ORIGINAL ARTICLE

Heterogeneity in Incidence Rates of Schizophrenia and Other Psychotic Syndromes

Findings From the 3-Center ÆSOP Study

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Context: Convention suggests uniformity of incidence of schizophrenia and other psychoses; variation would have implications for their causes and biological characteristics.

Objective: To investigate variability in the incidence of psychotic syndromes in terms of place, ethnicity, age, and sex.

Design: Three-center, prospective, comprehensive survey of clinically relevant first-onset psychotic syndromes over a 2-year period (1997-1999). Census data provided the denominator.

Setting: Southeast London, Nottingham, and Bristol, England.

Participants: One million six hundred thousand person-years yielded 568 subjects aged 16 to 64 years with clinically relevant psychotic syndromes.

Main Outcome Measures: The World Health Organization Psychosis Screen and the Schedules for Clinical Assessment in Neuropsychiatry to classify, blind to ethnicity, all *DSM-IV* psychotic syndromes and the subclasses of schizophrenia, other nonaffective disorders, affective disorders, and substance-induced psychosis.

Results: All syndromes showed a characteristic age distribution. Schizophrenia was significantly more common in men (incidence rate ratio [IRR], 2.3 [95% confidence interval (CI), 1.7-3.1]); affective disorders occurred equally in men and women (IRR, 1.0 [95% CI, 0.7-1.3]). All psychoses were more common in the black and minority ethnic group (crude IRR, 3.6 [95% CI, 3.0-4.2]). Differences in age, sex, and study center accounted for approximately a quarter of this effect (adjusted IRR, 2.9 [95% CI, 2.4-3.5]) in each psychosis outcome. The age-sex standardized incidence rate for all psychoses was higher in Southeast London (IRR, 49.4 [95% CI, 43.6-55.3]) than Nottingham (IRR, 23.9 [95% CI, 20.6-27.2]) or Bristol (IRR, 20.4 [95% CI, 15.1-25.7]). Rates of all outcomes except affective disorders remained significantly higher in Southeast London when the model was expanded to control for ethnicity.

Conclusions: There is significant and independent variation of incidence of schizophrenia and other psychoses in terms of sex, age, ethnicity, and place. This confirms that environmental effects at the individual, and perhaps neighborhood level, may interact together and with genetic factors in the etiology of psychosis.

Arch Gen Psychiatry. 2006;63:250-258

DOUBT REMAINS AS TO whether the incidence of schizophrenia varies according to the classic epidemiological dimensions of time, place, and person.[1-5] Several studies suggest considerable variability while others,[6] including the World Health Organization (WHO) 10-country study,[7] have been interpreted as indicating homogeneity. There is even less confidence about affective psychoses and bipolar disorder.[8] This uncertainty is important because variation is an important tool for understanding and investigating the causes of psychosis. Apparent lack of geographical variation has led to emphasis on genetic factors, whereas heterogeneity would support environmental causes that most likely interact with the genome. We present results from a large epidemiological study designed to answer the question of variation in incidence.

Incident psychotic syndromes are relatively rare. Many epidemiological studies of first-episode schizophrenia have been based or interpreted at the national level,[1,4,9,10] ignoring potentially important differences in incidence at a subregional level. Several studies[11-13] and a systematic review[14] demonstrate an increased risk of schizophrenia in urban compared with rural areas, supporting the hypothesis that factors in the urban environment may play a part in causation.[15-18]

Migrants may be particularly exposed to the effects of urbanicity, the related but distinct effects of social deprivation, and

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other unknown factors. High incidence rates compared with the host population have been reported in people of African Caribbean origin in the United Kingdom[19-21] and in immigrants to other European countries.[22-25] Disentangling and understanding the relationship between specific environmental factors, summarized by urban and socioeconomic dimensions, and the excess of psychoses in migrant populations are important in terms of understanding causation.

The Ætiology and Ethnicity in Schizophrenia and Other Psychoses (ÆSOP) study was designed to investigate these problems using identical methods and diagnostic criteria in 3 English study centers (Southeast London, Nottingham, and Bristol) with heterogeneous populations. The methods draw on the WHO 10-country study[7] and previous epidemiological investigations in our centers.[7,19,20,26-28]

METHODS

The ÆSOP study is a large, population-based case-control study conducted over 2 years in 3 study centers in England. Two centers (Southeast London and Bristol) were exclusively urban; the third (Nottingham) was a mixture of urban, suburban, and rural environments. Herein, we present data on the incident cases. Ethical approval was obtained from the local research ethics committee in each study center.

POPULATION AT RISK

When the study began in 1997, the study areas were initially defined in terms of 1991 census electoral wards covered by participating mental health services in each study center. Census Area Statistic (CAS) wards (approximately 5700) superseded electoral wards (approximately 4600) in 1998 and were used in the 2001 census. The study included 33 CAS wards in Lambeth and Southwark in Southeast London, 95 CAS wards in Nottingham, and 52 CAS wards in central Bristol (a list of these wards is available on request). We used these 180 CAS wards and the 2001 census to estimate the population at risk in our analyses.

In accordance with the case inclusion criteria, all people between 16 and 64 years of age at the time of the census (April 29, 2001) were included to estimate the population at risk for our analyses. The census population was doubled in Southeast London and Nottingham to account for the 2-year study period and multiplied by 0.75 in Bristol, where cases were surveyed over 9 months. This estimates the true populations that were available during the study period, from which we aimed to ascertain all those who developed a clinically relevant psychotic syndrome.

CASE ASCERTAINMENT

We identified everyone between 16 and 64 years of age living in our study areas who made contact with mental health services because of a first episode of any probable psychosis, nonpsychotic mania, or bipolar disorder. It took place over 24 months in Southeast London and Nottingham (September 1997-August 1999) and the first 9 months of this period in Bristol.

All potential cases who made contact with psychiatric services for the first time (including adult community mental health teams, inpatient units, forensic services, learning disability services, adolescent mental health services, and drug and alcohol units) were screened. The study team contacted health service bases weekly to identify all potential contacts. There were regular training events for health staff. The initial inclusion criteria were based on those used in the WHO study[7]: age between 16 and 64 years; resident within the 3 study areas; absence of an organic medical cause (*DSM-IV* 293.xx) or profound learning disability; presence of hallucinations, delusions, thought disorder, bizarre or disturbed behavior, negative syndrome, mania, or clinical suspicion of psychosis; and no previous contact with psychiatric services for psychotic symptoms.

A leakage study, based on the methods used by Cooper et al,[28] was conducted after the survey period to identify subjects missed by the screening process. This included checking with psychiatrists involved in private practice, checking with private psychiatric hospitals in the study areas, reviewing all new mental health service registration forms held in the medical records department, and interrogating computerized information systems. All subjects who had been given a diagnosis of any psychotic syndrome or schizotypal, paranoid, or schizoid personality disorder were identified. Case notes were reviewed and clinical staff interviewed. Those subjects who were in their first episode of illness meeting these criteria were identified and went on to the subsequent stages of the protocol. Ethical approval was not obtained in Bristol to conduct a leakage study and so this process was completed in the Nottingham and London study centers only.

Subjects who passed the screen underwent a battery of assessments including the Schedules for Clinical Assessment in Neuropsychiatry (SCAN)[29]; a modified Personal and Psychiatric History Schedule[29]; and a schedule developed to record sociodemographic data. We completed the SCAN Item Group Checklist for all subjects who declined an interview, based on case notes and information from clinical staff.

Diagnoses were allocated by consensus agreement from a panel of psychiatrists at each study center, including a principal investigator and the clinical researcher who conducted the individual assessments. This researcher presented the clinical information, blind to ethnicity of the subject, to the panel, which comprised members from a variety of ethnic groups. Diagnoses were made using this and information from the case notes, item ratings in SCAN, and collateral histories, according to *DSM-IV*.[30] These diagnoses were categorized in 5 ways: all psychoses, affective psychoses (*DSM-IV* 296.x4, 296.4, 296.89), nonaffective psychoses (*DSM-IV* 295.xx, 297.xx, 298.8, 298.9), schizophrenia (*DSM-IV* 295.xx) (including schizophreniform and schizoaffective disorder), and substance-induced psychoses (SIPs) (*DSM-IV* 291.3, 291.5, 292.11, 292.12).

Ethnicity was ascribed using all available information, including self-ascription, place of birth, and parental place of birth. Two researchers (J.B.K. and P.F.) independently rated ethnicity, with discrepancies agreed by consensus with a third (P.B.J.). We created a dichotomous ethnicity variable (black and minority ethnic [BME] vs white British, according to the 2001 census) as used by the National Institute for Mental Health in England (London).[31] This classification includes the white non-British (predominantly Irish and European) group in the BME category.

INTERRATER RELIABILITY

Researchers were trained in the SCAN interview on a WHO-approved course and established prestudy reliability using independent rating of videotaped interviews. Principal investigators in each center produced independent diagnostic ratings on 20 case vignettes chosen at random from the entire sample. The κ scores ranged from 1.0 for psychosis as a category to 0.6 to 0.8 for individual diagnoses. Interrater reliability was also high for ethnicity classification ($\kappa = 0.94$).

STATISTICAL ANALYSES

Descriptive epidemiological data are reported for the 5 diagnostic categories. This included the age and sex distribution and ethnic composition of the sample. The estimated denominator population was stratified similarly.

Table 1. Sample and Denominator Population Characteristics by Study Center

Characteristic	Study Center			Total
	London	Nottingham	Bristol	
Total denominator*	565 576 (34.7)	808 412 (49.6)	257 454 (15.7)	**1 631 442** (100)
Sex				
Men	277 196 (49.0)	402 820 (49.8)	128 412 (49.9)	**808 428** (49.6)
Women	288 380 (51.0)	405 592 (50.2)	129 042 (50.1)	**823 014** (50.4)
Ethnicity				
White	363 856 (64.3)	739 708 (91.5)	240 509 (93.4)	**1 344 073** (82.4)
BME group	201 720 (35.7)	68 704 (8.5)	16 945 (6.6)	**287 369** (17.6)
Area, hectares	4382 (4.6)	70 008 (74.0)	20 201 (15.4)	**94 591**
Total cases†	308 (54.2)	203 (35.8)	57 (10.0)	**568** (100)
Sex				
Men	173 (56)	121 (60)	39 (68)	**333** (59)
Women	135 (44)	82 (40)	18 (32)	**235** (41)
Ethnicity				
White	109 (35.4)	157 (77.3)	38 (66.7)	**304** (53.5)
BME group	199 (64.6)	46 (22.8)	19 (33.3)	**264** (46.5)

Abbreviation: BME, black and minority ethnic.
*Values are expressed as denominator population (percentage) of person-years. Two-year study: London and Nottingham; 9-month study: Bristol. To obtain persons at risk (compared with person-years), divide the denominator by 2 in the London and Nottingham studies and by 0.75 in the Bristol study.
†Values are expressed as number (percentage) of cases.

Both crude and age-sex–adjusted incidence rates were calculated with their 95% confidence intervals (CIs) for each study center. Rates are presented per 100 000 person-years. Analyses were conducted using Stata (version 8).[32]

Direct standardization was used to compare incidence rates between study centers and to obtain age-sex–adjusted rates of psychoses. This is the preferred method of standardization for small numbers.[33] Rates in each study center were standardized using the 2001 census population of England and Wales stratified by sex and age (age bands: 16-19, 20-29, 30-39, 40-49, and 50-64 years).

Poisson regression was conducted to examine potential differences in the incidence of psychoses between study centers, having controlled for age and sex and having introduced ethnicity as a potential explanatory variable. Interaction terms were fitted between variables where appropriate. The Southeast London study center was used as the baseline for reported incidence rate ratios (IRRs); these are presented as 1/IRR, giving positive effects that are easier to interpret.

RESULTS

Table 1 presents the estimated denominator population, adjusted for length of follow-up in each study center. The total number of person-years was 1 631 442, more than 5% of the relevant English population, to which women contributed 50.4%. Nottingham contributed approximately half (49.6%) of the person-years; Southeast London and Bristol contributed 34.7% and 15.7%, respectively. The BME group contributed 35.7% of the person-years in Southeast London, greater than the proportion of the BME population in both Nottingham (8.5%) and Bristol (6.6%). African and African Caribbean communities constituted 41.9% of the BME population; those of white Irish or European or Indian Subcontinent origin contributed 27.9% and 13.6%, respectively.

Six hundred twenty-six people passed the initial screen during the survey period or were identified through the leakage study. We excluded 58 people on the basis of further information: a likely *DSM-IV* organic psychotic disorder (n=6); probable nonpsychotic disorder (n=18); previous contact with mental health services visit (n=7); refusal (n=2); no responses, no information or notes, diagnosis not possible (n=11); and outside study area (n=14).

A total of 568 cases from the 3 study centers met inclusion criteria. Table 1 also presents basic demographic characteristics of these cases by study center. More than half (308 [54.2%]) were from Southeast London; 35.8% (n=203), from Nottingham; and 10% (n=57), from Bristol. Overall, 59% of cases were men. This varied nonsignificantly between study centers ($\chi^2=2.4$; $P=.30$), from 56% in Southeast London to 68% in Bristol. Sixty-six cases (11.6%) came through the leakage studies in Nottingham (n=40) and Southeast London (n=26), a proportion almost identical to previous studies.[20] These cases were remarkably similar to those subjects identified in the initial survey, giving little clue as to why they were not identified initially (data available on request).

AGE AT FIRST CONTACT

For all psychoses, the mean age at first contact was significantly younger for men (29.6 years [95% CI, 28.4-30.7 years]) than women (32.6 years [95% CI, 31.1-34.0 years]). For men (median age, 27 years [interquartile range, 22-34 years]) and women (median age, 30 years [interquartile range, 24-39]), median age was lower than mean age, confirming the positively skewed age distribution for psychoses (ie, young age at first contact). More than 76% of men and 63% of women in the sample made first contact with mental health services before 35 years of age (**Figure 1**). By age 40 years, these proportions were more than 85% and 75%, respectively. Similar patterns were observed separately for nonaffective and affective psychoses.

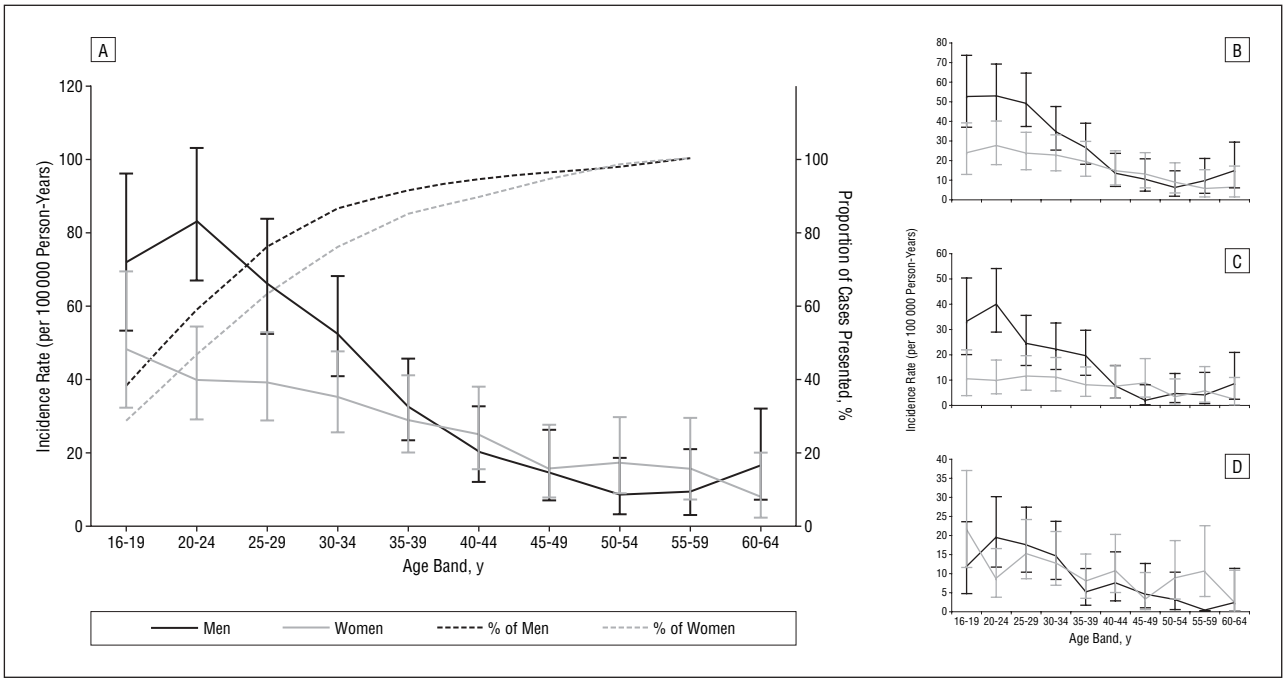

Figure 1. Cumulative proportion of all psychoses by age and sex and age-specific incidence rates of selected psychoses by sex. A, All psychoses. B, Nonaffective psychoses. C, Schizophrenia. D, Affective disorders.

DIAGNOSES

Figure 2 shows the distribution of cases by diagnosis. Sixty-seven percent of cases received a diagnosis of nonaffective psychosis; 37%, *DSM-IV* schizophrenia; and 30%, *DSM-IV* other nonaffective psychoses. Twenty-eight percent of the sample received a diagnosis of affective psychosis. More than half of these were cases of depression with psychotic features (53%); the remainder received a diagnosis of bipolar disorder. The remaining 5% of cases in the total sample were diagnosed with an SIP. Sixty-nine percent of both cases with schizophrenia and SIPs were men, but for other psychoses, sex differences were more modest (men, 54%). Just more than half of all cases of affective psychosis were women (52%).

Table 2 presents the crude and age-sex–standardized incidence of different psychoses for the combined study areas and by each study center. The IRR comparing study centers, adjusted for age and sex of the total study population, is also presented in Table 2.

All Psychoses

The overall incidence rate (λ) of all psychotic disorders in the ÆSOP study was 34.8 per 100 000 person-years (95% CI, 32.1-37.8). This figure varied between study centers such that the crude incidence of first-onset psychoses in Southeast London (λ=54.5 [95% CI, 48.7-60.9]) was more than twice that observed in Nottingham (λ=25.1 [95% CI, 21.9-28.8]) or Bristol (λ=22.1 [95% CI, 17.1-28.7]). Standardization for age and sex did not significantly alter this pattern. The rate of psychoses in Southeast London was significantly higher than in Nottingham (1/IRR, 2.0 [95% CI, 1.7-2.5]) or Bristol (1/IRR, 2.5 [95% CI, 1.7-3.3]).

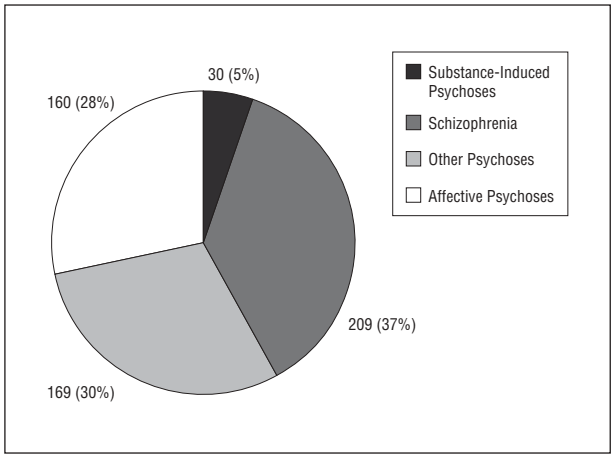

Figure 2. Distribution of cases by diagnosis in the Ætiology and Ethnicity in Schizophrenia and Other Psychoses (ÆSOP) study.

Nonaffective Psychosis and Schizophrenia

The adjusted incidence rates described earlier are presented graphically in **Figure 3**, along with rates for specific psychotic disorders using the data presented in Table 2. After adjustment for age and sex, the incidence of nonaffective disorders remained significantly higher in Southeast London (λ=37.4 [95% CI, 32.3-42.5]) than Nottingham (λ=13.1 [95% CI, 10.6-15.5]) or Bristol (λ=13.2 [95% CI, 8.9-17.4]). This effect was independently present for both schizophrenia and other nonaffective psychoses (Figure 3).

Affective Psychoses

The crude incidence of affective psychoses in the sample was 9.8 per 100 000 person-years (Table 2).

Table 2. Incidence Rate of Various Psychoses by Study Center*

	Crude Rate	Adjusted Rate (95% CI)	IRR (95% CI)
Psychoses			
Overall (n = 568)	34.8	32.1 (29.4-34.8)	. . .
London	54.5	49.4 (43.6-55.3)	1.0
Nottingham	25.1	23.9 (20.6-27.2)	0.5 (0.4-0.6)
Bristol	22.1	20.4 (15.1-25.7)	0.4 (0.3-0.6)
Nonaffective psychoses			
Overall (n = 378)	23.2	21.3 (19.1-23.5)	. . .
London	40.5	37.4 (32.3-42.5)	1.0
Nottingham	13.9	13.1 (10.6-15.5)	0.3 (0.3-0.4)
Bristol	14.4	13.2 (8.9-17.4)	0.4 (0.2-0.5)
Schizophrenia			
Overall (n = 209)	12.8	11.7 (10.1-13.3)	. . .
London	21.6	20.1 (16.3-23.9)	1.0
Nottingham	8.2	7.6 (5.8-9.4)	0.4 (0.3-0.5)
Bristol	8.2	7.2 (4.1-10.3)	0.4 (0.2-0.6)
Affective psychoses			
Overall (n = 160)	9.8	9.2 (7.7-10.6)	. . .
London	14.0	12.0 (9.2-14.8)	1.0
Nottingham	8.2	8.0 (6.1-9.9)	0.7 (0.5-0.9)
Bristol	5.8	5.6 (2.7-8.4)	0.5 (0.3-0.8)
Substance-induced psychoses			
Overall (n = 30)	1.8	1.6 (1.0-2.2)	. . .

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; ellipses, not applicable.
*Per 100 000 person-years.

Table 3. Incidence Rate Ratios (IRRs) for Psychoses for Select Risk Factors

Risk Factor	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)*	*P* Value for Interaction
Men (vs women)			
All psychoses	1.4 (1.2-1.7)	1.5 (1.3-1.8)	.05†
Nonaffective psychoses	1.7 (1.4-2.1)	1.8 (1.4-2.2)	.46†
Schizophrenia	2.3 (1.7-3.1)	2.4 (1.8-3.2)	.05†
Affective psychoses	0.9 (0.7-1.3)	1.0 (0.7-1.3)	.04†
BME group (vs white British)			
All psychoses	3.6 (3.0-4.2)	2.9 (2.4-3.5)	. . .
Nonaffective psychoses	4.0 (3.3-5.0)	3.0 (2.4-3.7)	. . .
Schizophrenia	4.6 (3.5-6.1)	3.6 (2.7-4.9)	. . .
Affective psychoses	3.6 (2.6-4.9)	3.2 (2.3-4.6)	. . .
Study center (vs London)			
Nottingham			
All psychoses	0.5 (0.4-0.6)	0.8 (0.6-0.9)	. . .
Nonaffective psychoses	0.3 (0.3-0.4)	0.6 (0.4-0.7)	. . .
Schizophrenia	0.4 (0.3-0.5)	0.7 (0.5-0.9)	. . .
Affective psychoses	0.6 (0.4-0.8)	1.0 (0.7-1.5)	. . .
Bristol			
All psychoses	0.4 (0.3-0.5)	0.7 (0.5-0.9)	. . .
Nonaffective psychoses	0.4 (0.3-0.5)	0.6 (0.4-0.9)	. . .
Schizophrenia	0.4 (0.2-0.6)	0.7 (0.4-1.1)	. . .
Affective psychoses	0.4 (0.2-0.7)	0.7 (0.4-1.3)	. . .

Abbreviations: BME, black and minority ethnic; CI, confidence interval; ellipses, not applicable.
*Adjusted for sex, age, ethnicity (BME), and study center as appropriate.
†*P* value reports age × sex interaction.

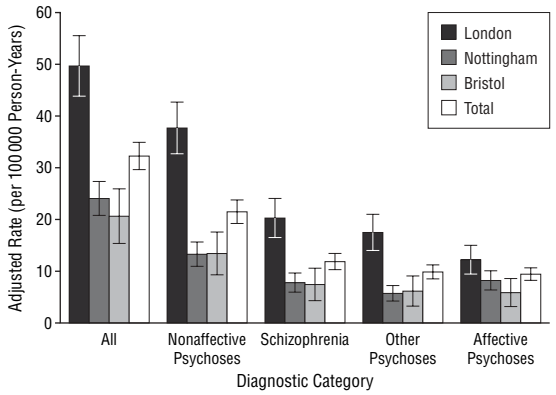

Figure 3. Age- and sex-adjusted rates (standardized using the 2001 census population of England and Wales) of psychoses by diagnostic category and study center. Error bars represent 95% confidence intervals.

After standardization for age and sex, the incidence in Southeast London was significantly higher than in Nottingham (1/IRR, 1.7 [95% CI, 1.1-2.0]) and Bristol (1/IRR, 2.0 [95% CI, 1.3-3.3]).

Substance-Induced Psychoses

The adjusted incidence of SIPs in the ÆSOP study was low: 1.6 per 100 000 person-years (95% CI, 1.0-2.2). Incidence was too low for meaningful intercenter comparisons to be made.

AGE- AND SEX-SPECIFIC INCIDENCE RATES

Table 3 presents unadjusted and adjusted IRRs for men and women. After controlling for age, study center, and ethnicity, the risk of all psychotic disorders, with the exception of affective psychoses, was greater for men than women.

For nonaffective psychoses, men were at 1.8-fold greater risk than women (95% CI, 1.4-2.2), having adjusted for the confounders mentioned earlier. There was no evidence of heterogeneity of risk between different age groups ($P=.60$). For all other outcomes, there was evidence that the risk for men was higher than women at younger ages, but as age increased, such differences disappeared. Evidence of this interaction is presented in Figure 1.

The highest incidence of psychoses for men occurred in the age band 20 to 24 years ($\lambda=82.8$ [95% CI, 66.7-102.8]), significantly higher than for women at this age (IRR, 2.0 [95% CI, 1.4-3.0]). For women, the highest observed rate was earlier, between 16 and 19 years of age ($\lambda=48.0$ [95% CI, 32.2-69.0]). The rate of psychoses for men declined beyond age 24 years, more sharply so than for the corresponding decrease in incidence for women. After age 35 years, there was no evidence of a sex difference in incidence rates, despite slightly raised point estimates of incidence for women older than 40 years.

An analogous pattern was observed for schizophrenia; men were again at greatest risk compared with women in the age band 20 to 24 years. The point estimate for this effect was greater than for all psychoses combined (IRR, 4.1), but with lower precision (95% CI, 2.0-8.5). The peak incidence for schizophrenia in women (age

25-29 years) was later than for men (age 20-24 years). Incidence was significantly greater for men compared with women for every age band before 40 to 44 years (from Poisson model; data not shown).

Differences were less clear in the age-specific IRRs for affective psychoses (Figure 1). The IRR is significantly greater for men than women in the age band 20 to 24 years (IRR, 2.3 [95% CI, 1.0-5.4]), as was apparent for the outcomes mentioned earlier. No statistically significant differences in risk between men and women were observed in any other age band, although peak incidence occurred earlier in women (age 16-19 years vs age 20-24 years).

ETHNICITY

Table 3 also presents unadjusted and adjusted IRRs for the BME group compared with the white British group for various diagnoses. For all psychoses, the unadjusted IRR for the BME group was 3.6 (95% CI, 3.0-4.2). This was reduced to 2.9 (95% CI, 2.4-3.5), having adjusted for age, sex, and study center, but remained highly significant.

A similar pattern was also observed for specific psychotic disorders (Table 3). Adjusted IRRs for the BME group were significantly elevated for schizophrenia (IRR, 3.6 [95% CI, 2.7-4.9]) and nonaffective (IRR, 3.0 [95% CI, 2.4-3.7]) and affective psychoses (IRR, 3.2 [95% CI, 2.3-4.6]).

EXPLAINING INTERCENTER DIFFERENCES

The effect of including ethnicity as an explanatory variable in addition to age and sex on the differences in rates between study centers is presented in Table 3. Some, but not all, of the variation in incidence between the 3 study centers is explained by the BME group. For all psychoses, the rate in Southeast London remained significantly higher than in either Nottingham (1/IRR, 1.3 [95% CI, 1.1-1.7]) or Bristol (1/IRR, 1.4 [95% CI, 1.1-2.0]), having adjusted for age, sex, and ethnicity. An identical pattern was observed for nonaffective disorders and schizophrenia (Table 3), although the IRR for schizophrenia in Bristol was just beyond statistical significance (1/IRR, 1.4 [95% CI, 0.9-2.0]). These effects were independently present for the white British and BME groups. Inspection of census data, stratified analyses, and modeling interaction terms involving the BME group and age indicated no evidence of modification of the study center effect by age or generation; this excluded overrepresentation of second or third generation migrants in London explaining the excess (data available on request). No significant differences in rates were observed between centers for affective disorders after adjustment for age, sex, and ethnicity.

COMMENT

PRINCIPAL FINDINGS

The findings demonstrate considerable heterogeneity in incidence rates of psychoses in terms of sex, age, ethnic group, and study center. There was a degree of confounding between these factors but each had independent effects on incidence. If we could explain these effects, we would understand more about the causes of these disorders.

In terms of the ÆSOP sample's age and sex composition, we replicated and confirmed the familiar age-at-first-contact patterns observed for schizophrenia and other mental disorders.[34-36] Our finding that most, but by no means all, cases of psychosis have manifested by age 35 years has direct relevance to early-intervention mental health services for first-episode psychoses that are being established in a number of countries. Many use age 35 years as an upper age limit, which will, inevitably, exclude some people; the majority will be only slightly older than this limit, preferentially women.

Regarding incidence, we have shown the classic excess for men at younger ages, followed by a later decline, with a nonsignificant rise in the incidence of psychoses for women older than 40. Overall, we found a greater risk of nonaffective disorders, including schizophrenia, for men compared with women, as confirmed by a recent meta-analysis.[37] The age-specific incidence of affective psychoses is less commonly investigated[34]; herein, we confirmed that, like schizophrenia, the most common onset is in early adulthood, but the pattern for men and women is much more similar. These distinctions are of relevance to putative explanations of the sex difference in schizophrenia (such as the estrogen protection hypothesis),[38-40] suggesting that this is not a mechanism that explains the age distribution of schizophrenia alone, and age, or factors associated with it, is a potent risk factor for all psychoses.

The incidence of all diagnoses was greater in Southeast London than Nottingham or Bristol after standardization for age and sex. These differences remained after further adjustment for ethnicity, except for affective disorders. This suggests truly "psychotogenic" effects of that environment or population stratification in terms of psychosis risk and needs exploring in further detail.

The observed 3-fold increased incidence of psychoses in the BME group compared with the white British group is important, particularly because this was found across study centers and broad diagnoses. A tendency to preferentially classify symptoms as schizophrenia in BME groups cannot have led to these findings; detailed examination is presented elsewhere (P.F., J.B.K., P.D., C.M., K.M., T.L., G.H., J.T., Alan Fung, PhD, J.H., R.M.M., G.L.H., J.P.L., P.B.J., unpublished data, September 1997-August 1999).

METHODOLOGICAL CONSIDERATIONS

This study has a number of strengths. To our knowledge, it is the first incidence study of psychoses to use the UK 2001 census to estimate the denominator population. This census was designed to avoid underenumeration of minority ethnic groups, men, and younger people,[41] problems that dogged previous data.[42] We acknowledge that the true dynamic population at risk over the survey period may have varied slightly, but we have no reason to believe that there was systematic bias. We minimized any misclassification by ethnic status in either our denominator or numerator populations by using a dichoto-

mous ethnicity variable with a very broad ethnic minority group (BME) and an easily definable comparator group.

To our knowledge, the study is one of the largest investigations of prospectively ascertained and clinically assessed first-episode psychoses. Consensus diagnoses were performed blind to ethnic status of the case. Cases included people from a wide range of mental health services with broad inclusion criteria, and leakage studies were conducted to minimize underascertainment.

Separate incidence rates have also been calculated for affective psychoses and SIPs. The broad psychosis category is relevant to planning contemporary early-intervention mental health service developments for first-episode psychosis.

MEANING OF THE FINDINGS

There was evidence of heterogeneity of incidence rates between study centers. Although several IRRs have been reported, the pattern and number of significant associations far exceed those that would have been expected by chance alone. Despite a shorter study period in Bristol, it is reassuring that the incidence of psychoses was consistent with rates observed in Nottingham. We have no reason to suppose that the differences between the study centers could have been explained by systematic bias either in estimating the population at risk or in ascertaining cases. Seasonal variation in inception rates[43] was not captured by the 9-month study in Bristol, but we do not believe this would have significantly altered our findings.

We have begun to explore differential incidence rates between study centers through Poisson modeling of some demographic variables. An excess incidence of psychoses remains apparent in Southeast London, having adjusted for age, sex, and ethnicity, all of which are associated with incidence and differed in the 3 populations we studied. The study center effect indicates that socioenvironmental risk factors not included herein, such as individual social class and social capital; psychological effects such as life events, achievements, and expectations; and neighborhood deprivation may be etiologically relevant in explaining the residual differences in incidence rates we observed, including intercenter and ethnic group effects. Differential exposure to biological factors, such as unknown environmental contaminants, diet,[44] or infectious agents,[45] can also not be ruled out. The results are not consistent with causal hypotheses suggesting that genetic factors alone are sufficient for the majority of psychosis; gene × environment interactions are much more likely.

COMPARISON WITH PREVIOUS STUDIES

Unlike some previous studies that have relied on case-register data,[46-48] or informal case referrals,[21] ÆSOP is a population-based first-episode study capturing all potential cases who made contact with mental health services within the catchment area(s), where we know they are not treated only in primary care.[49] We have not included subclinical, subsyndromal psychotic symptoms that may occur in the general population, a phenotype presently attracting interest.[50,51] However, the nosological and phenomenological status of such symptoms remains unclear, particularly with respect to whether they evolve into formal psychotic syndromes. It seems clear that help seeking and contact with mental health services mark an important inflexion on any proposed continuum of psychosis in the general population. Our broad inclusion criteria and diagnostic approach included subjects with individual psychotic symptoms and what are sometimes called "at-risk mental states" for psychosis defined on a quantitative scale, who also contacted mental health services. These individuals would have been classified as having psychotic diagnoses within the *DSM-IV* "other psychoses" category. Thus, the ÆSOP study includes the widest possible range of psychotic conditions that result in mental health service contact.

To our knowledge, the administrative incidence reported in this study is among the highest observed using consistent methods and standardized diagnoses in Western countries, even after adjustment for age and sex. Few studies have presented the combined rate of all psychoses, which should be considered an important outcome in current clinical practice. It is, however, more relevant herein to discuss observed rates of separate psychoses where more comparative literature is available. For comparability with previous studies, we calculated the *International Statistical Classification of Diseases, 10th Revision*[52] incidence of F20 schizophrenia in our study centers (data not shown). Incidence in Southeast London, after adjustment for age and sex, was 25.3 per 100 000 person-years. This is comparable with the very highest rates of schizophrenia previously observed in the United Kindgom[14,47,53,54] and counters recent suggestions that the incidence of schizophrenia is in decline,[4,10] providing some support to the contrary.[55]

The results demonstrate the relative position of syndromal schizophrenia within the totality of first-episode psychoses. At just more than one third of cases, it was not much more common than affective and other psychoses at first episode. Two recent studies indicated an evolution of diagnosis over the first few years of psychosis toward schizophrenia and, to a lesser extent, the affective psychoses, away from substance-induced and acute syndromes.[56,57] Our first-contact study probably underestimates the true, or ultimate, rate of the schizophrenia syndrome because some cases would have remained undifferentiated at initial examination. Clinically, this reinforces the need for periodic reformulation of diagnosis. The notion of preventing syndromes evolving into schizophrenia is attractive but needs empirical support that should take into account broader outcomes as well as diagnosis.

The excess incidence of nonaffective disorders in Southeast London compared with Nottingham or Bristol is consistent with a dose-response relationship with urbanicity demonstrated in several recent studies.[16,17] Ethnicity did not explain this association. Socioenvironmental risk factors that have previously been hypothesized to account for this include urban birthplace,[16] social capital,[58] neighborhood environment,[59] or restricted social networks.[60] It will be important to consider these and other explanations for this excess in highly urban areas, such as Southeast London, in future research.

We have also shown that the BME group is at greater risk of psychoses. This population not only includes nonwhite ethnic groups, but non-British white groups, suggesting rates may be raised across all ethnic groups. An increased risk of psychoses in minority ethnic groups has been frequently demonstrated in Europe[22,24] and the United Kingdom, particularly for the African Caribbean group.[19,20] This has led to hypotheses that migration and associated stresses may increase the risk of developing a psychosis either for the migrant or for subsequent generations.[25,61] The increase in psychoses for the BME group observed in this study does not refute this hypothesis. We found no evidence to support the hypothesis that the increased rate in Southeast London was due to an excess of second or third generation migrants. Risk factors associated with migration and ethnicity are likely to be modified by the neighborhood-level effects discussed earlier, and the association with psychoses is unlikely to be a simple one. We have already shown differences between ethnic groups in terms of pathways to care[62,63] and will, in the future, address the interface between neighborhood-level effects, migration, and ethnicity to understand how these affect the risk of first-onset psychoses for different groups.

CONCLUSIONS

The incidence of schizophrenia and other psychotic syndromes is not uniform in terms of age, sex, ethnic group, and place. Exploratory Poisson modeling suggests that very high rates of psychoses are present in the uniformly urban London study area compared with 2 other UK study centers, even after adjustments for age, sex, and ethnicity. This multidimensional heterogeneity has implications for policy, mental health service development, and the biological characteristics of the psychoses. It sets the scene for future investigation using the more detailed assessments of individual and geographical characteristics that are available in the ÆSOP study to examine causation.

Submitted for Publication: April 26, 2005; final revision received July 5, 2005; accepted July 28, 2005.
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Funding/Support: This study was funded by grants from the Medical Research Council, London, England, and the Stanley Medical Research Institute, Bethesda, Md.
Acknowledgment: We would like to thank the staff in the mental health services who helped in the case ascertainment and the research subjects. We gratefully acknowledge advice from the late R. E. Kendell, FRCPsych, regarding the design of the study. We wish to acknowledge the contributions of the entire ÆSOP study team, listed online at http://www.psychiatry.cam.ac.uk/aesop.

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