

COVID-19 & Mental illness

England And Denmark

Student :Pi-Ling Wang 王碧玲

Advisor :Professor Sheng-Hsiang Lin 林聖翔

Date : 20250416 pm



Ashley Wang

Vaccination and mental illness. Multiple choice



Paper 1

COVID-19 and Mental Illnesses in Vaccinated and Unvaccinated People

Venexia M. Walker, PhD; Praveetha Patalay, PhD; Jose Ignacio Cuitun Coronado, PhD; Rachel Denholm, PhD; Harriet Forbes, PhD; Jean Stafford, PhD; Bettina Moltrecht, PhD; Tom Palmer, PhD; Alex Walker, PhD; Ellen J. Thompson, PhD; Kurt Taylor, PhD; Genevieve Cezard, PhD; Elsie M. F. Horne, PhD; Yinghui Wei, PhD; Marwa Al Arab, PhD; Rochelle Knight, MSc; Louis Fisher, MSc; Jon Massey, PhD; Simon Davy, PhD; Amir Mehrkar, MRCP; Seb Bacon, BA; Ben Goldacre, MRCPsych; Angela Wood, PhD; Nishi Chaturvedi, PhD; John Macleod, PhD; Ann John, MD; Jonathan A. C. Sterne, PhD; for the Longitudinal Health and Wellbeing COVID-19 National Core Study

JAMA Psychiatry. [2024](#);81(11):1071-1080. doi:10.1001/jamapsychiatry.2024.2339

Paper 2

COVID-19 and Risk for Mental Disorders Among Adults in Denmark

Vardan Nersesjan, MD; Rune H. B. Christensen, MSc, PhD; Daniel Kondziella, MD, DMSc, Dr Philos; Michael E. Benros, MD, PhD

JAMA Psychiatry. [2023](#);80(8):778-786. doi:10.1001/jamapsychiatry.2023.1265

Prospective cohort study and COVID 19, a novel disease identified in 2020.

2023 **JOURNAL IMPACT FACTOR**

22.5



Paper1:First Author



Venexia Walker ✓

Epidemiologist

Bristol, England, United Kingdom

317 connections

 **Connect**

+ Follow



About

I am an epidemiologist at the University of Bristol Medical Research Council Integrative Epidemiology Unit, UK and the University of Pennsylvania Perelman School of Medicine, USA. My research covers causal inference using electronic health record data and Mend...see more



Paper 2 : First Author



Vardan Nersesjan

PHD Student and Medical Doctor

Biological and Precision Psychiatry - Mental Health Centre Copenhagen,
CPH University Hospital · Københavns Universitet
Copenhagen, Capital Region of Denmark, Denmark

263 connections

Paper 1

JAMAPsychiatry | Original Investigation

England

COVID-19 and Mental Illnesses in Vaccinated and Unvaccinated People





Background

Paper 2 (2023) : nationwide data is lacking

COVID-19 → Subsequent mental illness

But

?

Limited

Paper 1 (2024)

COVID-19 and status of vaccination

Objective



Vaccination

COVID-19 and Severity
(hospitalized)

Sex, Age, Ethnicity, Index of
multiple deprivation (IMD).

Mental illness (aHR)

- **depression**
- **serious mental illness**

(E.x. schizophrenia,
schizoaffective disorder,
bipolar disorder, and
psychotic depression)

Study Design : 3 cohorts

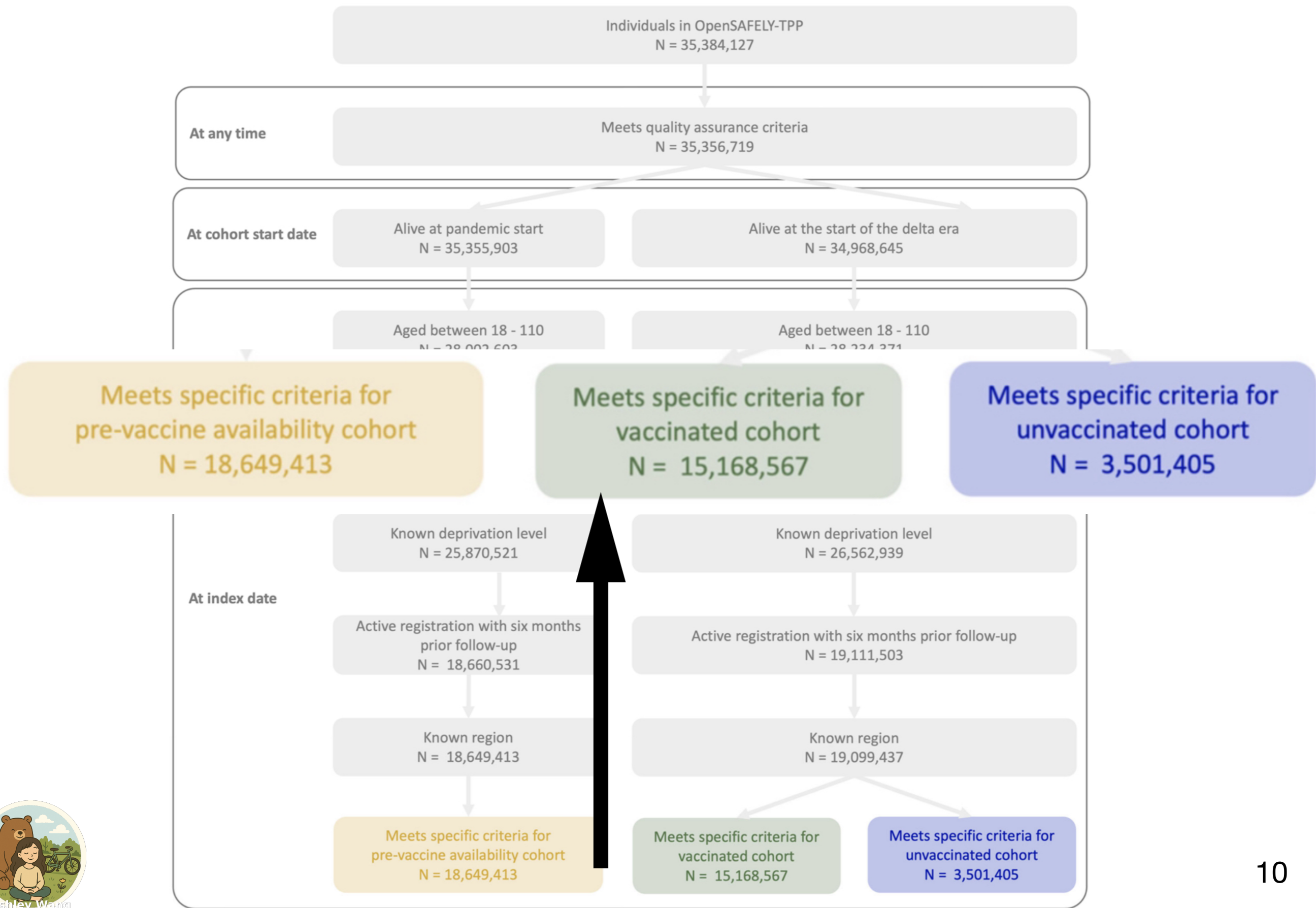
Data Resource :

OpenSAFELY-TPP platform of the UK National Health Service (NHS), covering approximately **24 million** patients in general practice. (Electronic medical record)

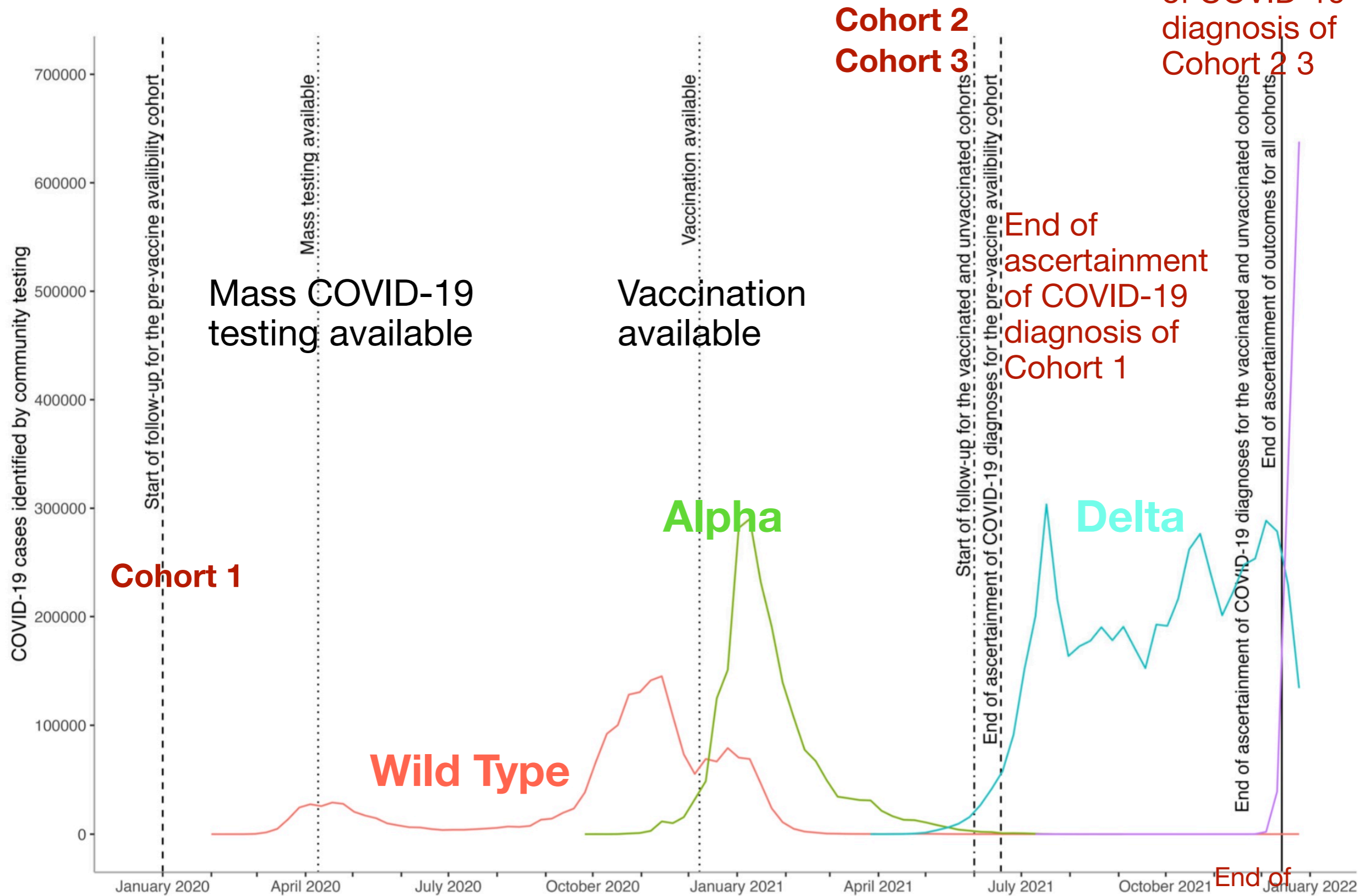
- Cohort 1** ● Before vaccine availability (January 1, 2020-December 14, 2021)
- Cohort 2** ● Vaccinated (June 1, 2021-December 14, 2021)
- Cohort 3** ● Unvaccinated (June 1, 2021-December 14, 2021)



eFigure 2: Diagram showing cohort construction.



eFigure 1: COVID-19 cases over time



End of
ascertainment
of COVID-19
diagnosis of
Cohort 2 3

End of
ascertainment
of COVID-19
diagnosis of
Cohort 1

End of
ascertainment of
outcome of all
cohorts



Statistical Analyses

Cox Proportional Hazards Model

Time period :day

Cohort 1	Cohort 2	Cohort 3
[0,28],[28,197], [197,365],[365,714]	[0,28],[28,197]	[0,28],[28,197]



Result 1/4

Dominant

Cohort1

Cohort2

Cohort3

Table 1. Patient Characteristics by Cohort

Characteristic	Pre-vaccine availability		Vaccinated		Unvaccinated	
	No. (%)	COVID-19 diagnoses	No. (%)	COVID-19 diagnoses	No. (%)	COVID-19 diagnoses
Total, No.	18 648 606	1 012 335	14 035 286	866 469	3 242 215	149 745
Sex						
Female	9 363 710 (50.2)	543 513	7 308 556 (52.1)	481 581	1 363 401 (42.1)	79 179
Male	9 284 896 (49.8)	468 825	6 726 730 (47.9)	384 891	1 878 814 (57.9)	70 569
Age range, y						
18-29	3 278 187 (17.6)	244 839	1 760 740 (12.5)	94 533	981 925 (30.3)	40 131
30-39	3 225 998 (17.3)	203 931	1 958 328 (14)	149 193	966 470 (29.8)	50 655
40-49	3 059 107 (16.4)	190 065	2 206 560 (15.7)	236 229	612 180 (18.9)	33 429
50-59	3 264 621 (17.5)	184 371	2 716 818 (19.4)	204 009	376 272 (11.6)	16 827
60-69	2 552 894 (13.7)	92 931	2 316 757 (16.5)	105 645	186 402 (5.7)	5625
70-79	2 066 329 (11.1)	51 573	1 980 447 (14.1)	54 057	80 546 (2.5)	1947
80-89	989 819 (5.3)	31 893	909 927 (6.5)	18 327	30 138 (0.9)	903
≥90	211 651 (1.1)	12 717	185 709 (1.3)	4479	8282 (0.3)	225
Ethnicity ^a						
Black	1 191 793 (6.4)	118 365	789 476 (5.6)	41 457	325 199 (10)	9609
South Asian	217 132 (1.2)	14 241	128 514 (0.9)	7521	81 017 (2.5)	3867
White	14 865 866 (79.7)	773 745	11 752 297 (83.7)	748 743	2 025 492 (62.5)	115 449
Mixed	423 111 (2.3)	20 301	237 383 (1.7)	10 641	190 874 (5.9)	4035
Other ^b	400 437 (2.1)	27 069	217 317 (1.5)	9585	173 014 (5.3)	7641
Missing	1 550 267 (8.3)	58 611	910 299 (6.5)	48 513	446 619 (13.8)	9141
IMD quintile						
1	3 574 653 (19.2)	247 365	2 273 863 (16.2)	135 945	958 877 (29.6)	45 795
2	3 690 808 (19.8)	219 063	2 617 493 (18.6)	158 889	775 318 (23.9)	35 445
3	4 042 896 (21.7)	203 055	3 111 723 (22.2)	186 855	652 380 (20.1)	29 619
4	3 809 548 (20.4)	183 015	3 065 889 (21.8)	191 499	498 458 (15.4)	22 515
5	3 530 701 (18.9)	159 837	2 966 318 (21.1)	193 275	357 182 (11)	16 371
Smoking						
Never	759 965 (4.1)	40 677	428 549 (3.1)	16 419	370 770 (11.4)	8415
Formerly	8 568 556 (45.9)	504 843	6 540 674 (46.6)	422 337	1 348 307 (41.6)	59 631
Currently	6 137 311 (32.9)	329 373	5 106 300 (36.4)	333 675	645 817 (19.9)	43 887
Missing	3 182 774 (17.1)	137 439	1 959 763 (14)	94 035	877 321 (27.1)	37 815
Region						
East	4 305 743 (23.1)	227 421	3 281 525 (23.4)	182 847	731 831 (22.6)	33 825
East Midlands	3 263 511 (17.5)	191 925	2 474 916 (17.6)	161 259	527 562 (16.3)	28 815
London	1 245 392 (6.7)	67 791	728 567 (5.2)	37 287	459 504 (14.2)	10 977
North East	889 507 (4.8)	60 369	663 394 (4.7)	48 891	137 238 (4.2)	7239
North West	1 658 370 (8.9)	109 887	1 270 319 (9.1)	88 227	220 722 (6.8)	12 045
South East	1 249 245 (6.7)	50 373	969 482 (6.9)	57 105	195 663 (6)	8853
South West	2 655 179 (14.2)	80 649	2 207 972 (15.7)	133 143	331 576 (10.2)	17 871
West Midlands	760 648 (4.1)	56 397	499 564 (3.6)	29 931	181 504 (5.6)	8223
Yorkshire	2 621 011 (14.1)	167 505	1 939 547 (13.8)	127 767	456 615 (14.1)	21 891
Care home resident	90 076 (0.5)	15 309	57 532 (0.4)	2835	3014 (0.1)	105

Abbreviation: IMD, Index of Multiple Deprivation (lower indicates more deprived).

^a Ethnicity data were reported because disparities in COVID-19 outcomes by

ethnic group have been reported.¹⁷

^b Other ethnicity groups were consolidated for disclosure control.



Result 1/3

Cohort 1 Cohort 2 Cohort 3

Table 2. Mental Illness Events Following Diagnosis of COVID-19 by Cohort, Overall, and by COVID-19 Severity

	Pre-vaccine availability (n = 18 648 606)		Vaccinated (n = 14 035 286)		Unvaccinated (n = 3 242 215)	
Outcome	Event/person-years	Incidence rate	Event/person-years	Incidence rate	Event/person-years	Incidence rate
Depression						
No COVID-19	1 278 435/33 058 669	3867	341 811/6 293 635	5431	54 903/1 207 059	4548
Hospitalized for COVID-19	6333/41 555	15 240	1395/2426	57 491	849/1636	51 902
Not hospitalized for COVID-19	44 499/897 194	4960	9741/156 195	6236	2061/25 034	8233
Serious mental illness						
No COVID-19	382 305/33 963 171	1126	85 917/6 359 387	1351	17 985/1 215 060	1480
Hospitalized for COVID-19	1653/47 219	3501	213/2705	7874	165/1796	9185
Not hospitalized for COVID-19	13 407/945 179	1418	2367/158 999	1489	573/25 466	2250

6333/41555=0.15240

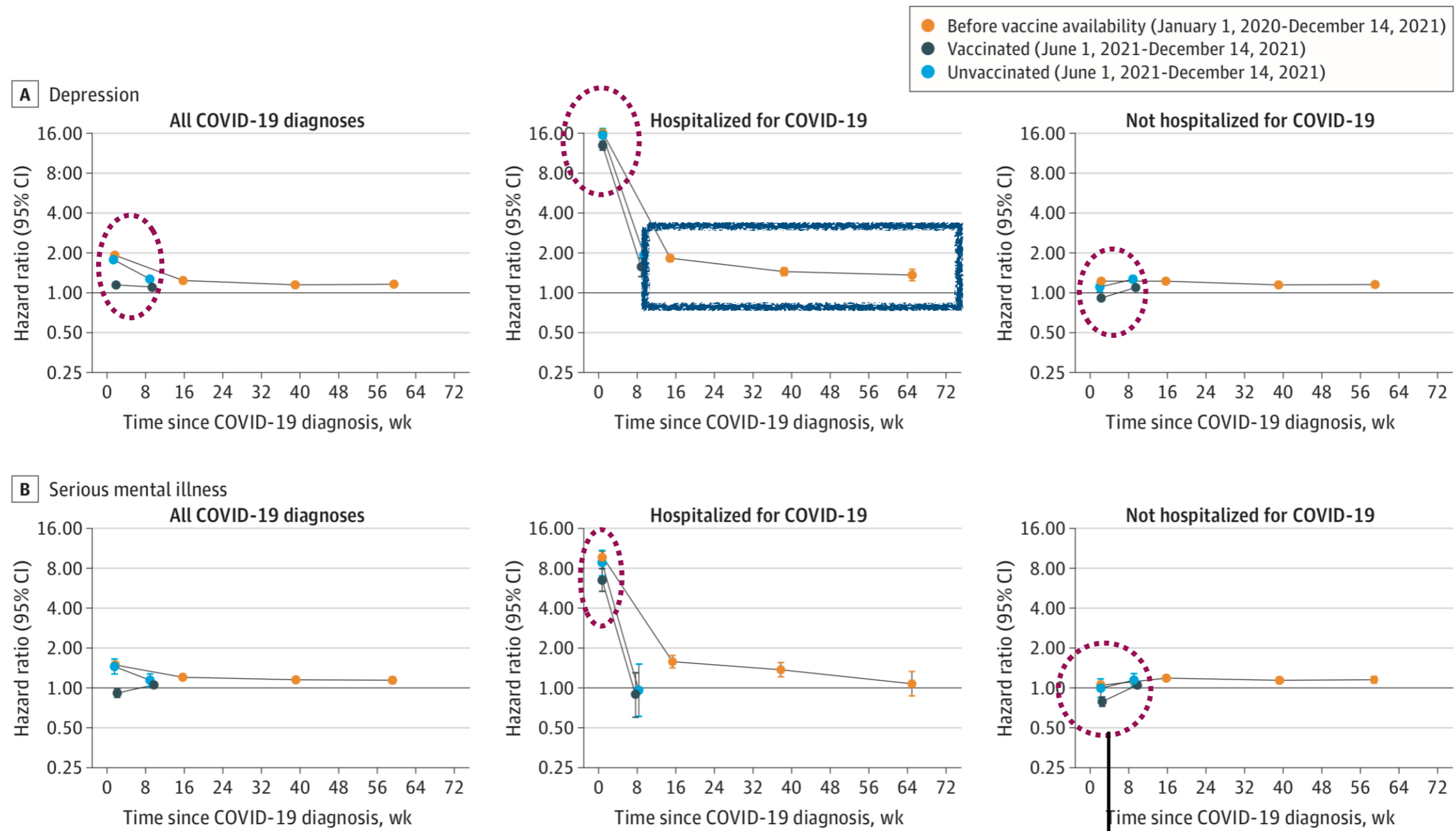
0.15240/100,000=15,240



Result 2/3

Cox model [0,28), [28,197)

Figure 1. Maximally Adjusted Hazard Ratios and 95% CIs for Depression and Serious Mental Illness Following Diagnosis of COVID-19, Overall, and by COVID-19 Severity

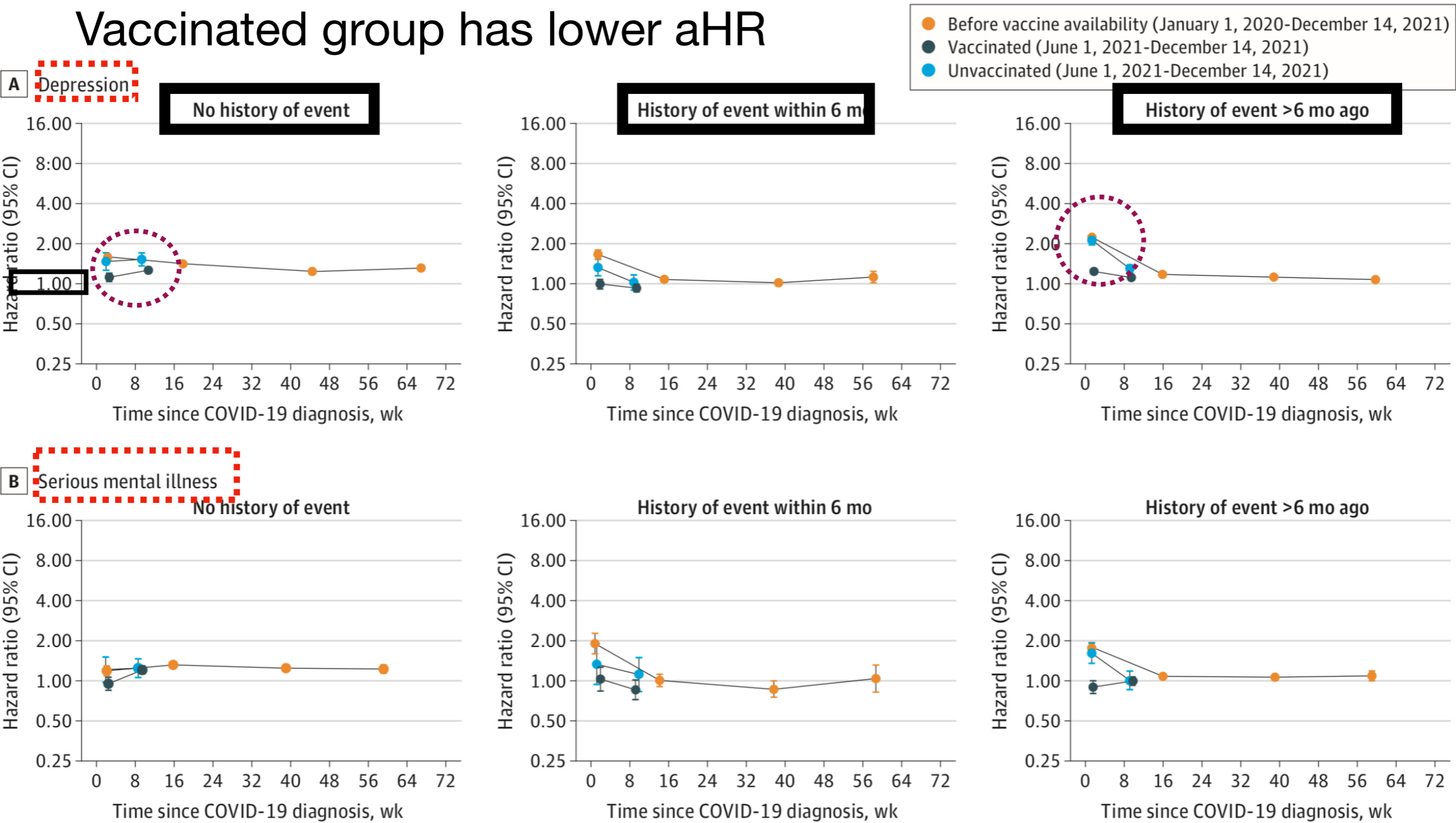




Result 3/3

Cox model [0,28), [28,197)

Figure 2. Maximally Adjusted Hazard Ratios and 95% CIs for Depression and Serious Mental Illness Following Diagnosis of COVID-19 by History of the Outcome



Strength and Limitation

Strengths:

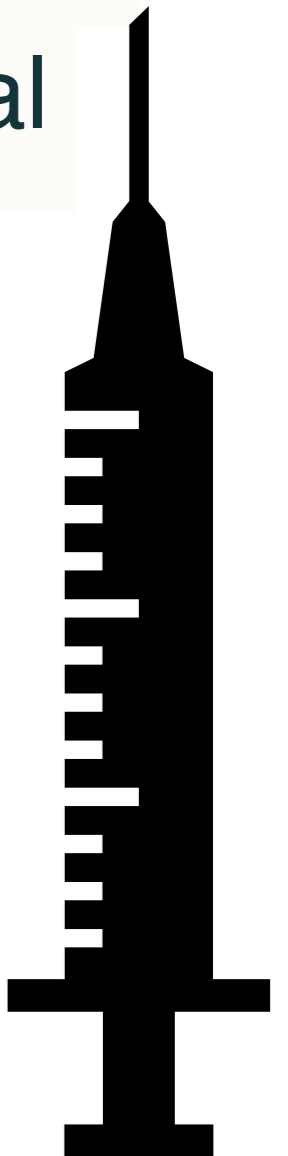
- the large sample size
- the relatively long duration of follow-up

Limitations:

- electronic health records are routinely collected data for health care provision and so only capture conditions diagnosed and recorded by the health care professional **rather than true incidence in the population.**
- Unvaccinated people may have been less likely to contact health services and to test for SARS-CoV-2 infection, leading to **underestimated effect.**

Conclusion

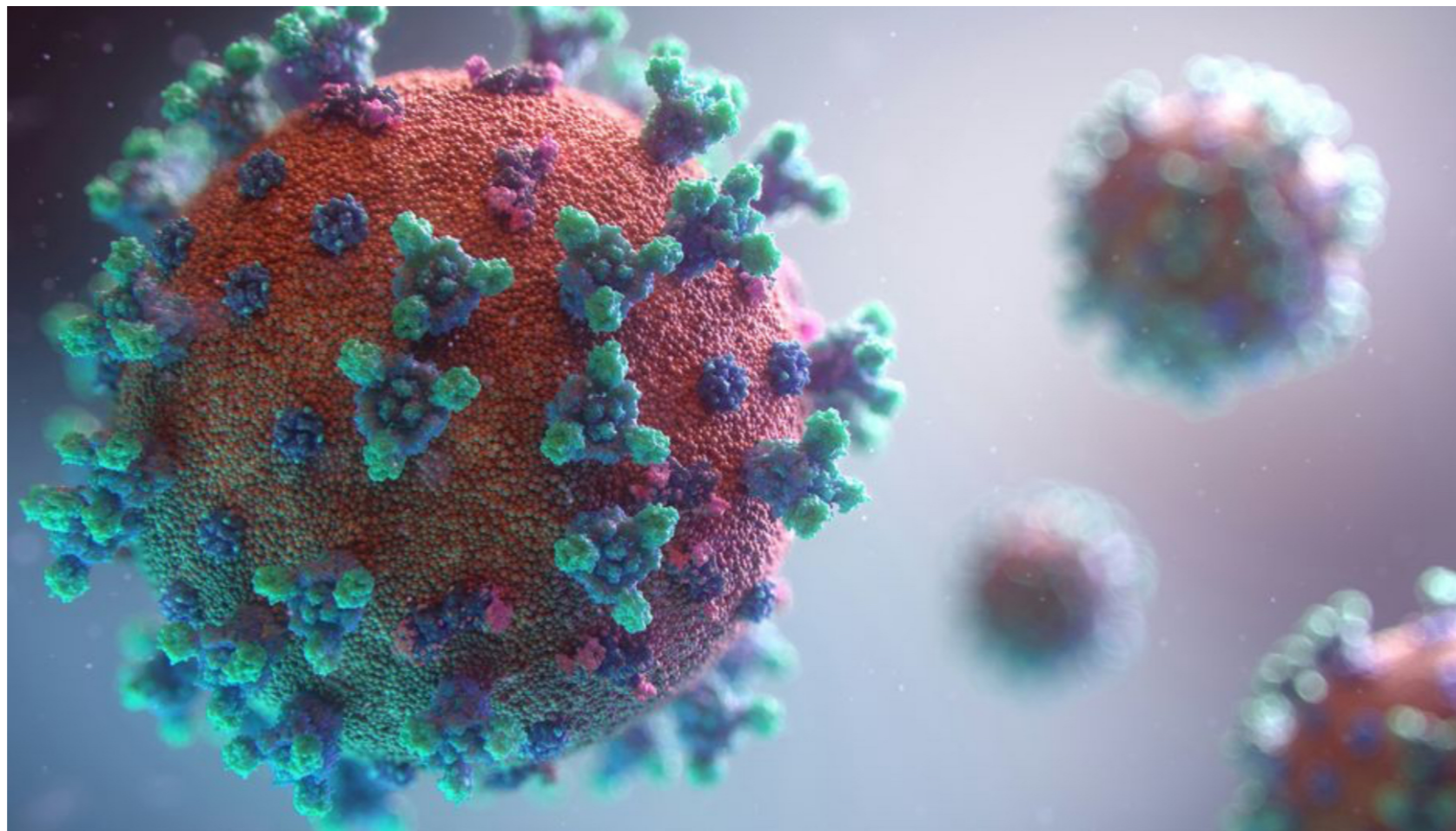
Vaccination may mitigate the adverse effects of COVID-19 on mental health, especially for high-risk groups such as individuals with a history of mental illness. The research supports promoting vaccination to protect psychological well-being.



Paper 2

JAMAPsychiatry | Original Investigation

COVID-19 and Risk for Mental Disorders Among Adults in Denmark



Objective

The Aims of this study

SARS-CoV 2 PCR test

- Positive
- Negative
- Non-testing (ref.)

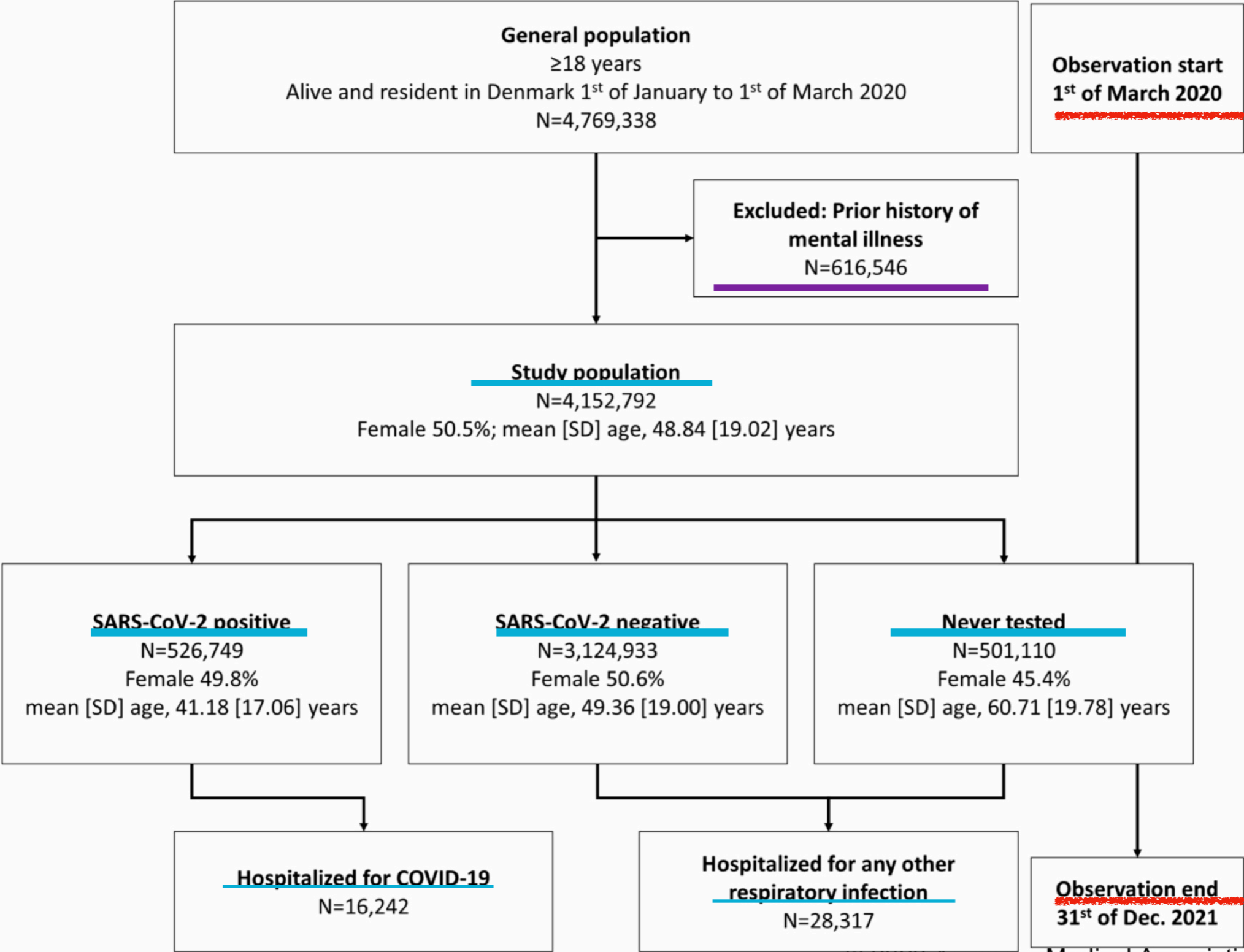
COVID-19

- Hospitalized
- Non-hospitalization

**Non-COVID-19
hospitalized**

- **Mental illness**
 - **Psychotropic medication**
- (HHR)**

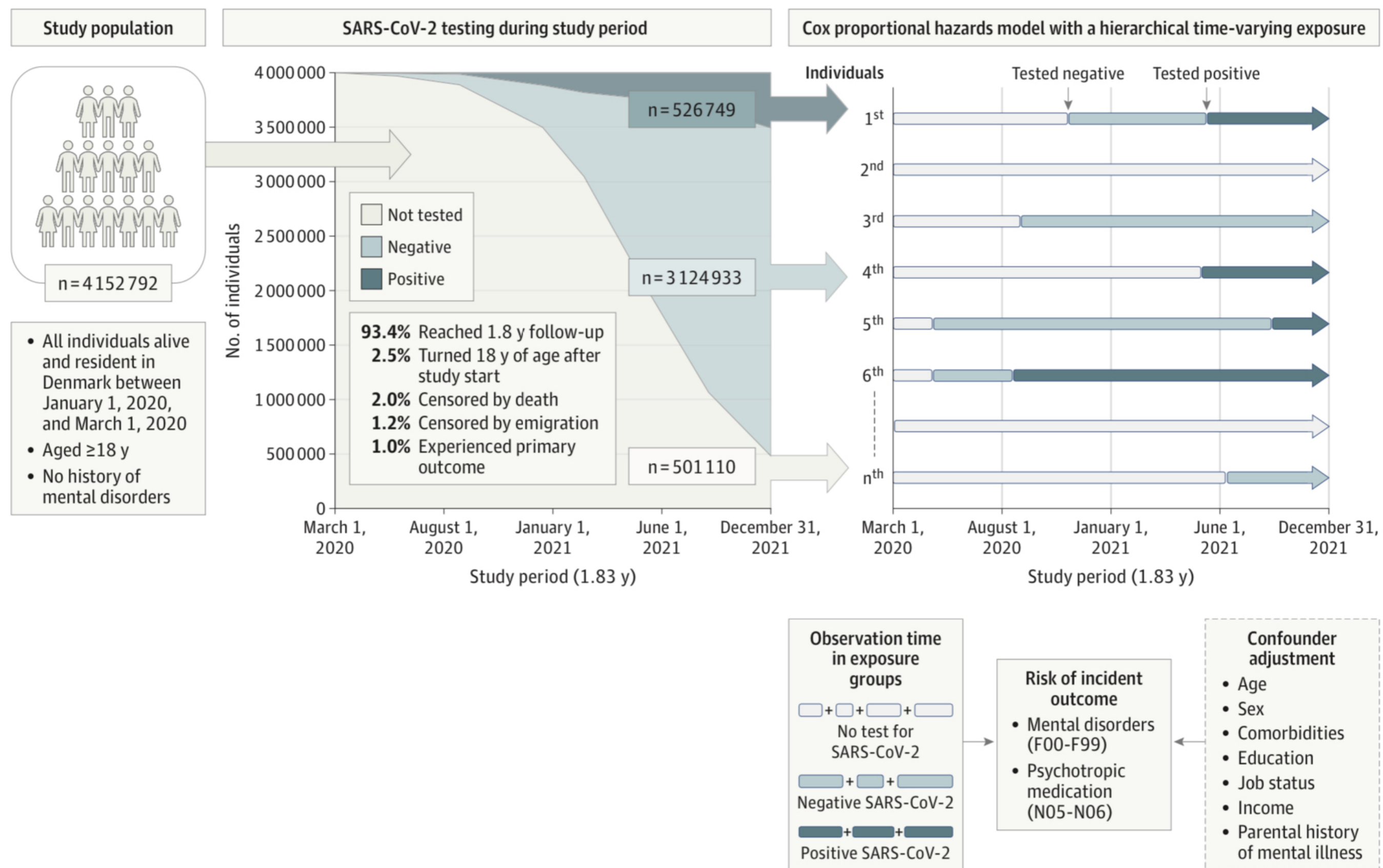
eFigure 3. Flowchart Over Study Population for Primary Outcome



© 2023 American Medical Association. All rights reserved.

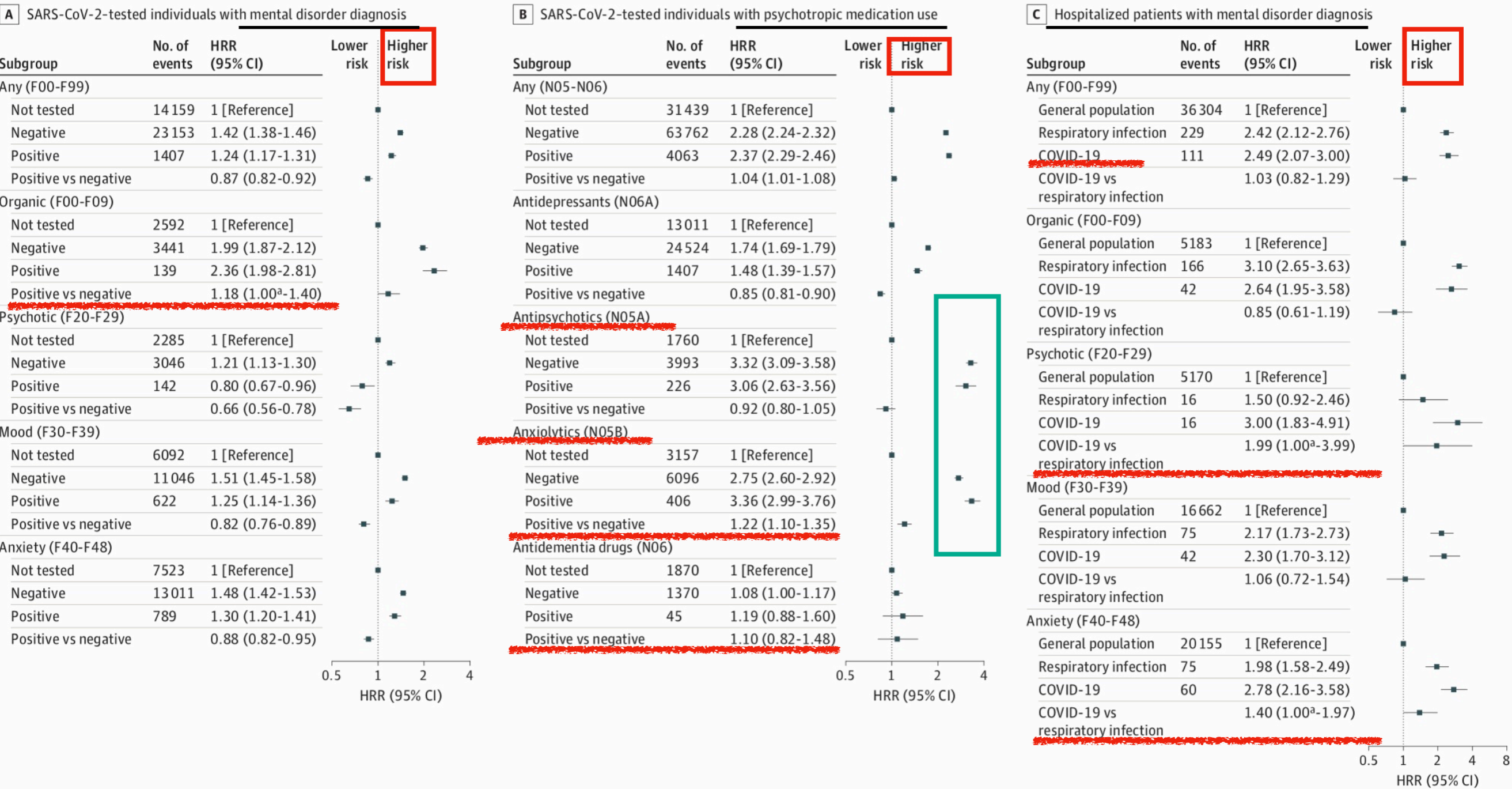
Paper 2 COVID-19 and Risk for Mental Disorders Among Adults in Denmark

Figure 1. Schematic Presentation of Study Design and Structure of Data Analysis



Result 1/3

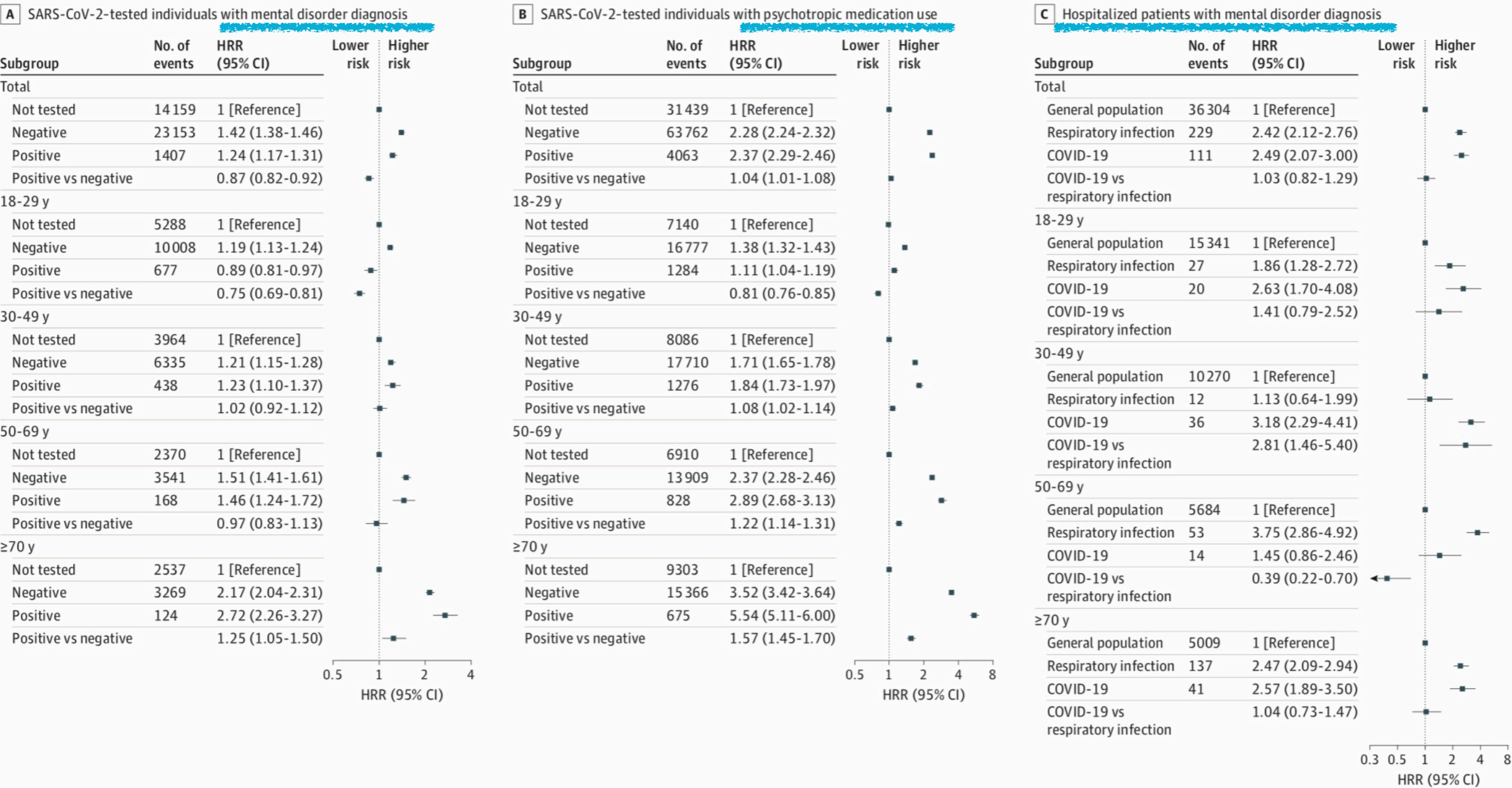
Figure 2. Risk of New-Onset Mental Disorder and Psychotropic Medication Use Among Individuals Tested for SARS-CoV-2 and Patients Hospitalized for COVID-19 or Other Respiratory Tract Infections



Result 2/3



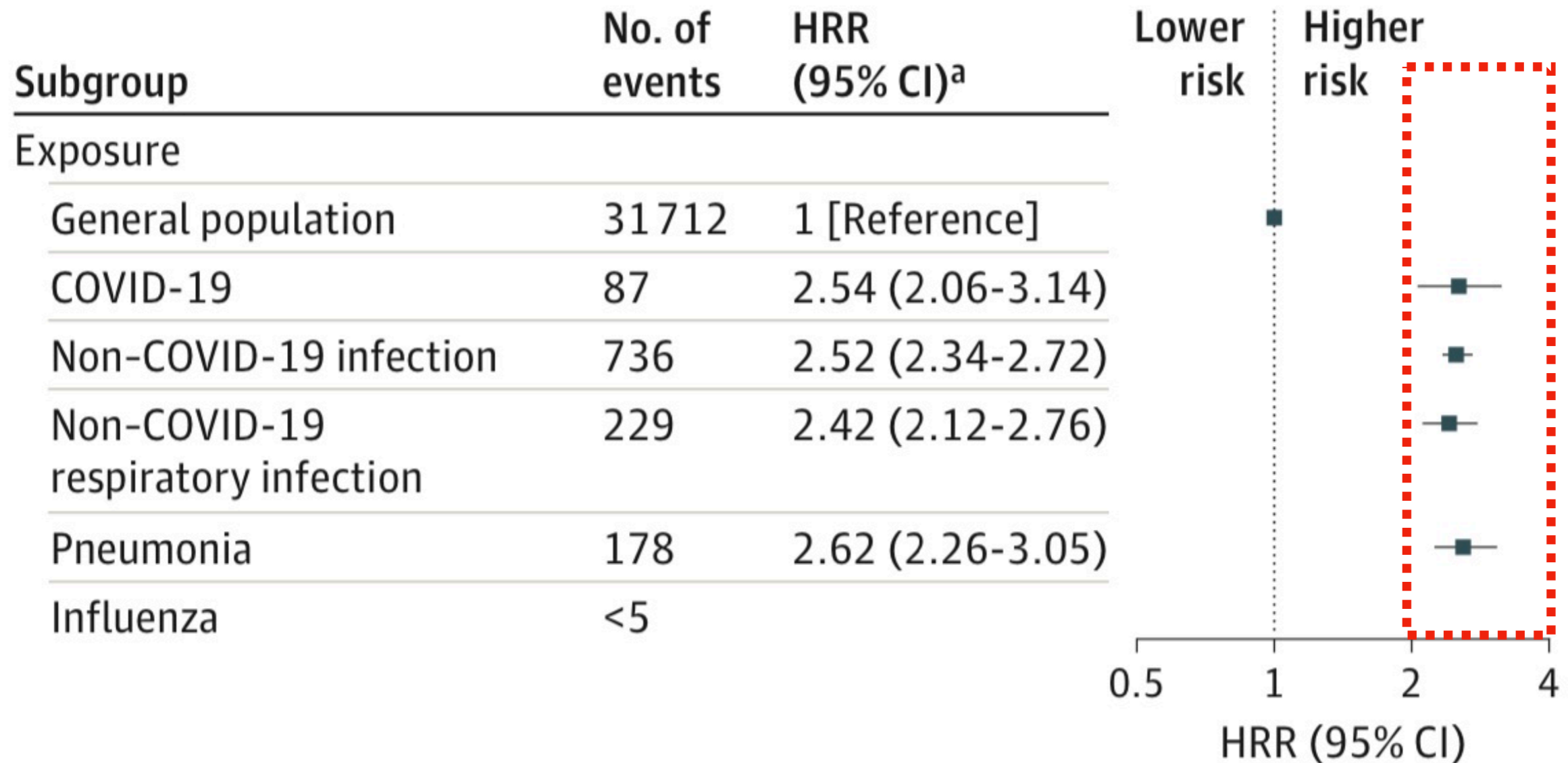
Figure 3. Risk of New-Onset Mental Disorder and Psychotropic Medication Use Among Individuals Tested for SARS-CoV-2 and Patients Hospitalized for COVID-19 Stratified in Age Groups





Result 3/3

Figure 4. Risk of New-Onset Mental Disorders After Hospitalization for COVID-19 or Non-COVID-19 Infections



Comparison



Study Type	Prospective cohort study
Method	<p>1. <u>Population/Sample</u>: The sample size of Paper 1 is larger than that of Paper 2.</p> <p>2. <u>Exclusion Criteria</u>: Paper 2 excludes individuals with a history of mental illness.</p> <p>3. <u>Statistical Analyses</u>: Cox proportional hazards model (adjusted Hazard Ratio [aHR], Hazard Rate Ratio [HRR]).</p> <p>4. <u>Observational Time</u>: The observational period differs in Paper 1, while it remains the same in Paper 2.(93.4%)</p>
Conclusion	The COVID-19 patients with hospitalized have more mental illness outcome.



Strengths and Limitations

Strengths

- This is a nationwide study conducted within a free healthcare system, enabling follow-up of all individuals.
- This approach reduces selection bias and enhances the generalizability of the findings.

Limitations

- **Behavioral Patterns**: Fear of COVID-19 and testing incentives may affect exposure and outcomes, but these factors are not fully captured in registries (e.g., anxiety-driven testing may increase anxiety disorder diagnoses).
- **Psychotropic Medication Use**: Outcomes may not solely reflect mental disorder treatment, as these drugs can treat insomnia, pain, or be used in palliative care; only ICD-10 F-chapter diagnoses were included.



Conclusion

In this Danish nationwide cohort study, **overall risk of new-onset mental disorders** in SARS-CoV-2–positive individuals **did not exceed the risk** among individuals with negative test results (except for those aged 70 years). However, when **hospitalized**, patients with **COVID-19** had markedly **increased risk compared with the general population**, but **comparable** to risk among patients hospitalized for non-**COVID-19** infections.

Slido

Email



Thank you





Paper 1

JAMA Psychiatry | **Original Investigation**

COVID-19 and Mental Illnesses in Vaccinated and Unvaccinated People

Venexia M. Walker, PhD; Praveetha Patalay, PhD; Jose Ignacio Cuitun Coronado, PhD; Rachel Denholm, PhD; Harriet Forbes, PhD; Jean Stafford, PhD; Bettina Moltrecht, PhD; Tom Palmer, PhD; Alex Walker, PhD; Ellen J. Thompson, PhD; Kurt Taylor, PhD; Genevieve Cezard, PhD; Elsie M. F. Horne, PhD; Yinghui Wei, PhD; Marwa Al Arab, PhD; Rochelle Knight, MSc; Louis Fisher, MSc; Jon Massey, PhD; Simon Davy, PhD; Amir Mehrkar, MRCP; Seb Bacon, BA; Ben Goldacre, MRCPsych; Angela Wood, PhD; Nishi Chaturvedi, PhD; John Macleod, PhD; Ann John, MD; Jonathan A. C. Sterne, PhD; for the Longitudinal Health and Wellbeing COVID-19 National Core Study

Comments on Paper 1

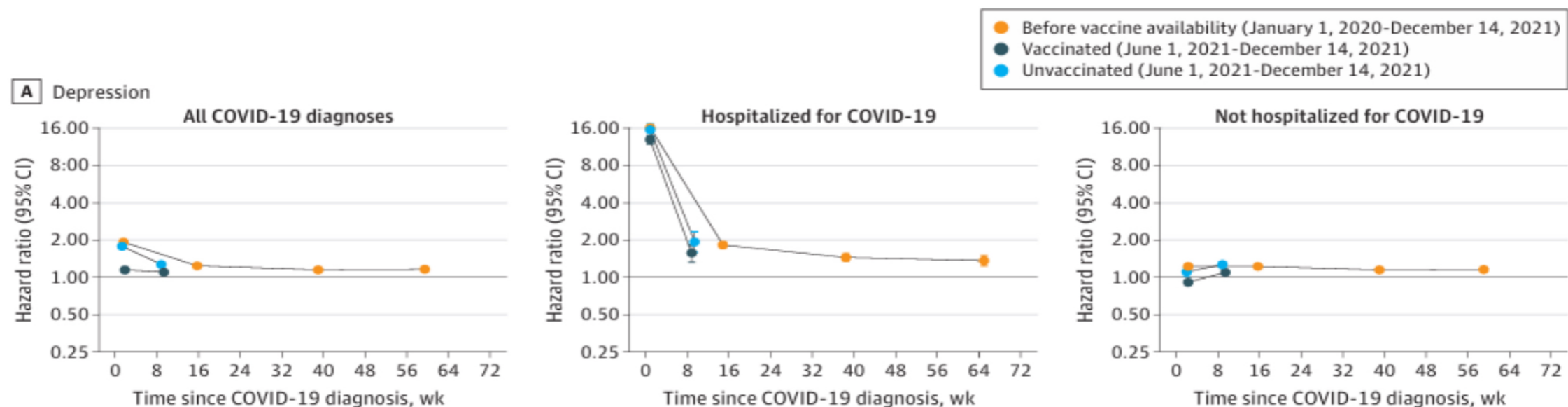
Swati Jain

T88127037

2nd Year PhD Student

COMMENT - 1

In the paper, it can be noted that the adjusted hazard ratios for mental health outcomes are significantly higher in patients with COVID-19 hospitalization, especially for depression on day 0.



Do you think these elevated risks primarily reflect the severity of the illness, or could they also be influenced by the increased healthcare contact and opportunity for diagnosis within the hospital setting? Would incorporating additional, alternative measures of COVID-19 severity help clarify the relative contributions of disease severity versus healthcare exposure in these associations?

COMMENT -2

As mentioned in discussion section **“we cannot exclude the possibility of unmeasured confounding, although we controlled for a wide range of demographic characteristics and prior morbidities”**.

Given the differences in healthcare-seeking behavior between vaccinated and unvaccinated groups, do you think these adjustments were sufficient to fully mitigate such unmeasured confounding? Do you believe that using a negative control group or alternative methods could further strengthen the causal interpretation of the findings?

Answer

Comment 1

- Illness Severity vs. Healthcare Contact:
- Data Limitation: Electronic health records (EHR)
- Suggestions for Clarity:
 - _Add severity measures (e.g., ICU admission, hospital days).
 - _Use stratification or propensity score matching to control healthcare contact bias.



International Journal of Epidemiology, 2016, 1866–1886

doi: 10.1093/ije/dyw314

Advance Access Publication Date: 20 January 2017

Original article



Approaches to causal inference

Triangulation in aetiological epidemiology

Debbie A Lawlor,^{1,2,*} Kate Tilling^{1,2} and George Davey Smith^{1,2}

¹MRC Integrative Epidemiology Unit at the University of Bristol, Bristol, UK and ²School of Social and Community Medicine, University of Bristol, Bristol, UK

Paper 2

COVID-19 and Risk for Mental Disorders Among Adults in Denmark

Commenter:

2nd Year PhD student

曾元聰(Yuan-Tsung Tseng)

20250416

Comment 1

In the actual analysis, the authors used a time-varying grouping based on each individual's test results. However, a single individual might undergo multiple tests or become **positive at different time points** during the follow-up.

Could these complex testing sequences be missing certain test records or introduce bias, thus affecting the estimated risk for mental disorders?

Comment 2

Compared to those who were tested (either negative or positive), individuals who never received a test may be older or have lower health awareness or **limited healthcare access**.

Could this difference lead to surveillance bias or selection bias?

- How did the authors attempt to address this issue in their model?