Supplementary file

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Supplementary table 1
List of Read codes used to define ischaemic heart disease

Read code	Description
G30y100	Acute papillary muscle infarction
G306.00	True posterior myocardial infarction
G350.00	Subsequent myocardial infarction of anterior wall
G33z400	Ischaemic chest pain
G34y000	Chronic coronary insufficiency
G312.00	Coronary thrombosis not resulting in myocardial infarction
G341.00	Aneurysm of heart
G32..00	Old myocardial infarction
G30X000	Acute ST segment elevation myocardial infarction
G30A.00	Mural thrombosis
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G309.00	Acute Q-wave infarct
Gyu3600	[X]Subsequent myocardial infarction of unspecified site
G341200	Aneurysm of coronary vessels
Gyu3200	[X]Other forms of acute ischaemic heart disease
G311500	Acute coronary syndrome
G311z00	Preinfarction syndrome NOS
G330.00	Angina decubitus
G382.00	Postoperative transmural myocardial infarction other sites
G34z.00	Other chronic ischaemic heart disease NOS
G311100	Unstable angina
G341.11	Cardiac aneurysm
G31y.00	Other acute and subacute ischaemic heart disease
G344.00	Silent myocardial ischaemia
G31y200	Subendocardial ischaemia
G33z000	Status anginosus
G34y100	Chronic myocardial ischaemia
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
G39..00	Coronary microvascular disease
G340000	Single coronary vessel disease
G34yz00	Other specified chronic ischaemic heart disease NOS
G30..00	Acute myocardial infarction
G304.00	Posterior myocardial infarction NOS
G3z..00	Ischaemic heart disease NOS
G30y000	Acute atrial infarction
G310.00	Postmyocardial infarction syndrome
G33z500	Post infarct angina
G35X.00	Subsequent myocardial infarction of unspecified site
G33zz00	Angina pectoris NOS
G311011	MI - myocardial infarction aborted

G30..17	Silent myocardial infarction
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
G30..16	Thrombosis - coronary
G340.11	Triple vessel disease of the heart
G30..15	MI - acute myocardial infarction
G340.12	Coronary artery disease
G343.00	Ischaemic cardiomyopathy
G36..00	Certain current complication follow acute myocardial infarct
G30..14	Heart attack
G30..13	Cardiac rupture following myocardial infarction (MI)
G301.00	Other specified anterior myocardial infarction
G30..12	Coronary thrombosis
Gyu3300	[X]Other forms of chronic ischaemic heart disease
G30..11	Attack - heart
G341300	Acquired atrioventricular fistula of heart
G311400	Worsening angina
Gyu3.00	[X]Ischaemic heart diseases
G307.00	Acute subendocardial infarction
G332.00	Coronary artery spasm
G30z.00	Acute myocardial infarction NOS
G380.00	Postoperative transmural myocardial infarction anterior wall
G311000	Myocardial infarction aborted
G32..12	Personal history of myocardial infarction
G32..11	Healed myocardial infarction
G31y300	Transient myocardial ischaemia
G33z100	Stenocardia
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
G30yz00	Other acute myocardial infarction NOS
G34..00	Other chronic ischaemic heart disease
G340100	Double coronary vessel disease
G331.00	Prinzmetal's angina
G383.00	Postoperative transmural myocardial infarction unspec site
G31yz00	Other acute and subacute ischaemic heart disease NOS
G33z600	New onset angina
G34y.00	Other specified chronic ischaemic heart disease
G31..00	Other acute and subacute ischaemic heart disease
G341000	Ventricular cardiac aneurysm
G301z00	Anterior myocardial infarction NOS
G30X.00	Acute transmural myocardial infarction of unspecif site
G301100	Acute anteroseptal infarction
G360.00	Haemopericardium/current comp folow acut myocard infarct
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
Gyu3000	[X]Other forms of angina pectoris
G38..00	Postoperative myocardial infarction

G307100	Acute non-ST segment elevation myocardial infarction
G330000	Nocturnal angina
G305.00	Lateral myocardial infarction NOS
G331.11	Variant angina pectoris
G351.00	Subsequent myocardial infarction of inferior wall
G34z000	Asymptomatic coronary heart disease
G310.11	Dressler's syndrome
G311300	Refractory angina
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
G340.00	Coronary atherosclerosis
G33z.00	Angina pectoris NOS
G30B.00	Acute posterolateral myocardial infarction
G31y000	Acute coronary insufficiency
G33z200	Syncope anginosa
G3...13	IHD - Ischaemic heart disease
G3...12	Atherosclerotic heart disease
G3...11	Arteriosclerotic heart disease
G302.00	Acute inferolateral infarction
G30y200	Acute septal infarction
G30y.00	Other acute myocardial infarction
G381.00	Postoperative transmural myocardial infarction inferior wall
G341z00	Aneurysm of heart NOS
G311.12	Impending infarction
G33z300	Angina on effort
G311.11	Crescendo angina
G35..00	Subsequent myocardial infarction
G33z700	Stable angina
G3y..00	Other specified ischaemic heart disease
G311.14	Angina at rest
G38z.00	Postoperative myocardial infarction, unspecified
G311.13	Unstable angina
G37..00	Cardiac syndrome X
G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
Gyu3500	[X]Subsequent myocardial infarction of other sites
G3...00	Ischaemic heart disease
G341100	Other cardiac wall aneurysm
G301000	Acute anteroapical infarction
G353.00	Subsequent myocardial infarction of other sites
G303.00	Acute inferoposterior infarction
G307000	Acute non-Q wave infarction
G33..00	Angina pectoris
G311.00	Preinfarction syndrome
G384.00	Postoperative subendocardial myocardial infarction
G311200	Angina at rest

G342.00	Atherosclerotic cardiovascular disease
G31y100	Microinfarction of heart
G330z00	Angina decubitus NOS
G308.00	Inferior myocardial infarction NOS
G341111	Mural cardiac aneurysm
G300.00	Acute anterolateral infarction

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Supplementary text 1

Latent class analysis

Latent class analysis is a statistical method for finding unobservable, or latent, subgroups within a population based on the similarity of patterns across multivariate categorical data (in this case comorbidities). This method was chosen over counts-based approaches (whether weighted or unweighted) as those methods are not able to distinguish between groups with the same number but different types of comorbidities. Furthermore, count-based measures have been shown to have poor predictability of outcomes such as emergency admissions (Wallace *et al*, 2016). It was also chosen over combinations of comorbidities given the very large number of groupings generated for all pair-wise combinations of 20 comorbidities, which would greatly inflate the risk of a type II error. Latent class analysis was preferred over other traditional clustering methods, as it is a model-based clustering approach that derives clusters using a probabilistic model that describes the distribution of the data as opposed to determining clusters based on a chosen distance measure. In latent class analysis, posterior probabilities are assigned to each individual based on the estimated model parameters and their observed scores. This allows for each individual to be allocated to the appropriate latent class based on their probability of membership and from this, the risk of mortality by cluster can be estimated (Hagenaars and McCutcheon, 2002)

As recommended by Busija *et al* (2019), there were 20 chronic conditions selected as comorbidities and these conditions all met the criteria from the Academy of Medical Sciences and the WHO in that they were either:

1. A physical non-communicable disease of long duration such as cardiovascular disease or cancer;
2. A mental health condition of long duration such as a mood disorder or dementia.

Latent class analysis was undertaken using generalised structural equation modelling in Stata. Models with class (cluster) size of 2-8 were run. The optimal number of clusters in the underlying data was selected based on a number of criteria:

1. Information criteria: while the eight cluster solution was preferred in all criteria of AIC, BIC, SSABIC, and log-likelihood, there was not a lot of added benefit for these criteria above the three cluster solution apart from entropy where a five cluster solution was preferred (**Supplementary table 2**).

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2. No small classes: the rule of thumb is that there is no cluster size below 5% of the study population. With six or more clusters, at least two of the clusters were 5% or below. The choice of five clusters meant that there was only one cluster that made up 3.1% of the population.
3. Domain-usefulness: In terms of clinical interpretability and meaningfulness, the five clusters are quite distinct and clinically interpretable with all patients in the smaller cluster having a diagnosis of COPD and two-thirds also having a diagnosis of asthma.

References

Busija L, Lim K, Szoeke C, Sanders KM, McCabe MP (2019). Do replicable profiles of multimorbidity exist? Systematic review and synthesis. Eur J Epidemiol *in press*.

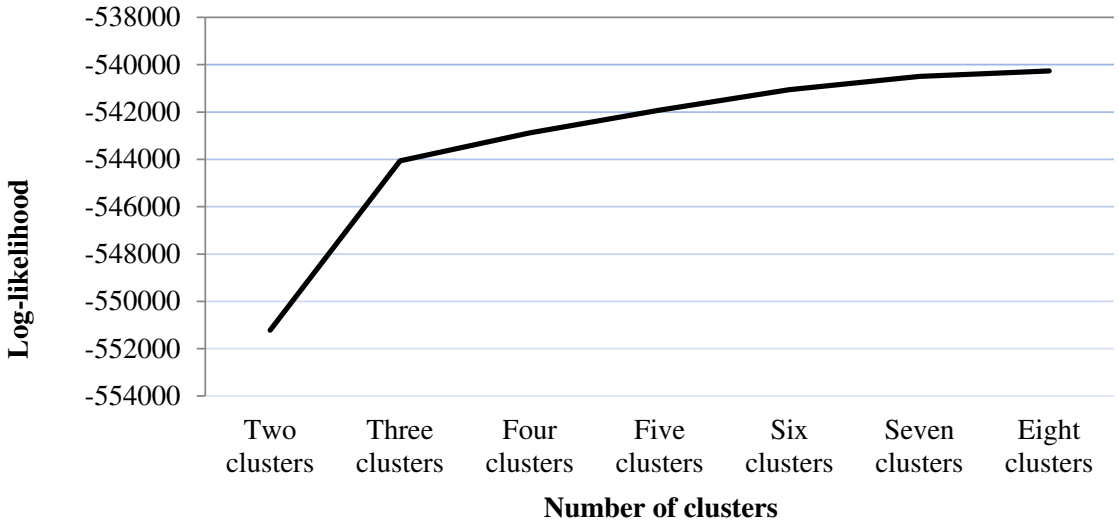
Hagenaars JA, and McCutcheon A L. (2002). Applied Latent Class Analysis. Cambridge: Cambridge University Press

Wallace E, McDowell R, Bennett K, Fahey T, Smith SM (2016). Comparison of count-based multimorbidity measures in predicting emergency admission and functional decline in older community-dwelling adults: a prospective cohort study. BMJ Open 6:e013089.

Supplementary table 2
Latent class model fit statistics

Model	Obs	Log likelihood	df	AIC	BIC	SSABIC	Entropy
Two clusters	92,186	-551219	41	1102521	1102907	1102777	0.463
Three clusters	92,186	-544058	62	1088240	1088825	1088628	0.591
Four clusters	92,186	-542877	83	1085920	1086703	1086439	0.547
Five clusters	92,186	-541924	104	1084056	1085037	1084706	0.603
Six clusters	92,186	-541050	125	1082350	1083529	1083132	0.589
Seven clusters	92,186	-540491	146	1081274	1082651	1082187	0.581
Eight clusters	92,186	-540268	167	1080871	1082446	1081915	0.588

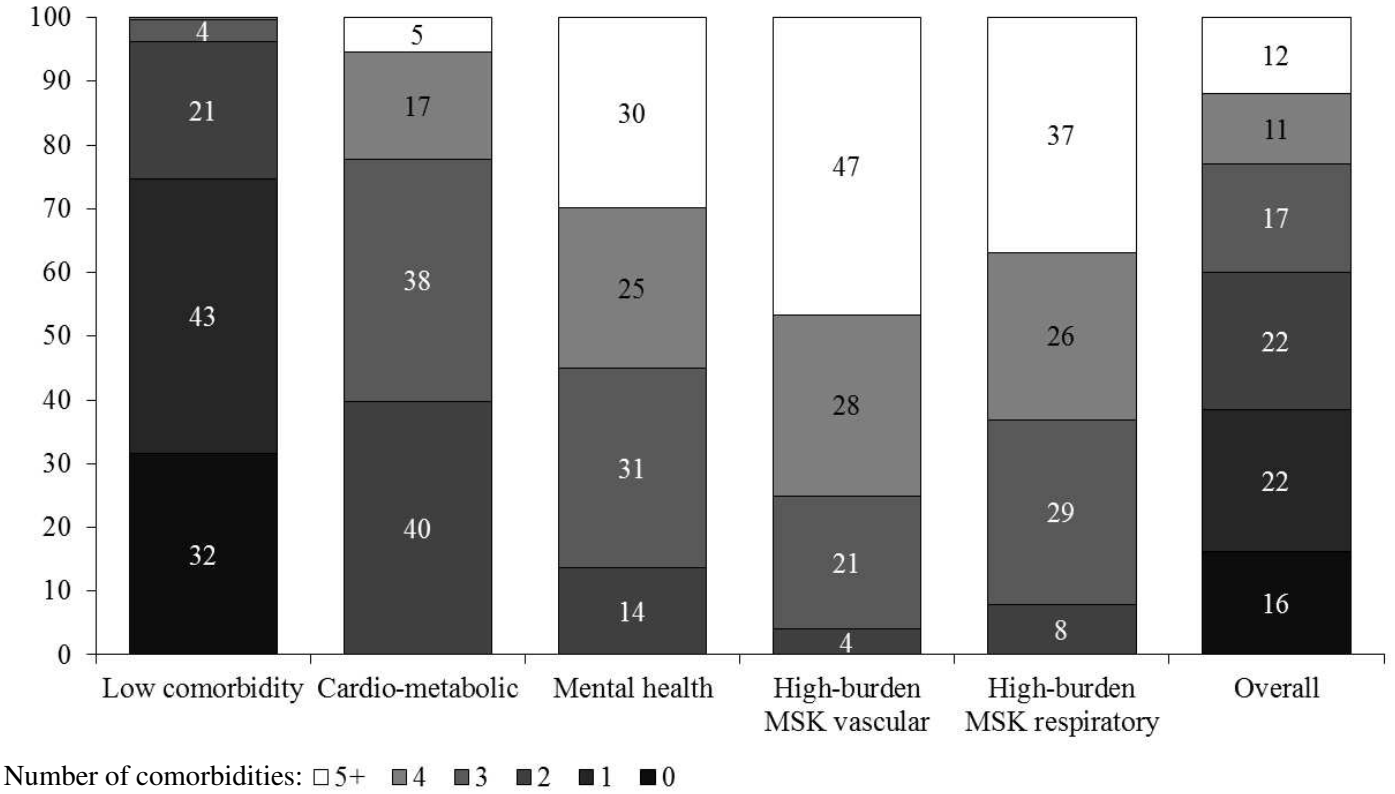
AIC, Akaike Information Criterion; BIC, Bayesian information criterion; SSABIC, sample size adjusted BIC



Supplementary figure 1
Plot of the log likelihood for the different latent class solutions

Supplementary table 3
Median (IQR) probability of group membership

	Median (IQR)
Low-burden	0.85 (0.57-0.96)
Cardio-metabolic	0.63 (0.53-0.71)
Mental health	0.89 (0.70-0.95)
High-burden musculoskeletal vascular	0.71 (0.54-0.87)
High-burden musculoskeletal respiratory	0.69 (0.50-0.83)



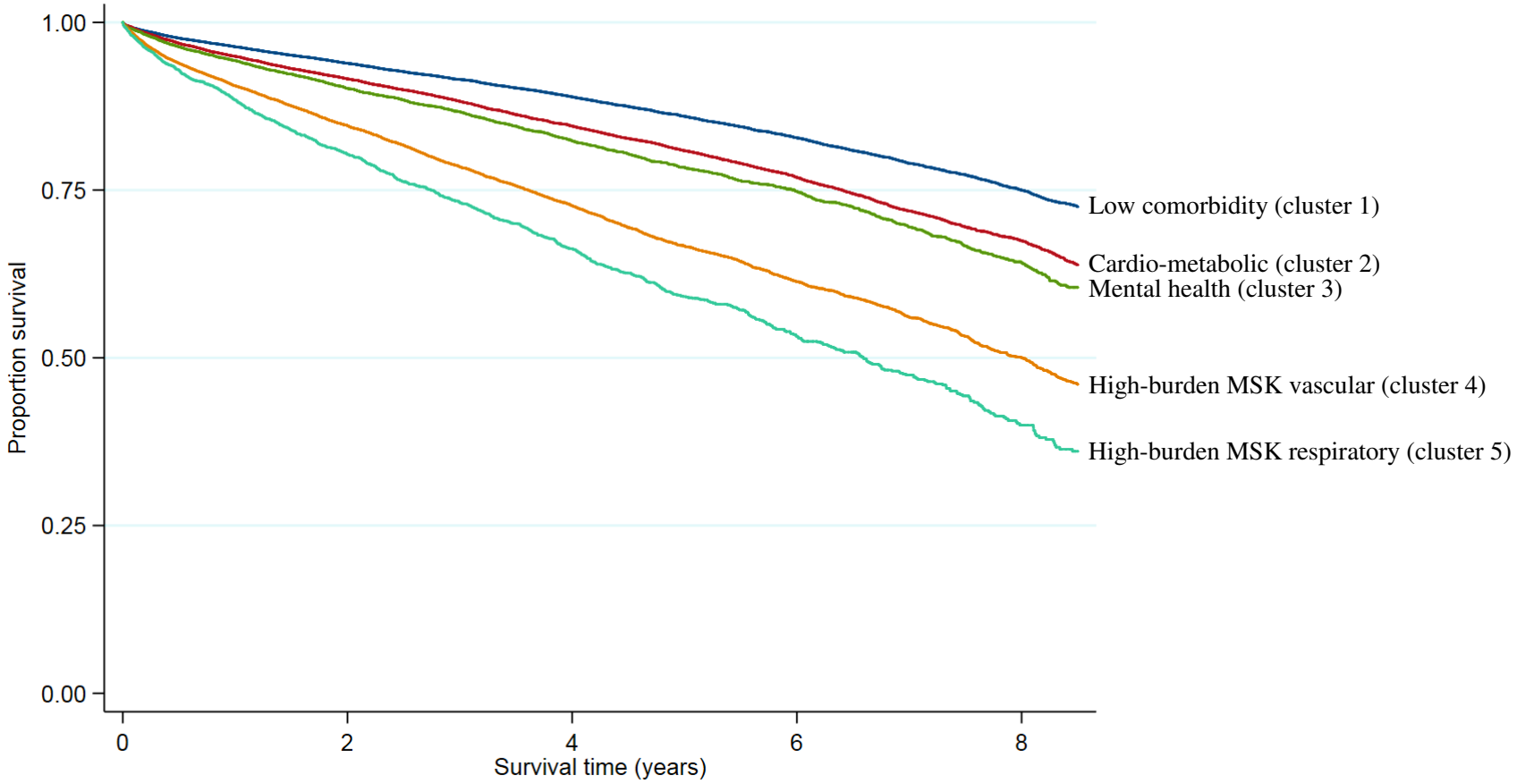
Supplementary figure 2
Distribution (%) of the number of comorbidities in patients with ischaemic heart disease according to comorbidity phenotype

Supplementary table 4
Distribution of the 20 comorbidities according to the five comorbidity clusters*

	Low-burden	Cardio-metabolic	Mental health	High-burden musculoskeletal vascular	High-burden musculoskeletal respiratory
Atrial fibrillation	1,146 (2.4%)	720 (3.8%)	455 (4.1%)	5,432 (45.1%)	362 (12.7%)
Heart failure	1,149 (2.4%)	84 (0.5%)	355 (3.2%)	4,395 (36.5%)	396 (13.8%)
Hypertension	10,222 (21.6%)	18,303 (97.0%)	5,166 (47.0%)	8,432 (70.0%)	1,290 (45.1%)
Stroke & TIA	778 (1.6%)	2,123 (11.3%)	1,000 (9.1%)	3,541 (29.4%)	329 (11.5%)
PVD	592 (1.3%)	1,499 (7.9%)	478 (4.4%)	1,341 (11.1%)	456 (15.9%)
Kidney disease	2,422 (5.1%)	6,661 (35.3%)	1,668 (15.2%)	7,632 (63.3%)	570 (19.9%)
Diabetes	2,453 (5.2%)	7,280 (38.6%)	1,758 (16.0%)	2,692 (22.3%)	325 (11.4%)
Hypothyroidism	1,568 (3.3%)	1,916 (10.2%)	1,487 (13.5%)	2,011 (16.7%)	185 (6.5%)
Osteoarthritis	4,214 (8.9%)	1,641 (8.7%)	2,067 (18.8%)	3,787 (31.4%)	752 (26.3%)
Osteoporosis	5,748 (12.1%)	6,585 (34.9%)	3,701 (33.7%)	5,430 (45.1%)	914 (31.9%)
Rheumatoid arthritis	442 (0.9%)	410 (2.2%)	285 (2.6%)	547 (4.5%)	150 (5.2%)
Dementia	163 (0.3%)	12 (0.1%)	105 (1.0%)	905 (7.5%)	21 (0.7%)
Epilepsy	728 (1.5%)	93 (0.5%)	377 (3.4%)	386 (3.2%)	66 (2.3%)
Cancer	1,997 (4.2%)	2,055 (10.9%)	669 (6.1%)	2,170 (18.0%)	374 (13.1%)
Asthma	3,158 (6.7%)	1,630 (8.6%)	1,938 (17.6%)	1,086 (9.0%)	1,769 (61.8%)
COPD	1,386 (2.9%)	492 (2.6%)	909 (8.3%)	1,070 (8.9%)	2,862 (100.0%)
Anxiety	3,371 (7.1%)	1,272 (6.7%)	8,822 (80.3%)	1,356 (11.3%)	525 (18.3%)
Depression	3,913 (8.3%)	1,079 (5.7%)	10,492 (95.5%)	1,843 (15.3%)	612 (21.4%)
Severe mental illness	226 (0.5%)	25 (0.1%)	829 (7.6%)	172 (1.4%)	38 (1.3%)
Chronic liver disease	260 (0.6%)	346 (1.8%)	271 (2.5%)	90 (0.8%)	66 (2.3%)

COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; TIA, transient ischaemic attack.

*Values are presented as *n* (%)



Supplementary figure 3

Long-term survival for the five comorbidity phenotypes. Adjusted Kaplan-Meier curves according to clusters of comorbidities where expected survival is set for those age 70 years.

Supplementary table 5
Hazards ratio of mortality by the presence of individual comorbidities

Comorbidity	Median (IQR) comorbidities	*n*	Deaths (%)	HR (95% CI) mortality	*P* value
Atrial fibrillation	4 (3 to 5)	8,115	3,041 (37%)	1.55 (1.49 to 1.62)	< 0.001
Heart failure	4 (3 to 5)	6,379	2,805 (44%)	1.91 (1.82 to 2.00)	< 0.001
Hypertension	3 (2 to 4)	43,413	10,291 (24%)	1.18 (1.14 to 1.22)	< 0.001
PVD	4 (3 to 5)	4,366	1,698 (39%)	1.64 (1.56 to 1.74)	< 0.001
Stroke & TIA	4 (3 to 5)	7,771	2,823 (36%)	1.53 (1.46 to 1.59)	< 0.001
Kidney disease	4 (3 to 5)	18,953	6,881 (36%)	1.38 (1.34 to 1.43)	< 0.001
Diabetes	3 (2 to 5)	14,508	3,706 (26%)	1.68 (1.62 to 1.75)	< 0.001
Hypothyroidism	4 (3 to 5)	7,167	1,619 (23%)	0.97 (0.93 to 1.02)	0.318
Osteoporosis	4 (2 to 5)	12,461	3,524 (28%)	1.31 (1.26 to 1.36)	< 0.001
Osteoarthritis	3 (2 to 5)	22,378	5,377 (24%)	0.94 (0.91 to 0.97)	< 0.001
Rheumatoid arthritis	4 (3 to 5)	1,834	584 (32%)	1.72 (1.57 to 1.88)	< 0.001
Dementia	4 (3 to 6)	1,206	643 (53%)	2.13 (1.96 to 2.32)	< 0.001
Epilepsy	3 (2 to 5)	1,650	387 (23%)	1.43 (1.29 to 1.59)	< 0.001
Cancer	3 (2 to 5)	7,265	2,547 (35%)	1.64 (1.57 to 1.72)	< 0.001
Asthma	3 (2 to 5)	9,581	2,008 (21%)	1.19 (1.14 to 1.25)	< 0.001
COPD	4 (3 to 5)	6,719	2,626 (39%)	1.88 (1.80 to 1.97)	< 0.001
Anxiety	3 (2 to 5)	15,346	2,648 (17%)	1.08 (1.04 to 1.13)	< 0.001
Depression	3 (2 to 5)	17,939	3,233 (18%)	1.20 (1.15 to 1.25)	< 0.001
Severe mental illness	4 (3 to 5)	1,290	324 (25%)	1.68 (1.49 to 1.90)	< 0.001
Chronic liver disease	4 (2 to 5)	1,033	224 (22%)	1.91 (1.65 to 2.20)	< 0.001

COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; TIA, transient ischaemic attack.

*Adjusted for age, sex. socioeconomic group, BMI, and smoking.

Supplementary table 6
Hazards ratio (95% CI) of mortality according to five comorbidity phenotypes at the time of ischaemic heart disease in sensitivity analysis

	Low	Cardio-metabolic	Mental health	High-burden musculoskeletal vascular	High-burden musculoskeletal respiratory
Overall					
Deaths	5,277	4,236	1,748	5,246	1,138
n	47,413	18,876	10,986	12,049	2,862
HR mortality (95% CI)*	1.00 (ref)	1.46 (1.39 to 1.52)	1.55 (1.46 to 1.64)	2.38 (2.28 to 2.49)	2.62 (2.45 to 2.79)
Among patients with complete data on covariates					
Deaths	3,969	3,545	1,466	4,230	970
n	37,778	16,289	9,583	10,082	2,502
HR mortality (95% CI)*	1.00 (ref)	1.51 (1.44 to 1.59)	1.54 (1.45 to 1.64)	2.48 (2.36 to 2.60)	2.65 (2.47 to 2.85)
Among patients with a diagnosis of MI					
Deaths	2,796	2,247	909	2,957	639
n	21,385	7,456	4,467	5,757	1,373
HR mortality (95% CI)*	1.00 (ref)	1.60 (1.51 to 1.70)	1.63 (1.52 to 1.75)	2.45 (2.31 to 2.59)	2.68 (2.45 to 2.92)

*Adjusted for age, sex. socioeconomic group, BMI, and smoking.