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Blood Eosinophils, Serum Cotinine, and Reported Asthma Attacks Across Three NHANES Releases: A Repeated Cross-Sectional Analysis

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Abstract

Background: Joint associations of blood eosinophils and cotinine with asthma attacks may differ from an incremental cotinine association. We examined these associations across separated US survey releases.

Methods: We analyzed NHANES 2005-2006, 2017-March 2020, and August 2021-August 2023. Participants aged ≥6 years with complete measurements and determinable questionnaire routing were categorized by eosinophils (<300/≥300 cells/μL) and cotinine (<0.05/0.05-<10 ng/mL). Survey logistic models adjusted for age, sex, race/ethnicity, poverty-income ratio, and body mass index. A duration-weighted pooled summary included categorical period adjustment. Standardized prevalence contrasts included coefficient and empirical-target uncertainty.

Results: Of 22,140 complete participants, 17,901 had cotinine <10 ng/mL, with 824 attack reports. The pooled joint-category association was aOR 2.90 (95% Confidence Interval (CI) 2.03-4.15). The incremental cotinine OR within high eosinophils was 1.28 (95% CI 0.86-1.89). The standardized additive contrast was 1.53 percentage points (95% CI -1.62 to 4.68). Among 1,767 current-asthma respondents, the joint-category OR was 1.53 (95% CI 0.94-2.51). Interaction intervals were wide. Exploratory upper-cotinine and recent-product-use restrictions retained the joint association but did not establish exposure source.

Conclusions: Joint high biomarker categories were associated with population reports of asthma attacks. Incremental cotinine and current-asthma associations remained inconclusive. Cross-sectional design, exposure-source ambiguity, and selection limit causal interpretation; these findings do not establish nicotine-specific effects or intervention benefits.

Keywords: Asthma; Eosinophils; Cotinine; NHANES; Cross-Sectional Studies; Interaction

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Abbreviations

aOR: adjusted Odds Ratio; BMI: Body Mass Index; CI: Confidence Interval; IgE: Immunoglobulin E; MEC: Mobile Examination Center; NHANES: National Health and Nutrition Examination Survey; NCHS: National Center for Health Statistics; OR: Odds Ratio; PIR: Poverty-Income Ratio; PSU: Primary Sampling Unit; RERI: Relative Excess Risk due to Interaction; SE: Standard Error

Introduction

Asthma encompasses heterogeneous patterns of inflammation and clinical expression [1]. Blood eosinophil counts have been associated with subsequent asthma burden, but peripheral counts alone do not define an airway phenotype [2]. Cotinine reflects nicotine uptake over a recent interval. Its interpretation depends on product use, exposure context, metabolism, and analytical thresholds; a single concentration does not uniquely identify passive exposure or active use [3, 4].

These distinctions motivate a descriptive question: how are joint eosinophil/cotinine categories associated with reported asthma attacks across separated survey releases? A joint-category OR compares two categories differing on both biomarkers. It does not isolate cotinine's contribution. An incremental comparison within high eosinophils and interaction estimates address separate questions. Interaction also depends on scale: an odds-based summary and an additive prevalence

contrast are not interchangeable [5].

We evaluated population reports of attacks, attacks conditional on reported current asthma, additive contrasts, and heterogeneity across the selected releases. These analyses were descriptive; no confirmatory pre-specification is claimed.

Materials and Methods

Data, participants, and selected-period mixture

NHANES is a nationally administered complex survey with interview, examination, and laboratory components. We used three public releases: 2005-2006, 2017-March 2020, and August 2021-August 2023. Official component codebooks document variable definitions and eligibility [6-9]. These are independent cross-sectional samples, not follow-up observations of a cohort.

Sequential eligibility required age ≥6, positive applicable survey weight, observed cotinine and eosinophils, observed BMI and Poverty-Income Ratio (PIR), and determinable asthma/attack routing. Full release frames were retained for domain variance estimation [10]. Table S1 reports flow and missingness; Tables S2-S3 describe retained/excluded samples.

Weights were WTMEC2YR in the baseline release, WTMECPRP in the pre-pandemic release, and WTPH2YR for post-pandemic blood analytes [7, 11]. The pooled summary scaled weights by release duration: 2/7.2, 3.2/7.2, and 2/7.2. This selected-period mixture represents 7.2 observed survey-years with calendar gaps. It neither represents every intervening year nor estimates a continuous temporal trajectory. Release-specific findings are therefore reported alongside the pooled secondary summary. Pooled models include categorical period indicators with baseline as the reference.

Outcomes and routing

The primary endpoint was a population report of an asthma attack during the previous 12 months, using lifetime asthma (MCQ010), current asthma (MCQ035), and attack (MCQ040) responses [6]. A respondent was a case when all required positive responses identified current asthma with a reported attack. This operational population endpoint therefore represents current asthma accompanied by a reported recent attack, rather than an attack question administered independently to every participant. Known negative upstream responses defined routed non-cases. Refused, unknown, or genuinely missing required responses were excluded; missing responses were not generally recoded as no.

The secondary domain required reported lifetime and current asthma and a valid attack response. It estimates attack occurrence among current-asthma respondents, not attack severity. Conditioning changes the population and can introduce selection bias if variables influence entry into that domain [12]. Differences between primary and secondary ORs cannot by themselves establish a causal explanation for attenuation.

Biomarkers, covariates, and missingness

The primary domain was cotinine <10 ng/mL. Within it, four categories crossed eosinophils <300 *versus* ≥300 cells/μL with cotinine <0.05 *versus* 0.05-<10 ng/mL. Categories are labeled low/low, high eosinophils only, higher cotinine only, and joint high. "Higher cotinine" is relative to the analytical boundary; it is not a verified environmental-exposure category. The ≥10 category is excluded from primary analyses without treating that cutoff as a universal smoking discriminator.

The thresholds are analytical conventions preserved for comparability with earlier analyses. The cited eosinophil cohort used a main comparison above *versus* at/below 400 cells/μL, rather than directly validating our 300 boundary [2]. The cotinine threshold study reported adult/adolescent optimal smoking discriminators near 3 ng/mL, with variation across groups; it does not validate a universal 10 threshold [3]. Upper- and lower-boundary diagnostics evaluate sensitivity without proving correct source classification.

Covariates were age, sex, categorical RIDRETH1 race/ethnicity (non-Hispanic White reference), continuous PIR, and continuous BMI. Adult obesity was defined as BMI ≥30 kg/m^2 among eligible adults aged ≥20 years; the denominator included all eligible adults, regardless of obesity status. Continuous BMI in regression was not treated as an adult obesity diagnosis for children. Baseline total IgE ≥100 kU/L was an exploratory alternative biomarker category restricted to measured IgE; the assay codebook does not establish this as a diagnostic atopy cutoff [8].

Complete-case domain analyses excluded missing biomarkers/covariates and unknown required routing. Release-specific retained/excluded summaries report unweighted characteristics and variable-specific observed denominators. Excluded people include those lacking applicable laboratory weights. Similarity in observed sample characteristics cannot demonstrate absence of selection bias. Missing biomarkers and unobserved selection mechanisms remain limitations; standard survey weights do not automatically correct analysis-specific missingness.

Models, uncertainty, and interaction

We fit weighted binomial logistic models using the survey strata/PSU design and Taylor linearization [10, 11]. Crude models included biomarker category; Model 1 added age, sex, and race/ethnicity; Model 2 added PIR and BMI. All pooled models included period. Domain restrictions were applied after constructing the full release design. Release identifiers kept pooled strata separate. The reference was the low/low biomarker category.

Design degrees of freedom were calculated as positive-weight PSUs minus strata. Regression confidence intervals used residual degrees of freedom, obtained by subtracting fitted non-intercept predictors from design degrees of freedom. Model-specific design summaries and covariance matrices are retained with the analysis. Small residual degrees of freedom in individual releases warrant caution.

The incremental cotinine OR within high eosinophils was $\exp(\beta_{11}-\beta_{10})$, with covariance included in its SE. OR-based RERI was $OR_{11}-OR_{10}-OR_{01}+1$; the OR-based synergy index was $(OR_{11}-1)/(OR_{10}+OR_{01}-2)$, when defined. Delta-method uncertainty used the relevant joint coefficient covariance. Odds-based measures do not automatically identify additive risk interaction, particularly where outcomes are common [5].

For a directly interpretable descriptive prevalence contrast, we averaged fitted probabilities under each category over the same weighted empirical covariate target within each release/domain. The additive contrast was $P_{11}-P_{10}-P_{01}+P_{00}$, in percentage points. Its primary uncertainty jointly linearized model coefficients and the empirical target distribution, including covariance, at the PSU level. Individual margin SEs/CIs and joint covariance matrices are

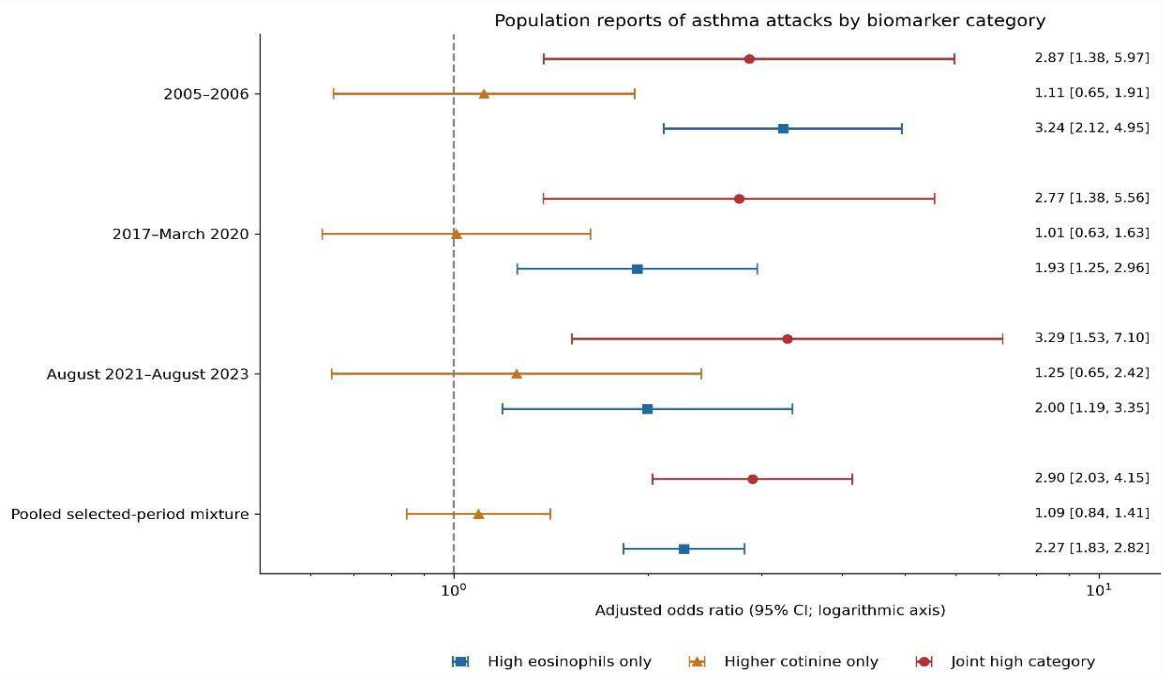


Figure 1: Fully adjusted attack ORs and residual-df confidence intervals for the three biomarker contrasts in each release and pooled mixture. Reference is low eosinophils/low cotinine; pooled models adjust for period. The axis is logarithmic. The figure describes population attack associations, not attack severity.

exported. Coefficient-only inference conditional on the observed target is retained as a labeled diagnostic. Standardization does not identify an intervention effect, and target distributions differ between releases.

A six-term period-by-category test was reported using both chi-square and design F references. It tests evidence of heterogeneity, not equivalence. Broad CIs or nonsignificant tests do not establish temporal stability or absence of biological interaction.

Sensitivity analyses

Additional analyses examined adults, post-pandemic MEC rather than phlebotomy weights, measured baseline IgE, a cotinine lower boundary of 0.10 ng/mL, eosinophil boundaries of 150/400 cells/μL, and quadratic age/BMI terms. Similarity under a quadratic specification indicates robustness to that tested form, not proof of no model bias. These analyses were introduced during review and are exploratory; multiplicity and selective-analysis limitations remain.

A selection-propensity diagnostic modeled BMI/PIR/routing retention among positive-weight laboratory-complete participants using age, age-squared, sex, race/ethnicity, release, and observed biomarker categories. Retained observations were inversely weighted by fitted retention probabilities clipped to [0.05,0.95]. Reported diagnostic intervals condition on these estimated weights and exclude nuisance-model estimation uncertainty. Retention exchangeability and correct propensity specification are unverified assumptions. This diagnostic cannot recover missing biomarkers or absent laboratory weights and does not replace primary inference.

Two focused diagnostics restricted cotinine to <3 ng/mL and restricted adults to no reported covered tobacco/nicotine product use in the previous five days. Questionnaire wording, routing, interview modes, and product coverage differ by release [9]. The pre-pandemic release concatenates its later separate e-cigarette question into a product checkbox; it does not contain the same e-cigarette variable as the post-pandemic file. Known negative screening responses were required, and reported e-cigarette use was excluded. Unknown responses did not establish non-use. These restrictions do not demonstrate lifetime abstinence or validate an environmental source, and questionnaire restriction changes the selected population.

Analyses used Python 3.13 and svy 0.33.1. Independently written weighted logistic models with stratified-PSU sandwich covariance reproduced primary estimates and standardized contrasts. Data preparation, model specifications, and software versions are retained in the reproducibility materials.

Results and Discussion

Participant derivation and descriptive contrasts

There were 37,841 enrolled participants across releases, yielding 22,140 complete analytical participants: 6,915 in 2005-2006, 9,298 in 2017-March 2020, and 5,927 in August 2021-August 2023. The primary cotinine <10 domain included 17,901 participants and 824 attack reports. The current-asthma primary-domain sample was 1,767. Figure 3 and Table S1 show the complete derivation.

Adult obesity percentages were 34.63%, 42.76%, and 40.71%. Attack prevalence in the cotinine-defined primary domain was 5.27%, 4.07%, and 4.94%. The baseline-to-post-pandemic attack endpoint contrast had p=0.5754; its separate ordinal release trend had p=0.6216. Table 1 gives all weighted means/proportions, SEs, and endpoint comparisons. Tables S2-S3 describe observed selection differences without resolving missingness bias.

Joint-category association and incremental cotinine contrast

The fully adjusted joint-category ORs versus low/low were 2.87 (95% CI 1.38-5.97; p=0.01624) in the baseline release, 2.77 (95% CI 1.38-5.56; p=0.007394) pre-pandemic, and 3.29 (95% CI 1.53-7.10;

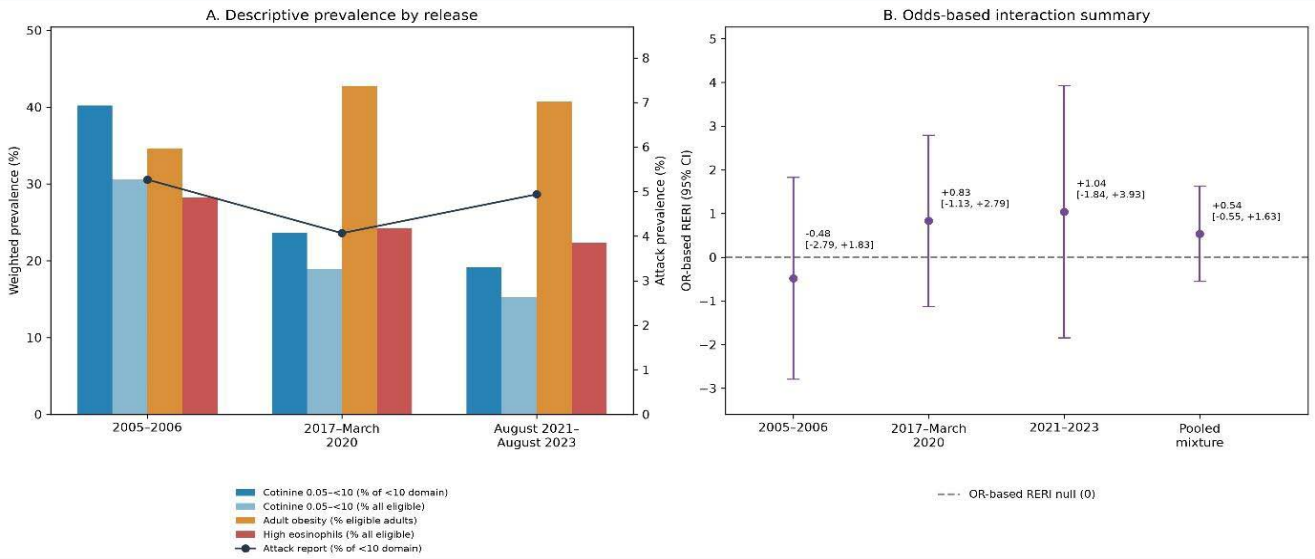


Figure 2: Panel A shows weighted cotinine-category prevalence in all eligible participants and the cotinine<10 domain, adult obesity among eligible adults, and high eosinophils; the second axis shows population attack prevalence in the cotinine<10 domain. Panel B shows OR-based RERI and delta-method confidence intervals; zero is the RERI null. This is distinct from standardized prevalence interaction and does not establish biological absence.

Table 1: Survey weighted characteristics.

Characteristic	2005-2006	2017-March 2020	August 2021-August 2023	Pooled mixture	Endpoint *p*
Complete sample, n	6,915	9,298	5,927	22,140	—
Cotinine <10 domain, n	5,605	7,532	4,764	17,901	—
Age, years	39.64 (0.78)	42.11 (0.64)	41.85 (0.57)	41.37 (0.39)	0.0294
Female, %	51.27 (0.39)	51.27 (0.89)	50.80 (0.62)	51.14 (0.45)	0.526
Adult obesity, %	34.63 (1.48)	42.76 (1.22)	40.71 (1.76)	40.01 (0.82)	0.013
PIR <1, %	12.48 (0.95)	14.08 (0.88)	14.58 (1.38)	13.79 (0.61)	0.21
High eosinophils, %	28.23 (0.85)	24.23 (0.53)	22.38 (0.75)	24.79 (0.42)	1.65×10^{-5}
Cotinine 0.05-<10, all eligible, %	30.55 (1.08)	18.93 (0.84)	15.26 (1.08)	21.05 (0.62)	5.31×10^{-10}
Cotinine 0.05-<10, <10 domain, %	40.22 (1.51)	23.62 (1.14)	19.15 (1.64)	26.68 (0.89)	2.46×10^{-9}
Cotinine ≥10, %	24.05 (1.16)	19.87 (0.98)	20.28 (1.38)	21.12 (0.67)	0.0488
Lifetime asthma, %	14.54 (0.66)	15.43 (0.62)	17.79 (0.57)	15.86 (0.37)	0.00105
Attack report, <10 domain, %	5.27 (0.41)	4.07 (0.46)	4.94 (0.42)	4.63 (0.26)	0.575

Values are weighted means or percentages (SE); Counts are unweighted. Endpoint *p* compares 2021-2023 with 2005-2006. Adult obesity: age ≥20 and BMI ≥30 kg/m^2. High eosinophils: ≥300 cells/μL. Cotinine units: ng/mL. PIR: Poverty-Income Ratio; SE: Standard Error

p=0.01263) post-pandemic. The pooled period-adjusted estimate was aOR 2.90 (95% CI 2.03-4.15; $p=3.548 \times 10^{-7}$). Table 2 provides crude, Model 1, and Model 2 estimates for all categories; Table S5 gives category counts, events, and weighted attack prevalence.

The pooled incremental cotinine contrast within high eosinophils was 1.28 (95% CI 0.86-1.89; *p*=0.2145). Its interval includes unity. A joint-category association therefore cannot be described as demonstrating an independent cotinine association, nor can these comparisons decompose the entire joint association into causal components.

Interaction and standardized prevalence

The pooled OR-based RERI was 0.54 (95% CI -0.55 to 1.63); the synergy index was 1.39 (95% CI 0.74 to 2.63). Release-specific interaction intervals were also wide. The pooled standardized prevalences were 3.48%, 7.50%, 3.78%, and 9.33% for low/low, high eosinophils only, higher cotinine only, and joint high. The standardized additive contrast was 1.53 percentage points (95% CI -1.62 to 4.68; *p*=0.3318), with joint SE 1.56 percentage points. Table S4 provides individual margin uncertainty.

The period-by-category chi-square statistic was 11.31 (df 6; *p*=0.0794), and the design F statistic was 1.88 (numerator df 6, denominator df 55; *p*=0.1000). These results do not establish equivalence or absence of meaningful heterogeneity.

Current-asthma domain

Among current-asthma respondents, the pooled joint-category OR was 1.53 (95% CI 0.94-2.51; *p*=0.08704). Reference-category weighted attack prevalence was 45.60%, illustrating that the outcome is much more common in this conditional population than in the population endpoint. Odds ratios should not be read as risk ratios in this domain. Conditioning, changed target population, and uncertainty limit direct comparison with primary results; Table 3 reports each release.

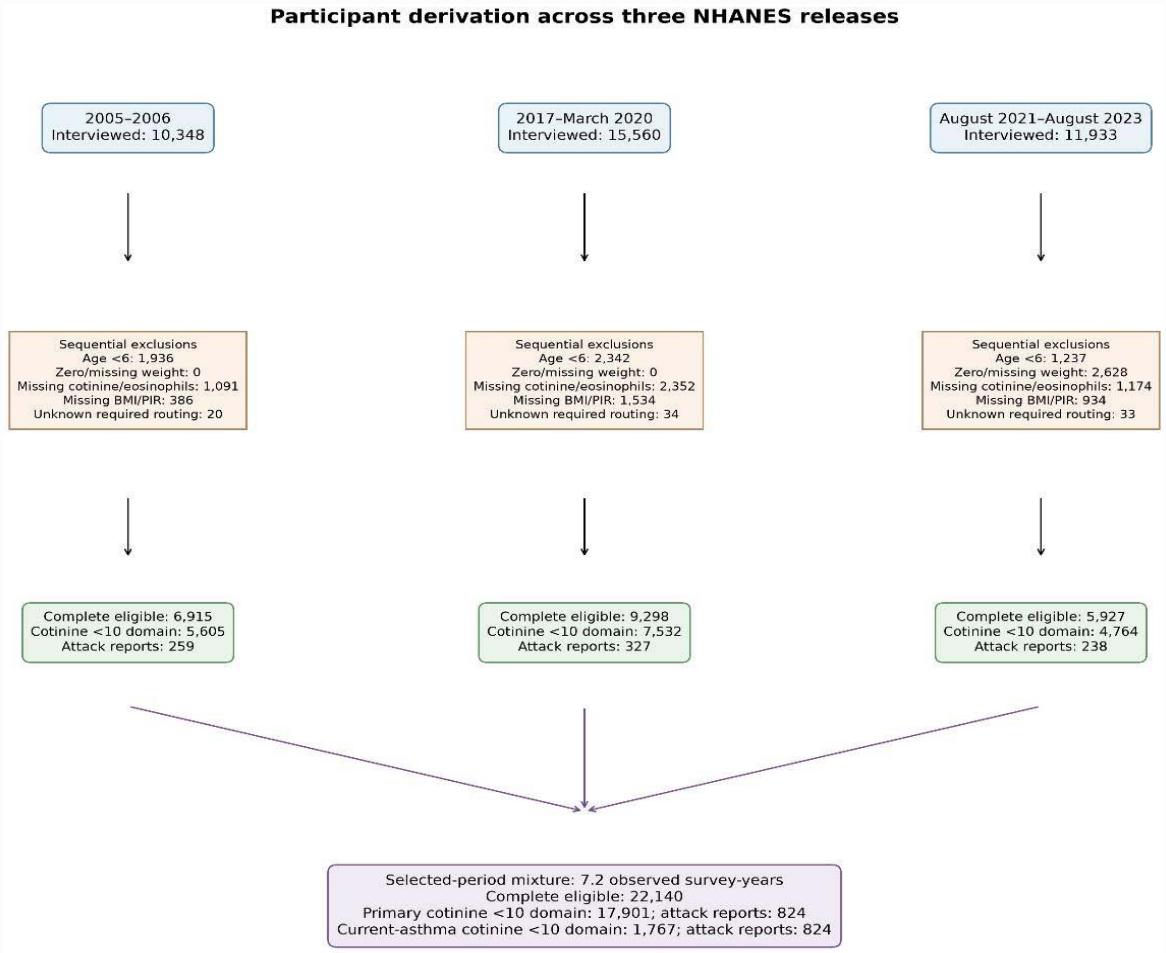


Figure 3: Unweighted participant derivation, sequential exclusions, and primary/current-asthma domain counts. The pooled box sums observed release counts; it does not imply longitudinal follow-up.

Exploratory diagnostics

With cotinine <3 ng/mL, the pooled diagnostic included 17,452 participants and 802 events; its joint-category estimate was 2.86 (95% CI 1.97-4.14; p=1.044 × 10^{-6}). The incremental cotinine contrast was 1.25 (95% CI 0.84-1.88; p=0.2651). The broad joint association persisted under this tested restriction, while the incremental contrast remained imprecise. This does not validate the original cutoff or identify exposure source.

The adult five-day reported non-use diagnostic included 10,736 participants and 446 events. Its joint-category estimate was 3.03 (95% CI 2.01-4.55; p=2.177 × 10^{-6}), and its incremental cotinine estimate was 1.60 (95% CI 0.98-2.62; p=0.05905). These results describe a more selected adult population with release-specific questionnaire limitations. Table 4 presents all exploratory specifications, including their estimates and uncertainty; similarity across tested alternatives does not eliminate residual confounding, missingness bias, or model dependence.

The selection-IPW diagnostic included 25,081 laboratory-complete participants in the retention model and 17,901 in the fitted attack domain. The joint-category OR was 2.89; its conditional-on-estimated-weights interval was 2.03-4.11. This bounded diagnostic does not resolve selection bias or provide complete uncertainty for an adjusted population estimate.

Interpretation and study limitations

The strongest descriptive result was the association between joint high biomarker categories and population reports of asthma attacks. Consistent point estimates across separated releases and exploratory specifications support reporting that association. They do not establish a stable biological mechanism, an independent nicotine effect, or an intervention benefit. The incremental cotinine contrast asks a narrower question and remained inconclusive. Higher eosinophil-associated ORs cannot be used to assign a proportion of the joint association without a justified decomposition.

The current-asthma analysis changes the estimand. It considers attack occurrence after conditioning on reported disease rather than the combined population pattern of disease and attacks. Conditioning can also introduce bias [12]. Common outcomes in the conditional population further complicate odds-based interpretation. These considerations help explain why primary and secondary findings should be presented separately; they do not prove the cause of their difference.

The standardized additive contrast adds a prevalence-scale description to the OR-based interaction summaries. Its uncertainty covers both model fitting and the observed weighted target distribution. All such calculations remain model-dependent descriptions of observed samples. Wide intervals permit a range

Table 2: Primary attack models 2005-2006.

Category	Crude OR (95% CI)	Model 1 aOR (95% CI)	Model 2 aOR (95% CI)
High eosinophils only	3.26 (2.35–4.50) $p=4.11 \times 10^{-6}$	3.33 (2.26–4.91) $p=0.000277$	3.24 (2.12–4.95) $p=0.00155$
Higher cotinine only	1.17 (0.76–1.79) $p=0.442$	1.15 (0.73–1.82) $p=0.486$	1.11 (0.65–1.91) $p=0.607$
Joint high	3.06 (1.84–5.07) $p=0.000423$	2.97 (1.65–5.36) $p=0.004$	2.87 (1.38–5.97) $p=0.0162$

Domain n=5,605; events=259; design df=15; Model 2 residual df=4. Reference: eosinophils <300 cells/μL and cotinine <0.05 ng/mL. Model 1 adjusts age, sex and race/ethnicity; Model 2 also adjusts PIR and BMI. All pooled models include period. OR: Odds Ratio; Aor: adjusted OR; CI: Confidence Interval; df: degrees of freedom

Table 2: Primary attack models 2017-March 2020.

Category	Crude OR (95% CI)	Model 1 aOR (95% CI)	Model 2 aOR (95% CI)
High eosinophils only	1.96 (1.32–2.91) $p=0.00188$	2.06 (1.38–3.07) $p=0.00155$	1.93 (1.25–2.96) $p=0.0055$
Higher cotinine only	1.18 (0.73–1.89) $p=0.486$	1.15 (0.69–1.90) $p=0.57$	1.01 (0.63–1.63) $p=0.967$
Joint high	3.18 (1.81–5.58) $p=0.000321$	3.31 (1.79–6.15) $p=0.000813$	2.77 (1.38–5.56) $p=0.00739$

Domain n=7,532; events=327; design df=25; Model 2 residual df=14. Reference: eosinophils <300 cells/μL and cotinine <0.05 ng/mL. Model 1 adjusts age, sex and race/ethnicity; Model 2 also adjusts PIR and BMI. All pooled models include period. OR: Odds Ratio; aOR: adjusted OR; CI: Confidence Interval; df: degrees of freedom

Table 2: Primary attack models August 2021-August 2023.

Category	Crude OR (95% CI)	Model 1 aOR (95% CI)	Model 2 aOR (95% CI)
High eosinophils only	1.97 (1.33–2.90) $p=0.0026$	2.08 (1.33–3.25) $p=0.00695$	2.00 (1.19–3.35) $p=0.0207$
Higher cotinine only	1.58 (1.00–2.52) $p=0.0512$	1.53 (0.88–2.64) $p=0.108$	1.25 (0.65–2.42) $p=0.399$
Joint high	3.73 (2.16–6.43) $p=0.000203$	3.77 (1.95–7.31) $p=0.00268$	3.29 (1.53–7.10) $p=0.0126$

Domain n=4,764; events=238; design df=15; Model 2 residual df=4. Reference: eosinophils <300 cells/μL and cotinine <0.05 ng/mL. Model 1 adjusts age, sex and race/ethnicity; Model 2 also adjusts PIR and BMI. All pooled models include period. OR: Odds Ratio; aOR: adjusted OR; CI: Confidence Interval; df: degrees of freedom

Table 2: Primary attack models pooled mixture.

Category	Crude OR (95% CI)	Model 1 aOR (95% CI)	Model 2 aOR (95% CI)
High eosinophils only	2.27 (1.85–2.78) $p=1.73 \times 10^{-10}$	2.38 (1.93–2.94) $p=1.26 \times 10^{-10}$	2.27 (1.83–2.82) $p=1.49 \times 10^{-9}$
Higher cotinine only	1.25 (0.96–1.62) $p=0.0935$	1.22 (0.93–1.59) $p=0.142$	1.09 (0.84–1.41) $p=0.493$
Joint high	3.19 (2.36–4.31) $p=4.21 \times 10^{-10}$	3.28 (2.36–4.54) $p=3.9 \times 10^{-9}$	2.90 (2.03–4.15) $p=3.55 \times 10^{-7}$

Domain n=17,901; events=824; design df=55; Model 2 residual df=42. Reference: eosinophils <300 cells/μL and cotinine <0.05 ng/mL. Model 1 adjusts age, sex and race/ethnicity; Model 2 also adjusts PIR and BMI. All pooled models include period. OR: Odds Ratio; aOR: adjusted OR; CI: Confidence Interval; df: degrees of freedom

Table 2: Continued incremental cotinine and interaction.

Release	Incremental cotinine aOR (95% CI)	OR based RERI (95% CI)	OR based S (95% CI)	Additive contrast pp (95% CI)
2005-2006	0.89 (0.43–1.82) $p=0.667$	-0.48 (-2.79 to +1.83)	0.80 (0.25–2.51)	-1.41 (-7.91 to +5.10) $p=0.581$
2017-March 2020	1.44 (0.68–3.05) $p=0.318$	+0.83 (-1.13 to +2.79)	1.89 (0.48–7.48)	+2.33 (-2.98 to +7.63) $p=0.362$
August 2021-August 2023	1.65 (0.59–4.59) $p=0.247$	+1.04 (-1.84 to +3.93)	1.84 (0.38–8.97)	+3.13 (-5.47 to +11.73) $p=0.37$
Pooled mixture	1.28 (0.86–1.89) $p=0.214$	+0.54 (-0.55 to +1.63)	1.39 (0.74–2.63)	+1.53 (-1.62 to +4.68) $p=0.332$

Incremental cotinine compares joint high with high eosinophils only. RERI, relative excess risk due to interaction, calculated from ORs; S: OR-based synergy index; pp: percentage points. Additive prevalence contrasts use joint coefficient/empirical-target PSU linearization. OR-based RERI and S do not directly establish risk-scale interaction

Table 3: Attack occurrence among respondents with current asthma.

Release	n	High eosinophils only aOR (95% CI)	Higher cotinine only aOR (95% CI)	Joint high aOR (95% CI)
2005-2006	513	1.27 (0.52–3.13) $p=0.497$	1.01 (0.46–2.21) $p=0.985$	1.44 (0.58–3.60) $p=0.332$
2017-March 2020	740	1.25 (0.67–2.32) $p=0.456$	0.66 (0.41–1.08) $p=0.0921$	1.40 (0.46–4.25) $p=0.521$
August 2021-August 2023	514	1.47 (0.77–2.82) $p=0.173$	1.26 (0.49–3.22) $p=0.538$	1.58 (0.70–3.57) $p=0.191$
Pooled mixture	1,767	1.32 (0.94–1.83) $p=0.103$	0.93 (0.67–1.28) $p=0.633$	1.53 (0.94–2.51) $p=0.087$

Same fully adjusted covariates as primary Model 2. Domain: cotinine <10 ng/mL and reported lifetime/current asthma with a valid attack response. These ORs measure attack occurrence, not severity. Reference: low/low biomarkers. aOR: adjusted Odds Ratio; CI: Confidence Interval

of interaction values; nondetection should not be interpreted as refutation of biological synergy. Likewise, the heterogeneity test cannot establish temporal equivalence.

Cotinine is particularly vulnerable to source ambiguity. Different

Table 4: Exploratory sensitivity analyses.

Specification	n	Joint category aOR (95% CI)	*p*
Adults ≥20 years	11,856	2.96 (2.02–4.33)	9.24×10^{-7}
Post-pandemic MEC weights	4,764	3.38 (1.60–7.14)	0.0107
Baseline IgE ≥100 kU/L	5,595	3.29 (1.29–8.38)	0.0242
Cotinine lower boundary 0.10	17,901	2.84 (1.98–4.07)	6.92×10^{-7}
Eosinophil boundary 150	17,901	2.39 (1.60–3.56)	6.96×10^{-5}
Eosinophil boundary 400	17,901	3.08 (2.03–4.66)	2.33×10^{-6}
Quadratic age and BMI	17,901	2.91 (2.04–4.15)	3.98×10^{-7}
Cotinine upper restriction <3	17,452	2.86 (1.97–4.14)	1.04×10^{-6}
Adult five-day reported non-use	10,736	3.03 (2.01–4.55)	2.18×10^{-6}
Selection IPW diagnostic	17,901	2.89 (2.03–4.11)	3.16×10^{-7}

Analyses were introduced during review and are exploratory. Eosinophil units: cells/μL; cotinine units: ng/mL. IgE is not a diagnostic atopy definition. MEC, mobile examination center; IPW: Inverse-Probability Weighting; IgE: Immunoglobulin E. IPW CIs condition on estimated/truncated weights and omit nuisance-model uncertainty. None of these diagnostics establishes absence of bias

nicotine products, replacement therapy, intermittent use, and environmental exposure can contribute to measured values [4]. The upper-cutoff and recent-use diagnostics probe specific restrictions but do not identify all active use or establish passive exposure. Avoidance or treatment recommendations cannot be inferred from these data; intervention questions require external evidence and designs suited to causal inference.

Limitations include cross-sectional temporality, self-reported diagnosis and attacks, possible exposure misclassification, threshold dependence, unmeasured clinical factors and residual confounding, complete-case selection, and differences in survey collection across releases. The selected-period mixture leaves calendar gaps and combines distinct target distributions. Total IgE is neither a complete atopy assessment nor available comparably across all releases. Exploratory analyses were chosen after results/reviews, and multiplicity was not controlled for confirmatory inference. Release-specific residual df are small and estimates can be unstable. Independent arithmetic checks establish reproducibility of specified calculations, not validity of all identifying assumptions.

Conclusion

Joint eosinophil/cotinine categories were associated with population reports of asthma attacks in the selected NHANES releases. Incremental cotinine, current-asthma, and interaction findings warrant cautious interpretation. The study supports descriptive biomarker-category associations while leaving exposure source, causation, and intervention effects unresolved.

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Ethics and Consent

This study analyzed de-identified public-use NHANES data. NHANES ethics and consent documentation applies to the original survey. The authors must confirm the institutionally applicable secondary-analysis ethics or exemption statement before submission; no local determination is asserted here.

Funding and Competing Interests

Author confirmation required.

Author Contributions

The final contributor roles and approval of all named authors require confirmation.

Data and Code Availability

The raw component files are publicly available from NCHS. Harmonized data, analytical scripts, model outputs, and verification materials are retained with this study. A public repository URL has not been supplied and must be confirmed before submission.

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