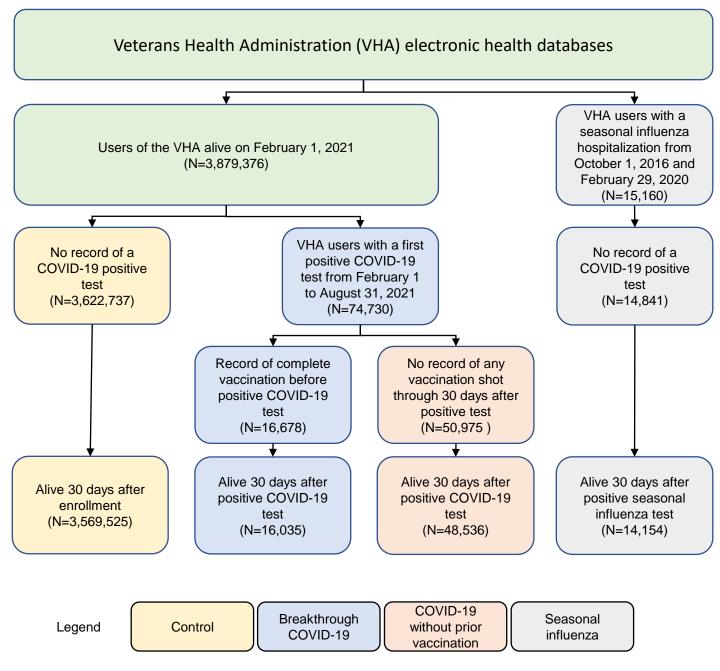
Extended data figure 1 Acute cornary disease -Atrial fibrillation -Atrial flutter Heart failure -Cardiovascular Myocardical infarction -Myocarditis -Tachycardia -Ventricular arrhythmias -Deep vein thrombosis -Other coagulation disorders -Coagulation Pulomary emoblism -Superfical venous thrombosis Fatigue - \vdash **Fatigue** Constipation or diarrhea Gastrointestinal **GERD** AKI Kidney CKD eGFR decline >=50% Anxiety Mood disorder Mental health Sleep disorder -Substance abuse - \vdash Diabetes -Metabolic Diabetes medications · Musculoskeletal Muscle or joint pain -Memory loss Smell loss Neurologic Stroke Cough -H Hypoxemia · **Pulmonary** Shortness of breath -5 10 20 30 Hazard ratio



Extended Data Figure 2

Extended Data Table 1: Demographic and health characteristics of those with breakthrough COVID-19 and the control

group.

Characteristic	Breakthrough COVID-19 (N=16,035)	Control (N=3,569,525)
Age, mean SD	66.62 (13.79)	63.82 (16.09)
Race, N (%)	, ,	
White	11,436 (71.32)	2,736,491 (76.66)
Black	3,395 (21.17)	665,774 (18.65)
Other	1,204 (7.51)	167,260 (4.69)
Sex, N (%)	, , ,	
Male	14,643 (91.32)	3,230,996 (90.52)
Female	1,391 (8.68)	338,529 (9.48)
ADIa, mean SD	52.41 (15.06)	51.78 (15.90)
Smoking status, N (%)	, ,	
Never	8,264 (51.54)	1,792,956 (50.23)
Former	4,674 (29.15)	936,518 (26.24)
Current	3,097 (19.31)	840,051 (23.53)
Long-term care, N (%)	246 (1.53)	21,814 (0.61)
Systolic blood pressure, mean SD	132.79 (19.07)	131.55 (16.78)
BMI, (mean SD)	30.80 (6.40)	30.90 (232.06)
Cerebrovascular disease, N (%)	1,380 (8.61)	161,188 (4.52)
Cancer, N (%)	2,073 (12.93)	228,989 (6.42)
Anxiety, N (%)	2,121 (13.23)	306,387 (8.58)
Chronic kidney disease, N (%)	2,309 (14.40)	492,848 (13.81)
Cardiovascular disease, N (%)	3,869 (24.13)	470,963 (13.19)
Dementia, N (%)	1,056 (6.59)	113,220 (3.17)
Depression, N (%)	1,753 (10.93)	250,405 (7.02)
Diabetes mellitus type 2, N (%)	6,150 (38.35)	845,115 (23.68)
Lung disease, N (%)	3,088 (19.26)	404,159 (11.32)
Peripheral artery disease, N (%)	348 (2.17)	32,931 (0.92)
Receipt of seasonal influenza vaccine in the year prior, N (%)	6,118 (38.15)	951,955 (26.67)
Number of inpatient visits, median (IQR)	0 (0, 0)	0 (0, 0)
Number of outpatient visits, median (IQR)	3 (2, 4)	2 (1, 3)
Number of blood chemistry panels, median (IQR)	2 (1, 4)	1 (0, 2)
Number of unique medications, median (IQR)	11 (6, 18)	5 (1, 11)
Vaccination type, N (%)	11 (3, 13)	0 (1, 11)
Ad26.COV2.S	1807 (11.3%)	-
mRNA-1273	6086 (38.0%)	-
BNT162b2	8142 (50.8%)	-
Incident breakthrough rates ^b , per 1000 persons at 6-months (95% CI)	31.12 (66.676)	
Overall	7.26 (7.25, 7.26)	-
Ad26.COV2.S	14.72 (14.70, 14.75)	-
mRNA-1273	5.57 (5.56, 5.57)	-
BNT162b2	8.31 (8.31, 8.31)	-
Calendar week of vaccination completion in 2021, median (IQR)	12 (9, 16)	-
Calendar week of vaccination completion in 2021, median (IQR)	31 (27, 33)	_
Time (in weeks) between completion of vaccination to positive	, ,	
COVID-19 test, median (IQR)	17 (10, 21)	-

All characteristics assessed in the year prior to testing positive for COVID-19, or equivalent T₀.

^aADI is a composite measure of socioeconomic deprivation that ranges from 0 (low deprivation) to 100 (high deprivation).

^bAmong those with record of complete vaccination in the VHA (N=3,165,714 overall; 205222 Ad26.COV2.S; 1358794 mRNA-1273; 1601597 BNT162b2)

ADI, Area Deprivation Index; BMI, body mass index; IQR, interquartile range; N, sample size; SD, standard deviation.

Extended Data Table 2: Demographic and health characteristics of those with breakthrough COVID-19 who were not hospitalized, those who were hospitalized during the acute phase of the disease, and the control group.

Characteristic	Not hospitalized ^a breakthrough COVID-19 (N=13,683)	Hospitalized ^a breakthrough COVDI- 19 (N=2,352)	Control (N=3,569,525)
Age, (mean SD)	65.68 (13.97)	72.14 (11.18)	63.82 (16.09)
Race, N (%)			
White	9,831 (71.85)	1,605 (68.24)	2,736,491 (76.66)
Black	2,823 (20.63)	572 (24.32)	665,774 (18.65)
Other	1,029 (7.52)	175 (7.44)	167,260 (4.69)
Sex, N (%)			
Male	12,389 (90.55)	2,254 (95.83)	3,230,996 (90.52)
Female	1,293 (9.45)	98 (4.17)	338,529 (9.48)
ADI ^b , (mean SD)	52.30 (15.13)	53.03 (14.67)	51.78 (15.90)
Smoking status, N (%)			
Never	7,178 (52.46)	1,086 (46.17)	1,792,956 (50.23)
Former	3,916 (28.62)	758 (32.23)	936,518 (26.24)
Current	2,589 (18.92)	508 (21.60)	840,051 (23.53)
Long-term care, N (%)	157 (1.15)	89 (3.78)	21,814 (0.61)
Systolic blood pressure, mean SD	132.47 (18.16)	134.65 (23.60)	131.55 (16.78)
BMI, (mean SD)	30.94 (6.29)	29.95 (6.91)	30.90 (232.06)
Cerebrovascular disease, N (%)	1,014 (7.41)	366 (15.56)	161,188 (4.52)
Cancer, N (%)	1,559 (11.39)	514 (21.85)	228,989 (6.42)
Anxiety, N (%)	1,690 (12.35)	431 (18.32)	306,387 (8.58)
Chronic kidney disease, N (%)	1,674 (12.23)	635 (27.00)	492,848 (13.81)
Cardiovascular disease, N (%)	2,963 (21.65)	906 (38.52)	470,963 (13.19)
Dementia, N (%)	737 (5.39)	319 (13.56)	113,220 (3.17)
Depression, N (%)	1,399 (10.22)	354 (15.05)	250,405 (7.02)
Diabetes mellitus type 2, N (%)	4,950 (36.18)	1,200 (51.02)	845,115 (23.68)
Lung disease, N (%)	2,349 (17.17)	739 (31.42)	404,159 (11.32)
Peripheral artery disease, N (%)	229 (1.67)	119 (5.06)	32,931 (0.92)
Receipt of seasonal influenza vaccine in the year prior, N (%)	5,080 (37.13)	1,038 (44.13)	951,955 (26.67)
Number of inpatient visits, median (IQR)	0 (0, 0)	0 (0, 1)	0 (0, 0)
Number of outpatient visits, median (IQR)	3 (2, 4)	4 (3, 5)	2 (1, 3)
Number of blood chemistry panels, median (IQR)	2 (1, 3)	4 (2, 9)	1 (0, 2)
Number of unique medications, median (IQR)	10 (6, 17)	17 (10, 23)	5 (1, 11)

All characteristics assessed in the year prior to testing positive for COVID-19, or equivalent T_0 .

^aHospitalization assessed during the acute phase of the disease.

^bADI is a composite measure of socioeconomic deprivation that ranges from 0 (low deprivation) to 100 (high deprivation).

ADI, Area Deprivation Index; BMI, body mass index; IQR, interquartile range; N, sample size; SD, standard deviation.

Extended Data Table 3: Demographic and health characteristics of those with breakthrough COVID-19 and those with COVID-19 without prior vaccination.

Characteristic	Breakthrough COVID-19 (N=16,035)	COVID-19 (N=48,536)
Age, mean SD	66.62 (13.79)	56.07 (15.72)
Race, N (%)		
White	11,436 (71.32)	34,537 (71.16)
Black	3,395 (21.17)	10,888 (22.43)
Other	1,204 (7.51)	3,111 (6.41)
Sex, N (%)		
Male	14,643 (91.32)	41,670 (85.85)
Female	1,391 (8.68)	6,866 (14.15)
ADIa, mean SD	52.41 (15.06)	53.38 (14.78)
Smoking status, N (%)		
Never	8,264 (51.54)	26,763 (55.14)
Former	4,674 (29.15)	10,806 (22.26)
Current	3,097 (19.31)	10,967 (22.60)
Long-term care, N (%)	246 (1.53)	409 (0.84)
Systolic blood pressure, mean SD	132.79 (19.07)	131.63 (17.55)
BMI, (mean SD)	30.80 (6.40)	31.21 (6.40)
Cerebrovascular disease, N (%)	1,380 (8.61)	2,045 (4.21)
Cancer, N (%)	2,073 (12.93)	2,763 (5.69)
Anxiety, N (%)	2,121 (13.23)	5,352 (11.03)
Chronic kidney disease, N (%)	2,309 (14.40)	3,042 (6.27)
Cardiovascular disease, N (%)	3,869 (24.13)	5,650 (11.64)
Dementia, N (%)	1,056 (6.59)	1,439 (2.96)
Depression, N (%)	1,753 (10.93)	4,775 (9.84)
Diabetes mellitus type 2, N (%)	6,150 (38.35)	11,664 (24.03)
Lung disease, N (%)	3,088 (19.26)	5,566 (11.47)
Peripheral artery disease, N (%)	348 (2.17)	429 (0.88)
Receipt of seasonal influenza vaccine in the year prior, N (%)	6,118 (38.15)	9,183 (18.92)
Number of inpatient visits, median (IQR)	0 (0, 0)	0 (0, 0)
Number of outpatient visits, median (IQR)	3 (2, 4)	2 (1, 3)
Number of blood chemistry panels, median (IQR)	2 (1, 4)	1 (1, 2)
Number of unique medications, median (IQR)	11 (6, 18)	7 (3, 12)
Week of 2021 that participant tested positive, median (IQR)	31 (27, 33)	17 (8, 30)
Care received at a medical center ^b , N (%)	10,333 (64.44)	29,717 (61.23)
Percent of hospital system beds occupied ^c , median (IQR)	0.43 (0.35, 0.49)	0.40 (0.33, 0.48)
Total number of hospital beds available in hospital system ^c , median (IQR)	407 (228, 610)	386 (227, 607)

All characteristics assessed in the year prior to testing positive for COVID-19, or equivalent T₀.

^aADI is a composite measure of socioeconomic deprivation that ranges from 0 (low deprivation) to 100 (high deprivation).

^bComplexity of the care system assessed whether participants receive care at a medical center vs an outpatient clinic. ^cAssessed as the average in the hospital system of care during the week of testing positive.

ADI, Area Deprivation Index; BMI, body mass index; IQR, interquartile range; N, sample size; SD, standard deviation.

Extended Data Table 4: Demographic and health characteristics of those with breakthrough COVID-19 who were hospitalized during the acute phase of the disease and those hospitalized with seasonal influenza.

Age, mean SD 72.14 (11.18) 69.61 (12.74) Race, N (%) White 1,605 (68.24) 10,339 (73.05) Black 572 (24.32) 3,172 (22.41) Other 175 (7.44) 643 (4.54) Sex, N (%) Male 2,254 (95.83) 13,351 (94.33) Female 98 (4.17) 803 (5.67) ADIª, mean SD 53.03 (14.66) 50.56 (15.47) Smoking status, N (%) Never 1,086 (46.17) 5,402 (38.17) Former 758 (32.23) 4,250 (30.03) Current 508 (21.6) 4,502 (31.81) Long-term care, N (%) 89 (3.78) 1,150 (8.13) Systolic blood pressure, (mean SD) 134.65 (23.59) 133.03 (23.57) BMI, (mean SD) 29.95 (6.91) 29.20 (6.98) Cerebrovascular disease, N (%) 366 (15.56) 2,043 (14.43) Cancer, N (%) 366 (15.66) 2,043 (14.43) Chronic kidney disease, N (%) 635 (27) 3,236 (22.86) Cardiovascular disease, N (%) 319 (13.56) 1,798	Characteristic	Breakthrough COVID-19 (N=2,352)	Seasonal Influenza (N=14,154)
White 1,605 (68.24) 10,339 (73.05) Black 572 (24.32) 3,172 (22.41) Other 175 (7.44) 643 (4.54) Sex, N (%) 175 (7.44) 643 (4.54) Sex, N (%) 175 (7.44) 643 (4.54) Male 2,254 (95.83) 13,351 (94.33) Female 98 (4.17) 803 (5.67) ADP, mean SD 53.03 (14.66) 50.56 (15.47) Smoking status, N (%) 1,086 (46.17) 5,402 (38.17) Former 758 (32.23) 4,250 (30.03) Current 508 (21.6) 4,502 (31.81) Long-term care, N (%) 89 (37.8) 1,150 (8.13) Systolic blood pressure, (mean SD) 134.65 (23.59) 133.03 (23.57) BMI, (mean SD) 29.95 (6.91) 29.20 (6.98) Cerebrovascular disease, N (%) 366 (15.56) 2,043 (14.43) Cancer, N (%) 366 (15.56) 2,043 (14.43) Anxiety, N (%) 431 (18.33) 3,097 (21.88) Chronic kidney disease, N (%) 635 (27) 3,236 (22.86) Chronic kidney disease, N (%) 635 (27) 3,236 (22.86) Dementia, N (%)	Age, mean SD	72.14 (11.18)	69.61 (12.74)
Black 572 (24.32) 3,172 (22.41) Other 175 (7.44) 643 (4.54) Sex, N (%) 175 (7.44) 643 (4.54) Sex, N (%) 2,254 (95.83) 13,351 (94.33) Female 98 (4.17) 803 (5.67) ADIa, mean SD 53.03 (14.66) 50.56 (15.47) Smoking status, N (%) 53.03 (14.66) 50.56 (15.47) Never 1,086 (46.17) 5,402 (38.17) Former 758 (32.23) 4,250 (30.03) Current 508 (21.6) 4,502 (31.81) Long-term care, N (%) 89 (3.78) 1,150 (8.13) Systolic blood pressure, (mean SD) 134.65 (23.59) 133.03 (23.57) BMI, (mean SD) 29.95 (6.91) 29.20 (6.98) Cerebrovascular disease, N (%) 366 (15.56) 2,043 (14.43) Anxiety, N (%) 431 (18.33) 3,097 (21.88) Chronic kidney disease, N (%) 635 (27) 3,236 (22.86) Cardiovascular disease, N (%) 635 (27) 3,236 (22.86) Cardiovascular disease, N (%) 354 (15.05) 2,242 (15.84) <td< td=""><td>Race, N (%)</td><td></td><td></td></td<>	Race, N (%)		
Other 175 (7.44) 643 (4.54) Sex, N (%) Male 2,254 (95.83) 13,351 (94.33) Female 98 (4.17) 803 (5.67) ADP, mean SD 53.03 (14.66) 50.56 (15.47) Smoking status, N (%) Smoking status, N (%) Never 1,086 (46.17) 5,402 (38.17) Former 758 (32.23) 4,250 (30.03) 20.03 </td <td>White</td> <td>1,605 (68.24)</td> <td>10,339 (73.05)</td>	White	1,605 (68.24)	10,339 (73.05)
Sex, N (%) Male 2,254 (95.83) 13,351 (94.33) Female 98 (4.17) 803 (5.67) ADI³, mean SD 53.03 (14.66) 50.56 (15.47) Smoking status, N (%) 1,086 (46.17) 5,402 (38.17) Former 758 (32.23) 4,250 (30.03) Current 508 (21.6) 4,502 (31.81) Long-term care, N (%) 89 (3.78) 1,150 (8.13) Systolic blood pressure, (mean SD) 134.65 (23.59) 133.03 (23.57) BMI, (mean SD) 29.95 (6.91) 29.20 (6.98) Cerebrovascular disease, N (%) 366 (15.56) 2,043 (14.43) Cancer, N (%) 431 (18.33) 3,097 (21.88) Chronic kidney disease, N (%) 635 (27) 3,236 (22.86) Cardiovascular disease, N (%) 906 (38.52) 5,527 (39.05) Dementia, N (%) 319 (13.56) 1,798 (12.7) Depression, N (%) 354 (15.05) 2,242 (15.84) Diabetes mellitus type 2, N (%) 1,200 (51.02) 6,273 (44.32) Lung disease, N (%) 739 (31.42) 5,851 (41.34) Peripheral artery disease, N (%)	Black	572 (24.32)	3,172 (22.41)
Male 2,254 (95.83) 13,351 (94.33) Female 98 (4.17) 803 (5.67) ADIª, mean SD 53.03 (14.66) 50.56 (15.47) Smoking status, N (%) 1,086 (46.17) 5,402 (38.17) Never 1,086 (46.17) 5,402 (38.17) Former 758 (32.23) 4,250 (30.03) Current 508 (21.6) 4,502 (31.81) Long-term care, N (%) 89 (3.78) 1,150 (8.13) Systolic blood pressure, (mean SD) 134.65 (23.59) 133.03 (23.57) BMI, (mean SD) 29.95 (6.91) 29.20 (6.98) Cerebrovascular disease, N (%) 366 (15.56) 2,043 (14.43) Cancer, N (%) 366 (15.56) 2,043 (14.43) Cancer, N (%) 431 (18.33) 3,097 (21.88) Chronic kidney disease, N (%) 635 (27) 3,236 (22.86) Cardiovascular disease, N (%) 635 (27) 3,236 (22.86) Cardiovascular disease, N (%) 319 (13.56) 1,798 (12.7) Depression, N (%) 319 (13.56) 1,798 (12.7) Depression, N (%) 354 (15.05) 2,242 (15.84) Diabetes mellitus type 2, N (%) 1,200 (51.02) <	Other	175 (7.44)	643 (4.54)
Female 98 (4.17) 803 (5.67) ADIP, mean SD 53.03 (14.66) 50.56 (15.47) Smoking status, N (%) 1,086 (46.17) 5,402 (38.17) Former 758 (32.23) 4,250 (30.03) Current 508 (21.6) 4,502 (31.81) Long-term care, N (%) 89 (3.78) 1,150 (8.13) Systolic blood pressure, (mean SD) 134.65 (23.59) 133.03 (23.57) BMI, (mean SD) 29.95 (6.91) 29.20 (6.98) Cerebrovascular disease, N (%) 366 (15.56) 2,043 (14.43) Cancer, N (%) 514 (21.85) 2,490 (17.59) Anxiety, N (%) 431 (18.33) 3,097 (21.88) Chronic kidney disease, N (%) 635 (27) 3,236 (22.86) Cardiovascular disease, N (%) 635 (27) 3,236 (22.86) Cardiovascular disease, N (%) 906 (38.52) 5,527 (39.05) Dementia, N (%) 319 (13.56) 1,798 (12.7) Depression, N (%) 354 (15.05) 2,242 (15.84) Diabetes mellitus type 2, N (%) 1,200 (51.02) 6,273 (44.32) Lung disease, N (%) 739 (31.42) <td>Sex, N (%)</td> <td></td> <td></td>	Sex, N (%)		
ADIª, mean SD 53.03 (14.66) 50.56 (15.47) Smoking status, N (%) Never 1,086 (46.17) 5,402 (38.17) Former 758 (32.23) 4,250 (30.03) Current 508 (21.6) 4,502 (31.81) Long-term care, N (%) 89 (3.78) 1,150 (8.13) Systolic blood pressure, (mean SD) 134.65 (23.59) 133.03 (23.57) BMI, (mean SD) 29.95 (6.91) 29.20 (6.98) Cerebrovascular disease, N (%) 366 (15.56) 2,043 (14.43) Cancer, N (%) 366 (15.56) 2,043 (14.43) Cancer, N (%) 514 (21.85) 2,490 (17.59) Anxiety, N (%) 431 (18.33) 3,097 (21.88) Chronic kidney disease, N (%) 635 (27) 3,236 (22.86) Cardiovascular disease, N (%) 906 (38.52) 5,527 (39.05) Dementia, N (%) 319 (13.56) 1,798 (12.7) Depression, N (%) 354 (15.05) 2,242 (15.84) Diabetes mellitus type 2, N (%) 1,200 (51.02) 6,273 (44.32) Lung disease, N (%) 739 (31.42) 5,851 (41.34) Peripheral artery disease, N (%) 119 (5.06) 665 (4.7) Receipt of seasonal influenza vaccine in the year prior, N (%) 1,038 (44.13) 7,021 (49.6) Number of inpatient visits, median (IQR) 0 (0, 1) 0 (0, 1) Number of blood chemistry panels, median (IQR) 4 (2, 9) 4 (2, 10)	Male	2,254 (95.83)	13,351 (94.33)
Smoking status, N (%) 1,086 (46.17) 5,402 (38.17) Former 758 (32.23) 4,250 (30.03) Current 508 (21.6) 4,502 (31.81) Long-term care, N (%) 89 (3.78) 1,150 (8.13) Systolic blood pressure, (mean SD) 134.65 (23.59) 133.03 (23.57) BMI, (mean SD) 29.95 (6.91) 29.20 (6.98) Cerebrovascular disease, N (%) 366 (15.56) 2,043 (14.43) Cancer, N (%) 514 (21.85) 2,490 (17.59) Anxiety, N (%) 431 (18.33) 3,097 (21.88) Chronic kidney disease, N (%) 635 (27) 3,236 (22.86) Cardiovascular disease, N (%) 906 (38.52) 5,527 (39.05) Dementia, N (%) 319 (13.56) 1,798 (12.7) Depression, N (%) 354 (15.05) 2,242 (15.84) Diabetes mellitus type 2, N (%) 1,200 (51.02) 6,273 (44.32) Lung disease, N (%) 739 (31.42) 5,851 (41.34) Peripheral artery disease, N (%) 119 (5.06) 665 (4.7) Receipt of seasonal influenza vaccine in the year prior, N (%) 1,038 (44.13) 7,021 (49.6) <	Female	98 (4.17)	803 (5.67)
Never 1,086 (46.17) 5,402 (38.17) Former 758 (32.23) 4,250 (30.03) Current 508 (21.6) 4,502 (31.81) Long-term care, N (%) 89 (3.78) 1,150 (8.13) Systolic blood pressure, (mean SD) 134.65 (23.59) 133.03 (23.57) BMI, (mean SD) 29.95 (6.91) 29.20 (6.98) Cerebrovascular disease, N (%) 366 (15.56) 2,043 (14.43) Cancer, N (%) 514 (21.85) 2,490 (17.59) Anxiety, N (%) 431 (18.33) 3,097 (21.88) Chronic kidney disease, N (%) 635 (27) 3,236 (22.86) Cardiovascular disease, N (%) 906 (38.52) 5,527 (39.05) Dementia, N (%) 319 (13.56) 1,798 (12.7) Depression, N (%) 354 (15.05) 2,242 (15.84) Diabetes mellitus type 2, N (%) 1,200 (51.02) 6,273 (44.32) Lung disease, N (%) 739 (31.42) 5,851 (41.34) Peripheral artery disease, N (%) 119 (5.06) 665 (4.7) Receipt of seasonal influenza vaccine in the year prior, N (%) 1,038 (44.13) 7,021 (49.6) Number of inpatient visits, median (IQR) 4 (3, 5) 4 (3, 5)	ADIa, mean SD	53.03 (14.66)	50.56 (15.47)
Former 758 (32.23) 4,250 (30.03) Current 508 (21.6) 4,502 (31.81) Long-term care, N (%) 89 (3.78) 1,150 (8.13) Systolic blood pressure, (mean SD) 134.65 (23.59) 133.03 (23.57) BMI, (mean SD) 29.95 (6.91) 29.20 (6.98) Cerebrovascular disease, N (%) 366 (15.56) 2,043 (14.43) Cancer, N (%) 514 (21.85) 2,490 (17.59) Anxiety, N (%) 431 (18.33) 3,097 (21.88) Chronic kidney disease, N (%) 635 (27) 3,236 (22.86) Cardiovascular disease, N (%) 906 (38.52) 5,527 (39.05) Dementia, N (%) 319 (13.56) 1,798 (12.7) Depression, N (%) 354 (15.05) 2,242 (15.84) Diabetes mellitus type 2, N (%) 1,200 (51.02) 6,273 (44.32) Lung disease, N (%) 739 (31.42) 5,851 (41.34) Peripheral artery disease, N (%) 119 (5.06) 665 (4.7) Receipt of seasonal influenza vaccine in the year prior, N (%) 1,038 (44.13) 7,021 (49.6) Number of inpatient visits, median (IQR) 0 (0, 1) 0 (0, 1)	Smoking status, N (%)		
Current 508 (21.6) 4,502 (31.81) Long-term care, N (%) 89 (3.78) 1,150 (8.13) Systolic blood pressure, (mean SD) 134.65 (23.59) 133.03 (23.57) BMI, (mean SD) 29.95 (6.91) 29.20 (6.98) Cerebrovascular disease, N (%) 366 (15.56) 2,043 (14.43) Cancer, N (%) 514 (21.85) 2,490 (17.59) Anxiety, N (%) 431 (18.33) 3,097 (21.88) Chronic kidney disease, N (%) 635 (27) 3,236 (22.86) Cardiovascular disease, N (%) 906 (38.52) 5,527 (39.05) Dementia, N (%) 319 (13.56) 1,798 (12.7) Depression, N (%) 354 (15.05) 2,242 (15.84) Diabetes mellitus type 2, N (%) 1,200 (51.02) 6,273 (44.32) Lung disease, N (%) 739 (31.42) 5,851 (41.34) Peripheral artery disease, N (%) 119 (5.06) 665 (4.7) Receipt of seasonal influenza vaccine in the year prior, N (%) 1,038 (44.13) 7,021 (49.6) Number of inpatient visits, median (IQR) 4 (3, 5) 4 (3, 5) Number of blood chemistry panels, median (IQR) 4 (2, 9)	Never	1,086 (46.17)	5,402 (38.17)
Long-term care, N (%) 89 (3.78) 1,150 (8.13) Systolic blood pressure, (mean SD) 134.65 (23.59) 133.03 (23.57) BMI, (mean SD) 29.95 (6.91) 29.20 (6.98) Cerebrovascular disease, N (%) 366 (15.56) 2,043 (14.43) Cancer, N (%) 514 (21.85) 2,490 (17.59) Anxiety, N (%) 431 (18.33) 3,097 (21.88) Chronic kidney disease, N (%) 635 (27) 3,236 (22.86) Cardiovascular disease, N (%) 906 (38.52) 5,527 (39.05) Dementia, N (%) 319 (13.56) 1,798 (12.7) Depression, N (%) 354 (15.05) 2,242 (15.84) Diabetes mellitus type 2, N (%) 1,200 (51.02) 6,273 (44.32) Lung disease, N (%) 739 (31.42) 5,851 (41.34) Peripheral artery disease, N (%) 119 (5.06) 665 (4.7) Receipt of seasonal influenza vaccine in the year prior, N (%) 1,038 (44.13) 7,021 (49.6) Number of inpatient visits, median (IQR) 0 (0, 1) 0 (0, 1) Number of blood chemistry panels, median (IQR) 4 (2, 9) 4 (2, 10)	Former	758 (32.23)	4,250 (30.03)
Systolic blood pressure, (mean SD) 134.65 (23.59) 133.03 (23.57) BMI, (mean SD) 29.95 (6.91) 29.20 (6.98) Cerebrovascular disease, N (%) 366 (15.56) 2,043 (14.43) Cancer, N (%) 514 (21.85) 2,490 (17.59) Anxiety, N (%) 431 (18.33) 3,097 (21.88) Chronic kidney disease, N (%) 635 (27) 3,236 (22.86) Cardiovascular disease, N (%) 906 (38.52) 5,527 (39.05) Dementia, N (%) 319 (13.56) 1,798 (12.7) Depression, N (%) 354 (15.05) 2,242 (15.84) Diabetes mellitus type 2, N (%) 1,200 (51.02) 6,273 (44.32) Lung disease, N (%) 739 (31.42) 5,851 (41.34) Peripheral artery disease, N (%) 119 (5.06) 665 (4.7) Receipt of seasonal influenza vaccine in the year prior, N (%) 1,038 (44.13) 7,021 (49.6) Number of inpatient visits, median (IQR) 0 (0, 1) 0 (0, 1) Number of blood chemistry panels, median (IQR) 4 (2, 9) 4 (2, 10)	Current	508 (21.6)	4,502 (31.81)
BMI, (mean SD) Cerebrovascular disease, N (%) Cancer, N (%) Anxiety, N (%) Cardiovascular disease, N (%) Dementia, N (%) Dementia, N (%) Depression, N (%) Diabetes mellitus type 2, N (%) Lung disease, N (%) Peripheral artery disease, N (%) Receipt of seasonal influenza vaccine in the year prior, N (%) Number of inpatient visits, median (IQR) Number of blood chemistry panels, median (IQR) Number of blood chemistry panels, median (IQR) Number of blood chemistry panels, median (IQR) At 1,29 At 29.20 (6.98) 29.20 (6.98	Long-term care, N (%)	89 (3.78)	1,150 (8.13)
BMI, (mean SD) 29.95 (6.91) 29.20 (6.98) Cerebrovascular disease, N (%) 366 (15.56) 2,043 (14.43) Cancer, N (%) 514 (21.85) 2,490 (17.59) Anxiety, N (%) 431 (18.33) 3,097 (21.88) Chronic kidney disease, N (%) 635 (27) 3,236 (22.86) Cardiovascular disease, N (%) 906 (38.52) 5,527 (39.05) Dementia, N (%) 319 (13.56) 1,798 (12.7) Depression, N (%) 354 (15.05) 2,242 (15.84) Diabetes mellitus type 2, N (%) 1,200 (51.02) 6,273 (44.32) Lung disease, N (%) 739 (31.42) 5,851 (41.34) Peripheral artery disease, N (%) 119 (5.06) 665 (4.7) Receipt of seasonal influenza vaccine in the year prior, N (%) 1,038 (44.13) 7,021 (49.6) Number of inpatient visits, median (IQR) 0 (0, 1) 0 (0, 1) Number of blood chemistry panels, median (IQR) 4 (3, 5) 4 (3, 5) Number of blood chemistry panels, median (IQR) 4 (2, 9) 4 (2, 10)	Systolic blood pressure, (mean SD)	134.65 (23.59)	133.03 (23.57)
Cancer, N (%) 514 (21.85) 2,490 (17.59) Anxiety, N (%) 431 (18.33) 3,097 (21.88) Chronic kidney disease, N (%) 635 (27) 3,236 (22.86) Cardiovascular disease, N (%) 906 (38.52) 5,527 (39.05) Dementia, N (%) 319 (13.56) 1,798 (12.7) Depression, N (%) 354 (15.05) 2,242 (15.84) Diabetes mellitus type 2, N (%) 1,200 (51.02) 6,273 (44.32) Lung disease, N (%) 739 (31.42) 5,851 (41.34) Peripheral artery disease, N (%) 119 (5.06) 665 (4.7) Receipt of seasonal influenza vaccine in the year prior, N (%) 1,038 (44.13) 7,021 (49.6) Number of inpatient visits, median (IQR) 0 (0, 1) 0 (0, 1) Number of blood chemistry panels, median (IQR) 4 (3, 5) 4 (3, 5) Number of blood chemistry panels, median (IQR) 4 (2, 9) 4 (2, 10)		29.95 (6.91)	29.20 (6.98)
Anxiety, N (%) Anxiety, N (%) Chronic kidney disease, N (%) Cardiovascular disease, N (%) Dementia, N (%) Dementia, N (%) Depression, N (%) Diabetes mellitus type 2, N (%) Lung disease, N (%) Peripheral artery disease, N (%) Receipt of seasonal influenza vaccine in the year prior, N (%) Number of outpatient visits, median (IQR) Number of blood chemistry panels, median (IQR) A31 (18.33) 3,097 (21.88) 431 (18.33) 3,097 (21.88) 3,097 (21.88) 3,097 (21.88) 3,097 (21.88) 431 (18.33) 3,097 (21.88) 3,097 (21.88) 431 (18.33) 3,097 (21.88) 431 (18.33) 3,097 (21.88) 431 (18.33) 3,097 (21.88) 431 (18.33) 3,097 (21.88) 431 (18.33) 3,097 (21.88) 431 (18.33) 3,097 (21.88) 404.88) 405.91 Auxiety disease, N (%) 407.91 Auxiety disease, N (%) 408.91 Auxiety disease, N (%) 409.61 Auxiety disease, N	Cerebrovascular disease, N (%)	366 (15.56)	2,043 (14.43)
Chronic kidney disease, N (%) 635 (27) 3,236 (22.86) Cardiovascular disease, N (%) 906 (38.52) 5,527 (39.05) Dementia, N (%) 319 (13.56) 1,798 (12.7) Depression, N (%) 354 (15.05) 2,242 (15.84) Diabetes mellitus type 2, N (%) 1,200 (51.02) 6,273 (44.32) Lung disease, N (%) 739 (31.42) 5,851 (41.34) Peripheral artery disease, N (%) 119 (5.06) 665 (4.7) Receipt of seasonal influenza vaccine in the year prior, N (%) 1,038 (44.13) 7,021 (49.6) Number of inpatient visits, median (IQR) 0 (0, 1) 0 (0, 1) Number of blood chemistry panels, median (IQR) 4 (3, 5) 4 (3, 5) Number of blood chemistry panels, median (IQR) 4 (2, 9) 4 (2, 10)	Cancer, N (%)	514 (21.85)	2,490 (17.59)
Cardiovascular disease, N (%) 906 (38.52) 5,527 (39.05) Dementia, N (%) 319 (13.56) 1,798 (12.7) Depression, N (%) 354 (15.05) 2,242 (15.84) Diabetes mellitus type 2, N (%) 1,200 (51.02) 6,273 (44.32) Lung disease, N (%) 739 (31.42) 5,851 (41.34) Peripheral artery disease, N (%) 119 (5.06) 665 (4.7) Receipt of seasonal influenza vaccine in the year prior, N (%) 1,038 (44.13) 7,021 (49.6) Number of inpatient visits, median (IQR) 0 (0, 1) 0 (0, 1) Number of blood chemistry panels, median (IQR) 4 (3, 5) 4 (3, 5) Number of blood chemistry panels, median (IQR) 4 (2, 9) 4 (2, 10)	Anxiety, N (%)	431 (18.33)	3,097 (21.88)
Dementia, N (%) 319 (13.56) 1,798 (12.7) Depression, N (%) 354 (15.05) 2,242 (15.84) Diabetes mellitus type 2, N (%) 1,200 (51.02) 6,273 (44.32) Lung disease, N (%) 739 (31.42) 5,851 (41.34) Peripheral artery disease, N (%) 119 (5.06) 665 (4.7) Receipt of seasonal influenza vaccine in the year prior, N (%) 1,038 (44.13) 7,021 (49.6) Number of inpatient visits, median (IQR) 0 (0, 1) 0 (0, 1) Number of outpatient visits, median (IQR) 4 (3, 5) 4 (3, 5) Number of blood chemistry panels, median (IQR) 4 (2, 9) 4 (2, 10)	Chronic kidney disease, N (%)	635 (27)	3,236 (22.86)
Depression, N (%) 354 (15.05) 2,242 (15.84) Diabetes mellitus type 2, N (%) 1,200 (51.02) 6,273 (44.32) Lung disease, N (%) 739 (31.42) 5,851 (41.34) Peripheral artery disease, N (%) 119 (5.06) 665 (4.7) Receipt of seasonal influenza vaccine in the year prior, N (%) 1,038 (44.13) 7,021 (49.6) Number of inpatient visits, median (IQR) 0 (0, 1) 0 (0, 1) Number of outpatient visits, median (IQR) 4 (3, 5) 4 (3, 5) Number of blood chemistry panels, median (IQR) 4 (2, 9) 4 (2, 10)	Cardiovascular disease, N (%)	906 (38.52)	5,527 (39.05)
Diabetes mellitus type 2, N (%) 1,200 (51.02) 6,273 (44.32) Lung disease, N (%) 739 (31.42) 5,851 (41.34) Peripheral artery disease, N (%) 119 (5.06) 665 (4.7) Receipt of seasonal influenza vaccine in the year prior, N (%) 1,038 (44.13) 7,021 (49.6) Number of inpatient visits, median (IQR) 0 (0, 1) 0 (0, 1) Number of outpatient visits, median (IQR) 4 (3, 5) 4 (3, 5) Number of blood chemistry panels, median (IQR) 4 (2, 9) 4 (2, 10)	Dementia, N (%)	319 (13.56)	1,798 (12.7)
Lung disease, N (%) 739 (31.42) 5,851 (41.34) Peripheral artery disease, N (%) 119 (5.06) 665 (4.7) Receipt of seasonal influenza vaccine in the year prior, N (%) 1,038 (44.13) 7,021 (49.6) Number of inpatient visits, median (IQR) 0 (0, 1) 0 (0, 1) Number of outpatient visits, median (IQR) 4 (3, 5) 4 (3, 5) Number of blood chemistry panels, median (IQR) 4 (2, 9) 4 (2, 10)	Depression, N (%)	354 (15.05)	2,242 (15.84)
Peripheral artery disease, N (%) Receipt of seasonal influenza vaccine in the year prior, N (%) Number of inpatient visits, median (IQR) Number of outpatient visits, median (IQR) Number of blood chemistry panels, median (IQR) 119 (5.06) 1,038 (44.13) 7,021 (49.6) 0 (0, 1) 0 (0, 1) 4 (3, 5) 4 (3, 5) 4 (2, 10)	Diabetes mellitus type 2, N (%)	1,200 (51.02)	6,273 (44.32)
Receipt of seasonal influenza vaccine in the year prior, N (%) Number of inpatient visits, median (IQR) Number of outpatient visits, median (IQR) Number of blood chemistry panels, median (IQR) 1,038 (44.13) 0 (0, 1) 0 (0, 1) 4 (3, 5) 4 (3, 5) 4 (2, 9) 4 (2, 10)	Lung disease, N (%)	739 (31.42)	5,851 (41.34)
Number of inpatient visits, median (IQR) Number of outpatient visits, median (IQR) Number of blood chemistry panels, median (IQR) 4 (3, 5) 4 (2, 9) 4 (2, 10)	Peripheral artery disease, N (%)	119 (5.06)	665 (4.7)
Number of outpatient visits, median (IQR) 4 (3, 5) 4 (3, 5) 4 (2, 9) 4 (2, 10)	Receipt of seasonal influenza vaccine in the year prior, N (%)	1,038 (44.13)	7,021 (49.6)
Number of blood chemistry panels, median (IQR) 4 (2, 9) 4 (2, 10)	Number of inpatient visits, median (IQR)	0 (0, 1)	0 (0, 1)
	Number of outpatient visits, median (IQR)	4 (3, 5)	4 (3, 5)
Number of unique medications, median (IQR) 17 (10, 23) 16 (10, 23)	Number of blood chemistry panels, median (IQR)	4 (2, 9)	4 (2, 10)
	Number of unique medications, median (IQR)	17 (10, 23)	16 (10, 23)

All characteristics assessed in the year prior to testing positive for COVID-19, or equivalent T₀.

ADI, Area Deprivation Index; BMI, body mass index; IQR, interquartile range; N, sample size; SD, standard deviation.

^aADI is a composite measure of socioeconomic deprivation that ranges from 0 (low deprivation) to 100 (high deprivation).

Extended Data Table 5: Risk of negative outcome controls in those with breakthrough COVID-19 compared to the control group.

Outcome	HR (95% CI)
Accidental injury or poisoning	1.02 (0.91, 1.13)
Atopic dermatitis	1.01 (0.93, 1.09)

Models were weighted for age, race, ADI, the number in the year prior to testing positive of outpatient visits, inpatient visits, unique medication prescriptions, and routine blood chemistry panels, prior history of receiving an influenza vaccination, smoking status, anxiety, cancer, cardiovascular disease, cerebrovascular disease, chronic kidney disease, dementia, depression, type 2 diabetes mellitus, chronic obstructive pulmonary disease, and peripheral artery disease, systolic blood pressure, and body mass index (BMI), as well as algorithmically selected high dimensional variables. HR, hazard ratio. CI, confidence interval.