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Reporting Summary

Nature Research 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 Research policies, see Authors & Referees 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	RNA sequencing bcl files were deconvoluted and converted to fastq format using Casava from Illumina. Fastq files were aligned to the Ensembl version of the human genome (GRCh38) (GenBank assembly accession id GCA_000001405.15), using TopHat (version 1.4.1). The single-paired flag was set to "single," while all other TopHat parameters were set to defaults. HTSeq-count was used to generate gene counts with mode as "Intersection (nonempty)" and minimum alignment quality set to 0 and otherwise set to default parameters.
Data analysis	All RNA sequencing analysis was completed using R versions 3.4.3 and 3.4.4 and the packages referenced in the manuscript. Network graphs were generated using Cytoscape version 3.5.1. Clinical data analysis was completed using SAS version 9.4.

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/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

RNA-sequencing data were deposited to the National Center for Biotechnology Information Gene Expression Omnibus with accession number GSE115824. All metadata from the study cohort have been deposited to ImmPort with accession number SDY1387. Data will be made public at the time of publication of 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	Sample size was determined using the R package RNASeqPower and confirmed using the R package PROPER. The following assumptions were made: An average RNA sequencing depth of 10 million reads per library, a type I error rate of 0.05 after multiple testing correction using the Benjamini-Hochberg procedure, and a biological CV for samples ranging between 0.20 and 0.45. The biological CV for samples was based on publicly available microarray data, which was then scaled to the extra variation expected in RNA sequencing data based on the publication "Utilizing RNA-Seq data for de novo coexpression network inference." (PMID: 22556371). The target study sample size was selected to allow us to detect effect sizes of at least 1.50 and higher with 80% power. Our enrollment target was set at 220 participants and our exacerbation event target was set at 32 exacerbations. The power calculation was approved by a NIAID statistician independent of the project.
Data exclusions	For data quality control, RNA sequencing data was retained only for samples that had > 0.66% counts aligned to the human genome, a median CV coverage < 1.5, and > 0.3 million counts. Individuals were excluded from the analysis if they did not report any cold events during the study, did not return to clinic for any cold events, or did not have any samples collected during cold events that produced RNA-sequencing data meeting these quality control metrics (see figure 1). From the RNA-sequencing data, genes were filtered to include only those that had a trimmed mean of M values (TMM) normalization count of at least 1 in at least 10% of libraries and were classified as protein coding using BioMart.
Replication	To cross validate our primary outcome results we did each of the following: 1) The cohort was split into a prespecified paired and unpaired analysis according to a predefined statistical analysis plan and the primary outcome calculated for each; 2) A bootstrap sensitivity analysis was performed though iterative subsetting of the full population. Each of these confirmed the primary outcome as presented in the manuscript.
Randomization	For the primary outcome, individuals/samples were organized into groups according to whether they were collected from individuals during cold symptom events that progressed to an asthma exacerbation defined as clinical symptoms that resulted in systemic corticosteroid use within 10 days of cold symptom onset, versus those events that resolved without treatment with systemic corticosteroids. The requirement for systemic corticosteroids and hence the group classification was monitored by an NIAID study manager independent of the study analysts. The group classification was provided to the analysts at the time of data analysis, and the analysis followed a prespecified statistical analysis plan. For the secondary outcome, individuals/samples were further subgrouped into virus associated or not virus associated depending on whether a virus was detected in the associated nasal lavage sample collecting during that cold symptom event. This subgrouping and secondary outcome was also done according to a prespecified statistical analysis plan.
Blinding	Group allocation was provided to the analysts at the time of data analysis and analyses were conducted according to a prespecified statistical analysis plan.

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
☒	☐ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data

Methods

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	An individual was eligible for enrollment if he or she: was 6 to 17 years of age; was diagnosed with asthma by a clinician greater than 1 year prior to recruitment; had at least 2 asthma exacerbation in the prior year (defined as a requirement for systemic corticosteroids and/or hospitalization); was treated with at least fluticasone 250 mcg 1 puff twice daily or its equivalent for those aged 6 to 11 years, or treated with at least Advair 250/50 mcg 1 puff twice daily or its equivalent for those aged 12 years and

	older; had peripheral blood eosinophils ≥ 150 per mm3; was a non-smoker; and had a parent/legal guardian sign a written informed consent and if applicable, signed the assent form, as per central IRB guidelines. Details of clinical characteristics are presented in Table 1.
Recruitment	Participants were recruited across 9 inner city sites in Boston, Chicago, Cincinnati, Dallas, Denver, Detroit, New York, St Louis, and Washington DC. Clinical sites utilized multiple recruitment sources throughout the trial. Sites reviewed lists of participants from previous Inner City Asthma Consortium (ICAC) trials who agreed to future contact as well as lists of potential participants from institutional Emergency Departments, clinics, and EPIC health software databases. Some sites also partnered with asthma and allergy providers in the community. Participants were also recruited through the ICAC Registry (RACR2/ICAC-25). Advertisements were placed in the institutions and around the community to elicit interest in the trial.
Ethics oversight	The study complied with all relevant ethical regulations. The study was approved by a central IRB (Western IRB), and a parent or legal guardian for each child signed written informed consent before completing study procedures.

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

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	The study was registered on clinicaltrials.gov as NCT02502890.
Study protocol	The full trail protocol can be accessed in ImmPort under accession number SDY1387
Data collection	The study sites for data collection are available at clinicaltrials.gov, NCT02502890. The study start was October 2015, recruitment ended October 2016, and study completion was January 2017.
Outcomes	Primary and secondary outcome measures were pre-defined in the study protocol and the statistical analysis plan available in ImmPort under accession number SDY1387.