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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Nab L, Parker EPK, Andrews CD, et al. Changes in COVID-19-related mortality across key demographic and clinical subgroups in England from 2020 to 2022: a retrospective cohort study using the OpenSAFELY platform. *Lancet Public Health* 2023; **8**: e364–77.

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Methods

Waves

Start and end dates of the first two pandemic waves were determined on the basis of infection incidence estimates published by the Office for National Statistics [1]. Of note, we refer to wave 2 as wave 2 (alpha) as the alpha variant was dominant in all but the first 3 months of wave 2 [2]. The start date of the third pandemic wave (May 28, 2021) was determined based on the day that the reported reproduction value was above 1 (1.0-1.1) and growth rates in England were positive (0-3). The end date of the third pandemic wave and start date of the fourth pandemic wave (14 December 2021 and 15 December 2021, respectively) was chosen as omicron became nationally dominant after this date [3]. The end date of the omicron wave (29 April 2022) was chosen because reported reproduction values and growth rates were below 1 and negative, respectively, for more than two months following that date. The start date and end date of wave 5 were chosen following the same rules [1].

Subgroups

We included age (grouped as 18-39, 40-49, 50-59, 60-69, 70-79 and ≥ 80 years for descriptive analysis), sex, ethnicity (White, Mixed, South Asian, Black, Other, Unknown), body mass index (BMI; categorised as not obese, class I [BMI 30-34.9kg/m²], II [35-39.9kg/m²], III [≥ 40 kg/m²]), smoking status (never, former, current), and IMD quintile (derived from the patient's postcode at lower super output area level). We also considered the following comorbidities: high blood pressure (systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90) or diagnosed hypertension, chronic respiratory diseases other than asthma, asthma (categorised as with or without recent use of oral steroids), chronic cardiac disease, diabetes (categorised according to the most recent glycated haemoglobin [HbA1c] recorded in the 15 months prior to the first day of the pandemic wave), non-haematological and haematological cancer, chronic kidney disease [CKD] or renal replacement therapy [RRT] (categorised based on estimated glomerular filtration rates of ≥ 60 [absent], < 60 and ≥ 45 [stage 3a], < 45 and ≥ 30 [stage 3b], < 30 and ≥ 15 [stage 4], and < 15 [stage 5] ml/min/1.73 m² using the most recent serum creatinine level recorded in the last 2 years prior to the first day of the pandemic wave, respectively, or diagnostic codes indicative of dialysis and kidney transplant), chronic liver disease, stroke, dementia, other neurological disease (motor neurone disease, myasthenia gravis, multiple sclerosis, Parkinson's disease, cerebral palsy, quadriplegia or hemiplegia, and progressive cerebellar disease), organ transplant (categorised as kidney transplant or other organ transplant), asplenia (splenectomy or a spleen dysfunction, including sickle cell disease), rheumatoid arthritis/lupus/psoriasis, learning disability, severe mental illness, and other immunosuppressive conditions. STP of the patient's general practice was included as a covariate to adjust for geographical variation in infection rates across the country.

Results

Participant selection

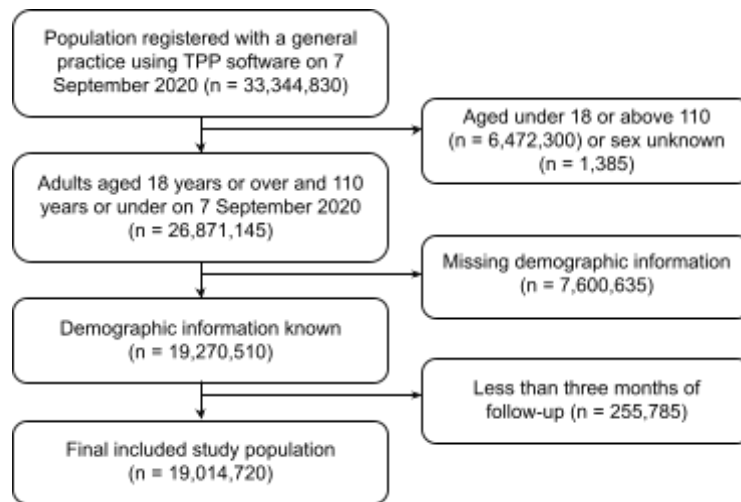


Figure S1. This diagram shows the number of people (n) excluded at different stages of cohort selection covering the second pandemic wave (7 September 2020 - 24 April 2021). All counts were rounded to the nearest five and may therefore not add up.

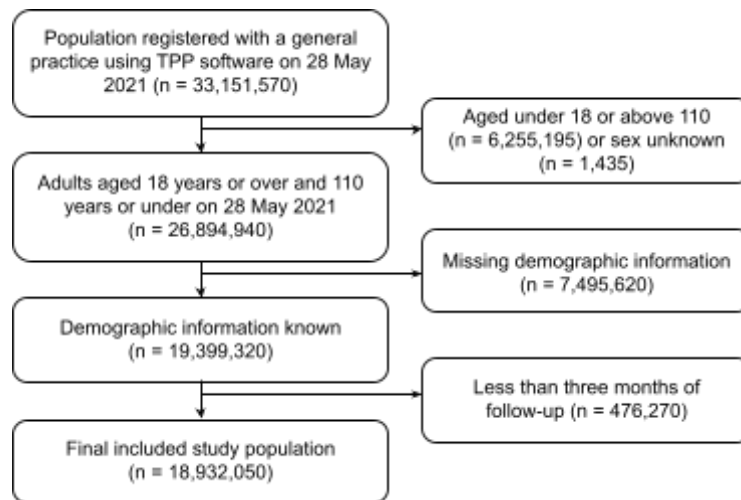


Figure S2. This diagram shows the number of people (n) excluded at different stages of cohort selection covering the third (delta) pandemic wave (28 May 2021 - 14 December 2021). All counts were rounded to the nearest five and may therefore not add up.

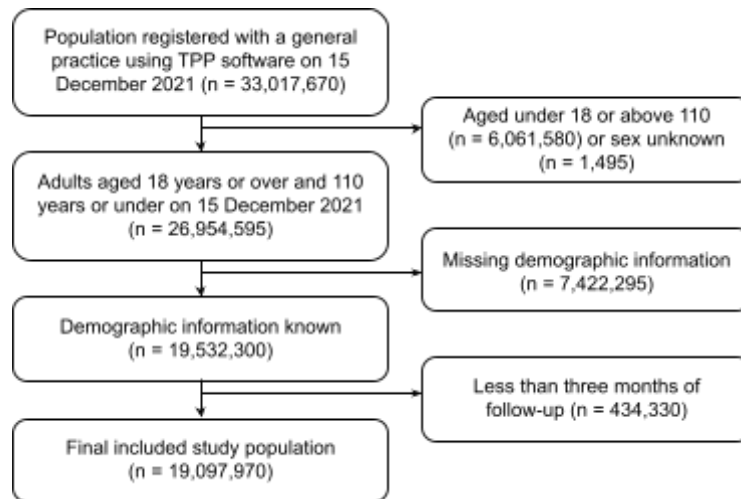


Figure S3. This diagram shows the number of people (*n*) excluded at different stages of cohort selection covering the third (omicron) pandemic wave (15 December 2021 - 29 April 2022). All counts were rounded to the nearest five and may therefore not add up.

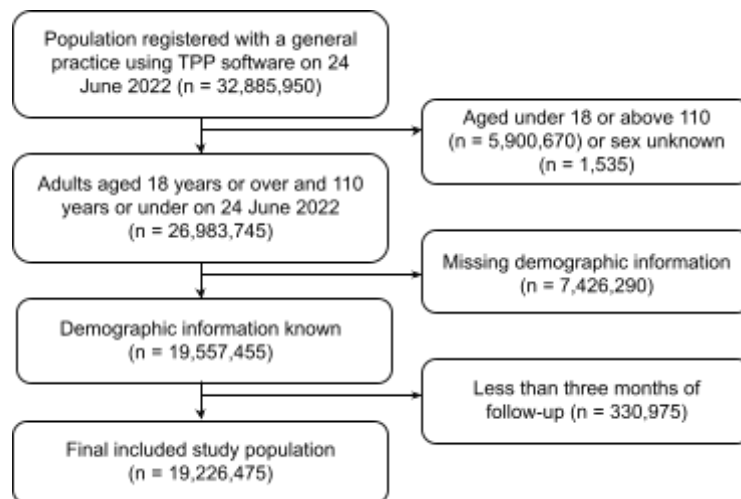


Figure S4. This diagram shows the number of people (*n*) excluded at different stages of cohort selection covering the fourth pandemic wave (24 June 2022 - 3 August 2022). All counts were rounded to the nearest five and may therefore not add up.

Absolute rate of death

Crude death rate

Table S1. Crude COVID-19-related death rates and 95% confidence intervals in OpenSAFELY-TPP, stratified by demographic and clinical subgroups in the first five pandemic waves in England (wave 1: March 23 to May 30, 2020; wave 2 (alpha): September 7, 2020 to April 24, 2021; wave 3 (delta): May 28 to December 14, 2021; wave 4 (omicron): December 15, 2021 to April 29, 2022; and wave 5: June 24 to August 3, 2022).

Subgroup	Category	Wave 1 (WT)		Wave 2 (alpha)		Wave 3 (delta)		Wave 4 (omicron)		Wave 5 (omicron)	
		Events (1000 person-years)*	Death rate per 1000 person-years	Events (1000 person-years)*	Death rate per 1000 person-years	Events (1000 person-years)*	Death rate per 1000 person-years	Events (1000 person-years)*	Death rate per 1000 person-years	Events (1000 person-years)*	Death rate per 1000 person-years
All	-	15,725 (3,512.4)	4.48 (4.41;4.55)	31,975 (11,875.4)	2.69 (2.66;2.72)	6,635 (10,337.2)	0.64 (0.63;0.66)	7,110 (7,043.6)	1.01 (0.99;1.03)	1,420 (2,104.4)	0.67 (0.64;0.71)
Age Group	18-39	65 (1,252.1)	0.05 (0.04;0.06)	210 (4,226.9)	0.05 (0.04;0.06)	155 (3,649.3)	0.04 (0.04;0.05)	80 (2,480.5)	0.03 (0.03;0.04)	15 (744)	0.02 (0.01;0.03)
	40-49	200 (572.7)	0.35 (0.3;0.4)	485 (1,936.7)	0.25 (0.23;0.27)	265 (1,674.9)	0.16 (0.14;0.18)	115 (1,140.8)	0.1 (0.08;0.12)	15 (338)	0.04 (0.02;0.07)
	50-59	665 (608.7)	1.09 (1.01;1.18)	1,550 (2,063)	0.75 (0.71;0.79)	590 (1,803.6)	0.33 (0.3;0.35)	335 (1,226.5)	0.27 (0.24;0.3)	55 (363.1)	0.15 (0.11;0.19)
	60-69	1,435 (475.3)	3.02 (2.86;3.18)	3,380 (1,615.9)	2.09 (2.02;2.16)	1,015 (1,423.5)	0.71 (0.67;0.76)	660 (975)	0.68 (0.63;0.73)	135 (292.7)	0.46 (0.38;0.54)
	70-79	3,560 (383.1)	9.29 (8.99;9.6)	7,505 (1,300.7)	5.77 (5.64;5.9)	1,710 (1,148.8)	1.49 (1.42;1.56)	1,550 (784.1)	1.98 (1.88;2.08)	315 (234.5)	1.34 (1.19;1.49)
	80 plus	9,795 (220.5)	44.41 (43.53;45.29)	18,850 (732.1)	25.75 (25.38;26.12)	2,895 (637.1)	4.54 (4.38;4.71)	4,370 (436.7)	10.01 (9.71;10.3)	885 (132.1)	6.7 (6.26;7.14)
Sex	Female	7,095 (1,765.4)	4.02 (3.93;4.11)	14,755 (5,963.9)	2.47 (2.43;2.51)	2,680 (5,195.8)	0.52 (0.5;0.54)	3,160 (3,527.4)	0.9 (0.86;0.93)	655 (1,053.4)	0.62 (0.57;0.67)
	Male	8,625 (1,747.1)	4.94 (4.83;5.04)	17,225 (5,911.5)	2.91 (2.87;2.96)	3,955 (5,141.4)	0.77 (0.75;0.79)	3,950 (3,516.2)	1.12 (1.09;1.16)	765 (1,051.1)	0.73 (0.68;0.78)
Ethnicity	White	14,035 (2,798.5)	5.02 (4.93;5.1)	28,605 (9,429.5)	3.03 (3;3.07)	5,750 (8,180.4)	0.7 (0.68;0.72)	6,580 (5,547.6)	1.19 (1.16;1.21)	1,325 (1,646.7)	0.8 (0.76;0.85)
	Mixed	95 (42.4)	2.24 (1.79;2.69)	175 (145.8)	1.2 (1.02;1.38)	45 (129.6)	0.35 (0.25;0.45)	40 (90.1)	0.44 (0.31;0.58)	[REDACTED]	[REDACTED]
	South Asian	780 (231.4)	3.37 (3.13;3.61)	1,900 (794.5)	2.39 (2.28;2.5)	465 (704)	0.66 (0.6;0.72)	225 (488.1)	0.46 (0.4;0.52)	50 (149.5)	0.33 (0.24;0.43)
	Black	345 (78.7)	4.39 (3.92;4.85)	510 (269.8)	1.89 (1.73;2.05)	165 (239.1)	0.69 (0.58;0.8)	110 (165.3)	0.67 (0.54;0.79)	10 (50.7)	0.2 (0.07;0.32)
	Other	170 (80.5)	2.11 (1.79;2.43)	265 (275.2)	0.96 (0.85;1.08)	90 (243.7)	0.37 (0.29;0.45)	50 (171.3)	0.29 (0.21;0.37)	10 (53.4)	0.19 (0.07;0.3)
	Unknown	300 (281)	1.07 (0.95;1.19)	515 (960.6)	0.54 (0.49;0.58)	120 (840.5)	0.14 (0.12;0.17)	105 (581.2)	0.18 (0.15;0.22)	20 (176.5)	0.11 (0.06;0.16)
Region	North East	930 (167.3)	5.56 (5.2;5.92)	1,815 (563.7)	3.22 (3.07;3.37)	485 (490)	0.99 (0.9;1.08)	385 (332.3)	1.16 (1.04;1.27)	70 (99.2)	0.71 (0.54;0.87)
	North West	1,885 (306.4)	6.15 (5.87;6.43)	3,025 (1,032.1)	2.93 (2.83;3.04)	740 (899.3)	0.82 (0.76;0.88)	695 (610.5)	1.14 (1.05;1.22)	135 (182.1)	0.74 (0.62;0.87)

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Subgroup	Category	Wave 1 (WT)		Wave 2 (alpha)		Wave 3 (delta)		Wave 4 (omicron)		Wave 5 (omicron)	
		Events (1000 person-years)*	Death rate per 1000 person-years	Events (1000 person-years)*	Death rate per 1000 person-years	Events (1000 person-years)*	Death rate per 1000 person-years	Events (1000 person-years)*	Death rate per 1000 person-years	Events (1000 person-years)*	Death rate per 1000 person-years
	Yorkshire and the Humber	2,290 (496.1)	4.62 (4.43;4.81)	4,285 (1,679.5)	2.55 (2.48;2.63)	1,165 (1,464.1)	0.8 (0.75;0.84)	1,025 (994.8)	1.03 (0.97;1.09)	210 (297.6)	0.71 (0.61;0.8)
	East Midlands	2,665 (612.8)	4.35 (4.18;4.51)	6,410 (2,067.4)	3.1 (3.02;3.18)	1,295 (1,796.7)	0.72 (0.68;0.76)	1,345 (1,222.1)	1.1 (1.04;1.16)	280 (366.3)	0.76 (0.67;0.85)
	West Midlands	905 (141.8)	6.38 (5.97;6.8)	1,725 (479.2)	3.6 (3.43;3.77)	340 (414.8)	0.82 (0.73;0.91)	295 (280.8)	1.05 (0.93;1.17)	65 (83.4)	0.78 (0.59;0.97)
	East of England	3,590 (811.8)	4.42 (4.28;4.57)	8,225 (2,748.6)	2.99 (2.93;3.06)	1,230 (2,389.7)	0.51 (0.49;0.54)	1,640 (1,623)	1.01 (0.96;1.06)	330 (481.1)	0.69 (0.61;0.76)
	London	1,040 (244.7)	4.25 (3.99;4.51)	1,375 (835.8)	1.65 (1.56;1.73)	305 (730.9)	0.42 (0.37;0.46)	295 (515.2)	0.57 (0.51;0.64)	55 (156.8)	0.35 (0.26;0.44)
	South East	850 (236.2)	3.6 (3.36;3.84)	1,985 (796.6)	2.49 (2.38;2.6)	360 (691.9)	0.52 (0.47;0.57)	410 (470.5)	0.87 (0.79;0.96)	75 (140.7)	0.53 (0.41;0.65)
	South West	1,565 (495.4)	3.16 (3;3.32)	3,130 (1,672.4)	1.87 (1.81;1.94)	720 (1,459.8)	0.49 (0.46;0.53)	1,020 (994.4)	1.03 (0.96;1.09)	195 (297.2)	0.66 (0.56;0.75)
IMD quintile	5 (least deprived)	2,555 (659.8)	3.87 (3.72;4.02)	5,250 (2,230.3)	2.35 (2.29;2.42)	945 (1,941.8)	0.49 (0.46;0.52)	1,155 (1,319.6)	0.88 (0.82;0.93)	250 (394.4)	0.63 (0.56;0.71)
	4	3,025 (726.6)	4.16 (4.01;4.31)	5,920 (2,456.2)	2.41 (2.35;2.47)	1,185 (2,139.5)	0.55 (0.52;0.59)	1,370 (1,459.5)	0.94 (0.89;0.99)	300 (436.1)	0.69 (0.61;0.77)
	3	3,190 (748.8)	4.26 (4.11;4.41)	6,630 (2,529.1)	2.62 (2.56;2.68)	1,245 (2,201.4)	0.57 (0.53;0.6)	1,495 (1,501.6)	1 (0.95;1.05)	290 (448.7)	0.65 (0.57;0.72)
	2	3,360 (698.6)	4.81 (4.65;4.97)	6,900 (2,361.9)	2.92 (2.85;2.99)	1,405 (2,055.5)	0.68 (0.65;0.72)	1,465 (1,402.5)	1.04 (0.99;1.1)	280 (420)	0.67 (0.59;0.74)
	1 (most deprived)	3,595 (678.7)	5.3 (5.12;5.47)	7,275 (2,297.9)	3.17 (3.09;3.24)	1,850 (1,998.9)	0.93 (0.88;0.97)	1,625 (1,360.3)	1.19 (1.14;1.25)	300 (405.3)	0.74 (0.66;0.82)
Body Mass Index	Not obese	12,085 (2,745.3)	4.4 (4.32;4.48)	23,665 (9,323.2)	2.54 (2.51;2.57)	4,385 (8,174.3)	0.54 (0.52;0.55)	5,645 (5,611)	1.01 (0.98;1.03)	1,140 (1,690)	0.67 (0.64;0.71)
	Obese I (30-34.9 kg/m²)	2,150 (461.2)	4.66 (4.46;4.86)	4,725 (1,531.4)	3.09 (3;3.17)	1,190 (1,293)	0.92 (0.87;0.97)	890 (854.7)	1.04 (0.97;1.11)	165 (246.7)	0.67 (0.57;0.77)
	Obese II (35-39.9 kg/m²)	920 (187.5)	4.91 (4.59;5.22)	2,010 (625.1)	3.22 (3.07;3.36)	550 (531.8)	1.03 (0.95;1.12)	330 (352.8)	0.94 (0.83;1.04)	60 (102.2)	0.59 (0.44;0.74)
	Obese III (40+ kg/m²)	565 (118.4)	4.77 (4.38;5.17)	1,575 (395.6)	3.98 (3.78;4.18)	510 (338.2)	1.51 (1.38;1.64)	240 (225.2)	1.07 (0.93;1.2)	45 (65.6)	0.69 (0.49;0.89)
Smoking status	Never and unknown	5,285 (1,765.1)	2.99 (2.91;3.07)	10,535 (6,000.8)	1.76 (1.72;1.79)	2,035 (5,240.2)	0.39 (0.37;0.41)	2,240 (3,583.8)	0.63 (0.6;0.65)	450 (1,078.2)	0.42 (0.38;0.46)
	Former	9,435 (1,148.3)	8.22 (8.05;8.38)	19,000 (3,867.2)	4.91 (4.84;4.98)	4,005 (3,385.1)	1.18 (1.15;1.22)	4,090 (2,306.6)	1.77 (1.72;1.83)	785 (689.3)	1.14 (1.06;1.22)

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		Events (1000 person- years)*	Death rate per 1000 person-years	Events (1000 person- years)*	Death rate per 1000 person-years	Events (1000 person- years)*	Death rate per 1000 person-years	Events (1000 person- years)*	Death rate per 1000 person-years	Events (1000 person- years)*	Death rate per 1000 person-years
	Current	1,005 (599)	1.68 (1.57;1.78)	2,440 (2,007.4)	1.22 (1.17;1.26)	595 (1,711.9)	0.35 (0.32;0.38)	780 (1,153.1)	0.68 (0.63;0.72)	180 (337)	0.53 (0.46;0.61)
Asthma	No asthma	13,550 (2,939.4)	4.61 (4.53;4.69)	27,135 (9,936.7)	2.73 (2.7;2.76)	5,535 (8,651.8)	0.64 (0.62;0.66)	6,090 (5,903.2)	1.03 (1.01;1.06)	1,205 (1,765.7)	0.68 (0.64;0.72)
	With no oral steroid use	1,710 (512.7)	3.34 (3.18;3.49)	3,850 (1,754.6)	2.19 (2.12;2.26)	950 (1,578.6)	0.6 (0.56;0.64)	840 (1,048)	0.8 (0.75;0.86)	165 (307.2)	0.54 (0.46;0.62)
	With oral steroid use	465 (60.3)	7.72 (7.01;8.42)	995 (184)	5.41 (5.07;5.74)	150 (106.7)	1.41 (1.18;1.63)	180 (92.4)	1.95 (1.66;2.23)	50 (31.5)	1.59 (1.15;2.03)
Diabetes	No diabetes	10,100 (3,158.9)	3.2 (3.14;3.26)	20,470 (10,683.8)	1.92 (1.89;1.94)	3,975 (9,253)	0.43 (0.42;0.44)	4,680 (6,283.5)	0.74 (0.72;0.77)	930 (1,869.2)	0.5 (0.47;0.53)
	Controlled	4,710 (299.6)	15.72 (15.27;16.17)	9,345 (952)	9.82 (9.62;10.02)	2,080 (826.9)	2.52 (2.41;2.62)	1,985 (617.7)	3.21 (3.07;3.35)	405 (196.6)	2.06 (1.86;2.26)
	Not controlled	275 (14.9)	18.47 (16.29;20.65)	580 (47.7)	12.16 (11.17;13.15)	120 (40.8)	2.94 (2.41;3.46)	85 (26.6)	3.2 (2.52;3.88)	15 (7.8)	1.93 (0.95;2.91)
	Without recent HbA1c measure	635 (39.1)	16.26 (14.99;17.52)	1,580 (191.8)	8.24 (7.83;8.64)	460 (216.5)	2.12 (1.93;2.32)	360 (115.8)	3.11 (2.79;3.43)	70 (30.9)	2.26 (1.73;2.79)
Chronic kidney disease or renal replacement therapy	No CKD or RRT	9,195 (3,323.7)	2.77 (2.71;2.82)	18,830 (11,263)	1.67 (1.65;1.7)	4,090 (9,796.7)	0.42 (0.4;0.43)	4,115 (6,674.3)	0.62 (0.6;0.64)	810 (1,992.5)	0.41 (0.38;0.43)
	CKD stage 3a	3,095 (125.7)	24.62 (23.76;25.49)	6,165 (409.5)	15.05 (14.68;15.43)	1,115 (360.5)	3.09 (2.91;3.27)	1,285 (245.1)	5.24 (4.96;5.53)	265 (74.3)	3.57 (3.14;4)
	CKD stage 3b	2,220 (46.1)	48.17 (46.16;50.17)	4,585 (148.3)	30.93 (30.03;31.82)	830 (131.4)	6.32 (5.89;6.75)	1,025 (90.4)	11.34 (10.65;12.04)	200 (27.3)	7.33 (6.32;8.35)
	CKD stage 4	860 (11)	78.38 (73.14;83.62)	1,750 (34.8)	50.25 (47.89;52.6)	355 (31.1)	11.43 (10.24;12.62)	485 (21.7)	22.31 (20.33;24.3)	95 (6.7)	14.13 (11.29;16.97)
	CKD stage 5	120 (1.2)	102.16 (83.88;120.43)	245 (3.7)	65.66 (57.44;73.88)	50 (3.4)	14.85 (10.73;18.97)	65 (2.4)	27.39 (20.73;34.04)	25 (0.8)	32.54 (19.78;45.29)
	RRT (dialysis)	180 (2.5)	72.33 (61.76;82.89)	280 (8.2)	33.97 (29.99;37.95)	90 (7.3)	12.26 (9.72;14.79)	80 (5.1)	15.8 (12.34;19.27)	10 (1.5)	6.5 (2.47;10.52)
	RRT	50 (2.3)	21.4	115 (7.8)	14.77	105 (6.8)	15.4	50 (4.6)	10.87	15 (1.4)	10.93

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Subgroup	Category	Wave 1 (WT)		Wave 2 (alpha)		Wave 3 (delta)		Wave 4 (omicron)		Wave 5 (omicron)	
		Events (1000 person-years)*	Death rate per 1000 person-years	Events (1000 person-years)*	Death rate per 1000 person-years	Events (1000 person-years)*	Death rate per 1000 person-years	Events (1000 person-years)*	Death rate per 1000 person-years	Events (1000 person-years)*	Death rate per 1000 person-years
	(transplant)		(15.47;27.33)		(12.07;17.46)		(12.46;18.35)		(7.86;13.88)		(5.4;16.45)
Organ transplant	No transplant	15,640 (3,508.7)	4.46 (4.39;4.53)	31,785 (11,862.8)	2.68 (2.65;2.71)	6,465 (10,326.1)	0.63 (0.61;0.64)	7,020 (7,036.1)	1 (0.97;1.02)	1,405 (2,102.2)	0.67 (0.63;0.7)
	Kidney transplant	65 (2.8)	23.4 (17.71;29.09)	145 (9.3)	15.58 (13.05;18.12)	130 (8.2)	15.91 (13.17;18.64)	70 (5.5)	12.66 (9.7;15.63)	15 (1.7)	9.07 (4.48;13.66)
	Other organ transplant	15 (1)	15.24 (7.53;22.95)	45 (3.3)	13.63 (9.65;17.61)	40 (2.9)	13.79 (9.52;18.07)	20 (2)	10.15 (5.7;14.59)	[REDACTED]	[REDACTED]
Hypertension		11,485 (1,182)	9.72 (9.54;9.89)	23,850 (3,946.2)	6.04 (5.97;6.12)	4,810 (3,451.5)	1.39 (1.35;1.43)	5,220 (2,336.1)	2.23 (2.17;2.3)	1,075 (697.7)	1.54 (1.45;1.63)
Chronic respiratory disease		3,205 (139.5)	22.97 (22.17;23.76)	6,975 (458.7)	15.21 (14.85;15.56)	1,615 (399.9)	4.04 (3.84;4.24)	1,705 (271.2)	6.29 (5.99;6.59)	375 (81.2)	4.62 (4.15;5.09)
Chronic cardiac disease		5,625 (231.1)	24.34 (23.7;24.98)	11,940 (765.3)	15.6 (15.32;15.88)	2,390 (671.7)	3.56 (3.42;3.7)	2,770 (458)	6.05 (5.82;6.27)	560 (137.6)	4.07 (3.73;4.41)
Cancer (non haematological)		2,705 (170.6)	15.86 (15.26;16.46)	5,790 (567.1)	10.21 (9.95;10.47)	1,080 (503.8)	2.14 (2.02;2.27)	1,480 (347)	4.27 (4.05;4.48)	315 (105.1)	3 (2.67;3.33)
Haematological malignancy		475 (20)	23.76 (21.63;25.9)	950 (66.8)	14.23 (13.32;15.13)	390 (59.3)	6.58 (5.93;7.24)	405 (40.7)	9.96 (8.99;10.93)	95 (12.3)	7.74 (6.19;9.3)
Chronic liver disease		285 (20.4)	14 (12.37;15.62)	655 (68.6)	9.55 (8.82;10.28)	185 (61.9)	2.99 (2.56;3.42)	180 (43.2)	4.17 (3.56;4.78)	35 (13.2)	2.65 (1.77;3.53)
Stroke		2,840 (73)	38.92 (37.49;40.35)	5,055 (241)	20.98 (20.4;21.55)	860 (213.4)	4.03 (3.76;4.3)	1,150 (146.9)	7.83 (7.37;8.28)	240 (44.6)	5.38 (4.7;6.06)
Dementia		1,465 (8.4)	174.97 (166.01;183.92)	1,985 (24.6)	80.63 (77.08;84.18)	225 (21.1)	10.65 (9.26;12.05)	385 (14.2)	27.06 (24.36;29.77)	60 (4.3)	14.04 (10.49;17.59)
Other neurological disease		1,035 (34.4)	30.12 (28.28;31.95)	1,795 (113.3)	15.84 (15.11;16.57)	280 (99)	2.83 (2.5;3.16)	405 (67.5)	6 (5.42;6.59)	85 (20.2)	4.2 (3.31;5.09)
Asplenia		55 (5.6)	9.81 (7.22;12.4)	140 (18.7)	7.47 (6.23;8.71)	20 (16.3)	1.22 (0.69;1.76)	30 (11.1)	2.7 (1.74;3.67)	10 (3.3)	3.01 (1.14;4.88)
Rheumatoid arthritis/ lupus/ psoriasis		1,385 (176.4)	7.85 (7.44;8.27)	2,950 (593.4)	4.97 (4.79;5.15)	745 (519.5)	1.43 (1.33;1.54)	715 (353.1)	2.02 (1.88;2.17)	145 (105.5)	1.37 (1.15;1.6)

Table S1. Crude COVID-19-related death rates and 95% confidence intervals in OpenSAFELY-TTP, stratified by demographic and clinical subgroups in the first five pandemic waves in England (wave 1: March 23 to May 30, 2020; wave 2 (alpha): September 7, 2020 to April 24, 2021; wave 3 (delta): May 28 to December 14, 2021; wave 4 (omicron): December 15, 2021 to April 29, 2022; and wave 5: June 24 to August 3, 2022).

Subgroup	Category	Wave 1 (WT)		Wave 2 (alpha)		Wave 3 (delta)		Wave 4 (omicron)		Wave 5 (omicron)	
		Events (1000 person-years)*	Death rate per 1000 person-years	Events (1000 person-years)*	Death rate per 1000 person-years	Events (1000 person-years)*	Death rate per 1000 person-years	Events (1000 person-years)*	Death rate per 1000 person-years	Events (1000 person-years)*	Death rate per 1000 person-years
Immunosuppressive condition		850 (43.4)	19.58 (18.26;20.89)	1,660 (146.1)	11.36 (10.81;11.91)	585 (130.7)	4.48 (4.11;4.84)	620 (91.4)	6.79 (6.25;7.32)	130 (28)	4.64 (3.84;5.44)
Learning disability		230 (19.8)	11.61 (10.11;13.11)	385 (67.4)	5.71 (5.14;6.28)	70 (61)	1.15 (0.88;1.42)	60 (42)	1.43 (1.07;1.79)	25 (12.7)	1.97 (1.2;2.75)
Severe mental illness		615 (41.6)	14.77 (13.61;15.94)	990 (140.6)	7.04 (6.6;7.48)	175 (124.6)	1.4 (1.2;1.61)	195 (85.1)	2.29 (1.97;2.61)	35 (25.4)	1.38 (0.92;1.83)

*All counts have been rounded to the nearest five and may therefore not add up; person-years have been rounded to the nearest five and the first decimal.
Abbreviations: WT wild type; CKD chronic kidney disease; RRT renal replacement therapy.

Standardised death rate

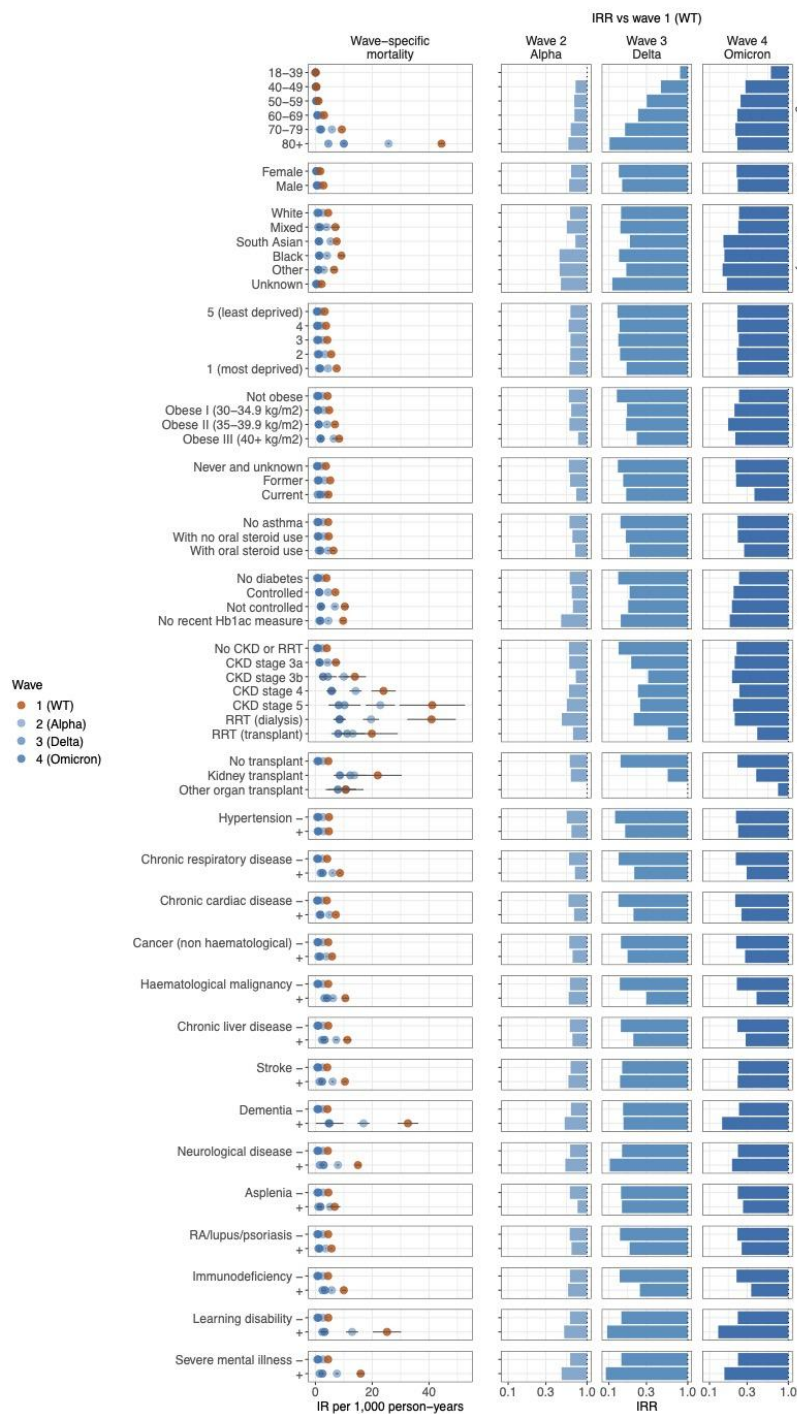


Figure S5. Sex- and age-standardised COVID-19-related death rates (IR) and 95% confidence intervals per 1,000 person-years in OpenSAFELY-TPP in the five pandemic waves (wave 1: March 23 to May 30, 2020; wave 2 (alpha): September 7, 2020 to April 24, 2021; wave 3 (delta): May 28 to December 14, 2021; wave 4 (omicron): December 15, 2021 to April 29, 2022; and wave 5: June 24 to August 3, 2022). Models were standardised for age and sex using the European standard population except for the death rates by age group (not standardised) and death rates by sex (standardised by age). The two columns on the right present the fold-changes in death rate (IRR) of wave 2 (alpha) vs 1 and wave 3 vs 1. Abbreviations: IMD, index of multiple deprivation; BMI, body mass index; SMK, smoking; CKD, chronic kidney disease; RRT, renal replacement therapy; Tx, transplant. The death rates presented in this figure can be found in table S1 of the Supplementary material.

Table S2. Sex- and age-standardised COVID-19-related death rates and 95% confidence intervals per 1,000 person-years in OpenSAFELY-TPP in the three pandemic waves (wave 1: March 23 to May 30, 2020; wave 2 (alpha): September 7, 2020 to April 24, 2021; wave 3 (delta): May 28 to December 14, 2021; wave 4 (omicron): December 15, 2021 to April 29, 2022; and wave 5: June 24 to August 3, 2022).

Subgroup	Category	Sex- and age-standardised COVID-19-related death rate* per 1,000 person-years (95% CI)				
		Wave 1 (WT)	Wave 2 (alpha)	Wave 3 (delta)	Wave 4 (omicron)	Wave 5 (omicron)
All	-	4.56 (4.49;4.64)	2.77 (2.73;2.8)	0.65 (0.64;0.67)	1.04 (1.01;1.06)	0.69 (0.65;0.72)
Age Group	18-39	0.05 (0.04;0.06)	0.05 (0.04;0.06)	0.04 (0.04;0.05)	0.03 (0.03;0.04)	0.02 (0.01;0.03)
	40-49	0.35 (0.3;0.4)	0.25 (0.23;0.27)	0.16 (0.14;0.18)	0.1 (0.08;0.12)	0.04 (0.02;0.07)
	50-59	1.09 (1.01;1.18)	0.75 (0.71;0.79)	0.33 (0.3;0.35)	0.27 (0.24;0.3)	0.15 (0.11;0.19)
	60-69	3.02 (2.86;3.18)	2.09 (2.02;2.16)	0.71 (0.67;0.76)	0.68 (0.63;0.73)	0.46 (0.38;0.54)
	70-79	9.29 (8.99;9.6)	5.77 (5.64;5.9)	1.49 (1.42;1.56)	1.98 (1.88;2.08)	1.34 (1.19;1.49)
	80 plus	44.41 (43.53;45.29)	25.75 (25.38;26.12)	4.54 (4.38;4.71)	10.01 (9.71;10.3)	6.7 (6.26;7.14)
Sex	Female	1.72 (1.68;1.76)	1.08 (1.06;1.1)	0.23 (0.22;0.24)	0.38 (0.37;0.4)	0.26 (0.24;0.28)
	Male	2.85 (2.79;2.91)	1.69 (1.66;1.71)	0.42 (0.41;0.44)	0.65 (0.63;0.68)	0.42 (0.39;0.45)
Ethnicity	White	4.48 (4.4;4.56)	2.73 (2.7;2.76)	0.64 (0.62;0.65)	1.06 (1.04;1.09)	0.71 (0.67;0.75)
	Mixed	7 (5.37;8.62)	3.89 (3.23;4.54)	0.98 (0.65;1.31)	1.62 (1.03;2.2)	[REDACTED]
	South Asian	7.46 (6.9;8.03)	5.31 (5.05;5.57)	1.38 (1.23;1.52)	1.12 (0.96;1.28)	0.84 (0.59;1.08)
	Black	9.13 (8.06;10.21)	4.08 (3.69;4.48)	1.23 (1.01;1.44)	1.41 (1.12;1.71)	0.56 (0.23;0.9)
	Other	6.55 (5.48;7.62)	2.94 (2.55;3.32)	1.09 (0.84;1.35)	0.96 (0.67;1.25)	0.54 (0.15;0.93)
	Unknown	2.17 (1.91;2.42)	1.01 (0.92;1.11)	0.24 (0.2;0.29)	0.36 (0.28;0.43)	0.25 (0.14;0.36)
Region	North East	5.72 (5.34;6.09)	3.47 (3.3;3.63)	1.02 (0.93;1.11)	1.22 (1.09;1.34)	0.72 (0.54;0.89)
	North West	6.09 (5.81;6.38)	2.92 (2.82;3.03)	0.79 (0.74;0.85)	1.13 (1.05;1.22)	0.73 (0.6;0.86)
	Yorkshire and the Humber	5.06 (4.84;5.27)	2.8 (2.72;2.89)	0.84 (0.79;0.89)	1.13 (1.05;1.2)	0.76 (0.65;0.87)
	East Midlands	4.46 (4.28;4.63)	3.19 (3.11;3.27)	0.73 (0.69;0.77)	1.13 (1.07;1.19)	0.77 (0.68;0.87)
	West Midlands	7.31 (6.82;7.8)	4.16 (3.96;4.37)	0.92 (0.82;1.02)	1.19 (1.05;1.33)	0.88 (0.66;1.1)
	East of England	4.46 (4.31;4.61)	3 (2.94;3.07)	0.52 (0.49;0.55)	1.02 (0.97;1.07)	0.7 (0.62;0.77)
	London	8.12 (7.6;8.63)	3.07 (2.9;3.24)	0.75 (0.66;0.84)	1.18 (1.04;1.32)	0.72 (0.53;0.92)
	South East	3.21 (2.98;3.43)	2.23 (2.13;2.33)	0.49 (0.44;0.54)	0.79 (0.71;0.87)	0.45 (0.35;0.56)
	South West	2.61 (2.47;2.74)	1.57 (1.51;1.62)	0.42 (0.39;0.45)	0.86 (0.8;0.91)	0.54 (0.46;0.62)
IMD quintile	5 (least deprived)	3.27 (3.14;3.4)	2.01 (1.95;2.06)	0.42 (0.39;0.45)	0.74 (0.69;0.78)	0.52 (0.45;0.58)
	4	3.73 (3.6;3.87)	2.18 (2.13;2.24)	0.51 (0.48;0.54)	0.84 (0.8;0.89)	0.62 (0.55;0.69)
	3	4.17 (4.02;4.32)	2.57 (2.5;2.63)	0.55 (0.52;0.58)	0.98 (0.92;1.03)	0.63 (0.56;0.7)
	2	5.55 (5.36;5.74)	3.4 (3.32;3.49)	0.77 (0.73;0.81)	1.24 (1.17;1.31)	0.79 (0.7;0.89)
	1 (most deprived)	7.45 (7.19;7.7)	4.45 (4.34;4.56)	1.25 (1.19;1.31)	1.72 (1.63;1.81)	1.04 (0.92;1.17)
	Body Mass Index	Not obese	4.27 (4.19;4.35)	2.51 (2.48;2.54)	0.54 (0.53;0.56)	1.01 (0.98;1.04)
Obese I (30-34.9 kg/m ²)		4.83 (4.6;5.06)	3.04 (2.95;3.14)	0.82 (0.76;0.87)	1 (0.92;1.07)	0.63 (0.52;0.74)
Obese II (35-39.9 kg/m ²)		6.84 (6.2;7.47)	4.08 (3.84;4.31)	1.13 (1.02;1.25)	1.18 (1.01;1.35)	0.71 (0.49;0.93)
Obese III (40+)		8.33 (7.13;9.53)	6.42 (5.83;7.02)	1.88 (1.62;2.15)	1.77 (1.33;2.22)	1.04 (0.61;1.46)

Table S2. Sex- and age-standardised COVID-19-related death rates and 95% confidence intervals per 1,000 person-years in OpenSAFELY-TPP in the three pandemic waves (wave 1: March 23 to May 30, 2020; wave 2 (alpha): September 7, 2020 to April 24, 2021; wave 3 (delta): May 28 to December 14, 2021; wave 4 (omicron): December 15, 2021 to April 29, 2022; and wave 5: June 24 to August 3, 2022).

Subgroup	Category	Sex- and age-standardised COVID-19-related death rate* per 1,000 person-years (95% CI)				
		Wave 1 (WT)	Wave 2 (alpha)	Wave 3 (delta)	Wave 4 (omicron)	Wave 5 (omicron)
	kg/m ²)					
Smoking status	Never and unknown	3.69 (3.58;3.81)	2.17 (2.12;2.21)	0.48 (0.46;0.5)	0.79 (0.75;0.82)	0.52 (0.47;0.58)
	Former	5.2 (5.09;5.31)	3.17 (3.12;3.22)	0.79 (0.76;0.81)	1.13 (1.1;1.17)	0.71 (0.66;0.77)
	Current	4.58 (4.21;4.94)	3.34 (3.16;3.52)	0.76 (0.68;0.85)	1.7 (1.54;1.86)	1.35 (1.09;1.61)
Asthma	No asthma	4.49 (4.42;4.57)	2.69 (2.65;2.72)	0.63 (0.61;0.64)	1.02 (0.99;1.05)	0.67 (0.63;0.71)
	With no oral steroid use	4.69 (4.46;4.93)	3.06 (2.95;3.16)	0.77 (0.72;0.83)	1.07 (0.99;1.14)	0.69 (0.58;0.8)
	With oral steroid use	6.33 (5.71;6.94)	4.48 (4.18;4.79)	1.16 (0.96;1.36)	1.74 (1.47;2.02)	1.42 (0.99;1.84)
Diabetes**	No diabetes	3.88 (3.8;3.96)	2.34 (2.3;2.37)	0.51 (0.49;0.53)	0.92 (0.89;0.95)	0.61 (0.57;0.65)
	Controlled	6.98 (6.74;7.22)	4.47 (4.35;4.59)	1.28 (1.2;1.36)	1.41 (1.33;1.48)	0.86 (0.77;0.96)
	Not controlled	10.34 (9.03;11.65)	6.84 (6.2;7.49)	1.82 (1.36;2.28)	1.99 (1.46;2.52)	1.03 (0.53;1.52)
	Without recent HbA1c measure	9.75 (8.96;10.54)	4.57 (4.33;4.81)	1.38 (1.19;1.57)	1.76 (1.57;1.95)	1.33 (1.01;1.65)
Chronic kidney disease or renal replacement therapy	No CKD or RRT	3.99 (3.9;4.08)	2.35 (2.32;2.39)	0.53 (0.51;0.55)	0.88 (0.85;0.91)	0.59 (0.55;0.64)
	CKD stage 3a	7.19 (5.71;8.67)	4.27 (3.56;4.97)	1.38 (0.98;1.79)	1.5 (1.18;1.82)	1.31 (0.25;2.37)
	CKD stage 3b	13.88 (9.96;17.8)	10 (8.05;11.95)	4.37 (1.26;7.47)	2.68 (1.85;3.51)	1.74 (1.19;2.29)
	CKD stage 4	23.97 (19.68;28.27)	14.14 (11.98;16.29)	5.61 (3.87;7.34)	5.74 (4.39;7.09)	7.23 (0.31;14.15)
	CKD stage 5	41.12 (29.56;52.68)	22.84 (17.67;28.01)	10.26 (4.59;15.93)	8.19 (4.88;11.51)	10.05 (4.5;15.6)
	RRT (dialysis)	40.88 (32.34;49.43)	19.57 (16.75;22.4)	8.46 (6.29;10.64)	8.54 (6.52;10.57)	4.76 (1.21;8.31)
	RRT (transplant)	19.85 (10.7;29)	13.17 (8.83;17.51)	11.15 (8.65;13.65)	8 (5.58;10.41)	5.96 (2.69;9.23)
Organ transplant	No transplant	4.55 (4.47;4.62)	2.75 (2.72;2.78)	0.64 (0.62;0.65)	1.03 (1;1.05)	0.68 (0.64;0.72)
	Kidney transplant	21.94 (13.52;30.36)	13.66 (9.41;17.92)	12.25 (9.73;14.77)	8.58 (6.39;10.77)	5.57 (2.58;8.56)
	Other organ transplant	10.66 (4.39;16.93)	10.71 (7.25;14.18)	10.61 (6.85;14.36)	7.88 (3.57;12.2)	[REDACTED]
Hypertension	No	4.75 (4.6;4.9)	2.63 (2.57;2.7)	0.57 (0.54;0.6)	1.03 (0.98;1.08)	0.61 (0.54;0.68)
	Yes	4.72 (4.62;4.81)	2.99 (2.94;3.03)	0.76 (0.73;0.78)	1.09 (1.06;1.12)	0.73 (0.69;0.78)
Chronic respiratory disease	No	4.13 (4.05;4.2)	2.44 (2.41;2.48)	0.55 (0.54;0.57)	0.89 (0.87;0.92)	0.57 (0.54;0.61)
	Yes	8.62 (8.17;9.06)	6.05 (5.81;6.29)	1.81 (1.66;1.95)	2.55 (2.33;2.76)	1.91 (1.46;2.36)
Chronic cardiac disease	No	4.01 (3.93;4.1)	2.33 (2.29;2.36)	0.53 (0.52;0.55)	0.85 (0.82;0.87)	0.56 (0.52;0.6)
	Yes	7.16 (6.88;7.44)	4.9 (4.75;5.05)	1.47 (1.33;1.6)	1.82 (1.71;1.93)	1.25 (1.06;1.44)
Cancer (non haematological)	No	4.5 (4.42;4.58)	2.68 (2.64;2.71)	0.64 (0.62;0.65)	0.98 (0.96;1.01)	0.64 (0.6;0.68)
	Yes	5.84 (5.51;6.17)	3.83 (3.64;4.02)	1.01 (0.88;1.14)	1.65 (1.48;1.82)	1.31 (1.06;1.55)
Haematological malignancy	No	4.5 (4.43;4.57)	2.73 (2.7;2.76)	0.62 (0.61;0.64)	1 (0.97;1.02)	0.65 (0.62;0.69)
	Yes	10.53 (9.37;11.69)	6.16 (5.68;6.64)	3.14 (2.74;3.54)	4.16 (3.66;4.66)	3.29 (2.39;4.18)

Table S2. Sex- and age-standardised COVID-19-related death rates and 95% confidence intervals per 1,000 person-years in OpenSAFELY-TPP in the three pandemic waves (wave 1: March 23 to May 30, 2020; wave 2 (alpha): September 7, 2020 to April 24, 2021; wave 3 (delta): May 28 to December 14, 2021; wave 4 (omicron): December 15, 2021 to April 29, 2022; and wave 5: June 24 to August 3, 2022).

Subgroup	Category	Sex- and age-standardised COVID-19-related death rate* per 1,000 person-years (95% CI)				
		Wave 1 (WT)	Wave 2 (alpha)	Wave 3 (delta)	Wave 4 (omicron)	Wave 5 (omicron)
Chronic liver disease	No	4.51 (4.44;4.59)	2.73 (2.7;2.76)	0.64 (0.62;0.66)	1.02 (1;1.04)	0.67 (0.64;0.71)
	Yes	11.21 (9.72;12.69)	7.31 (6.67;7.95)	2.29 (1.91;2.66)	3.22 (2.59;3.86)	2.23 (1.38;3.07)
Stroke	No	4.14 (4.07;4.22)	2.56 (2.53;2.59)	0.61 (0.6;0.63)	0.96 (0.94;0.99)	0.63 (0.59;0.67)
	Yes	10.38 (9.83;10.92)	6.03 (5.67;6.39)	1.44 (1.27;1.61)	2.36 (2.02;2.69)	1.51 (1.24;1.78)
Dementia	No	4.23 (4.15;4.3)	2.64 (2.61;2.67)	0.64 (0.62;0.65)	1 (0.98;1.02)	0.67 (0.63;0.7)
	Yes	32.56 (28.91;36.2)	16.92 (14.79;19.05)	4.99 (0.09;9.89)	4.7 (3.79;5.6)	2.05 (1.32;2.78)
Other neurological disease	No	4.36 (4.29;4.43)	2.66 (2.63;2.7)	0.64 (0.62;0.65)	1 (0.98;1.03)	0.66 (0.62;0.7)
	Yes	14.96 (13.95;15.96)	7.93 (7.52;8.33)	1.54 (1.33;1.74)	2.89 (2.59;3.2)	2.15 (1.65;2.65)
Asplenia	No	4.56 (4.49;4.63)	2.76 (2.73;2.79)	0.65 (0.64;0.67)	1.04 (1.01;1.06)	0.68 (0.65;0.72)
	Yes	6.76 (4.76;8.75)	5.12 (4.21;6.02)	0.99 (0.51;1.48)	1.8 (1.14;2.47)	1.9 (0.59;3.22)
Rheumatoid arthritis/ lupus/ psoriasis	No	4.48 (4.4;4.55)	2.7 (2.67;2.73)	0.62 (0.61;0.64)	1.01 (0.98;1.03)	0.66 (0.62;0.7)
	Yes	5.67 (5.35;5.98)	3.6 (3.47;3.74)	1.04 (0.96;1.11)	1.45 (1.34;1.56)	1.02 (0.84;1.2)
Immunosuppressive condition	No	4.45 (4.37;4.52)	2.7 (2.67;2.73)	0.61 (0.6;0.63)	0.98 (0.95;1)	0.64 (0.61;0.68)
	Yes	9.98 (9.24;10.72)	5.73 (5.44;6.03)	2.47 (2.24;2.7)	3.37 (3.08;3.65)	2.4 (1.89;2.9)
Learning disability	No	4.51 (4.44;4.58)	2.74 (2.71;2.77)	0.65 (0.63;0.66)	1.03 (1.01;1.06)	0.68 (0.64;0.71)
	Yes	25.2 (20.2;30.2)	12.91 (10.76;15.05)	2.4 (1.45;3.35)	3.25 (2.18;4.31)	4.22 (2.03;6.41)
Severe mental illness	No	4.44 (4.37;4.51)	2.71 (2.68;2.74)	0.64 (0.63;0.66)	1.02 (1;1.05)	0.68 (0.64;0.71)
	Yes	15.93 (14.54;17.32)	7.57 (7.05;8.1)	1.46 (1.21;1.7)	2.46 (2.07;2.85)	1.44 (0.93;1.95)

* Models were standardised for age and sex using the European standard population except for the death rates by age group (not standardised) and death rates by sex (standardised by age).

** HbA1c classification based on the latest measure within 15 months before baseline.

Abbreviations: WT wild type; CKD chronic kidney disease; RRT renal replacement therapy.

Relative hazard of death

Table S3. Relative hazard of COVID-19-related death and 95% confidence intervals (95%CI) in OpenSAFELY-TPP in the five pandemic waves in England (wave 1: March 23 to May 30, 2020; wave 2 (alpha): September 7, 2020 to April 24, 2021; wave 3 (delta): May 28 to December 14, 2021; wave 4 (omicron): December 15, 2021 to April 29, 2022; and wave 5: June 24 to August 3, 2022).

Subgroup	Category	Relative hazard of COVID-19-related death* (95%CI)				
		Wave 1 (WT)	Wave 2 (alpha)	Wave 3 (delta)	Wave 4 (omicron)	Wave 5 (omicron)
Age Group	18-39	0.04 (0.03;0.06)	0.06 (0.06;0.07)	0.13 (0.11;0.15)	0.12 (0.09;0.15)	0.12 (0.07;0.22)
	40-49	0.31 (0.26;0.36)	0.33 (0.3;0.36)	0.47 (0.41;0.55)	0.36 (0.29;0.45)	0.3 (0.17;0.53)
	50-59	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	60-69	2.85 (2.6;3.12)	2.83 (2.67;3.01)	2.21 (2;2.44)	2.53 (2.22;2.88)	3.05 (2.23;4.16)
	70-79	9.06 (8.34;9.84)	7.95 (7.53;8.4)	4.75 (4.32;5.21)	7.48 (6.65;8.42)	8.9 (6.7;11.83)
	80 plus	44.8 (41.42;48.47)	36.59 (34.74;38.54)	15.25 (13.95;16.66)	39.16 (35.02;43.78)	45.92 (35.04;60.18)
Sex	Female	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Male	1.71 (1.66;1.77)	1.61 (1.57;1.64)	1.86 (1.77;1.96)	1.75 (1.67;1.84)	1.64 (1.48;1.83)
Ethnicity	White	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Mixed	1.52 (1.24;1.87)	1.49 (1.29;1.73)	1.56 (1.17;2.09)	1.37 (1;1.88)	0.17 (0.02;1.24)
	South Asian	1.47 (1.36;1.59)	2.02 (1.92;2.12)	1.99 (1.8;2.2)	1.02 (0.89;1.17)	1.07 (0.8;1.44)
	Black	1.75 (1.56;1.95)	1.45 (1.33;1.59)	2 (1.7;2.34)	1.33 (1.09;1.61)	0.71 (0.4;1.26)
	Other	1.25 (1.07;1.46)	1.07 (0.95;1.21)	1.54 (1.25;1.89)	0.85 (0.64;1.12)	0.65 (0.32;1.31)
	Unknown	0.45 (0.4;0.5)	0.36 (0.33;0.4)	0.38 (0.32;0.46)	0.33 (0.27;0.4)	0.33 (0.21;0.51)
IMD quintile	5 (least deprived)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	4	1.16 (1.1;1.23)	1.11 (1.07;1.16)	1.21 (1.11;1.32)	1.16 (1.07;1.25)	1.19 (1;1.41)
	3	1.32 (1.25;1.39)	1.33 (1.28;1.38)	1.37 (1.26;1.5)	1.34 (1.24;1.45)	1.22 (1.03;1.45)
	2	1.71 (1.62;1.8)	1.74 (1.68;1.8)	1.86 (1.71;2.02)	1.69 (1.56;1.82)	1.49 (1.25;1.77)
	1 (most deprived)	2.11 (2;2.23)	2.2 (2.12;2.28)	2.76 (2.54;2.99)	2.33 (2.15;2.52)	1.99 (1.67;2.37)
Body Mass Index	Not obese	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Obese I (30-34.9 kg/m ²)	1.17 (1.11;1.22)	1.27 (1.23;1.31)	1.54 (1.45;1.65)	1 (0.93;1.08)	0.92 (0.79;1.09)
	Obese II (35-39.9 kg/m ²)	1.71 (1.6;1.83)	1.81 (1.73;1.9)	2.26 (2.07;2.47)	1.26 (1.12;1.41)	1.15 (0.89;1.49)
	Obese III (40+ kg/m ²)	2.66 (2.44;2.9)	3.51 (3.34;3.7)	4.78 (4.35;5.25)	2.29 (2.01;2.61)	2.18 (1.63;2.94)
Smoking status	Never and unknown	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Former	1.43 (1.38;1.48)	1.46 (1.43;1.5)	1.64 (1.55;1.73)	1.44 (1.37;1.52)	1.37 (1.22;1.55)
	Current	1.2 (1.12;1.28)	1.41 (1.35;1.48)	1.32 (1.21;1.45)	2.28 (2.1;2.48)	2.8 (2.34;3.35)
Asthma	No asthma	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	With no oral steroid use	1.09 (1.03;1.14)	1.18 (1.14;1.22)	1.28 (1.19;1.37)	1.1 (1.02;1.18)	1.1 (0.94;1.3)
	With oral steroid use	1.47 (1.34;1.61)	1.75 (1.64;1.86)	1.94 (1.65;2.28)	1.8 (1.55;2.09)	2.26 (1.7;2.99)
Diabetes**	No diabetes	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Controlled	1.61 (1.55;1.67)	1.79 (1.74;1.83)	2.24 (2.12;2.36)	1.48 (1.4;1.56)	1.4 (1.24;1.58)
	Not controlled	2.61 (2.3;2.95)	2.81 (2.58;3.06)	3.67 (3.04;4.43)	2.07 (1.66;2.58)	2.01 (1.23;3.29)

Table S3. Relative hazard of COVID-19-related death and 95% confidence intervals (95%CI) in OpenSAFELY-TPP in the five pandemic waves in England (wave 1: March 23 to May 30, 2020; wave 2 (alpha): September 7, 2020 to April 24, 2021; wave 3 (delta): May 28 to December 14, 2021; wave 4 (omicron): December 15, 2021 to April 29, 2022; and wave 5: June 24 to August 3, 2022).

Subgroup	Category	Relative hazard of COVID-19-related death* (95%CI)				
		Wave 1 (WT)	Wave 2 (alpha)	Wave 3 (delta)	Wave 4 (omicron)	Wave 5 (omicron)
Age Group	18-39	0.04 (0.03;0.06)	0.06 (0.06;0.07)	0.13 (0.11;0.15)	0.12 (0.09;0.15)	0.12 (0.07;0.22)
	40-49	0.31 (0.26;0.36)	0.33 (0.3;0.36)	0.47 (0.41;0.55)	0.36 (0.29;0.45)	0.3 (0.17;0.53)
	50-59	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	60-69	2.85 (2.6;3.12)	2.83 (2.67;3.01)	2.21 (2;2.44)	2.53 (2.22;2.88)	3.05 (2.23;4.16)
	70-79	9.06 (8.34;9.84)	7.95 (7.53;8.4)	4.75 (4.32;5.21)	7.48 (6.65;8.42)	8.9 (6.7;11.83)
	80 plus	44.8 (41.42;48.47)	36.59 (34.74;38.54)	15.25 (13.95;16.66)	39.16 (35.02;43.78)	45.92 (35.04;60.18)
Sex	Female	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Male	1.71 (1.66;1.77)	1.61 (1.57;1.64)	1.86 (1.77;1.96)	1.75 (1.67;1.84)	1.64 (1.48;1.83)
	Without recent HbA1c measure	2.23 (2.06;2.42)	1.89 (1.8;1.99)	2.32 (2.1;2.56)	1.82 (1.63;2.03)	2.02 (1.58;2.59)
Chronic kidney disease or renal replacement therapy	No CKD or RRT	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	CKD stage 3a	1.31 (1.25;1.37)	1.41 (1.37;1.45)	1.67 (1.56;1.79)	1.27 (1.19;1.35)	1.26 (1.09;1.46)
	CKD stage 3b	1.71 (1.63;1.8)	1.98 (1.92;2.05)	2.57 (2.37;2.79)	1.82 (1.69;1.96)	1.75 (1.49;2.07)
	CKD stage 4	2.54 (2.36;2.73)	2.98 (2.83;3.14)	4.37 (3.9;4.9)	3.23 (2.93;3.57)	3.07 (2.46;3.83)
	CKD stage 5	4.56 (3.81;5.46)	5.77 (5.09;6.54)	7.55 (5.68;10.02)	5.92 (4.62;7.58)	11 (7.42;16.32)
	RRT (dialysis)	8.28 (7.13;9.6)	7.23 (6.43;8.13)	12.47 (10.12;15.35)	9.02 (7.23;11.26)	5.6 (3;10.45)
	RRT (transplant)	7.07 (5.34;9.37)	8.31 (6.91;9.98)	29.22 (24.02;35.54)	17.58 (13.37;23.12)	22.01 (12.71;38.11)
Organ transplant	No transplant	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Kidney transplant	7.53 (5.92;9.58)	7.89 (6.69;9.3)	27.42 (23.03;32.64)	18.4 (14.55;23.27)	18.03 (10.63;30.59)
	Other organ transplant	3.25 (1.96;5.4)	5.12 (3.85;6.82)	18.58 (13.61;25.37)	9.92 (6.39;15.39)	2.49 (0.35;17.71)
	Hypertension	1.02 (0.98;1.05)	1.17 (1.14;1.2)	1.39 (1.31;1.47)	1.07 (1.02;1.13)	1.2 (1.05;1.36)
	Chronic respiratory disease	1.89 (1.82;1.97)	2.18 (2.12;2.24)	2.79 (2.64;2.96)	2.46 (2.33;2.6)	2.77 (2.46;3.12)
	Chronic cardiac disease	1.56 (1.51;1.62)	1.82 (1.78;1.86)	2.13 (2.02;2.25)	1.86 (1.77;1.96)	1.88 (1.68;2.11)
	Cancer (non haematological)	1.13 (1.08;1.18)	1.25 (1.21;1.28)	1.25 (1.17;1.34)	1.4 (1.32;1.48)	1.49 (1.32;1.69)
	Haematological malignancy	1.99 (1.82;2.18)	2 (1.87;2.13)	4.41 (3.98;4.89)	3.76 (3.4;4.15)	4.3 (3.48;5.31)
	Chronic liver disease	2.65 (2.36;2.98)	2.99 (2.77;3.23)	3.59 (3.1;4.15)	3.54 (3.05;4.1)	3.32 (2.37;4.64)
	Stroke	2.09 (2.01;2.18)	1.91 (1.85;1.97)	1.82 (1.69;1.96)	1.84 (1.73;1.96)	1.89 (1.64;2.18)
	Dementia	5.06 (4.78;5.34)	3.81 (3.64;3.99)	2.79 (2.44;3.2)	3.22 (2.9;3.58)	2.43 (1.87;3.15)
	Other neurological disease	3.2 (3.01;3.41)	2.88 (2.75;3.02)	2.3 (2.04;2.59)	2.89 (2.61;3.2)	3.05 (2.45;3.79)
	Asplenia	1.52 (1.16;1.98)	1.92 (1.62;2.26)	1.39 (0.9;2.13)	1.86 (1.3;2.66)	2.74 (1.42;5.28)
	Rheumatoid arthritis/ lupus/ psoriasis	1.29 (1.22;1.36)	1.36 (1.31;1.41)	1.71 (1.58;1.84)	1.47 (1.36;1.59)	1.5 (1.27;1.78)
	Immunosuppressive condition	2.04 (1.9;2.19)	2.01 (1.92;2.12)	3.76 (3.45;4.1)	3.3 (3.04;3.59)	3.3 (2.75;3.96)
	Learning disability	8.69 (7.62;9.91)	6.98 (6.31;7.72)	4.12 (3.25;5.23)	4.63 (3.58;5.99)	9.89 (6.59;14.86)
	Severe mental illness	3.73 (3.44;4.04)	3.04 (2.85;3.24)	2.39 (2.06;2.77)	2.67 (2.31;3.08)	2.41 (1.72;3.38)

Table S3. Relative hazard of COVID-19-related death and 95% confidence intervals (95%CI) in OpenSAFELY-TPP in the five pandemic waves in England (wave 1: March 23 to May 30, 2020; wave 2 (alpha): September 7, 2020 to April 24, 2021; wave 3 (delta): May 28 to December 14, 2021; wave 4 (omicron): December 15, 2021 to April 29, 2022; and wave 5: June 24 to August 3, 2022).

Subgroup	Category	Relative hazard of COVID-19-related death* (95%CI)				
		Wave 1 (WT)	Wave 2 (alpha)	Wave 3 (delta)	Wave 4 (omicron)	Wave 5 (omicron)
Age Group	18-39	0.04 (0.03;0.06)	0.06 (0.06;0.07)	0.13 (0.11;0.15)	0.12 (0.09;0.15)	0.12 (0.07;0.22)
	40-49	0.31 (0.26;0.36)	0.33 (0.3;0.36)	0.47 (0.41;0.55)	0.36 (0.29;0.45)	0.3 (0.17;0.53)
	50-59	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	60-69	2.85 (2.6;3.12)	2.83 (2.67;3.01)	2.21 (2;2.44)	2.53 (2.22;2.88)	3.05 (2.23;4.16)
	70-79	9.06 (8.34;9.84)	7.95 (7.53;8.4)	4.75 (4.32;5.21)	7.48 (6.65;8.42)	8.9 (6.7;11.83)
	80 plus	44.8 (41.42;48.47)	36.59 (34.74;38.54)	15.25 (13.95;16.66)	39.16 (35.02;43.78)	45.92 (35.04;60.18)
Sex	Female	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Male	1.71 (1.66;1.77)	1.61 (1.57;1.64)	1.86 (1.77;1.96)	1.75 (1.67;1.84)	1.64 (1.48;1.83)

* Models were adjusted for age using a 4-knot cubic spline, except for estimation of age group relative hazards of death; adjusted for sex, except for estimation of sex group relative hazards of death; and stratified by region.

** HbA1c classification based on the latest measure within 15 months before baseline.

Abbreviations: WT wild type; CKD chronic kidney disease; RRT renal replacement therapy.

Immunity levels by vaccination status

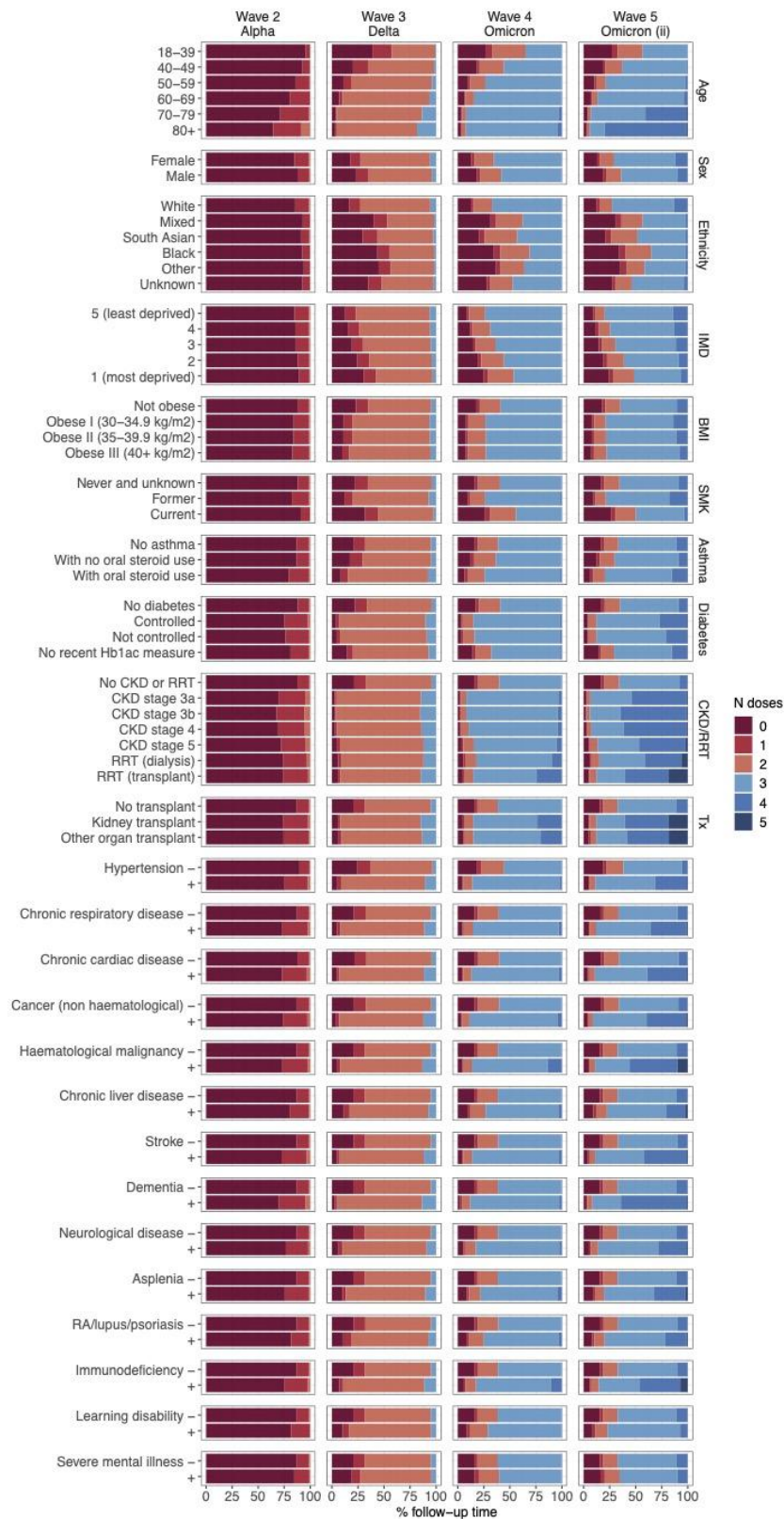


Figure S6. Percentage of follow-up time on 0-5 vaccination doses in wave 2-5 (wave 2 (alpha): September 7, 2020 to April 24, 2021; wave 3 (delta): May 28 to December 14, 2021; wave 4 (omicron): December 15, 2021 to April 29, 2022; and wave 5: June 24 to August 3, 2022). Abbreviations: IMD, index of multiple deprivation; BMI, body mass index; SMK, smoking; CKD, chronic kidney disease; RRT, renal replacement therapy; Tx, transplant. The percentages presented in this figure can be found in table S4 of the Supplementary material.

Table S4. Follow-up in 1,000 person-years on 1 dose, 2 doses and 3 doses or more of the SARS-CoV-2 vaccination, stratified by demographic and clinical subgroups in four pandemic waves in England (wave 2 (alpha): September 7, 2020 to April 24, 2021; wave 3 (delta): May 28 to December 14, 2021; wave 4 (omicron): December 15, 2021 to April 29, 2022; and wave 5: June 24 to August 3, 2022).

Subgroup	Category	Follow up in 1,000 person-years (% of total)															
		Wave 2 (alpha)			Wave 3 (delta)				Wave 4 (omicron)				Wave 5 (omicron)				
		Total	1 dose	2 doses or more	Total	1 dose	2 doses	≥ 3 doses	Total	1 dose	2 doses	≥ 3 doses	Total	1 dose	2 doses	≥ 3 doses	
All	-	11875.4	1447.1 (12%)	128.2 (1%)	10337.2	1131 (11%)	6583.2 (64%)	505.5 (5%)	7043.6	214.6 (3%)	1372 (19%)	4348.5 (62%)	2104.4	64.2 (3%)	290 (14%)	1418.3 (67%)	
Age Group	18-39	4226.9	172.4 (4%)	15.5 (0%)	3649.3	680.7 (19%)	1512 (41%)	36.5 (1%)	2480.5	143.4 (6%)	794.8 (32%)	864.4 (35%)	744	42.4 (6%)	177.7 (24%)	322.7 (43%)	
	40-49	1936.7	140.3 (7%)	12 (1%)	1674.9	249.8 (15%)	1049.4 (63%)	34.8 (2%)	1140.8	31.6 (3%)	267.5 (23%)	635.3 (55%)	338	9.3 (3%)	52.8 (16%)	213.5 (63%)	
	50-59	2063	266.9 (13%)	15.3 (1%)	1803.6	135.6 (8%)	1402.2 (78%)	70.5 (4%)	1226.5	20.2 (2%)	181.2 (15%)	902.5 (74%)	363.1	6.3 (2%)	34.3 (9%)	285.4 (78%)	
	60-69	1615.9	308.7 (19%)	8.9 (1%)	1423.5	46.7 (3%)	1186.3 (83%)	92 (6%)	975	10.6 (1%)	79.6 (8%)	822.5 (84%)	292.7	3.6 (1%)	15.8 (5%)	254.1 (87%)	
	70-79	1300.7	359.9 (28%)	14.9 (1%)	1148.8	11.2 (1%)	939.5 (82%)	155.6 (14%)	784.1	5.4 (1%)	30.5 (4%)	721.1 (92%)	234.5	1.7 (1%)	6.3 (3%)	218.2 (93%)	
	80 plus	732.1	198.8 (27%)	61.6 (8%)	637.1	7 (1%)	493.7 (77%)	116.2 (18%)	436.7	3.4 (1%)	18.4 (4%)	402.6 (92%)	132.1	0.9 (1%)	3.2 (2%)	124.4 (94%)	
Sex	Female	5963.9	817.2 (14%)	79.7 (1%)	5195.8	527.8 (10%)	3466.5 (67%)	293.2 (6%)	3527.4	101.2 (3%)	666.5 (19%)	2302 (65%)	1053.4	30.6 (3%)	139.6 (13%)	746.5 (71%)	
	Male	5911.5	629.9 (11%)	48.6 (1%)	5141.4	603.2 (12%)	3116.6 (61%)	212.3 (4%)	3516.2	113.5 (3%)	705.4 (20%)	2046.3 (58%)	1051.1	33.6 (3%)	150.4 (14%)	671.7 (63%)	
Ethnicity	White	9429.5	1269.3 (13%)	112.9 (1%)	8180.4	847 (10%)	5528.3 (68%)	453 (6%)	5547.6	148.8 (3%)	983.5 (18%)	3717.8 (67%)	1646.7	43.2 (3%)	197 (12%)	1199.3 (73%)	
	Mixed	145.8	9.6 (7%)	0.8 (1%)	129.6	17 (13%)	58 (45%)	2.7 (2%)	90.1	4.7 (5%)	23.1 (26%)	33.9 (37%)	27.6	1.5 (5%)	5.6 (20%)	11.9 (43%)	
	South Asian	794.5	66.5 (8%)	6.7 (1%)	704	102.1	375 (53%)	20.1 (3%)	488.1	25.2 (5%)	152.6	209.5	149.5	7.8 (5%)	38.3 (26%)	72.3 (49%)	

Table S4. Follow-up in 1,000 person-years on 1 dose, 2 doses and 3 doses or more of the SARS-CoV-2 vaccination, stratified by demographic and clinical subgroups in four pandemic waves in England (wave 2 (alpha): September 7, 2020 to April 24, 2021; wave 3 (delta): May 28 to December 14, 2021; wave 4 (omicron): December 15, 2021 to April 29, 2022; and wave 5: June 24 to August 3, 2022).

Subgroup	Category	Follow up in 1,000 person-years (% of total)															
		Wave 2 (alpha)			Wave 3 (delta)				Wave 4 (omicron)				Wave 5 (omicron)				
		Total	1 dose	2 doses or more	Total	1 dose	2 doses	≥ 3 doses	Total	1 dose	2 doses	≥ 3 doses	Total	1 dose	2 doses	≥ 3 doses	
						(14%)					(31%)	(43%)					
	Black	269.8	19.3 (7%)	1.5 (1%)	239.1	28.3 (12%)	101.2 (42%)	4.9 (2%)	165.3	10 (6%)	46.5 (28%)	51.4 (31%)	50.7	3 (6%)	12.6 (25%)	17.7 (35%)	
	Other	275.2	15.3 (6%)	1.5 (1%)	243.7	27.9 (11%)	100.8 (41%)	5 (2%)	171.3	7.5 (4%)	39 (23%)	61.8 (36%)	53.4	3.1 (6%)	9.3 (17%)	22.2 (41%)	
	Unknown	960.6	67 (7%)	4.7 (0%)	840.5	108.8 (13%)	419.9 (50%)	19.7 (2%)	581.2	18.4 (3%)	127.3 (22%)	274.2 (47%)	176.5	5.7 (3%)	27.1 (15%)	94.8 (54%)	
IMD quintile	5 (least deprived)	2230.3	311.6 (14%)	29.2 (1%)	1941.8	198.2 (10%)	1377.8 (71%)	119.3 (6%)	1319.6	25.3 (2%)	203.1 (15%)	973.8 (74%)	394.4	8.1 (2%)	36.7 (9%)	314.2 (79%)	
	4	2456.2	326.8 (13%)	30 (1%)	2139.5	222.1 (10%)	1457.5 (68%)	120.2 (6%)	1459.5	34.2 (2%)	249.3 (17%)	1004.7 (69%)	436.1	10.8 (2%)	48.3 (11%)	325.6 (74%)	
	3	2529.1	318 (13%)	28 (1%)	2201.4	236.6 (11%)	1431.1 (65%)	111.7 (5%)	1501.6	41.8 (3%)	281.6 (19%)	959.3 (64%)	448.7	12.8 (3%)	57.9 (13%)	312.3 (69%)	
	2	2361.9	263.9 (11%)	22.6 (1%)	2055.5	235 (11%)	1232.7 (60%)	86.9 (4%)	1402.5	49.7 (4%)	304.9 (22%)	780.9 (56%)	420	14.8 (4%)	67.6 (16%)	257.5 (61%)	
	1 (most deprived)	2297.9	226.8 (10%)	18.4 (1%)	1998.9	239 (12%)	1084.1 (54%)	67.5 (3%)	1360.3	63.7 (5%)	333.1 (24%)	629.8 (47%)	405.3	17.8 (4%)	79.6 (20%)	208.9 (51%)	
Body Mass Index	Not obese	9323.2	1050.5 (11%)	100.7 (1%)	8174.3	947 (12%)	4966.1 (61%)	376.3 (5%)	5611	182.1 (3%)	1132.3 (20%)	3299.6 (59%)	1690	55.1 (3%)	242.4 (14%)	1092.7 (64%)	
	Obese I (30-34.9 kg/m²)	1531.4	235.7 (15%)	17.9 (1%)	1293	113.2 (9%)	957.2 (74%)	80.5 (6%)	854.7	19.1 (2%)	140.4 (16%)	627.4 (73%)	246.7	5.4 (2%)	27.6 (11%)	194 (78%)	
	Obese II (35-39.9 kg/m²)	625.1	95.4 (15%)	6.3 (1%)	531.8	47.3 (9%)	396.6 (75%)	30.5 (6%)	352.8	8.1 (2%)	60.5 (17%)	257.1 (73%)	102.2	2.3 (2%)	11.9 (12%)	80.3 (78%)	

Table S4. Follow-up in 1,000 person-years on 1 dose, 2 doses and 3 doses or more of the SARS-CoV-2 vaccination, stratified by demographic and clinical subgroups in four pandemic waves in England (wave 2 (alpha): September 7, 2020 to April 24, 2021; wave 3 (delta): May 28 to December 14, 2021; wave 4 (omicron): December 15, 2021 to April 29, 2022; and wave 5: June 24 to August 3, 2022).

Subgroup	Category	Follow up in 1,000 person-years (% of total)															
		Wave 2 (alpha)			Wave 3 (delta)				Wave 4 (omicron)				Wave 5 (omicron)				
		Total	1 dose	2 doses or more	Total	1 dose	2 doses	≥ 3 doses	Total	1 dose	2 doses	≥ 3 doses	Total	1 dose	2 doses	≥ 3 doses	
	Obese III (40+ kg/m²)	395.6	65.5 (17%)	3.4 (1%)	338.2	23.4 (7%)	263.4 (78%)	18.3 (5%)	225.2	5.4 (2%)	38.8 (17%)	164.3 (73%)	65.6	1.5 (2%)	8 (12%)	51.1 (78%)	
Smoking status	Never and unknown	6000.8	649.2 (11%)	60.4 (1%)	5240.2	632.8 (12%)	3209.3 (61%)	226.6 (4%)	3583.8	110.2 (3%)	746.9 (21%)	2138.1 (60%)	1078.2	34.8 (3%)	156.8 (15%)	708.2 (65%)	
	Former	3867.2	624.2 (16%)	58.4 (2%)	3385.1	274.8 (8%)	2467.4 (73%)	237.4 (7%)	2306.6	45.8 (2%)	342.1 (15%)	1700.5 (73%)	689.3	13.4 (2%)	68.4 (10%)	541.7 (79%)	
	Current	2007.4	173.7 (9%)	9.5 (0%)	1711.9	223.3 (13%)	906.4 (53%)	41.5 (2%)	1153.1	58.7 (5%)	283 (25%)	509.8 (44%)	337	16 (5%)	64.8 (19%)	168.3 (49%)	
Asthma	No asthma	9936.7	1201.5 (12%)	107.9 (1%)	8651.8	933.7 (11%)	5457.3 (63%)	424.1 (5%)	5903.2	177.4 (3%)	1137.5 (19%)	3614.4 (61%)	1765.7	53.8 (3%)	241.5 (14%)	1178.1 (67%)	
	With no oral steroid use	1754.6	211.1 (12%)	17.3 (1%)	1578.6	189.8 (12%)	1043.7 (66%)	73.4 (5%)	1048	34.7 (3%)	219.2 (21%)	665.4 (64%)	307.2	9.7 (3%)	44.9 (15%)	215.1 (70%)	
	With oral steroid use	184	34.5 (19%)	3 (2%)	106.7	7.5 (7%)	82.1 (77%)	8.1 (8%)	92.4	2.5 (3%)	15.2 (17%)	68.5 (74%)	31.5	0.8 (2%)	3.7 (12%)	25 (80%)	
Diabetes	No diabetes	10683.8	1188.3 (11%)	103.7 (1%)	9253	1091.1 (12%)	5708.4 (62%)	402.6 (4%)	6283.5	203.4 (3%)	1288 (20%)	3722.4 (59%)	1869.2	60.7 (3%)	271.4 (15%)	1217.3 (65%)	
	Controlled	952	214.8 (23%)	20.9 (2%)	826.9	25.8 (3%)	683.2 (83%)	84 (10%)	617.7	7.9 (1%)	63 (10%)	525.4 (85%)	196.6	2.6 (1%)	14.2 (7%)	172.2 (88%)	
	Not controlled	47.7	10.6 (22%)	0.7 (2%)	40.8	1.4 (3%)	34.1 (84%)	3.6 (9%)	26.6	0.4 (1%)	3 (11%)	22.2 (84%)	7.8	0.1 (1%)	0.6 (7%)	6.8 (87%)	
	Without recent HbA1c measure	191.8	33.4 (17%)	2.9 (2%)	216.5	12.7 (6%)	157.5 (73%)	15.4 (7%)	115.8	3 (3%)	17.9 (15%)	78.3 (67%)	30.9	0.8 (3%)	3.8 (12%)	21.9 (71%)	
Chronic kidney disease or renal replacement	No CKD or RRT	11263	1286 (11%)	100.4 (1%)	9796.7	1122.4 (11%)	6144.6 (63%)	427 (4%)	6674.3	211.5 (3%)	1351.4 (20%)	4011.2 (60%)	1992.5	63.3 (3%)	286.1 (14%)	1313.8 (66%)	

Table S4. Follow-up in 1,000 person-years on 1 dose, 2 doses and 3 doses or more of the SARS-CoV-2 vaccination, stratified by demographic and clinical subgroups in four pandemic waves in England (wave 2 (alpha): September 7, 2020 to April 24, 2021; wave 3 (delta): May 28 to December 14, 2021; wave 4 (omicron): December 15, 2021 to April 29, 2022; and wave 5: June 24 to August 3, 2022).

Subgroup	Category	Follow up in 1,000 person-years (% of total)															
		Wave 2 (alpha)			Wave 3 (delta)				Wave 4 (omicron)				Wave 5 (omicron)				
		Total	1 dose	2 doses or more	Total	1 dose	2 doses	≥ 3 doses	Total	1 dose	2 doses	≥ 3 doses	Total	1 dose	2 doses	≥ 3 doses	
therapy	CKD stage 3a	409.5	107.8 (26%)	17.4 (4%)	360.5	5.6 (2%)	293.4 (81%)	51.9 (14%)	245.1	2 (1%)	13 (5%)	224.9 (91%)	74.3	0.6 (1%)	2.5 (3%)	69.5 (93%)	
	CKD stage 3b	148.3	39.7 (27%)	8.1 (5%)	131.4	1.9 (1%)	106.3 (81%)	20.1 (15%)	90.4	0.8 (1%)	4.9 (5%)	82.9 (92%)	27.3	0.2 (1%)	0.9 (3%)	25.7 (93%)	
	CKD stage 4	34.8	8.9 (26%)	1.8 (5%)	31.1	0.6 (2%)	25.2 (81%)	4.4 (14%)	21.7	0.2 (1%)	1.5 (7%)	19.5 (90%)	6.7	0.1 (1%)	0.3 (4%)	6.2 (93%)	
	CKD stage 5	3.7	0.9 (24%)	0.2 (4%)	3.4	0.1 (3%)	2.7 (80%)	0.4 (12%)	2.4	0 (2%)	0.2 (10%)	2 (84%)	0.8	0 (2%)	0.1 (7%)	0.6 (87%)	
	RRT (dialysis)	8.2	1.9 (23%)	0.3 (3%)	7.3	0.2 (3%)	5.8 (79%)	0.9 (12%)	5.1	0.1 (2%)	0.5 (11%)	4.2 (82%)	1.5	0 (2%)	0.1 (8%)	1.3 (85%)	
	RRT (transplant)	7.8	1.9 (24%)	0.1 (2%)	6.8	0.2 (2%)	5.3 (77%)	1 (15%)	4.6	0.1 (1%)	0.4 (9%)	3.9 (85%)	1.4	0 (1%)	0.1 (6%)	1.3 (88%)	
Organ transplant	No transplant	11862.8	1444 (12%)	128 (1%)	10326.1	1130.7 (11%)	6574.6 (64%)	503.9 (5%)	7036.1	214.5 (3%)	1371.3 (19%)	4342.1 (62%)	2102.2	64.2 (3%)	289.9 (14%)	1416.3 (67%)	
	Kidney transplant	9.3	2.2 (24%)	0.2 (2%)	8.2	0.2 (2%)	6.3 (77%)	1.2 (15%)	5.5	0.1 (1%)	0.5 (9%)	4.7 (85%)	1.7	0 (1%)	0.1 (6%)	1.4 (88%)	
	Other organ transplant	3.3	0.8 (24%)	0 (1%)	2.9	0.1 (3%)	2.2 (78%)	0.4 (13%)	2	0 (2%)	0.2 (8%)	1.7 (84%)	0.6	0 (1%)	0 (6%)	0.5 (87%)	
Hypertension	No	7929.2	699.6 (9%)	53.7 (1%)	6885.7	933.4 (14%)	3923.2 (57%)	211 (3%)	4707.5	178.6 (4%)	1101.6 (23%)	2487.3 (53%)	1406.8	53.6 (4%)	235.9 (17%)	835.9 (59%)	
	Yes	3946.2	747.4 (19%)	74.6 (2%)	3451.5	197.6 (6%)	2660 (77%)	294.7 (9%)	2336.1	36 (2%)	270.4 (12%)	1861.2 (80%)	697.7	10.7 (2%)	54.1 (8%)	582.3 (84%)	
Chronic respiratory disease	No	11416.7	1336.6 (12%)	116.4 (1%)	9937.3	1119.7 (11%)	6259.3 (63%)	460.6 (5%)	6772.3	210.9 (3%)	1348 (20%)	4116.9 (61%)	2023.3	63.2 (3%)	285 (14%)	1346.8 (67%)	
	Yes	458.7	110.4 (24%)	11.8 (3%)	399.9	11.3 (3%)	323.8 (81%)	45 (11%)	271.2	3.8 (1%)	24 (9%)	231.6 (85%)	81.2	1.1 (1%)	5 (6%)	71.5 (88%)	

Table S4. Follow-up in 1,000 person-years on 1 dose, 2 doses and 3 doses or more of the SARS-CoV-2 vaccination, stratified by demographic and clinical subgroups in four pandemic waves in England (wave 2 (alpha): September 7, 2020 to April 24, 2021; wave 3 (delta): May 28 to December 14, 2021; wave 4 (omicron): December 15, 2021 to April 29, 2022; and wave 5: June 24 to August 3, 2022).

Subgroup	Category	Follow up in 1,000 person-years (% of total)															
		Wave 2 (alpha)			Wave 3 (delta)				Wave 4 (omicron)				Wave 5 (omicron)				
		Total	1 dose	2 doses or more	Total	1 dose	2 doses	≥ 3 doses	Total	1 dose	2 doses	≥ 3 doses	Total	1 dose	2 doses	≥ 3 doses	
Chronic cardiac disease	No	11110.1	1264.4 (11%)	104.7 (1%)	9665.5	1114.1 (12%)	6038.4 (62%)	426.8 (4%)	6585.6	209.2 (3%)	1335.4 (20%)	3951.1 (60%)	1966.8	62.6 (3%)	282.5 (14%)	1295.4 (66%)	
	Yes	765.3	182.7 (24%)	23.5 (3%)	671.7	16.9 (3%)	544.8 (81%)	78.8 (12%)	458	5.4 (1%)	36.6 (8%)	397.4 (87%)	137.6	1.6 (1%)	7.5 (5%)	122.8 (89%)	
Cancer (non haematological)	No	11308.2	1315.1 (12%)	112.3 (1%)	9833.4	1116.1 (11%)	6175.1 (63%)	445.3 (5%)	6696.5	211.4 (3%)	1348 (20%)	4040.7 (61%)	1999.4	63.3 (3%)	285.5 (14%)	1322.3 (66%)	
	Yes	567.1	132 (23%)	16 (3%)	503.8	14.9 (3%)	408 (81%)	60.3 (12%)	347	3.3 (1%)	23.9 (7%)	307.8 (89%)	105.1	1 (1%)	4.5 (4%)	96 (92%)	
Haematological malignancy	No	11808.6	1431 (12%)	126.5 (1%)	10277.9	1129.4 (11%)	6536.3 (64%)	497.8 (5%)	7002.9	214.1 (3%)	1368.8 (20%)	4313.3 (62%)	2092.2	64.1 (3%)	289.3 (14%)	1407.4 (67%)	
	Yes	66.8	16 (24%)	1.8 (3%)	59.3	1.6 (3%)	46.9 (79%)	7.7 (13%)	40.7	0.5 (1%)	3.2 (8%)	35.1 (87%)	12.3	0.1 (1%)	0.7 (5%)	10.9 (89%)	
Chronic liver disease	No	11806.8	1434.3 (12%)	127.5 (1%)	10275.3	1127.2 (11%)	6536.3 (64%)	501.1 (5%)	7000.4	213.4 (3%)	1365.7 (20%)	4316.8 (62%)	2091.3	63.9 (3%)	288.6 (14%)	1408 (67%)	
	Yes	68.6	12.8 (19%)	0.8 (1%)	61.9	3.7 (6%)	46.9 (76%)	4.4 (7%)	43.2	1.2 (3%)	6.3 (15%)	31.6 (73%)	13.2	0.4 (3%)	1.4 (11%)	10.2 (77%)	
Stroke	No	11634.4	1388.9 (12%)	120.4 (1%)	10123.8	1125.2 (11%)	6410.4 (63%)	480.5 (5%)	6896.6	212.6 (3%)	1359.8 (20%)	4221.7 (61%)	2059.8	63.7 (3%)	287.6 (14%)	1378.6 (67%)	
	Yes	241	58.2 (24%)	7.9 (3%)	213.4	5.8 (3%)	172.7 (81%)	25 (12%)	146.9	2 (1%)	12.2 (8%)	126.6 (87%)	44.6	0.6 (1%)	2.5 (6%)	39.7 (89%)	
Dementia	No	11850.7	1440.7 (12%)	127.2 (1%)	10316.1	1130.5 (11%)	6566 (64%)	502.7 (5%)	7029.3	214.4 (3%)	1370.9 (20%)	4335.9 (62%)	2100.2	64.2 (3%)	289.8 (14%)	1414.3 (67%)	
	Yes	24.6	6.4 (26%)	1.1 (4%)	21.1	0.5 (2%)	17.2 (81%)	2.8 (13%)	14.2	0.2 (2%)	1.1 (8%)	12.5 (88%)	4.3	0.1 (2%)	0.2 (5%)	3.9 (91%)	
Other neurological	No	11762	1422.8	126.2 (1%)	10238.2	1127.4	6502.7	496.8 (5%)	6976.1	213.6 (3%)	1364.9	4292.8	2084.2	63.9 (3%)	288.6	1400.8	

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Subgroup	Category	Follow up in 1,000 person-years (% of total)															
		Wave 2 (alpha)			Wave 3 (delta)				Wave 4 (omicron)				Wave 5 (omicron)				
		Total	1 dose	2 doses or more	Total	1 dose	2 doses	≥ 3 doses	Total	1 dose	2 doses	≥ 3 doses	Total	1 dose	2 doses	≥ 3 doses	
disease			(12%)			(11%)	(64%)				(20%)	(62%)			(14%)	(67%)	
	Yes	113.3	24.3 (21%)	2.1 (2%)	99	3.6 (4%)	80.5 (81%)	8.7 (9%)	67.5	1.1 (2%)	7.1 (10%)	55.7 (82%)	20.2	0.3 (2%)	1.4 (7%)	17.5 (86%)	
Asplenia	No	11856.6	1442.8 (12%)	127.9 (1%)	10320.9	1130.4 (11%)	6570.7 (64%)	503.8 (5%)	7032.5	214.4 (3%)	1370.8 (19%)	4339.8 (62%)	2101.1	64.2 (3%)	289.7 (14%)	1415.6 (67%)	
	Yes	18.7	4.3 (23%)	0.3 (2%)	16.3	0.5 (3%)	12.5 (76%)	1.7 (10%)	11.1	0.2 (2%)	1.2 (11%)	8.7 (78%)	3.3	0.1 (2%)	0.3 (9%)	2.7 (81%)	
Rheumatoid arthritis/ lupus/ psoriasis	No	11282	1346 (12%)	119.4 (1%)	9817.7	1091.1 (11%)	6197.6 (63%)	466.9 (5%)	6690.4	207.2 (3%)	1320.2 (20%)	4083.7 (61%)	1998.9	62.2 (3%)	279.4 (14%)	1334.1 (67%)	
	Yes	593.4	101 (17%)	8.8 (1%)	519.5	39.8 (8%)	385.5 (74%)	38.6 (7%)	353.1	7.4 (2%)	51.8 (15%)	264.7 (75%)	105.5	2.1 (2%)	10.6 (10%)	84.2 (79%)	
Immunosuppressive condition	No	11729.2	1414.3 (12%)	125 (1%)	10206.5	1126.5 (11%)	6481.3 (64%)	490.6 (5%)	6952.2	213.1 (3%)	1362.9 (20%)	4273 (62%)	2076.4	63.8 (3%)	288 (14%)	1394.3 (67%)	
	Yes	146.1	32.7 (22%)	3.2 (2%)	130.7	4.5 (3%)	101.9 (78%)	15 (11%)	91.4	1.5 (2%)	9.1 (10%)	75.4 (82%)	28	0.4 (2%)	2 (7%)	23.9 (85%)	
Learning disability	No	11808	1435.1 (12%)	127.8 (1%)	10276.2	1127.1 (11%)	6535 (64%)	502.7 (5%)	7001.5	213.4 (3%)	1364.6 (19%)	4318.6 (62%)	2091.8	63.9 (3%)	288.5 (14%)	1408.5 (67%)	
	Yes	67.4	11.9 (18%)	0.4 (1%)	61	3.9 (6%)	48.2 (79%)	2.8 (5%)	42	1.2 (3%)	7.4 (18%)	29.8 (71%)	12.7	0.3 (3%)	1.5 (12%)	9.7 (77%)	
Severe mental illness	No	11734.8	1426.1 (12%)	127.1 (1%)	10212.6	1120.6 (11%)	6498.3 (64%)	500 (5%)	6958.5	210.9 (3%)	1356 (19%)	4297 (62%)	2079	63.2 (3%)	286.4 (14%)	1401.6 (67%)	
	Yes	140.6	20.9 (15%)	1.1 (1%)	124.6	10.4 (8%)	84.9 (68%)	5.5 (4%)	85.1	3.7 (4%)	16 (19%)	51.5 (61%)	25.4	1 (4%)	3.6 (14%)	16.6 (65%)	

*Person-years have been rounded to the nearest five and the first decimal.
Abbreviations: CKD chronic kidney disease; RRT renal replacement therapy.

Codelists

Table S5. All codelists can be found at <https://codelists.opensafely.org/codelist/> following the links below. Further details of how these codes are combined are available in the project study definition and subsequent analysis R scripts at https://github.com/opensafely/covid_mortality_over_time.

Name	URL	Accessed on
ethnicity	https://codelists.opensafely.org/codelist/opensafely/ethnicity/2020-04-27/	2022-02-23
smoking-clear	https://codelists.opensafely.org/codelist/opensafely/smoking-clear/2020-04-29/	2022-02-23
hypertension	https://codelists.opensafely.org/codelist/opensafely/hypertension/2020-04-28/	2022-02-23
chronic-respiratory-disease	https://codelists.opensafely.org/codelist/opensafely/chronic-respiratory-disease/2020-04-10/	2022-02-23
asthma-diagnosis	https://codelists.opensafely.org/codelist/opensafely/asthma-diagnosis/2020-04-15/	2022-02-23
asthma-oral-prednisolone-medication	https://codelists.opensafely.org/codelist/opensafely/asthma-oral-prednisolone-medication/2020-04-27/	2022-02-23
chronic-cardiac-disease	https://codelists.opensafely.org/codelist/opensafely/chronic-cardiac-disease/2020-04-08/	2022-02-23
diabetes	https://codelists.opensafely.org/codelist/opensafely/diabetes/2020-04-15/	2022-02-23
glycated-haemoglobin-hba1c-tests-ifcc	https://codelists.opensafely.org/codelist/opensafely/glycated-haemoglobin-hba1c-tests-ifcc/6d7287f8/	2022-03-09
haematological-cancer	https://codelists.opensafely.org/codelist/opensafely/haematological-cancer/2020-04-15/	2022-02-23
lung-cancer	https://codelists.opensafely.org/codelist/opensafely/lung-cancer/2020-04-15/	2022-02-23
cancer-excluding-lung-and-haematological	https://codelists.opensafely.org/codelist/opensafely/cancer-excluding-lung-and-haematological/2020-04-15/	2022-02-23
dialysis	https://codelists.opensafely.org/codelist/opensafely/dialysis/3ce108ac/	2022-02-23
kidney-transplant	https://codelists.opensafely.org/codelist/opensafely/kidney-transplant/2020-07-15/	2022-03-03
egfr	https://codelists.opensafely.org/codelist/pincer/egfr/v1.8/	2022-03-03
chronic-liver-disease	https://codelists.opensafely.org/codelist/opensafely/chronic-liver-disease/2020-06-02/	2022-02-23
stroke-updated	https://codelists.opensafely.org/codelist/opensafely/stroke-updated/2020-06-02/	2022-02-23
dementia	https://codelists.opensafely.org/codelist/opensafely/dementia/2020-04-22/	2022-02-23
other-neurological-conditions	https://codelists.opensafely.org/codelist/opensafely/other-neurological-conditions/2020-06-02/	2022-02-23
other-organ-transplant	https://codelists.opensafely.org/codelist/opensafely/other-organ-transplant/79caeeec/	2022-03-09
asplenia	https://codelists.opensafely.org/codelist/opensafely/asplenia/2020-06-02/	2022-02-23
sickle-cell-disease	https://codelists.opensafely.org/codelist/opensafely/sickle-cell-disease/2020-04-14/	2022-02-23
ra-sle-psoriasis	https://codelists.opensafely.org/codelist/opensafely/ra-sle-psoriasis/2020-04-14/	2022-02-23
aplastic-anaemia	https://codelists.opensafely.org/codelist/opensafely/aplastic-anaemia/2020-04-24/	2022-02-23
immdx_cov	https://codelists.opensafely.org/codelist/primis-covid19-vacc-uptake/immdx_cov/v1/	2022-03-10
immrx	https://codelists.opensafely.org/codelist/primis-covid19-vacc-uptake/immrx/v1/	2022-03-10
ld_cod	https://codelists.opensafely.org/codelist/nhsd-primary-care-domain-refsets/ld_cod/20210127/	2022-02-24

sev_mental	https://codelists.opensafely.org/codelist/primis-covid19-vacc-uptake/sev_mental/v1/	2022-02-24
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Administrative

Information governance

NHS England is the data controller for OpenSAFELY-TPP; TPP is the data processor; all study authors using OpenSAFELY have the approval of NHS England. This implementation of OpenSAFELY is hosted within the TPP environment which is accredited to the ISO 27001 information security standard and is NHS IG Toolkit compliant.[4]

Patient data has been pseudonymised for analysis and linkage using industry standard cryptographic hashing techniques; all pseudonymised datasets transmitted for linkage onto OpenSAFELY are encrypted; access to the platform is via a virtual private network (VPN) connection, restricted to a small group of researchers; the researchers hold contracts with NHS England and only access the platform to initiate database queries and statistical models; all database activity is logged; only aggregate statistical outputs leave the platform environment following best practice for anonymisation of results such as statistical disclosure control for low cell counts.[5]

The OpenSAFELY research platform adheres to the obligations of the UK General Data Protection Regulation (GDPR) and the Data Protection Act 2018. In March 2020, the Secretary of State for Health and Social Care used powers under the UK Health Service (Control of Patient Information) Regulations 2002 (COPI) to require organisations to process confidential patient information for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the COVID-19 outbreak and incidents of exposure; this sets aside the requirement for patient consent.[6] This was extended in July 2022 for the NHS England OpenSAFELY COVID-19 research platform.[7] In some cases of data sharing, the common law duty of confidence is met using, for example, patient consent or support from the Health Research Authority Confidentiality Advisory Group.[8]

Taken together, these provide the legal bases to link patient datasets on the OpenSAFELY platform. GP practices, from which the primary care data are obtained, are required to share relevant health information to support the public health response to the pandemic, and have been informed of the OpenSAFELY analytics platform.

Transparency

The guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data access and verification

Access to the underlying identifiable and potentially re-identifiable pseudonymised electronic health record data is tightly governed by various legislative and regulatory frameworks, and restricted by best practice. The data in OpenSAFELY is drawn from General Practice data across England where TPP is the Data Processor. TPP developers (CB, JC, JP, FH, and SH) initiate an automated process to create pseudonymised records in the core OpenSAFELY database, which are copies of key structured data tables in the identifiable records. These are linked onto key external data resources that have also been pseudonymised via SHA-512 one-way hashing of NHS numbers using a shared salt. Bennett Institute for Applied Data Science developers and PIs (BG, CEM, SCJB, AJW, WJH, DE, PI, SD, GH, BBC, RMS, ID, TW, TO, SM, CLS, LB and EJW) holding contracts with NHS England have access to the OpenSAFELY pseudonymised data tables as needed to develop the OpenSAFELY tools. These tools in turn enable researchers with OpenSAFELY Data Access Agreements to write and execute code for data management and data analysis without direct access to the underlying raw pseudonymised patient data, and to review the outputs of this code. All code for the full data management pipeline—from raw data to completed results for this analysis—and for the OpenSAFELY platform as a whole

is available for review at github.com/OpenSAFELY. We invite people to email to team@opensafely.org to discuss applying for access to the platform.

The data management and analysis code for this paper was led by LN and contributed to by EPKP, CDA, WJH, LF and AJW.

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