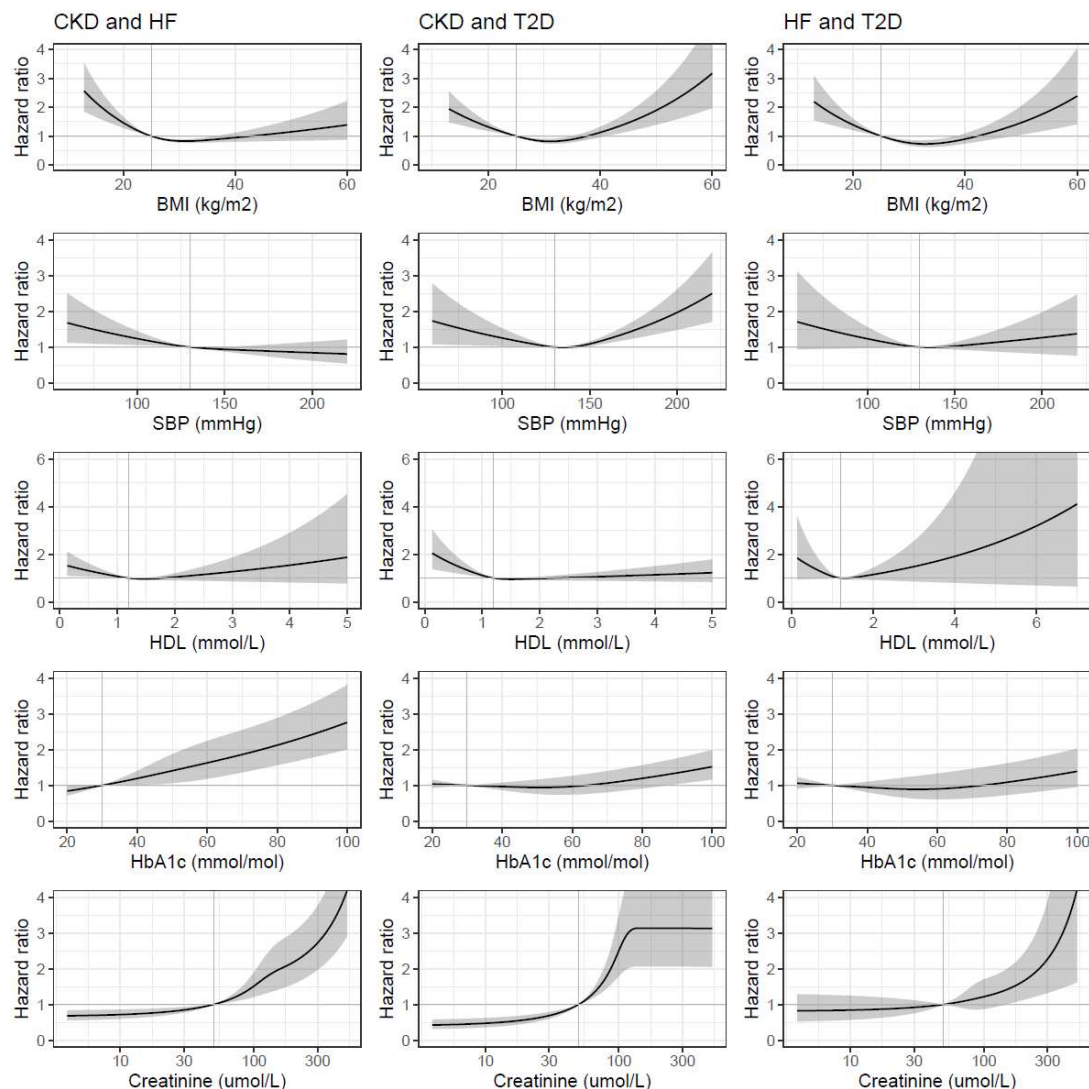


**Figure S4: Risk of cardiovascular death in disease pairs of heart failure, chronic kidney disease and type 2 diabetes, using multivariable Cox regression models on multiply imputed data.**



\*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.

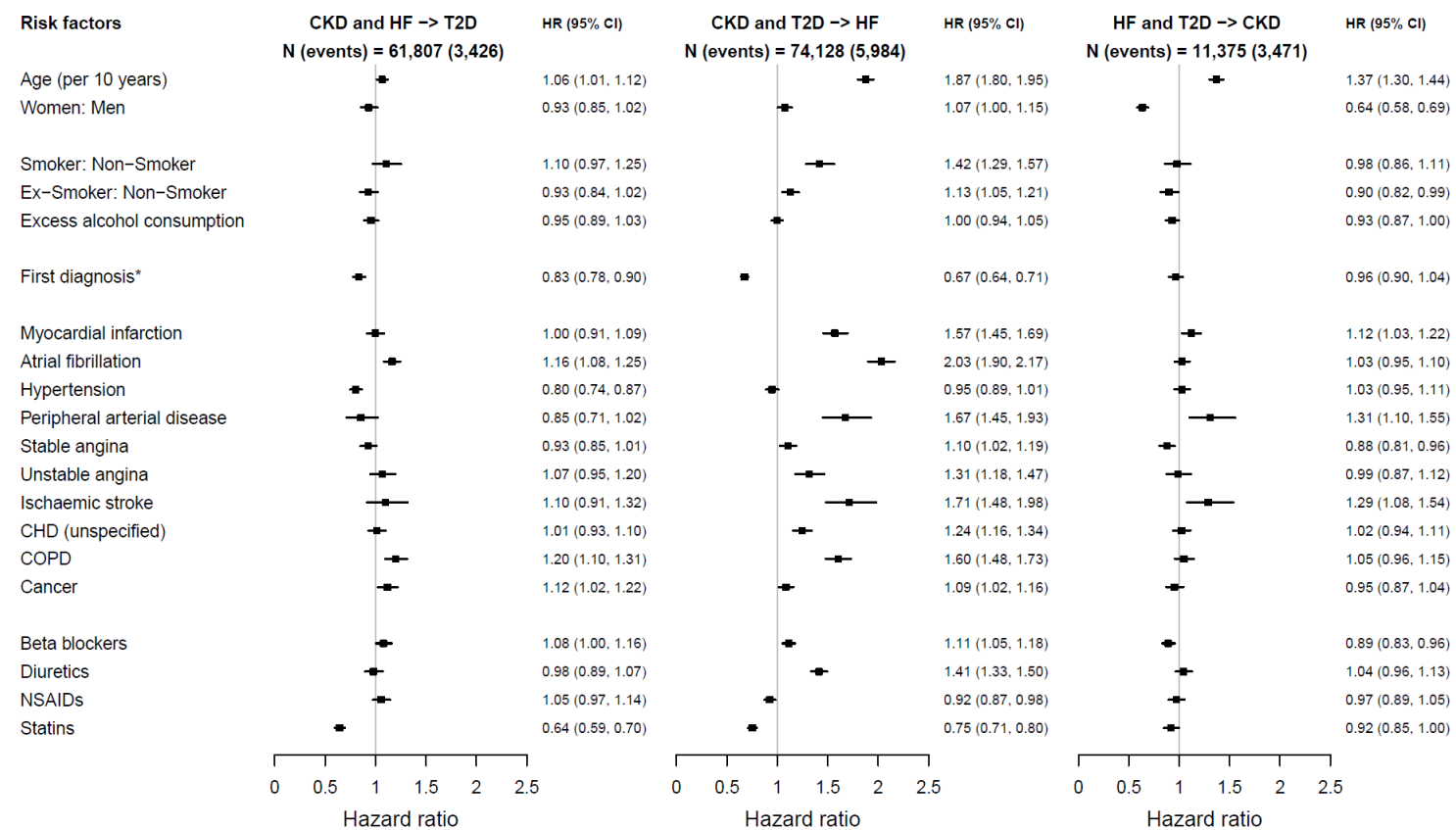
**Figure S5: Restricted cubic splines to model continuous biomarkers in the multivariable Cox regression models on multiple imputed data: Risk of cardiovascular death in disease pairs of heart failure, chronic kidney disease and type 2 diabetes**



Note: The reference value for each risk factor was BMI: 25kg/m<sup>2</sup>, 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.



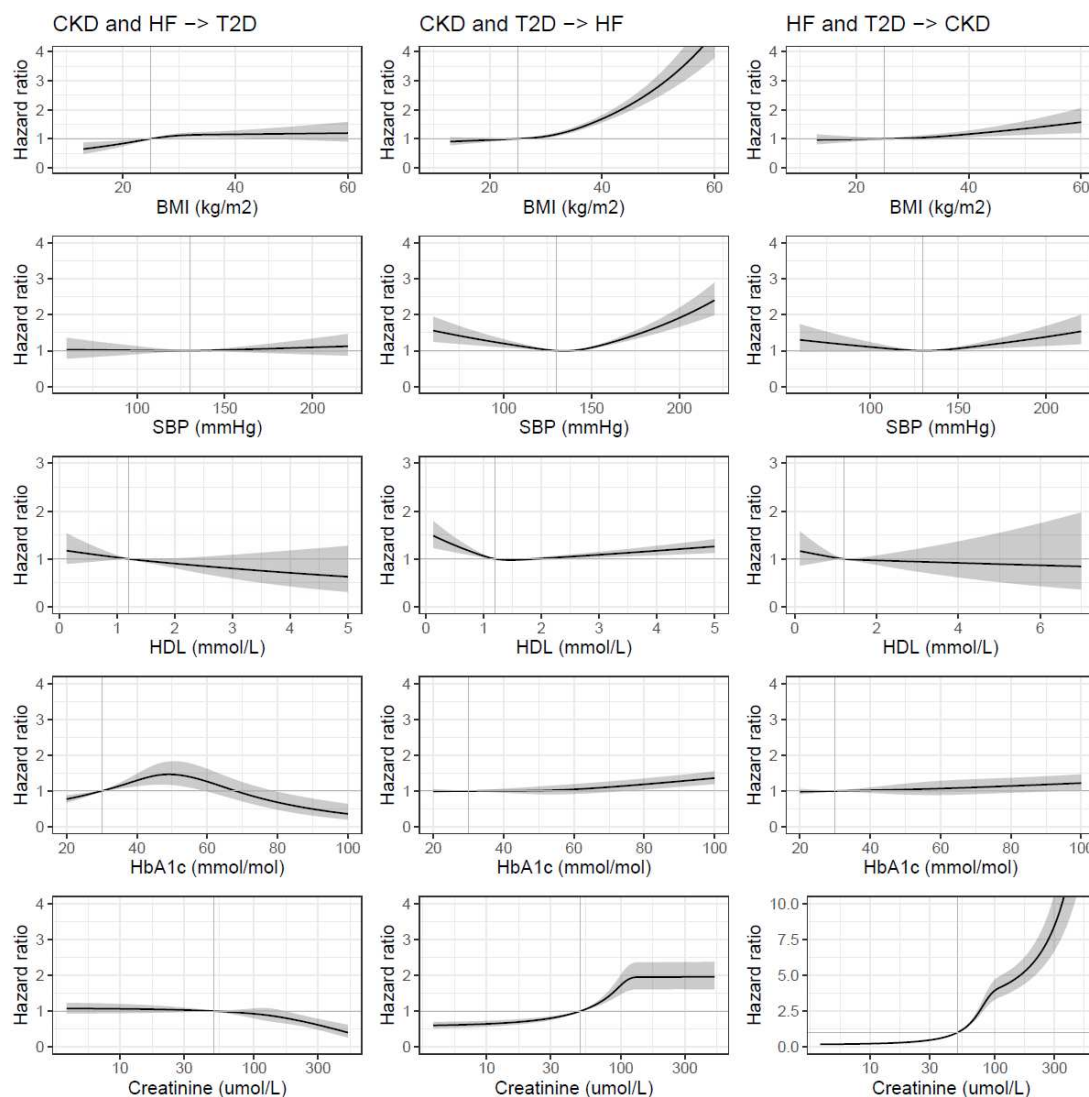
**Figure S6: Risk factors for developing third condition in disease pairs of heart failure, chronic kidney disease and type 2 diabetes, using multivariable Cox regression models on multiply imputed data, in the subgroup of the study population aged >60 years at baseline**



\*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.

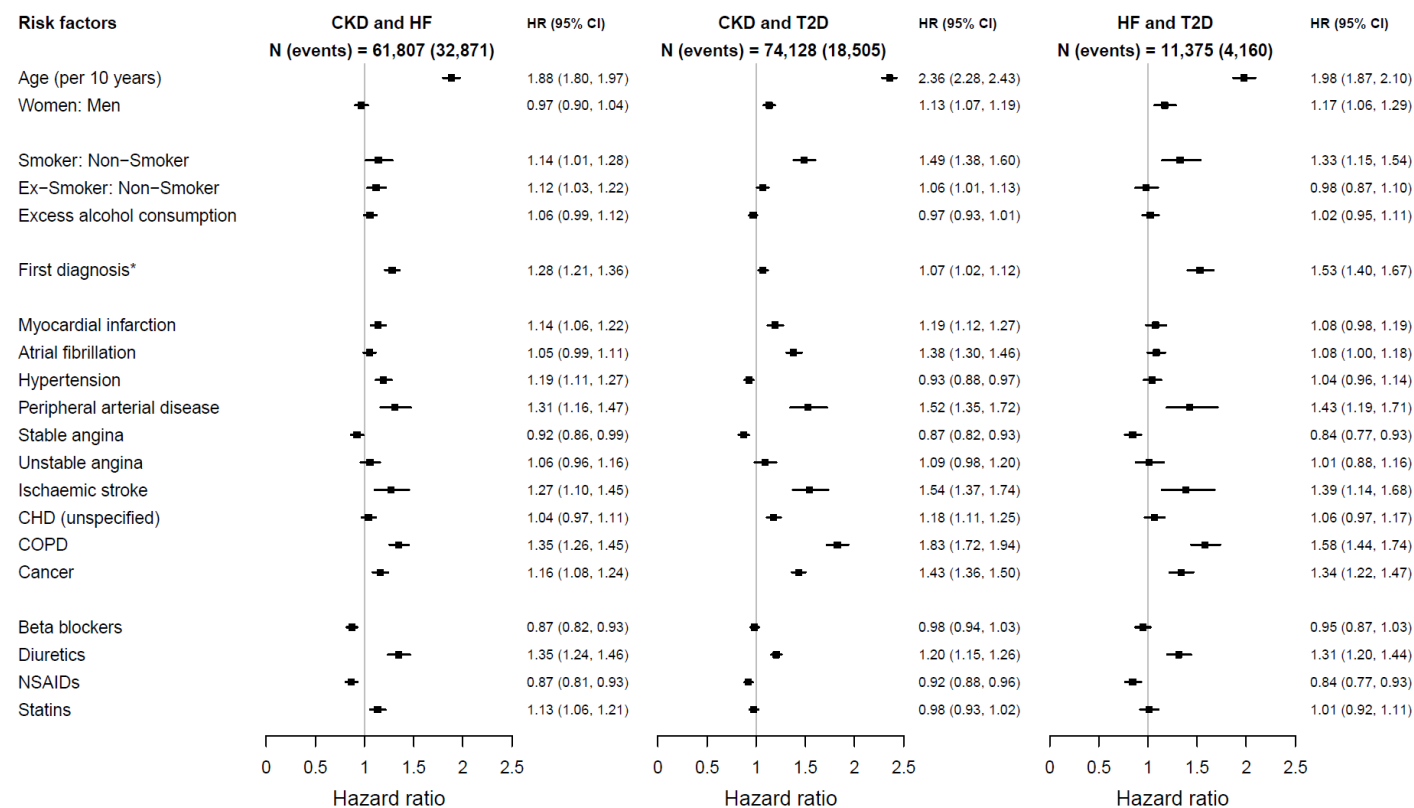
Note: The upper and lower limits for each point are the 95% confidence intervals. These models were also adjusted for the continuous variables modelled using restricted cubic splines displayed in figure S7.

**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/m<sup>2</sup>, 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

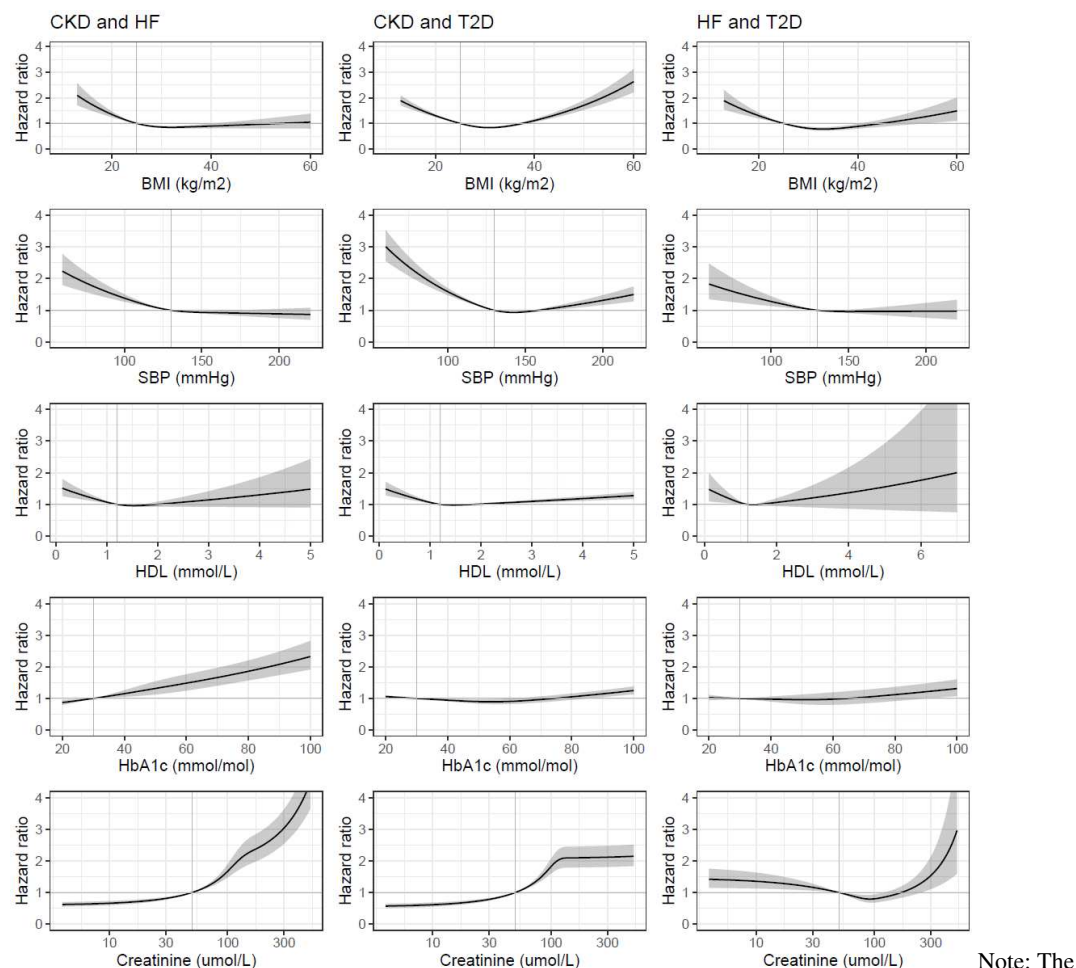
**Figure S8: Risk factors for all-cause mortality in disease pairs of heart failure, chronic kidney disease and type 2 diabetes, using multivariable Cox regression models on multiply imputed data, in the subgroup of the study population aged >60 years at baseline**



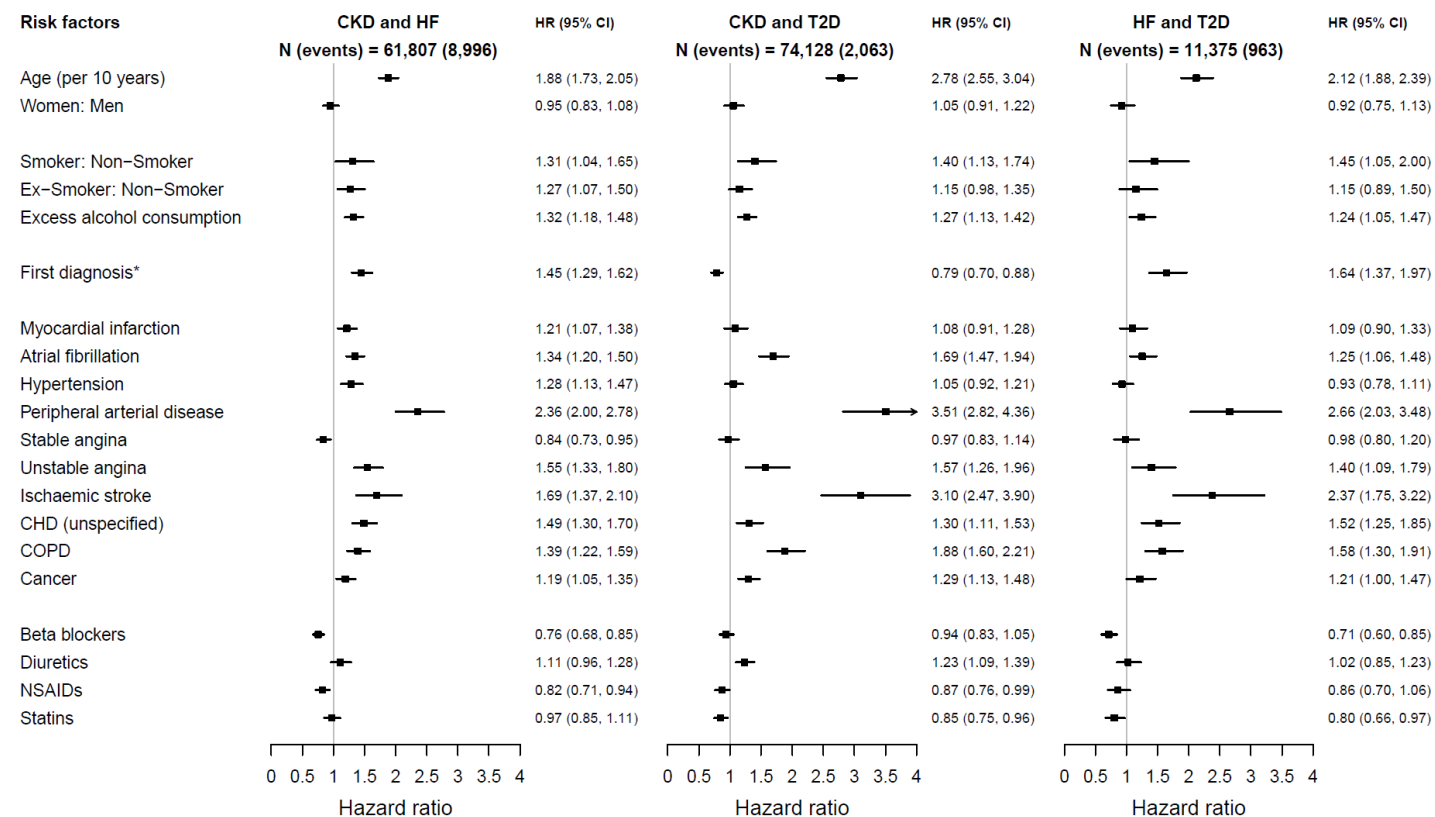
\*For first diagnosis, HF is the reference group for CKD and HF, CKD is the reference group for CKD and T2D and HF is the reference group for HF and T2D.

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**



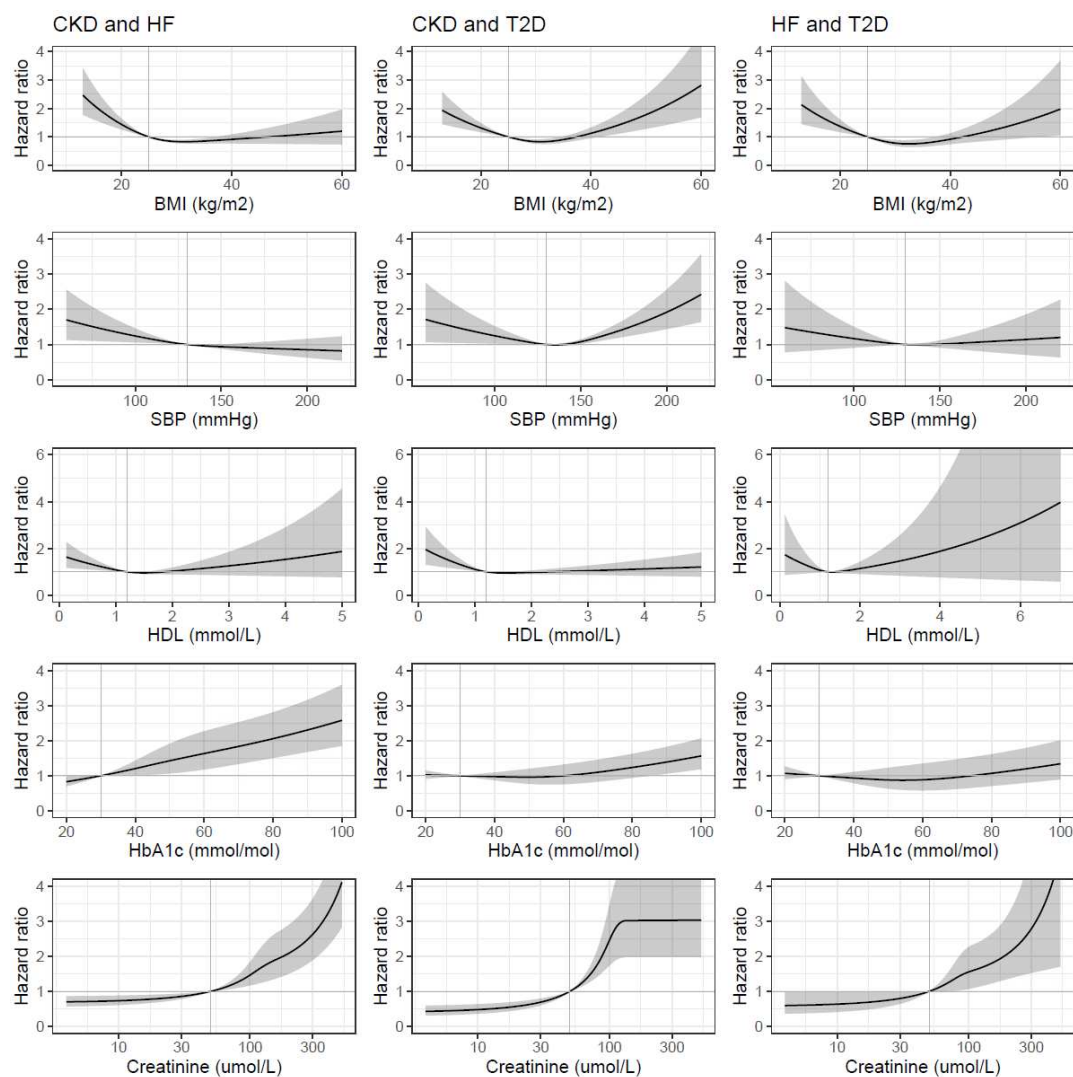
**Figure S10: Risk factors for cardiovascular death in disease pairs of heart failure, chronic kidney disease and type 2 diabetes, using multivariable Cox regression models on multiply imputed data, in the subgroup of the study population aged >60 years at baseline**



\*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.

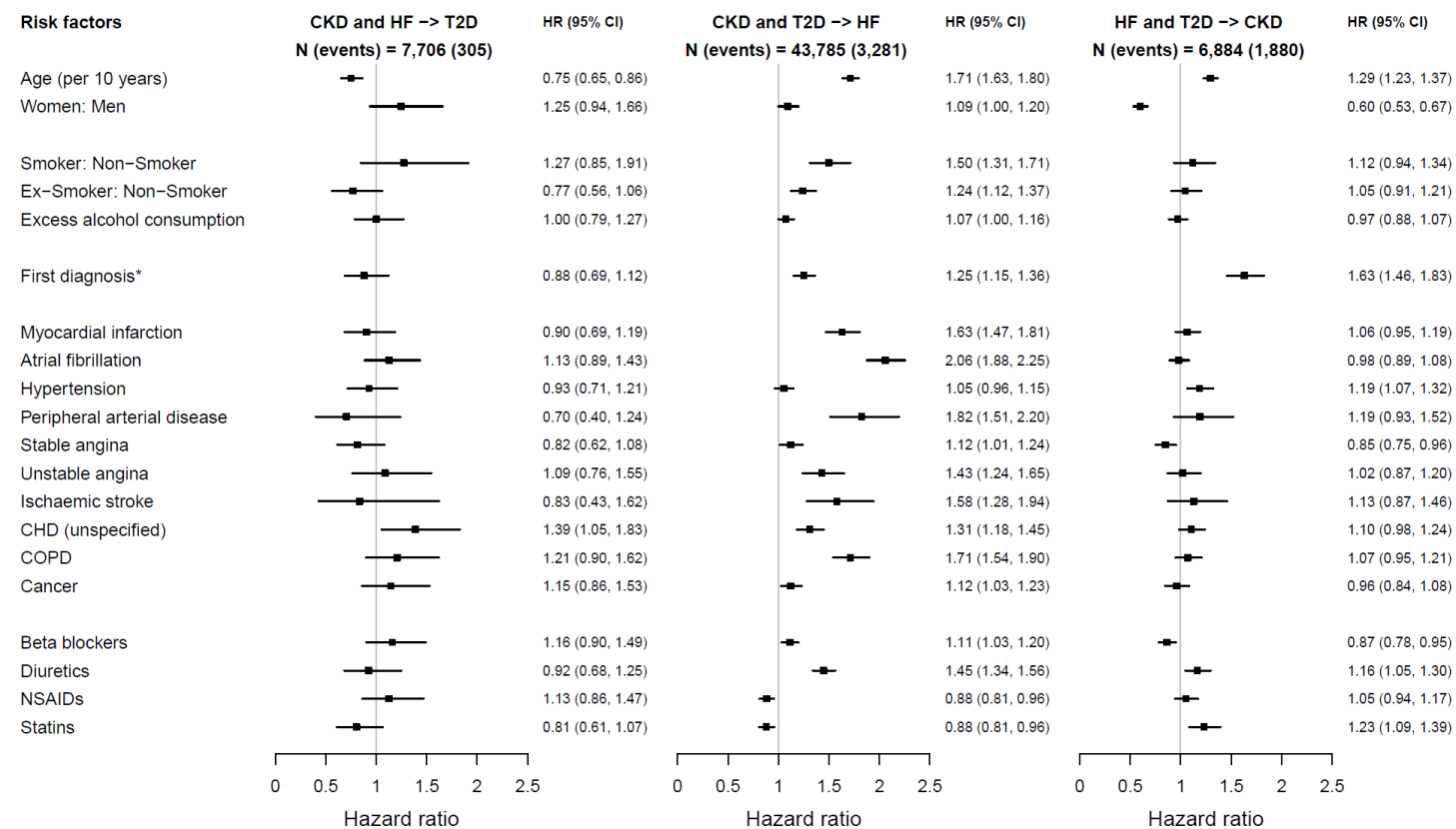
Note: The upper and lower limits for each point are the 95% confidence intervals. These models were also adjusted for the continuous variables modelled using restricted cubic splines displayed in figure S11.

**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/m<sup>2</sup>, SBP: 130mmHg, HDL: .1.2mmol/L, HbA1c: 30 mmol/mol and creatinine: 50umol/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

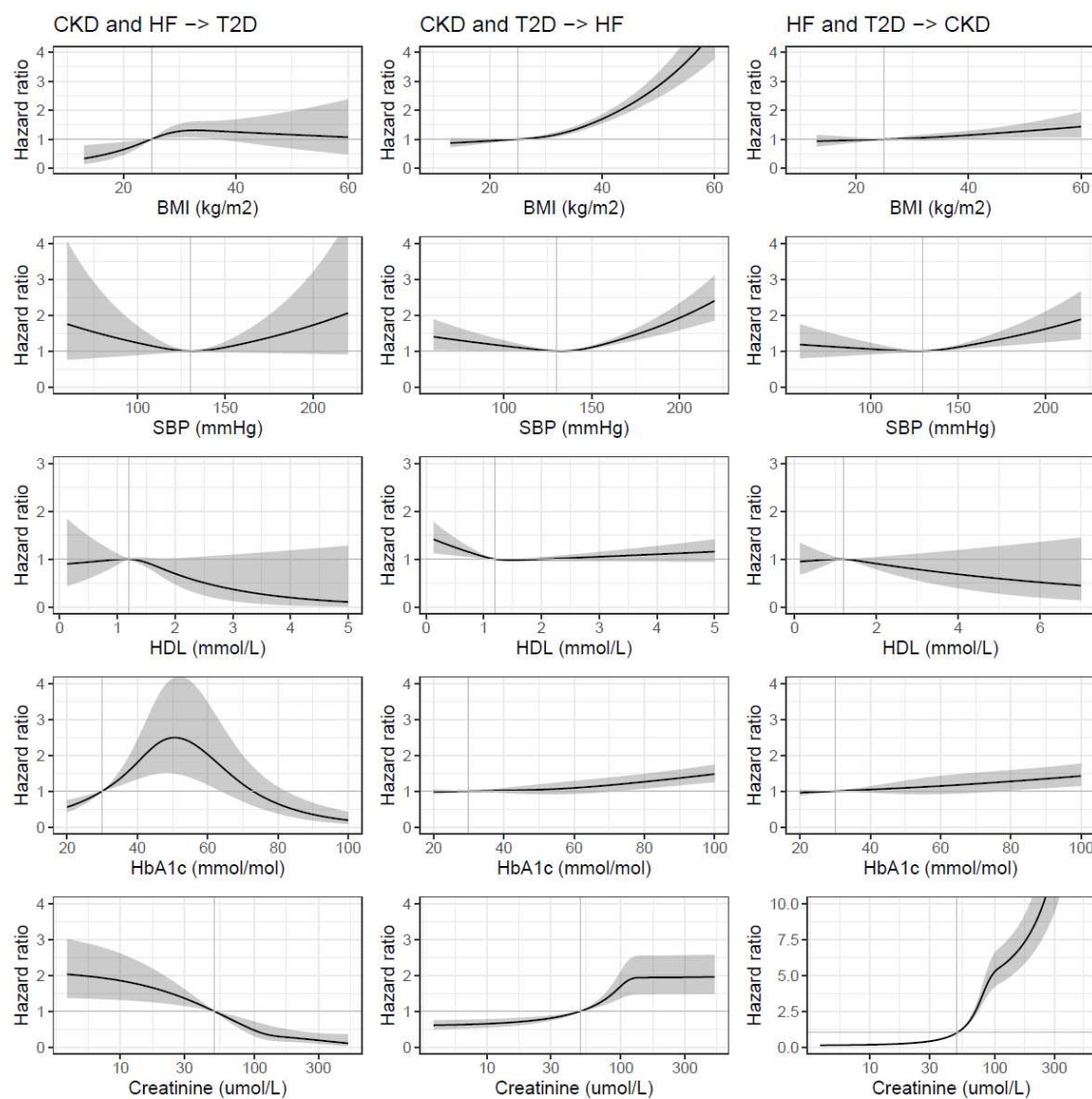
**Figure S12: Risk factors for developing third condition in disease pairs of heart failure, chronic kidney disease and type 2 diabetes, using multivariable Cox regression models on complete case data.**



\*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.

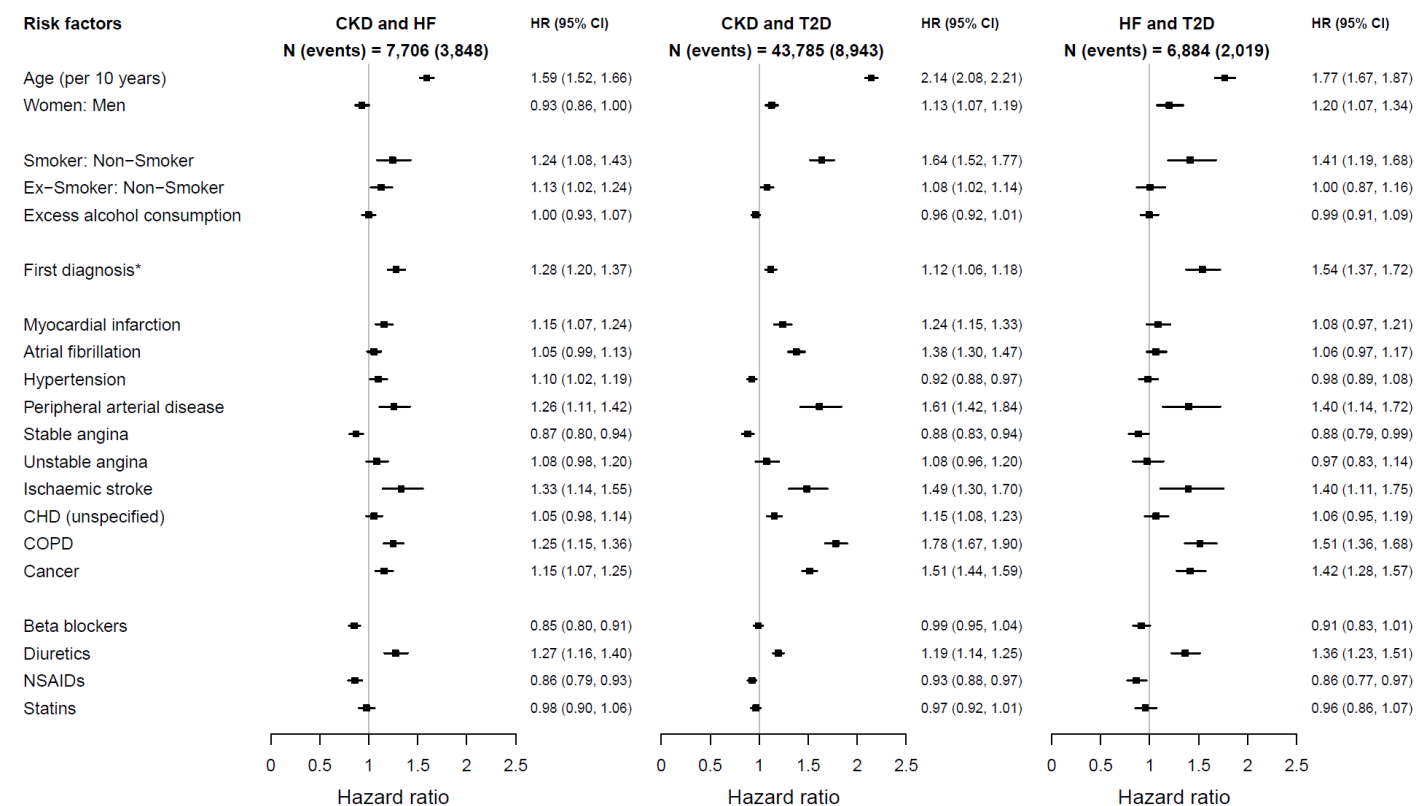
**Figure S13: Restricted cubic splines to model continuous biomarkers in the multivariable Cox regression models on complete case data: Risk factors for developing a third condition in disease pairs of heart failure, chronic kidney disease and type 2 diabetes**



Note: The reference value for each risk factor was BMI: 25kg/m<sup>2</sup>, 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



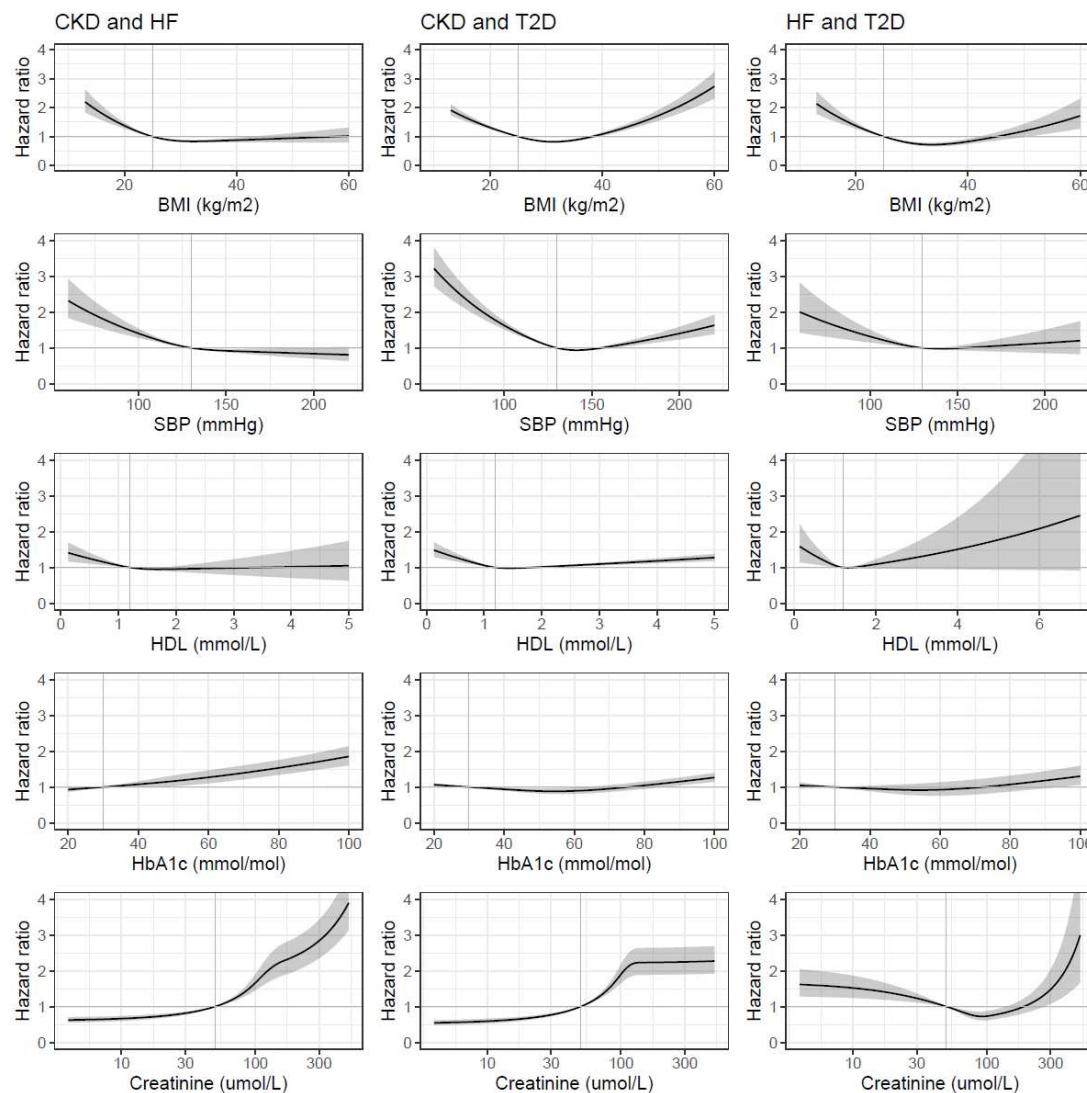
**Figure S14: Risk of all-cause mortality in disease pairs of heart failure, chronic kidney disease and type 2 diabetes, using multivariable Cox regression models on complete case data**



\*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.

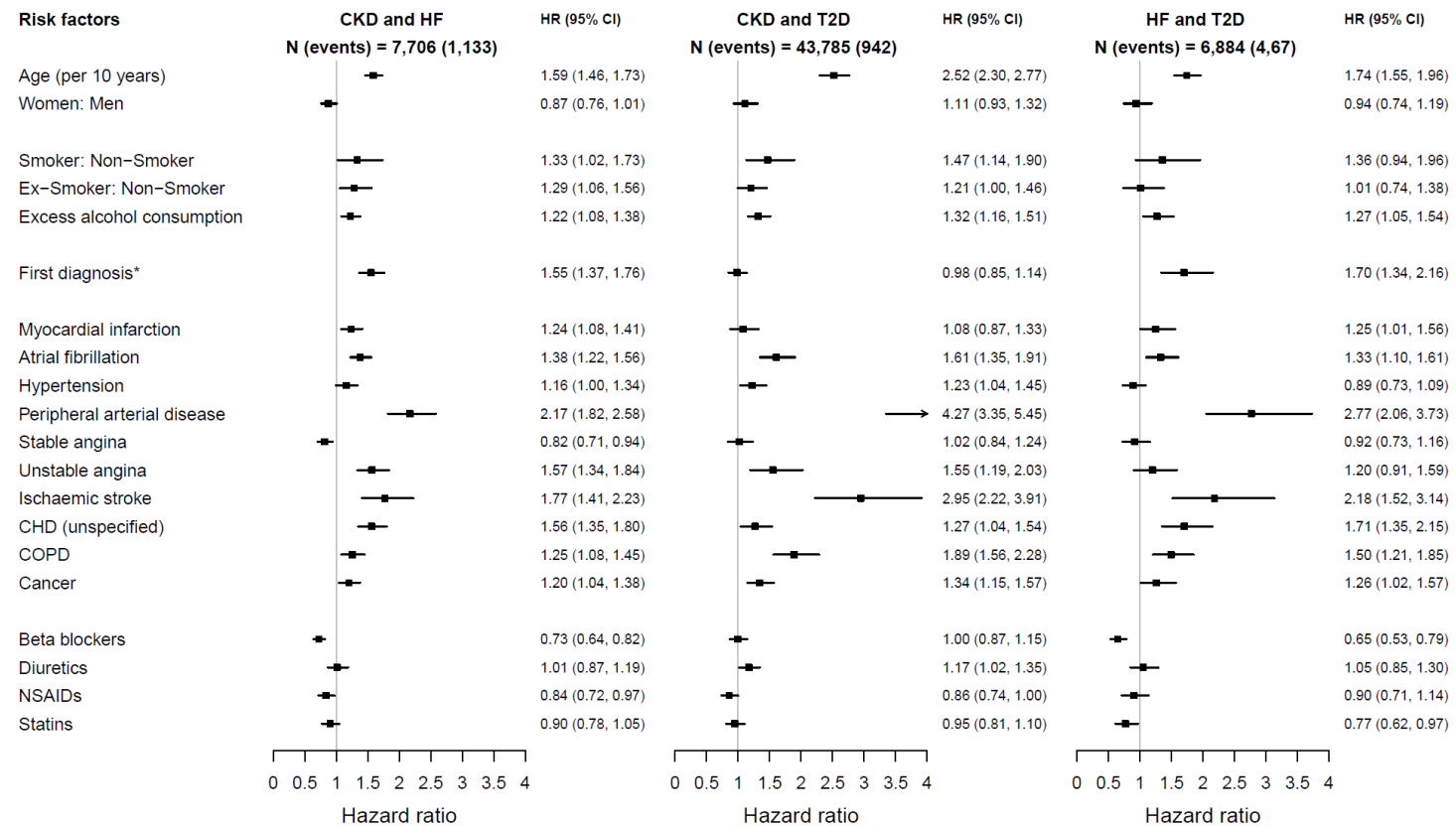
Note: The upper and lower limits for each point are the 95% confidence intervals. These models were also adjusted for the continuous variables modelled using restricted cubic splines displayed in figure S15.

**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<sup>2</sup>, 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 S14.

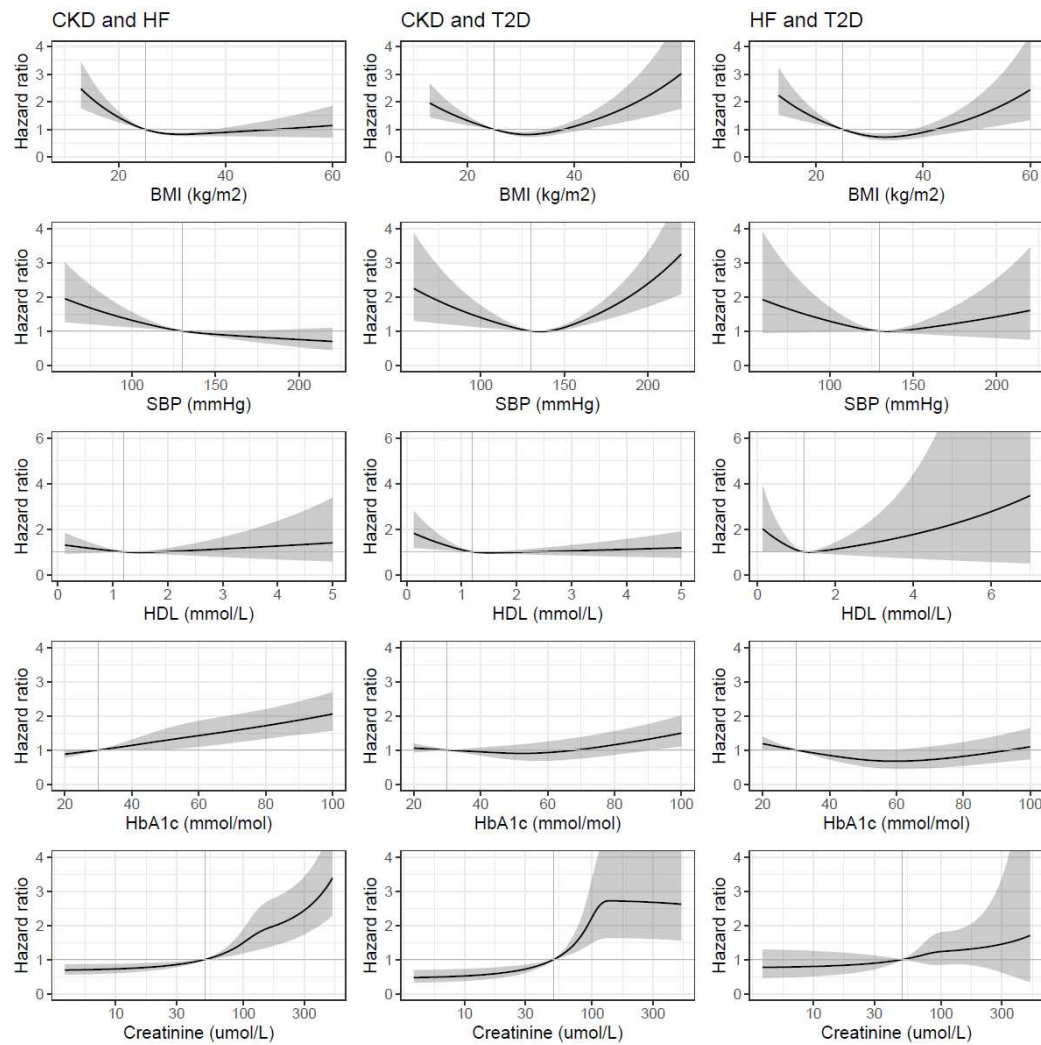
**Figure S16: Risk of cardiovascular death in disease pairs of heart failure, chronic kidney disease and type 2 diabetes, using multivariable Cox regression models on complete case data**



\*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.

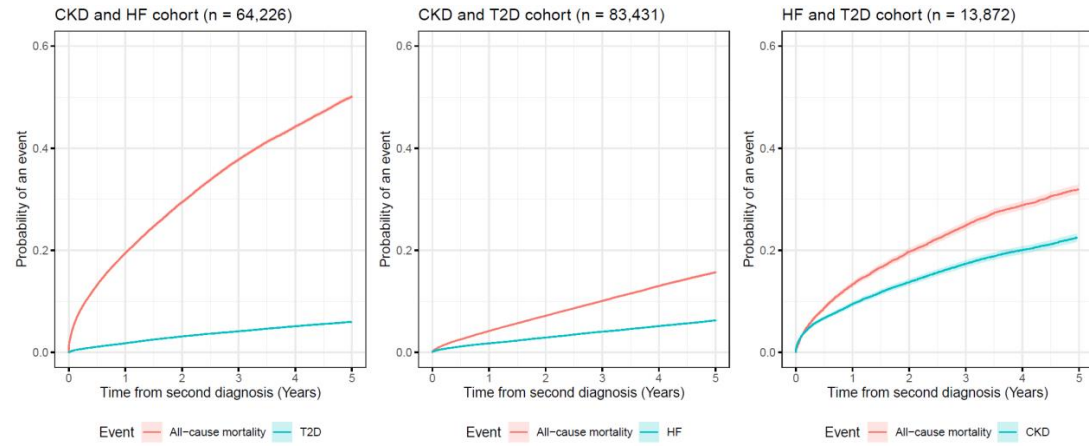
Note: The upper and lower limits for each point are the 95% confidence intervals. These models were also adjusted for the continuous variables modelled using restricted cubic splines displayed in figure S17.

**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**

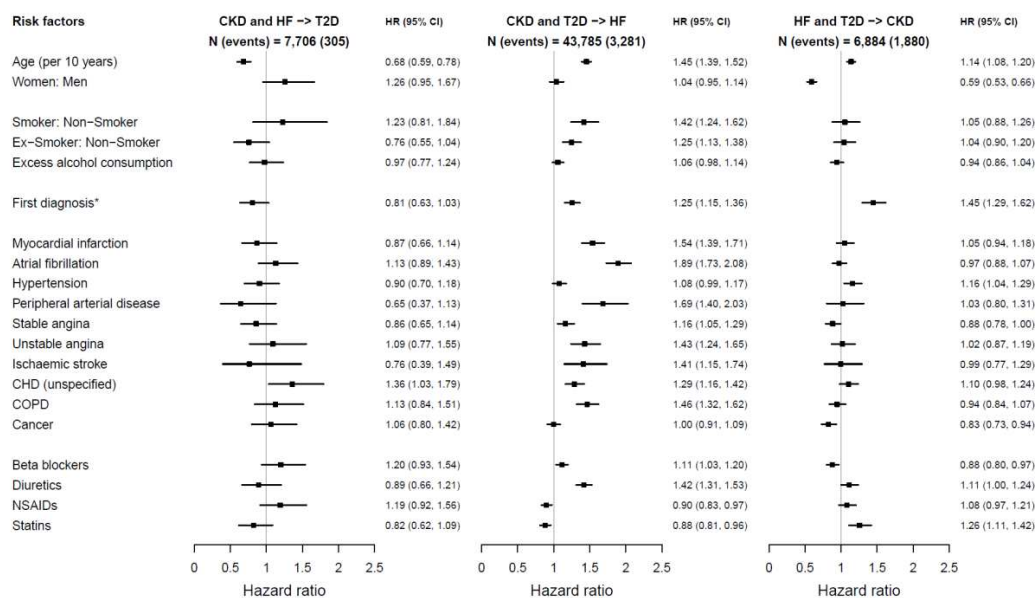


Note: The reference value for each risk factor was BMI: 25kg/m<sup>2</sup>, SBP: 130mmHg, HDL: 1.2mmol/L, HbA1c: 30 mmol/mol and creatinine: 50µmol/L. The shaded area in each panel is the 95% confidence interval. All estimates are from the fully adjusted model including the risk factors displayed in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



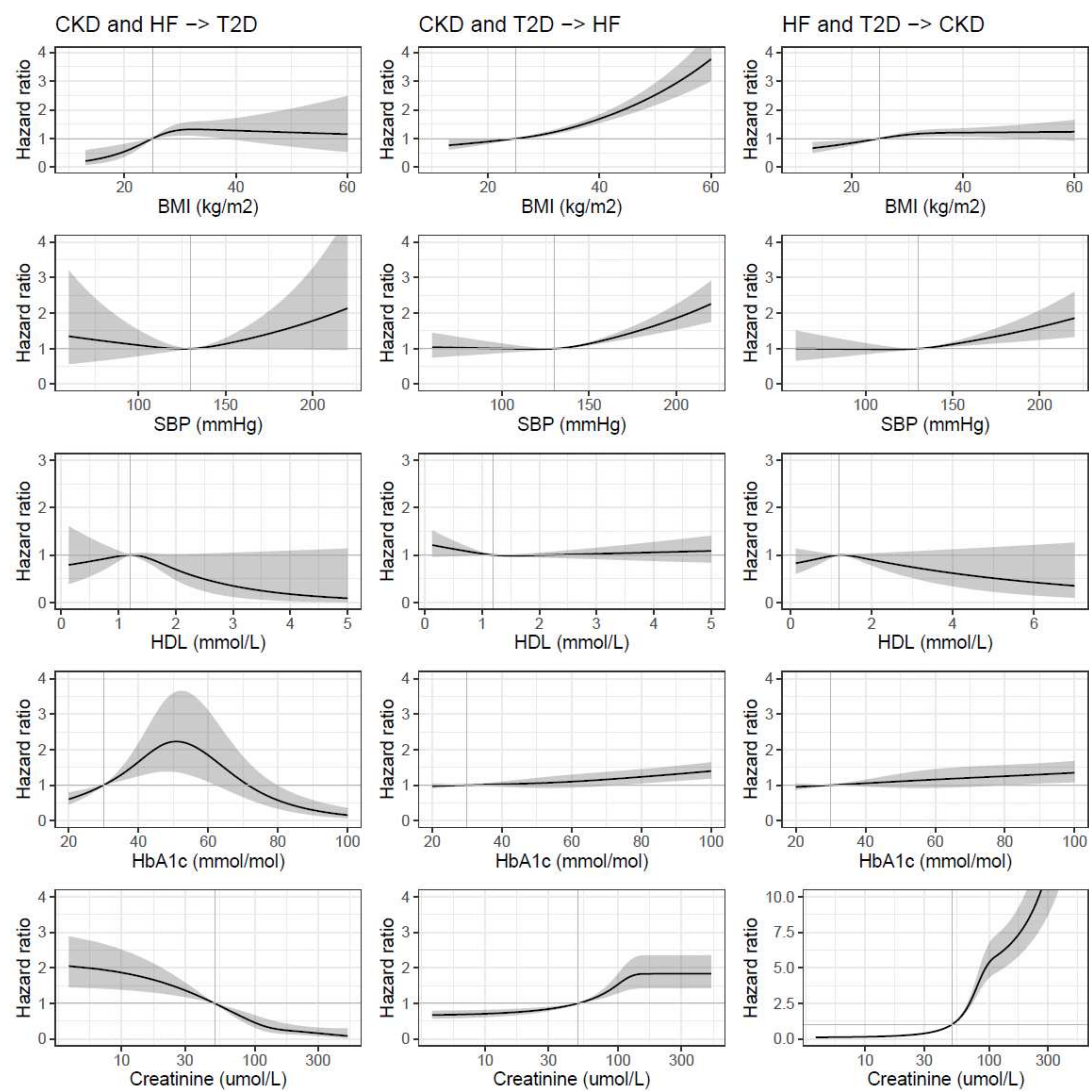
**Figure S19: Risk factors for developing third condition in disease pairs of heart failure, chronic kidney disease and type 2 diabetes, using multivariable Fine and Grey regression models on complete case data.**



\*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.

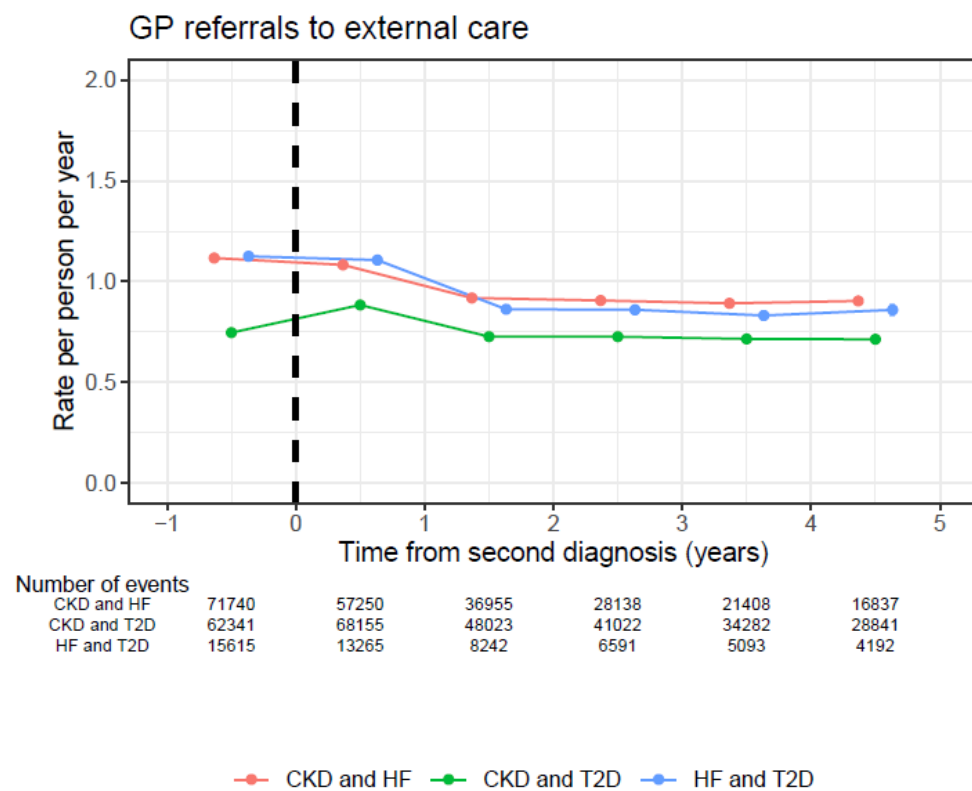
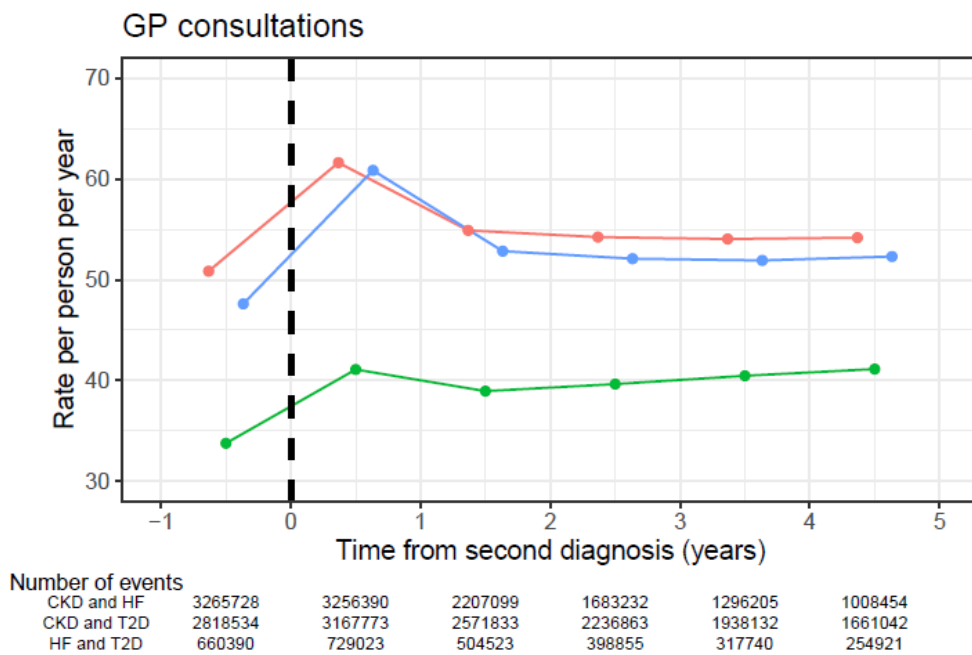
Note: The upper and lower limits for each point are the 95% confidence intervals. These models were also adjusted for the continuous variables modelled using restricted cubic splines displayed in figure S20.

**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**



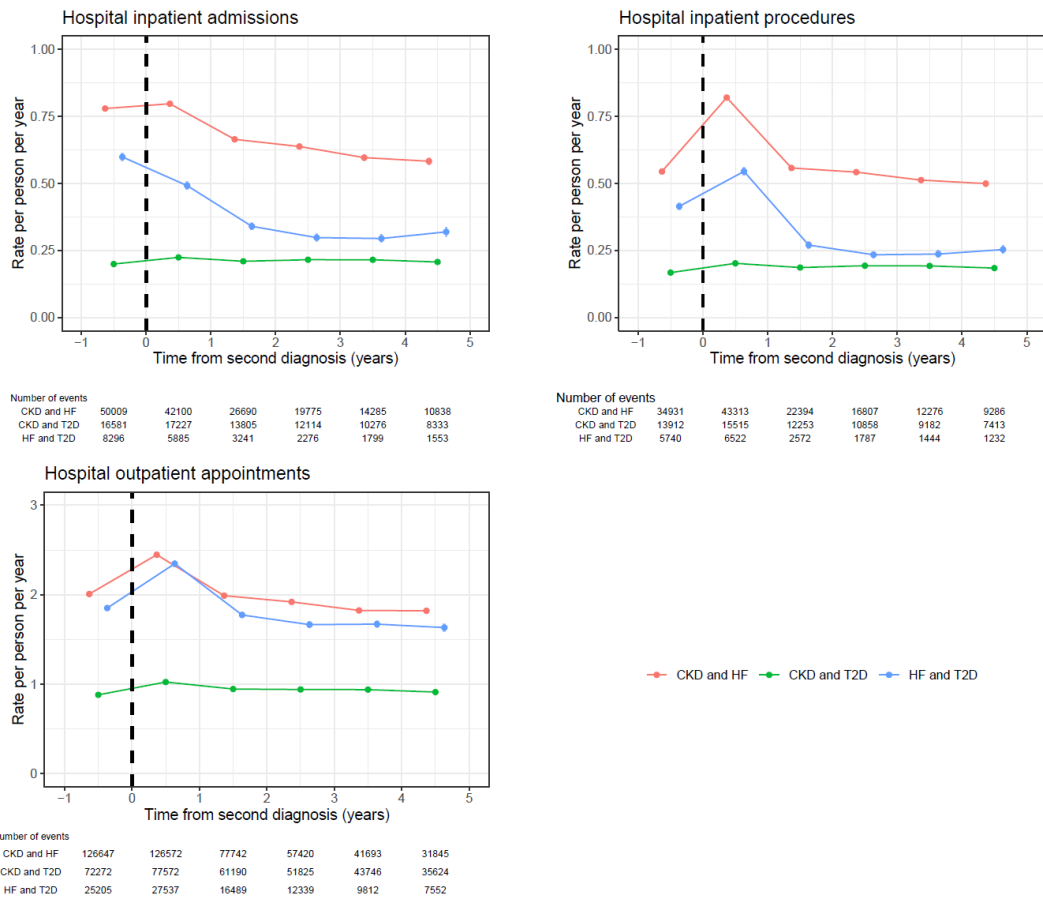
Note: The reference value for each risk factor was BMI: 25kg/m<sup>2</sup>, SBP: 130mmHg, HDL: 1.2mmol/L, HbA1c: 30 mmol/mol and creatinine: 50umol/L. The shaded area in each panel is the 95% confidence interval. All estimates are from the fully adjusted models including the risk factors displayed in figure S19.

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





**Figure S22: Observed rate of healthcare utilisation in hospital setting**



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