Online Supplement

eTable 1. Model-Based IPTW Model Coefficients

Covariate	Coefficient	Standard Error	95% CI Low	95% CI High
Age: 18-24	-0.79	0.02	-0.83	-0.75
Age: 25-34	-0.43	0.02	-0.46	-0.40
Age: 50-64	0.43	0.01	0.41	0.46
Age: 65+	1.07	0.02	1.04	1.10
Acute Kidney Injury	-0.23	0.03	-0.29	-0.17
CCI: 1-2	0.06	0.01	0.03	0.09
CCI: 3-4	0.13	0.02	0.08	0.18
CCI: 5-10	0.17	0.03	0.11	0.23
CCI: 11+	0.19	0.09	0.03	0.36
Chronic Lung Disease	0.04	0.02	0.00	0.07
Congestive Heart Failure	0.10	0.06	-0.01	0.22
COVID In Sep 2021	0.13	0.02	0.10	0.16
COVID In Oct 2021	0.32	0.02	0.29	0.36
COVID In Nov 2021	0.40	0.02	0.37	0.44
COVID In Dec 2021	0.70	0.02	0.66	0.73
COVID In Jan 2022	1.28	0.02	1.24	1.32
Data Partner A	0.35	0.03	0.29	0.40
Data Partner B	0.26	0.06	0.14	0.37
Data Partner C	0.35	0.04	0.27	0.43
Data Partner D	0.70	0.07	0.57	0.84
Data Partner E	0.46	0.06	0.36	0.57
Data Partner F	0.10	0.03	0.05	0.15
Data Partner G	0.72	0.03	0.66	0.79
Data Partner H	-0.12	0.05	-0.21	-0.02
Data Partner I	0.54	0.05	0.45	0.64
Data Partner K	0.03	0.02	-0.01	0.06
Diabetes Complicated	0.05	0.03	0.01	0.10
Diabetes Uncomplicated	0.08	0.02	0.04	0.12
Gender: Male	-0.14	0.01	-0.16	-0.12
Heart Failure	-0.09	0.05	-0.19	0.01
Immunocompromised	0.57	0.05	0.47	0.68
Intercept	-1.09	0.02	-1.13	-1.05
Kidney Disease	0.18	0.02	0.14	0.23
Myocardial Infarction	-0.15	0.03	-0.21	-0.08
Race/Ethnicity: Asian	0.90	0.04	0.82	0.99
Race/Ethnicity: Black	-0.43	0.02	-0.47	-0.40
Race/Ethnicity: Hispanic	0.14	0.02	0.10	0.18
Race/Ethnicity: Pacific Islander	-0.20	0.14	-0.47	0.06
Race/Ethnicity: Other	-0.39	0.04	-0.46	-0.32
Race/Ethnicity: Unknown	-0.02	0.04	-0.11	0.07
SDOH: 0-45	-0.30	0.07	-0.44	-0.16
SDOH: 56-65	0.69	0.02	0.66	0.72
SDOH: 65+	1.11	0.03	1.04	1.17
SDOH: Missing	0.20	0.03	0.15	0.25
SDOH: Other	0.20	0.02	0.17	0.24
Tobacco Smoker	-0.55	0.03	-0.60	-0.50

eTable 2. Clinic-Based IPTW Model Coefficients

Covariate	Coefficient	Standard Error	95% CI Low	95% CI High
Age: 18-24	-0.75	0.04	-0.83	-0.67
Age: 25-34	-0.34	0.03	-0.40	-0.28
Age: 50-64	0.24	0.03	0.18	0.29
Age: 65+	0.69	0.03	0.63	0.76
Acute Kidney Injury	-0.30	0.05	-0.39	-0.20
CCI: 1-2	0.09	0.03	0.04	0.15
CCI: 3-4	0.18	0.04	0.09	0.26
CCI: 5-10	0.25	0.05	0.14	0.35
CCI: 11+	0.28	0.12	0.04	0.51
Chronic Lung Disease	0.06	0.03	0.00	0.11
Congestive Heart Failure	0.10	0.10	-0.10	0.30
COVID In Sep 2021	0.17	0.04	0.10	0.24
COVID In Oct 2021	0.33	0.04	0.25	0.42
COVID In Nov 2021	0.38	0.05	0.29	0.47
COVID In Dec 2021	0.89	0.04	0.82	0.96
COVID In Jan 2022	1.29	0.03	1.23	1.35
Data Partner A	0.28	0.03	0.22	0.33
Data Partner C	0.28	0.04	0.20	0.36
Data Partner D	0.62	0.07	0.49	0.76
Data Partner G	0.62	0.03	0.55	0.69
Data Partner I	0.59	0.05	0.49	0.69
Diabetes Complicated	0.10	0.05	0.01	0.19
Diabetes Uncomplicated	0.09	0.04	0.01	0.17
Gender: Male	-0.19	0.02	-0.23	-0.14
Heart Failure	-0.09	0.09	-0.27	0.09
Immunocompromised	0.81	0.08	0.67	0.96
Intercept	-0.95	0.04	-1.03	-0.88
Kidney Disease	0.19	0.04	0.11	0.27
Myocardial Infarction	-0.11	0.05	-0.22	-0.01
Race/Ethnicity: Asian	0.66	0.09	0.49	0.83
Race/Ethnicity: Black	-0.36	0.03	-0.41	-0.31
Race/Ethnicity: Hispanic	-0.24	0.04	-0.33	-0.16
Race/Ethnicity: Pacific Islander	-0.52	0.25	-1.02	-0.02
Race/Ethnicity: Other	-0.68	0.07	-0.82	-0.55
Race/Ethnicity: Unknown	-0.23	0.07	-0.36	-0.10
SDOH: 0-45	-0.51	0.18	-0.87	-0.16
SDOH: 56-65	0.69	0.02	0.65	0.74
SDOH: 65+	1.33	0.06	1.22	1.44
SDOH: Missing	-0.40	0.08	-0.56	-0.25
SDOH: Other	-0.06	0.05	-0.15	0.04
Tobacco Smoker	-0.65	0.03	-0.72	-0.58

eTable 3. Model-based Logistic Regression, All Coefficients

Covariate	Coefficient	Standard Error	95% CI Low	95% CI High
Age: 18-24	-1.45	0.14	-1.72	-1.17
Age: 25-34	-0.80	0.07	-0.94	-0.65
Age: 50-64	0.17	0.05	0.08	0.27
Age: 65+	0.16	0.06	0.04	0.28
Acute Kidney Injury	0.27	0.09	0.09	0.46
Chronic Lung Disease	1.06	0.05	0.96	1.15
Congestive Heart Failure	-0.25	0.16	-0.56	0.06
COVID In Sep 2021	-0.06	0.05	-0.16	0.05
COVID In Oct 2021	-0.21	0.07	-0.34	-0.07
COVID In Nov 2021	-0.17	0.07	-0.32	-0.03
COVID In Dec 2021	-0.32	0.07	-0.45	-0.18
COVID In Jan 2022	-0.78	0.07	-0.92	-0.64
Data Partner A	0.11	0.08	-0.05	0.27
Data Partner B	-0.18	0.22	-0.60	0.24
Data Partner C	-0.12	0.13	-0.37	0.13
Data Partner D	-0.78	0.23	-1.22	-0.33
Data Partner E	-0.61	0.23	-1.06	-0.17
Data Partner F	-0.50	0.07	-0.64	-0.36
Data Partner G	-0.02	0.12	-0.26	0.21
Data Partner H	0.01	0.13	-0.26	0.27
Data Partner I	0.94	0.14	0.67	1.21
Data Partner K	-1.54	0.05	-1.64	-1.43
Diabetes Complicated	-0.08	0.09	-0.26	0.10
Diabetes Uncomplicated	0.28	0.08	0.13	0.43
Gender: Male	-0.21	0.04	-0.30	-0.13
Heart Failure	0.64	0.13	0.38	0.90
Immunocompromised	0.00	0.12	-0.23	0.23
Intercept	-3.08	0.07	-3.21	-2.95
Kidney Disease	0.03	0.09	-0.16	0.21
Myocardial Infarction	-0.06	0.10	-0.26	0.13
Race/Ethnicity: Asian	0.11	0.27	-0.41	0.64
Race/Ethnicity: Black	0.01	0.05	-0.10	0.11
Race/Ethnicity: Hispanic	-0.14	0.09	-0.31	0.03
Race/Ethnicity: Pacific Islander	0.38	0.28	-0.16	0.93
Race/Ethnicity: Other	-0.43	0.17	-0.77	-0.09
Race/Ethnicity: Unknown	-0.12	0.17	-0.45	0.20
Tobacco Smoker	-0.03	0.07	-0.16	0.10
Vaccination Status	-0.36	0.04	-0.44	-0.28

eTable 4. Clinic-based Logistic Regression, All Coefficients

Covariate	Coefficient	Standard Error	95% CI Low	95% CI High
Age: 18-24	-1.19	0.25	-1.67	-0.71
Age: 25-34	-0.63	0.15	-0.93	-0.33
Age: 50-64	0.16	0.12	-0.06	0.39
Age: 65+	0.25	0.13	0.00	0.50
Acute Kidney Injury	0.31	0.19	-0.06	0.68
Chronic Lung Disease	0.69	0.11	0.48	0.89
Congestive Heart Failure	0.34	0.36	-0.35	1.04
COVID In Sep 2021	-0.26	0.12	-0.49	-0.02
COVID In Oct 2021	-0.41	0.17	-0.75	-0.08
COVID In Nov 2021	-0.25	0.16	-0.57	0.06
COVID In Dec 2021	-0.54	0.15	-0.83	-0.24
COVID In Jan 2022	-0.89	0.13	-1.15	-0.64
Data Partner A	-0.17	0.13	-0.43	0.09
Data Partner C	0.19	0.18	-0.16	0.54
Data Partner D	-0.06	0.27	-0.59	0.46
Data Partner G	0.33	0.13	0.08	0.59
Data Partner I	1.34	0.16	1.03	1.65
Diabetes Complicated	-0.10	0.19	-0.48	0.28
Diabetes Uncomplicated	0.11	0.18	-0.24	0.46
Gender: Male	-0.11	0.10	-0.30	0.08
Heart Failure	-0.23	0.34	-0.90	0.44
Immunocompromised	0.06	0.24	-0.42	0.53
Intercept	-3.73	0.12	-3.97	-3.50
Kidney Disease	0.16	0.15	-0.14	0.47
Myocardial Infarction	-0.48	0.24	-0.96	-0.01
Race/Ethnicity: Asian	0.32	0.31	-0.28	0.92
Race/Ethnicity: Black	-0.40	0.13	-0.67	-0.14
Race/Ethnicity: Hispanic	-0.11	0.19	-0.47	0.26
Race/Ethnicity: Other	0.03	0.25	-0.47	0.53
Race/Ethnicity: Unknown	0.06	0.25	-0.43	0.55
Tobacco Smoker	-0.22	0.15	-0.51	0.08
Vaccination Status	-0.36	0.09	-0.53	-0.20

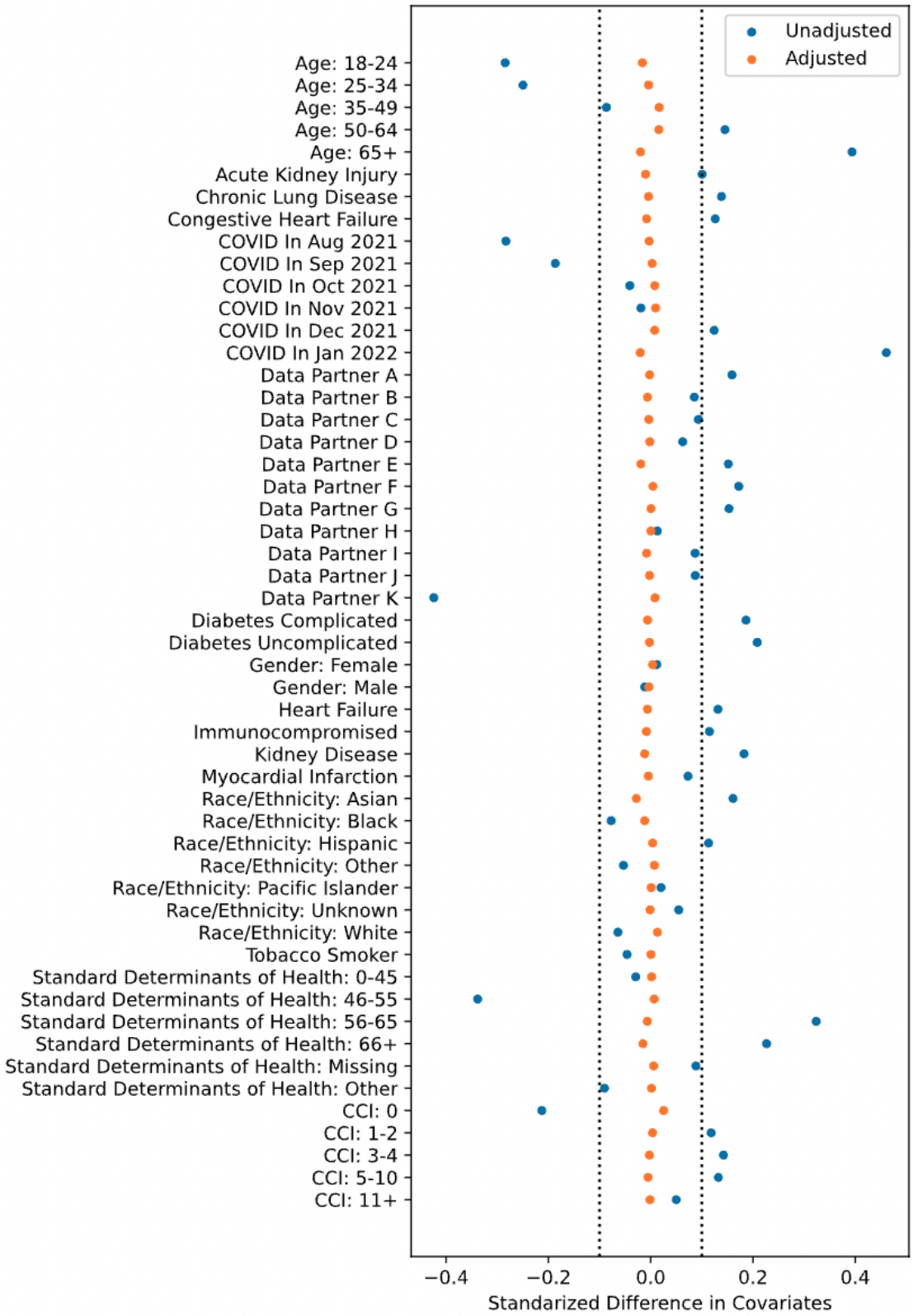
eTable 5. Model-based Proportional Hazards, All Coefficients

Covariate	Coefficient	Standard Error	95% CI Low	95% CI High
Age: 18-24	-2.70	0.42	-3.52	-1.88
Age: 25-34	-0.89	0.10	-1.08	-0.70
Age: 50-64	0.25	0.07	0.13	0.38
Age: 65+	0.27	0.08	0.12	0.42
Acute Kidney Injury	0.18	0.12	-0.05	0.41
Chronic Lung Disease	1.02	0.06	0.90	1.14
Congestive Heart Failure	-0.28	0.16	-0.59	0.04
COVID In Sep 2021	-0.06	0.07	-0.21	0.08
COVID In Oct 2021	-0.11	0.09	-0.30	0.07
COVID In Nov 2021	0.09	0.09	-0.09	0.27
COVID In Dec 2021	0.16	0.09	-0.03	0.34
COVID In Jan 2022	-0.19	0.11	-0.42	0.03
Data Partner A	0.33	0.09	0.15	0.51
Data Partner B	-0.32	0.23	-0.77	0.12
Data Partner C	-0.13	0.16	-0.44	0.18
Data Partner D	1.46	0.82	-0.15	3.06
Data Partner E	-0.52	0.38	-1.28	0.23
Data Partner F	-1.10	0.18	-1.45	-0.74
Data Partner G	-0.10	0.18	-0.46	0.26
Data Partner H	0.21	0.15	-0.08	0.51
Data Partner I	0.64	0.20	0.25	1.03
Data Partner K	-1.13	0.07	-1.27	-0.98
Diabetes Complicated	-0.04	0.10	-0.24	0.17
Diabetes Uncomplicated	0.27	0.09	0.10	0.44
Gender: Male	0.24	0.11	0.02	0.46
Heart Failure	0.65	0.15	0.34	0.95
Immunocompromised	0.15	0.16	-0.16	0.47
Kidney Disease	-0.07	0.11	-0.28	0.14
Myocardial Infarction	0.03	0.12	-0.19	0.26
Race/Ethnicity: Asian	0.33	0.38	-0.41	1.07
Race/Ethnicity: Black	0.04	0.07	-0.09	0.17
Race/Ethnicity: Hispanic	-0.12	0.12	-0.35	0.11
Race/Ethnicity: Other	-0.31	0.20	-0.71	0.09
Race/Ethnicity: Unknown	-0.16	0.27	-0.69	0.37
Tobacco Smoker	0.02	0.09	-0.16	0.19
Vaccination Status	-0.47	0.05	-0.58	-0.37
Time * Gender: Male	-0.00	0.00	-0.01	-0.00
Time * Age: 18-24	0.01	0.00	0.00	0.02
Time * Data Partner D	-0.02	0.01	-0.04	-0.00
Time * Data Partner F	0.01	0.00	0.00	0.01

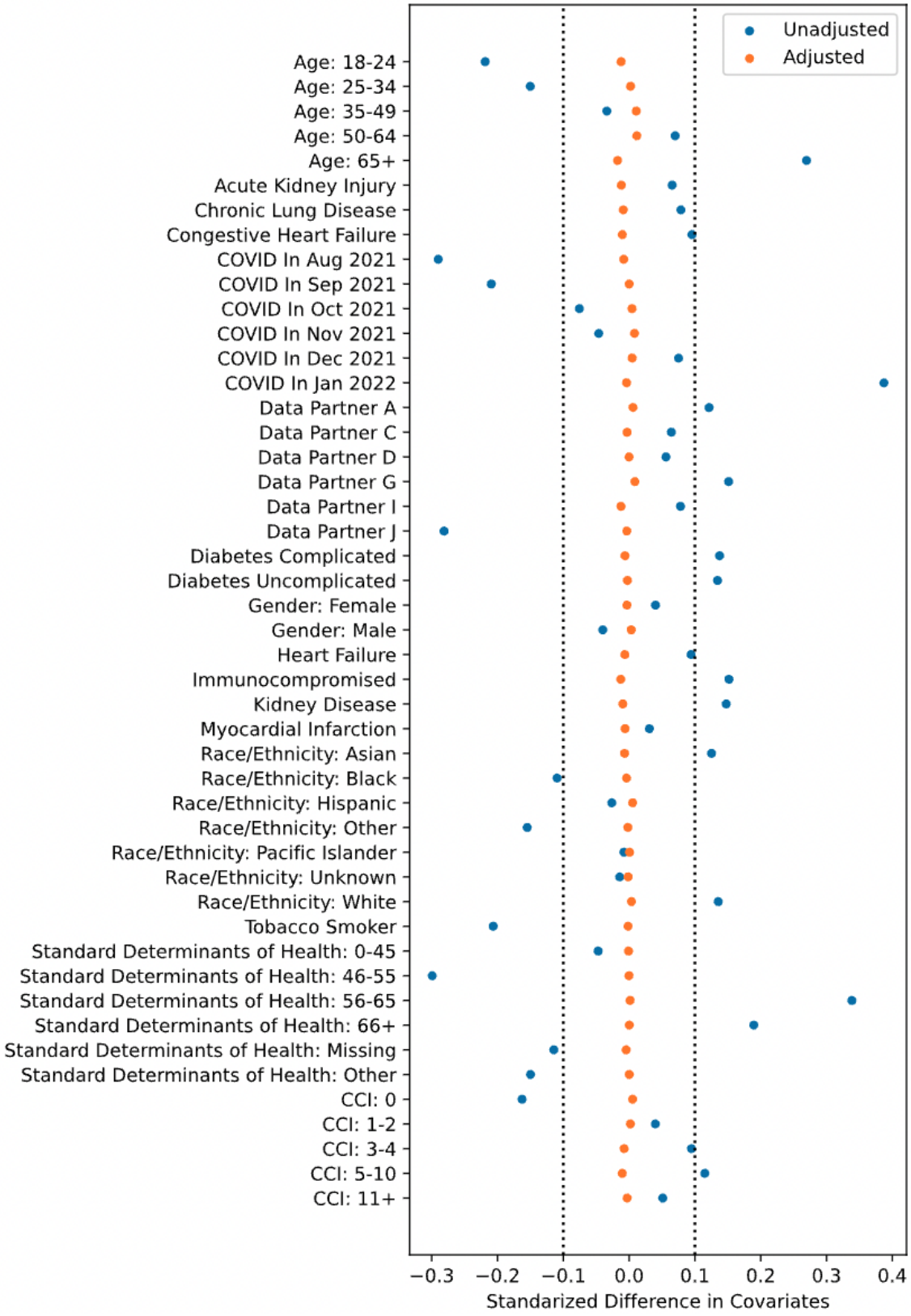
eTable 6. Clinic-based Proportional Hazards, All Coefficients

Covariate	Coefficient	Standard Error	95% CI Low	95% CI High
Age: 18-24	-1.26	0.30	-1.86	-0.67
Age: 25-34	-0.55	0.18	-0.91	-0.19
Age: 50-64	0.26	0.14	-0.01	0.53
Age: 65+	0.31	0.16	0.00	0.62
Acute Kidney Injury	0.41	0.19	0.03	0.78
Chronic Lung Disease	0.76	0.12	0.52	0.99
Congestive Heart Failure	0.09	0.39	-0.68	0.86
COVID In Sep 2021	-0.06	0.14	-0.34	0.21
COVID In Oct 2021	-0.27	0.20	-0.67	0.13
COVID In Nov 2021	-0.13	0.21	-0.55	0.29
COVID In Dec 2021	-0.29	0.20	-0.67	0.09
COVID In Jan 2022	-0.48	0.15	-0.76	-0.19
Data Partner A	-0.03	0.14	-0.30	0.23
Data Partner C	0.26	0.22	-0.18	0.69
Data Partner D	-0.09	0.29	-0.66	0.48
Data Partner G	0.18	0.17	-0.14	0.51
Data Partner I	1.32	0.17	0.98	1.66
Diabetes Complicated	-0.10	0.23	-0.56	0.35
Diabetes Uncomplicated	0.10	0.21	-0.31	0.51
Gender: Male	-0.12	0.10	-0.32	0.09
Heart Failure	0.00	0.36	-0.71	0.71
Immunocompromised	0.09	0.24	-0.39	0.56
Kidney Disease	0.16	0.16	-0.16	0.47
Myocardial Infarction	-0.56	0.25	-1.04	-0.08
Race/Ethnicity: Asian	0.52	0.44	-0.34	1.38
Race/Ethnicity: Black	-0.38	0.15	-0.68	-0.09
Race/Ethnicity: Hispanic	-0.16	0.22	-0.58	0.27
Race/Ethnicity: Other	0.13	0.30	-0.45	0.72
Race/Ethnicity: Unknown	0.23	0.31	-0.38	0.85
Tobacco Smoker	-0.26	0.18	-0.61	0.09
Vaccination Status	-0.41	0.10	-0.60	-0.22

eFigure 1. Differences in standardized covariates in the model-based cohort between vaccinated and unvaccinated groups before (unadjusted) and after (adjusted) IPTW.



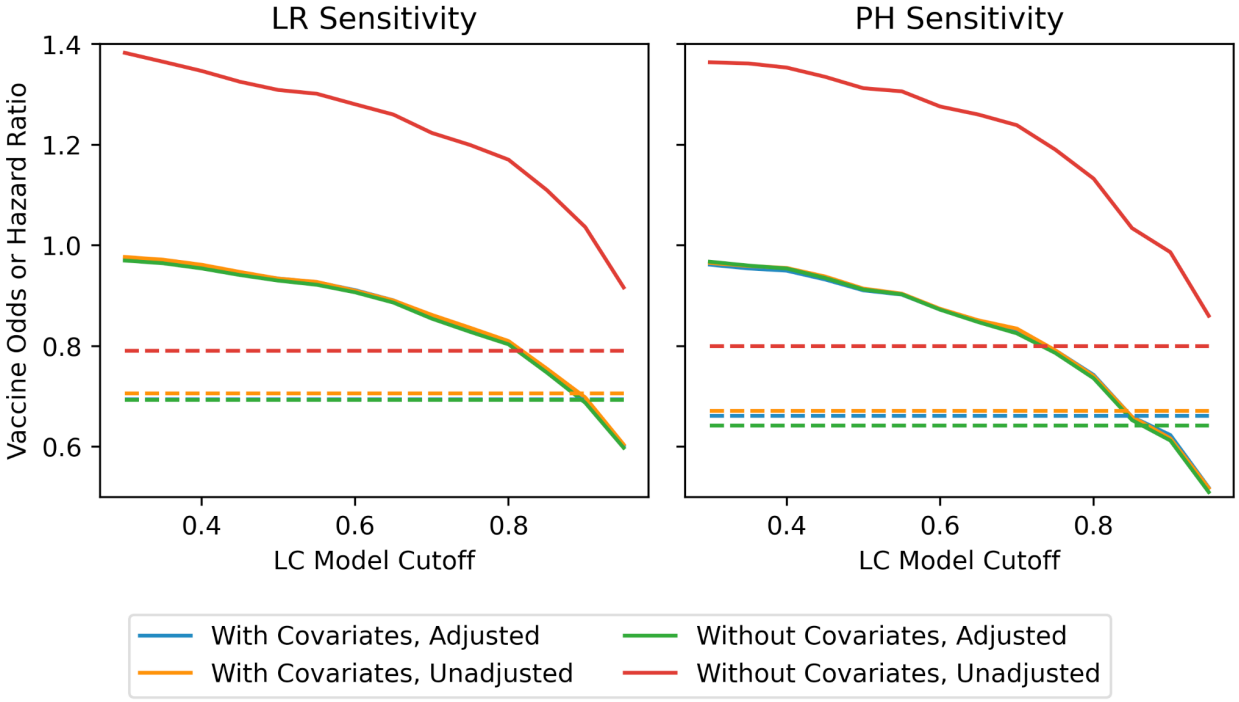
eFigure 2. Differences in standardized covariates in the clinic-based cohort between vaccinated and unvaccinated groups before (unadjusted) and after (adjusted) IPTW.



eTable 7. Associations of Age with Vaccination and Long COVID

	Age at COVID Index Date	Overall	Fully Vaccinated	Unvaccinated	With Long COVID	Without Long COVID
Model-based Cohort	All	199498 (100.0)	87099 (100.0)	112399 (100.0)	3405 (100.0)	196093 (100.0)
	18-24	20701 (10.4)	4922 (5.7)	15779 (14.0)	71 (2.1)	20630 (10.5)
	25-34	36729 (18.4)	11382 (13.1)	25347 (22.6)	292 (8.6)	36437 (18.6)
	35-49	53883 (27.0)	21646 (24.9)	32237 (28.7)	984 (28.9)	52899 (27.0)
	50-64	50887 (25.5)	25332 (29.1)	25555 (22.7)	1175 (34.5)	49712 (25.4)
	65+	37298 (18.7)	23817 (27.3)	13481 (12.0)	883 (25.9)	36415 (18.6)
Clinic-based Cohort	All	47752 (100.0)	26567 (100.0)	21185 (100.0)	706 (100.0)	47046 (100.0)
	18-24	4522 (9.5)	1753 (6.6)	2769 (13.1)	22 (3.1)	4500 (9.6)
	25-34	8557 (17.9)	4078 (15.3)	4479 (21.1)	68 (9.6)	8489 (18.0)
	35-49	12445 (26.1)	6748 (25.4)	5697 (26.9)	194 (27.5)	12251 (26.0)
	50-64	12356 (25.9)	7235 (27.2)	5121 (24.2)	232 (32.9)	12124 (25.8)
	65+	9872 (20.7)	6753 (25.4)	3119 (14.7)	190 (26.9)	9682 (20.6)

eFigure 3. Sensitivity analysis results for logistic regression (LR) and proportional hazards (PH), full LC Model threshold range. Odds ratios for the vaccination coefficient are shown for LR, hazard ratios for the vaccination coefficient are shown for PH. Dashed lines are results from the clinic-based cohort, where the LC model cutoff is not relevant. Solid lines are results from the model-based cohort.



eDiscussion

We do not interpret the associations between vaccination and long COVID here as causal, as we fail to fully account for two important conditions: unconfoundedness and latent variables.

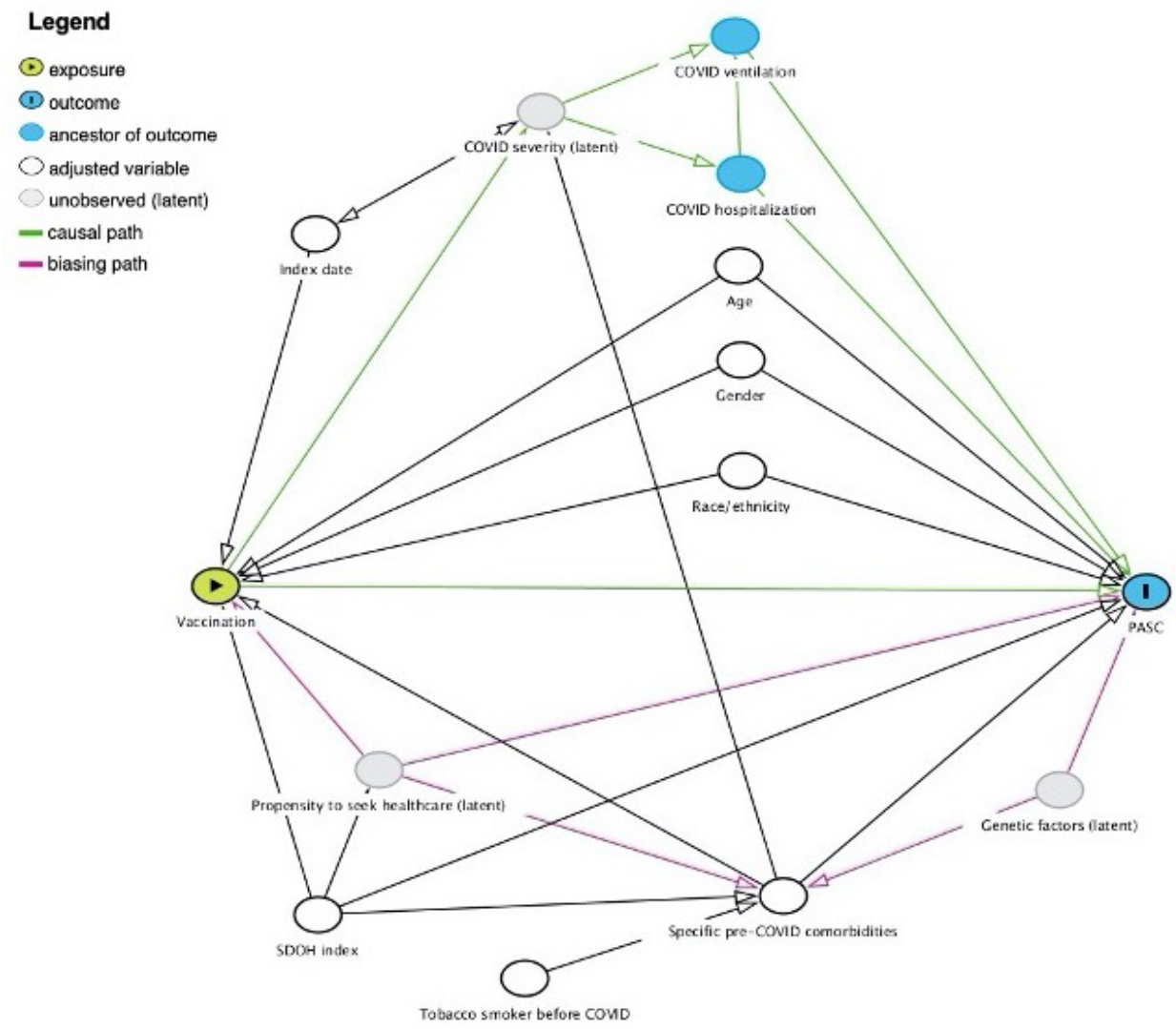
Unconfoundedness

Under certain assumptions, associations in IPTW-adjusted models can be interpreted as causal effects, even when treatment is not randomly assigned.[1,2] If we are willing to assume that there are no unmeasured confounders, IPTW satisfies the condition of exchangeability: the treatment and control groups differ in outcome only due to the treatment. We attempt to satisfy this assumption by controlling for the measured confounders outlined in eTables 1 and 2 in our treatment model. Nevertheless, we do not assume that there are no further confounders, largely due to the field's nascent understanding of long COVID. For example, a small cohort study suggested that reactivation of latent viruses may contribute to long COVID, but we do not include past viral infections in the treatment model.[3] Furthermore, some of the latent variables in our causal model are unobserved confounders, as discussed further below.

Latent Variables

To assess the feasibility of interpreting our results causally, we developed a simplified, theoretical causal model of COVID-19 and long COVID. This model is illustrated with a directed acyclic graph (DAG) in eFigure 4 and reveals latent variables that present an obstacle to estimating the causal effect of COVID-19 vaccination on long COVID. Of particular concern is patient propensity to seek healthcare, which affects the likelihood that both COVID-19 vaccination and long COVID will be observed, and is common in research using electronic health records.[4]

eFigure 4: Directed acyclic graph (DAG) of a simplified, theoretical causal model of COVID-19 vaccination and long COVID.



eReferences

1. Hernán MA, Robins JM. Estimating causal effects from epidemiological data. *J Epidemiol Community Health*. 2006;60(7):578-586.

2. Chesnaye NC, Stel VS, Tripepi G, et al. An introduction to inverse probability of treatment weighting in observational research. *Clin Kidney J*. 2022;15(1):14-20.

3. Su Y, Yuan D, Chen DG, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell*. 2022;185(5):881-895.e20.

4. Farmer R, Mathur R, Bhaskaran K, Eastwood SV, Chaturvedi N, Smeeth L. Promises and pitfalls of electronic health record analysis. *Diabetologia*. 2018;61(6):1241-1248.