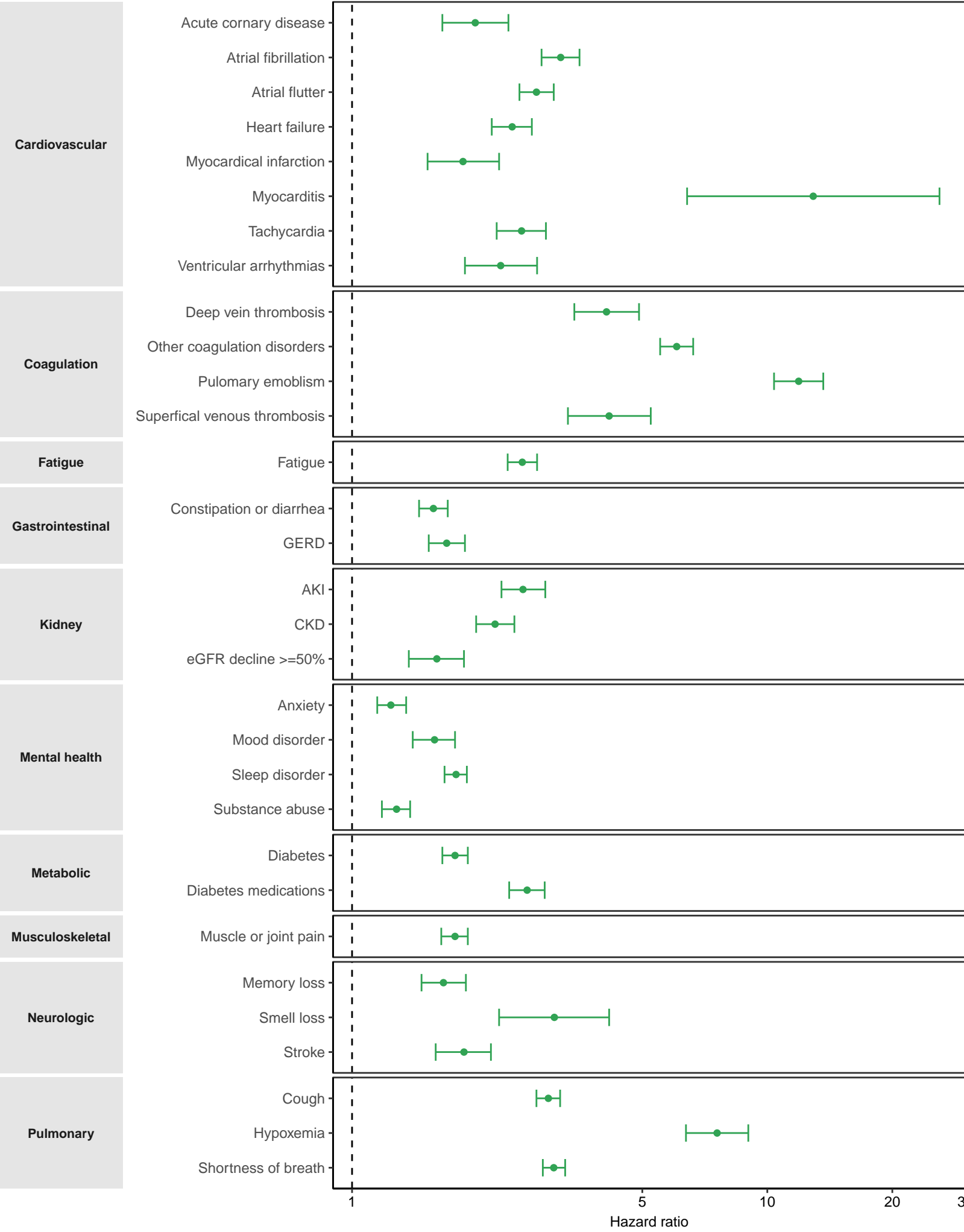
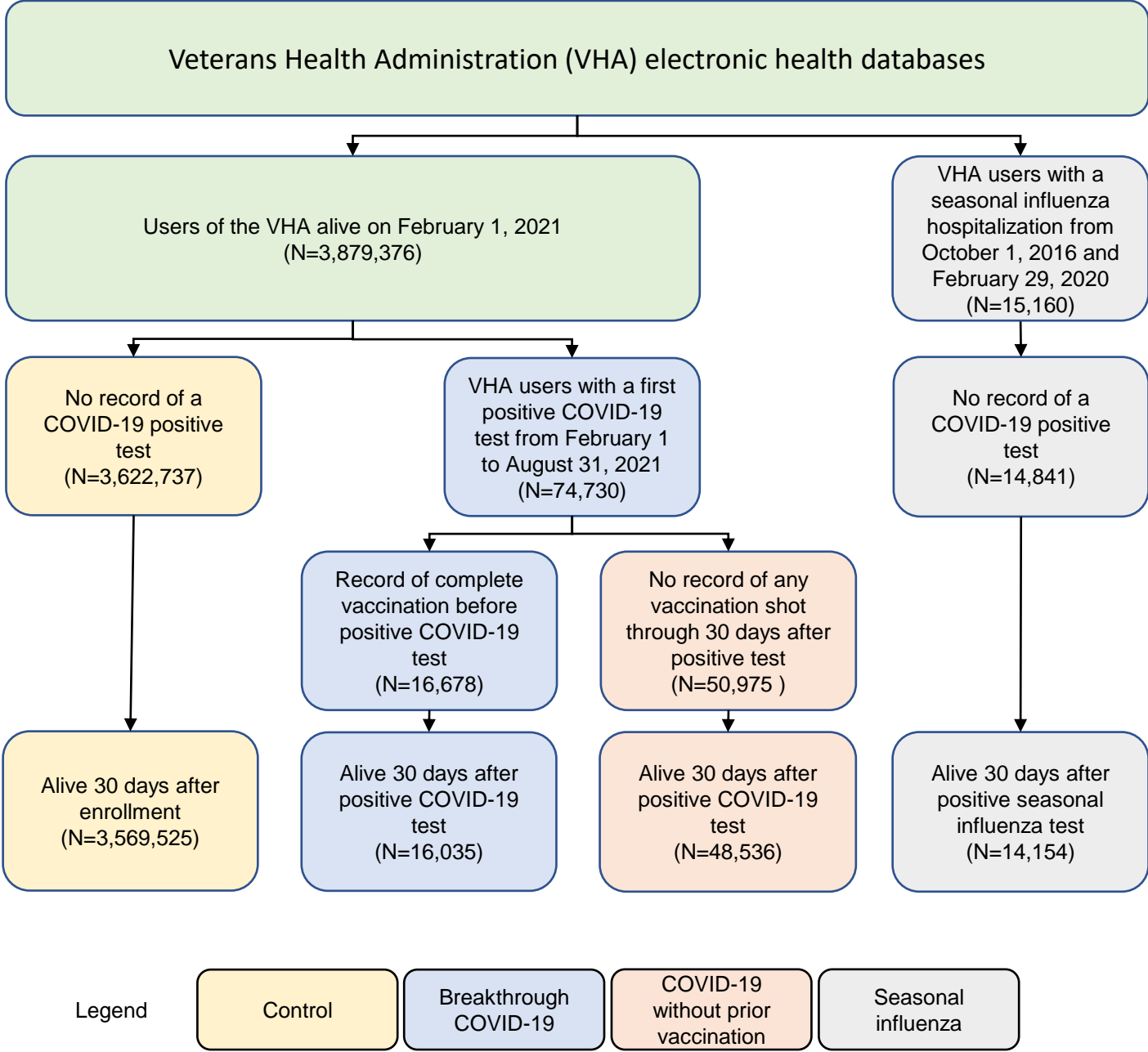


Extended data figure 1





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)
ADI ^a , 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 (%)		
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)		
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 breakthrough infection 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 T ₀ .		
^a ADI is a composite measure of socioeconomic deprivation that ranges from 0 (low deprivation) to 100 (high deprivation).		
^b Among 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 COVID- 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 .			
^a Hospitalization assessed during the acute phase of the disease.			
^b ADI 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)
ADl ^a , 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)
<p>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.</p>		

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.

Characteristic	Breakthrough COVID-19 (N=2,352)	Seasonal Influenza (N=14,154)
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)
ADI ^a , 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 (%)	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 outpatient visits, median (IQR)	4 (3, 5)	4 (3, 5)
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 T ₀ . ^a ADI 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 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.	