

## Fever and acute brief psychosis in urban and rural settings in north India

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**Background** This case–control study used data from Chandigarh, North India to investigate the association between antecedent fever and acute brief psychosis.

**Aims** To assess whether antecedent fever may be a biological correlate of acute brief psychosis, and contribute to the nosology of acute brief psychosis.

**Method** The study was based in an incidence cohort from two catchment areas, an urban and a rural site, that were part of the World Health Organization Determinants of Outcome study. The cases ( $n=17$ ) met criteria for acute brief psychosis; controls ( $n=40$ ) were patients with other acute and subacute psychoses. The Life Events Schedule was used to determine the presence of antecedent fever.

**Results** The crude odds ratio for fever as a risk factor for acute brief psychosis was 6.2 ( $P=0.004$ ). The odds ratio in a logistic regression analysis – adjusted for site, gender and CATEGO classification – was 11.2 ( $P=0.003$ ).

**Conclusions** Antecedent fever may be a biological correlate of acute brief psychosis. This finding supports the validity of this entity, and has implications for its aetiology and diagnosis.

**Declaration of interest** Supported by the National Institute of Mental Health, USA.

"The majority of male admissions to Mulago Mental Hospital give a history of sudden, severe confusion, restlessness, wandering, violence, destruction of crops, and arson. After recovery, half of these cases give a history of preceding fever . . ." (Tewfik, 1958).

This study examines the association between antecedent fever and acute brief psychosis in one urban and one rural setting in north India. The investigation follows on previous work that has established a higher incidence of acute brief psychosis in developing than in industrialised country settings (e.g. Susser & Wanderling, 1994). Other studies have provided preliminary findings suggesting an association between antecedent fever and acute psychosis in developing country settings (Tewfik, 1958; Day *et al*, 1987; Srikanth *et al*, 1994; Collins *et al*, 1996; Malhotra *et al*, 1998). The current study examines this association in an incident cohort in Chandigarh, India, using a thorough and standardised documentation of fever history, an *a priori* case definition of acute brief psychosis (Susser *et al*, 1996) and carefully defined controls with other acute or subacute psychoses.

### METHODS

This study was based in the urban and rural Chandigarh sites of the World Health Organization (WHO) Determinants of Outcome Study (DOS). This WHO study, extensively described elsewhere (Jablensky *et al*, 1992), sought to determine the incidence of schizophrenia in 13 developing and industrialised country sites. Investigators at each site aimed to include all new-onset non-affective psychoses presenting for treatment of any kind; thus, it was a substantially representative sample.

### Sites

Among the developing country sites, a complete cohort of incident cases ( $n=209$ ) was recruited only from the urban and rural

sites in Chandigarh, north India (Jablensky *et al*, 1992). Urban Chandigarh (approximate population 348 000 in 1980) is one of the most recently constructed cities in India, and is renowned for its design by the Swiss architect Le Corbusier. The rural catchment area (approximate population 104 000 in 1980) in Chandigarh is a green, fertile region in Ambala District (Haryana State) in the foothills of the Himalayas (Day *et al*, 1987), in which the communities are more prosperous than in many rural Indian locales.

### Subjects

The present analysis of the Chandigarh data was restricted to the patients of the WHO Life Events Sub-Study, for whom systematic data on antecedent fever were available. As described elsewhere (Day *et al*, 1987), this Sub-Study was designed to investigate the role of stressful life events in the precipitation of psychosis. It was restricted to patients with acute or subacute psychoses, defined by symptom onsets of one of three types: onset of florid psychotic symptoms over the course of seven days without prodromal symptoms; onset of symptoms over seven days, but preceded by a prodrome; and onset of psychotic symptoms over more than seven days, but within one month. Patients with 'organic' psychosis or substance-induced psychosis were excluded.

The Life Events Sub-Study enrolled 67 patients (urban  $n=41$ , rural  $n=26$ ) (Day *et al*, 1987). Ninety-one patients met criteria for inclusion in the Sub-Study; however, because of patient volume, not all eligible subjects could be interviewed, as detailed elsewhere (Day *et al*, 1987). The present analysis included the 57 (85%) patients (urban  $n=34$ , rural  $n=23$ ) who were followed up to 12 months and had a non-affective ICD-9 diagnosis (World Health Organization, 1978); specifically, all of these subjects had ICD-9 295 diagnoses (295.2, 295.3, 295.4 or 295.9).

### Definition of cases and controls

The 57 patients included in the present analysis were divided into two groups: cases, comprising patients with acute brief psychosis; and controls, comprising all other patients. Note that as a result of the inclusion criteria for the Life Events Sub-Study, controls also had (other) acute or subacute psychoses.

We have previously demonstrated that the operational criteria of the ICD-10 (World Health Organization, 1992) acute and transient psychotic disorders fail to capture most cases of acute brief psychosis in this setting (Susser *et al*, 1998). We did not therefore rely upon these ICD-10 diagnoses to define cases. Instead, cases were defined, in accord with our previously established criteria (Susser *et al*, 1996) for acute brief psychosis or non-affective acute remitting psychosis (NARP), as: (a) non-affective – ICD-9 diagnosis at onset was a non-affective psychotic disorder, and no affective syndrome developed within two years of onset; (b) acute onset – a florid psychotic state developed within less than one week with no prodrome; (c) remitting – the patient fully recovered from the index episode within six months, and did not relapse within two years of onset; (d) psychosis – psychotic symptoms were present but were not required to meet symptom criteria for schizophrenia. For the present analysis the sample was defined on the basis of a 12-month follow-up, so the criteria were modified by substituting 12 months for two years.

### Assessment of case v. control status

To classify the patients of the Life Events sub-study as cases or controls, using the above criteria, we utilised data from comprehensive assessments conducted at baseline and again at 12-month follow-up as part of the WHO study. These included ICD-9 diagnoses; at baseline, a research psychiatrist administered the Present State Examination (Wing *et al*, 1974) and completed the Diagnostic and Prognostic Schedule (Jablensky *et al*, 1992). These also included ratings of onset and course in the Psychiatric and Personal History Schedule (Jablensky *et al*, 1992), a standardised instrument administered by a research social worker at baseline and at 12-month follow-up. As previously reported, ratings of symptoms, onset and course demonstrated good reliability in the WHO study (Jablensky *et al*, 1992).

Seventeen patients met the case criteria, eleven in the urban and six in the rural sample. The controls were all 40 remaining patients, 23 in the urban and 17 in the rural sample.

### Assessment of exposure

All subjects were rated for presence or absence of fever in the original sub-study using the Life Events Schedule (LES). This

is a semi-structured instrument based on an unpublished version of the Bedford Instrument, developed by Brown and colleagues (Brown & Harris, 1978; Day *et al*, 1987). The instrument recorded “relevant changes” occurring in the subject’s life during the 12 weeks preceding the onset of psychosis, along with the time at which the event occurred (recorded as number of weeks preceding the onset of psychotic symptoms) (Day *et al*, 1987). Data were gathered from subjects and key informants.

The LES enquires specifically about “the onset of any serious physical illness” (Day *et al*, 1987). When a history of fever was elicited, a specific aetiology of the fever was not required. Frequently, however, the aetiology and course of the fever were described; for example, “Patient develops pneumonia with fever of 105–106 (°F; 40.5–41°C). Treated by GPs (general practitioners) in a general hospital. Illness lasts about 10 days”. The majority of fevers recorded accompanied significant illnesses. In all patients the fever had resolved before the onset of psychotic symptoms.

After the LES interviews were completed, they were reviewed by one of the authors (R.D.), who completed summary ratings and a narrative which described the onset of illness and the life events. The summary ratings included a rating on fever which was used in the present analysis. The LES interviewers and this rater were blind to the specific hypotheses of the current study.

### Data analysis

After classifying each case and control according to exposure (fever *v.* no fever) status, we computed odds ratios for fever as a risk factor for acute brief psychosis *v.* other acute/sub-acute psychosis. The data were first examined without stratification. We computed the crude odds ratio with 95% confidence intervals (CIs) derived using Taylor series. Statistical significance was tested using a  $\chi^2$  statistic.

Stratified analyses were then conducted. The sample was stratified in three ways: by site, urban *v.* rural; by gender, men *v.* women; and by CATEGO classification, S+ *v.* non-S+. S+ is a diagnostic classification of the CATEGO computer program which is intended to represent core schizophrenic psychosis, including Schneiderian symptoms (Wing *et al*, 1974) and was prominent in previous WHO reports on this study. In each of the three stratified

analyses we computed summary Mantel-Haenszel odds ratios and  $\chi^2$  statistics; the Mantel-Haenszel odds ratio and  $\chi^2$  statistic provide an odds ratio and significance test which are adjusted for the stratification variable.

We also conducted a logistic regression analysis. This analysis enabled us to calculate an odds ratio for fever as a risk factor for acute brief psychosis that was adjusted for site, gender and CATEGO classification. The logistic regression analysis also enabled us to examine interactions. However, interaction terms for fever by site, fever by gender, and fever by CATEGO S+ were not significant and were not included in the model reported here (these data are available upon request from P.Y.C.).

## RESULTS

The demographic data for 17 cases and 40 controls are shown in Table 1. A summary of the fever histories is shown in Table 2.

### Crude odds ratio

Eight (47%) of 17 cases had a history of fever *v.* five (13%) of 40 controls ( $\chi^2=8.09$ , d.f.=1,  $P=0.004$ ). The odds ratio was 6.2 (95% CI: 1.4, 29.7).

### Mantel-Haenszel odds ratios

There was a consistent association between antecedent fever and acute brief psychosis across sites, genders and CATEGO classification (Table 3). The association was statistically significant when adjusted for site, gender and CATEGO classification separately. Within individual strata, where numbers are small, the trend was always evident, although not always statistically significant.

### Logistic regression analysis

In the logistic regression analysis the odds ratio for fever, adjusted for gender, site and CATEGO classification together, was 11.2 (95% CI: 2.2, 55.4) (Table 4).

## DISCUSSION

These data demonstrate a strong association (odds ratio=6.2) between antecedent fever and acute brief psychosis in an incidence cohort in Chandigarh, India. The association was found in comparable samples of two distinct sites, the urban and rural catchment areas, which differ with respect

**Table 1** Gender and age groups of cases of acute brief psychosis and controls in Chandigarh, India

	Urban		Rural	
	Cases n (%)	Controls n (%)	Cases n (%)	Controls n (%)
<b>Gender</b>				
Male	3 (27)	10 (43)	4 (67)	6 (35)
Female	8 (73)	13 (57)	2 (33)	11 (65)
<b>Age group</b>				
15–24	7 (64)	18 (78)	6 (100)	6 (53)
25–34	4 (36)	5 (22)	0 (0)	5 (29)
35+	0 (0)	0 (0)	0 (0)	3 (18)
<b>Total</b>	11	23	6	17

**Table 2** Fever descriptions from Life Events Schedule narratives for cases and controls

Cases
1. Patient suffered from fever and was treated by a physician with penicillin
2. Patient develops pneumonia with fever 40.5–41°C; treated by physician in a general hospital
3. Patient has fever of 40°C for 3–4 days; treated by physician
4. Patient has a malarial fever; treated in a general hospital
5. Patient has malarial fever lasting 3–5 days; treated by physician
6. Malarial fever lasting one day, treated by physician
7. Patient has fever lasting 3–4 days, treated by physician
8. Malarial fever, lasts 2–3 days; treated by physician
Controls
1. Malarial fever lasting more than a month. Treated in hospital
2. Patient has a high-grade fever with sore throat and vomiting. Illness lasts one week, treated by three physicians
3. Patient has a fever of unknown origin of 39–40°C for 4–5 days
4. Patient suffers high fever for 4–5 days; treated with chloroquine
5. Patient contracts typhoid fever and is ill for two weeks; treated by physician

to socio-economic factors (Varma *et al*, 1997). Note that fever was not concurrent with the onset of psychotic symptoms in these cases, but occurred and resolved in the 12 weeks preceding the emergence of psychotic symptoms.

### Characteristics of acute brief psychosis

The above finding indicates that antecedent fever may be a biological correlate of acute brief psychosis but not other forms of acute and sub-acute psychosis, which were used as controls. Along with long-term course, phenomenology and epidemiology, biological correlates provide a means to differentiate among psychiatric conditions that share some features. In

our previous studies, acute brief psychosis (as defined here) has also been shown to differ from other acute and sub-acute psychoses in terms of its excellent long-term prognosis (Susser *et al*, 1998), its distinct phenomenological characteristics such as modal duration of two to four months (Susser *et al*, 1995), and its epidemiological determinants such as socio-cultural and gender-related variations in incidence (Susser & Wanderling, 1994; also further details available from the author upon request).

### Implications for aetiology

These data suggest the need to study the potential role for fever in the causation of acute brief psychosis. The temporal

relationship is consistent with causation: fever precedes psychosis. On epidemiological grounds, fever is plausible considering the increased incidence of acute psychoses in developing countries and the greater morbidity of febrile infectious illnesses in these environments. With regard to biology, viral infections such as influenza and the herpes simplex virus have been associated with psychotic symptoms (Torrey, 1991). It is possible that the stress of recent illness and fever may lead to reactivation of a latent virus – resulting in an acute and short-lived manifestation of psychotic symptoms (Lycke & Ziegler, 1983). Another possibility is that acute infection and fever initiate an auto-antibody response that predisposes to development of psychotic symptoms in the weeks after the fever itself subsides.

There are, however, alternative interpretations. The association may be confounded, for instance, if poor nutrition or trauma predisposes to both high fever and subsequent psychosis. There may be subtle, premorbid manifestations of illness that predispose individuals to develop fever prior to the onset of psychosis. It is also conceivable that fever may protect against more severe forms of psychosis, and is therefore more frequently associated with acute brief psychosis than with the other psychoses that served as controls in this study.

In addition, while the data shown in this report suggest an association between antecedent fever and acute brief psychosis, it is still possible that this association is not specific to acute brief psychosis as a distinct nosological entity, but instead applies to one of its defining characteristics such as acute onset (within a week) or brief duration (less than six months). In that case we would expect a higher frequency of antecedent fever among controls with acute onset or brief duration respectively. To examine this possibility we conducted two further analyses. First we compared the occurrence of antecedent fever in controls with and without acute onset. In the second analysis we compared the occurrence of antecedent fever in controls with and without brief duration of symptoms. The results of these analyses (available from P.Y.C.) confirmed that in this study, antecedent fever was not associated with acute mode of onset or brief duration *per se* but with a disorder, namely acute brief psychosis, which has these characteristics.

**Table 3** Association of fever with acute brief psychosis: odds ratio across strata defined by site, gender and CATEGO<sup>1</sup> diagnosis in Chandigarh, India

Strata	Sample	Exposure		Odds ratio	95% CI for odds ratio	Mantel-Haenszel statistics <sup>2</sup>		
		Fever	No fever			Odds ratio	$\chi^2$	P
<b>Site</b>						6.3	6.27	0.012
Urban	Cases	4	7					
	Controls	3	20	3.8	0.5, 30.2			
Rural	Cases	4	2					
	Controls	2	15	15.0	1.1, 326.1			
<b>Gender</b>						6.0	6.02	0.014
Male	Cases	3	4					
	Controls	3	13	3.3	0.3, 36.4			
Female	Cases	5	5					
	Controls	2	22	11.0	1.3, 119.9			
<b>CATEGO<sup>1</sup></b>						11.1	8.06	0.005
S+	Cases	3	6					
	Controls	0	14	15.6	0.8, 67.0			
Non-S+	Cases	5	3					
	Controls	5	21	7.0	0.96, 58.6			

1. CATEGO, see Wing *et al* (1974).

2. Mantel-Haenszel odds ratio and significance test adjusted for the stratification variable.

**Table 4** Results of the logistic regression analysis for fever as a risk factor for acute brief psychosis controlling for gender, site and CATEGO<sup>1</sup> diagnosis in Chandigarh, India

Explanatory variables	Coefficient	P	Odds ratio	95% CI for odds ratio
Fever (present v. absent)	2.41	0.003	11.2	2.2, 55.4
Gender (male v. female)	-0.18	0.791	0.8	0.2, 3.1
Site (urban v. rural)	0.38	0.589	1.5	0.4, 5.6
CATEGO <sup>1</sup> (S+ v. non-S+)	1.42	0.058	4.1	1.0, 17.9

1. CATEGO, see Wing *et al* (1974).

### Implications for the ICD

The ICD-10 introduced the novel grouping of acute and transient psychotic disorders. This advance is especially important for developing country settings where psychosis with acute onset and short duration is among the most common forms of psychosis. At the same time, it has been shown that the ICD-10 criteria for acute and transient psychotic disorders are not readily applicable in developing country settings (Susser *et al*, 1995, 1998). This is due in part to the modal duration of 2-4 months for acute brief psychosis in these settings; duration is often longer than the 1-3 months specified in the ICD-10 for specific diagnoses in the grouping of acute and transient psychotic disorders. Results from the

present study provide further support for the concept underlying this grouping - namely, that a distinctive group of non-affective psychoses with acute onset and short duration can be differentiated from other acute psychoses and from schizophrenia and affective psychoses.

### Limitations

First, the number of subjects in the study was relatively small, and this was more pronounced on stratification. Despite the small sample size, however, the odds ratios were large in magnitude across subgroups. Second, the Life Events data do not consistently reveal the aetiologies of fever; however, they do provide careful documentation of fever histories. Third,

these findings are not independent of previous preliminary findings from Chandigarh samples (Day *et al* 1987; Collins *et al*, 1996; Malhotra *et al*, 1998); none the less, this study represents a significant advance, as previous studies did not include a well-defined control group and systematically documented fever histories. Fourth, to maximise the sample size, we modified our criteria for this sample of acute brief psychosis by using one-year follow-up data. If we restrict the analysis to cases and controls followed up for two years, the association between fever and acute brief psychosis remains (odds ratio=4.5), although it is not as strong. Finally, acute brief psychosis may require the interaction of fever with other potential aetiologies for its expression. Previous literature has explored the relationship of acute psychoses to stressful life events, socio-cultural factors, childbirth and seasonality of birth, as well as antecedent fever (Day *et al*, 1987; Collins *et al*, 1996; Malhotra *et al*, 1998). These other possible aetiologies may be particularly relevant to acute brief psychoses that occur in industrialised country settings in the absence of fever.

### ACKNOWLEDGEMENTS

This paper is based on the data obtained during the participation of the authors in the Determinants of Outcome of Severe Mental Disorder Study (DOS), sponsored and funded by the World Health Organization through the WHO Collaborating Center in Mental Health, Chandigarh, India, and the participating field research centres (also supported by the National Institute of Mental Health, USA, grant MH29969).

The chief collaborating investigators in the 12 field research centres of this study were: Aarhus - E. Stromgren; Agra - K. C. Dube; Cali - C. Leon; Chandigarh - N. N. Wig (1976-1980) and V. Varma (1980-present); Dublin - D. Walsh; Honolulu - A. Marsella and M. Katz; Ibadan - M. Olatawura; Moscow - R. A. Nadzharov and N. N. Zharikov; Nagasaki - R. Takahashi (1976-1984) and Y. Nakane (1984-present); Nottingham - J. E. Cooper; Prague - L. Hanzlicek (1976-1981) and C. Skoda (1982-present); Rochester - L. C. Wynne and T. Gift.

At WHO headquarters, Geneva, the study was coordinated by N. Sartorius (Principal Investigator) and A. Jablensky (Co-Principal Investigator).

The authors are also grateful to the health administrators and the field staff of Chandigarh Union Territory, and Raipur Rani Block, Ambala District, Haryana, for their help and cooperation in conducting this study, which was also supported in part by NIMH training grant 5-T32-MH19126 and NIMH grant IP20-MH50727.

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## CLINICAL IMPLICATIONS

- Antecedent fever may be a biological correlate of acute brief psychosis in developing countries.
- It is important to consider physical as well as psychosocial stress as a potential aetiology of acute brief psychosis.
- The concept underlying “acute and transient psychotic disorders” of ICD–10 is sound – namely, a group of psychoses with acute onset and short duration which are separable from other psychoses. However, the operational criteria for those diagnoses need refinement.

## LIMITATIONS

- The number of subjects in this study was small for analyses in specific strata.
- While the occurrence of fever was systematically documented, the cause of the fever was not consistently documented.
- Since the specific ICD–10 criteria for acute and transient psychotic disorders were not applicable in this setting, we relied upon our criteria for acute brief psychosis, which adhere to the spirit but not the letter of the ICD–10 grouping.

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(First received 31 July 1998, final revision 18 January 1999, accepted 28 January 1999)

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