

Supplementary Material

Supplementary methods

COVID-19 event Phenotyping

COVID-19 positive tests were defined as a positive result from national testing data (SGSS), encompassing tests from NHS hospitals for those with a clinical need and healthcare workers (known as ‘Pillar 1’) and swab testing from the wider population (known as ‘Pillar 2’). COVID-19 primary care diagnoses were identified from primary care (GDPPR) using SNOMED-CT terms. COVID-19 hospital admissions were defined as any hospital admission recorded in CHES (COVID-19 specific hospitalisations data) or admissions with a COVID-19 diagnosis in HES APC or SUS as primary or other listed cause of hospitalisation.

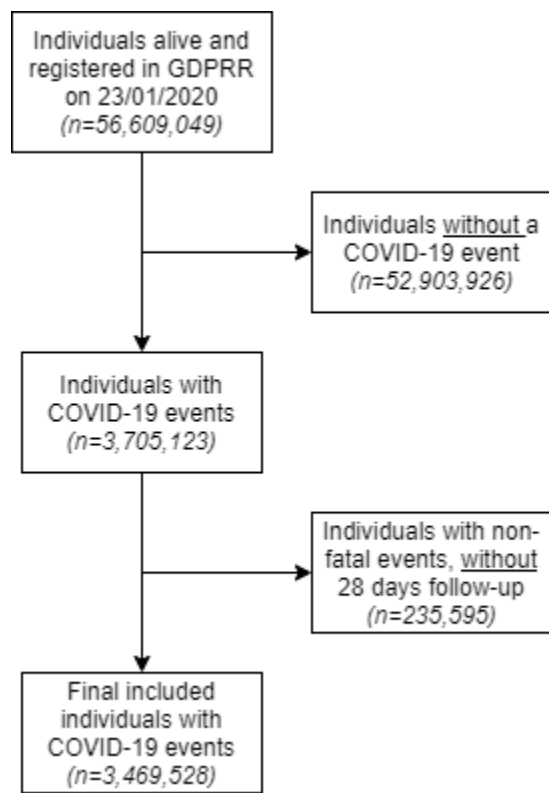
Provision of critical care was ascertained from several sources: a) patients with an ICU admission recorded in CHES or patients with an ICU admission (defined as an entry within HES Adult Critical Care) within the same admission as HES APC, b) patients receiving NIV, identified using the OPCS4 code E85.2 (Non-invasive ventilation NEC) or E85.6 (Continuous positive airway pressure), from SUS or HES APC, or a positive number of days receiving basic respiratory support in HES Adult Critical Care, or ‘*high flow nasal oxygen*’ or ‘*non invasive mechanical ventilation*’ recorded in CHES, c) patients receiving Intermittent Mandatory Ventilation (IMV) were identified using OPCS4 code E85.1 (Invasive ventilation) or X56 (Intubation of trachea), in SUS or HES APC, or a non-zero entry for days receiving advanced respiratory support from HES Adult Critical Care, or ‘*invasive mechanical ventilation*’ recorded in CHES, d) patients receiving Extracorporeal Membrane Oxygenation (ECMO) identified using OPCS4 X58.1 (Extracorporeal membrane oxygenation) in SUS or HES APC or ‘*respiratory support ECMO*’ recorded in CHES.

Fatal COVID-19 events were identified from ONS Civil Registration of Deaths and secondary care (HES APC, SUS) and defined as: a) a suspected or confirmed COVID-19 diagnosis ICD-10 term present in any position on the death certificate, b) death within 28-days of the first recorded COVID-19 event (positive test, diagnosis or admission), irrespective of the cause of death recorded on the death certificate, or c) a COVID-19 hospital admission with a discharge method or destination denoting death, irrespective of cause and duration after the index event. See supplementary table 2 for the specific codes used.

Phenotype definitions were reviewed by clinicians, health data scientists and epidemiologists and validated by quantifying cross-EHR source concordance and checking consistency of findings with established risk factors from the literature, in keeping with the CALIBER approach¹⁰.

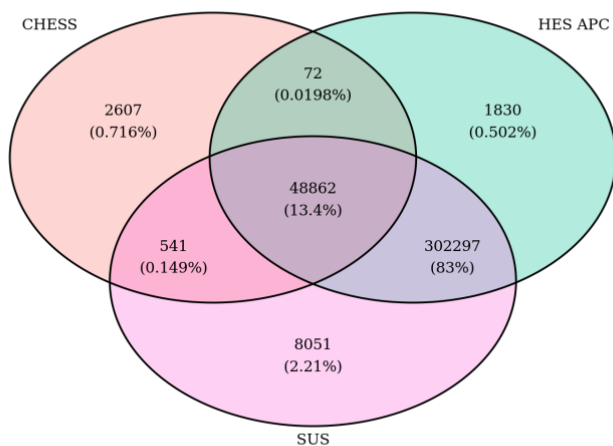
Ethical and Regulatory Approvals

Data access approval was granted to the CVD-COVID-UK consortium (under project proposal CCU013 High-throughput electronic health record phenotyping approaches) through the NHS Digital online Data Access Request Service¹⁶ (ref. DARS-NIC-381078-Y9C5K). For full detail see supplementary methods. The BHF Data Science Centre approvals and oversight board deemed that this project's work fell within the scope of the consortium's ethical and regulatory approvals. Analyses were conducted by three approved researchers (JHT, CT, SD) via secure remote access to the TRE. Only summarised, aggregate results were exported, following manual review by the NHS Digital ‘safe outputs’ escrow service, to ensure no output placed in the public domain contains information that may be used to identify an individual⁷. The North East-Newcastle and North Tyneside 2 research ethics committee provided ethical approval for the CVD-COVID-UK research programme (REC No 20/NE/0161).

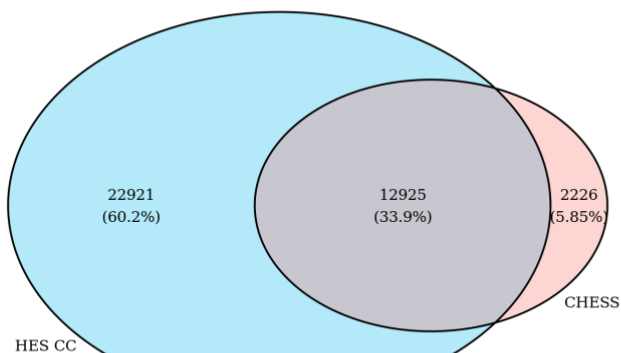
Supplementary Figures

Supplement figure 1: Flowchart of cohort design showing the number of records/individuals
Excluded individuals at different stages and the identification of cases and the final study population.

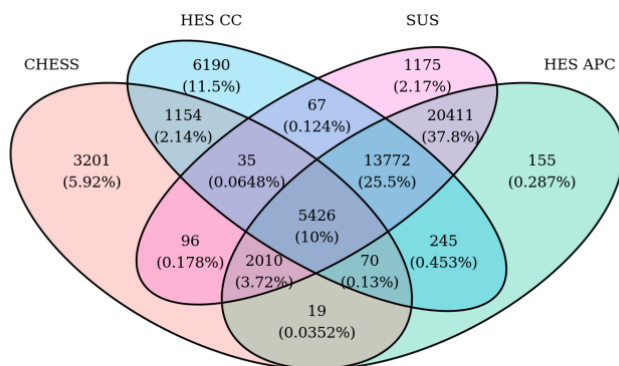
a) COVID-19 Hospitalisation



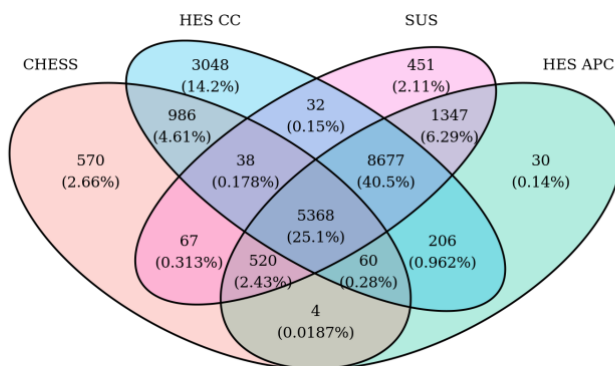
b) COVID-19 ICU Admission



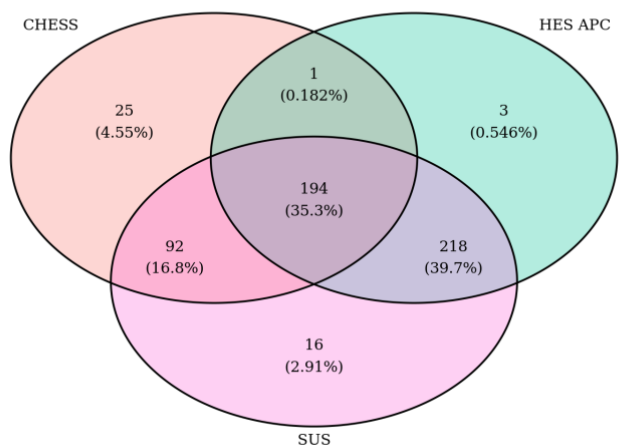
c) NIV treatment



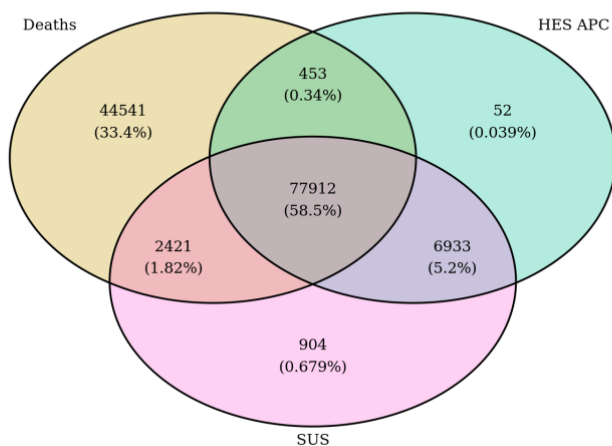
d) IMV treatment



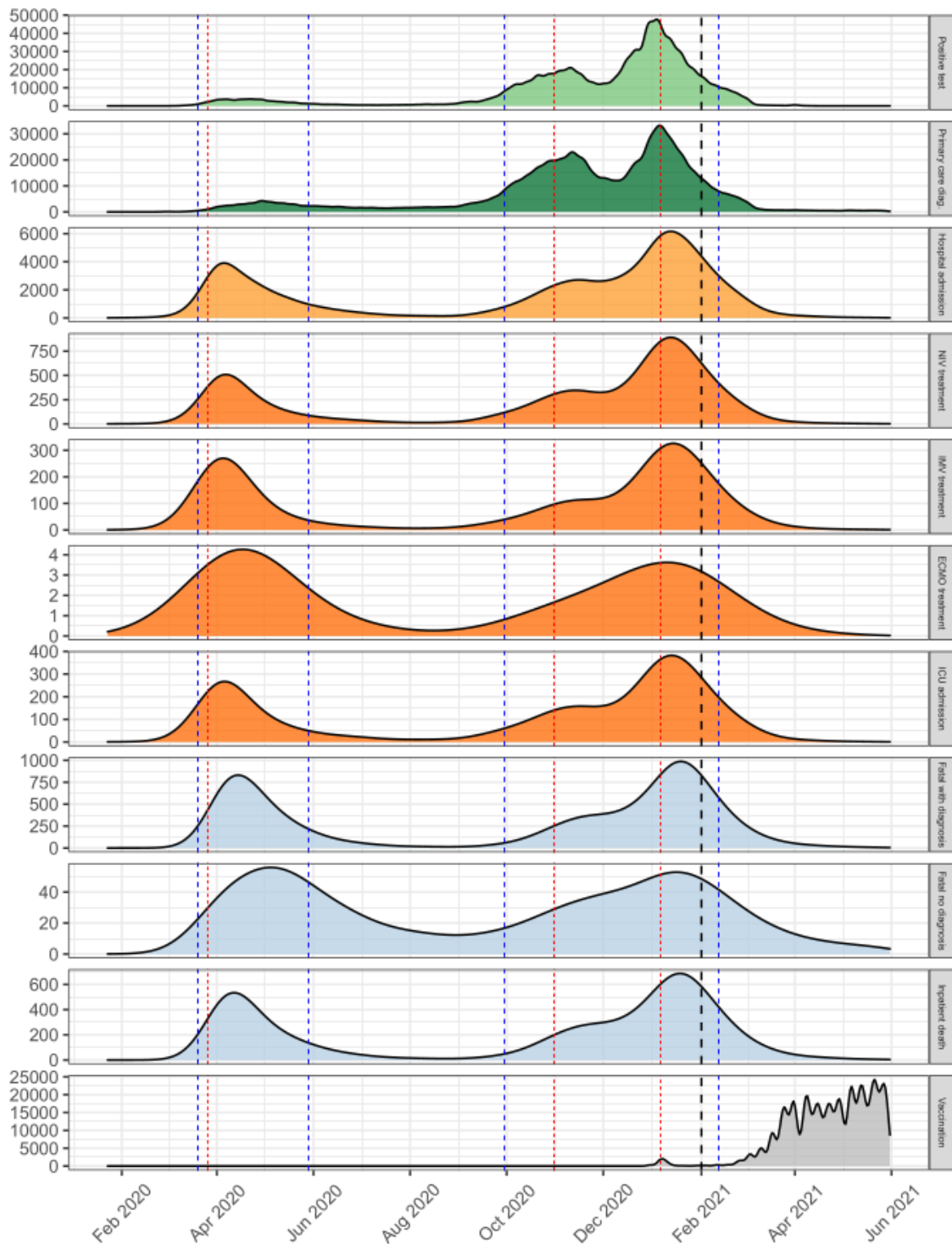
e) ECMO treatment



f) COVID-19 inpatient deaths

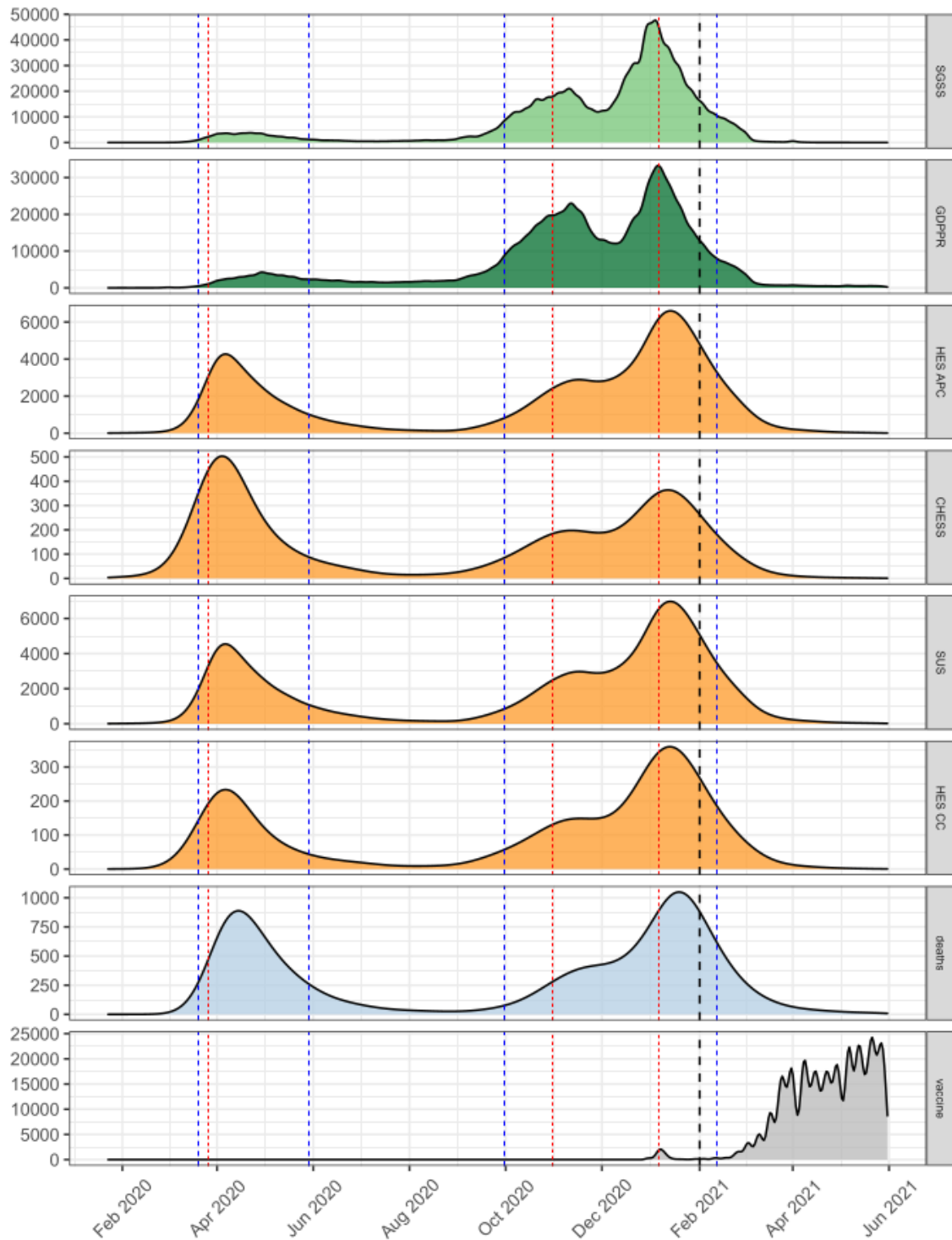
**Supplement figure 2: Venn Diagrams illustrating the numbers of individuals experiencing each COVID-19 event.**

Positive tests, primary care diagnoses and deaths with COVID-19 diagnosis, or within 28 days of a positive test, are not shown as these are derived from a single data source.



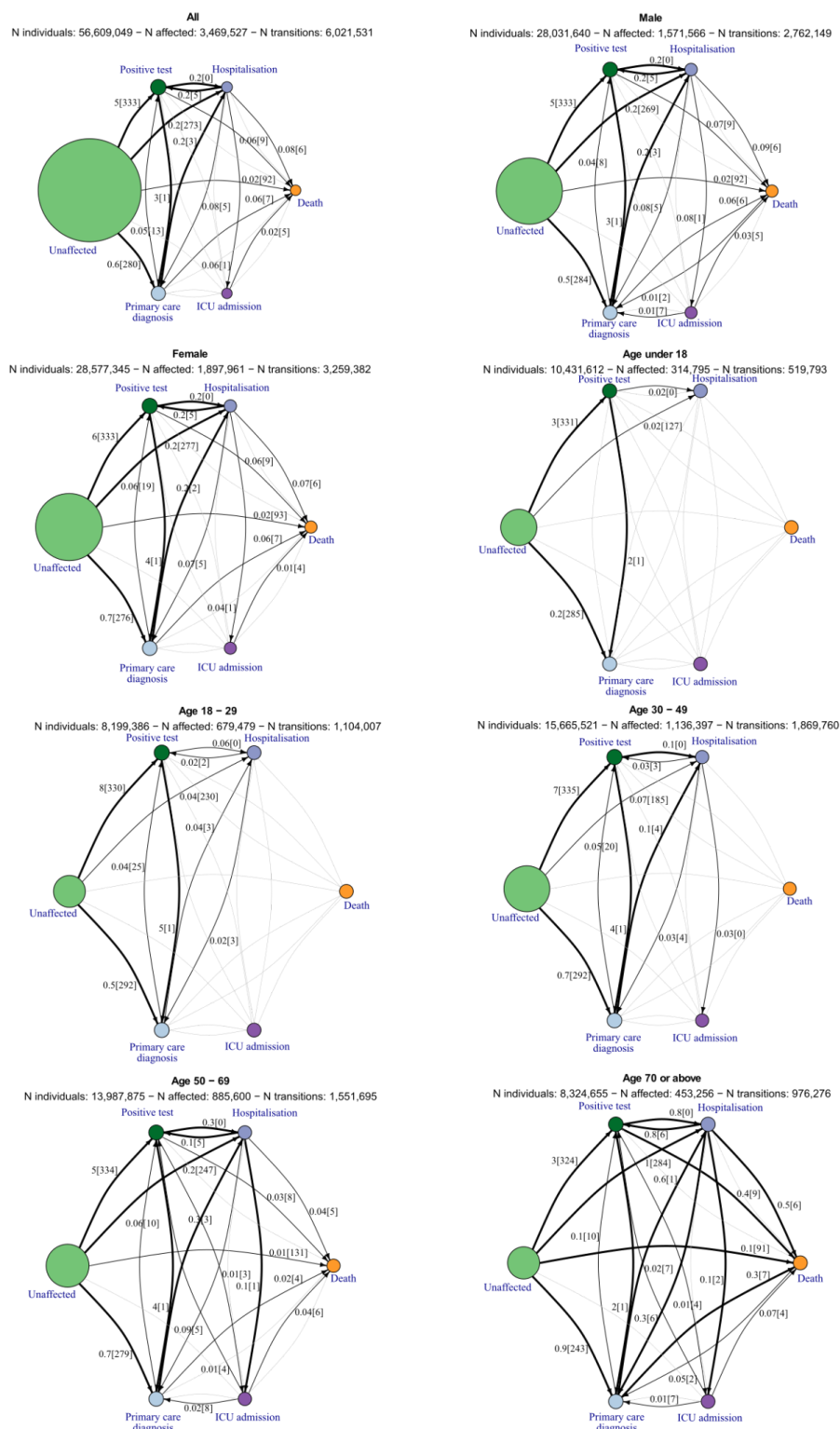
Supplement figure 3: Timeline of COVID-19 event phenotypes.

Kernel density estimation plot showing unique events per individual per date, a person may have multiple events of the same type at different dates. Vaccination shows the date of the second dosage. Red vertical lines indicate the official English lockdown dates (26.03.2020, 31.10.2020 & 06.01.2021). Blue vertical lines indicate our study definition of wave 1 (20.03.2020 - 29.05.2020) and wave 2 (30.09.2020 - 12.02.2021). Black vertical line indicates the date used to explore the effects of vaccination on COVID-19 phenotypes.



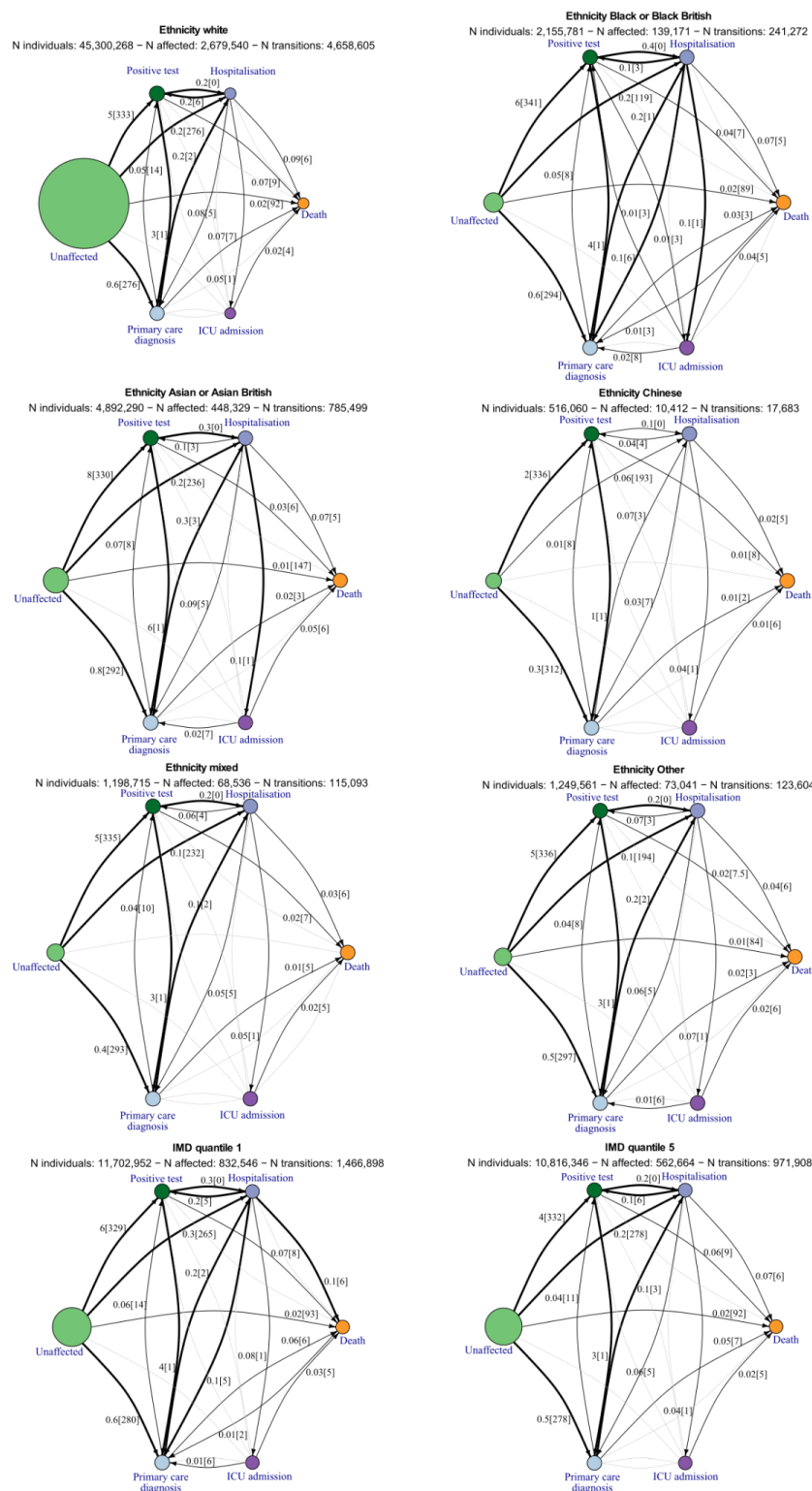
Supplement figure 4: Timeline plots showing COVID-19 events, stratified by data source.

A person may have multiple events from the same source at different dates. Vaccination shows the date of the second dosage. Red vertical lines indicate the official English lockdown dates (26.03.2020, 31.10.2020 & 06.01.2021). Blue vertical lines indicate our study definition of wave 1 (20.03.2020 - 29.05.2020) and wave 2 (30.09.2020 - 12.02.2021). Black vertical line indicates the date used to explore the effects of vaccination on COVID-19 phenotypes.



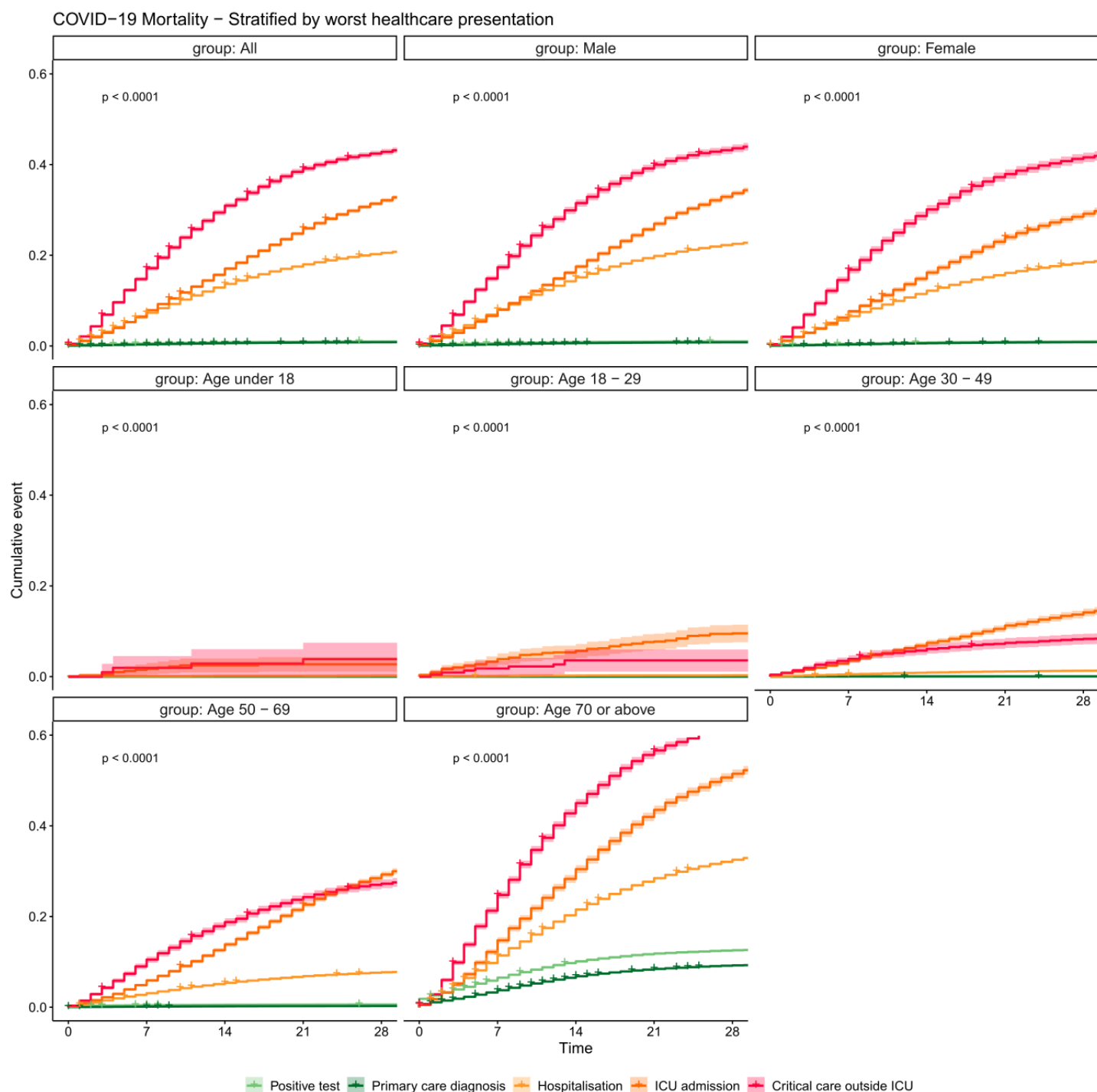
Supplement figure 5: COVID-19 trajectory networks by gender and age groups.

Networks show percentage of individuals transitioning and the median number of days passing between severity phenotypes stratified on sex and age groups. The size of the circles represent the number of individuals with that event relative to the total study population size of 56.6 million. Numbers on arrows are the percentage of individuals with the given transition (relative to N individuals in the group) and in square brackets median days between events across all individuals with that transition. Median days between unaffected and other severity phenotypes are larger, as these represent days from study start and the particular event. Thick arrows represent transitions occurring in $\geq 0.1\%$. Thin black arrows represent transitions occurring in $\geq 0.01\%$. Any transitions occurring in fewer than 0.01% are not shown. N affected = N individuals with COVID-19.



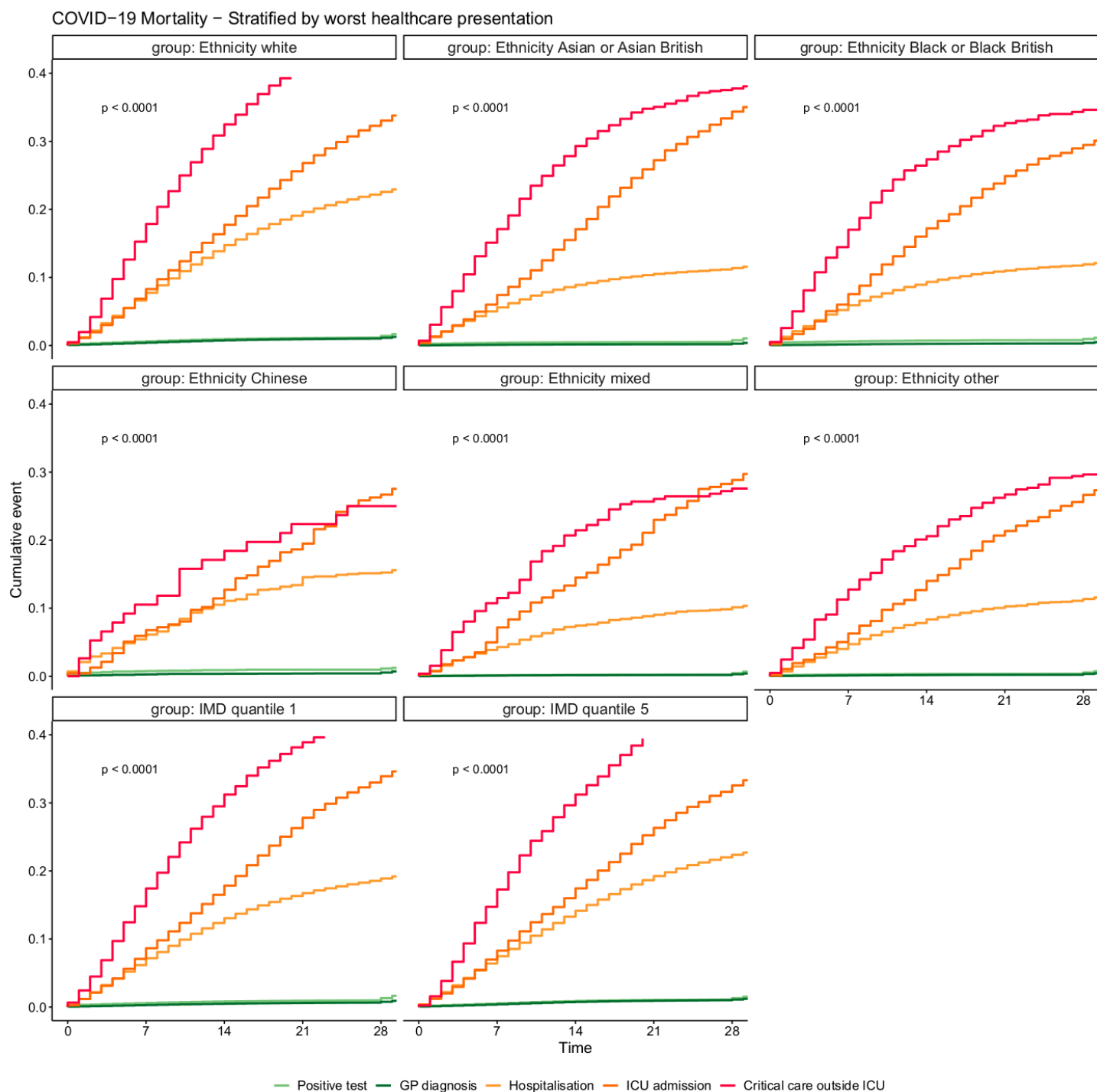
Supplement figure 6: COVID-19 trajectory networks by ethnicity and IMD.

Networks show showing percentage of individuals transitioning and the median number of days passing between severity phenotypes stratified on sex and age groups. The size of the circles represent the number of individuals with that event relative to the total study population size of 56.6 million. Numbers on arrows are the percentage of individuals with the given transition (relative to N individuals in the group) and in square brackets median days between events across all individuals with that transition. Median days between unaffected and other severity phenotypes are larger, as these represent days from study start and the particular event. Thick arrows represent transitions occurring in $\geq 0.1\%$. Thin black arrows represent transitions occurring in $\geq 0.01\%$. Any transitions occurring in fewer than 0.01% are not shown. N affected = N individuals with COVID-19.



Supplement figure 7: Kaplan Meier plot of COVID-19 mortality by gender and age groups.

Curves are stratified by worst healthcare presentation, here listed in increasing order of severity; positive test (light green), primary care diagnosis (dark green), hospitalisation (orange) and ICU admission (blue). Note the ICU admission group does not include patients who received critical care outside of ICU wards. Shaded areas represent 95% confidence intervals in all panels.



Supplement figure 8: Kaplan Meier plot of COVID-19 mortality by ethnicity and IMD level.

Curves are stratified by worst healthcare presentation, here listed in increasing order of severity; positive test (light green), primary care diagnosis (dark green), hospitalisation (orange) and ICU admission (blue). Note the ICU admission group does not include patients who received critical care outside of ICU wards. Shaded areas represent 95% confidence intervals in all panels.

Supplementary Tables

Supplement table 1: Number of individuals identified from each data source stratified by COVID-19 event and as total individuals across all data sources.

Date ranges shown for all included data sources after filtering as per cohort definition (see Figure 1).

Data	SGSS	GDPPR	HES APC	SUS	CHESS	HES CC	Deaths	Total
Min. Date	2020-01-24	2020-01-23	2020-01-23	2020-01-23	2020-01-23	2020-01-28	2020-01-30	2020-01-23
Max. Date	2021-05-31	2021-05-31	2021-05-31	2021-05-31	2021-05-31	2021-05-28	2021-05-31	2021-05-31
Positive test	3,114,784							3,114,784
GP diagnosis		2,363,507						2,363,507
Hospitalisation			353,061	359,751	52,082			364,260
ECMO treatment			416	520	312			549
ICU admission					15,151	35,846		38,072
IMV treatment			16,212	16,500	7,613	18,415		21,404
NIV treatment			42,108	42,992	12,011	26,959		54,026
Inpatient Death			85,350	88,170				88,675
Fatal with diagnosis							125,327	125,327
Death without diagnosis							13,083	13,083

Supplement table 2: COVID-19 codes & frequencies.

Codes appearing with a frequency <5 are masked as '<5' to protect privacy.

COVID-19 Event	Code	Terminology	Description	Source	n
01 Covid positive test			pillar 2	SGSS	2694960
01 Covid_positive_test			pillar 1	SGSS	741785
01 GP covid diagnosis	12405810 00000104	SNOMED	Severe acute respiratory syndrome coronavirus 2 ribonucleic acid detected (finding)	GDPPR	2127470
01 GP covid diagnosis	13007210 00000109	SNOMED	Coronavirus disease 19 caused by severe acute respiratory syndrome coronavirus 2 confirmed by laboratory test (situation)	GDPPR	419647
01 GP covid diagnosis	10085410 00000105	SNOMED	Coronavirus ribonucleic acid detection assay (observable entity)	GDPPR	257399
01 GP covid diagnosis	12407510 00000100	SNOMED	Coronavirus disease 19 caused by severe acute respiratory syndrome coronavirus 2 (disorder)	GDPPR	193545
01 GP covid diagnosis	13215410 00000108	SNOMED	Severe acute respiratory syndrome coronavirus 2 immunoglobulin G detected (finding)	GDPPR	67791
01 GP covid diagnosis	13227810 00000102	SNOMED	Severe acute respiratory syndrome coronavirus 2 antigen detection result positive (finding)	GDPPR	65011
01 GP covid diagnosis	18674700 9	SNOMED	Coronavirus infection (disorder)	GDPPR	43078
01 GP covid diagnosis	13006810 00000102	SNOMED	Assessment using coronavirus disease 19 severity scale (procedure)	GDPPR	28030
01 GP covid diagnosis	13007310 00000106	SNOMED	Coronavirus disease 19 caused by severe acute respiratory syndrome coronavirus 2 confirmed using clinical diagnostic criteria (situation)	GDPPR	22156
01 GP covid diagnosis	12405110 00000106	SNOMED	Detection of severe acute respiratory syndrome coronavirus 2 using polymerase chain reaction technique (procedure)	GDPPR	16496
01 GP covid diagnosis	12405510 00000105	SNOMED	Pneumonia caused by severe acute respiratory syndrome coronavirus 2 (disorder)	GDPPR	12199
01 GP covid diagnosis	12407410 00000103	SNOMED	Severe acute respiratory syndrome coronavirus 2 serology (observable entity)	GDPPR	9873
01 GP covid diagnosis	13217610 00000103	SNOMED	Severe acute respiratory syndrome coronavirus 2 immunoglobulin A detected (finding)	GDPPR	7095
01 GP covid diagnosis	13228710 00000109	SNOMED	Severe acute respiratory syndrome coronavirus 2 antibody detection result positive (finding)	GDPPR	5568
01 GP covid diagnosis	13006310 00000101	SNOMED	Coronavirus disease 19 severity score (observable entity)	GDPPR	5054
01 GP covid diagnosis	12405410 00000107	SNOMED	Infection of upper respiratory tract caused by severe acute respiratory syndrome coronavirus 2 (disorder)	GDPPR	3421
01 GP covid diagnosis	10294810 00000103	SNOMED	Coronavirus nucleic acid detection assay (observable entity)	GDPPR	2578
01 GP covid diagnosis	13006710 00000104	SNOMED	Coronavirus disease 19 severity scale (assessment scale)	GDPPR	2059
01 GP covid diagnosis	13215510 00000106	SNOMED	Severe acute respiratory syndrome coronavirus 2 immunoglobulin M detected (finding)	GDPPR	1799
01 GP covid diagnosis	12404010 00000105	SNOMED	Antibody to severe acute respiratory syndrome coronavirus 2 (substance)	GDPPR	576

01 GP covid diagnosis	12404210				
	00000101	SNOMED	Serotype severe acute respiratory syndrome coronavirus 2 (qualifier value)	GDPPR	263
01 GP covid diagnosis	12405710				
	00000101	SNOMED	Gastroenteritis caused by severe acute respiratory syndrome coronavirus 2 (disorder)	GDPPR	230
01 GP covid diagnosis	12405310				
	00000103	SNOMED	Myocarditis caused by severe acute respiratory syndrome coronavirus 2 (disorder)	GDPPR	165
01 GP covid diagnosis	13213410				
	00000103	SNOMED	Arbitrary concentration of severe acute respiratory syndrome coronavirus 2 immunoglobulin G in serum (observable entity)	GDPPR	162
01 GP covid diagnosis	12403910				
	00000107	SNOMED	Antigen of severe acute respiratory syndrome coronavirus 2 (substance)	GDPPR	150
01 GP covid diagnosis	13213310				
	00000107	SNOMED	Arbitrary concentration of severe acute respiratory syndrome coronavirus 2 total immunoglobulin in serum (observable entity)	GDPPR	105
01 GP covid diagnosis	13213010				
	00000101	SNOMED	Severe acute respiratory syndrome coronavirus 2 ribonucleic acid qualitative existence in specimen (observable entity)	GDPPR	99
01 GP covid diagnosis	12405610				
	00000108	SNOMED	Encephalopathy caused by severe acute respiratory syndrome coronavirus 2 (disorder)	GDPPR	70
01 GP covid diagnosis	13212410				
	00000105	SNOMED	Cardiomyopathy caused by severe acute respiratory syndrome coronavirus 2 (disorder)	GDPPR	23
01 GP covid diagnosis	13213510				
	00000100	SNOMED	Arbitrary concentration of severe acute respiratory syndrome coronavirus 2 immunoglobulin M in serum (observable entity)	GDPPR	21
01 GP covid diagnosis	12405210				
	00000100	SNOMED	Otitis media caused by severe acute respiratory syndrome coronavirus 2 (disorder)	GDPPR	17
01 GP covid diagnosis	13213210				
	00000105	SNOMED	Severe acute respiratory syndrome coronavirus 2 immunoglobulin G qualitative existence in specimen (observable entity)	GDPPR	15
01 GP covid diagnosis	13213110				
	00000104	SNOMED	Severe acute respiratory syndrome coronavirus 2 immunoglobulin M qualitative existence in specimen (observable entity)	GDPPR	11
01 GP covid diagnosis	13218110				
	00000105	SNOMED	Severe acute respiratory syndrome coronavirus 2 immunoglobulin A qualitative existence in specimen (observable entity)	GDPPR	<5
01 GP covid diagnosis	12081400				
	5	SNOMED	Coronavirus antibody (substance)	GDPPR	<5
01 GP covid diagnosis	13212010				
	00000107	SNOMED	Coronavirus disease 19 caused by severe acute respiratory syndrome coronavirus 2 health issues simple reference set (foundation metadata concept)	GDPPR	<5
01 GP covid diagnosis	13211810				
	00000108	SNOMED	Coronavirus disease 19 caused by severe acute respiratory syndrome coronavirus 2 record extraction simple reference set (foundation metadata concept)	GDPPR	<5
01 GP covid diagnosis	12403810				
	00000105	SNOMED	Severe acute respiratory syndrome coronavirus 2 (organism)	GDPPR	<5
01 GP covid diagnosis	13218010				
	00000108	SNOMED	Arbitrary concentration of severe acute respiratory syndrome coronavirus 2 immunoglobulin A in serum (observable entity)	GDPPR	<5
01 GP covid diagnosis	12404110				
	00000107	SNOMED	Ribonucleic acid of severe acute respiratory syndrome coronavirus 2 (substance)	GDPPR	<5
01 GP covid diagnosis	13211910				
	00000105	SNOMED	Coronavirus disease 19 caused by severe acute respiratory syndrome coronavirus 2 procedures simple reference set (foundation metadata concept)	GDPPR	<5
02 Covid admission	U07.1	ICD10	Confirmed COVID19	SUS	667110
02 Covid admission	U07.1	ICD10	Confirmed COVID19	HES APC	654497
02 Covid admission	U07.2	ICD10	Suspected COVID19	SUS	64012
02 Covid admission	U07.2	ICD10	Suspected COVID19	HES APC	58567
02 Covid admission			HospitalAdmissionDate IS NOT null	CHESS	55454
03 ECMO treatment	X58.1	OPCS	Extracorporeal membrane oxygenation	SUS	588
03 ECMO treatment	X58.1	OPCS	Extracorporeal membrane oxygenation	HES APC	461
03 ECMO treatment			RespiratorySupportECMO == Yes	CHESS	379
03 ICU admission			id is in hes_cc table	HES CC	44990
03 ICU admission			DateAdmittedICU IS NOT null	CHESS	16291
03 IMV treatment			ARESSUPDAYS > 0	HES CC	22835
03 IMV treatment	E85.1	OPCS	Invasive ventilation	SUS	18716
03 IMV treatment	E85.1	OPCS	Invasive ventilation	HES APC	18018
03 IMV treatment			Invasivemechanicalventilation == Yes	CHESS	8382
03 IMV treatment	X56	OPCS	Intubation of trachea	SUS	451
03 IMV treatment	X56	OPCS	Intubation of trachea	HES APC	414
03 NIV treatment	E85.6	OPCS	Continuous positive airway pressure	SUS	36857
03 NIV treatment	E85.6	OPCS	Continuous positive airway pressure	HES APC	36175
03 NIV treatment			bressupdays > 0	HES CC	30785
03 NIV treatment	E85.2	OPCS	Non-invasive ventilation NEC	SUS	17622
03 NIV treatment	E85.2	OPCS	Non-invasive ventilation NEC	HES APC	16242
03 NIV treatment			Highflownasaloxxygen OR NoninvasiveMechanicalventilation == Yes	CHESS	12280
04 Covid inpatient death			DISCHARGE_METHOD_HOSPITAL_PROVIDER_SPELL = 4 (Died)	SUS	89811
04 Covid inpatient death			DISMETH = 4 (Died)	HES APC	85328
04 Covid inpatient death			DISCHARGE_DESTINATION_HOSPITAL_PROVIDER_SPELL = 79 (Not applicable - PATIENT died or still birth)	SUS	155
04 Covid inpatient death			DISDEST = 79 (Not applicable - PATIENT died or still birth)	HES APC	108

04_Fatal_with_covid_diagnosis	U071	ICD10		deaths	123154
04_Fatal_with_covid_diagnosis	U072	ICD10		deaths	4032
04_Fatal_without_covid_diagnosis			ONS death within 28 days	deaths	13085

Supplement table 3: 270 CALIBER phenotypes, aggregated into 16 categories

Table shows the number of individuals within the study cohort identified from GPPR (SNOMED-CT) and HES APC (ICD-10, OPCS-4).

Category	Phenotype	Individuals
benign neoplasm cin	benign neoplasm of colon rectum anus and anal ...	82,933
benign neoplasm cin	benign neoplasm of ovary	53,602
benign neoplasm cin	benign neoplasm and polyp of uterus	30,807
benign neoplasm cin	benign neoplasm of stomach and duodenum	25,003
benign neoplasm cin	haemangioma any site	10,885
benign neoplasm cin	carcinoma in situ cervical	4,351
benign neoplasm cin	benign neoplasm of brain and other parts of ce...	2,665
cancers	myelodysplastic syndromes	284,874
cancers	primary malignancy other organs	231,644
cancers	primary malignancy other skin and subcutaneous...	220,826
cancers	primary malignancy breast	104,193
cancers	primary malignancy cervical	46,985
cancers	primary malignancy prostate	19,692
cancers	primary malignancy colorectal and anus	14,410
cancers	primary malignancy malignant melanoma	9,706
cancers	non-hodgkin_lymphoma	7,830
cancers	secondary malignancy other organs	7,438
cancers	primary_malignancy_bladder	7,001
cancers	monoclonal gammopathy of undetermined signific...	6,665
cancers	leukaemia	6,051
cancers	hodgkin_lymphoma	5,570
cancers	multiple myeloma and malignant plasma cell neo...	5,301
cancers	primary malignancy lung and trachea	4,401
cancers	secondary malignancy bone	4,272
cancers	primary malignancy kidney and ureter	3,438
cancers	primary malignancy uterine	3,011
cancers	secondary malignancy lung	2,875
cancers	secondary malignancy liver and intrahepatic bi...	2,643
cancers	primary malignancy testicular	2,442
cancers	primary malignancy ovarian	2,300
cancers	primary malignancy oro-pharyngeal	2,097
cancers	polycythaemia vera	2,049
cancers	primary malignancy thyroid	1,871
cancers	secondary malignancy retroperitoneum and perit...	1,536
cancers	primary_malignancy_oesophageal	1,039
cancers	primary_malignancy_brain_other_cns_and_intracr...	1,006
cancers	secondary malignancy lymph nodes	780
cancers	primary_malignancy_liver	748
cancers	secondary malignancy brain other_cns_and_intra...	746
cancers	primary malignancy stomach	720
cancers	secondary malignancy pleura	564
cancers	primary malignancy pancreatic	506
cancers	primary malignancy bone and articular cartilage	399
cancers	secondary malignancy bowel	397
cancers	primary malignancy biliary tract	313
cancers	secondary malignancy adrenal gland	303
cancers	primary malignancy mesothelioma	68
cancers	primary malignancy multiple independent sites	8
diseases of the circulatory system	hypertension	568,174
diseases of the circulatory system	coronary heart disease not otherwise specified	161,781
diseases of the circulatory system	stable angina	110,546
diseases of the circulatory system	atrial fibrillation	102,862
diseases of the circulatory system	myocardial infarction	88,821
diseases of the circulatory system	heart failure	58,762
diseases of the circulatory system	stroke_nos	51,193

diseases of the circulatory system	transient ischaemic attack	47,975
diseases of the circulatory system	ischaemic stroke	45,939
diseases of the circulatory system	peripheral arterial disease	43,035
diseases of the circulatory system	unstable angina	40,536
diseases of the circulatory system	supraventricular tachycardia	26,549
diseases of the circulatory system	venous thromboembolic disease excl pe	23,853
diseases of the circulatory system	right bundle branch block	23,775
diseases of the circulatory system	left bundle branch block	20,374
diseases of the circulatory system	atrioventricular block first degree	18,001
diseases of the circulatory system	abdominal aortic aneurysm	12,956
diseases of the circulatory system	raynauds syndrome	8,368
diseases of the circulatory system	secondary pulmonary hypertension	7,782
diseases of the circulatory system	other cardiomyopathy	7,318
diseases of the circulatory system	atrioventricular block complete	7,014
diseases of the circulatory system	pericardial effusion noninflammatory	6,956
diseases of the circulatory system	intracerebral haemorrhage	6,031
diseases of the circulatory system	ventricular tachycardia	5,824
diseases of the circulatory system	atrioventricular block second degree	5,009
diseases of the circulatory system	dilated cardiomyopathy	4,659
diseases of the circulatory system	sick sinus syndrome	4,226
diseases of the circulatory system	subdural haematoma - nontraumatic	3,302
diseases of the circulatory system	primary pulmonary hypertension	3,139
diseases of the circulatory system	trifascicular block	2,015
diseases of the circulatory system	bifascicular block	1,992
diseases of the circulatory system	hypertrophic cardiomyopathy	1,897
diseases of the circulatory system	subarachnoid haemorrhage	863
diseases of the circulatory system	pulmonary embolism	433
diseases of the circulatory system	rheumatic valve dz	140
diseases of the digestive system	abdominal hernia	115,615
diseases of the digestive system	oesophagitis and oesophageal ulcer	72,309
diseases of the digestive system	appendicitis	62,962
diseases of the digestive system	cholecystitis	52,391
diseases of the digestive system	fatty liver	28,930
diseases of the digestive system	anal fissure	18,229
diseases of the digestive system	barretts oesophagus	17,253
diseases of the digestive system	peritonitis	16,205
diseases of the digestive system	coeliac disease	15,883
diseases of the digestive system	liver fibrosis sclerosis and cirrhosis	12,408
diseases of the digestive system	anorectal fistula	12,332
diseases of the digestive system	cholangitis	7,607
diseases of the digestive system	pancreatitis	7,509
diseases of the digestive system	anorectal prolapse	7,076
diseases of the digestive system	portal hypertension	5,661
diseases of the digestive system	gastro-oesophageal reflux disease	4,892
diseases of the digestive system	volvulus	4,277
diseases of the digestive system	angiodysplasia of colon	3,155
diseases of the digestive system	autoimmune liver disease	2,894
diseases of the digestive system	oesophageal varices	2,709
diseases of the digestive system	alcoholic liver disease	2,163
diseases of the digestive system	diaphragmatic hernia	2,067
diseases of the digestive system	hepatic failure	1,464
diseases of the digestive system	peptic ulcer disease	1,381
diseases of the digestive system	diverticular disease of intestine acute and ch...	184
diseases of the ear	hearing loss	5,970
diseases of the ear	tinnitus	5,063
diseases of the ear	meniere disease	3,930
diseases of the endocrine system	diabetes	280,896
diseases of the endocrine system	obesity	203,250
diseases of the endocrine system	hypo or hyperthyroidism	171,787
diseases of the endocrine system	polycystic ovarian syndrome	24,459
diseases of the endocrine system	syndrome of inappropriate secretion of antidiu...	19,025
diseases of the endocrine system	hyperparathyroidism	7,433
diseases of the endocrine system	cystic fibrosis	864
diseases of the eye	diabetic ophthalmic complications	202,348
diseases of the eye	cataract	177,536
diseases of the eye	glaucoma	33,775
diseases of the eye	macular degeneration	32,503

diseases_of_the_eye	retinal_detachments_and_breaks	15,994
diseases_of_the_eye	ptosis of eyelid	7,665
diseases_of_the_eye	anterior_and_intermediate_uveitis	3,172
diseases_of_the_eye	keratitis	567
diseases_of_the_eye	scleritis and episcleritis	449
diseases_of_the_eye	posterior uveitis	260
diseases_of_the_eye	retinal vascular occlusions	99
diseases_of_the_eye	visual impairment and blindness	54
diseases_of_the_genitourinary_system	acute kidney injury	106,099
diseases_of_the_genitourinary_system	menorrhagia and polymenorrhoea	85,377
diseases_of_the_genitourinary_system	urolithiasis	58,758
diseases_of_the_genitourinary_system	obstructive and reflux uropathy	29,746
diseases_of_the_genitourinary_system	urinary incontinence	29,696
diseases_of_the_genitourinary_system	postmenopausal bleeding	23,098
diseases_of_the_genitourinary_system	end stage renal disease	17,055
diseases_of_the_genitourinary_system	dysmenorrhoea	16,493
diseases_of_the_genitourinary_system	glomerulonephritis	15,858
diseases_of_the_genitourinary_system	hydrocoele incl infected	14,197
diseases_of_the_genitourinary_system	endometrial hyperplasia and hypertrophy	13,294
diseases_of_the_genitourinary_system	postcoital and contact bleeding	12,034
diseases_of_the_genitourinary_system	non-acute cystitis	5,603
diseases_of_the_genitourinary_system	erectile dysfunction	2,680
diseases_of_the_genitourinary_system	tubulo-interstitial nephritis	1,408
diseases_of_the_genitourinary_system	undescended testicle	33
diseases_of_the_genitourinary_system	male infertility	13
diseases_of_the_respiratory_system	asthma	528,582
diseases_of_the_respiratory_system	copd	85,731
diseases_of_the_respiratory_system	allergic and chronic rhinitis	68,720
diseases_of_the_respiratory_system	chronic sinusitis	60,075
diseases_of_the_respiratory_system	sleep apnoea	41,581
diseases_of_the_respiratory_system	pulmonary collapse excl pneumothorax	30,531
diseases_of_the_respiratory_system	hypertrophy of nasal turbinates	18,848
diseases_of_the_respiratory_system	bronchiectasis	17,719
diseases_of_the_respiratory_system	aspiration pneumonitis	13,829
diseases_of_the_respiratory_system	other interstitial pulmonary diseases with fib...	10,684
diseases_of_the_respiratory_system	pleural plaque	6,469
diseases_of_the_respiratory_system	respiratory failure	2,013
diseases_of_the_respiratory_system	asbestosis	803
diseases_of_the_respiratory_system	pleural effusion	94
diseases_of_the_respiratory_system	pneumothorax	25
diseases_of_the_respiratory_system	nasal polyp	0
haematological immunological conditions	vitamin b12 deficiency anaemia	<5
haematological immunological conditions	secondary or other thrombocytopaenia	14,326
haematological immunological conditions	splenomegaly	9,774
haematological immunological conditions	sickle-cell trait	6,587
haematological immunological conditions	thalassaemia trait	5,871
haematological immunological conditions	hyposplenism	4,498
haematological immunological conditions	primary or idiopathic thrombocytopaenia	4,208
haematological immunological conditions	thalassaemia	3,606
haematological immunological conditions	thrombophilia	3,570
haematological immunological conditions	agranulocytosis	3,304
haematological immunological conditions	sickle-cell anaemia	2,816
haematological immunological conditions	secondary polycythaemia	2,635
haematological immunological conditions	aplastic anaemias	2,196
haematological immunological conditions	immunodeficiencies	1,984
haematological immunological conditions	sarcoidosis	1,520
haematological immunological conditions	other haemolytic anaemias	383
haematological immunological conditions	other anaemias	179
haematological immunological conditions	iron deficiency anaemia	65
infectious_diseases	bacterial diseases excl tb	238,377
infectious_diseases	other or unspecified infectious organisms	238,106
infectious_diseases	hiv	219,038
infectious_diseases	urinary tract infections	199,628
infectious_diseases	viral diseases excl chronic hepatitis hiv	65,332
infectious_diseases	infections of other or unspecified organs	56,208
infectious_diseases	lower respiratory tract infections	53,756
infectious_diseases	infection of other or unspecified genitourinar...	20,132

infectious diseases	infection of skin and subcutaneous tissues	17,584
infectious diseases	infections of the digestive system	17,376
infectious diseases	other nervous system infections	9,924
infectious diseases	infection of male genital system	6,650
infectious diseases	eve infections	6,574
infectious diseases	infections of the heart	3,877
infectious diseases	infection of bones and joints	3,861
infectious diseases	infection of anal and rectal regions	3,435
infectious diseases	infection of liver	3,045
infectious diseases	chronic viral hepatitis	2,543
infectious diseases	parasitic infections	2,027
infectious diseases	mycoses	1,856
infectious diseases	ear and upper respiratory tract infections	1,783
infectious diseases	meningitis	1,763
infectious diseases	septicaemia	1,572
infectious diseases	tuberculosis	1,216
infectious diseases	encephalitis	538
infectious diseases	rheumatic fever	239
mental health disorders	depression	638,222
mental health disorders	bipolar affective disorder and mania	396,659
mental health disorders	anxiety disorders	261,938
mental health disorders	other psychoactive substance misuse	135,585
mental health disorders	alcohol problems	96,206
mental health disorders	dementia	91,367
mental health disorders	intellectual disability	39,980
mental health disorders	schizophrenia schizotypal and delusional disor...	23,940
mental health disorders	autism and aspergers syndrome	23,504
mental health disorders	hyperkinetic disorders	14,624
mental health disorders	anorexia and bulimia nervosa	3,046
mental health disorders	personality disorders	201
mental health disorders	delirium not induced by alcohol and other psyc...	82
musculoskeletal conditions	osteoporosis	73,899
musculoskeletal conditions	spondylosis	66,395
musculoskeletal conditions	carpal tunnel syndrome	51,553
musculoskeletal conditions	fracture of wrist	44,024
musculoskeletal conditions	enthesopathies synovial disorders	42,187
musculoskeletal conditions	fracture of hip	37,679
musculoskeletal conditions	spinal stenosis	29,367
musculoskeletal conditions	rheumatoid arthritis	26,342
musculoskeletal conditions	intervertebral disc disorders	17,427
musculoskeletal conditions	polymyalgia rheumatica	12,729
musculoskeletal conditions	collapsed vertebra	9,801
musculoskeletal conditions	spondylolisthesis	9,590
musculoskeletal conditions	fibromatoses	9,186
musculoskeletal conditions	psoriatic arthropathy	4,769
musculoskeletal conditions	giant cell arteritis	3,233
musculoskeletal conditions	sjogrens disease	2,627
musculoskeletal conditions	enteropathic arthropathy	462
musculoskeletal conditions	gout	46
musculoskeletal conditions	systemic sclerosis	12
musculoskeletal conditions	lupus erythematosus local and systemic	0
neurological conditions	epilepsy	54,629
neurological conditions	postviral fatigue syndrome neurasthenia and fi...	31,424
neurological conditions	peripheral neuropathies excluding cranial nerv...	28,445
neurological conditions	diabetic neurological complications	23,834
neurological conditions	parkinsons disease	13,097
neurological conditions	bells palsy	8,268
neurological conditions	disorders of autonomic nervous system	3,624
neurological conditions	intracranial hypertension	3,226
neurological conditions	trigeminal neuralgia	3,178
neurological conditions	essential tremor	2,934
neurological conditions	myasthenia gravis	1,533
neurological conditions	motor neuron disease	951
perinatal conditions	slow fetal growth or low birth weight	24,016
perinatal conditions	prematurity	15,232
perinatal conditions	congenital malformations of cardiac septa	13,995
perinatal conditions	high birth weight	6,720

perinatal conditions	post-term infant	3,426
perinatal conditions	patent ductus arteriosus	2,857
perinatal conditions	downs syndrome	2,713
perinatal conditions	intrauterine hypoxia	1,143
perinatal conditions	spina bifida	896
skin conditions	seborrheic dermatitis	<5
skin conditions	dermatitis atopc contact other unspecified	70,563
skin conditions	pilonidal cyst sinus	15,805
skin conditions	actinic keratosis	11,061
skin conditions	psoriasis	4,603
skin conditions	hidradenitis suppurativa	3,261
skin conditions	acne	2,036
skin conditions	rosacea	1,435
skin conditions	lichen planus	67

Supplement table 4: Demographic overview of deceased patients

Table is stratified by individuals identified with or without a formal COVID-19 diagnosis listed on the death certificate, and/or COVID-19 inpatient deaths, as compared with the total population of all patients with a COVID-19 event.

	Fatal with COVID-19 diagnosis	Fatal without COVID-19 diagnosis	COVID-19 Inpatient death	COVID-19 Death no hospital contact	COVID-19 Death no hospital contact - Wave 1	COVID-19 Death no hospital contact - Wave 2	All COVID events
n	125327 (3.6)	13083 (0.4)	88675 (2.6)	39510 (1.1)	16325 (6.2)	19951 (0.7)	3469528 (100)
Sex							
Female	57287 (45.7)	6350 (48.5)	36424 (41.1)	21971 (55.6)	8830 (54.1)	11546 (57.9)	1897963 (54.7)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Age							
Under 18	20 (0)	20 (0.2)	27 (0)	19 (0)	6 (0)	10 (0.1)	337664 (9.7)
Age 18 - 29	165 (0.1)	38 (0.3)	136 (0.2)	70 (0.2)	27 (0.2)	35 (0.2)	694821 (20)
Age 30 - 49	2328 (1.9)	357 (2.7)	1864 (2.1)	733 (1.9)	217 (1.3)	416 (2.1)	1134935 (32.7)
Age 50 - 69	18465 (14.7)	2035 (15.6)	15769 (17.8)	3867 (9.8)	1295 (7.9)	2036 (10.2)	862436 (24.9)
>= 70	104349 (83.3)	10633 (81.3)	70879 (79.9)	34821 (88.1)	14780 (90.5)	17454 (87.5)	439672 (12.7)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ethnicity							
White	109568 (87.4)	11972 (91.5)	76036 (85.7)	36092 (91.3)	14947 (91.6)	18205 (91.2)	2679545 (77.2)
Asian or asian british	8569 (6.8)	584 (4.5)	7109 (8)	1572 (4)	513 (3.1)	885 (4.4)	448341 (12.9)
Black or black british	3763 (3)	248 (1.9)	2972 (3.4)	869 (2.2)	412 (2.5)	414 (2.1)	139152 (4)
Chinese	303 (0.2)	23 (0.2)	229 (0.3)	85 (0.2)	42 (0.3)	38 (0.2)	10417 (0.3)
Mixed and others	2221 (1.8)	179 (1.4)	1755 (2)	521 (1.3)	257 (1.6)	221 (1.1)	141580 (4.1)
Unknown ethnicity	903 (0.7)	77 (0.6)	574 (0.6)	371 (0.9)	154 (0.9)	188 (0.9)	50493 (1.5)
IMD Fifths (%)							
1 (most deprived)	29198 (23.3)	2992 (22.9)	21821 (24.6)	7892 (20)	3380 (20.7)	3849 (19.3)	832581 (24)
5 (least deprived)	21018 (16.8)	2330 (17.8)	14002 (15.8)	7651 (19.4)	3201 (19.6)	3922 (19.7)	562638 (16.2)
Unknown	111 (0.1)	12 (0.1)	58 (0.1)	53 (0.1)	25 (0.2)	23 (0.1)	2911 (0.1)
COVID-19 events							
COVID-19 positive test	106941 (85.3)	5365 (41)	79670 (89.8)	23567 (59.6)	6405 (39.2)	15913 (79.8)	3114784 (89.8)
GP COVID-19 diagnosis	52286 (41.7)	5029 (38.4)	31525 (35.6)	19527 (49.4)	5933 (36.3)	11563 (58)	2363507 (68.1)
COVID-19 admission	91308 (72.9)	7593 (58)	88657 (100)	0 (0)	0 (0)	0 (0)	364260 (10.5)
ICU admission	14429 (11.5)	619 (4.7)	15074 (17)	0 (0)	0 (0)	0 (0)	38072 (1.1)
NIV treatment	21899 (17.5)	773 (5.9)	22498 (25.4)	0 (0)	0 (0)	0 (0)	54026 (1.6)
IMV treatment	10596 (8.5)	422 (3.2)	11153 (12.6)	0 (0)	0 (0)	0 (0)	21404 (0.6)
ECMO treatment	194 (0.2)	1 (0)	204 (0.2)	0 (0)	0 (0)	0 (0)	549 (0)
Fatal with COVID-19 diagnosis	125327 (100)	0 (0)	80786 (91.1)	34018 (86.1)	15100 (92.5)	17310 (86.8)	125327 (3.6)
Fatal without COVID-19 diagnosis	0 (0)	13083 (100)	5391 (6.1)	5490 (13.9)	1223 (7.5)	2641 (13.2)	13083 (0.4)
COVID-19 inpatient death	80786 (64.5)	5391 (41.2)	88675 (100)	17 (0)	17 (0.1)	0 (0)	88675 (2.6)

Supplement table 5: Primary diagnosis on death certificate for deceased patients

Table shows the top 10 most frequent primary diagnosis on the death certificate for individuals dying with or without a COVID-19 diagnosis. After removal of duplicates and missing; 125,869 primary diagnosis was found for the 123,648 individuals with COVID-19 on the death certificate, and 12,569 primary diagnosis for the 12,547 dying without COVID-19 on the death certificate within 28 days of a COVID-19 event.

COVID on the death certificate			Without COVID on the death certificate		
ICD10	Description	N (%)	ICD10	Description	N (%)
U071	COVID-19 Confirmed	109603 (87.5%)	F03	Unspecified dementia	890 (6.8%)
U072	COVID-19 Suspected	3514 (2.8%)	J189	Pneumonia	710 (5.4%)
F03	Unspecified dementia	1218 (1%)	C349	Cancer of bronchus and lung	659 (5%)
I259	Chronic ischemic heart disease	709 (0.6%)	J440	COPD	443 (3.4%)
C349	Cancer of bronchus and lung	685 (0.5%)	I259	Chronic ischemic heart disease	436 (3.3%)
G309	Alzheimer's disease	643 (0.5%)	I64	Stroke	421 (3.2%)
I64	Stroke	639 (0.5%)	G309	Alzheimer's disease	388 (3%)
I219	Acute myocardial infarction	531 (0.4%)	I219	Acute myocardial infarction	361 (2.8%)
F019	Dementia	499 (0.4%)	F019	Dementia	309 (2.4%)
J440	COPD	314 (0.3%)	C61	Malignant neoplasm of prostate	283 (2.2%)