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PANIC ATTACKS AND THE RISK OF PSYCHOSIS

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OBJECTIVE: To determine the association between panic attack and the risk of psychosis among young adults in the community.

METHOD: Data were drawn from a 21-year longitudinal birth cohort study (n = 1,265). Negative binomial regression models were used to determine the association between panic attacks in adolescence (age 15-21) and the risk of psychotic symptoms.

RESULTS: Having a panic attack in the preceding three years was associated with elevated rates of psychotic symptoms at ages 18 (rate ratio = 2.81; 95% CI = 1.92-4.13) and 21 (rate ratio = 3.01; 95% CI = 2.10-4.33). These associations were adjusted for differences in previous psychotic symptoms, comorbid anxiety, depression and substance use disorders and a range of other potential confounding factors using a generalized estimating equation model. This analysis showed that after adjustment for confounding factors, having a panic attack was still associated with an increased rate of psychotic symptoms (rate ratio = 1.51; 95% CI 1.14-2.02).

CONCLUSIONS: Panic attack is associated with increased risk of psychotic symptoms among young adults in the community. Much of the relationship between panic attacks and psychotic symptoms appears to be explained by common risk factors and psychiatric comorbidity. However, these data provide the first evidence of an independent association between panic attacks and the risk of onset of psychosis in the community. Replication of these findings is needed, as are future studies that further investigate the mechanism of this association.

Findings from several recent studies suggest that panic attacks and psychotic disorders co-occur more often than would be expected by chance (1-10). The mechanism of this association is not known. It may be that panic attacks lead to a heightened vulnerability for the onset of psychotic illness through destabilizing effects of severe anxiety on physical, emotional, and cognitive functioning (11-13). It is also possible that psychotic symptoms lead to panic attacks, as clinical data have suggested that psychotic episodes can precede and predict onset of specific anxiety disorders (i.e., post-traumatic stress disorder (PTSD)) (14). Alternatively, it could be that a third factor is associated with increased risk of the co-occurrence of panic attacks and psychotic symptoms. Some possible third factors include early environmental risk factors for psychopathology (e.g., low socioeconomic status), and comorbid mental disorders (e.g., major depression), as well as genetic influences.

Previous epidemiologic data show that anxiety disorders, especially panic attacks and panic disorder, are more common than expected among individuals with non-affective psychosis and schizophrenia in the community (5-8). Recent cross-sectional data have also suggested that there is an association between panic attacks and symptoms of schizophrenia among youth (age 9-17) (15) as well as an association between early-onset panic attacks are associated with a greater odds of psychosis, compared with that associated with panic attacks with later onset (8). Data from community samples also suggest a significant association between panic and symptoms of paranoia among adults in the community (6). There are also data from epidemiologic samples to suggest that symptoms of schizophrenia at early ages may lead to anxiety disorders (16). Findings from clinical samples suggest that anxiety disorders (e.g., PTSD, obsessive-compulsive disorder (OCD), panic disorder) occur more often than would be expected among patients with psychotic

illness (2, 5, 9). Moreover, clinical data suggest that panic attack may be associated with poorer response to treatment and increase in specific symptoms (e.g., hostility) among psychotic patients (17, 18).

While previous data cumulatively suggest an association between panic attack and psychosis, and the majority of epidemiologic data suggest that the onset of anxiety disorders and symptoms begin prior to the onset of affective, substance, and psychotic disorders (19-21), several methodological shortcomings have limited the ability of these findings to provide information about the nature of this association. Specifically, previous studies, both epidemiologic and clinical, examining the relationship between panic and psychotic disorders have been limited to the exclusive use of cross-sectional data. Therefore it has not been possible to determine whether and to what degree panic attacks may increase the risk of psychosis. Second, previous looking at the association between panic attacks and psychotic symptoms come from clinical studies of adults with severe mental disorders for which they are receiving treatment. These findings are therefore not generalizable to the community as it may be that observed associations result from factors associated with selection into treatment, severity of illness, or treatment-related factors, rather than true exposure-disease relationships. Third, studies to date have not included data on early environmental risk factors, which may be responsible for a general increase in all types of psychopathology, as well as the risk for both panic and psychotic symptoms. Fourth, previous studies have been limited to adult samples, yet the period of greatest risk of onset of psychosis is during late adolescence and early adulthood. The goal of the current study is to determine the association between panic attacks and the risk of psychosis among young adults in the community. First, the study will determine whether panic attacks are associated with an increased risk of psychotic symptoms among young

adults in the community. Second, the study will determine the specificity of this association (i.e., whether the relationship persists after adjusting for comorbid mental disorders at baseline) and whether the association is independent of the effects of early environmental risk factors for psychopathology. We hypothesized that panic attacks would be associated with an increased risk of psychotic symptoms. Based on previous data, we expected that this association would persist independent of comorbid mental disorders and other early environmental risk factors for psychopathology.

METHOD

Participants

The data described in this report were gathered during the course of the Christchurch Health and Development Study (CHDS). The CHDS is a longitudinal study of an unselected birth cohort of 1,265 children (635 males, 630 females) born in the Christchurch, New Zealand, urban region in mid-1977. This cohort has now been studied at birth, 4 months, 1 year and annual intervals to age 16 years, and again at ages 18 and 21 years. The present analysis is based on a sample of 1,053 individuals for whom information on panic attacks and psychotic symptoms was available at age 18 or 21 years. This sample represented 84% of the original birth cohort. However, since not all participants were assessed at both ages the observed sample numbers vary between age 18 (N = 1,025) and age 21 (N = 1,011).

Psychotic symptoms

At ages 18 and 21 years, sample members were administered a comprehensive mental health interview designed to assess a number of aspects of the individual's mental health and

psychosocial adjustment. As part of this interview participants were questioned on current (over the past month) psychotic symptomology using items from the Symptoms Checklist 90 (SCL 90) (22). A series of 10 items were extracted from the SCL 90 to provide a measure of psychotic symptoms. These items related to hallucinations, delusions, and alienation. The items are shown in Table 1. As previously reported (23), the fit of the items to a uni-dimensional scale was tested using methods of confirmatory factor analysis. This analysis showed that at each age, the items formed a single scale. For the adjusted model, the model scale scores were estimated using the unweighted sum of symptoms. An unweighted sum was used because: a) the scale had a clear interpretation and b) the unweighted sum was highly correlated ($r > .95$) with the least squares estimate of the factor score. The reliability of the scale score was estimated using coefficient alpha and the scale was found to have moderate internal consistency ($\alpha = .76$ at age 18; $\alpha = .73$ at age 21).

Panic attack

As part of the assessment at ages 16, 18 and 21 years, sample members were questioned about their experience of panic attacks and related symptomatology using items from the Composite International Diagnostic Interview (CIDI) (24). In particular, participants were asked on how many occasions, if any, they “had a spell or attack in which you all of a sudden felt frightened, anxious or uneasy in a situation where most people would not be anxious or afraid,” since the previous assessment. Those who reported an attack were questioned about the symptomology associated with their most severe attack(s) using CIDI items to assess DSM-IV symptom criteria. In addition, participants were asked to describe the setting and circumstances in which the attack(s) occurred. Using this information sample members were classified on DSM-IV criteria for panic

attack in each of the periods 15-18 years and 18-21 years. These assessments showed that 6.8% of the sample met DSM-IV criteria for panic attack during the interval from 15-18 years and 6.4% during the interval from 18-21 years. These prevalence rates are consistent with previous epidemiologic data (21).

Confounding Factors

To control for the association between panic attacks and psychotic symptoms for both fixed and time-dynamic sources of confounding the following measures were selected from the database of the study.

- a) Prior psychotic symptoms. Psychotic symptoms at the time of the preceding assessments were included as confounding factors. Thus, for 18 years, psychotic symptoms at age 15 years were controlled for and for 21 years psychotic symptoms at age 18 years were controlled.
- b) Other time dynamic confounders. As part of the mental health interview at ages 18 and 21, sample members were assessed on standardized symptom criteria for major depression, anxiety disorders (including generalized anxiety disorder, specific phobia, social phobia and agoraphobia) and substance use disorders based on the relevant sections of the CIDI. This information was used to classify participants according to DSM-IV diagnoses for anxiety disorders, major depression, alcohol and illicit drug dependence, in the preceding 12 months. In addition, parallel to questions on mental health, information was also obtained on other time dynamic aspects of the individual's lifestyle including exposure to adverse life events and the extent of affiliations with deviant peers.
- c) Fixed factors. A wide range of measures of social, family, and individual functioning that were assessed prior to age 18 and were correlated with either panic attack or psychotic symptoms

were considered in the analysis. These factors included: measures of family sociodemographic background (parental ages, parental education levels, family socioeconomic status, and family living standards); family functioning (parental conflict, adverse family life events, quality of parental attachments, exposure to childhood sexual and physical abuse); parental adjustment (parental depressive and anxiety disorders, alcohol problems, criminality, illicit drug use); individual characteristics (gender, childhood neuroticism, child IQ).

Statistical Analysis

In the first stage of the analysis (Table 2) mean psychotic symptoms were compared for those reporting and not reporting panic attacks. The strength of association between panic attacks and psychotic symptoms was described by the incidence rate ratio (IRR) and corresponding 95% confidence interval. In the second stage of the analysis the association between panic attack and psychotic symptoms was adjusted for confounding factors using a negative binomial generalized estimating equation (GEE) model (25). The model fitted was:

$$\log(Y_{it}) = B_0 + B_1X_{it} + B_2Y_{it-k} + \sum B_j Z_{ijt} + \sum B_l Z_{il}$$

where Y_{it} was the rate of psychotic symptoms for the i th subject at time t , X_{it} was the corresponding measure of panic attack for subject i at time t , Y_{it-k} was a measure of psychotic symptoms at the preceding assessment, Z_{ijt} were a set of time dynamic confounders (e.g., depression, anxiety disorders, substance use disorders) and Z_{il} were a set of fixed confounders (e.g., family, social and individual characteristics). The fitted model assumed an unstructured correlation matrix of residuals across time. Model fitting was conducted using STATA 6.0 (26). From this model the estimated adjusted IRR and 95% confidence interval for the effect of panic attacks on psychotic symptoms were obtained.

RESULTS

a) The association between psychotic symptoms and panic attack.

Table 2 shows the mean rates of psychotic symptoms at ages 18 and 21 for those with and without panic attacks in the preceding 36 months. The table also reports the incidence rate ratio (IRR) and corresponding 95% CI for each age. The IRR estimates show that at age 18, those reporting a panic attack in the preceding 3 years had rates of psychotic symptoms that were 2.81 times higher than those who did not have a panic attack ($p < .0001$). Similarly, at age 21, having a panic attack was associated with a 3.01 times increase in the rate of psychotic symptoms ($p < .0001$). The results show clearly elevated rates of psychotic symptoms for those with panic attacks.

b) Covariate adjusted results.

To examine the association between panic attacks and psychotic symptoms after adjustment for confounding factors a GEE model was fitted to the data (see Methods). This approach modelled the relationship between panic attack and psychotic symptoms taking into account a series of fixed and time-dynamic confounders. These confounders included: (a) measures of preceding psychotic symptoms; (b) comorbid measures of depression, anxiety and substance use disorders, and other time dynamic factors; and (c) measures of fixed social, family, and individual characteristics (see Table 3).

The results of this analysis are given in Table 3, which reports the estimated model parameter for the effect of panic attack on psychotic symptoms, with the corresponding standard error and test of significance and the adjusted IRR (95% confidence interval). The Table shows that even

following the adjustment for confounding factors (including previous symptom levels), the associations between panic attack and psychotic symptoms remained statistically significant ($p = .004$). Those with a panic attack had estimated rates of psychotic symptoms that were 1.51 (95% CI 1.14-2.02) times higher than those who did not have a panic attack. The results in Table 3 show estimates of the IRR when all covariates were taken into account. Similar results were obtained when a reduced model containing only significant covariates (i.e., depression, social phobia, agoraphobia, alcohol dependence, cannabis dependence, previous psychotic symptoms, deviant peer affiliations, family conflict, family SES, life events in past 12 months, neuroticism) were included in the analysis. For this model, the adjusted IRR was 1.52 (95% CI 1.15-2.00).

DISCUSSION

The results of this study confirm findings from previous clinical and epidemiologic research suggesting comorbidity between panic attacks and psychotic symptoms (1-10). Young people prone to panic attacks had rates of psychotic symptoms that were approximately three times those of young people without panic attacks. In part, this association was explained by other factors that were associated with panic attacks and psychotic symptoms. These factors included depression, social phobia, agoraphobia, alcohol dependence, cannabis dependence, previous psychotic symptoms, deviant peer affiliations, family conflict, family SES, life events in the past 12 months, and neuroticism. After controlling for sources of confounding, the association between panic attacks and psychotic symptoms persisted albeit in an attenuated form with young people prone to panic attacks having rates of psychotic symptoms that were 1.5 times higher than those not prone to panic attacks. These findings provide some evidence that this link is not simply due to a relationship between psychotic symptoms and psychiatric morbidity in general but that there is

specificity in the link between panic and psychosis. These results also extend previous findings by permitting the examination of the nature and strength of how panic attacks, changing over time, are associated with psychotic symptoms over time among young people in the community.

Potential limitations of this study should be considered when interpreting results. Specifically, it is important to note that the study examines the development of psychotic symptoms rather than the development of specific psychotic disorders, such as schizophrenia. Therefore, a potential ambiguity in the present study concerns the interpretation of psychotic symptoms. It is clear that the scale used is a uni-dimensional measure of symptoms. However, the link between affirmative response to these items and frank psychotic symptoms is unclear. Nevertheless, the validity of our findings is supported by parallel clinical and epidemiologic evidence from previous studies linking panic attacks and psychosis. First, results from several clinical studies have documented strong and consistent links between panic attacks and severe psychotic illness, including schizophrenia and schizoaffective disorder (2-4, 9, 10, 12). Second, data from several epidemiologic reports have shown an association between panic attacks and psychotic symptoms in the community (5-8). The convergence of these two lines of evidence clearly supports the view that panic attacks and psychotic symptoms form comorbid symptom sets.

While our findings provide new information on the nature and strength of the relationship between panic attacks and psychotic symptoms, they do not reveal the exact mechanism of this association. The possibility that panic attacks lead to increased vulnerability to the onset of psychotic symptoms is consistent with our results. This could occur through increased perceptual disturbances (e.g., depersonalization) and reality distortion (e.g., fear of dying) associated with

severe anxiety. Previous data showing linkages between panic and paranoia, as well as common effects of trauma in increasing depersonalization, which can characterize both panic and psychosis, are consistent with this likelihood (10, 14). It is also conceivable that panic attack reflects a prodrome or early phase of psychotic disorders. The onset of panic attack is often characterized by a fear of going mad or going crazy, which is one of the 13 panic symptoms (27). This is consistent with previous epidemiologic data, which suggest that this panic symptom is significantly more common among adults with panic attacks and schizophrenia, compared with those with panic without schizophrenia, among adults in the community (15). Though previous investigations have examined possible prodromes of psychosis, they have focused on depressive symptoms, cognitive symptoms (e.g., inattention), social withdrawal, and bizarre behaviour, but no previous studies have included an examination of panic, or other severe anxiety. Another possibility is that this co-occurrence is a result of common shared genetic or environmental effects. However, the persistence of the association, using the analytic strategy with adjustment for multiple confounders suggests that these common influences are not solely responsible for the increased risk of psychosis conferred by panic attack. Similarly, another plausible explanation could be that common influences of some substances (e.g., cocaine) on neurochemical processes may influence the onset of both psychosis and panic attacks. Since our data show that the relationship persists independent of the effects of substance use disorders, as well, this is unlikely to be the unifying factor, though substance use may still contribute to the association.

Extreme fear, in conjunction with certain inherited vulnerabilities or environmental circumstances, may result in the onset of psychosis. Panic attack may provide a marker of the initial manifestation, initiation, or a risk factor for the onset of psychosis in some proportion of cases.

Future research in several areas that build upon these results may be worthwhile. First, replication of these findings with data that can more definitively address the direction of causality is needed. Second, future studies that can improve our understanding of the precise nature of this association may be helpful in identifying strategies for intervention. Third, studies that investigate whether treatment of panic attack decreases the risk of psychotic symptoms, as has been suggested with major depression, may be of value in efforts to prevent or delay onset of psychotic illness.

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Table 1: Rates (%) of psychotic symptoms in past month at age 18, 21 years

Symptom	18 years	21 years
	% (N)	% (N)
The idea that someone else can control your thoughts	3.6 (37)	4.7 (48)
Hearing voices that other people do not hear	2.0 (20)	1.7 (17)
Other people being aware of your private thoughts	8.7 (89)	6.5 (66)
Having thoughts that are not your own	2.8 (28)	2.9 (29)
Having ideas or beliefs that others do not share	18.1 (186)	18.8 (180)
The ideal that something is seriously wrong with your body	7.7 (79)	8.8 (89)
Never feeling close to another person	7.3 (75)	7.7 (78)
The idea that something is wrong with your mind	6.3 (65)	7.0 (71)
Feeling that other people cannot be trusted	15.0 (154)	15.7 (159)
Feeling that you are watched or talked about by others	15.0 (154)	19.5 (197)

¹ Total sample assessed at age 18 N=1,025; at age 21 N=1,011

Table 2: Mean psychotic symptoms (past month) at age 18, 21 years by panic attack (past 36 months)

Age		Panic Attack		p	Rate Ratio	(95% CI)
		No	Yes			
18 years	Mean	.77	2.17	p<.0001	2.81	(1.92-4.13)
	(N)	(955)	(70)			
21 years	Mean	.82	2.49	p<.0001	3.01	(2.10-4.33)
	(N)	(946)	(65)			

Table 3: Estimated association between panic attack and psychotic symptoms after adjustment for confounding factors ¹

Regression Parameter		p	Rate Ratio	(95% CI)
B	(se)			
.416	(.146)	p = .004	1.51	1.14-2.02

¹ Confounding factors included:

- a) Psychotic symptoms at the previous assessment.
- b) Other time dynamic covariates including: major depression, generalized anxiety disorder, social phobia, specific phobia, and agoraphobia, alcohol, cannabis, and other illicit drug dependence, exposure to adverse life events, and deviant peer affiliations
- c) Fixed covariates including: gender, maternal age, maternal education, family socioeconomic status, family living standards, parental conflict, adverse family life events, quality of parental attachments, exposure to childhood sexual or physical abuse, parental depressive and anxiety disorders, parental alcohol problems, parental drug use, childhood neuroticism, and child IQ.

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