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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	This study utilized Limited Data Set (Level 3) data from the N3C dataset with Structured Query Language (SQL) and R programming languages (version 4.2.2). All data of this study is available in the N3C Data Enclave for researchers with an approved protocol and data use request from an institutional review board. Data access is governed by the National Institutes of Health. More information on the enclave and instructions for data access can be found at https://covid.cd2h.org/for-researchers.
Data analysis	All analyses were conducted within the N3C enclave using Structured Query Language (SQL) and R programming languages (version 4.2.2). The analytical code used in this study is available at the GitHub repository: https://github.com/yuanyp25/SCCS_vaccine_ADs, and has been archived on Zenodo with the following DOI: https://doi.org/10.5281/zenodo.15666388.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

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Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Sex (biological sex, categorized as male or female) was included in the statistical description of the study population. Subgroup analyses were conducted to assess potential differences in outcomes between male and female participants. The data on sex were derived from electronic health records. No explicit data on gender identity were collected, and the analysis did not distinguish between biological sex and social gender. In the subgroup analysis stratified by sex, the XBB.1.5-containing COVID-19 mRNA vaccines were not associated with a statistically significant increase in any of the 14 AESIs within the 28-day risk period compared to the reference periods.
Reporting on race, ethnicity, or other socially relevant groupings	Race and ethnicity data were collected from self-reported information or electronic health records. Categories included White, Black or African American, Asian, Hispanic or Latino, and Other. These data were used to describe the baseline characteristics of the study population. A self-controlled case series design was employed to account for potential confounders by using within-individual comparisons. Limitations of the study include incomplete race and ethnicity data for some participants and the potential for misclassification due to self-reporting.
Population characteristics	Overall, the study population consisted of 244,494 adult individuals (mean age: 61.14 years, standard deviation [SD]: 16.93 years; 59.4% female, 72.6% white) who received the XBB.1.5-containing COVID-19 mRNA vaccines between September 11, 2023, and June 1, 2024, in the USA. Among the participants, 55.4% received the vaccines from Moderna (n=141,495), while 44.6% received vaccines from Pfizer-BioNTech (n=102,999).
Recruitment	We included patients who had received any documented dose of the XBB.1.5-containing COVID-19 mRNA vaccine in the N3C dataset. Patients were excluded if they (1) were not continuously observed for the 365 days prior to the vaccination date through the end of follow-up (June 1, 2024), as defined by the observation period of the OMOP CDM; (2) were younger than 18 years old as of the XBB.1.5 COVID-19 mRNA vaccination date; (3) had received a prior COVID-19 vaccination less than 28 days before the XBB.1.5 dose; or (4) lacked any previously documented COVID-19 vaccination in the N3C dataset dating back to December, 2020, which was considered a potential indicator of incomplete vaccine records or non-continuous observation; (5)with missing any data in demographics.
Ethics oversight	Data usage for this study was authorized by N3C (DUR-36ED2AE) and reviewed and approved by the Medical School Institutional Review Board (IRB) at the University of Michigan (HUM00243962).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The sample size for the study was determined based on patient data from the National COVID Cohort Collaborative (N3C). Initially, 341,931 patients who received at least one dose of an XBB.1.5-containing COVID-19 mRNA vaccine were identified.
Data exclusions	Exclusions were applied based on the following criteria: 341,931 patients with receipt of XBB.1.5 containing COVID-19 mRNA vaccines in N3C Excluded 4202 missing data, 38859 younger than 18 years old, 40714 not being continuous observed, 34 received prior COVID-19 vaccines less than 28 days before, 13628 lacked any priorly documented COVID-19 vaccination finally 244,494 patients included.

Replication	To verify the reproducibility of the experimental findings, the cohort selection and data extraction process were independently repeated by a second researcher, yielding identical results. Statistical analyses were cross-validated by a different team member, who ran the same scripts and obtained the same outcomes. Subgroup analyses (e.g., by gender and vaccine brand) were conducted and confirmed the consistency of results across different population groups. Additionally, all data cleaning steps were independently reviewed, and no discrepancies were found. All attempts to replicate the findings were successful, with no results that could not be reproduced.
Randomization	This study used a self-controlled case series design to account for potential confounders by using within-individual comparisons. No study groups were divided.
Blinding	In this study, participants were not randomly allocated into experimental groups, as the study used a self-controlled case series (SCCS) design. Instead of assigning participants to separate groups, each individual served as their own control, allowing for within-individual comparisons. This design controls for confounding factors such as age, genetics, and baseline health conditions, as they remain constant within each participant throughout the study period. Therefore, random allocation and group-based control were not necessary, and the SCCS approach effectively accounted for these covariates.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*