Asthma and Panic in Young Adults
A 20-Year Prospective Community Study

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Rationale: **Psychologic factors are increasingly recognized to influence the onset and course of asthma. Previous cross-sectional community-based studies have provided evidence for a relatively specific association between asthma and panic.** ***Objectives:*** **To examine concurrent and longitudinal associations between asthma and panic in young adults.** ***Measurements and Main Results:*** **Prospective community-based cohort study of young adults (n = 591) followed between ages 19 and 40. Information was derived from six subsequent semi-structured diagnostic interviews conducted by professionals. Cross-sectionally (over the whole study period), asthma was more strongly associated with panic disorder (odds ratio [OR] = 4.0; 95% confidence interval [CI], 1.7, 9.3) than with any panic, which included panic disorder and panic attacks (OR = 2.1; 95% CI, 1.1, 4.5). Longitudinally, after adjusting for potentially confounding variables, active asthma predicted subsequent panic disorder (OR = 4.5; 95% CI, 1.1, 20.1), and the presence of panic disorder predicted subsequent asthma activity (OR = 6.3; 95% CI, 2.8, 14.0). Asthma predicted any panic (OR = 2.7; 95% CI, 1.1, 7.1), whereas any panic did not predict subsequent asthma activity. Associations were stronger in smokers than in nonsmokers, and stronger in women than in men. Smoking, early-childhood anxiety, and a family history of allergy were important confounders of the asthma–panic association.** ***Conclusions:*** **This is the first long-term follow-up study on asthma and panic. It showed dose–response-type relationships between panic and asthma, and bidirectional longitudinal associations between the two conditions. It provided evidence for familial factors and smoking as possible shared etiologic explanations.**

Keywords: anxiety; child development; respiratory tract disease; sex; smoking

Asthma is a major health problem, with evidence of rising prevalence over the last several decades (1, 2). Environmental factors, such as indoor allergens and air pollution, play important roles in asthma. Psychologic factors are increasingly recognized to influence the onset and course of asthma. Previous cross-sectional community-based studies have provided evidence for a relatively specific association between the prevalence of asthma and panic (3–6). However, cross-sectional studies have been limited in their ability to increase our understanding of these mechanisms because of very different definitions of panic and lack of information about the temporal association between asthma and panic. To date, only one brief (1 year) longitudinal community-based study on asthma and panic in adults (6) has been published, which reported that asthma increased the risk of panic. Long-term follow-up of community samples is necessary to elucidate potentially causal relationships of comorbid conditions and directionality.

The previous longitudinal study showed that asthma increases the risk of panic (6). Several mechanisms may explain the possible association between asthma and panic. Having asthma, which can be a potentially life-threatening condition, may increase the level of anxiety, which may lead in some vulnerable individuals to panic, possibly through dyspnea-induced fear conditioning and derangement of respiratory receptor set-point (7, 8). Asthma medication can have anxiogenic properties (9), and anxiety may further enhance the use of asthma medication (10). In addition, there is evidence for shared etiologic factors that increase the risk of both asthma and panic (e.g., elevated rates of atopy in the offspring of panic disorder probands) (11). Smoking may be a relatively specific shared risk factor for both asthma and panic. Smoking seems to increase the risk of panic (12), and smoking increases the risk of onset and recurrence of asthma, impairs response to asthma treatment, and worsens the pulmonary long-term outcome in patients with asthma (13–15). Another potentially shared etiologic factor is stress during childhood, which seems to increase risk of onset and recurrence of both asthma and panic (16–20). Associations between panic/fear and increased requests for as-needed medications and treatments (10), with high-frequency emergency room visits for respiratory symptoms (21), and increased asthma-related rehospitalization rates (22) underline the relevance of the asthma–panic comorbidity in clinical practice.

The major goal of this study is to test the hypothesis that asthma is associated with the subsequent occurrence of panic, which is based on a previous longitudinal study (6). Further goals are to explore potential associations between panic and later asthma, and to examine confounders and determinants of asthma–panic associations. Data were derived from the Zurich Cohort Study, which comprises a cohort of 4,547 subjects (2,201 men, 2,346 women) representative of the canton of Zurich in Switzerland, who were assessed in 1978 with a psychologic symptom questionnaire, the Symptom Checklist 90-R (SCL-90-R) (23), and a questionnaire for sociodemographic data. The study is based on a stratified sample with an overrepresentation of risk cases for psychiatric disorders. The diagnostic instrument used in the Zurich study was the Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology (SPIKE), a semistructured interview for psychiatric and medical conditions and health habits, which was developed for epidemiologic studies (24). Health professionals with extensive clinical training administered the SPIKE in the participants' homes (25). Asthma was diagnosed on the basis of self-reported asthmalike symptoms and self-report of physician's asthma diagnosis. Diagnoses of psychiatric disorders were made by algorithms

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based on the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-III*, *DSM-III-R*, and *DSM-IV*) (26, 27). Some of the results of this study were reported in the form of an abstract (28).

METHODS

Sample

To increase the probability of psychiatric disorders, a subsample of 591 subjects (292 men, 299 women) was selected from the screening sample (n = 4,547) for interview, with two-thirds consisting of high scorers (defined by the 85th percentile or more of the SCL-90-R) and a random sample of those with scores below the 85th percentile. Informed consent was obtained from subjects according to the requirements of the Swiss National Science Foundation. The screening took place in 1978 at age 19, the first and second interviews in 1979 and 1981, the third and fourth interviews in 1986 and 1988, the fifth interview in 1993, and the sixth in 1999.

Across 20 years, 62.1% of the follow-up sample (n = 591) continued to participate in the study and the following proportions participated in specific numbers of interviews: 47% in all six interviews, 63% in five interviews, 74% in four interviews, 82% in three interviews, and 91.4% in at least two interviews. Those who had dropped out did not differ significantly from the 1999 participants regarding the risk group at study entry and major variables of this study at baseline, including asthma, allergic rhinitis, panic, other anxiety disorders, major depression, early-childhood anxiety, and smoking (analyzed by χ^2 tests). Women participated more regularly and more frequently in interviews than men, but men showed a higher rate of recurrence to the study ("hoppers") than women (29).

Assessment of Asthma and Allergic Rhinitis

At each interview, subjects were asked about the occurrence of allergic rhinitis, urticaria, eczema, asthma attacks, or asthmalike breathing problems in the last 12 months. In addition, at each interview the participant was asked if a physician had ever given them the diagnosis of asthma. A person was considered to have active asthma at a specific interview if he or she met two criteria: first, reported asthma attacks or asthmalike breathing problems during the 12 months before the interview; second, reported ever receiving physician's diagnosis of asthma at any interview. All subjects diagnosed with asthma also reported treatment by a physician for asthma, and 95.3% of them received antiasthma medication during at least one of the 12-month periods covered by the interviews.

Assessment of Panic and Childhood Anxiety

From information collected at each interview, we classified individuals into two overlapping categories according to *DSM-III* and *DSM-III-R*: (*1*) panic disorder, including subjects who had recurrent unexplained panic attacks (at least one attack/week during 4 subsequent weeks) during the 12 months before the interview, and (*2*) any panic, which included subjects with either panic disorder or panic attacks (30).

At the first interview in 1979, childhood anxiety symptoms were assessed in all subjects of the follow-up sample. Because anxiety symptoms occurring in the first years of life are reported to be associated with atopic disorders (11), we defined a binary predictor variable "early-childhood anxiety" as whether or not the subject experienced anxiety symptoms before age 6. The childhood history section of the first interview also assessed several aspects of childhood behavior and emotional functioning retrospectively, including anxious temperament as experienced by subjects and observed by others during school years (31).

Statistical Analyses

Because both asthma and panic are chronic diseases that typically develop in childhood and adolescence (i.e., before the first interview of the present study), we primarily modeled disease activity instead of disease incidence to ensure good reliability and power of the analyses.

To test the hypothesis that asthma is related to later panic, we modeled associations between cumulative exposure to asthma and later panic disorder, while controlling for potentially confounding variables of the asthma–panic comorbidity. To test for a dose–response type of relationship, we alternatively used any panic (including panic disorder and panic attacks) as outcome variable. To explore the relationship between panic and later asthma, we used the same model with panic as a time-varying predictor variable and asthma as an outcome variable. To account for the correlated outcomes from longitudinal observations on the same subject, we calculated robust estimates of repeated measures by generalized estimating equations (32) with subject as cluster, and a first-order autoregressive within-cluster correlation structure. Time-variant and time-invariant covariates were selected on the basis of previous studies on respiratory illness/asthma and panic (7, 12, 33–39). Sex and regular smoking (smoking daily or almost daily) were selected as potential effect modifiers (40, 41), and all multivariate analyses were conducted on the whole sample, on men and women separately, and on smokers and nonsmokers separately. To evaluate for the impact of missing data on the results, we fit multivariate models that included only subjects who had participated in all interviews. This led to some minor changes in the model parameter estimates, which did not alter the interpretation of the results.

To estimate stability and predictive associations between asthma and panic across subsequent interviews, we applied five log-linear models, including four binary disease variables (asthma and any panic) and their six two-way interactions from two adjacent waves. This analytic strategy is described in greater detail in another article on the Zurich Cohort Study (42). SAS for Windows, release 8.02 (SAS Institute, Inc., Cary, NC), was used for all statistical analyses. The macro COLLIN from SAS-L was used to calculate collinearity diagnostics from a variance–covariance matrix of the generalized estimating equation models (43).

RESULTS

Cross-sectional Comorbidity of Asthma and Panic

In the stratified study sample with an overrepresentation of risk cases for psychiatric disorders, the 12-month prevalence of active asthma increased from 1.9% at the 1979 interview to 4.6% at the 1999 interview, whereas panic disorder ranged from 1.1 to 2.8% with no apparent pattern (Table 1). Despite these different annual patterns, the 20-year cumulative prevalence of asthma (7.3%) and panic disorder (7.8%) were similar, whereas any panic was almost three times as high at 20.5%. As expected, subjects of the SCL-90-R high-scorer sample had an increased risk for panic disorder (odds ratio [OR] = 5.5; 95% confidence interval [CI], 3.6–8.5), whereas scoring high on the SCL-90-R at baseline was not associated with having asthma at baseline (OR = 0.9; 95% CI, 0.5–1.4) or developing asthma during the study period (OR = 0.8; 95% CI, 0.6–1.1). Panic disorder was associated with female sex (OR = 2.2; 95% CI, 1.1–4.2) and with regular smoking (OR = 2.4; 95% CI, 1.2–4.7), whereas asthma was not associated with female sex (OR = 1.1; 95% CI, 0.6–2.1) and was weakly associated with smoking (OR = 1.9; 95% CI, 1.0–3.6). Among subjects with asthma, 20.9% had panic disorder and 32.6% had any panic. In addition, 19.6% of individuals with panic disorder had asthma, and 11.6% of individuals with any panic had asthma (not shown in Table 1). Asthma was more strongly associated with panic disorder (OR = 4.0; 95% CI, 1.7–9.3) than with any panic (OR = 2.1; 95% CI, 1.1–4.5). When controlling for sex, smoking, social class, early-childhood anxiety, family history of panic, and family history of allergy as potentially confounding variables, the estimate of the panic disorder–asthma association was considerably reduced (OR = 3.2; 95% CI, 1.3–7.9); a family history of allergy, smoking, and early-childhood anxiety emerged as the strongest confounders. When controlling for early-childhood anxiety, other childhood variables, including behavioral problems, sexual abuse, parental income, and single parent, did not influence the asthma–panic association.

Multivariate Analyses of Longitudinal Associations

We next looked at the longitudinal relation between asthma and panic. Initially, we tested for the relatedness of variables at

TABLE 1. PREVALENCE OF INDIVIDUAL CONDITIONS AND ODDS RATIO OF ASTHMA VERSUS PANIC, CUMULATIVE AND AT EACH INTERVIEW

Year	N	Asthma (%)	Allergic Rhinitis (%)	Panic Disorder (%)	Any Panic (%)	Regular Smoking (%)	Asthma versus Panic Disorder, OR (*95% CI*)*	Asthma versus Any Panic, OR (*95% CI*)*
Cumulative prevalence								
1979–1999	591	7.3	27.8	7.8	20.5	49.1	4.0 (1.7–9.3)†	2.1 (1.1–4.5)§
1979	591	1.9	15.7	2.2	8.1	21.8	—‡	3.3 (0.6–16.9)
1981	456	2.4	16.7	1.1	4.2	39.7	—‡	1.7 (0.2–14.4)
1986	457	3.7	16.4	2.8	5.5	39.2	1.7 (0.2–14.1)	2.0 (0.4–9.4)
1988	424	3.5	18.9	2.8	9.7	38.4	—‡	0.7 (0.1–5.6)
1993	407	4.7	18.4	1.5	4.9	38.6	4.8 (0.5–45.3)	2.7 (0.6–13.3)
1999	367	4.6	22.1	1.4	4.4	37.7	—‡	1.3 (0.2–10.3)

Definition of abbreviations: CI = confidence interval; N = number of subjects; OR = odds ratio.
* Associations, adjusted for sex and stratified sampling.
† $p < 0.01$.
‡ None of the subjects with symptomatic asthma had panic disorder in the same year.
§ $p < 0.05$.

baseline: early-childhood anxiety was associated with panic disorder (OR = 4.2; 95% CI, 1.2–14.6) and any panic (OR = 3.5; 95% CI, 1.6–7.9), whereas anxious temperament, anxiety disorders other than panic, and major depression were not associated with panic disorder or any panic at baseline. Asthma at baseline was not associated with baseline mood or anxiety variables. In the first models, we looked at the ability of asthma to predict panic disorder and panic disorder to predict asthma. Identical models were run replacing panic disorder with any panic, including panic attacks and panic disorder.

Asthma and Panic Disorder

As shown in Table 2, asthma (OR = 4.5; 95% CI, 1.1–20.1), anxious temperament (OR = 4.2; 95% CI, 2.0–8.7), female sex (OR = 2.6; 95% CI, 1.2–5.5), anxiety disorders other than panic (OR = 2.1; 95% CI, 1.0–4.5), and smoking (OR = 2.0; 95% CI, 1.0–3.9) were predictive of subsequent panic disorder. Although the presence of allergy in parents and siblings was not significantly associated with the occurrence of panic disorder, the exclusion of this variable increased the magnitude and significance of the OR of asthma to predict subsequent panic disorder (OR unadjusted for family history of allergy = 6.3; 95% CI, 1.9–20.9; $p < 0.001$). Panic disorder in parents or siblings, early-childhood anxiety, substance-use disorders other than smoking, and allergic rhinitis were not associated with later panic disorder. The associations between asthma and later panic disorder remained significant in women and in smokers, whereas there were no such associations in men and in nonsmokers. Sex-by-asthma and smoking-by-asthma interactions were not significant. A secondary multivariate longitudinal analyses with regular smoking as an outcome variable revealed that anxiety disorders other than panic were a significant predictor of later regular smoking (OR = 1.5;

TABLE 2. LONGITUDINAL MODELS OF ASTHMA AND PANIC DISORDER (n = 591)

Fixed* and Lagged† Predictors	Frequency (%)§	No. of Observations‖	Predictors of Panic Disorder, OR (*95% CI*)	Predictors of Asthma, OR (*95% CI*)
Age, unit = 10 yr	—		0.6 (0.5–0.9)¶	1.4 (0.8–23)
Female sex*	50.6	1,794	2.3 (1.1–5.0)¶	1.6 (0.6–4.1)
Asthma†	7.3	124	4.5 (1.1–20.1)¶	—
Allergic rhinitis†	27.8	480	0.4 (0.1–1.1)	9.6 (4.4–21.3)**
Panic disorder†	7.8	143	—	6.3 (2.8–14.0)**
GAD, phobias, OCD†	34.2	578	2.1 (1.0–4.5)¶	1.5 (0.8–2.8)
Major depression†	32.5	546	0.6 (0.3–1.4)	1.1 (0.5–2.6)
Regular smoking†	49.1	1,086	2.0 (1.0–4.0)¶	0.5 (0.2–1.1)
Alcohol abuse/dependence†	21.2	301	1.0 (0.3–3.1)	0.2 (0.1–0.6)††
Drug abuse/dependence†	11.0	115	0.7 (0.1–8.9)	0.5 (0.2–1.4)
Anxious temperament*	12.4	438	4.3 (2.1–8.9)¶	0.4 (0.1–1.6)
Childhood anxiety*	8.6	306	0.9 (0.3–2.5)	4.8 (1.7–13.3)††
Family history of allergy*‡	28.7	1,018	1.8 (0.9–3.9)	1.1 (0.5–2.5)
Family history of panic*‡	7.9	280	1.5 (0.6–3.9)	1.0 (0.2–3.9)

Definition of abbreviations: CI = confidence interval; GAD = generalized anxiety disorder; OCD = obsessive-compulsive disorder; OR = odds ratio.
Multivariate models were also adjusted for the outcome variable at baseline, socioeconomic status, and stratified sampling.
* Time-invariant exposure variable.
† Cumulative time-varying exposure variable preceding the outcome variable.
‡ Family history includes allergy/panic attacks in first-degree relatives.
§ Frequency = unweighted percentage of subjects in the study sample (100%: n = 591).
‖ Number of observations (repeated measures) as used in the analysis (total number of observations: 3,546).
¶ $p < 0.05$.
** $p < 0.001$.
†† $p < 0.01$.

95% CI, 1.1–2.1), whereas asthma and panic did not predict later regular smoking.

Conversely, the presence of panic disorder at an interview predicted subsequent asthma activity (OR = 6.3; 95% CI, 2.8–14.0). Allergic rhinitis (OR = 9.6; 95% CI, 4.4–21.3) and early-childhood anxiety (OR = 4.8; 95% CI, 1.7–13.3) also predicted subsequent asthma activity. Alcohol abuse/dependence was negatively associated with later asthma. Age, sex, anxiety disorders other than panic, and major depression were not associated with later asthma. Analyses stratified by sex showed that the association between panic disorder and later asthma was stronger in women (OR = 7.5; 95% CI, 2.7–20.8) than in men (OR = 3.7; 95% CI, 1.1–12.7; sex-by-panic disorder interaction did not reach statistical significance). Smoking status did not importantly influence the associations between the exposure variables and asthma.

Asthma and Any Panic

Identical models in which panic disorder was replaced with any panic are shown in Table 3. Asthma activity predicted the subsequent appearance of any panic (OR = 2.7; 95% CI, 1.1–7.1). In addition, age, anxiety disorders other than panic, smoking, alcohol abuse/dependence, anxious temperament, and a family history of allergy were predictive of any panic. Removal of the family history of allergy variable had an important effect on the asthma–any panic association (OR unadjusted for family history of allergy = 3.9; 95% CI, 1.6–9.4; $p < 0.01$). In contrast, any panic was not predictive of subsequent asthma, whereas allergic rhinitis, early-childhood anxiety, and alcohol abuse/dependence were associated with subsequent asthma activity as in the panic disorder model.

Subsequent analyses were run using models stratified by either smoking status or sex. Asthma activity remained predictive of any panic (panic disorder and panic attacks) among smokers (OR = 3.5; 95% CI, 1.0–13.4) but was no longer statistically significant among nonsmokers (OR = 2.1; 95% CI, 0.5–8.5). Stratifying by sex revealed asthma activity remained predictive of any panic among women (OR = 2.9; 95% CI, 1.1–8.6) but lost statistical significance among men (OR = 1.9; 95% CI, 0.2–19.6); in men, a family history of panic emerged as a significant predictor of any panic (OR = 2.9; 95% CI, 1.3–6.5; $p < 0.01$). Sex-by-asthma and smoking-by-asthma interactions were not significant. Smoking and sex did not affect the lack of association between any panic and later asthma.

Associations across Subsequent Interviews

The results from the five log-linear models, each of which included binary variables for asthma and any panic from two adjacent interviews, showed that asthma was a more stable condition (stability estimates, i.e., ORs derived from parameters of two-way interactions between dichotomous asthma variables of two adjacent interviews, ranged from 34.7 to 59.0) than panic (stability estimates between 3.9 and 11.6). Associations between panic and subsequent asthma were particularly strong in the first four interviews, whereas associations between asthma and subsequent panic were most prominent between the fourth and the fifth interview. There was no apparent effect of age on stability and concurrent associations of asthma and panic. Longitudinal associations tended to be stronger than concurrent associations across the study period.

DISCUSSION

This is the first long-term follow-up study looking at longitudinal relationships between asthma and panic in a community sample of young adults. This study consistently showed associations between asthma activity and panic. Longitudinal associations were generally stronger than concurrent associations. Consistent with our hypothesis, asthma was associated with later panic. An exploratory analysis showed that panic was associated with later asthma. A family history of allergy, smoking, and early-childhood anxiety were important confounders of the asthma–panic association. The analyses of adjacent interviews (i.e., at different ages separately) confirmed the results of the longitudinal analyses (i.e., over

TABLE 3. LONGITUDINAL MODELS OF ASTHMA AND ANY PANIC (n = 591)

Fixed* and Lagged† Predictors	Frequency (%)§	No.of Observations‖	Predictors of Any Panic, OR (*95% CI*)	Predictors of Asthma, OR (*95% CI*)
Age, unit = 10 yr	—		0.6 (0.5–0.9)¶	1.4 (0.8–2.3)
Female sex*	50.6	1,794	2.2 (1.3–3.5)**	1.6 (0.6–4.1)
Asthma†	7.3	124	2.7 (1.1–7.1)¶	—
Allergic rhinitis†	27.8	480	0.6 (0.3–1.0)	9.4 (4.3–20.9)††
Any panic†	20.5	403	—	1.3 (0.5–3.0)
GAD, phobias, OCD†	34.2	578	1.8 (1.1–2.8)¶	1.5 (0.8–2.9)
Major depression†	32.5	546	1.1 (0.6–1.8)	1.1 (0.5–2.6)
Regular smoking†	49.1	1,086	1.6 (1.0–2.5)¶	0.6 (0.3–1.3)
Alcohol abuse/dependence†	21.2	301	2.3 (1.1–4.5)¶	0.3 (0.1–0.7)**
Drug abuse/dependence†	11.0	115	1.0 (0.3–3.6)	0.6 (0.2–2.4)
Anxious temperament*	12.4	438	2.9 (1.7–5.0)††	0.5 (0.1–1.6)
Childhood anxiety*	8.6	306	0.6 (0.3–1.3)	4.3 (1.6–11.8)**
Family history of allergy*‡	28.7	1,018	1.8 (1.1–2.9)¶	1.2 (0.5–2.7)
Family history of panic*‡	7.9	280	1.4 (0.7–3.0)	1.0 (0.3–3.7)

For definition of abbreviations, *see* Table 2.

Multivariate models were also adjusted for the outcome variable at baseline, socioeconomic status, and stratified sampling.

* Time-invariant exposure variable.

† Cumulative time-varying exposure variable preceding the outcome variable.

‡ Family history includes allergy/panic attacks in first-degree relatives.

§ Frequency = unweighted percentage of subjects in the study sample (100%: n = 591).

‖ Number of observations (repeated measures) as used in the analysis (total number of observations: 3,546).

¶ $p < 0.05$.

** $p < 0.01$.

†† $p < 0.001$.

the whole study period), and showed that the asthma-enhancing properties of panic might be particularly important in adults younger than 30 years, and that the risk of recurrence of asthma was considerably higher than the risk of recurrence of panic.

Cross-sectionally, we found a dose–response-type relationship between asthma and panic. Longitudinally, the association between asthma and panic disorder was bidirectional, whereas the relation was unidirectional when using the broader definition of panic, including sporadic panic attacks and panic disorder. These results suggest that there needs to be a minimum "intensity" of panic as seen in panic disorder to affect asthma. Our findings seem to be at odds with a previous community study, which did not find a dose–response relationship between panic severity and asthma (44); however, this study had a cross-sectional design and did not control for potentially shared causative mechanisms.

An interesting secondary finding is the relation of asthma to early-childhood anxiety. Although there is growing evidence for associations between childhood-onset anxiety disorders and adult mood and anxiety disorders (34, 45), the strong and consistent association with adult asthma was not expected. However, this finding has to be interpreted with caution because it is based on retrospective data and the specific details of the early-childhood anxiety were not available. Therefore, no conclusion about the temporal order can be made (e.g., childhood asthma may have contributed to early-childhood anxiety). The relatively strong association between early-childhood anxiety and panic at baseline may have contributed to the apparent lack of association between early-childhood anxiety and the development of adult panic (i.e., it appeared that most of those who were going to develop panic after childhood anxiety already had panic at age 20).

The two basic mechanisms of comorbidity include causal and shared etiologic explanations. Causal mechanisms can be either direct, or indirect—that is, the primary disease contributes to risk factors of the secondary disease. Longitudinal associations and dose–response relationships suggest the involvement of causal mechanisms (46). Having asthma, which can be a potentially life-threatening condition, may increase the level of anxiety, which may lead in some vulnerable individuals to panic. Moreover, asthma medication can have anxiogenic properties (9), and anxiety may further enhance the use of asthma medication (10). These mechanisms appeared to be independent of asthma severity (9). However, our finding that longitudinal associations were stronger than concurrent associations suggest long-term anxiogenic mechanisms, including dyspnea-induced fear conditioning and derangement of respiratory receptor set-point (7, 8), are playing a role.

Conversely, we also found a relatively strong association between panic disorder and later asthma. Possible direct mechanisms for panic disorder relating to asthma disease activity include the following: The majority of patients with asthma suffer from exercise-induced asthma (47, 48). Exercise-induced asthma is an asthma attack brought on by 6 to 8 minutes of vigorous exercise. Cooling of the airways or changes in lung-fluid osmolarity are speculated to be the cause (49). It is the rapid, prolonged respiration rather than the exercise itself that brings on exercise-induced asthma (50). Given that panic disorder (or at least a subtype of panic disorder) is associated with chronically increased respiration (51), hyperventilation may be one potential mechanism of the long-term dose–response-type effect of panic on asthma. Adherence to asthma medication may be an indirect pathway involved here. Psychologic disorders have been associated with less adherence to asthma medication regimes (52). This could result in less control of asthma symptoms both cross-sectionally and longitudinally. Finally, the positive association between anxiety and respiratory symptom reporting (53), and potential misinterpretation of panic symptoms as asthma symptoms, may also contribute to this direction of comorbidity.

In addition to mechanisms that increase risk of one condition by the other condition, shared etiologic factors may be involved in the asthma–panic comorbidity. Although smoking did not appear to be a predictor of the development of asthma in adjusted longitudinal models, smoking was associated with later panic and appeared to be an important confounder of the asthma–panic association. Previous epidemiologic and clinical studies showed that daily smoking was associated with increased risk for later onset of panic attacks or panic disorder (12, 54, 55). It has been hypothesized that smoking increases the risk of panic by altering receptor sensitivity in the carotid body by the carbon monoxide in cigarettes, and that misinterpretation of physical symptoms related to nicotine consumption or withdrawal might trigger panic attacks (12, 55). One study, measuring respiratory patterns in smoking and nonsmoking patients with panic disorder, suggested that smoking was a critical factor in the onset or maintenance of panic disorder by increasing irregularity in baseline respiratory patterns (56). The current study adds to previous reports that smoking may considerably enhance the effects of asthma in the development and maintenance of panic.

The relatively strong confounding effect of a family history of allergy on cross-sectional and longitudinal associations between asthma and panic suggests a genetic link between these conditions. Because the family history of allergy was assessed by self-report of the study subjects, this result has to be interpreted with caution. Moreover, previous studies have consistently shown that early parenting problems, behavior problems, and other forms of acute and chronic stress are associated with increased risk of onset and recurrence of both asthma and panic (16–20), suggesting shared environmental factors in the etiology of both conditions. The relatively strong confounding effect of childhood anxiety might reflect such early environmental risk factors; however, it might also represent early symptoms of asthma associated with anxiety reflecting a childhood precursor of the adult asthma–panic comorbidity.

The findings of this study have potentially important implications on asthma management. The possibility that appropriate treatment of panic attacks has the potential to decrease future asthma activity is suggested by the predictive ability of a panic disorder on subsequent asthma activity. This additional benefit can be added to the already known association of panic with increased request for as-needed medications and treatments (10), with high-frequency emergency room visits for respiratory symptoms (21), and with increased asthma-related rehospitalization rates (22). Identification of the appropriate patients with asthma who would benefit from treatment of their comorbid panic is an important next step because our findings clearly showed a more broad-based definition of panic was not associated with future asthma attacks.

The strengths of this study include the following factors: The community-based sample was important in that clinic-based studies are uninformative when investigating anxiety-related medical conditions related to selection biases. The longitudinal study design allowed for distinguishing antecedent (predictors) from consequent (outcomes); in addition, the results of this study expand the findings of a previous longitudinal community study (6). Because there are no generally accepted objective measurements of asthma that are appropriate for population-based studies, self-report of a physician's diagnosis, as used in this study, seems to be adequate and consistent with recent state-of-the-art epidemiologic studies in asthma (57, 58). The high percentage of subjects with asthma treated with antiasthma medication, the lack of positive association between risk for psychologic

syndromes (SCL-90-R high-scorer sample vs. SCL-90-R low-scorer sample) and asthma, together with previous evidence for a lack of association between anxiety and self-reported diagnosis of asthma (59) support the reliability of the asthma data as used in the present study. A European community health survey showed a 12-month prevalence rate of diagnosed asthma (self-report of either having an asthma attack or currently receiving asthma medication) of 5.4% in Basel, Switzerland (60), and a relatively recent Swiss questionnaire survey revealed that 2.3% of young adults had current asthma as confirmed by their general practitioner (61). Taking into account the slightly different diagnostic criteria among the studies, the 12-month prevalence rates found in the current study of between 1.9 and 4.6% seem to be consistent with the survey data on the general population of Switzerland.

However, several methodologic limitations have to be noted: most important, the assessments of asthma symptoms and asthma diagnosis were based on self-report and were not validated by objective measures such as FEV_1 or by physical examination by a study physician. Therefore, some cases of asthma may represent misreport of asthmalike symptoms. These misdiagnoses may have led to an overestimation of asthma–panic associations. The study did not include sufficient information on asthma severity or treatment issues. The assessment of childhood symptoms was based on retrospective recall. That women were more likely to have a greater number of study interviews than men may have contributed to higher estimates of asthma–panic associations in women relative to men, and the number of cases was small to test for cross-sectional associations over a 12-month period. Additional limitations may reduce the generalizability of the results. These include the inclusion of a single age cohort, an attrition rate of 38%, and a sampling method that increased the probability of psychiatric disorders.

These data provide initial evidence for the involvement of bidirectional, dose–response-type mechanisms in the asthma–panic relationships and preliminary evidence for smoking and familial factors, including early-childhood anxiety and a family history of allergy as possible shared etiologic factors. More epidemiologic research is needed on the sequence of onset of these disorders, to evaluate the roles played by disease severity and subtypes of asthma and panic, and to replicate the association between childhood anxiety and asthma. Another unexplored area is familial and common environmental factors involved in both asthma and panic. Experimental research will be necessary to test the hypotheses generated by the observational studies. Finally, clinical research is needed to find out which asthma treatment components might increase or decrease the risk of panic, and to evaluate whether detection and treatment of panic improves asthma, increases quality of life in patients with asthma, and reduces asthma-related health care costs.

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