Supplementary Information

Long Covid after Breakthrough COVID-19: the post-acute sequelae of breakthrough COVID-19

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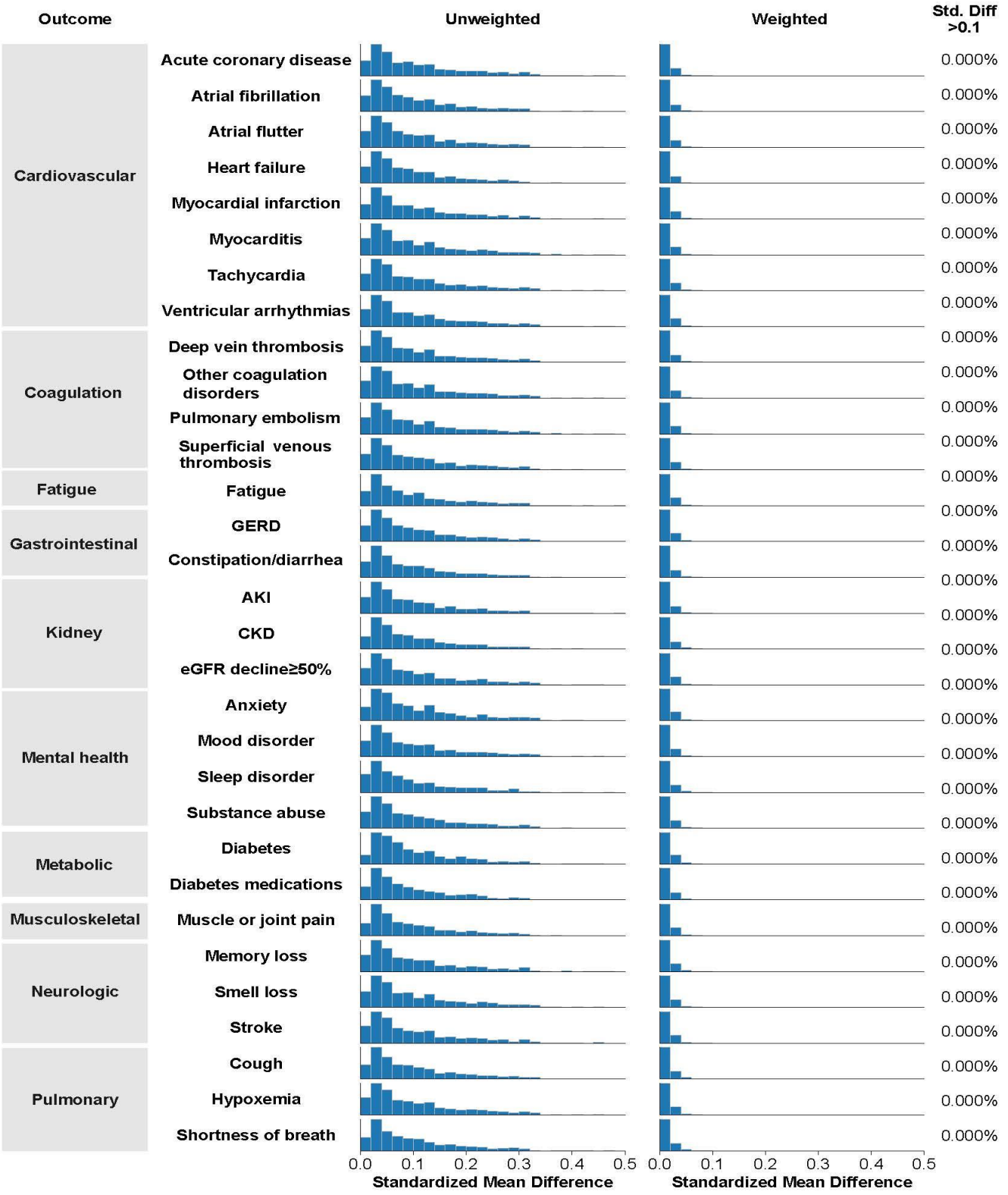
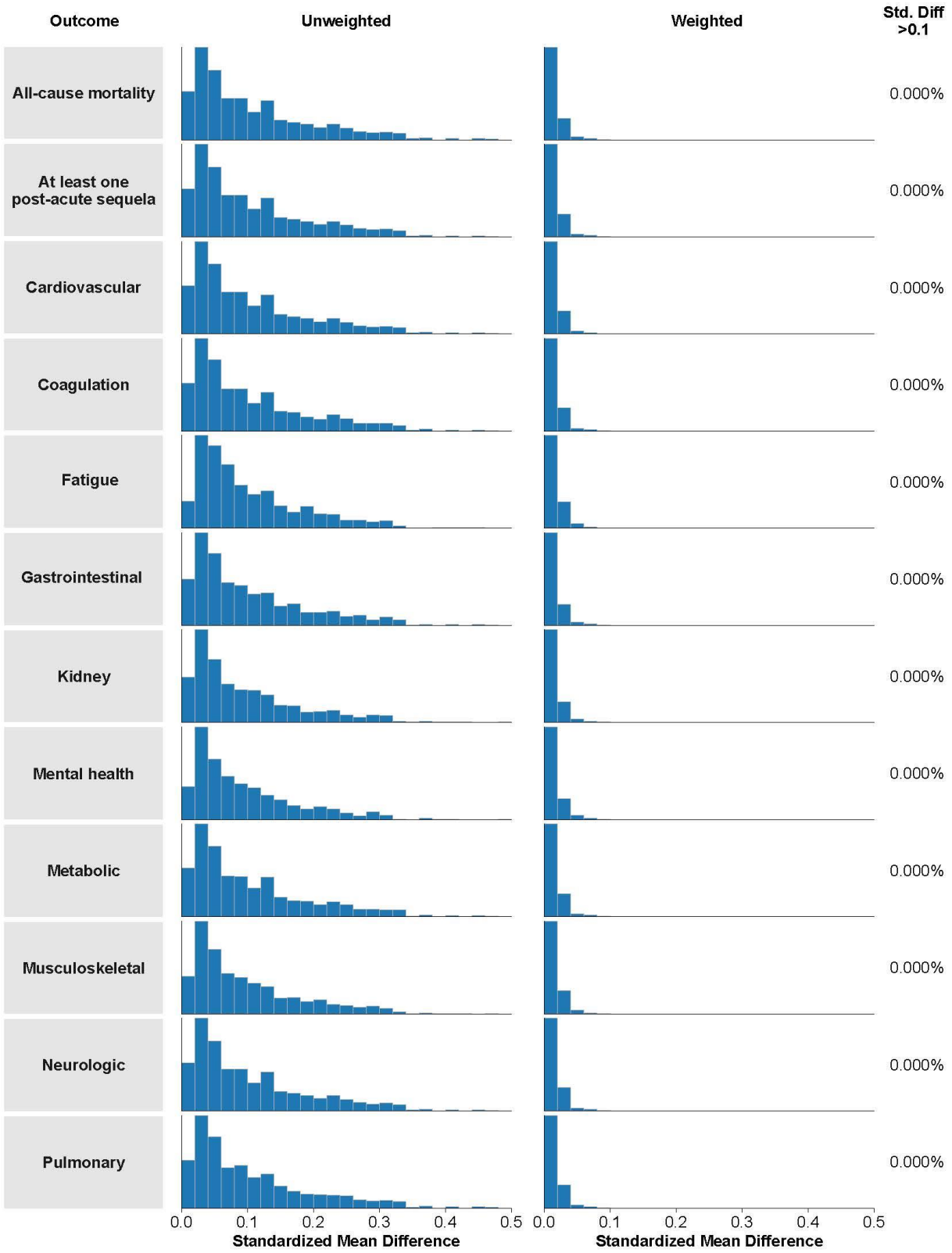
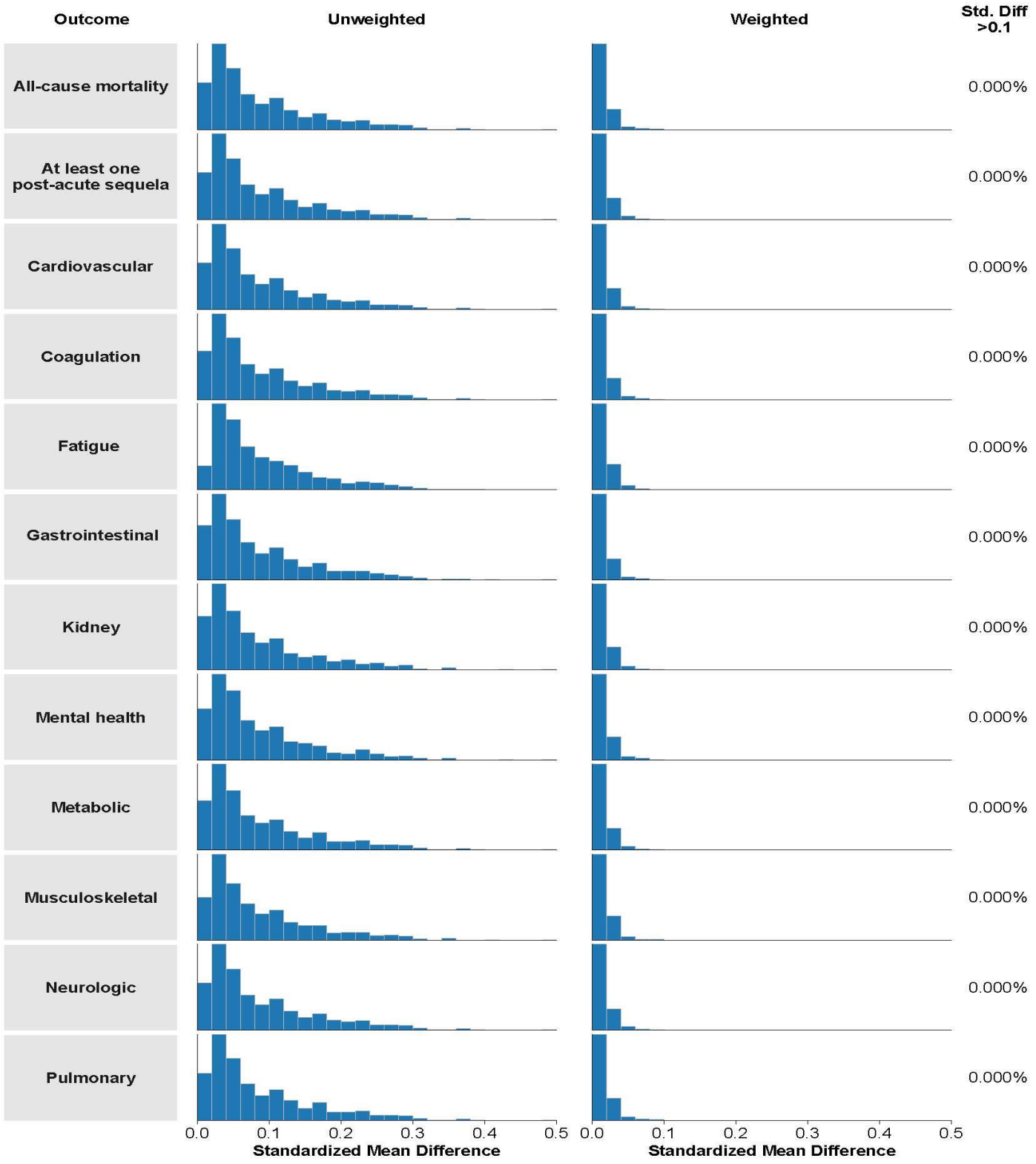


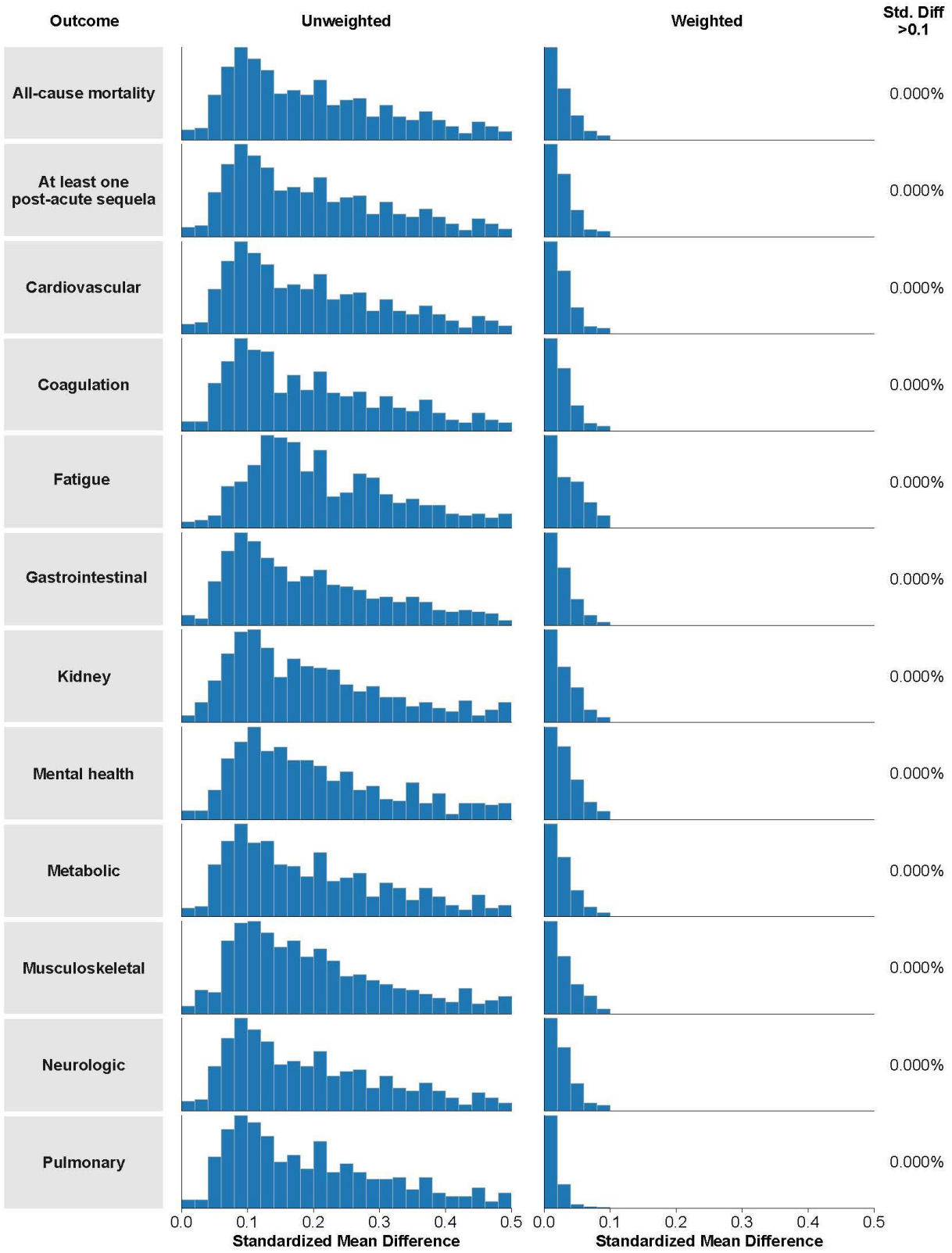
Supplementary Figure 1: Standardized mean differences between those with breakthrough COVID-19 and the control group before and after weighting by post-acute sequela. Histograms of the distribution of standardized mean differences before and after weighting of the predefined as well high dimensional covariates are presented. All standardized mean differences were assessed, for the corresponding outcome, in a cohort with no prior history of the outcome. Percentage of standardized mean differences after weighting that displayed evidence of imbalance (>0.1) is presented. Std. Diff, standardized mean difference; GERD, gastroesophageal reflux disease; AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.



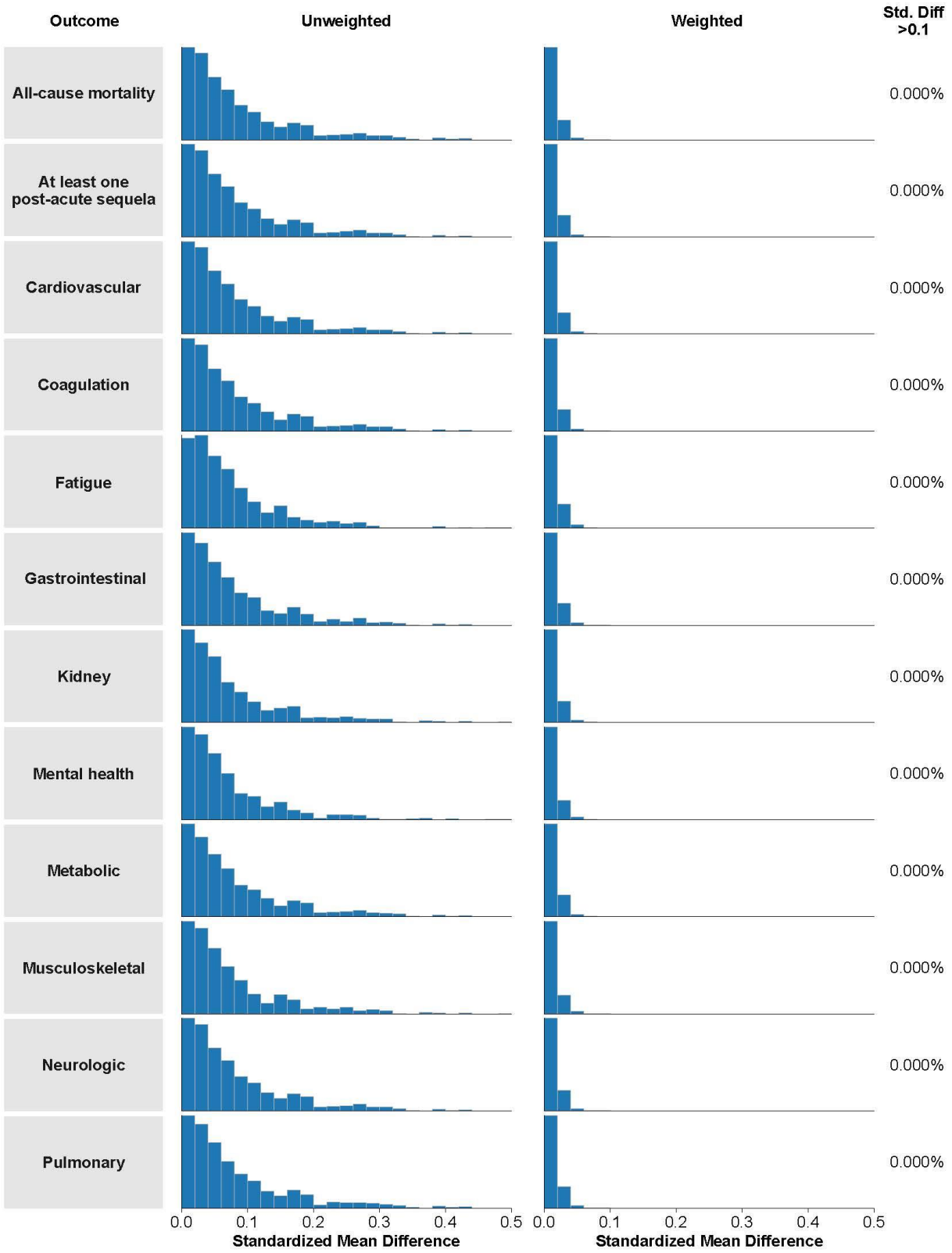
Supplementary Figure 2: Standardized mean differences between those with breakthrough COVID-19 and the control group before and after weighting by organ system. Histograms of the distribution of standardized mean differences before and after weighting of the predefined as well high dimensional covariates are presented. All standardized mean differences were assessed, for the corresponding outcome, in a cohort with no prior history of the outcome. Percentage of standardized mean differences after weighting that displayed evidence of imbalance (>0.1) is presented. Std. Diff, standardized mean difference.



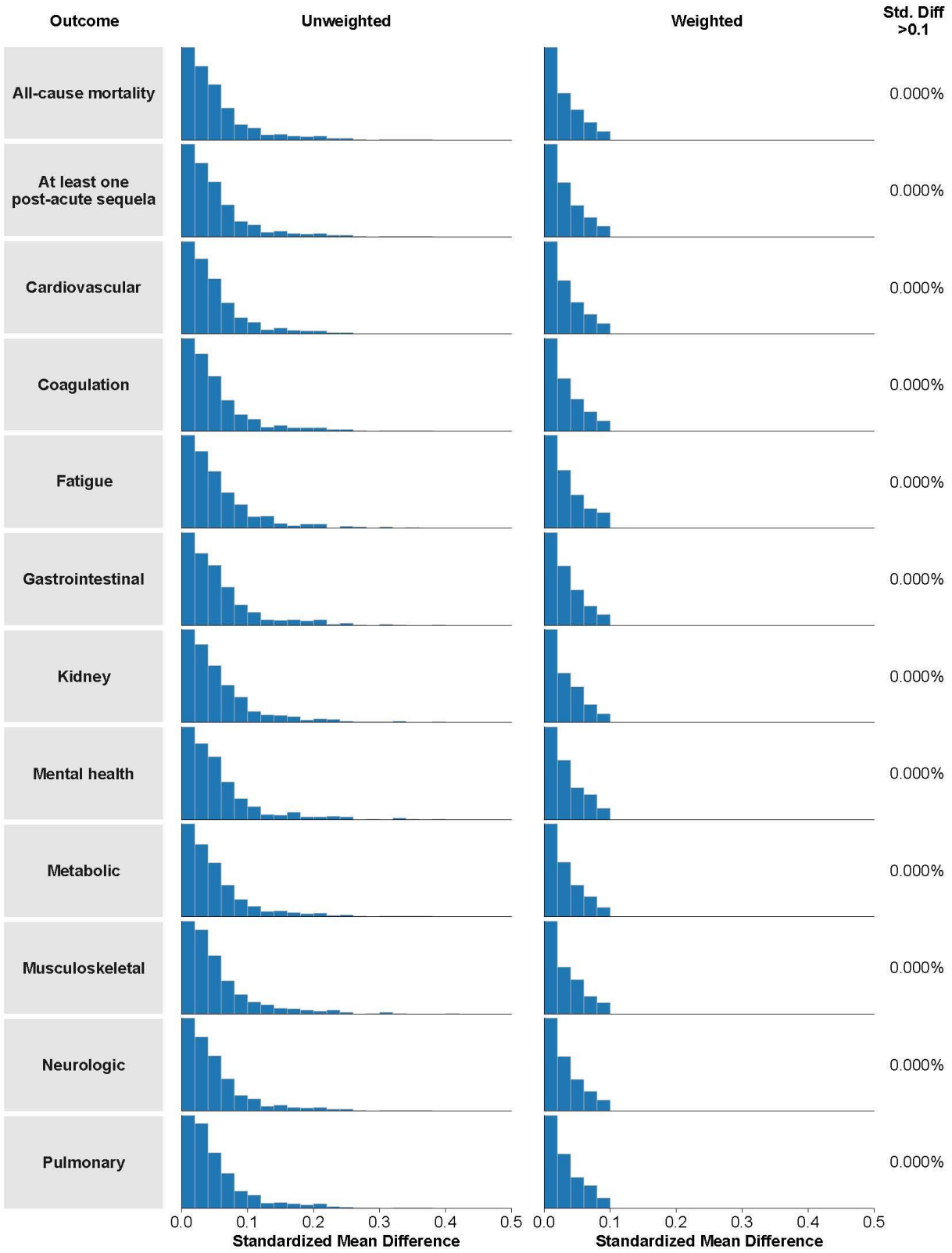
Supplementary Figure 3: Standardized mean differences between those with breakthrough COVID-19 not hospitalized during the acute phase of the illness and the control group before and after weighting by organ system. Histograms of the distribution of standardized mean differences before and after weighting of the predefined as well high dimensional covariates are presented. All standardized mean differences were assessed, for the corresponding outcome, in a cohort with no prior history of the outcome. Percentage of standardized mean differences after weighting that displayed evidence of imbalance (>0.1) is presented. Std. Diff, standardized mean difference.



Supplementary Figure 4: Standardized mean differences between those with breakthrough COVID-19 hospitalized during the acute phase of the illness and the control group before and after weighting by organ system. Histograms of the distribution of standardized mean differences before and after weighting of the predefined as well high dimensional covariates are presented. All standardized mean differences were assessed, for the corresponding outcome, in a cohort with no prior history of the outcome. Percentage of standardized mean differences after weighting that displayed evidence of imbalance (>0.1) is presented. Std. Diff, standardized mean difference.



Supplementary Figure 5: Standardized mean differences between those with breakthrough COVID-19 and those with COVID-19 by organ system. Histograms of the distribution of standardized mean differences before and after weighting of the predefined as well high dimensional covariates are presented. All standardized mean differences were assessed, for the corresponding outcome, in a cohort with no prior history of the outcome. Percentage of standardized mean differences after weighting that displayed evidence of imbalance (>0.1) is presented. Std. Diff, standardized mean difference.



Supplementary Figure 6: Standardized mean differences between those with breakthrough COVID-19 hospitalized during the acute phase of the illness and those hospitalized with seasonal influenza before and after weighting by organ system. Histograms of the distribution of standardized mean differences before and after weighting of the predefined as well high dimensional covariates are presented. All standardized mean differences were assessed, for the corresponding outcome, in a cohort with no prior history of the outcome. Percentage of standardized mean differences after weighting that displayed evidence of imbalance (>0.1) is presented. Std. Diff, standardized mean difference.

Supplementary Table 1: Characteristics and standardized mean differences of those with breakthrough COVID-19 compared to the control group after weighting.

Characteristic	Breakthrough COVID-19 (N=16,035)	Control (N=3,569,525)	Standardized mean difference
Age, (mean SD)	66.60 (13.81)	66.60 (13.88)	0.00
Race, N (%)			
White	11447 (71.39)	2548284 (71.39)	0.00
Black	3393 (21.16)	755311 (21.16)	0.00
Other	1195 (7.45)	265930 (7.45)	0.00
Sex, N (%)			
Male	14642 (91.31)	3259333 (91.31)	0.00
Female	1393 (8.69)	310192 (8.69)	0.00
ADI[a], (mean SD)	52.46 (15.06)	52.46 (15.03)	0.00
Smoking status, N (%)			
Never	8242 (51.40)	1834736 (51.40)	0.00
Former	4668 (29.11)	1039089 (29.11)	0.00
Current	3124 (19.48)	695343 (19.48)	0.00
Long-term care, N (%)	257 (1.60)	57112 (1.60)	0.00
Systolic blood pressure, (mean SD)	132.71 (19.09)	132.71 (19.01)	0.00
BMI, (mean SD)	30.80 (6.39)	30.80 (7.86)	0.00
Cerebrovascular disease, N (%)	1376 (8.58)	306265 (8.58)	0.00
Cancer, N (%)	2072 (12.92)	461183 (12.92)	0.00
Anxiety, N (%)	2118 (13.21)	471534 (13.21)	0.00
Chronic kidney disease, N (%)	2312 (14.42)	514726 (14.42)	0.00
Cardiovascular disease, N (%)	3864 (24.10)	860256 (24.10)	0.00
Dementia, N (%)	1068 (6.66)	237730 (6.66)	0.00
Depression, N (%)	1749 (10.91)	389435 (10.91)	0.00
Diabetes mellitus type 2, N (%)	6137 (38.27)	1366057 (38.27)	0.00
Lung disease, N (%)	3096 (19.31)	689275 (19.31)	0.00
Peripheral artery disease, N (%)	348 (2.17)	77459 (2.17)	0.00
Number of inpatient visits in the year prior to t0, (mean SD)	0.30 (0.99)	0.30 (1.00)	0.00
Number of outpatient visits in the year prior to t0, (mean SD)	3.16 (1.45)	3.16 (1.47)	0.00
Number of eGFR measures in the year prior to t0, (mean SD)	3.70 (6.16)	3.70 (8.92)	0.00
Number of unique medications in the year prior to t0, (mean SD)	12.61 (8.81)	12.61 (8.87)	0.00

Cohort weighted by the combination of an inverse probability of censoring due to death weight and overlap weight for probability of group membership.
Weighting conducted in cohort in the analyses of the at least one post-acute sequela outcome.
[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; N, sample size; SD, standard deviation; eGFR, estimated glomerular filtration rate

Supplementary Table 2: Risk and 6-month burden of death, at least one post-acute sequelae, and post-acute sequelae by organ system in breakthrough COVID-19 compared to the control group.

Outcome	HR (95% CI)	Breakthrough COVID-19 burden per 1000 persons at 6-months (95% CI)	Control burden per 1000 persons at 6-months (95% CI)	Excess burden per 1000 persons at 6-months (95% CI)
Death	1.53 (1.36, 1.72)	33.49 (29.80, 37.62)	22.04 (19.60, 24.77)	11.45 (7.77, 15.58)
At least one post-acute sequelae	1.59 (1.53, 1.65)	299.02 (289.39, 308.90)	200.38 (193.49, 207.49)	98.64 (89.01, 108.51)
Cardiovascular	2.01 (1.85, 2.20)	63.30 (58.19, 68.84)	31.93 (29.32, 34.78)	31.37 (26.26, 36.91)
Coagulation	2.93 (2.52, 3.42)	20.40 (17.53, 23.74)	7.01 (6.01, 8.16)	13.40 (10.53, 16.73)
Fatigue	2.16 (1.92, 2.43)	37.07 (33.01, 41.62)	17.32 (15.40, 19.47)	19.75 (15.69, 24.30)
Gastrointestinal	1.48 (1.34, 1.64)	53.50 (48.48, 59.03)	36.36 (32.92, 40.15)	17.15 (12.12, 22.67)
Kidney	1.92 (1.69, 2.18)	40.92 (36.11, 46.36)	21.58 (19.02, 24.48)	19.34 (14.53, 24.78)
Mental health	1.42 (1.32, 1.53)	86.55 (80.69, 92.83)	61.62 (57.39, 66.15)	24.94 (19.07, 31.21)
Metabolic	1.46 (1.29, 1.66)	49.52 (43.79, 55.98)	34.18 (30.20, 38.68)	15.34 (9.61, 21.80)
Musculoskeletal	1.75 (1.57, 1.95)	48.29 (43.39, 53.73)	27.86 (25.00, 31.03)	20.44 (15.54, 25.87)
Neurologic	1.79 (1.55, 2.06)	25.19 (21.84, 29.04)	14.19 (12.30, 16.37)	11.00 (7.65, 31.14)
Pulmonary	2.33 (2.16, 2.50)	88.62 (82.62, 95.03)	39.09 (36.38, 42.00)	49.53 (43.53, 55.94)

Models were adjusted 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.
Burdens are presented per 1000 persons at 6 months of follow-up.

Supplementary Table 3: Risk and 6-month burden of post-acute sequelae in breakthrough COVID-19 compared to the control group.

Outcome	HR (95% CI)	Breakthrough COVID-19 burden per 1000 persons at 6-months (95% CI)	Control burden per 1000 persons at 6-months (95% CI)	Excess burden per 1000 persons at 6-months (95% CI)
Acute coronary disease	1.99 (1.55, 2.55)	7.13 (5.56, 9.15)	3.60 (2.80, 4.61)	3.51 (1.94, 5.52)
Acute kidney injury	2.12 (1.81, 2.48)	25.35 (21.74, 29.54)	12.04 (10.32, 14.05)	13.30 (9.70, 17.50)
Anxiety	1.21 (1.03, 1.43)	17.81 (15.16, 20.92)	14.72 (12.52, 17.30)	3.09 (0.44, 6.20)
Atrial fibrillation	2.99 (2.60, 3.44)	28.66 (24.96, 32.91)	9.68 (8.42, 11.13)	18.99 (15.28, 23.23)
Atrial flutter	2.33 (2.03, 2.67)	27.39 (23.88, 31.41)	11.86 (10.33, 13.62)	15.53 (12.02, 19.55)
Chronic kidney disease	2.42 (2.07, 2.84)	27.03 (23.12, 31.60)	11.24 (9.60, 13.16)	15.79 (11.88, 20.36)
Constipation or diarrhea	1.50 (1.34, 1.69)	42.98 (38.28, 48.25)	28.77 (25.61, 32.33)	14.21 (9.51, 19.47)
Cough	2.43 (2.18, 2.71)	46.59 (41.88, 51.83)	19.44 (17.45, 21.66)	27.15 (22.44, 32.38)
Deep vein thrombosis	3.50 (2.71, 4.52)	5.80 (4.50, 7.48)	1.66 (1.29, 2.14)	4.14 (2.84, 5.82)
Diabetes	1.46 (1.29, 1.66)	49.52 (43.79, 55.98)	34.18 (30.20, 38.68)	15.34 (9.61, 21.80)
Diabetes medications	1.86 (1.59, 2.18)	23.04 (19.72, 26.93)	12.43 (10.63, 14.54)	10.62 (7.29, 14.50)
eGFR decline ≥50%	1.28 (1.03, 1.58)	13.73 (11.11, 16.95)	10.75 (8.70, 13.28)	2.98 (0.36, 6.21)
Fatigue	2.16 (1.92, 2.43)	37.07 (33.01, 41.62)	17.32 (15.40, 19.47)	19.75 (15.69, 24.30)
Gastroesophageal reflux disease	1.42 (1.18, 1.70)	15.50 (12.91, 18.60)	10.98 (9.14, 13.18)	4.52 (1.93, 7.63)
Heart failure	1.88 (1.61, 2.20)	18.52 (15.85, 21.64)	9.91 (8.47, 11.58)	8.62 (5.95, 11.74)
Hypoxemia	3.05 (2.49, 3.74)	9.95 (8.12, 12.19)	3.27 (2.67, 4.02)	6.68 (4.84, 8.92)
Memory loss	1.51 (1.27, 1.78)	20.08 (16.99, 23.72)	13.38 (11.31, 15.82)	6.70 (3.61, 10.35)
Mood disorder	1.63 (1.34, 2.00)	12.81 (10.49, 15.64)	7.85 (6.43, 9.59)	4.95 (2.63, 7.78)
Muscle or joint pain	1.75 (1.57, 1.95)	48.29 (43.39, 53.73)	27.86 (25.00, 31.03)	20.44 (15.54, 25.87)
Myocardial infarction	1.99 (1.52, 2.59)	6.55 (5.03, 8.53)	3.31 (2.54, 4.31)	3.25 (1.72, 5.23)
Myocarditis	2.76 (0.37, 20.75)	0.20 (0.03, 1.51)	0.07 (0.01, 0.55)	0.13 (-0.05, 1.44)
Other coagulation disorders	2.90 (2.45, 3.42)	18.38 (15.59, 21.67)	6.38 (5.41, 7.53)	12.00 (9.21, 15.29)
Pulmonary embolism	4.37 (3.37, 5.68)	5.45 (4.20, 7.07)	1.25 (0.96, 1.62)	4.20 (2.95, 5.82)
Shortness of breath	2.24 (2.02, 2.48)	54.78 (49.62, 60.45)	24.85 (22.48, 27.47)	29.93 (24.77, 35.60)
Sleep disorder	1.72 (1.55, 1.91)	54.31 (49.05, 60.11)	31.92 (28.8, 35.37)	22.39 (17.13, 28.19)
Smell loss	1.74 (0.90, 3.38)	0.99 (0.51, 1.93)	0.57 (0.29, 1.11)	0.42 (-0.06, 1.36)
Stroke	1.42 (1.12, 1.81)	8.45 (6.66, 10.71)	5.93 (4.68, 7.53)	2.51 (0.72, 4.78)
Substance abuse	1.15 (0.99, 1.33)	24.67 (21.31, 28.55)	21.48 (18.55, 24.86)	3.19 (-0.17, 7.07)
Superficial venous thrombosis	2.30 (1.62, 3.27)	3.87 (2.72, 5.50)	1.69 (1.19, 2.40)	2.19 (1.04, 3.82)
Tachycardia	1.62 (1.27, 2.06)	8.99 (7.09, 11.41)	5.56 (4.38, 7.06)	3.43 (1.52, 5.84)
Ventricular arrhythmias	1.97 (1.50, 2.59)	7.12 (5.43, 9.35)	3.62 (2.76, 4.76)	3.50 (1.80, 5.73)

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. Burdens are presented per 1000 persons at 6 months of follow-up.
ADI, area deprivation index.

Supplementary Table 4: Characteristics and standardized mean differences of those with breakthrough COVID-19 not hospitalized during the acute phase of the disease compared to the control group after weighting.

Characteristic	Non-hospitalized* breakthrough COVID-19 (N=13,683)	Control (N=3,569,525)	Standardized Mean Difference
Age, (mean SD)	65.64 (13.99)	65.64 (14.06)	0.00
Race, N (%)			
White	9845 (71.95)	2568273 (71.95)	0.00
Black	2816 (20.58)	734608 (20.58)	0.00
Other	1022 (7.47)	266644 (7.47)	0.00
Sex, N (%)			0.00
Male	12390 (90.55)	3232205 (90.55)	0.00
Female	1293 (9.45)	337320 (9.45)	0.00
ADI[a], (mean SD)	52.33 (15.12)	52.33 (15.09)	0.00
Smoking status, N (%)			0.00
Never	7155 (52.29)	1866505 (52.29)	0.00
Former	3916 (28.62)	1021598 (28.62)	0.00
Current	2612 (19.09)	681422 (19.09)	0.00
Long-term care, N (%)	161 (1.18)	42120 (1.18)	0.00
Systolic blood pressure, (mean SD)	132.43 (18.16)	132.43 (18.17)	0.00
BMI, (mean SD)	30.94 (6.29)	30.95 (7.95)	0.00
Cerebrovascular disease, N (%)	10134 (7.41)	264502 (7.41)	0.00
Cancer, N (%)	1564 (11.43)	407997 (11.43)	0.00
Anxiety, N (%)	1691 (12.36)	441193 (12.36)	0.00
Chronic kidney disease, N (%)	1676 (12.25)	437267 (12.25)	0.00
Cardiovascular disease, N (%)	2958 (21.62)	771731 (21.62)	0.00
Dementia, N (%)	740 (5.41)	193111 (5.41)	0.00
Depression, N (%)	1393 (10.18)	363378 (10.18)	0.00
Diabetes mellitus type 2, N (%)	4940 (36.10)	1288599 (36.10)	0.00
Lung disease, N (%)	2353 (17.20)	613958 (17.20)	0.00
Peripheral artery disease, N (%)	230 (1.68)	59968 (1.68)	0.00
Number of inpatient visits in the year prior to t0, (mean SD)	0.19 (0.68)	0.19 (0.68)	0.00
Number of outpatient visits in the year prior to t0, (mean SD)	3.03 (1.40)	3.03 (1.42)	0.00
Number of eGFR measures in the year prior to t0, (mean SD)	3.01 (4.60)	3.01 (7.56)	0.00
Number of unique medications in the year prior to t0, (mean SD)	11.79 (8.37)	11.79 (8.41)	0.00

Cohort weighted by the combination of an inverse probability of censoring due to death weight and overlap weight for probability of group membership.
Weighting conducted in cohort in the analyses of the at least one post-acute sequela outcome.
[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; N, sample size; SD, standard deviation; eGFR, estimated glomerular filtration rate.

Supplementary Table 5: Characteristics and standardized mean differences of those with breakthrough COVID-19 hospitalized during the acute phase of the disease compared to the control group after weighting.

Characteristic	Hospitalized* breakthrough COVID-19 (N=2,352)	Control (N=3,569,525)	Standardized Mean Difference
Age, (mean SD)	72.28 (11.26)	72.28 (11.34)	0.00
Race, N (%)			
White	1603 (68.15)	2432631 (68.15)	0.00
Black	574 (24.41)	871321 (24.41)	0.00
Other	175 (7.44)	265573 (7.44)	0.00
Sex, N (%)			
Male	2253 (95.80)	3419605 (95.80)	0.00
Female	99 (4.20)	149920 (4.20)	0.00
ADI[s], (mean SD)	53.22 (14.65)	53.22 (14.63)	0.00
Smoking status, N (%)			
Never	1083 (46.04)	1643409 (46.04)	0.00
Former	754 (32.07)	1144747 (32.07)	0.00
Current	515 (21.89)	781369 (21.89)	0.00
Long-term care, N (%)	102 (4.35)	155274 (4.35)	0.00
Systolic blood pressure, (mean SD)	134.26 (23.85)	134.26 (23.65)	0.00
BMI, (mean SD)	29.91 (6.93)	29.91 (14.46)	0.00
Cerebrovascular disease, N (%)	367 (15.59)	556489 (15.59)	0.00
Cancer, N (%)	520 (22.10)	788865 (22.10)	0.00
Anxiety, N (%)	433 (18.41)	657150 (18.41)	0.00
Chronic kidney disease, N (%)	643 (27.34)	975908 (27.34)	0.00
Cardiovascular disease, N (%)	922 (39.18)	1398540 (39.18)	0.00
Dementia, N (%)	338 (14.35)	512227 (14.35)	0.00
Depression, N (%)	359 (15.27)	545066 (15.27)	0.00
Diabetes mellitus type 2, N (%)	1207 (51.33)	1832237 (51.33)	0.00
Lung disease, N (%)	756 (32.14)	1147245 (32.14)	0.00
Peripheral artery disease, N (%)	121 (5.14)	183474 (5.14)	0.00
Number of inpatient visits in the year prior to t0, (mean SD)	0.95 (1.86)	0.95 (2.26)	0.00
Number of outpatient visits in the year prior to t0, (mean SD)	3.95 (1.50)	3.95 (1.54)	0.00
Number of eGFR measures in the year prior to t0, (mean SD)	7.94 (11.23)	7.94 (15.32)	0.00
Number of unique medications in the year prior to t0, (mean SD)	17.54 (9.79)	17.54 (10.02)	0.00

Cohort weighted by the combination of an inverse probability of censoring due to death weight and overlap weight for probability of group membership.
Weighting conducted in cohort in the analyses of the at least one post-acute sequela outcome.
[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; N, sample size; SD, standard deviation; eGFR, estimated glomerular filtration rate

Supplementary Table 6: Risk and 6-month burden of death, at least one post-acute sequelae, and post-acute sequelae by organ system in breakthrough COVID-19 not hospitalized during the acute phase compared to the control group.

Outcome	HR (95% CI)	Not hospitalized[a] breakthrough COVID-19 burden per 1000 persons at 6-months (95% CI)	Control burden per 1000 persons at 6-months (95% CI)	Excess burden per 1000 persons at 6-months (95% CI)
Death	1.20 (1.02, 1.40)	23.35 (19.94, 27.33)	19.58 (16.71, 22.92)	3.77 (0.36, 7.76)
At least one post-acute sequelae	1.30 (1.24, 1.36)	248.54 (238.47, 258.96)	197.19 (188.93, 205.76)	51.35 (41.29, 61.77)
Cardiovascular	1.40 (1.24, 1.57)	43.57 (38.84, 48.86)	31.35 (27.93, 35.19)	12.22 (7.49, 17.51)
Coagulation	1.97 (1.59, 2.43)	13.27 (10.74, 16.40)	6.77 (5.48, 8.37)	6.50 (3.97, 9.62)
Fatigue	1.30 (1.10, 1.55)	21.91 (18.47, 25.97)	16.85 (14.21, 19.99)	5.05 (1.62, 9.11)
Gastrointestinal	1.17 (1.03, 1.34)	41.19 (36.18, 46.87)	35.28 (30.98, 40.17)	5.90 (0.90, 11.59)
Kidney	1.30 (1.10, 1.55)	28.80 (24.27, 34.16)	22.18 (18.68, 26.32)	6.62 (2.10, 11.98)
Mental health	1.14 (1.04, 1.25)	71.03 (65.16, 77.41)	62.52 (57.33, 68.17)	8.51 (2.64, 14.89)
Metabolic	1.29 (1.12, 1.49)	43.45 (37.77, 49.96)	33.87 (29.42, 38.98)	9.58 (3.90, 16.09)
Musculoskeletal	1.20 (1.03, 1.39)	32.66 (28.25, 37.75)	27.34 (23.64, 31.61)	5.33 (0.91, 10.41)
Neurologic	1.30 (1.07, 1.57)	17.80 (14.73, 21.50)	13.73 (11.36, 16.59)	4.07 (1.00, 7.77)
Pulmonary	1.85 (1.69, 2.03)	69.29 (63.49, 75.59)	38.06 (34.82, 41.58)	31.23 (25.43, 37.54)

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, as well as algorithmically selected high dimensional variables.
Burdens are presented per 1000 persons at 6 months of follow-up.
[a]Hospitalization status assessed during the acute phase of the disease.
ADI, area deprivation index.

Supplementary Table 7: Risk and 6-month burden of death, at least one post-acute sequelae, and post-acute sequelae by organ system in breakthrough COVID-19 hospitalized during the acute phase compared to the control group.

Outcome	HR (95% CI)	Hospitalized* breakthrough COVID-19 burden per 1000 persons at 6-months (95% CI)	Control burden per 1000 persons at 6-months (95% CI)	Excess burden per 1000 persons at 6-months (95% CI)
Death	2.12 (1.77, 2.53)	86.29 (72.82, 102.11)	41.71 (35.06, 49.57)	44.59 (31.12, 60.41)
At least one post-acute sequelae	2.91 (2.72, 3.13)	551.79 (526.63, 577.30)	240.73 (226.37, 255.85)	311.06 (285.90, 336.57)
Cardiovascular	3.89 (3.41, 4.44)	162.27 (143.66, 183.02)	44.52 (39.11, 50.67)	117.75 (99.14, 138.50)
Coagulation	5.38 (4.24, 6.82)	58.56 (46.45, 73.70)	11.16 (8.80, 14.13)	47.40 (35.29, 62.54)
Fatigue	4.55 (3.80, 5.45)	125.59 (106.00, 148.49)	29.08 (24.34, 34.73)	96.51 (76.92, 119.40)
Gastrointestinal	2.62 (2.23, 3.09)	117.44 (100.60, 136.88)	46.52 (39.62, 54.58)	70.92 (54.09, 90.36)
Kidney	4.30 (3.54, 5.22)	116.19 (96.69, 139.32)	28.31 (23.37, 34.28)	87.88 (68.38, 111.01)
Mental health	2.76 (2.42, 3.14)	164.17 (145.78, 184.63)	62.92 (55.50, 71.30)	101.25 (82.86, 121.70)
Metabolic	2.59 (1.98, 3.37)	90.81 (70.42, 116.74)	36.14 (27.84, 46.86)	54.67 (34.28, 80.60)
Musculoskeletal	3.65 (3.07, 4.33)	137.60 (117.07, 161.39)	39.79 (33.58, 47.13)	97.81 (77.28, 121.59)
Neurologic	3.19 (2.56, 3.98)	62.98 (50.80, 77.96)	20.17 (16.20, 25.10)	42.81 (30.64, 57.79)
Pulmonary	4.18 (3.68, 4.75)	192.38 (171.46, 215.50)	49.79 (43.96, 56.36)	142.59 (121.68, 165.71)

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. Burdens are presented per 1000 persons at 6 months of follow-up.
*Hospitalization status assessed during the acute phase of the disease.
ADI, area deprivation index.

Supplementary Table 8: Characteristics and standardized mean differences of those with breakthrough COVID-19 compared to those with COVID-19 without prior vaccination after weighting.

Characteristic	Breakthrough COVID-19 (N=16,035)	COVID-19 (N=48,536)	Standardized Mean Difference
Age, (mean SD)	62.84 (14.67)	62.84 (14.70)	0.00
Race, N (%)			
White	11468 (71.52)	34713 (71.52)	0.00
Black	3423 (21.35)	10362 (21.35)	0.00
Other	1145 (7.14)	3465 (7.14)	0.00
Sex, N (%)			
Male	14270 (88.99)	43192 (88.99)	0.00
Female	1765 (11.01)	5344 (11.01)	0.00
ADI[a], (mean SD)	53.15 (14.83)	53.15 (14.78)	0.00
Smoking status, N (%)			
Never	8495 (52.98)	25714 (52.98)	0.00
Former	4169 (26.00)	12619 (26.00)	0.00
Current	3371 (21.02)	10202 (21.02)	0.00
Long-term care, N (%)	215 (1.34)	650 (1.34)	0.00
Systolic blood pressure, (mean SD)	132.36 (18.54)	132.36 (18.44)	0.00
BMI, (mean SD)	30.93 (6.42)	30.93 (6.42)	0.00
Cerebrovascular disease, N (%)	1074 (6.70)	3252 (6.70)	0.00
Cancer, N (%)	1554 (9.69)	4703 (9.69)	0.00
Anxiety, N (%)	1977 (12.33)	5984 (12.33)	0.00
Chronic kidney disease, N (%)	1676 (10.45)	5072 (10.45)	0.00
Cardiovascular disease, N (%)	2978 (18.57)	9013 (18.57)	0.00
Dementia, N (%)	771 (4.81)	2335 (4.81)	0.00
Depression, N (%)	1653 (10.31)	5004 (10.31)	0.00
Diabetes mellitus type 2, N (%)	5219 (32.55)	15798 (32.55)	0.00
Lung disease, N (%)	2518 (15.70)	7620 (15.70)	0.00
Peripheral artery disease, N (%)	245 (1.53)	743 (1.53)	0.00
Number of inpatient visits in the year prior to t0, (mean SD)	0.22 (0.83)	0.22 (0.83)	0.00
Number of outpatient visits in the year prior to t0, (mean SD)	2.85 (1.36)	2.85 (1.36)	0.00
Number of eGFR measures in the year prior to t0, (mean SD)	2.88 (4.76)	2.88 (5.53)	0.00
Number of unique medications in the year prior to t0, (mean SD)	10.78 (8.07)	10.78 (8.04)	0.00
Week of 2021 that participant tested positive, (mean SD)	26.65 (7.49)	26.65 (7.53)	0.00
Care received at a medical center[b], N (%)	77 (0.48)	233 (0.48)	0.00
Percent of hospital system beds occupied[c], (mean SD)	20.85 (0.13)	63.10 (0.13)	0.00
Total number of hospital beds available in hospital system[+], (mean SD)	461.81 (305.51)	461.81 (305.35)	0.00

Cohort weighted by the combination of an inverse probability of censoring due to death weight and overlap weight for probability of group membership. Weighting conducted in cohort in the analyses of the at least one post-acute sequela outcome.

[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; N, sample size; SD, standard deviation; eGFR, estimated glomerular filtration rate.

[b]Complexity of the care system assessed by whether participants receive care at a medical center vs an outpatient clinic. [c]Assessed as the average in the hospital system of care during the week of testing positive.

Supplementary Table 9: Risk and 6-month burden of death, at least one post-acute sequelae, and post-acute sequelae by organ system in breakthrough COVID-19 compared to those with COVID-19 without prior vaccination.

Outcome	HR (95% CI)	Breakthrough COVID-19 burden per 1000 persons at 6-months (95% CI)	COVID-19 burden per 1000 persons at 6-months (95% CI)	Excess burden per 1000 persons at 6-months (95% CI)
Death	0.65 (0.55, 0.76)	24.42 (20.81, 28.65)	37.39 (31.89, 43.82)	-12.97 (-16.58, -8.74)
At least one post-acute sequelae	0.87 (0.83, 0.92)	252.41 (240.76, 264.52)	283.01 (270.21, 296.27)	-30.60 (-42.25, -18.49)
Cardiovascular	0.80 (0.71, 0.91)	47.95 (42.53, 54.05)	59.48 (52.78, 66.99)	-11.52 (-16.95, -5.42)
Coagulation	0.54 (0.44, 0.66)	15.11 (12.38, 18.44)	27.64 (22.67, 33.69)	-12.53 (-15.26, -9.20)
Fatigue	0.83 (0.70, 0.98)	27.02 (22.93, 31.82)	32.46 (27.56, 38.22)	-5.45 (-9.54, -0.64)
Gastrointestinal	0.96 (0.82, 1.12)	48.06 (41.18, 56.04)	50.04 (42.89, 58.34)	-1.98 (-8.85, 6.00)
Kidney	0.90 (0.77, 1.05)	39.37 (33.87, 45.76)	43.75 (37.65, 50.81)	-4.37 (-9.87, 2.01)
Mental health	0.96 (0.87, 1.06)	79.13 (71.89, 87.07)	82.16 (74.66, 90.39)	-3.03 (-10.27, 4.90)
Metabolism	0.81 (0.69, 0.96)	34.50 (29.42, 40.47)	42.20 (35.99, 49.44)	-7.68 (-12.77, -1.72)
Musculoskeletal	0.90 (0.77, 1.05)	35.37 (30.31, 41.25)	39.41 (33.79, 45.94)	-4.04 (-9.10, 1.84)
Neurologic	0.92 (0.76, 1.13)	21.66 (17.76, 26.39)	23.41 (19.21, 28.52)	-1.75 (-5.65, 2.98)
Pulmonary	0.75 (0.68, 0.83)	68.78 (62.64, 75.50)	90.75 (82.74, 99.50)	-21.97 (-28.12, -15.25)

Models were adjusted 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, body mass index (BMI), week of testing positive for COVID-19, complexity of the hospital system receiving care at, average number of hospital beds occupied in the hospital system of the week testing positive, and total number of hospital beds in the hospital system of the week testing positive, as well as algorithmically selected high dimensional variables.
Burdens are presented per 1000 persons at 6 months of follow-up.
ADI, area deprivation index.

Supplementary Table 10: Characteristics and standardized mean differences of those with breakthrough COVID-19 hospitalized during the acute phase of the disease compared to those hospitalized with seasonal influenza after weighting.

Characteristic	Breakthrough COVID-19 (N=2,352)	Seasonal Influenza (Weighted N=14,154)	Standardized Mean Difference
Age, (mean SD)	71.80 (11.46)	71.80 (11.62)	0.00
Race, N (%)			
White	1627 (69.19)	9793 (69.19)	0.00
Black	565 (24.04)	3403 (24.04)	0.00
Other	159 (6.77)	958 (6.77)	0.00
Sex, N (%)			
Male	2248 (95.57)	13527 (95.57)	0.00
Female	104 (4.43)	627 (4.43)	0.00
ADI[a], (mean SD)	52.68 (14.79)	52.68 (14.73)	0.00
Smoking status, N (%)			
Never	1062 (45.17)	6393 (45.17)	0.00
Former	750 (31.88)	4512 (31.88)	0.00
Current	540 (22.95)	3249 (22.96)	0.00
Long-term care, N (%)	99 (4.22)	598 (4.23)	0.00
Systolic blood pressure, (mean SD)	134.39 (23.61)	134.39 (23.35)	0.00
BMI, (mean SD)	29.81 (6.90)	29.81 (6.93)	0.00
Cerebrovascular disease, N (%)	365 (15.52)	2197 (15.52)	0.00
Cancer, N (%)	495 (21.04)	2977 (21.04)	0.00
Anxiety, N (%)	445 (18.92)	2678 (18.92)	0.00
Chronic kidney disease, N (%)	619 (26.33)	3727 (26.33)	0.00
Cardiovascular disease, N (%)	911 (38.75)	5485 (38.75)	0.00
Dementia, N (%)	318 (13.52)	1914 (13.52)	0.00
Depression, N (%)	357 (15.17)	2147 (15.17)	0.00
Diabetes mellitus type 2, N (%)	1173 (49.87)	7059 (49.87)	0.00
Lung disease, N (%)	774 (32.93)	4661 (32.93)	0.00
Peripheral artery disease, N (%)	117 (4.96)	702 (4.96)	0.00
Receipt of seasonal influenza vaccine in the year prior, N (%)	1065 (45.3)	6412 (45.3)	0.00
Number of inpatient visits in the year prior to t0, (mean SD)	0.94 (1.88)	0.94 (1.86)	0.00
Number of outpatient visits in the year prior to t0, (mean SD)	3.93 (1.50)	3.93 (1.50)	0.00
Number of eGFR measures in the year prior to t0, (mean SD)	7.74 (10.31)	7.74 (9.47)	0.00
Number of unique medications in the year prior to t0, (mean SD)	17.39 (9.74)	17.39 (9.71)	0.00

Cohort weighted by the combination of an inverse probability of censoring due to death weight and overlap weight for probability of group membership.
Weighting conducted in cohort in the analyses of the at least one post-acute sequela outcome.
[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; N, sample size; SD, standard deviation; eGFR, estimated glomerular filtration rate

Supplementary Table 11: Risk and 6-month burden of death, at least one post-acute sequelae, and post-acute sequelae by organ system in breakthrough COVID-19 hospitalized during the acute phase compared to those hospitalized with seasonal influenza.

Outcome	HR (95% CI)	Hospitalized[a] breakthrough COVID-19 burden per 1000 persons at 6-months (95% CI)	Seasonal influenza burden per 1000 persons at 6-months (95% CI)	Excess burden per 1000 persons at 6-months (95% CI)
Death	1.47 (1.28, 1.69)	92.47 (80.89, 105.60)	63.77 (59.50, 68.02)	28.70 (24.45, 32.97)
At least one post-acute sequelae	1.15 (1.09, 1.22)	543.26 (522.99, 563.78)	493.23 (484.02, 502.28)	50.03 (40.98, 59.24)
Cardiovascular	1.19 (1.07, 1.33)	178.72 (161.95, 197.02)	152.19 (145.29, 159.04)	26.53 (19.68, 33.43)
Coagulation	2.07 (1.71, 2.51)	62.99 (52.36, 75.68)	30.90 (27.31, 34.47)	32.09 (28.52, 35.67)
Fatigue	1.54 (1.35, 1.77)	132.82 (116.93, 150.68)	88.16 (82.19, 94.09)	44.66 (38.73, 50.63)
Gastrointestinal	1.23 (1.08, 1.41)	169.43 (150.10, 190.95)	139.75 (131.95, 147.49)	29.68 (21.94, 37.48)
Kidney	1.42 (1.20, 1.68)	138.78 (118.61, 162.05)	99.75 (92.92, 106.53)	39.03 (32.25, 45.86)
Mental health	1.42 (1.28, 1.58)	181.95 (165.27, 200.10)	131.75 (125.32, 138.12)	50.20 (48.83, 56.63)
Metabolic	1.63 (1.29, 2.06)	88.36 (70.62, 110.29)	55.02 (48.93, 61.07)	33.34 (27.29, 39.43)
Musculoskeletal	1.49 (1.30, 1.70)	134.75 (118.85, 152.58)	92.71 (86.52, 98.86)	42.04 (35.89, 48.23)
Neurologic	1.47 (1.23, 1.77)	70.91 (59.49, 84.43)	48.65 (44.39, 52.90)	22.26 (18.02, 26.52)
Pulmonary	1.15 (1.04, 1.27)	188.59 (172.19, 206.35)	166.12 (159.01, 173.16)	22.47 (15.42, 29.58)

Models were adjusted 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, body mass index (BMI), as well as algorithmically selected high dimensional variables.
Burdens are presented per 1000 persons at 6 months of follow-up.
[a]Hosptialization status assessed during the acute phase of the disease.
ADI, area deprivation index.

Supplementary Table 12: Risk and 6-month burden of post-acute sequelae in COVID-19 compared to the control group.

Outcome	HR (95% CI)
Acute coronary disease	1.98 (1.65, 2.38)
Acute kidney injury	2.58 (2.29, 2.92)
Anxiety	1.24 (1.15, 1.35)
Atrial fibrillation	3.18 (2.86, 3.53)
Atrial flutter	2.78 (2.53, 3.06)
Chronic kidney disease	2.21 (1.99, 2.46)
Constipation or diarrhea	1.57 (1.45, 1.70)
Cough	2.97 (2.78, 3.17)
Deep vein thrombosis	4.10 (3.43, 4.91)
Diabetes	1.77 (1.65, 1.90)
Diabetes medications	2.64 (2.39, 2.91)
eGFR decline ≥50%	1.60 (1.37, 186)
Fatigue	2.57 (2.37, 2.79)
Gastroesophageal reflux disease	1.69 (1.53, 1.87)
Heart failure	2.43 (2.17, 2.71)
Hypoxemia	7.57 (6.37, 9.00)
Memory loss	1.66 (1.47, 1.88)
Mood disorder	1.58 (1.40, 1.77)
Muscle or joint pain	1.77 (1.64, 1.90)
Myocardial infarction	1.85 (1.52, 2.26)
Myocarditis	12.90 (6.41, 25.98)
Other coagulation disorders	6.05 (5.52, 6.63)
Pulmonary embolism	11.90 (10.38, 13.64)
Shortness of breath	3.06 (2.88, 3.26)
Sleep disorder	1.78 (1.67, 1.89)
Smell loss	3.07 (2.26, 4.16)
Stroke	1.86 (1.59, 2.16)
Substance abuse	1.28 (1.18, 1.38)
Superficial venous thrombosis	4.16 (3.31, 5.24)
Tachycardia	2.56 (2.23, 2.93)
Ventricular arrhythmias	2.28 (1.87, 2.79)

Models were adjusted 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, as well as algorithmically selected high dimensional variables.
ADI, area deprivation index.