

Covid Phenotyping

May 5th 2022

OHDSI APAC Community Call Gowtham Rao



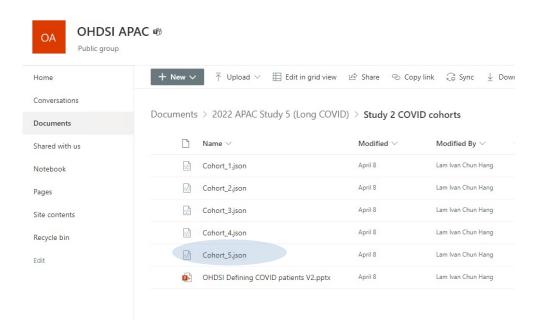
Agenda

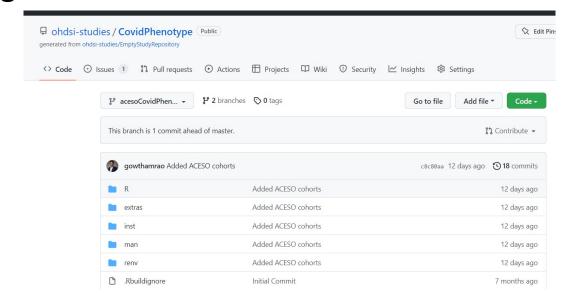
- ACESO project from HKU Cohort definitions Covid-19
- Orientation to Cohort Diagnostics
- Science of Phenotyping Measurement errors
- Review the Covid Phenotypes using Cohort Diagnostics
- How to pick the best cohort definition for Covid-19



ACESO project from Hong Kong University

The study title is 'Comparison of mortality, morbidities & healthcare resources utilization between patients with and without a diagnosis of COVID-19',







ACESO project from Hong Kong University **Covid-19 Cohort Definitions**

Id	Name	Logic Description
184 [1]	[ACESO] Covid 1 - Testing with 365d prior observation time after 2020	Earliest date a person was tested for Covid-19 with a 365 days prior observation on or after January 1 st 2020
185 [2]	[ACESO] Covid 2 - Testing positive with 365d prior observation time after 2020	Earliest date a person was tested for Covid-19 with a 365 days prior observation on or after January 1 st 2020 With test positive result between 0 to 7 days
186 [3]	[ACESO] Covid 3 - Testing positive or condition with 365d - after 2020	Earliest date a person was tested for Covid-19 with a 365 days prior observation on or after January 1 st 2020 With test positive result OR diagnosis of COVID between 0 to 7 days
187 [4]	[ACESO] Covid 4 - Testing positive or condition 2 with 365d - after 2020	Earliest date a person was tested with positive result for Covid-19 OR diagnosis of COVID 19 with a 365 days prior observation on or after January 1st 2020
188 [5]	[ACESO] Covid 5 - Testing positive or no negative with 365d - after 2020	Earliest date a person was tested with positive result for Covid-19 OR diagnosis of COVID 19 but no negative covid result within 3 days with a 365 days prior observation on or after January 1st 2020



Covid Phenotyping options

Positive

Positive & Negative

Lab only

Negative

No result

Diagnosis only

Lab AND Diagnosis

Lab OR Diagnosis



Not a theoretical problem

1 – test result positive

2 – test result negative

3 – both positive and negative

Empirical decision – 3 days

Debate -3d to +3d 0d to +3d

num_records 💌	dp5 ▼	dp4 ▼	dp3 ▼	dp2 ▼	dp1 ▼	d0 ▼	dm1 ▼	dm2 🔻	dm3 🔻	dm4 ▼	dm5 🔻
179,999	0	0	0	0	0	0	0	0	0	0	0
113,970	0	0	0	0	0	1	0	0	0	0	0
69,805	0	0	0	0	1	0	0	0	0	0	0
36,805	0	0	0	1	0	0	0	0	0	0	0
16,733	0	0	0	0	X 2	0	0	0	0	0	0
11,810	0	0	0	0	0	X 2	0	0	0	0	0
10,156	0	0	1	0	0	0	0	0	0	0	0
8,686	0	0	0	X 2	0	0	0	0	0	0	0
6,708	0	0	0	0	0	0	1	0	0	0	0
4,510	0	0	X 2	0	0	0	0	0	0	0	0
3,547	0	1	0	0	0	0	0	0	0	0	0
3,283	0	0	0	0	1	1	0	0	0	0	0
2,977	0	0	0	0	0	0	0	1	0	0	0
2,656	0	2	0	0	0	0	0	0	0	0	0
2,441	0	0	0	0	0	0	0	0	1	0	0
2,207	0	0	0	0	※ 2	X 2	0	0	0	0	0
2,149	0	0	0	0	0	0	0	0	0	1	0
2,114	2	0	0	0	0	0	0	0	0	0	0
1,867	1	0	0	0	0	0	0	0	0	0	0
1,846	0	0	0	0	0	0	0	0	0	0	1
947	0	0	0	X 2	X 2	0	0	0	0	0	0
695	0	0	0	1	1	0	0	0	0	0	0
652	0	0	0	1	0	1	0	0	0	0	0
644	0	0	0	0	0	1	1	0	0	0	0
629	0	0	0	0	0	3	0	0	0	0	0
598	0	0	0	0	0	0	2	0	0	0	0
539	0	0	0	0	2	1	0	0	0	0	0
477	0	0	0	0	0	0	0	2	0	0	0
438	0	0	0	2	0	2	0	0	0	0	0
433	0	0	0	0	0	0	0	0	2	0	0
415	0	0	0	0	3	0	0	0	0	0	0

#JoinTheJourney



OHDSI Phenotype Development Workgroup

Id	Name	Logic Description
	COVID-19 diagnosis and SARS-CoV-2 test (1pos) (0neg) within 3d 47 (3Pe, 7Era)	Persons with concurrent diagnosis and SARS-Cov-2 positive test results, within 3 days of each other AND the absence of a negative SARS-Cov-2 test result between diagnosis or test date and 3 days after that date
	COVID-19 diagnosis and SARS-CoV-2 test (1pos) within 3d (3Pe, 46 7Era)	Persons with concurrent diagnosis and SARS-Cov-2 positive test results, within 3 days of each other
	58 SARS-CoV-2 test positive result (3Ps, 21Era)	Persons with a positive lab measurement based on SARS-CoV-2 test
	SARS-CoV-2 test (1pos) or COVID-19 diagnosis with (1pos or 0 neg 56-3d to 3d) (3Ps, 21Era)	Persons with a positive lab measurement based on SARS-CoV-2 test or a provider documented Covid-19 diagnosis with no negative test result between the 3 days prior to and upto 3 days after the date of diagnosis - any recurrent event within 21 days is considered to be part of the original disease episode
	SARS-CoV-2 test (1pos) or COVID-19 diagnosis with (1pos or 0 neg 85 od to 3d) (3Ps, 21Era)	Persons with a positive lab measurement based on SARS-CoV-2 test or a provider documented Covid-19 diagnosis with no negative test result between the date of the diagnosis and upto 3 days after the date of diagnosis - any recurrent event within 21 days is considered to be part of the original disease episode
	SARS-CoV-2 test (1pos) or COVID-19 diagnosis with (1pos or 0 neg 84 0d to 3d) (3Ps, 180Era)	Persons with a positive lab measurement based on SARS-CoV-2 test or a provider documented Covid-19 diagnosis with no negative test result between the date of the diagnosis and upto 3 days after the date of diagnosis - any recurrent event within 180 days is considered to be part of the original disease episode
	55 COVID-19 diagnosis or SARS-CoV-2 test (1pos) (3Ps, 21Era)	Persons with a provider documented diagnosis for Covid-19 or a positive lab measurement based on SARS-CoV-2 test
	44 COVID-19 diagnosis (3Pe, 7Era)	Persons with a provider documented diagnosis for Covid-19
	45 COVID-19 diagnosis with SARS-Cov-2 test (-3d to 3d) (3Pe, 21Era)	Persons with a provider documented diagnosis for Covid-19 with a lab measurement result for a SARS-Cov-2 test within 3 of diagnosis
	59 COVID-19 diagnosis with no SARS-CoV-2 test (3Ps, 21Era)	Persons with a provider documented diagnosis for Covid-19 with NO measurement result for a SARS-Cov-2 test within 3 of diagnosis
	COVID-19 diagnosis and SARS-CoV-2 test (Opos upto 3d, 1neg 48 within 3d) (3Pe, 7Era)	Persons with a provider documented diagnosis for Covid-19 with NO lab measurement POSITIVE result for a SARS-Cov-2 test AND a NEGATIVE results for a SARS-Cov-2 within 3 days after diagnosis







Many scenarios ranked from sensitive to specific by intuition

Specific

Covid Measurement		Covid Diagnosis	Temporal
+ve, no -ve	AND	Diagnosis	-3d to 3d/0d to 3d
+ve	AND	Diagnosis	-3d to 3d/0d to 3d
+ve, no -ve			-3d to 3d/0d to 3d
+ve			
+ve, no -ve	OR	Diagnosis, (no –ve/missing)	-3d to 3d/0d to 3d
+ve, no -ve (2)	OR	Diagnosis, (no –ve) (2)	-3d to 3d/0d to 3d
+ve (1)	OR	Diagnosis, (no –ve/tested- missing) (2)	-3d to 3d/0d to 3d
+ve (1)	OR	Diagnosis, (no –ve) (2)	-3d to 3d/0d to 3d
+ve (1)	OR	Diagnosis (1)	
		Diagnosis (1), (no – ve/tested-missing) (2)	
,		Diagnosis (1), (no –ve) (2)	
		Diagnosis (1)	

Phenotype Algorithms classify subjects in data sources into groups called Cohorts – "Cohort Definition"

Cohort is a set of persons who satisfy a criteria for a certain period of time (cohort_start_date – cohort_end_date)

Are subject to misclassification errors - threats to reliable evidence.

Misclassification errors are estimated using sensitivity, specificity, positive predictive value (PPV), negative predictive value

Quantifying vs. knowing the origin of misclassification errors



Sensitive

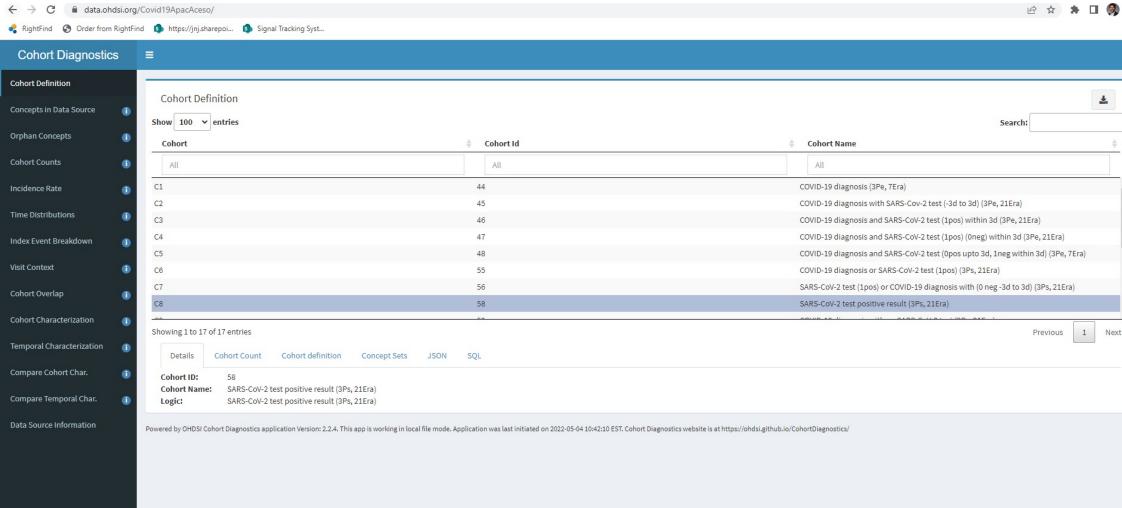


Theoretical Framework of Phenotype Evaluation

- **Sensitivity error** we may say that a given cohort has sensitivity errors, if we observe evidence that there are persons in the data source who may have the phenotype of interest but <u>are not identified by the PA</u>.
- **Specificity error** we may say that a given cohort has specificity errors, if we observe evidence that subjects identified by the PA do not have the phenotype of interest.
- Index-date misclassification we may say that a given cohort has indexdate misclassification error, if we observe evidence that subjects identified by the PA have incorrect designation of event start date.

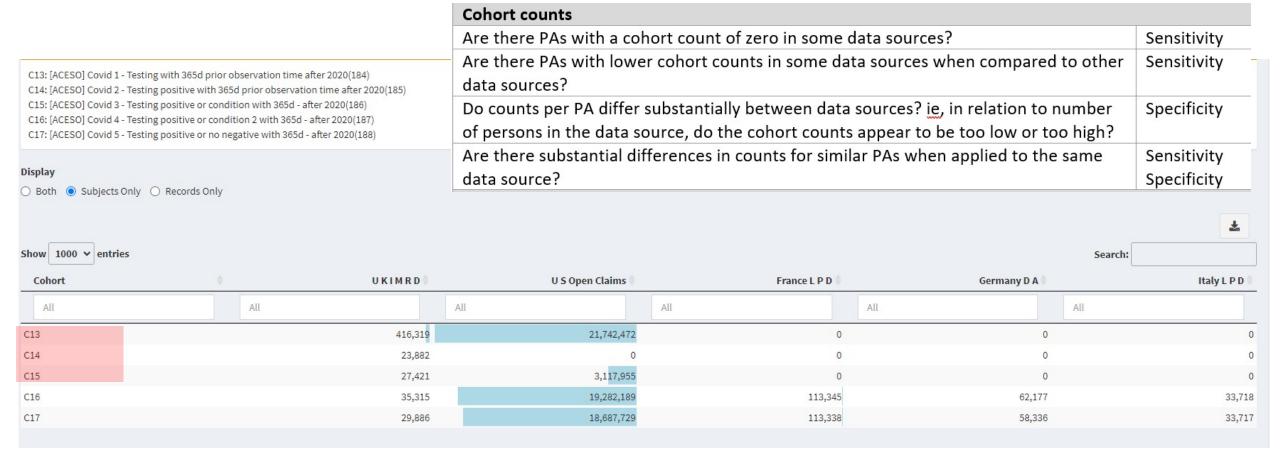


Cohort Diagnostics Tool - overview



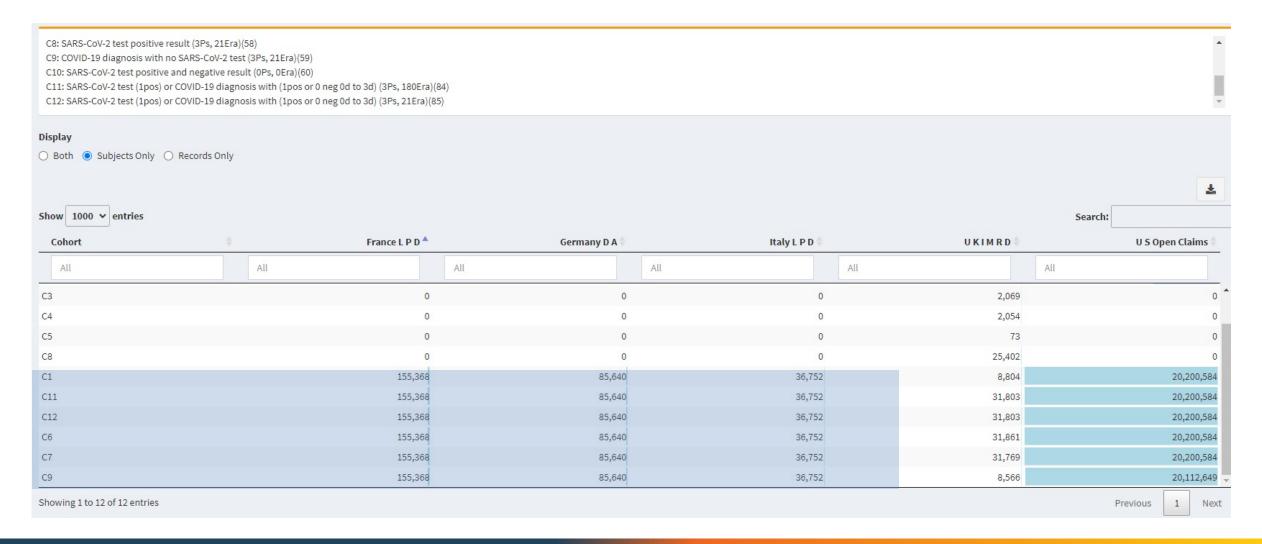


ACESO project from Hong Kong University Cohort Counts





ACESO project from Hong Kong University Cohort Counts



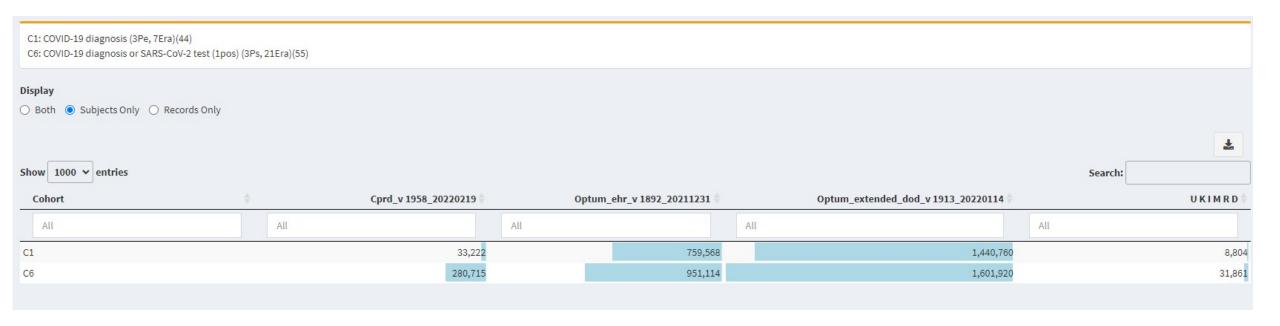


Lab don't matter for most datasources





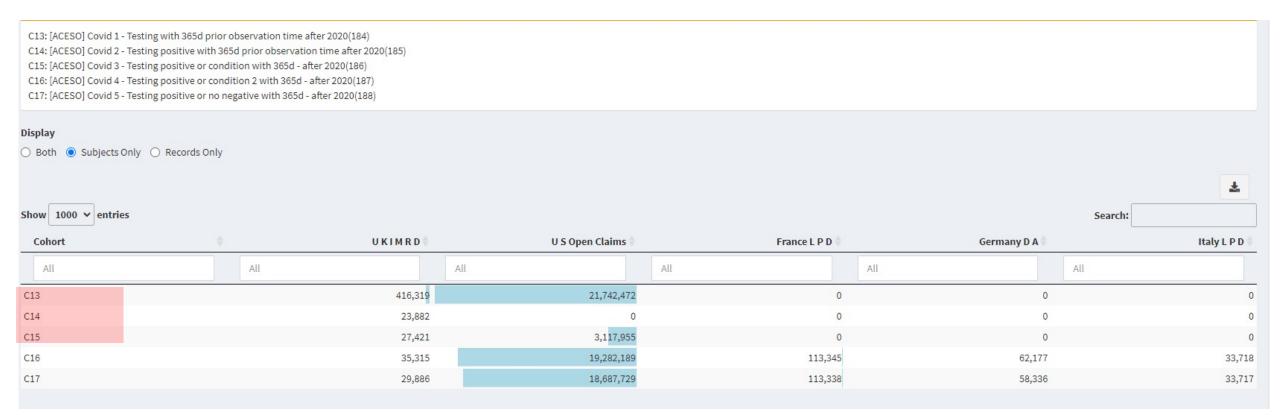
But labs are important



Data sources that don't have LAB have sensitivity errors



Test OR Condition



Cohort Definitions SHOULD include CONDITION or TEST as entry event criteria

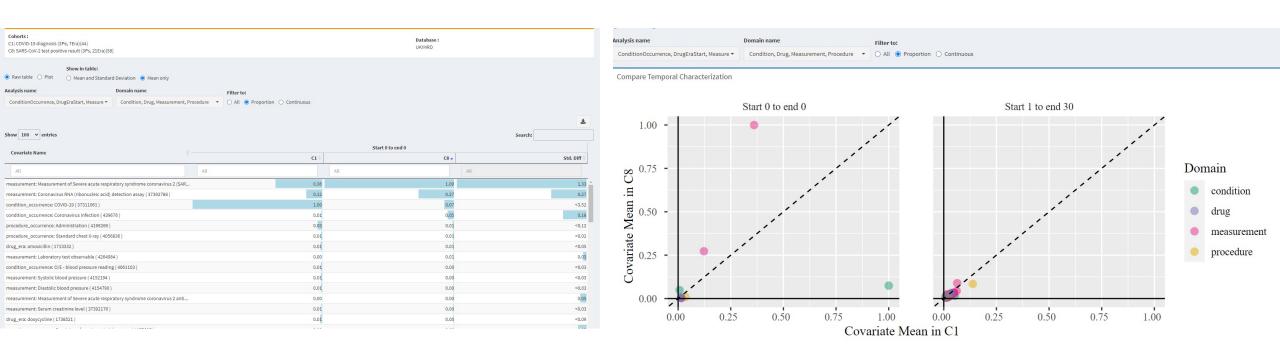
X test only

X Condition only





UKIMRD – Compare cohort with diagnosis ONLY vs Positive Test only



No Difference





Majority failed Cohort Count Diagnostics (Sensitivity errors)

cohort	cohortId cohortName	Fail
C1	Campaning will require data course with lab	X
C2	Comparing will require data source with lab	X
C3 C4 C5	results	X X X
C6	55 COVID-19 diagnosis or SARS-CoV-2 test (1pos) (3Ps, 21Era)	
C7	56 SARS-CoV-2 test (1pos) or COVID-19 diagnosis with (0 neg -3d to 3d) (3Ps, 21Era)	
C8	58 SARS-CoV-2 test positive result (3Ps, 21Era)	X
C9	59 COVID-19 diagnosis with no SARS-CoV-2 test (3Ps, 21Era)	X
C10	60 SARS-CoV-2 test positive and negative result (0Ps, 0Era)	X
C11	84 SARS-CoV-2 test (1pos) or COVID-19 diagnosis with (1pos or 0 neg 0d to 3d) (3Ps, 180Era)	
C12	85 SARS-CoV-2 test (1pos) or COVID-19 diagnosis with (1pos or 0 neg 0d to 3d) (3Ps, 21Era)	
C13	184 [ACESO] Covid 1 - Testing with 365d prior observation time after 2020	X
C14	185 [ACESO] Covid 2 - Testing positive with 365d prior observation time after 2020	X
C15	186 [ACESO] Covid 3 - Testing positive or condition with 365d - after 2020	X
C16	187 [ACESO] Covid 4 - Testing positive or condition 2 with 365d - after 2020	
C17	188 [ACESO] Covid 5 - Testing positive or no negative with 365d - after 2020	



Data Sources with Lab measurements



Have similar sensitivity





Theoretical Framework of Phenotype Evaluation

- **Sensitivity error** we may say that a given cohort has sensitivity errors, if we observe evidence that there are persons in the data source who may have the phenotype of interest but <u>are not identified by the PA</u>.
- Specificity error we may say that a given cohort has specificity errors, if we observe evidence that subjects identified by the PA do not have the phenotype of interest.
- Index-date misclassification we may say that a given cohort has indexdate misclassification error, if we observe evidence that subjects identified by the PA have incorrect designation of event start date.



Not a theoretical problem

1 – test result positive

2 – test result negative

3 – both positive and negative

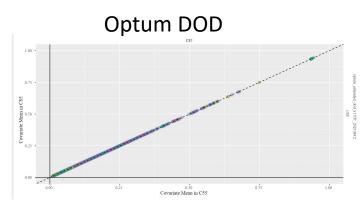
Empirical decision – 3 days

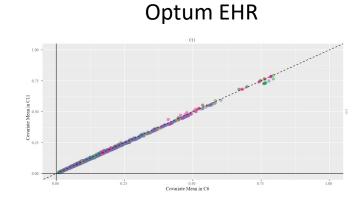
Debate
-3d to +3d
0d to +3d

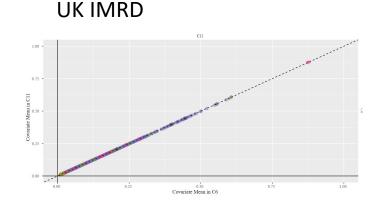
num_records 💌	dp5 ▼	dp4 ▼	dp3 ▽	dp2 ▼	dp1 ▼	d0 ▼	dm1 ▼	dm2 ▼	dm3 ▼	dm4 ▼	dm5 💌
179,999	0	0	0	0	0	0	0	0	0	0	0
113,970	0	0	0	0	0	1	0	0	0	0	0
69,805	0	0	0	0	1	0	0	0	0	0	0
36,805	0	0	0	1	0	0	0	0	0	0	0
16,733	0	0	0	0	X 2	0	0	0	0	0	0
11,810	0	0	0	0	0	※ 2	0	0	0	0	0
10,156	0	0	1	0	0	0	0	0	0	0	0
8,686	0	0	0	X 2	0	0	0	0	0	0	0
6,708	0	0	0	0	0	0	1	0	0	0	0
4,510	0	0	X 2	0	0	0	0	0	0	0	0
3,547	0	1	0	0	0	0	0	0	0	0	0
3,283	0	0	0	0	1	1	0	0	0	0	0
2,977	0	0	0	0	0	0	0	1	0	0	0
2,656	0	2	0	0	0	0	0	0	0	0	0
2,441	0	0	0	0	0	0	0	0	1	0	0
2,207	0	0	0	0	X 2	X 2	0	0	0	0	0
2,149	0	0	0	0	0	0	0	0	0	1	0
2,114	2	0	0	0	0	0	0	0	0	0	0
1,867	1	0	0	0	0	0	0	0	0	0	0
1,846	0	0	0	0	0	0	0	0	0	0	1
947	0	0	0	X 2	X 2	0	0	0	0	0	0
695	0	0	0	1	1	0	0	0	0	0	0
652	0	0	0	1	0	1	0	0	0	0	0
644	0	0	0	0	0	1	1	0	0	0	0
629	0	0	0	0	0	3	0	0	0	0	0
598	0	0	0	0	0	0	2	0	0	0	0
539	0	0	0	0	2	1	0	0	0	0	0
477	0	0	0	0	0	0	0	2	0	0	0
438	0	0	0	2	0	2	0	0	0	0	0
433	0	0	0	0	0	0	0	0	2	0	0
415	0	0	0	0	3	0	0	0	0	0	0



Baseline characteristics Very little difference







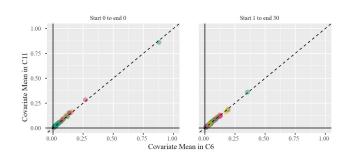
Very little difference at baseline on covariates NOT directly related to covid

i.e. ignore covid testing, respiratory covariates like pneumonia, SpO2, radiology etc

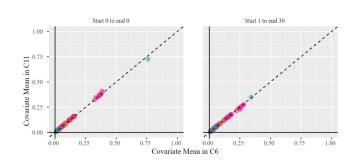


Index date and 1 to 30 days after Very little difference

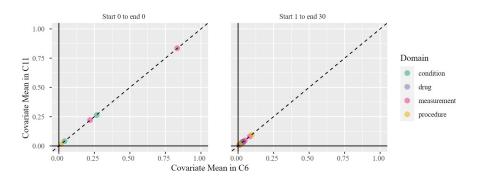
Optum DOD



Optum EHR

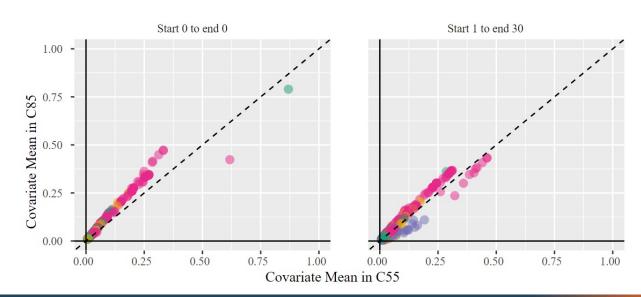


UK IMRD



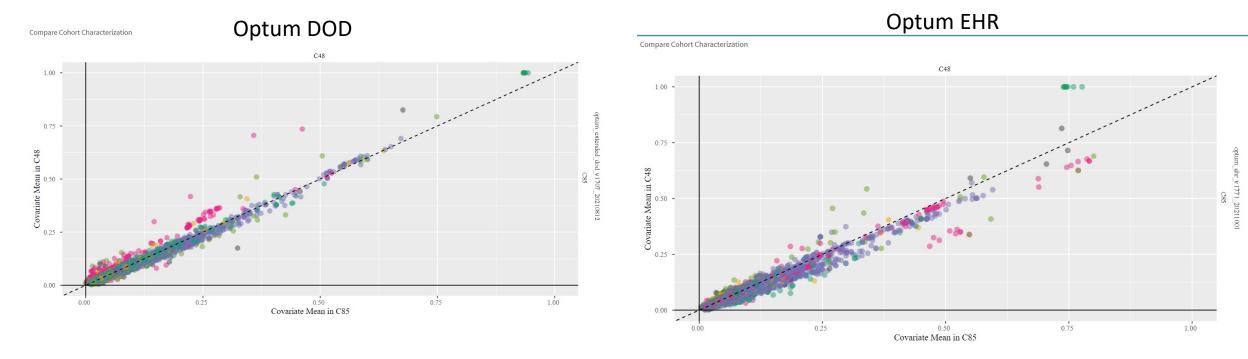
Columbia University Medical Center

Compare Temporal Characterization





Baseline characteristics No negative test vs Marginal (negative test)



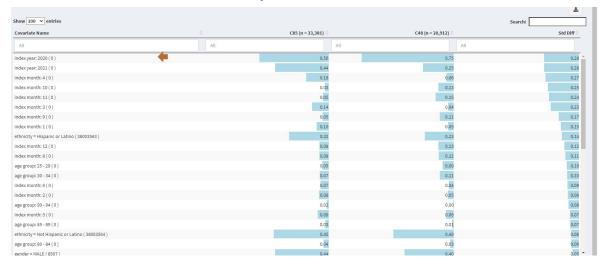
We observe differences at baseline on covariates NOT directly related to covid

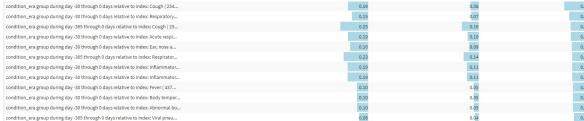
i.e. ignore covid testing, respiratory covariates like pneumonia, SpO2, radiology etc



Baseline characteristics No negative test vs Marginal (negative test)

Columbia University Medical Center





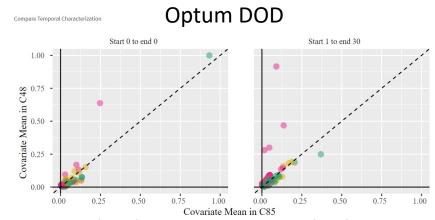
Optum EHR



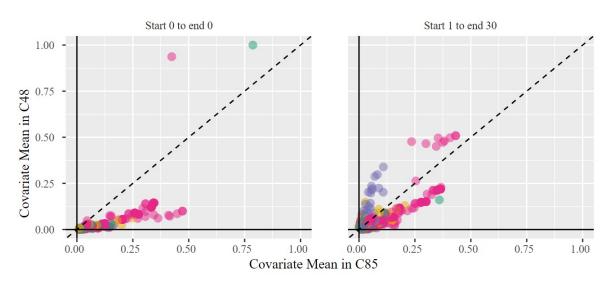
procedure_occurrence during day -30 through 0 days relative to index: Radiologic	0.24	0.04	0.44
procedure_occurrence during day -365 through 0 days relative to index: Radiologi	0.33	0.10	0.41
condition_era group during day -365 through 0 days relative to index: Viral pneu	0.18	0.02	0.40
condition_era group during day -365 through 0 days relative to index: Viral lowe	0.18	0.02	0.40
measurement during day -30 through 0 days relative to index: Oxygen saturation i	0.50	0.24	0.39
measurement during day -30 through 0 days relative to index: Respiratory rate (0.43	0.19	0.38
condition_era group during day -365 through 0 days relative to index: Viral resp	0.19	0.03	0.38
condition_era group during day -365 through 0 days relative to index: Lower resp	0.20	0.03	0.38
condition_era group during day -365 through 0 days relative to index: Infective	0.18	0.03	0.38
condition_era group during day -30 through 0 days relative to index: Respiratory	0.18	0.02	0.38
condition era group during day -365 through 0 days relative to index: Infectious	0.19	0.03	0.37

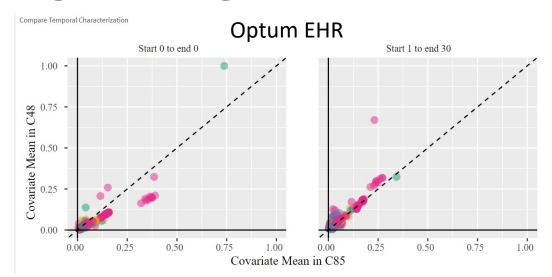


Index date and 1 to 30 days after No negative test vs Marginal (negative test)



Compare Temporal Characte Columbia University Medical Center



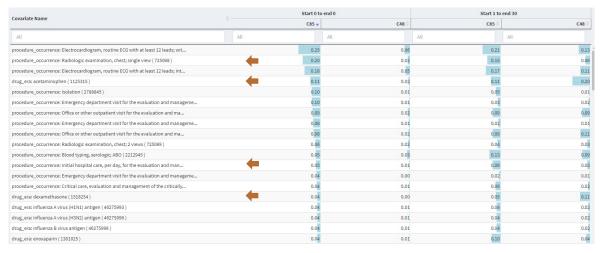




Index date and 1 to 30 days after No negative test vs Marginal (negative test)

Columbia University Medical Center

Optum EHR



Covariate Name	Start 0	to end 0	Start 1 to	o end 30
Covariate Name	C85 v	C48 🗇	C85 🕏	C48 🏺
All	All	All	All	All
condition_occurrence: COVID-19 (37311061)	0.7	1.00	0.36	0.16
measurement: Systolic blood pressure (3004249)	0.4	7 0.10	0.43	0.51
measurement: Diastolic blood pressure (3012888)	0.4	7 0.10	0.43	0.51
measurement: Heart rate (3027018)	0.4	0.09	0.41	0.50
measurement: SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by NAA	0.4	2 0.94	0.25	0.26
measurement: Oxygen saturation in Arterial blood by Pulse oximetry (40762499)	0.4	2 0.07	0.38	0.47
measurement: Body temperature (3020891)	0.4	0.08	0.38	0.48
measurement: Respiratory rate (3024171)	0.3	0.06	0.35	0.45
measurement: Hemoglobin [Mass/volume] in Blood (3000963)	0.3	0.14	0.37	0.23
measurement: Body weight (3025315)	0.3	4 0.08	0.35	0.50
measurement: Hematocrit [Volume Fraction] of Blood by Automated count (3023314	0.3	0.14	0.36	0.22
measurement: Leukocytes [#/volume] in Blood by Automated count (3000905)	0.3	0.14	0.36	0.22
measurement: Platelets [#/volume] in Blood by Automated count (3024929)	0.3	0.14	0.36	0.22
measurement: MCHC [Mass/volume] by Automated count (3009744)	0.3	0.14	0.36	0.22
measurement: MCH [Entitic mass] by Automated count (3012030)	0.3	0.14	0.36	0.22
measurement: Erythrocyte distribution width [Ratio] by Automated count (3019897	0.3	0.14	0.36	0.22
measurement: Engthrocytes (#/volume) in Blood by Automated count (2020/16)	0.3	0.14	0.26	0.22

	end 0	Start 1 to end 30		
C85 ▼	C48 🛊	C85 🖣	C48 🗦	
All	All	All	All	
0.13	0.06	0.10	0.08	
0.11	0.07	0.07	0.05	
0.10	0.06	0.06	0.08	
0.09	0.06	0.06	0.06	
0.09	0.06	0.04	0.03	
0.09	0.05	0.11	0.13	
80.0	0.03	80.0	0.09	
0.08	0.04	0.06	0.05	
0.07	0.04	0.05	0.10	
0.06	0.03	0.05	0.09	
0.06	0.03	0.02	0.02	
0.05	0.03	0.03	0.02	
0.04	0.01	0.04	0.05	
0.04	0.04	0.06	0.06	
0.04	0.06	0.01	0.05	
0.04	0.02	0.02	0.02	
0.04	0.02	0.03	0.03	
0.04	0.02	0.01	0.01	
	0.13 0.11 0.10 0.09 0.08 0.08 0.08 0.08 0.08 0.04 0.04 0.04	All	All	

Covariate Name	Start 0 to end 0			Start 1 to end 30		
Covariate Name	V.S.	C85 ▼	C48 🗦	C85 🛡	C48 \$	
All	All		All	All	All	
measurement: Body temperature (3020891)		0.39	0.21	0.25	0.29	
measurement: SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by NAA		0.39	0.32	0.23	0.67	
measurement: Systolic blood pressure (3004249)		0.37	0.20	0.27	0.32	
measurement: Diastolic blood pressure (3012888)		0.37	0.20	0.27	0.32	
measurement: Pulse intensity of Unspecified artery palpation (3045980)		0.37	0.20	0.26	0.31	
measurement: Oxygen [Partial pressure] in Blood (3027315)		0.36	0.20	0.24	0.28	
measurement: Body weight (3025315)		0.36	0.18	0.24	0.30	
measurement: Body mass index (BMI) [Ratio] (3038553)		0.34	0.18	0.24	0.30	
measurement: Respiratory rate (3024171)		0.34	0.19	0.23	0.27	
measurement: Body height (3036277)		0.32	0.16	0.21	0.26	
measurement: Leukocytes [#/volume] in Blood (3010813)		0.16	0.11	0.18	0.18	
measurement: Erythrocytes [#/volume] in Blood (3026361)			0.11	0.17	0.19	
measurement: Glucose [Mass/volume] in Serum or Plasma (3004501)			0.11	0.18	0.19	
measurement: Hemoglobin [Mass/volume] in Blood (3000963)		0.16	0.11	0.17	0.18	
measurement: Hematocrit [Volume Fraction] of Blood (3009542)			0.11	0.17	0.18	
measurement: Platelets [#/volume] in Blood (3007461)		0.16	0.11	0.17	0.18	



Recommended

- Provider documented diagnosis of COVID-19
- OR
- COVID-19 positive test result
- NO COVID-19 negative test result between 0 to 3 days