Published in final edited form as:

J Allergy Clin Immunol Pract. 2019 April ; 7(4): 1367–1369.e1. doi:10.1016/j.jaip.2018.10.039.

Anxiety and non-eosinophilic asthma among adults in the United States

Yueh-Ying Han, PhD¹, Erick Forno, MD, MPH¹, and Juan C. Celedón, MD, DrPH, FAACAP¹

¹Division of Pediatric Pulmonary Medicine, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh, Pittsburgh, PA

To the Editor:

In the U.S., 7.6% of adolescents and adults report depression in any two-week period, and 7.6% of adults report current asthma¹. Depression and anxiety have been associated with asthma in adults^{2,3}. Whether this is explained by eosinophilic inflammation or other (non-eosinophilic mediated) mechanisms (i.e. dysregulation of the hypothalamic pituitary axis, persistent secretion of cortisol and catecholamines, and down-regulation of the glucocorticoid and β 2-adrenergic receptors) is unclear³.

A previous study of 30 adults with mild asthma showed that acute on chronic stress was associated with increased eosinophils in blood and sputum⁴. Although those findings must be cautiously interpreted due to small sample size, we hypothesized that depression or anxiety would have different effects on asthma according to the presence or absence of peripheral blood eosinophilia. We tested this hypothesis among U.S. adults participating in the National Health and Nutrition Examination Survey (NHANES).

NHANES is a cross-sectional nationwide survey designed to assess the health and nutrition of the noninstitutionalized U.S. population⁵, using a stratified multistage probability design to select a representative sample of such population. As part of the study design, ethnic minorities (non-Hispanic blacks, Hispanics and Asians), low-income whites, and persons 80 years and older are oversampled to increase statistical power for data analysis in these groups. Informed consent is obtained from all study participants. NHANES is approved by the Institutional Review Board of the National Center for Health Statistics of the Center for Disease Control and Prevention.

Adults aged 20 to 79 years who participated in the 2007–2008, 2009–2010, or 2011–2012 NHANES study cycles were included in the current analysis.

Corresponding author: Juan C. Celedón, MD, DrPH, FAACAP, Division of Pediatric Pulmonary Medicine, Children's Hospital of Pittsburgh of UPMC, 4401 Penn Avenue, Pittsburgh, PA 15224, Phone: 412.692.8429; Fax: 412.692.7636, juan.celedon@chp.edu.

Clinical Implications: Our findings suggest that anxiety influences the pathogenesis of asthma through non-eosinophilic mediated mechanisms.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Depression was measured using the 9-item Patient Health Questionnaire (PHQ-9), a self-administered screening instrument with questions about the frequency of depressive symptoms over the past 2 weeks⁶. Response categories for the 9-item instrument were scored from 0 to 3 (0="not at all," 1="several days," 2="more than half the days," and 3="nearly every day"). The total PHQ-9 score is based on the sum of the points for each question, and thus ranges from 0 to 27. Depression severity was classified as minimal (PHQ-9 score <5), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (≥ 20). A PHQ-9 score of 15 or higher (comprising moderately severe to severe depression) is consistent with major depression⁶. NHANES participants were also asked the number of days that they had felt worried, tense, or anxious in the previous 30 days. As in previous work³, anxiety symptoms (which can accompany depression) were then categorized as binary (at or above the upper quartile [7 days] vs the lowest 3 quartiles [≤ 6 days]) for the number of days feeling anxious in the previous month. Current asthma was defined as having been diagnosed with asthma by a doctor or health professional and still having asthma. Subjects with current asthma were classified as having eosinophilic and non-eosinophilic asthma according to peripheral blood eosinophils ≥ 4% vs. < 4%, respectively. Controls were participants without current asthma.

Primary sampling units and strata for the complex NHANES survey design were taken into account for data analysis. Sampling weights, stratification, and clusters provided in the NHANES data set were incorporated into the analysis to obtain proper estimates and their standard errors. Wald chi-square tests and t-tests were used for bivariate analyses. Logistic regression was used for the multivariable analysis of depression or anxiety and non-eosinophilic or eosinophilic asthma. All models were adjusted for age, gender, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other), and annual household income (< vs. ≥ \$20,000 per year). Other covariates considered for inclusion in the multivariate models were educational attainment [<12th grade (includes 12th grade without diploma), completed high school or had a graduate education diploma, completed some college or an Associate in Arts degree, and college degree or higher], health insurance, family history of asthma, body mass index (BMI), smoking status (never, former, or current), and pack-years of smoking. Covariates that were significant at $P < 0.05$ or that changed the effect estimate (the odds ratio) by ≥ 10% were retained in the final models. All statistical analyses were conducted using the SAS SURVEY procedure and SAS 9.4 software (SAS Institute Inc., Cary, NC).

There were 14,076 adults aged 20–79 years who completed the PHQ-9 and anxiety questions, and who could be classified as controls or having non-eosinophilic vs. eosinophilic asthma. The main characteristics of the study participants are presented in Table 1. Compared with controls (n=12,969), participants with non-eosinophilic asthma (n=800) were significantly more likely to be female, non-Hispanic white, and current smokers, and to have: health insurance coverage, family history of asthma, lower annual income and educational level, a higher BMI, anxiety, more pack-years of smoking, and more severe depressive symptoms than controls. Similar findings were obtained when comparing subjects with eosinophilic asthma (n=307) with controls.

Table 2 shows the results of the multivariable analysis of the variables (depressive symptoms, major depression, and anxiety) and outcomes (non-eosinophilic and eosinophilic asthma) of interest. In this analysis, participants with mild to severe depressive symptoms had significantly higher odds of non-eosinophilic asthma than those with minimal or no depressive symptoms (**Model 1**, *P* for linear trend <0.01). Anxiety (**Model 2**) and major depression (**Model 3**) were each significantly associated with 1.4–1.7 times increased odds of non-eosinophilic asthma. Moreover, both major depression and anxiety were independently associated with 1.3–1.5 times increased odds of non-eosinophilic asthma when included in the same model (**Model 4**).

Table 2 shows that neither depressive symptoms nor major depression were significantly associated with eosinophilic asthma (**models 1, 3 and 4**), but that the magnitude of the associations was similar to those for non-eosinophilic asthma. Thus, the non-significant findings for eosinophilic asthma are likely due to smaller sample size. In contrast, the magnitude and significance of the association between anxiety and eosinophilic asthma were markedly lower than those for non-eosinophilic asthma (i.e. odds ratio of ~1, **models 2 and 4**). Similar results were obtained in a confirmatory analysis defining eosinophilic and non-eosinophilic asthma by using peripheral blood eosinophil counts of ≥ 300 and < 300 cells/ μ L, respectively (data not shown).

We further examined whether depression or anxiety was associated with peripheral blood eosinophilia ($\geq 4\%$) among the 1,107 participants with asthma (Table E1). In this analysis, anxiety was significantly associated with 0.67 times decreased odds of eosinophilia among subjects with asthma. Neither depressive symptoms nor major depression were significantly associated with eosinophilia.

We cannot assess temporal relationships in this cross-sectional study, and lack data on sputum eosinophils or antidepressant use (to further classify asthma or depression). Moreover, we had limited statistical power to detect a significant association between depression and eosinophilic asthma. Nonetheless, our overall findings suggest that depression is linked to both eosinophilic and non-eosinophilic asthma, but that anxiety is only linked to non-eosinophilic asthma. Longitudinal studies should help define whether and how anxiety affects non-eosinophilic asthma, including its sub-phenotypes (e.g., neutrophilic, obesity-related, pauci-granulocytic, and environmentally-induced)⁷.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Declaration of funding and conflicts of interest: Dr. Forno's contribution was supported by grants from the U.S. National Institutes of Health (NIH, HL125666), Children's Hospital of Pittsburgh, and the Klosterfrau Foundation. Dr. Celedón's contribution was supported by grants from the U.S. NIH (HL117191, HL119952, and MD011764). Dr. Celedón has received research materials from Merck and GSK (inhaled steroids), and Pharmavite (vitamin D and placebo capsules), to provide medications at no cost to participants in NIH-funded studies, unrelated to the current work. The other authors report no conflicts of interest.

References

1. <https://www.cdc.gov/nchs/data/databriefs/db303.pdf>. Accessed on May 2 of 2018.
2. Wong KO, Hunter Rowe B, Douwes J, Senthilselvan A. Asthma and wheezing are associated with depression and anxiety in adults: an analysis from 54 countries. *Pulmonary medicine*. 2013;2013:929028. [PubMed: 23577252]
3. Han YY, Forno E, Marsland AL, Miller GE, Celedon JC. Depression, asthma, and bronchodilator response in a nationwide study of US adults. *J Allergy Clin Immunol Pract*. 2016;4(1):68–73 e61. [PubMed: 26563676]
4. Rosenkranz MA, Esnault S, Christian BT, Crisafi G, Gresham LK, Higgins AT, et al. Mind-body interactions in the regulation of airway inflammation in asthma: A PET study of acute and chronic stress. *Brain Behav Immun* 2016; 58:18–30. [PubMed: 27039241]
5. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey (NHANES) Survey Methods and Analytic Guidelines. 2018; <https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx>. Accessed April 30, 2018.
6. Kroenke K, Spitzer RL. The PHQ-9: a new depression and diagnostic severity measure. *Psych Annals*. 2002;32:509–521.
7. Carr TF, Zeki AA, Kraft M. Eosinophilic and noneosinophilic Asthma. *Am J Respir Crit Care Med* 2018;197(1):22–37. [PubMed: 28910134]

Table 1-

Characteristics of study participants by asthma status, NHANES 2007–2012

Characteristics	Controls n=12,969	Non-eosinophilic asthma n=800	Eosinophilic asthma n=307
Age (years)	45.7 ± 0.4	45.5 ± 0.7	48.5 ± 1.1 [‡]
Male gender	6608 (50.4)	270 (33.8) [‡]	135 (45.5)
Race/ethnicity			
Non-Hispanic white	5538 (68.1)	386 (70.3) [‡]	153 (74.3) [‡]
Non-Hispanic Black	2792 (11.0)	209 (14.2)	75 (12.5)
Mexican American/other Hispanic	3570 (14.3)	149 (9.3)	62 (10.1)
Other	1069 (6.6)	56 (6.1)	17 (3.1)
Education			
< 12 th grade (includes 12 th grade without diploma)	3416 (17.3)	225 (18.8) [‡]	90 (20.1)
High school/GES/AA	6653 (53.5)	437 (58.3)	155 (49.5)
College and above	2889 (29.2)	138 (22.9)	62 (30.3)
Had health insurance coverage	9537 (79.1)	650 (84.5) [‡]	253 (83.1)
Annual household income \$20,000	2643 (13.9)	254 (23.9) [‡]	97 (23.2) [‡]
Body mass index (BMI, kg/m ²)	28.7 ± 0.1	31.0 ± 0.3 [‡]	30.4 ± 0.6 [‡]
Smoking status			
Never	7089 (55.0)	376 (48.6) [‡]	132 (44.2) [‡]
Former	3011 (23.9)	190 (23.3)	97 (35.5)
Current	2862 (21.1)	234 (28.1)	78 (20.2)
Pack-years of smoking	7.7 ± 0.4	11.3 ± 1.1 [‡]	10.7 ± 1.5 [‡]
Family history of asthma	2300 (17.8)	347 (42.6) [‡]	128 (44.8) [‡]
Peripheral blood eosinophils (cells/μL)	194.7 ± 1.9	166 ± 4.1 [‡]	450 ± 16.6 [‡]
Peripheral blood eosinophils (percent, %)	2.8 ± 0.02	2.2 ± 0.05 [‡]	6.3 ± 0.2 [‡]
Felt anxious 7 days in the past 30 days	3219 (25.3)	340 (38.7) [‡]	108 (28.7)
PHQ-9 score	2.9 ± 0.1	4.9 ± 0.2 [‡]	4.4 ± 0.5 [‡]
Depression severity [*]			
Minimal	9901 (66.1)	448 (61.3) [‡]	178 (65.2) [‡]
Mild	1927 (12.17)	190 (21.6)	67 (20.9)
Moderate	724 (4.0)	82 (9.1)	33 (6.9)
Moderately severe	303 (1.6)	55 (5.9)	19 (4.1)
Severe	114 (0.6)	25 (2.1)	10 (2.9)

Results are shown as mean ± standard error (SE) for continuous variables, and as N (%) for binary variables.

^{*} Depression severity is defined using the Patient Health Questionnaire-9 (PHQ-9) score: 0–4=minimal; 5–9=mild; 10–14=moderate; 15–19=moderately severe, 20=severe

[‡] P<0.05 or

[‡]P<0.01 for the comparison between subjects with non-eosinophilic or eosinophilic asthma and controls.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2 –

Multivariable analyses of depression or anxiety and asthma (non-eosinophilic and eosinophilic) in the 2007–2012 NHANES

	Model 1	Model 2	Model 3	Model 4
Odds ratio (95% CI), two-sided P-value				
Non-eosinophilic asthma (n=800) *				
Depression severity				
Minimal	1.0	-	-	-
Mild	1.54 (1.16, 2.05)[†]			
Moderate	1.68 (1.17, 2.41)[†]			
Major depression **	2.05 (1.44, 2.91)[†]			
Anxiety	-	1.41 (1.10, 1.80)[†]	-	1.34 (1.03, 1.74)[†]
Major depression *	-	-	1.74 (1.24, 2.44)[†]	1.49 (1.02, 2.18)[†]
Eosinophilic asthma (n=307) *				
Depression severity				
Minimal	1.0			
Mild	1.38 (0.83, 2.31)			
Moderate	1.62 (0.96, 2.73)			
Major depression *	1.70 (0.87, 3.32)			
Anxiety		1.03 (0.74, 1.43)	-	0.98 (0.70, 1.36)
Major depression *	-	-	1.51 (0.87, 2.62)	1.53 (0.88, 2.66)

All models adjusted for age, gender, race/ethnicity, annual household income, family history of asthma, body mass index, smoking status, and pack-years of smoking.

* Non-eosinophilic asthma was defined as asthma and <4% eosinophils in peripheral blood; eosinophilic asthma was defined as asthma and ≥4% eosinophils in peripheral blood. Control subjects are the comparison group in all analyses.

** Major depression: Patient Health Questionnaire-9 (PHQ-9) score ≥15

[†]P<0.05

[‡]P<0.01