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.


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.

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Doubt remains as to whether the incidence of schizophrenia varies according to the classic epidemiological dimensions of time, place, and person. Several studies suggest considerable variability while others, including the World Health Organization (WHO) 10-country study, have been interpreted as indicating homogeneity. There is even less confidence about affective psychoses and bipolar disorder. 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, ignoring potentially important differences in incidence at a subregional level. Several studies and a systematic review 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. Migrants may be particularly exposed to the effects of urbanicity, the related but distinct effects of social deprivation, and...
other unknown factors. High incidence rates compared with the host population have been reported in people of African Caribbean origin in the United Kingdom\textsuperscript{10-21} and in immigrants to other European countries.\textsuperscript{22-23} 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\textsuperscript{7} and previous epidemiological investigations in our centers.\textsuperscript{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, non-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.,\textsuperscript{26} 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)\textsuperscript{29}, a modified Personal and Psychiatric History Schedule\textsuperscript{30}, 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.\textsuperscript{30} These diagnoses were categorized in 5 ways: all psychoses, affective psychoses (DSM-IV 296.x4, 296.4, 296.89), non-affective psychoses (DSM-IV 293.xx, 297.xx, 298.8, 298.9), schizophrenia (DSM-IV 295.x) (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).\textsuperscript{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 \( \kappa \) 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.
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.

Positive effects that are easier to interpret.

dence rate ratios (IRRs); these are presented as 1/IRR, giving

don study center was used as the baseline for reported inci-
dences in the incidence of psychoses between study centers,

fitted between variables where appropriate. The Southeast Lon-

cinity as a potential explanatory variable. Interaction terms were

having controlled for age and sex and having introduced eth-

ses 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

rates are presented per 100 000 person-years. Analy-

s were conducted using Stata (version 8).32

Both crude and age-sex–adjusted incidence rates were cal-

culated with their 95% confidence intervals (CIs) for each study

center. Rates are presented per 100 000 person-years. Analy-

s 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 strati-

fied 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 dif-

ferences in the incidence of psychoses between study centers,

having controlled for age and sex and having introduced ethnic-

ity as a potential explanatory variable. Interaction terms were

fitted between variables where appropriate. The Southeast Lon-
Figure 2 shows the distribution of cases by diagnosis. Sixty-seven percent of cases received a diagnosis of non-affective 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 (\( \lambda \)) 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 (\( \lambda = 54.5 \) [95% CI, 48.7-60.9]) was more than twice that observed in Nottingham (\( \lambda = 25.1 \) [95% CI, 21.9-28.8]) or Bristol (\( \lambda = 22.1 \) [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, 2.3 [95% CI, 1.7-3.3]).

All Psychoses

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 (\( \lambda = 37.4 \) [95% CI, 32.3-42.5]) than Nottingham (\( \lambda = 13.1 \) [95% CI, 10.6-15.5]) or Bristol (\( \lambda = 13.2 \) [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*

<table>
<thead>
<tr>
<th>Psychoses</th>
<th>Overall (n = 568)</th>
<th>London</th>
<th>Nottingham</th>
<th>Bristol</th>
<th>Crude Rate</th>
<th>Adjusted Rate (95% CI)</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>34.8</td>
<td>32.1 (29.4-34.8)</td>
<td>...</td>
</tr>
<tr>
<td>Nonaffective psychoses</td>
<td>Overall (n = 378)</td>
<td>23.2</td>
<td>21.9 (19.1-23.5)</td>
<td>...</td>
<td>40.5</td>
<td>37.4 (32.3-42.5)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>London</td>
<td>13.9</td>
<td>13.1 (10.6-15.5)</td>
<td>0.3 (0.3-0.4)</td>
<td>14.3</td>
<td>13.2 (8.9-17.4)</td>
<td>0.4 (0.2-0.5)</td>
</tr>
<tr>
<td></td>
<td>Bristol</td>
<td>12.8</td>
<td>11.7 (10.1-13.3)</td>
<td>...</td>
<td>12.0</td>
<td>12.0 (9.2-14.8)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; ellipses, not applicable.

*Per 100,000 person-years.

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, 1.1-2.1]) 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.

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

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Unadjusted IRR (95% CI)</th>
<th>Adjusted IRR (95% CI)*</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (vs women)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All psychoses</td>
<td>1.4 (1.2-1.7)</td>
<td>1.5 (1.3-1.8)</td>
<td>.05†</td>
</tr>
<tr>
<td>Nonaffective psychoses</td>
<td>1.7 (1.4-2.1)</td>
<td>1.8 (1.4-2.2)</td>
<td>.46†</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>2.3 (1.7-3.1)</td>
<td>2.4 (1.8-3.2)</td>
<td>.05†</td>
</tr>
<tr>
<td>Affective psychoses</td>
<td>0.9 (0.7-1.3)</td>
<td>1.0 (0.7-1.3)</td>
<td>.04†</td>
</tr>
<tr>
<td>BME group (vs white British)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All psychoses</td>
<td>3.6 (3.0-4.2)</td>
<td>2.9 (2.4-3.5)</td>
<td>...</td>
</tr>
<tr>
<td>Nonaffective psychoses</td>
<td>4.0 (3.3-5.0)</td>
<td>3.0 (2.4-3.7)</td>
<td>...</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>4.6 (3.6-5.1)</td>
<td>3.6 (2.7-4.9)</td>
<td>...</td>
</tr>
<tr>
<td>Affective psychoses</td>
<td>3.6 (2.6-4.9)</td>
<td>3.2 (2.3-4.6)</td>
<td>...</td>
</tr>
<tr>
<td>All psychoses</td>
<td>1.4 (1.2-1.7)</td>
<td>1.5 (1.3-1.8)</td>
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<td>.04†</td>
</tr>
</tbody>
</table>

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.

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 (λ = 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 (λ = 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, 2.0-8.3). The peak incidence for schizophrenia in women (age
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. 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. The age-specific incidence of affective psychoses is less commonly investigated; 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), 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 South-east 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, problems that dogged previous data. 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-
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 ÅSOP 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 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 Kingdom 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.6,17 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 non-white 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 and the United Kingdom, particularly for the African Caribbean group. 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. 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 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.

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