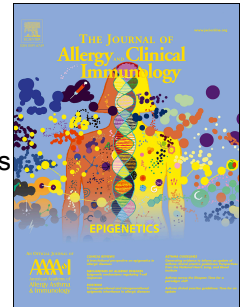


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Asthma as an Outcome: Exploring Multiple Definitions of Asthma across Birth Cohorts in the ECHO Children's Respiratory and Environmental Workgroup (CREW)

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**Asthma as an Outcome: Exploring Multiple Definitions of Asthma across Birth Cohorts
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Conflict of Interest Statement

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CAPSULE SUMMARY

Asthma definitions vary widely across research studies and feature a trade-off between inclusivity and precision. Harmonizing definitions across multiple asthma birth cohort studies highlights these challenges.

Word Count: 26 (max=30)

KEY WORDS

asthma, asthma prevalence, pediatric asthma, birth cohort

To The Editor:

Every birth cohort study investigating risk factors for the development of asthma relies on specific criteria for classifying children as asthmatic or not, but these criteria vary widely across studies, as there is no gold standard set of diagnostic criteria nor an objective test for asthma. Researchers make independent, yet informed, decisions about the data elements they need and are able to collect to achieve their research objectives given available resources. Cohorts with only questionnaire data available, such as The International Study of Asthma and Allergies in Childhood (ISAAC), rely on parent-reported physician diagnosis of asthma.¹ Some studies have used lung function and airway hyperresponsiveness in their asthma definition criteria, while others have used reports of wheezing symptoms, asthma medication use, and health care data. Often, studies use a combination of the above to identify children with asthma. A comprehensive review of birth cohort asthma definitions found 60 different asthma definitions among 122 studies.² In addition to the varying prevalence of asthma due to the definition used, identification of risk factors for asthma may also vary based on how the outcome is defined and the age at which it is applied, potentially leading to inconsistent findings across birth cohorts.

The Children's Respiratory Research and Environment Workgroup (CREW) is a consortium of 12 U.S birth cohort studies³ which are part of the larger Environmental Influences on Child Health Outcomes (ECHO) program of the National Institutes of Health (<http://echochildren.org/>). The combined study participants of the CREW consortium represent a diverse national sample of children recruited over the past 30+ years into cohort studies specifically designed to study the role of early life environmental risk factors on asthma development. Some of the cohorts recruited participants from the general population, while others selected participants based on parental histories of asthma or allergy or parental atopy. One of the goals of CREW is to

combine and harmonize extant data across all of the cohorts. Understanding the extent of heterogeneity in asthma definitions is an essential early step in the process towards building a harmonized definition of asthma.

We used data from 9 of the CREW cohorts to examine how the prevalence of asthma in middle childhood (age 5-10 years) varies by applying different outcome definitions, where possible.

After examining all of the definitions used across all 9 cohorts (Table E1 in the Online Repository), 4 definitions of asthma were chosen for comparison across multiple cohorts:

DEFINITION 1: Positive response to “Has a doctor or other health professional ever told you your child has asthma?” at any time up to the assessment age.

DEFINITION 2: A parent-reported physician diagnosis of asthma as above plus a parental report of ≥ 1 wheezing episode in the past 12 months.

DEFINITION 3: A parent-reported physician diagnosis of asthma as above or report of asthma medication use (both controllers and rescue albuterol) in the past year.

DEFINITION 4: FEV_1 reversibility $\geq 12\%$ or bronchial hyperresponsiveness (methacholine $PC_{20} \leq 4$ mg/ml).

A single analyst (TG) pooled the data and applied the four asthma definitions to each cohort. In order to ensure that observed differences were due to changes in definition and not to changing population sizes, the cohort analysis populations were restricted to those children who had data for all definitions possible for that cohort. If a cohort did not collect a given data element at all (e.g. clinical pulmonary function measurements), that definition was not used for that cohort.

Descriptive statistics were calculated as median with interquartile range (median, IQR:25th, 75th) for continuous variables, and frequency and percentages for categorical variables. We used a Venn diagram to graphically display the overlap in children defined as asthmatic using the different asthma definitions. All analyses were performed using R version 3.4.0 (<http://www.R-project.org>).

Demographic characteristics of the cohorts are shown in Table I. Each cohort sent data for a particular time point, usually that for which a primary determination of asthma was previously done. Ages ranged from about 5 years to 7 years of age, with the exception of the WHEALS study which provided data from a 10-year assessment.

Only two definitions could be applied to all 9 cohorts: physician diagnosis (Definition 1) and physician diagnosis plus wheeze (Definition 2). As expected, prevalence based on Definition 2 (“current” versus “ever” asthma) was lower across all the cohorts (range from 2-13 percentage points). Physician diagnosis or asthma medication use (Definition 3) was applied to six of the nine cohorts, and always resulted in higher prevalence than Definition 1 (range from 1-6 percentage points). The definition based on tests of reversibility or hyperresponsiveness (Definition 4) could only be applied to three cohorts. Prevalence based on Definition 4 was the lowest of the four definitions for one cohort and the highest for two of the cohorts (Figure 1). Thus, in addition to varying in inclusivity, the different definitions identified distinct subsets of children as having asthma (Figure E1 in the Online Repository).

Without an objective test or even a gold-standard set of clinical diagnostic criteria for asthma, research studies are not consistent in operationalizing their definition of disease. In our application of 4 different asthma definitions to data from 9 of the CREW birth cohorts, we found substantial differences in asthma prevalence. Further, the definitions identified distinct groups of

children, such that certain definitions miss children that others pick up. In addition, because of the availability of data, only 2 out of 4 of the definitions could be applied post-hoc to all studies, making harmonization of outcome definitions challenging.

As shown in the van Wonderen review article,² researchers often choose combinations of variables to determine asthma in their study populations as they strive to identify all the asthmatics while simultaneously excluding the non-asthmatics. The URECA cohort, in particular, used a complex set of and/or criteria to identify the children with asthma in their population at seven years of age.⁴ An approach like this, e.g. creating standard “building blocks” that could be assembled depending on the research question, may hold promise, but is next to impossible to apply post hoc to datasets from other studies that did not ask the same questions or include the same procedures.

This work highlights the need to develop consensus guidelines for asthma definitions and to promote the use of standardized data collection elements to ensure the ability to compare studies and achieve reproducibility and rigor.

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247

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249

250 Table I. Demographic characteristics of participating CREW birth cohorts.
251

	CCCEH (N=727)	TCRS (N=1246)	IIS (N=482)	COAST (N=259)	URECA (N=485)	CCAAPS (N=617)	EHAAS (N=438)	WHEALS (N=1258)	CAS (N=835)
<u>Race/Ethnicity</u>									
Hispanic	65%	26%	26%	3%	20%	1%	6%	7%	0%
Non-Hispanic White	0%	59%	58%	87%	1%	66%	80%	26%	95%
Non-Hispanic Black	35%	2%	2%	4%	72%	16%	7%	63%	2%
Other/Mixed	0%	13%	14%	6%	7%	16%	8%	5%	4%
<u>Sex</u>									
Male	48%	49%	48%	57%	51%	55%	54%	50%	49%
Female	52%	51%	52%	43%	49%	45%	46%	50%	51%
Mean Age in Years at Asthma Assessment (SD)	7.0 (6.0-9.0)	6.2 (5.8-6.5)	5.1 (5.0-5.2)	6.0 (6.0-6.0)	7.0 (6.9-7.2)	6.8 (6.7-7.0)	7.0 (7.0-7.0)	10.2 (9.5-10.8)	6.7 (6.6-6.8)
Type of Eligibility*	General	General	General	Family History	Family History	Family History	Family History	General	General
Percent w/Asthma in Original Cohort Publication	31%	10%	12%	28%	29%	16%	8%	13%	10%

252
253 *Detailed eligibility criteria are given in Table E1 in the Online Supplement.

254 **Figure Legends**

255 Figure 1. Changes in asthma prevalence across each cohort for varying definitions of asthma.

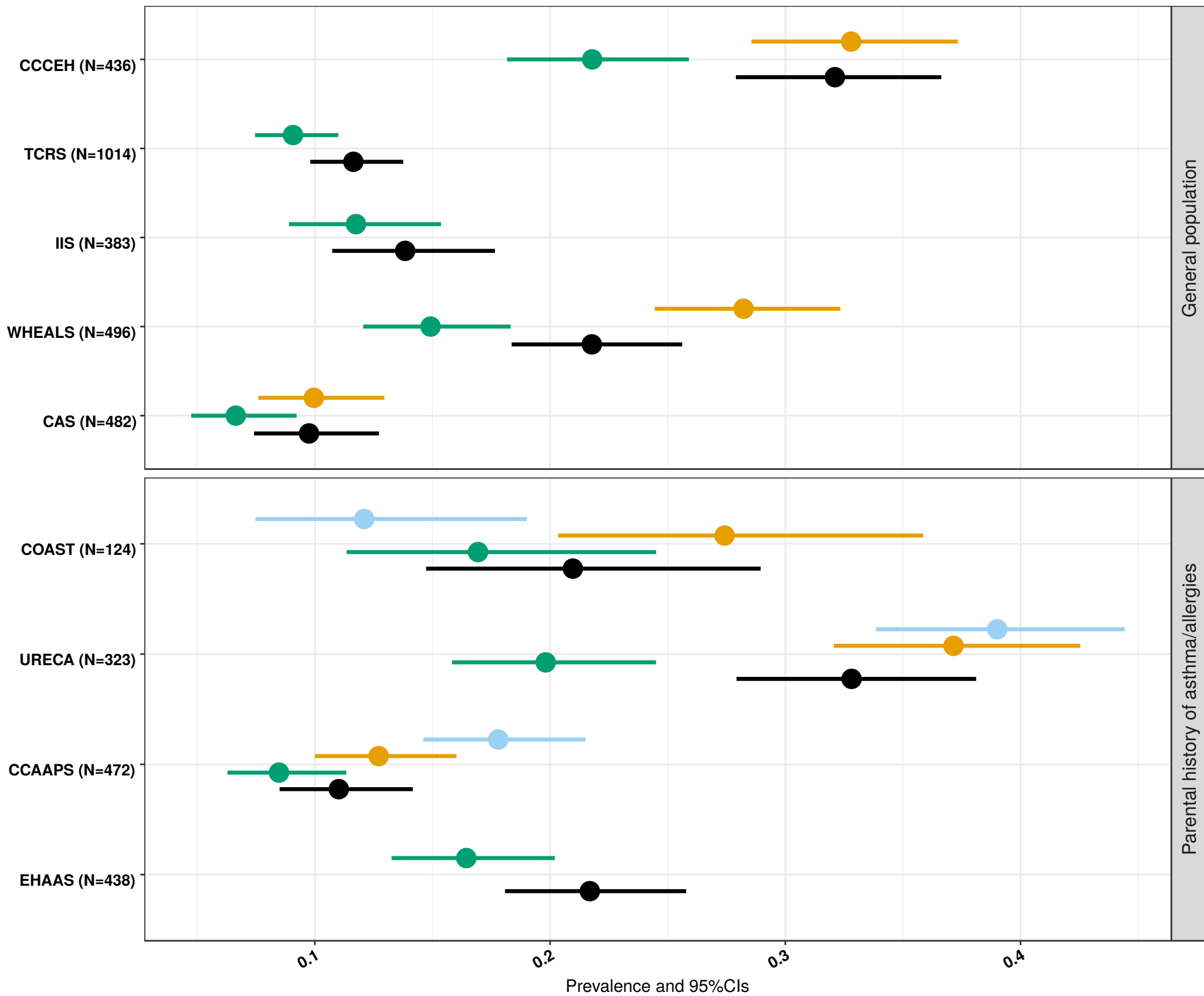
256 (Definition 1= Doctor diagnosis of asthma; Definition 2 = Doctor diagnosis of asthma +

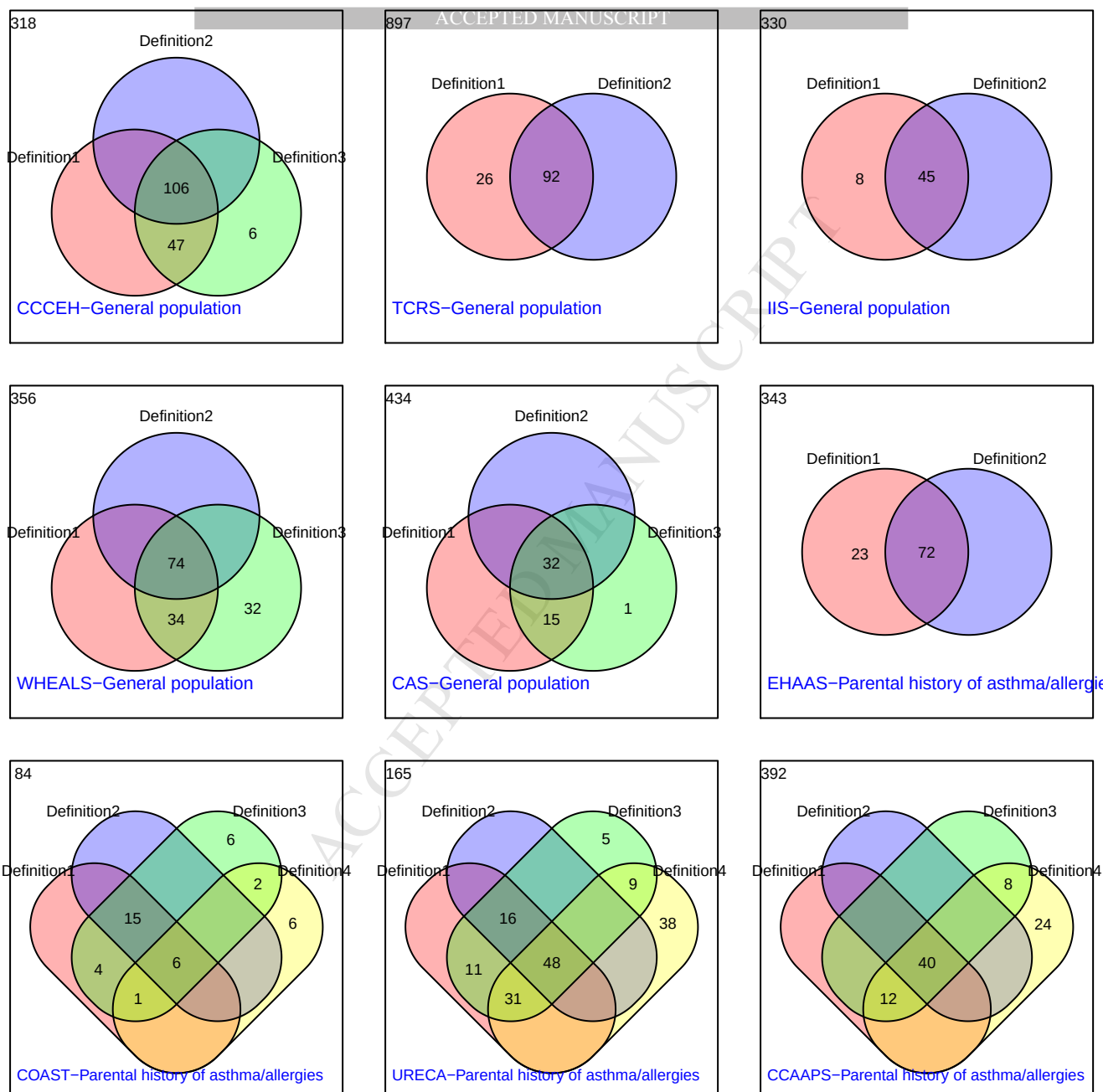
257 wheezing in the past 12 months; Definition 3 = Doctor diagnosis of asthma or asthma medication

258 use in the past year; Definition 4 = FEV1 reversibility or bronchial hyperresponsiveness).

259

Definition 1 Definition 2 Definition 3 Definition 4





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Online Repository

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Table E1. Definitions of asthma (age 5-10 years) for each CREW birth cohort.

Cohort	Cohort Name	Institution	City	Original Cohort Asthma Definition	Key Eligibility Criteria
CCCEH ¹	Columbia Center for Children's Environmental Health	Columbia University Medical Center	New York	Parent-reported physician diagnosis of asthma or report of wheeze or use of asthma medications in past year.	Women 18–35 years old, who self-identified as African American or Dominican and had resided in northern Manhattan or the South Bronx for at least 1 year before pregnancy. Women were excluded from enrollment into the cohort if they reported active smoking, used other tobacco products or illicit drugs, had diabetes, hypertension, or known HIV, or had their first prenatal visit after 20 weeks gestation.
TCRS ²	Tucson Children's Respiratory Study	University of Arizona	Tucson	Physician-diagnosed asthma with report of asthma attacks/episodes or wheezing in past year.	Newborns whose parents were patients of Group Health Medical Associates in Tucson, AZ.
IIS ³	The Infant Immune Study	University of Arizona	Tucson	Physician-diagnosed asthma with report of asthma attacks/episodes, wheezing, or asthma medication use in past year.	Participants were healthy children born to women who planned to obtain care for their newborns from collaborating pediatricians.
COAST ⁴	Childhood Origins of Asthma Study	University of Wisconsin	Madison	Physician-diagnosed asthma, or use of albuterol for asthma attacks/episodes or wheezing, or asthma controller medication use, or having a step-up plan, or use of prednisone in past year.	At least one parent was required to have respiratory allergies (defined as one or more positive aeroallergen skin tests) and/or a history of physician-diagnosed asthma. Delivery at ≥ 34 weeks of gestation.

URECA ⁵	Urban Environment and Childhood Asthma	John's Hopkins University School of Medicine	Baltimore	1) Parent-reported physician diagnosis of asthma between age 4 and 7 years, combined with asthma symptoms or the use of asthma controller medication for 6 of the past 12 months; 2) Methacholine PC20 $\leq$ 4 mg/ml or albuterol reversibility of FEV1 $\geq$ 10%, combined with asthma symptoms or use of asthma controller medication for 6 of the past 12 months; or 3) The report in the past 12 months of $\geq$ 2 wheezing episodes, $\geq$ 2 doctor visits for asthma/wheeze, $\geq$ 1 hospitalization for asthma/wheeze, or the use of controller medications for 6 of the past 12 months.	At least one parent was required to have had a previous physician diagnosis of asthma, hay fever, or eczema (captured by maternal report). Delivery at $\geq$ 34 weeks of gestation. Residence in a census tract with $\geq$ 20% poverty at the time of birth.
		Boston University School of Medicine	Boston		
		Columbia University Medical Center	New York		
		St. Louis Children's Hospital	St. Louis		
CCAAPS ⁶	Cincinnati Childhood Allergy and Air Pollution Study	Cincinnati Children's Hospital	Cincinnati	Physician-diagnosed asthma with evidence of bronchoreactivity or reversibility.	Delivery at 35+ weeks gestation At least one parent with current allergy symptoms and SPT positive to at least one aeroallergen Live less than 400 meters or greater than 1500 meters from a major highway
EHAAS ^{7,8}	Epidemiology of Home Allergens and Asthma Study	Harvard University	Cambridge	Physician-diagnosed asthma with report of asthma attacks/episodes or	Children with a history of asthma or allergy in at least one parent.

				wheezing in past year.	
WHEALS ⁹	Wayne County Health Environment Allergy and Asthma Longitudinal Study	Henry Ford Health System	Detroit	Parental report of physician-diagnosed asthma.	Women were eligible for inclusion in the study if they were in their second or third trimester of pregnancy, were between 21 and 49 years of age, and lived in a predefined cluster of ZIP codes in Detroit and its surrounding suburbs and attending one of 5 obstetric clinics.
CAS ^{10,11}	Childhood Allergy/Asthma Study	Henry Ford Health System	Detroit	Parental report of physician-diagnosed asthma.	Women 18 years and older having prenatal visits in a geographically circumscribed suburban Detroit health maintenance organization (HMO).

Figure Legends

Figure E1. Overlap among asthma definitions for each cohort. The numbers represent the number of children, and each Venn diagram shows the number of children in that cohort not diagnosed with asthma by any definition in the upper left-hand corner. (Definition 1= Doctor diagnosis of asthma; Definition 2 = Doctor diagnosis of asthma + wheezing in the past 12 months; Definition 3 = Doctor diagnosis of asthma or asthma medication use in the past year; Definition 4 = FEV1 reversibility or bronchial hyperresponsiveness).

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immunology : official publication of the American College of Allergy, Asthma, & Immunology 2003;90:41-4.

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