

Supplemental File

Frailty and comorbidity in predicting community COVID-19 mortality in the UK Biobank: the effect of sampling

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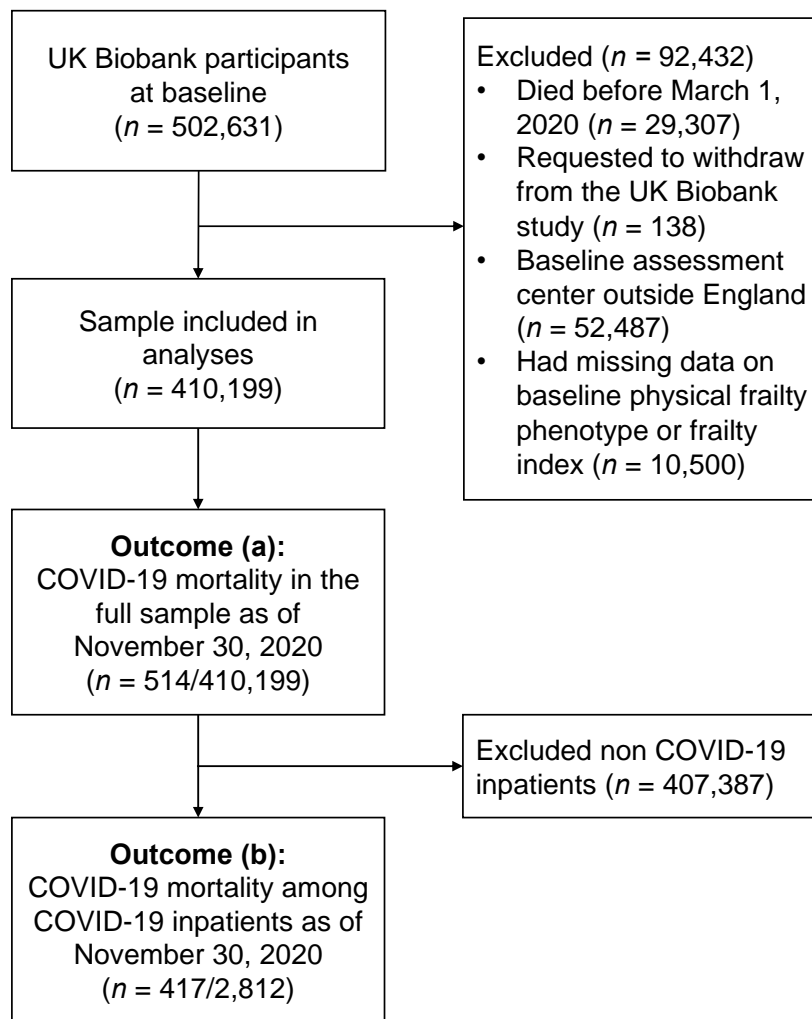
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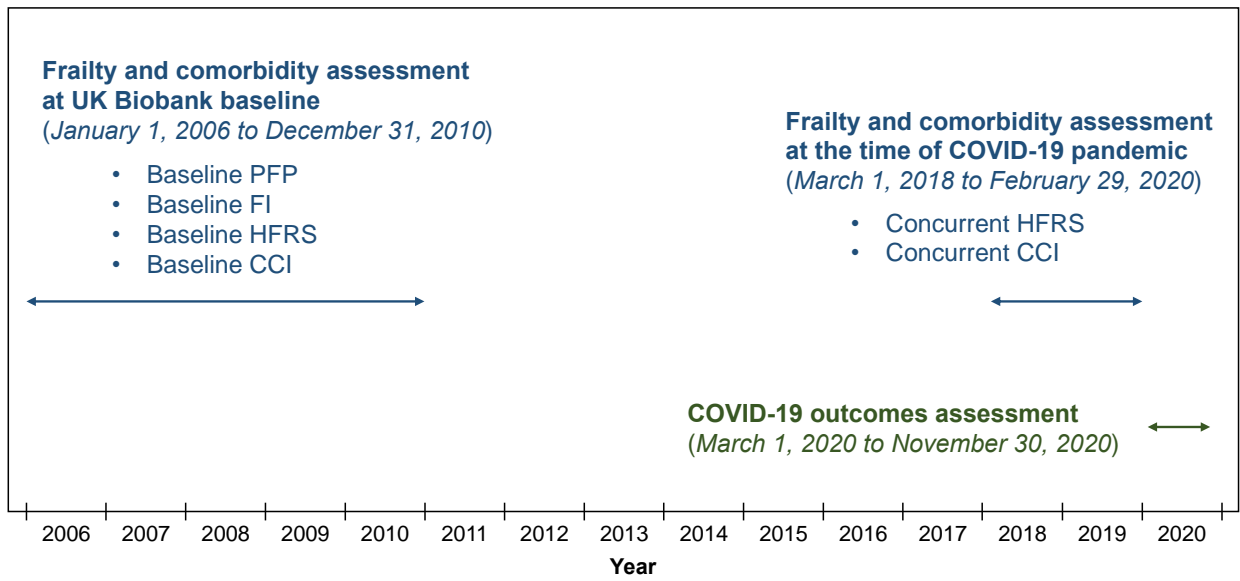
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Supplementary Figure S1. Flowchart of selection of the study samples from the UK Biobank



Supplementary Figure S2. Assessment timeline in the UK Biobank

Abbreviations: *CCI*, Charlson Comorbidity Index; *FI*, frailty index; *HFRS*, Hospital Frailty Risk Score; *PFP*, physical frailty phenotype

Supplementary Table S1. List of the five frailty criteria for construction of the physical frailty phenotype

Frailty criteria	Measurement	Scoring
Weight loss	Self-reported question: “Compared with one year ago, has your weight changed?”	Yes, lost weight=1; other=0
Exhaustion	Self-reported question: “Over the past two weeks, how often have you felt tired or had little energy?”	More than half the days or nearly every day=1; other=0
Slowness	Self-reported question: “How would you describe your usual walking pace?”	Slow=1; other=0
Low physical activity	Self-reported physical activity questionnaire, categorized into 4 levels: (i) none – no physical activity in the last 4 weeks (ii) low – light DIY activity (e.g., pruning, watering the lawn) only in the last 4 weeks (iii) medium – heavy DIY activity (e.g., weeding, lawn mowing, carpentry and digging), walking for pleasure, or other exercises in the last 4 weeks (iv) high – strenuous sports in the last 4 weeks	None or light activity with a frequency of once per week or less=1; medium or heavy activity, or light activity more than once per week=0
Weakness	Measured grip strength	Sex and body mass index (BMI) adjusted cutoffs: <u>Men:</u> ≤29 kg for BMI ≤24; ≤30 kg for BMI 24.1–26; ≤30 kg for BMI 26.1–28; or ≤32 kg for BMI >28 <u>Women:</u> ≤17 kg for BMI ≤23; ≤17.3 kg for BMI 23.1–26; ≤18 kg for BMI 26.1–29; or ≤21 kg for BMI >29

Supplementary Table S2. List of the 49 frailty items and scoring for construction of the frailty index

#	Frailty item	Scoring
1	Glaucoma	No=0; Yes=1
2	Cataracts	No=0; Yes=1
3	Hearing difficulty	No=0; Yes/completely deaf=1
4	Migraine	No=0; Yes=1
5	Dental problems (ulcers, painful gums, bleeding gums, loose teeth, toothache, dentures)	None=0; Any=1
6	Self-rated health	Excellent=0; Good=0.25; Fair=0.5; Poor=1
7	Fatigue: frequency of tiredness/lethargy in last two weeks	Not at all=0; Several days=0.25; More than half=0.5; Nearly every day=1
8	Sleep: experience of sleeplessness/insomnia	Never/rarely=0; Sometimes=0.5; Usually=1
9	Depressed feelings: frequency in last two weeks	Not at all=0; Several days=0.5; More than half=0.75; Nearly every day=1
10	Self-described nervous personality	No=0; Yes=1
11	Severe anxiety/panic attacks	No=0; Yes=1
12	Common to feel loneliness	No=0; Yes=1
13	Sense of misery (ever/never)	No=0; Yes=1
14	Infirmity: long-standing illness or disability	No=0; Yes=1
15	Falls in last year	No falls=0; one fall=0.5; more than one=1
16	Fractures/broken bones in last five years	No=0; Yes=1
17	Diabetes	No=0; Yes=1
18	Myocardial infarction	No=0; Yes=1
19	Angina	No=0; Yes=1
20	Stroke	No=0; Yes=1
21	High blood pressure	No=0; Yes=1
22	Hypothyroidism	No=0; Yes=1
23	Deep-vein thrombosis	No=0; Yes=1
24	High cholesterol	No=0; Yes=1
25	Breathing: wheeze in last year	No=0; Yes=1
26	Pneumonia	No=0; Yes=1
27	Chronic bronchitis/emphysema	No=0; Yes=1
28	Asthma	No=0; Yes=1
29	Rheumatoid arthritis	No=0; Yes=1
30	Osteoarthritis	No=0; Yes=1
31	Gout	No=0; Yes=1
32	Osteoporosis	No=0; Yes=1
33	Hay fever, allergic rhinitis or eczema	No=0; Yes=1
34	Psoriasis	No=0; Yes=1
35	Any cancer diagnosis	No=0; Yes=1
36	Multiple cancers diagnosed	No/single cancer=0; Multiple cancers=1
37	Chest pain	No=0; Yes=1
38	Head and/or neck pain	No=0; Yes=1
39	Back pain	No=0; Yes=1
40	Stomach/abdominal pain	No=0; Yes=1
41	Hip pain	No=0; Yes=1
42	Knee pain	No=0; Yes=1
43	Whole-body pain	No=0; Yes=1
44	Facial pain	No=0; Yes=1
45	Sciatica	No=0; Yes=1
46	Gastric reflux	No=0; Yes=1
47	Hiatus hernia	No=0; Yes=1
48	Gall stones	No=0; Yes=1
49	Diverticulitis	No=0; Yes=1

Supplementary Table S3. List of the 109 ICD-10 codes and assigned weights for construction of the Hospital Frailty Risk Score

#	ICD-10 code	Description	Weight
1	F00	Dementia in Alzheimer's disease	7.1
2	G81	Hemiplegia	4.4
3	G30	Alzheimer's disease	4.0
4	I69	Sequelae of cerebrovascular disease (secondary codes)	3.7
5	R29	Other symptoms and signs involving the nervous and musculoskeletal systems (R29.6 Tendency to fall)	3.6
6	N39	Other disorders of urinary system (includes urinary tract infection and urinary incontinence)	3.2
7	F05	Delirium, not induced by alcohol and other psychoactive substances	3.2
8	W19	Unspecified fall	3.2
9	S00	Superficial injury of head	3.2
10	R31	Unspecified hematuria	3.0
11	B96	Other bacterial agents as the cause of diseases classified to other chapters (secondary code)	2.9
12	R41	Other symptoms and signs involving cognitive functions and awareness	2.7
13	R26	Abnormalities of gait and mobility	2.6
14	I67	Other cerebrovascular diseases	2.6
15	R56	Convulsions, not elsewhere classified	2.6
16	R40	Somnolence, stupor and coma	2.5
17	T83	Complications of genitourinary prosthetic devices, implants and grafts	2.4
18	S06	Intracranial injury	2.4
19	S42	Fracture of shoulder and upper arm	2.3
20	E87	Other disorders of fluid, electrolyte and acid- base balance	2.3
21	M25	Other joint disorders, not elsewhere classified	2.3
22	E86	Volume depletion	2.3
23	R54	Senility	2.2
24	Z50	Care involving use of rehabilitation procedures	2.1
25	F03	Unspecified dementia	2.1
26	W18	Other fall on same level	2.1
27	Z75	Problems related to medical facilities and other health care	2.0
28	F01	Vascular dementia	2.0
29	S80	Superficial injury of lower leg	2.0
30	L03	Cellulitis	2.0
31	H54	Blindness and low vision	1.9
32	E53	Deficiency of other B group vitamins	1.9
33	Z60	Problems related to social environment	1.8
34	G20	Parkinson's disease	1.8
35	R55	Syncope and collapse	1.8
36	S22	Fracture of rib(s), sternum and thoracic spine	1.8
37	K59	Other functional intestinal disorders	1.8
38	N17	Acute renal failure	1.8
39	L89	Decubitus ulcer	1.7
40	Z22	Carrier of infectious disease	1.7
41	B95	Streptococcus and staphylococcus as the cause of diseases classified to other chapters	1.7
42	L97	Ulcer of lower limb, not elsewhere classified	1.6
43	R44	Other symptoms and signs involving general sensations and perceptions	1.6
44	K26	Duodenal ulcer	1.6
45	I95	Hypotension	1.6
46	N19	Unspecified renal failure	1.6
47	A41	Other septicemia	1.6
48	Z87	Personal history of other diseases and conditions	1.5
49	J96	Respiratory failure, not elsewhere classified	1.5
50	X59	Exposure to unspecified factor	1.5
51	M19	Other arthrosis	1.5
52	G40	Epilepsy	1.5
53	M81	Osteoporosis without pathological fracture	1.4

Supplementary Table S3. (continued)

#	ICD-10 code	Description	Weight
54	S72	Fracture of femur	1.4
55	S32	Fracture of lumbar spine and pelvis	1.4
56	E16	Other disorders of pancreatic internal secretion	1.4
57	R94	Abnormal results of function studies	1.4
58	N18	Chronic renal failure	1.4
59	R33	Retention of urine	1.3
60	R69	Unknown and unspecified causes of morbidity	1.3
61	N28	Other disorders of kidney and ureter, not elsewhere classified	1.3
62	R32	Unspecified urinary incontinence	1.2
63	G31	Other degenerative diseases of nervous system, not elsewhere classified	1.2
64	Y95	Nosocomial condition	1.2
65	S09	Other and unspecified injuries of head	1.2
66	R45	Symptoms and signs involving emotional state	1.2
67	G45	Transient cerebral ischemic attacks and related syndromes	1.2
68	Z74	Problems related to care-provider dependency	1.1
69	M79	Other soft tissue disorders, not elsewhere classified	1.1
70	W06	Fall involving bed	1.1
71	S01	Open wound of head	1.1
72	A04	Other bacterial intestinal infections	1.1
73	A09	Diarrhea and gastroenteritis of presumed infectious origin	1.1
74	J18	Pneumonia, organism unspecified	1.1
75	J69	Pneumonitis due to solids and liquids	1.0
76	R47	Speech disturbances, not elsewhere classified	1.0
77	E55	Vitamin D deficiency	1.0
78	Z93	Artificial opening status	1.0
79	R02	Gangrene, not elsewhere classified	1.0
80	R63	Symptoms and signs concerning food and fluid intake	0.9
81	H91	Other hearing loss	0.9
82	W10	Fall on and from stairs and steps	0.9
83	W01	Fall on same level from slipping, tripping and stumbling	0.9
84	E05	Thyrotoxicosis [hyperthyroidism]	0.9
85	M41	Scoliosis	0.9
86	R13	Dysphagia	0.8
87	Z99	Dependence on enabling machines and devices	0.8
88	U80	Agent resistant to penicillin and related antibiotics	0.8
89	M80	Osteoporosis with pathological fracture	0.8
90	K92	Other diseases of digestive system	0.8
91	I63	Cerebral Infarction	0.8
92	N20	Calculus of kidney and ureter	0.7
93	F10	Mental and behavioral disorders due to use of alcohol	0.7
94	Y84	Other medical procedures as the cause of abnormal reaction of the patient	0.7
95	R00	Abnormalities of heartbeat	0.7
96	J22	Unspecified acute lower respiratory infection	0.7
97	Z73	Problems related to life-management difficulty	0.6
98	R79	Other abnormal findings of blood chemistry	0.6
99	Z91	Personal history of risk-factors, not elsewhere classified	0.5
100	S51	Open wound of forearm	0.5
101	F32	Depressive episode	0.5
102	M48	Spinal stenosis (secondary code only)	0.5
103	E83	Disorders of mineral metabolism	0.4
104	M15	Polyarthritis	0.4
105	D64	Other anemias	0.4
106	L08	Other local infections of skin and subcutaneous tissue	0.4
107	R11	Nausea and vomiting	0.3
108	K52	Other noninfective gastroenteritis and colitis	0.3
109	R50	Fever of unknown origin	0.1

Abbreviation: *ICD-10*, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision

Supplementary Table S4. List of the 17 comorbidities, assigned weights and associated ICD-10 codes for construction of Charlson Comorbidity Index

#	Condition	ICD-10 code	Weight
1	Myocardial infarction	I21, I22, I25.2	1
2	Congestive heart failure	I50	1
3	Peripheral vascular disease	I71, I73.9, I79.0, R02, Z95.8, Z95.9	1
4	Cerebral vascular disease	G45, G46, I60–I64, I67–I69	1
5	Dementia	F00–F02, F05.1	1
6	Pulmonary disease	J40–J47, J60–J67	1
7	Connective tissue disorder	M05, M06, M32–M34, M35.3	1
8	Peptic ulcer	K25–K28	1
9	Liver disease	K70.2, K70.3, K71.7, K73, K74	1
10	Diabetes	E10–E14, excluding subdivisions 2–5	1
11	Diabetes complications	E10–E14, subdivisions 2–5	2
12	Paraplegia	G04.1, G81, G82	2
13	Renal disease	N01, N03, N18, N19, N25, N05.2–N05.6, N07.2–N07.4,	2
14	Cancer	C00–C41, C43, C45–C76, C81–C85, C88, C90–C97	2
15	Metastatic cancer	C77–C80	3
16	Severe liver disease	K72.1, K72.9, K76.6, K76.7	3
17	Acquired immune deficiency syndrome	B20–B24	6

Abbreviations: *ICD-10*, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision

Supplementary Table S5. Characteristics of individuals with and without hospital data

Characteristic	With hospital data (n=354,268)	Without hospital data ^a (n=55,931)	<i>p</i> ^b
Deaths, n (%)	3,144 (0.9)	42 (0.1)	<0.001
Age (year), mean \pm SD	68.0 \pm 8.1	65.0 \pm 7.7	<0.001
Age category, n (%)			<0.001
<65	124,902 (35.3)	27,749 (49.6)	
65–74	147,627 (41.7)	22,021 (39.4)	
\geq 75	81,739 (23.1)	6,161 (11.0)	
Sex, n (%)			<0.001
Female	197,432 (55.7)	28,586 (51.1)	
Male	156,836 (44.3)	27,345 (48.9)	
Ethnicity, n (%)			<0.001
White	333,290 (94.4)	52,067 (93.4)	
Asian	8,185 (2.3)	1,546 (2.8)	
Black	6,197 (1.8)	1,080 (1.9)	
Others	5,400 (1.5)	1,041 (1.9)	
Smoking status, n (%)			<0.001
Never	192,891 (54.6)	34,685 (62.2)	
Previous	124,964 (35.4)	16,235 (29.1)	
Current	35,142 (10.0)	4,869 (8.7)	
Education, n (%)			<0.001
Low	60,138 (17.2)	5,155 (9.3)	
Intermediate	179,642 (51.2)	27,362 (49.3)	
High	110,910 (31.6)	22,992 (41.4)	
Income, n (%)			<0.001
<£18,000	69,392 (23.0)	6,766 (13.7)	
£18,000–30,999	78,696 (26.0)	10,408 (21.1)	
£31,000–51,999	79,159 (26.2)	13,808 (28.0)	
\geq £52,000	75,079 (24.8)	18,300 (37.1)	
Townsend deprivation quintile, n (%)			<0.001
1 (least deprived)	70,422 (19.9)	11,934 (21.4)	
2	72,140 (20.4)	11,604 (20.8)	
3	71,409 (20.2)	11,259 (20.2)	
4	70,930 (20.0)	11,172 (20.0)	
5 (most deprived)	68,960 (19.5)	9,890 (17.7)	
Baseline PFP, n (%)			<0.001
Non-frail	200,997 (56.7)	37,644 (67.3)	
Pre-frail	140,037 (39.5)	17,676 (31.6)	
Frail	13,234 (3.7)	611 (1.1)	
Baseline FI, n (%)			<0.001
Relatively fit	18,262 (5.2)	6,742 (12.1)	
Less fit	127,287 (35.9)	29,051 (51.9)	
Least fit	162,490 (45.9)	18,523 (33.1)	
Frail	46,229 (13.1)	1,615 (2.9)	

^a Resided in England at baseline and without hospital data between 1980 and 2020

^b Based on t-tests for continuous variables and χ^2 -tests for categorical variables

Abbreviations: *FI*, frailty index; *PFP*, physical frailty phenotype; *SD*, standard deviation

Supplementary Table S6. Spearman’s rank correlation coefficients among different frailty and comorbidity measures

Variable	Baseline PFP	Baseline FI	Baseline HFRS	Baseline CCI	Concurrent HFRS	Concurrent CCI
Baseline PFP ^{a,b}	1					
Baseline FI ^b	0.338*	1				
Baseline HFRS ^b	0.131*	0.213*	1			
Baseline CCI ^b	0.132*	0.235*	0.326*	1		
Concurrent HFRS ^b	0.120*	0.199*	0.161*	0.139*	1	
Concurrent CCI ^b	0.128*	0.224*	0.143*	0.229*	0.551*	1

^a PFP is considered as a continuous variable of the total score across the five criteria (score ranges from 0 to 5)

^b Baseline PFP, FI, HFRS, and CCI were calculated using data at the UK Biobank baseline, and concurrent HFRS and CCI using data at the time of the COVID-19 pandemic

* $p < 0.001$

Abbreviations: *CCI*, Charlson Comorbidity Index; *FI*, frailty index; *HFRS*, hospital frailty risk score; *PFP*, physical frailty phenotype

Supplementary Table S7. Associations of the different frailty and comorbidity measures with being COVID-19 positive and COVID-19 inpatient

Model ^a		COVID-19 positive OR (95% CI)	COVID-19 inpatient OR (95% CI)
Baseline PFP ^b	Non-frail	1	1
	Pre-frail	1.25 (1.19–1.31)*	1.57 (1.45–1.70)*
	Frail	1.96 (1.77–2.17)*	3.67 (3.20–4.20)*
Baseline FI ^b	Relatively fit	1	1
	Less fit	1.11 (0.99–1.23)	1.43 (1.14–1.79)*
	Least fit	1.35 (1.22–1.50)*	2.19 (1.75–2.74)*
	Frail	2.05 (1.82–2.30)*	4.49 (3.57–5.66)*
Baseline HFRS ^b	Low risk	1	1
	Intermediate risk	1.91 (1.67–2.19)*	2.94 (2.48–3.48)*
	High risk	3.43 (2.00–5.89)*	7.16 (4.00–12.82)*
Baseline CCI ^b	Continuous	1.23 (1.20–1.27)*	1.41 (1.36–1.46)*
Concurrent HFRS ^b	Low risk	1	1
	Intermediate risk	2.23 (2.03–2.45)*	3.84 (3.41–4.31)*
	High risk	9.02 (8.10–10.04)*	15.25 (13.45–17.30)*
Concurrent CCI ^b	Continuous	1.30 (1.28–1.32)*	1.47 (1.44–1.50)*

^a All models were adjusted for age (continuous) and sex

^b Baseline PFP, FI, HFRS, and CCI were calculated using data at the UK Biobank baseline, and concurrent HFRS and CCI using data at the time of the COVID-19 pandemic

* Significant with a false discovery rate corrected significance level at 0.048

Abbreviations: *CCI*, Charlson Comorbidity Index; *CI*, confidence interval; *FI*, frailty index; *HFRS*, Hospital Frailty Risk Score; *OR*, odds ratio; *PFP*, physical frailty phenotype

Supplementary Table S8. Predictive accuracies of age, sex, frailty and comorbidity measures for COVID-19 mortality in the full sample and COVID-19 inpatients

Model	Full sample (n=410,199)			COVID-19 inpatients (n=2,812) ^a		
	AUC (95% CI)	% diff. with model 1	<i>p</i> ^b	AUC (95% CI)	% diff. with model 1	<i>p</i> ^b
1 Age + sex	0.77 (0.76–0.79)	-	-	0.71 (0.69–0.74)	-	-
2 Age + sex + baseline PFP ^c	0.79 (0.77–0.81)	+1.6%	<0.001	0.71 (0.69–0.74)	+0.1%	0.61
3 Age + sex + baseline FI ^c	0.79 (0.78–0.81)	+2.0%	<0.001	0.71 (0.69–0.74)	+0.1%	0.63
4 Age + sex + baseline HFRS ^c	0.78 (0.76–0.80)	+0.4%	0.019	0.71 (0.69–0.74)	+0.2%	0.33
5 Age + sex + baseline CCI ^c	0.79 (0.77–0.81)	+1.4%	<0.001	0.72 (0.69–0.74)	+0.2%	0.11
6 Age + sex + concurrent HFRS ^c	0.83 (0.81–0.85)	+5.2%	<0.001	0.72 (0.69–0.74)	+0.5%	0.16
7 Age + sex + concurrent CCI ^c	0.83 (0.82–0.85)	+6.0%	<0.001	0.73 (0.71–0.75)	+1.6%	0.004

^a The COVID-19 inpatient subsample is nested within the full sample

^b *p*-values for pairwise comparisons with model 1

^c Baseline PFP, FI, HFRS, and CCI were calculated using data at the UK Biobank baseline, and concurrent HFRS and CCI using data at the time of the COVID-19 pandemic

Abbreviations: *AUC*, area under the receiver operating characteristic curves; *CCI*, Charlson Comorbidity Index; *CI*, confidence interval; *FI*, frailty index; *HFRS*, Hospital Frailty Risk Score; *PFP*, physical frailty phenotype

Supplementary Table S9. Associations of the different frailty and comorbidity measures with mortality due to COVID-19 and other causes in the full sample and COVID-19 inpatients

Model ^a		Full sample (n=410,199)		COVID-19 inpatients (n=2,812) ^b	
		COVID-19 mortality OR (95% CI)	Other deaths ^c OR (95% CI)	COVID-19 mortality OR (95% CI)	Other deaths ^c OR (95% CI)
Baseline PFP ^d	Non-frail	1	1	1	1
	Pre-frail	1.69 (1.40–2.03)*	1.39 (1.28–1.50)*	1.07 (0.85–1.35)	1.23 (0.83–1.84)
	Frail	4.37 (3.24–5.90)*	3.02 (2.62–3.49)*	1.35 (0.94–1.96)	1.26 (0.65–2.44)
Baseline FI ^d	Relatively fit	1	1	1	1
	Less fit	1.64 (0.89–3.04)	1.08 (0.88–1.34)	1.06 (0.50–2.27)	0.48 (0.17–1.32)
	Least fit	2.33 (1.27–4.28)*	1.43 (1.16–1.76)*	0.95 (0.45–2.00)	0.56 (0.21–1.46)
	Frail	5.27 (2.85–9.74)*	2.26 (1.82–2.80)*	1.25 (0.59–2.67)	0.57 (0.21–1.54)
Baseline HFRS ^d	Low risk	1	1	1	1
	Intermediate risk	2.22 (1.48–3.32)*	2.50 (2.10–2.97)*	0.72 (0.43–1.21)	1.16 (0.55–2.46)
	High risk	5.12 (1.26–20.79)*	4.21 (2.06–8.59)*	0.49 (0.06–3.93)	No observation
Baseline CCI ^d	Continuous	1.47 (1.36–1.58)*	1.42 (1.37–1.47)*	1.18 (1.06–1.31)*	0.89 (0.70–1.14)
Concurrent HFRS ^d	Low risk	1	1	1	1
	Intermediate risk	5.41 (4.29–6.83)*	7.86 (7.14–8.65)*	1.64 (1.21–2.21)*	2.41 (1.48–3.92)*
	High risk	24.17 (19.24–30.35)*	24.82 (22.23–27.72)*	1.53 (1.13–2.08)*	2.62 (1.63–4.22)*
Concurrent CCI ^d	Continuous	1.64 (1.58–1.70)*	1.85 (1.82–1.88)*	1.21 (1.14–1.27)*	1.32 (1.22–1.42)*

^a Associations were assessed using multinomial logistic regression models, in which “COVID-19 mortality” and “other deaths” were compared to those who were alive as of November 30, 2020. All models were adjusted for age (continuous) and sex

^b The COVID-19 inpatient subsample is nested within the full sample

^c Other deaths are individuals died between March 1 and November 30, 2020 whose primary and contributory causes of death do not include COVID-19

^d Baseline PFP, FI, HFRS, and CCI were calculated using data at the UK Biobank baseline, and concurrent HFRS and CCI using data at the time of the COVID-19 pandemic

* Significant with a false discovery rate corrected significance level at 0.031

Abbreviations: *CCI*, Charlson Comorbidity Index; *CI*, confidence interval; *FI*, frailty index; *HFRS*, Hospital Frailty Risk Score; *OR*, odds ratio; *PFP*, physical frailty phenotype