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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
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☐ | ☒ | 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
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ | 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 Data were collected remotely from participants using REDCap.

Data analysis All statistical analyses were performed using R version 4.3.2 (R Foundation for Statistical Computing) in RStudio 2023.12.1+402 (RStudio, Inc; Boston, MA). We used publicly available R packages for all analyses, which are described/referenced in the methods.

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](#)

The raw data underlying the figures in the main text are available in the Supplementary Datasets. Due to ethical restrictions and to protect participant confidentiality, the complete datasets are available under restricted access. Deidentified individual participant data (including data dictionaries), study protocols, the statistical analysis plan, and the informed consent form can be obtained by submitting a request to the corresponding author (cfrivold@uw.edu), subject to approval by the Institutional Review Board of the University of Washington and the CASCADIA Steering Committee. Access will be granted for a period of one year,

with the option to renew, to researchers with a methodologically sound proposal for use in achieving the goals outlined in the approved proposal. Requests will be reviewed within 30 days.

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 and gender were self-reported in the enrollment survey. These variables were included as part of the descriptive statistics to describe our study population including RSV illness outcomes by sex and gender, but no analyses were adjusted for sex or gender. Sex and gender were not considered in the study design. Sex- and gender-based analyses were not performed because these variables were not our exposure/outcome of interest or potential confounders identified a priori. Consent was obtained for sharing de-identified individual-level data. Overall, 58.7% of participants were female (n=1899/3237). The study population included individuals in the following self-reported gender groups: 40.3% male, 56.0% female, 1.4% transgender, and 2.2% other.

Reporting on race, ethnicity, or other socially relevant groupings

We included self-reported race (American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or other Pacific Islander; White; Multiracial; Other) and Hispanic ethnicity (yes/no) as part of the descriptive statistics to describe our study population including by RSV illness outcome status in Table 1.

Potential confounders were identified a priori using a directed acyclic graph and included age at enrollment (6 months-1 year; 2-4 years; 5-12 years; 13-17 years; 18-50 years); school/daycare attendance (yes/no); and self-reported immunocompromised status (yes/no). These confounders were adjusted for in the proportional hazards regression analyses. Model fits accounted for possible within-household correlation and included a baseline hazard stratified by 2-week intervals to account for seasonality. Additional statistical methods are detailed in the methods section of the main text and the Supplemental Information.

Population characteristics

This study included 3,237 individuals in 1,188 households. Most participants (77.2%) shared a kitchen or living space with 2-4 individuals, including 2-4 children (69.7%); 24 individuals lived alone. Overall this study included individuals in the following age groups: 6 months-1 year (n=100); 2-4 years (n=233); 5-12 years (n=933); 13-17 years (n=351); 18-50 years (n=1620).

Recruitment

Potential participants were recruited through a variety of strategies. For instance, recruitment information and a link to the study website for further information and eligibility screening were distributed to past study participants who agreed to be contacted about future research studies and KPNW health plan members. Recruitment information was also distributed through local schools, daycares, community-based organizations, and pediatric clinics. Physical flyers were posted throughout the community and study staff attended community events such as health fairs where they shared flyers and answered questions about the study. A social media campaign was launched via paid ads on Facebook and Instagram as well as unpaid ads via Twitter and LinkedIn. Press releases were broadly disseminated with information about the study through the study sites. Prospective participants could complete the enrollment screener electronically on the study website and eligible individuals were contacted to schedule a consent visit (online or in-person). Recruitment materials were also translated into several languages and the study included staff members bilingual in Spanish, Amharic, and Tigrinya which facilitated increased uptake in these populations.

Although efforts were made to recruit participants from diverse backgrounds and to increase representation across different socioeconomic strata, our study population was relatively homogeneous with most participants from households with higher socioeconomic status and few reporting comorbidities. As such, our results may not be generalizable to the overall U.S. population or specific high-risk groups such as infants <6 months, older adults, or individuals with comorbidities.

All participants were compensated for their time in completing study activities as follows:

KNPW: \$10 for every month participant completed all weekly nasal swabs (can be up to \$120 per year) and \$25 for each blood sample.

UW: \$10 for every month participant completed all weekly swabs for the month (can be up to \$120 per year). Participant received \$20 if they were ill and completed a full course of illness swabs. Participants received \$25 for each blood sample along with an additional \$25 to cover travel costs for each visit for a blood draw.

Ethics oversight

The study protocol was reviewed and approved by the Kaiser Permanente Inter-regional Institutional Review Board, with reliance from University of Washington (UW) and Seattle Children's Research Institute (See 45 C.F.R. part 46.114; 21 C.F.R. part 56.114).

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

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Behavioural & social sciences study design

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

Study description	Prospective cohort study using quantitative data.
Research sample	We used data from the first year of the CASCADIA study (June 2022-May 2023), a community-based prospective cohort study of households in the states of Washington and Oregon in the United States. We included participants who completed an enrollment survey, attended a baseline blood draw appointment (regardless of blood draw success), and provided at least one nasal swab by May 31, 2023. To complement other studies focused on the highest-risk groups and align with the target populations of other RSV vaccines in the pipeline, we recruited individuals 6 months-50 years who are underrepresented in studies of RSV burden. Among 3,237 participants, the proportion of participants with RSV illness by age group was as follows: 6 months to 1 year (24.0%; n=24/100); 2-4 years (24.5%; n=57/233); 5-12 years (11.4%; n=106/933); 13-17 years (5.4%; n=19/351); 18-50 years (6.1%; n=99/1620).
Sampling strategy	This manuscript describes a secondary analysis of the CASCADIA study, which aimed to evaluate COVID-19 vaccine effectiveness. The sample size calculations were based on this primary outcome. The power analysis was based on the following assumptions: the number of study subjects among age 5 to < 18 years is 2400, and the number of adult study subjects is 1100; the SARS-CoV-2 incidence rate (i.e., the 'background' rate of infection) is 4.02%, vaccine uptake is predicted to be between 50% and 90%, the average cluster size is 2 (i.e., 2 children per family), alpha level is 0.05, and power is 80%. The target sample size was assumed to also be sufficient to evaluate other common respiratory illnesses such as RSV as described in this manuscript.
Data collection	Informed consent was obtained for all adult participants. For pediatric participants, informed consent was obtained from the minor's parent or legal guardian. We also obtained assent from children aged 7-17. If a participant turned 18 while participating in the study, we then consented these individuals as adults. Upon enrollment, participants (or their parent/guardian) completed an enrollment survey on demographic characteristics and health status, and attended a baseline blood draw appointment. Nasal swab kits were mailed to participants' homes with instructions for self- and parent/guardian-collection. Participants completed weekly online symptom surveys and home nasal swabs regardless of symptoms. Participants could also report new or worsening symptoms at any time; if this occurred >72 hours after their last swab, they were prompted to collect another swab. Participants with a reported illness or a positive test for SARS-CoV-2, influenza A, or RSV Subtype A (RSV A) completed additional surveys about symptoms, care-seeking, and absenteeism. Data were collected remotely using REDCap. Nasal swab PCR testing Mid-turbinate nasal swabs (RHINOstic™) were collected and shipped dry without preservative or media to UW. RSV A, influenza A, and SARS-CoV-2 testing was performed on all samples via RT-qPCR as previously described. Additionally, multipathogen testing was performed using a multiplex RT-qPCR assay including RSV A/B on swabs from participants who reported symptoms within 72 hours of swab collection, and swabs with a positive/inconclusive result for any virus during the first phase of testing. We defined an RSV-positive swab as a cycle threshold (Ct) value ≤37 for RSV RT-qPCR testing and a relative cycle threshold (Crt) <28 for multipathogen testing. We considered all inconclusive results as positive for the analysis. Crt values were used as a proxy for semiquantitative viral load. RSV antibody assays RSV pre-F IgG levels were measured in serum samples using an ECLIA with plates pre-coated with RSV pre-F antigen (Mesoscale Diagnostics). Pediatric serum samples were also tested using an RSV subtype A microneutralization assay and reported in standardized units based on the World Health Organization's first international standard for antiserum to RSV (16/284).
Timing	June 2022-May 2023
Data exclusions	We excluded individuals who screened eligible, but never fully enrolled in the study since all study procedures were not performed and/or participants did not consent to participate. Of the 9,851 who screened eligible, 3363 consented, and 3237 met the analysis inclusion criteria. Participants contributed person-time at risk during the weeks they self-collected a nasal swab beginning on the date of their first nasal swab collection. We restricted our analysis to participants who contributed >5 days of follow-up from the date of their first nasal swab collection.
Non-participation	Weekly swabbing compliance was high; participants missed a median of 2 weekly swab instances (range: 0-46 weeks). Participant retention was also high, with 96.4% remaining in the study at the end of the analytic period.
Randomization	This was an observational study; participants were not randomized. In our proportional hazards analysis, we adjusted for potential confounders identified a priori using a direct acyclic graph.

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, mosaicism, off-target gene editing) were examined.