Depression and Risk of Incident Asthma in Adults

The CARDIA Study

Wendy M. Brunner¹, Pamela J. Schreiner², Akshay Sood³, and David R. Jacobs, Jr.²

¹Asthma Program, Chronic Disease and Environmental Epidemiology Section, Minnesota Department of Health, St. Paul, Minnesota; ²Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota; and ³Department of Internal Medicine, University of New Mexico Health Sciences Center School of Medicine, Albuquerque, New Mexico

Abstract

Rationale: Asthma is associated with depression, but the temporality of the association has not been established.

Objectives: To examine the association between prevalent elevated depressive symptoms and incident asthma, and between prevalent asthma and incident elevated depressive symptoms in a cohort of young and middle-aged adults.

Methods: We examined the longitudinal association between asthma and depressive symptoms bidirectionally in the Coronary Artery Risk Development in Young Adults (CARDIA) cohort. First, 3,614 participants, free of asthma, were classified by elevated depressive symptoms at the CARDIA Year-5 exam ($n = 856$ elevated vs. 2,758 not elevated; ages 23–35 yr) and followed for 20 years to incident asthma. Then, 3,016 participants, free of elevated depressive symptoms, were classified by self-reported current asthma status ($n = 188$ prevalent vs. 2,828 not prevalent) at the CARDIA Year-5 exam and followed for 20 years until onset of elevated depressive symptoms.

Measurements and Main Results: The relative hazard of incident asthma among those with elevated depressive symptoms was 1.26 (95% confidence interval [CI] = 1.02–1.56) after adjustment for covariates. When depressive status was modeled as the total number

of reports of elevated depressive symptoms before the onset of asthma, the adjusted hazard ratio was 1.15 (95% CI = 1.02–1.29). The hazard of incident elevated depressive symptoms for those with asthma was no different than the hazard in those without asthma (adjusted hazard ratio = 0.92; 95% CI = 0.70–1.20).

Conclusions: This longitudinal observational study points to depression as a marker of risk for incident adult-onset asthma. On the other hand, prevalent asthma is not associated with incident adult-onset depression.

Keywords: adult; asthma; depression

At a Glance Commentary

Scientific Knowledge on the Subject: Cross-sectional studies consistently show an association between asthma and depression, but the temporality of this association has not been established.

What This Study Adds to the Field: This longitudinal observational study points to depression as a marker of risk for incident adult-onset asthma. On the other hand, prevalent asthma is not associated with incident adult-onset depression.

Depression is a common mental health condition with 15.7% of U.S. adults reporting having ever been diagnosed with a depressive disorder and 8.7% reporting

current depressive symptoms (1). These figures are consistent with the 2003 National Comorbidity Survey Replication, which found a 16.2% lifetime prevalence of

major depressive disorder and 6.6% prevalence of 12-month major depressive disorder (2). Similarly, asthma affects 39.5 million Americans, including 29.0 million

(Received in original form July 23, 2013; accepted in final form January 21, 2014)

Supported by the National Heart, Lung, and Blood Institute, The Coronary Artery Risk Development in Young Adults Study (CARDIA) contracts HHSN268201300025C, HHSN268201300026C, HHSN268201300027C, HHSN268201300028C, HHSN268201300029C, and HHSN268200900041C.

Author Contributions: W.M.B., P.J.S., and D.R.J. made substantial contributions to conception and design of the study and acquisition of data. W.M.B. performed the data analysis and drafted the article. All four authors made substantial contributions to analysis and interpretation of data, and to critical review and revision of the manuscript.

Correspondence and requests for reprints should be addressed to Wendy M. Brunner, M.S., Ph.D., Chronic Disease and Environmental Epidemiology Section, Minnesota Department of Health, P.O. Box 64882, St. Paul, MN 55164-0882. E-mail: wendy.brunner@state.mn.us

Am J Respir Crit Care Med Vol 189, Iss 9, pp 1044–1051, May 1, 2014

Copyright © 2014 by the American Thoracic Society

Originally Published in Press as DOI: 10.1164/rccm.201307-1349OC on January 23, 2014

Internet address: www.atsjournals.org

adults (3), and 300 million people worldwide (4). The annual U.S. medical expenditure attributable to asthma among adults is about \$18 billion (5). The burden of depression and asthma in the United States is high (6, 7).

Cross-sectional studies consistently show an association between asthma and depression (1, 8–12); however, temporality of the association has not been established (13). Mental health problems can impact awareness of and adherence to the treatment of asthma; thus, depression is associated with poor asthma control, which can lead to an increase in asthma exacerbations (14–16). A shift in T helper type 2 immune response due to dysregulation of the hypothalamic–pituitary–adrenal axis in response to chronic stress has been cited as a likely biological mechanism by which depression and asthma are causally related (17–19).

The objectives of this study were to examine the association between asthma and depressive symptoms bidirectionally, looking at the association between prevalent elevated depressive symptoms and incident asthma, and the association between prevalent current asthma and incident elevated depressive symptoms in a cohort of young and middle-aged adults. We hypothesized that elevated depressive symptoms predict development of adult-onset asthma and, to a lesser degree, that prevalent asthma is associated with development of elevated depressive symptoms. Some of the results of this analysis have been previously reported in the form of an abstract (20).

Methods

Study Population

The Coronary Artery Risk Development in Young Adults (CARDIA) is a multicenter prospective study of trends and determinants of cardiovascular risk factors from young adulthood. The CARDIA study participants were recruited in 1985–86 at the ages of 18–30 years from the cities of Birmingham, Alabama, Chicago, Illinois, Oakland, California, and Minneapolis, Minnesota. Individuals were randomly selected from census tracts (Chicago and Minneapolis), telephone exchanges (Birmingham), and Kaiser-Permanente membership lists (Oakland). There were

5,115 participants at baseline, with 72% of the surviving cohort participating at Year 25 ($n = 3,499$). Participants returned to the study centers for follow-up examinations at 2, 5, 7, 10, 15, 20, and 25 years after the Year-0 examination. A total of 86% of the cohort attended the Year-5 exam, the starting point for the analyses in the present study. The cohort was designed to be balanced by race (black and white), sex, age, and education (21).

Measurement of Asthma

Asthma history was assessed using the questions, “Have you ever had asthma?,” “Was it confirmed by a doctor?,” and “Do you still have it?” at Years 0 and 2, and “Has a doctor or nurse ever said that you have asthma?” followed by “Have you had this [asthma] in the past year?” at Years 7–25. Asthma history was not queried at Year 5. Asthma medication use was assessed at every examination. Subjects were asked to bring their medications to study visits. Trained study personnel physically verified the medication bottles/inhalers, when available. The medications were then independently reviewed against a pharmaceutical database and multiple respiratory physician experts classified the drugs as asthma related. “Incident asthma” was defined by a new report of asthma medication use and/or self-reported provider diagnosis of asthma (22). “Prevalent current asthma” at Years 0, 2, 7, 10, 15, 20, and 25 was defined as having a provider diagnosis of asthma and reporting either asthma symptoms in the past year or current asthma medication use. “Prevalent current asthma” at Year 5 was based on current asthma medication use only.

Measurement of Depressive Symptoms

Depressive symptoms were measured at Exam Years 5, 10, 15, 20, and 25 using the Center for Epidemiologic Studies Depression Scale (CES-D), a self-administered screening test consisting of 20 items used to evaluate the degree of depressive symptoms in the past 7 days (23). The reliability of this test ranges from 0.85 to 0.90 (23). Each item on the scale ranges from zero to three points, for a maximum of 60, with higher scores indicating a higher degree of depressive symptoms. The items are designed to measure four domains: depressed affect, positive affect, somatic, and interpersonal relations (23). CES-D

scores are not a surrogate for a clinical diagnosis of depression; instead, they are designed to capture dysthymia in nonclinical, population-based studies. CES-D scores of 16 or higher have been validated as a cutoff to indicate major depression, with a 6% false-positive rate, and 36.4% false-negative rate when compared with diagnosis from a structured interview (24).

We also obtained information on antidepressant medication use to capture individuals being treated for depression. Subjects’ medications were cross-referenced with a pharmaceutical database to identify those classified as antidepressants. For this analysis, we defined elevated depressive symptoms as a CES-D score of 16 or higher and/or self-reported antidepressant medication use. We defined incident elevated depressive symptoms as the first report of elevated depressive symptoms. Because CES-D scores were first measured at Year 5, we used Year 5 as the baseline for both of the analyses.

Covariates

The following covariates were examined as potential confounders of the asthma/depressive symptoms association. Sociodemographic data (age, sex, race, education) were collected by questionnaire. Physical activity was assessed by asking how often the participant participated in 13 specific activities during the past year. Frequency of activity was weighted by intensity to come up with an overall physical activity score, expressed in exercise units (25). Smoking status was classified as current, former, or never-smoker. Height (cm) without shoes was measured using a vertical ruler, weight (kg) in light clothing was measured using a calibrated balance beam scale, and body mass index (BMI; kg/m^2) was calculated.

Statistical Methods

Before conducting the bidirectional analyses, we examined the cross-sectional association between prevalent current asthma and depressive symptom status (elevated vs. not elevated) at Years 10, 15, 20, and 25 using logistic regression.

Longitudinal analysis #1: prevalent depressive symptoms as a marker of risk for incident asthma. We classified participants by depressive symptom status (elevated vs. not elevated) at Year 5 and followed to

incident asthma, lost to follow-up, or the Year-25 exam. We included all CARDIA participants having data on depressive symptoms at Year 5 and excluded those who reported a provider diagnosis of asthma at Years 0 or 2, or asthma medication use at Year 5, as well as those missing data on covariates of interest at Year 5.

We modeled the association between depressive symptom status at Year 5 and incident asthma using Cox proportional hazards models, adjusting for covariates. Anticipating that the association between depressive symptoms and incident asthma might be driven by obesity, we also ran this model limited to nonobese participants (i.e., BMI < 30). Because CES-D scores were measured at five exams, we conducted a secondary analysis in which depressive symptom status was allowed to vary by time in an extended Cox model (26). In this “cumulative exposure” model, depressive symptom status was defined as the total number of instances of elevated symptoms before development of asthma.

Longitudinal analysis #2: prevalent current asthma as a marker of risk for incident depressive symptoms. We classified participants by asthma status (prevalent current asthma at any of Exam Years 0, 2, or 5 vs. not prevalent current asthma at Years 0, 2, or 5) and followed them to incident elevated depressive symptoms, lost to follow-up, or the Year 25 exam. We included participants free of elevated depressive symptoms at Year 5 and excluded participants who were missing information on asthma status, depressive symptom status, or other covariates of interest at Year 5.

We calculated the relative hazard of incident elevated depressive symptoms in participants by the presence or absence of prevalent current asthma at Years 0, 2, or 5, adjusting for covariates. Because asthma status was measured at every follow-up exam starting at Year 5, we also modeled asthma status in terms of “cumulative exposure” based on the number of reports of prevalent asthma before development of incident elevated depressive symptoms as a secondary analysis. This allows for asthma to be analyzed as an episodically active disease that can go into periods of remission.

For each analysis, we compared characteristics of the groups at Year 5 using χ^2 test for categorical variables and *t* test for continuous variables. We tested for

Table 1: Odds of Elevated Depressive Symptoms* among Participants with and without Prevalent Current Asthma† by Examination Year

Examination Year	Unadjusted OR (95% CI)	Adjusted OR (95% CI)‡
10	1.52 (1.15–2.01)	1.40 (1.04–1.88)
15	1.57 (1.19–2.08)	1.39 (1.03–1.87)
20	1.91 (1.44–2.51)	1.61 (1.20–2.15)
25	1.82 (1.40–2.37)	1.41 (1.06–1.87)

Definition of abbreviations: CI = confidence interval; OR = odds ratio.

*Center for Epidemiologic Studies Depression Scale (CES-D) score ≥ 16 or antidepressant medication use versus CES-D score < 16 and no antidepressant use.

†Provider diagnosed asthma and current symptoms or asthma medication use.

‡Cross-sectional analysis adjusted for concurrent age, sex, race, study center, smoking status, body mass index, education, and physical activity.

multiplicative interactions by sex and race. Violation of the proportional hazards assumption was tested by examining the interaction of depression symptom status with follow-up time in the first analysis, and

the interaction of asthma status with follow-up time in the second analysis. Two-sided *P* values were used to assess statistical significance. Analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Table 2: Characteristics of Coronary Artery Risk Development in Young Adults Participants without Prevalent Ever-Asthma by Depressive Symptom Status at Year 5 (*n* = 3,614)

	Elevated Depressive Symptoms (<i>n</i> = 856)	Not Elevated Depressive Symptoms (<i>n</i> = 2,758)	<i>P</i> Value
Sex, %			
Female	549 (64.1)	1,457 (52.8)	<0.0001
Male	307 (35.9)	1,301 (47.2)	
Age, mean (SD)	29.8 (3.7)	30.1 (3.6)	0.02
Race, %			
African American	502 (58.6)	1,206 (43.7)	<0.0001
White	354 (41.4)	1,552 (56.3)	
Smoking status, %			
Never-smoker	443 (51.8)	1,666 (60.4)	<0.0001
Former smoker	107 (12.5)	396 (14.4)	
Current smoker	306 (35.7)	696 (25.2)	
BMI			
<25	408 (47.7)	1,479 (53.6)	<0.0001
25–29	237 (27.7)	805 (29.2)	
30+	211 (24.6)	474 (17.2)	
Study center, %			
Birmingham	173 (20.2)	650 (23.6)	0.03
Chicago	178 (20.8)	598 (21.7)	
Minneapolis	274 (32.0)	751 (27.2)	
Oakland	231 (27.0)	759 (27.5)	
Education status, %			
Less than high school	83 (9.7)	129 (4.7)	<0.0001
High school	262 (30.6)	639 (23.2)	
Some college	261 (30.5)	809 (29.3)	
College or more	250 (29.2)	1,181 (42.8)	
Physical activity score, exercise units, mean (SD)	336.5 (267.3)	394.1 (298.9)	<0.0001
Incident asthma, <i>n</i>	130 (15.2)	299 (10.8)	
Person-years of follow up	13,804	46,824	
Unadjusted rate per 1,000 person-years	9.4	6.4	0.0003

Definition of abbreviation: BMI = body mass index.

All CARDIA participants gave informed consent for participation in the cohort. The CARDIA study was approved by the Institutional Review Boards at each of the CARDIA study sites.

Results

We found statistically significant associations between prevalent current asthma and elevated depressive symptom status cross-sectionally without and with adjustment for covariates at Exam Years 10, 15, 20, and 25, as shown in Table 1. That is, participants with prevalent asthma during young adulthood and middle age had 39–61% higher odds of elevated depressive symptoms than those without asthma.

Longitudinal Analysis #1: Prevalent Depressive Symptoms as a Marker of Risk for Incident Asthma

There were 3,614 participants with complete information on Year-5 depressive symptom status who did not have prevalent current asthma at Year 5 (current asthma prevalence was 4.5, 5.2, and 3.5% at Years 0, 2, and 5, respectively). Table 2 lists characteristics of eligible participants by depressive symptom status at Year 5. Elevated depressive symptoms were more likely among participants who were black, female, obese, less educated, less physically active, and among those with incident asthma. Among those with elevated depressive symptom status at Year 5, the incidence rate of asthma was 9.4 per 1,000 person-years compared with 6.4 per 1,000 person-years for those whose depressive symptom status was not elevated.

As shown in Table 3, the relative hazard of incident asthma for those with versus those without elevated depressive symptoms at Year 5 was 1.47 (95% confidence interval [CI] = 1.20–1.81). However, after adjusting for covariates, the hazard ratio (HR) decreased to 1.26 (95% CI = 1.02–1.56).

Sex, BMI, and education were independent predictors of incident asthma in the multivariable model. The analysis was repeated in participants free of prevalent ever-asthma at baseline rather than prevalent current asthma, and the results were unchanged (unadjusted HR = 1.48 [95% CI = 1.18–1.86] and adjusted HR = 1.24 [95% CI = 0.98–1.56]). When the incident asthma analysis was limited to nonobese participants, the adjusted HR was

Table 3: Relative Hazard of Incident Asthma by Depressive Symptom Status ($n = 3,614$)

	Relative Hazard (95% CI)	P Value
Unadjusted model		
Baseline depressive symptom status	1.47 (1.20–1.81)	0.0002
Multivariable model		
Baseline depressive symptom status, adjusted	1.26 (1.02–1.56)	0.03
Age, 4 yr*	0.97 (0.87–1.07)	0.52
Female	1.93 (1.55–2.41)	<0.0001
White	0.95 (0.76–1.18)	0.62
Study center		
Birmingham	Ref.	
Chicago	1.11 (0.83–1.50)	0.49
Minneapolis	1.18 (0.88–1.57)	0.27
Oakland	1.30 (0.99–1.72)	0.06
Smoking status		
Never-smoker	Ref.	
Former smoker	1.18 (0.94–1.49)	0.41
Current smoker	1.23 (0.85–1.50)	0.15
BMI		
<25	Ref.	
25–29	1.19 (0.95–1.50)	0.14
30+	1.41 (1.10–1.81)	0.01
Education		
<High school	Ref.	
High school	0.74 (0.51–1.09)	0.13
Some college	0.64 (0.43–0.95)	0.03
College or more	0.66 (0.44–0.99)	0.05
Physical activity score, 299 exercise units*	0.999 (0.90–1.11)	0.99

Definition of abbreviations: BMI = body mass index; CI = confidence interval.

*One SD.

1.28 (95% CI = 1.00–1.65). The Cox proportional hazards assumption—that the HR is constant over time—was not violated in this analysis ($P = 0.35$). Interactions by race ($P = 0.58$) and sex ($P = 0.32$) were also not statistically significant.

Using the cumulative exposure model, which weights depressive symptom status by the number of reports, the unadjusted HR was 1.25 (95% CI = 1.12–1.39; Table 4). After adjusting for the same covariates listed above, the HR decreased to 1.15 (95% CI = 1.02–1.29), but remained statistically significant.

To assess the impact of missing asthma cases at Year 5, we conducted a sensitivity analysis using reports of asthma at Year 7 and age at diagnosis to impute asthma status at Year 5 (i.e., using age at diagnosis to identify those individuals who developed asthma between the Year-2 and the Year-5 exams). The results from this sensitivity analysis in which 15 additional asthma cases were excluded at baseline ($n = 3,550$; unadjusted HR = 1.59 [95% CI = 1.25–2.03]; and adjusted HR = 1.30 [95% CI = 1.01–1.67]) did not differ substantially from the results

Table 4: Relative Hazard of Incident Asthma by Time-Varying Depressive Symptom Status ($n = 3,614$)

Cumulative Exposure Model	Relative Hazard (95% CI)	P Value
Depressive symptom status, unadjusted	1.25 (1.12–1.39)	<0.0001
Depressive symptom status, adjusted*	1.15 (1.02–1.29)	0.02

Definition of abbreviation: CI = confidence interval.

*Adjusted for age, sex, race, study center, smoking status, body mass index, education, and physical activity.

Table 5: Characteristics of Coronary Artery Risk Development in Young Adults Study Participants by Asthma Status at Year 5 Examination among Participants without Elevated Depressive Symptoms (*n* = 3,016)

	Prevalent Current Asthma (<i>n</i> = 188)	Not Prevalent Current Asthma (<i>n</i> = 2,828)	<i>P</i> Value
Sex, <i>n</i> (%)			
Female	116 (61.7)	1,504 (53.2)	0.02
Male	72 (38.3)	1,324 (46.8)	
Age, mean (SD)	30.0 (3.6)	30.1 (3.6)	0.69
Race, <i>n</i> (%)			
African American	90 (47.9)	1,237 (43.7)	0.27
White	98 (52.1)	1,591 (56.3)	
Smoking status, <i>n</i> (%)			
Current smoker	49 (26.1)	714 (25.3)	0.30
Former smoker	34 (18.1)	405 (14.3)	
Never-smoker	105 (55.9)	1,709 (60.4)	
BMI			
<25	85 (45.2)	1,520 (53.8)	0.004
25–29	53 (28.2)	820 (29.0)	
30+	50 (26.6)	488 (17.3)	
Study center, <i>n</i> (%)			
Birmingham	31 (16.5)	662 (23.4)	0.02
Chicago	35 (18.6)	621 (22.0)	
Minneapolis	53 (28.2)	755 (26.7)	
Oakland	69 (36.7)	790 (27.9)	
Education, <i>n</i> (%)			
Less than high school	9 (4.8)	134 (4.7)	0.76
High school	49 (26.1)	648 (22.9)	
Some college	55 (29.3)	830 (29.4)	
College or more	75 (39.9)	1,216 (43.0)	
Physical activity score, exercise units, mean (SD)	360.6 (290.1)	391.1 (299.1)	0.18
Incident elevated depressive symptoms, <i>n</i> (%)	55 (29.3)	848 (30.0)	
Person-years of follow-up	3,205	47,995	
Unadjusted rate per 1,000 person-years	17.2	17.7	0.83

For definition of abbreviation, see Table 2.

that were based on using medications only to define asthma status at Year 5 in Table 3.

Longitudinal Analysis #2: Prevalent Current Asthma as a Marker of Risk for Incident Depressive Symptoms

There were 3,016 participants with complete information on Year-5 asthma status who were free of elevated depressive symptoms at Year 5. Table 5 lists the characteristics of eligible participants by asthma status at Year 5. Asthma status at Year 5 differed significantly only by study center. Among those with prevalent current asthma at Year 5, the unadjusted incidence rate of elevated depressive symptoms was 17.2 per 1,000, and among participants without asthma, the rate was 17.7 per 1,000.

Interactions by sex (*P* = 0.95) and race (*P* = 0.25) were not statistically significant. As shown in Table 6, the relative hazard

of developing elevated depressive symptoms for those with versus those without prevalent current asthma at Year 5 was 0.97 (95% CI = 0.74–1.28). There was little difference after adjusting for covariates (HR = 0.92 [95% CI = 0.70–1.20]).

When asthma status was weighted by the number of reports of prevalent current asthma, the HR increased slightly, but was not statistically significant in either the unadjusted (HR = 1.05 [95% CI = 0.97–1.13]) or adjusted (HR = 1.03 [95% CI = 0.95–1.11]) models (Table 7). In a sensitivity analysis, when prevalent ever-asthma was used to define asthma status rather than prevalent current asthma, the results were unchanged, with an unadjusted HR of 0.96 (95% CI = 0.78–1.19) and adjusted HR of 0.92 (95% CI = 0.75–1.14).

Female sex, education, and current smoking were all independent predictors of

incident elevated depressive symptoms after adjustment for the other covariates. The Cox proportional hazards assumption was not violated in this analysis (*P* = 0.89).

Discussion

We observed that prevalent depressive symptoms are a marker of risk for incident asthma, when we defined depressive symptom status as the participant's status at baseline and also when depressive status was weighted by the number of reports of elevated symptoms before incident asthma. Our findings are consistent with two prospective studies that demonstrated an association between prevalent depression and incident asthma. Loerbroks and colleagues (27) found that increasing depressive symptoms and decreasing social support were independently associated with development of asthma in 40- to 65-year-olds with a median of 8.5 years of follow-up. The authors suggest that these associations are more likely to be operating along direct inflammatory pathways rather than indirectly by way of health behaviors. In an examination of the incidence of chronic diseases among people with and without major depression, using data from the Canadian National Population Health Survey, Patten and colleagues (28) reported that having major depression was associated with development of asthma (adjusted HR = 2.1, with 8 yr of follow-up). Interestingly, the authors found a higher incidence of conditions associated with pain, inflammation, and/or autonomic reactivity (i.e., asthma, chronic obstructive pulmonary disease [COPD], and heart disease) among people with major depression, whereas the incidence of cataracts, peptic ulcers, and thyroid disease was not elevated for people with depression. Further, increased psychological stress results in decreased lung function, increased airway inflammation, and poor treatment plan adherence in asthma (16, 29), and, conversely, remission from depression is associated with improved asthma control (30, 31).

Approximately 12% of our study population developed incident asthma over 20 years of follow-up (7.1 per 1,000 person-years). This is consistent with previously published estimates from the CARDIA cohort (10-yr incidence = 5.6% [22]; annual

Table 6: Relative Hazard of Incident Elevated Depressive Symptoms by Asthma Status ($n = 3,016$)

	Relative Hazard (95% CI)	P Value
Unadjusted model		
Prevalent current asthma	0.97 (0.74–1.28)	0.84
Multivariable model		
Prevalent current asthma	0.92 (0.70–1.20)	0.53
Age, 4 yr*	1.07 (0.99–1.15)	0.08
Female	1.51 (1.31–1.74)	<0.0001
White	1.12 (0.97–1.29)	0.13
Study center		
Birmingham	Ref.	
Chicago	0.93 (0.76–1.14)	0.50
Minneapolis	0.97 (0.80–1.17)	0.74
Oakland	1.10 (0.92–1.33)	0.31
Education		
<High school	Ref.	
High school	0.79 (0.60–1.05)	0.11
Some college	0.60 (0.45–0.80)	0.001
College or more	0.50 (0.37–0.67)	<0.0001
Smoking status		
Never-smoker	Ref.	
Current smoker	1.24 (1.06–1.46)	0.01
Former smoker	0.99 (0.81–1.20)	0.89
BMI		
<25	Ref.	
25–29	0.95 (0.81–1.11)	0.51
30+	0.98 (0.82–1.18)	0.83
Physical activity score, 299 exercise units*	0.96 (0.90–1.04)	0.30

For definition of abbreviation, see Table 2.

*One SD.

incidence rate = 1.4% for women and 0.8% for men [32]), but higher than estimates for 2006–2008 from the Centers for Disease Control and Prevention for states participating in the Asthma Call-Back Survey (annual adult asthma incidence rate = 3.8/1,000) (33). This difference may be related to the disproportionately high percentages of black and obese individuals in CARDIA. These subpopulations are at particularly high risk for adult-onset asthma (32). The Black Women's Health Study reported incidence rates of 4.7 per 1,000 person-years when incident asthma was defined

as new onset of self-reported physician diagnosis and asthma medication use at least 3 d/wk, and 9.2 per 1,000 person-years when the definition did not require medication use (34).

We did not find evidence for an association between prevalent asthma and subsequent development of depressive symptoms. Asthma is an intermittent illness, and most participants in our community-based study had intermittent or mild persistent disease (35). It is possible that prevalent severe persistent asthma is associated with subsequent development of depression. It is also possible that our

cohort was not old enough (ages 23–35 yr at Year 5 through 43–55 yr at Year 25) to see an independent depressive effect for asthma. In a community sample of older people (ages 55–85 yr), Bisschop and colleagues (36) found that chronic respiratory disease was associated with an increase in depressive symptoms (as measured by CES-D scores) over 6 years of follow up. In a longitudinal study of adults with asthma (mean age = 44 yr), Katz and colleagues (37) showed that people with asthma who perceived low control of their disease were more likely than people with higher perceived control to develop depressive symptoms.

The mechanism by which depression may “cause” asthma is unclear. Although multiple pathways have been hypothesized, central nervous system, autonomic nervous system, shared comorbidities and exposures, inflammatory, and neuroendocrine mechanisms are thought to be likely (19). One potential central nervous system pathway involves the insular and anterior cingulate cortices (i.e., brain regions implicated in the regulation of emotion) that influence the development and persistence of symptom expression in asthma via changes in airway efferent neural activity (38). Others have suggested that depression is associated with autonomic dysregulation in the form of cholinergic activation, which, in turn, leads to airway constriction (39–41). Conversely, happiness affects autonomic patterns that may relieve airway constriction (41). It has also been suggested that the association between depression and incident asthma may be explained by either a shared comorbidity, such as obesity, or a shared environmental exposure, such as cigarette smoking (19, 42). These explanations, however, are unlikely, as our findings persist when the analysis is limited to nonobese participants or when BMI and/or smoking are included as covariates in our multivariable analyses. We are, however, unable to examine the effect of *in utero* cigarette smoke exposure, which is a risk factor for both depression and asthma in the offspring (43, 44). Depression is also associated with high systemic levels of inflammatory cytokines, particularly TNF- α , which, in turn, has a pathogenic role in asthma (45, 46). Finally, a potential neuroendocrine mechanism involves depression-related alteration in the hypothalamic–pituitary–adrenal axis that

Table 7: Relative Hazard of Incident Elevated Depressive Symptoms by Time-Varying Asthma Status ($n = 3,016$)

Cumulative Exposure Model	Relative Hazard (95% CI)	P Value
Asthma status, unadjusted	1.05 (0.97–1.13)	0.26
Asthma status, adjusted*	1.03 (0.95–1.11)	0.46

For definition of abbreviation, see Table 4.

*Adjusted for age, sex, race, study center, smoking status, body mass index, education, and physical activity.

results in endogenous glucocorticoid resistance. This, in turn, could increase vulnerability to asthma onset by biasing the immune system toward a T helper type 2 response (47, 48). Although this neuroendocrine mechanism is unconfirmed, Van Lieshout and colleagues (19) consider it to represent the most plausible causal link between the two conditions.

The major strength of this study is the ability to examine the temporality of the association between asthma and depressive symptoms over a 20-year period. Further strengths include the large sample size, many years of follow-up with good retention, and the availability of data on potential confounders, such as obesity and smoking. Finally, having repeated measurements of depressive symptoms and asthma status allowed for a more complete exposure history in each analysis.

A potential limitation involves our incident asthma definition that was based on self-reported provider-diagnosed asthma, which may have misclassification bias, as compared with objective tests. However, self-reported asthma has been shown to be valid in epidemiologic studies when the question asks about physician diagnosis (49). Furthermore, this misclassification of asthma diagnosis is likely nondifferential

(50). Asthma self-report may include early COPD, particularly among smokers, resulting in artificially high rates of incident asthma. This is an unlikely explanation, because most subjects in CARDIA had normal spirometric data (35). Excluding subjects with asthma with normal spirometry and focusing on only those with abnormal spirometry would decrease the power of the study and increase the potential of misclassification related to COPD, particularly in later years. Furthermore, recall bias may misclassify age of onset of disease and erroneously classify pediatric disease on recrudescence as incident adult-onset disease. However, 95.2% of subjects with asthma consistently classified their disease onset status at subsequent examination visits (32). There could have been recall bias for asthma by depression status (i.e., those with elevated depressive symptoms could be more likely to report asthma onset).

Recall bias related to the medication component of the asthma definitions was minimized by trained research assistants verifying pill containers and inhalers. Similarly, antidepressant medications were verified; however, it is possible that reported medications classified as antidepressants in the pharmaceutical database could have

been used for purposes other than treating depression.

The CARDIA cohort may not be representative of the U.S. population, but is still a relevant cohort, because it is representative of urban and suburban populations in the United States. Although the degree of asthma in a cohort study may not be severe, it represents how asthma and depressive symptoms relate in a large number of community-dwelling individuals.

Conclusions

This observational study, with 20 years of follow up, provides evidence that chronic depressive symptoms are associated with the development of adult-onset asthma in middle-aged adults. Thus, it is important for health care providers to be aware of the potential for new-onset asthma in their patients with depression. It is also possible that controlling depression may lead to newer preventative strategies for asthma in adults. There was no evidence for an association between prevalent current asthma in young adults and incident elevated depressive symptoms through middle age. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1. Strine TW, Mokdad AH, Balluz LS, Gonzalez O, Crider R, Berry JT, Kroenke K. Depression and anxiety in the United States: findings from the 2006 Behavioral Risk Factor Surveillance System. *Psychiatr Serv* 2008;59:1383–1390.
2. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS; National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 2003;289:3095–3105.
3. American Lung Association. Trends in asthma morbidity and mortality. 2012 [accessed 2013 Oct 28]. Available from: <http://www.lungusa.org/finding-cures/our-research/trend-reports/asthma-trend-report.pdf>
4. World Health Organization. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach. 2007 [accessed 2013 Oct 28]. Available from: http://www.who.int/gard/publications/GARD_Manual/en/index.html
5. Sullivan PW, Ghushchyan VH, Slejko JF, Belozeroff V, Globe DR, Lin SL. The burden of adult asthma in the United States: evidence from the Medical Expenditure Panel Survey. *J Allergy Clin Immunol* 2011;127:363–369.e1–3.
6. Gotlib IH, Hammen CL, eds. Handbook of depression, 2nd ed. New York: Guilford Press; 2009.
7. Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson CA, Liu X. Trends in asthma prevalence, health care use, and mortality in the United States, 2001–2010. *NCHS Data Brief* 2012;(94):1–8.
8. Ortega AN, Feldman JM, Canino G, Steinman K, Alegria M. Co-occurrence of mental and physical illness in US Latinos. *Soc Psychiatry Psychiatr Epidemiol* 2006;41:927–934.
9. Rubin NJ. Severe asthma and depression. *Arch Fam Med* 1993;2:433–440.
10. Goldney RD, Ruffin R, Fisher LJ, Wilson DH. Asthma symptoms associated with depression and lower quality of life: a population survey. *Med J Aust* 2003;178:437–441.
11. Rimington LD, Davies DH, Lowe D, Pearson MG. Relationship between anxiety, depression, and morbidity in adult asthma patients. *Thorax* 2001;56:266–271.
12. Loerbroeks A, Herr RM, Subramanian S, Bosch JA. The association of asthma and wheezing with major depressive episodes: an analysis of 245,727 women and men from 57 countries. *Int J Epidemiol* 2012;41:1436–1444.
13. Mannino DM. Doc, my asthma (depression) has gotten me down (wheezing). *Chest* 2008;134:1116–1117.
14. Strine TW, Mokdad AH, Balluz LS, Berry JT, Gonzalez O. Impact of depression and anxiety on quality of life, health behaviors, and asthma control among adults in the United States with asthma, 2006. *J Asthma* 2008;45:123–133.
15. Opolski M, Wilson I. Asthma and depression: a pragmatic review of the literature and recommendations for future research. *Clin Pract Epidemiol Ment Health* 2005;1:18.
16. Cluley S, Cochrane GM. Psychological disorder in asthma is associated with poor control and poor adherence to inhaled steroids. *Respir Med* 2001;95:37–39.
17. Chun TH, Weitzen SH, Fritz GK. The asthma/mental health nexus in a population-based sample of the United States. *Chest* 2008;134:1176–1182.
18. Scott KM, Von Korff M, Ormel J, Zhang MY, Bruffaerts R, Alonso J, Kessler RC, Tachimori H, Karam E, Levinson D, et al. Mental disorders among adults with asthma: results from the World Mental Health Survey. *Gen Hosp Psychiatry* 2007;29:123–133.

19. Van Lieshout RJ, Bienenstock J, MacQueen GM. A review of candidate pathways underlying the association between asthma and major depressive disorder. *Psychosom Med* 2009;71:187–195.
20. Brunner W, Schreiner P, Jacobs D, Sood A. Association between asthma and depressive symptoms in the Coronary Artery Risk Development in Young Adults (CARDIA) Cohort [abstract]. *Am J Epidemiol* 2012;175:S130.
21. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR Jr, Liu K, Savage PJ. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol* 1988;41:1105–1116.
22. Beckett WS, Jacobs DR Jr, Yu X, Iribarren C, Williams OD. Asthma is associated with weight gain in females but not males, independent of physical activity. *Am J Respir Crit Care Med* 2001;164:2045–2050.
23. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1977;1:385–401.
24. Myers JK, Weissman MM. Use of a self-report symptom scale to detect depression in a community sample. *Am J Psychiatry* 1980;137:1081–1084.
25. Sidney S, Jacobs DR Jr, Haskell WL, Armstrong MA, Dimicco A, Oberman A, Savage PJ, Slattery ML, Sternfeld B, Van Horn L. Comparison of two methods of assessing physical activity in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Epidemiol* 1991;133:1231–1245.
26. Kleinbaum DG, Klein M. Survival analysis: a self-learning text. New York: Springer; 2005.
27. Loerbroks A, Apfelbacher CJ, Bosch JA, Stürmer T. Depressive symptoms, social support, and risk of adult asthma in a population-based cohort study. *Psychosom Med* 2010;72:309–315.
28. Patten SB, Williams JV, Lavorato DH, Modgill G, Jetté N, Eliasziw M. Major depression as a risk factor for chronic disease incidence: longitudinal analyses in a general population cohort. *Gen Hosp Psychiatry* 2008;30:407–413.
29. Liu LY, Coe CL, Swenson CA, Kelly EA, Kita H, Busse WW. School examinations enhance airway inflammation to antigen challenge. *Am J Respir Crit Care Med* 2002;165:1062–1067.
30. Brown ES, Vigil L, Khan DA, Liggin JD, Carmody TJ, Rush AJ. A randomized trial of citalopram versus placebo in outpatients with asthma and major depressive disorder: a proof of concept study. *Biol Psychiatry* 2005;58:865–870.
31. Lechin F, van der Dijs B, Orozco B, Jara H, Rada I, Lechin ME, Lechin AE. Neuropharmacologic treatment of bronchial asthma with the antidepressant tianeptine: a double-blind, crossover placebo-controlled study. *Clin Pharmacol Ther* 1998;64:223–232.
32. Sood A, Qualls C, Schuyler M, Arynchyn A, Alvarado JH, Smith LJ, Jacobs DR Jr. Adult-onset asthma becomes the dominant phenotype among women by age 40 years: the longitudinal CARDIA study. *Ann Am Thorac Soc* 2013;10:188–197.
33. Winer RA, Qin X, Harrington T, Moorman J, Zahran H. Asthma incidence among children and adults: findings from the Behavioral Risk Factor Surveillance system asthma call-back survey—United States, 2006–2008. *J Asthma* 2012;49:16–22.
34. Coogan PF, Yu J, O'Connor GT, Brown TA, Cozier YC, Palmer JR, Rosenberg L. Experiences of racism and the incidence of adult-onset asthma in the Black Women's Health Study. *Chest* [published ahead of print] 25 Jul 2013; DOI: 10.1378/chest.13–665.
35. Sood A, Dominic E, Qualls C, Steffes MW, Thyagarajan B, Smith LJ, Lewis CE, Jacobs DR Jr. Serum adiponectin is associated with adverse outcomes of asthma in men but not in women. *Front Pharmacol* 2011;2:55.
36. Bisschop MI, Kriegsman DM, Deeg DJ, Beekman AT, van Tilburg W. The longitudinal relation between chronic diseases and depression in older persons in the community: the Longitudinal Aging Study Amsterdam. *J Clin Epidemiol* 2004;57:187–194.
37. Katz PP, Morris A, Julian L, Omachi T, Yelin EH, Eisner MD, Blanc PD. Onset of depressive symptoms among adults with asthma: results from a longitudinal observational cohort. *Prim Care Respir J* 2010;19:223–230.
38. Rosenkranz MA, Davidson RJ. Affective neural circuitry and mind-body influences in asthma. *Neuroimage* 2009;47:972–980.
39. Galil N. Depression and asthma in children. *Curr Opin Pediatr* 2000;12:331–335.
40. Janowsky DS, el-Yousef MK, Davis JM. Acetylcholine and depression. *Psychosom Med* 1974;36:248–257.
41. Miller BD, Wood BL. Influence of specific emotional states on autonomic reactivity and pulmonary function in asthmatic children. *J Am Acad Child Adolesc Psychiatry* 1997;36:669–677.
42. Goodwin RD, Bandiera FC, Steinberg D, Ortega AN, Feldman JM. Asthma and mental health among youth: etiology, current knowledge and future directions. *Expert Rev Respir Med* 2012;6:397–406.
43. Wu LT, Anthony JC. Tobacco smoking and depressed mood in late childhood and early adolescence. *Am J Public Health* 1999;89:1837–1840.
44. Ng SP, Zelikoff JT. Smoking during pregnancy: subsequent effects on offspring immune competence and disease vulnerability in later life. *Reprod Toxicol* 2007;23:428–437.
45. Berry MA, Hargadon B, Shelley M, Parker D, Shaw DE, Green RH, Bradding P, Brightling CE, Wardlaw AJ, Pavord ID. Evidence of a role of tumor necrosis factor alpha in refractory asthma. *N Engl J Med* 2006;354:697–708.
46. Khairova RA, Machado-Vieira R, Du J, Manji HK. A potential role for pro-inflammatory cytokines in regulating synaptic plasticity in major depressive disorder. *Int J Neuropsychopharmacol* 2009;12:561–578.
47. Pariante CM, Miller AH. Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biol Psychiatry* 2001;49:391–404.
48. Sternberg EM. Neuroendocrine regulation of autoimmune/inflammatory disease. *J Endocrinol* 2001;169:429–435.
49. Torén K, Brisman J, Järnholm B. Asthma and asthma-like symptoms in adults assessed by questionnaires: a literature review. *Chest* 1993;104:600–608.
50. Aaron SD, Vandemheen KL, Boulet LP, McIvor RA, Fitzgerald JM, Hernandez P, Lemiere C, Sharma S, Field SK, Alvarez GG, et al.; Canadian Respiratory Clinical Research Consortium. Overdiagnosis of asthma in obese and nonobese adults. *CMAJ* 2008;179:1121–1131.