ORIGINAL ARTICLE

Summer Birth and Deficit Schizophrenia

A Pooled Analysis From 6 Countries

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Background: In some reports, summer birth has been associated with deficit schizophrenia. Deficit schizophrenia and nondeficit schizophrenia also differ in several other ways.

Objective: To conduct a combined analysis of the published and unpublished data sets from the northern hemisphere that relate deficit and nondeficit schizophrenia to month of birth.

Data Sources: Studies of season of birth in which it was possible to make a deficit/nondeficit categorization.

Study Selection: Published studies with samples of convenience and all known population-based studies with the deficit/nondeficit categorization were included. The studies came from 6 countries.

Data Extraction: Three published studies of samples of convenience, 2 population-based prevalence studies, and 5 population-based studies that approximated incident samples were included. Month of birth was compared for deficit and nondeficit schizophrenia, using meta-analytic fixed-effects models.

Data Synthesis: A group x month goodness-of-fit χ^2 showed a significant difference between deficit and nondeficit subjects in season of birth ($P < .001$) in the studies that approximated incidence. This difference was largely due to an increase in deficit schizophrenia births in June and July (odds ratio, 1.9; 95% confidence interval, 1.3-2.9). Similar results were found in the prevalence studies. A similar pattern was found in 2 of the 3 samples of convenience, but when combined, these 3 samples did not show a significant deficit/nondeficit difference.

Conclusions: Deficit schizophrenia has a season of birth pattern that differs from that of nondeficit schizophrenia. This analysis supports the notion of a separate disease within schizophrenia.

Arch Gen Psychiatry. 2004;61:985-989

SCHIZOPHRENIA IS A CLINICALLY heterogeneous disorder and may consist of a group of diseases with overlapping clinical features but different etiologies and, to some extent, different pathophysiologies. The association of different risk factors with different clinical features would be an important step in defining subgroups that are more homogeneous relative to their pathophysiology.

Winter birth was first reported to be a risk factor for schizophrenia in 1929, and there have been many replications of this association in different sites.[1] Clinical characteristics that have been associated with winter birth include paranoid subtype and a more benign course of illness, although these have not always been found.[2,3]

The clinical features associated with winter birth differ from those of patients with deficit schizophrenia, a group defined by primary, enduring negative symptoms and a relatively severe form of the illness.[4] Consistent with this suggestion of a deficit/nondeficit difference in season of birth, a summer birth excess in patients with deficit schizophrenia has also been found in several studies.[5-8] Confirmation of a different risk factor profile for deficit and nondeficit groups would support the hypothesis that the deficit group represents an etiologically distinct form of schizophrenia and would be consistent with other evidence that deficit and nondeficit patients with schizophrenia also differ relative to course of illness, biological correlates, and treatment response.[9]

An important limitation of the existing studies of the summer birth effect is sample size. The deficit schizophrenia group comprises 15% to 20% of schizophrenia cases in epidemiological samples. If, for instance, 30% of nondeficit patients are born in the summer, one would need 86 deficit and 344 nondeficit cases

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to have 80% power to detect an odds ratio of 2.[10] However, previous studies of summer birth and deficit schizophrenia have often used smaller samples.

In the present study, we pooled data from the previously published studies as well as unpublished data. We performed a separate analysis for samples of convenience, prevalence studies, and studies approximating incidence, as well as a pooled analysis to produce a total estimate of the season effect in deficit schizophrenia.

METHODS

Data came from studies that made the deficit/nondeficit categorization within schizophrenia on the basis of the Schedule for the Deficit Syndrome (SDS), the Proxy for the Deficit Syndrome (PDS),[6-9,11] or a consensus medical record review diagnosis. The SDS[12] is a semistructured interview for the identification of primary and enduring negative symptoms and is the standard method for identifying patients with deficit schizophrenia. Administration of the SDS is usually not feasible in large epidemiological samples, so medical record review and the PDS[11] have also been used. The present analysis includes data from 6 studies in which the PDS was used.[8,13,14] The PDS quantifies the combination of typical negative symptoms and diminished emotionality, and it generates a score for each subject. On the basis of prevalence assumptions, cutoff points for deficit and nondeficit groups are defined. The validity of the categorizations is then tested by comparing the 2 diagnostic groups' clinical features. This approach has also been validated by comparison with SDS diagnoses.[11] Details on the validation procedures are included in the original publications.[8,11,13,14] Methods for the medical record reviews are discussed below. Where possible, the present analyses were conducted with samples meeting *DSM* criteria for schizophrenia; however, for some of these studies, *DSM* criteria were not used.

Studies were categorized based on the sampling method: convenience samples, population-based prevalence samples, and population-based samples with incident cases or samples that approximated incidence. Data came from 2 prevalence epidemiological samples in the northern hemisphere[6,7] and from 2 articles with results from 3 samples of convenience.[5,15] Data from the studies approximating incidence came from previously published studies (Camberwell,[8] Dumfries and Galloway,[14] and Cantabria[13]), the Suffolk County Mental Health Project (a previous publication was based on a partial Suffolk County Mental Health Project sample[5]), and unpublished data from the Roscommon Family Study.[16] Studies were conducted with institutional review board approval for each site.

SAMPLES OF CONVENIENCE

Samples of convenience came from the Maryland Psychiatric Research Center, the *DSM-IV*[17] Field Trial,[5] and a French multicenter study.[15] All 3 of these studies used the SDS in patients with *DSM-III*[18] schizophrenia.

PREVALENCE STUDIES

The first population-based study of prevalent cases came from Nithsdale,[6,7] a town in the region of Dumfries and Galloway in Scotland. There was overlap between this sample and the Dumfries and Galloway incidence study described below. However, this was probably small because the study in Dumfries and Galloway used a registry to identify patients, whereas in the Nithsdale study, on May 1, 1996, all patients with an *International Classification of Diseases, Ninth Revision (ICD-9)*[19] diagnosis of schizophrenia in Nithsdale were identified by the key informant method.

The other prevalence data[7] came from the 5-site Epidemiological Catchment Area study. In that study, psychiatric symptoms were assessed with the National Institute of Mental Health Diagnostic Interview Schedule (DIS), administered by lay interviewers.[20] Because there was little agreement between the Diagnostic Interview Schedule diagnosis and the psychiatrist's ascertainment of schizophrenia, this analysis used an alternative definition based on the number of psychotic symptoms. There is a suggestion that this strategy yielded a categorization closer to the clinician's assessment.[21] For details, see the original publication.[7]

In both prevalence studies, the deficit/nondeficit categorization was made using the PDS.

POPULATION-BASED STUDIES APPROXIMATING INCIDENCE

Roscommon, Ireland

The Roscommon Family Study was a population registry–based family study of affective and psychotic disorders in Roscommon County, western Ireland,[22] and therefore it approximated an incidence sample. Schizophrenia diagnoses used a best-estimate procedure and *DSM-III-R*[23] criteria. The deficit/nondeficit categorization was based on review of clinical information by 2 independent raters[16]; interrater reliability for this categorization was calculated in a subset of 12 subjects (92% agreement, $\kappa = 0.82$). Raters were blind as to the month of birth. A total of 137 subjects with schizophrenia and simple schizophrenia were included; in this sample, simple schizophrenia appeared to be genetically related to schizophrenia.[24]

Camberwell, England

Cases from the Camberwell Study were based on the Camberwell Cumulative Psychiatry Case Register, which recorded contacts with psychiatric services in an area of southern London, England.[25] Records were reviewed using the Operational Criteria Checklist for Psychotic Illness, and diagnoses were generated using a computerized algorithm (OPCRIT[26]). A previous publication on season of birth in this sample used Research Diagnostic Criteria[8]; data presented here used *DSM-III* diagnoses for schizophrenia. The PDS was used to distinguish deficit and nondeficit subjects.

Dumfries and Galloway, Scotland

This sample included all patients coming in contact with psychiatric services in Dumfries and Galloway from 1979 to 1998 who had a diagnosis of schizophrenia or schizoaffective disorder. The Operational Criteria Checklist for Psychotic Illness was completed based on review of medical records for each subject[26]; subjects had an OPCRIT *DSM-IV* diagnosis of schizophrenia. The PDS was used to categorize subjects as having deficit or nondeficit schizophrenia.[14]

Cantabria, Spain

The Cantabria First Episode Schizophrenia Study[27] included all patients diagnosed as having a psychotic disorder in treatment facilities in the Autonomous Community of Cantabria in Spain. A Spanish translation of the Present State Examination[28] was used to generate a CATEGO diagnosis. Subjects with a diagnosis of schizophrenia or paranoid psychosis were included; *DSM* diagnoses were not available. The PDS was used to distinguish deficit and nondeficit subjects.[13]

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Suffolk County, New York, United States

The Suffolk County Mental Health Project assessed patients with a first episode of psychotic symptoms in Suffolk County, New York, at the time of first treatment and at 6- and 24-month follow-ups.[29] Structured rating scales and notes from interviews were reviewed. At least 2 of 3 raters (R.W.B., W.T.C., and B.K.) reviewed each subject's information; if those 2 raters did not agree on the categorization, the third rater reviewed the information and a consensus was reached. Raters were blind to month of birth. Of 182 subjects with a *DSM* diagnosis of schizophrenia, 151 were categorized as nondeficit, 27 as deficit, and 4 were not categorized owing to insufficient information. A previous publication of Suffolk County birth data was based on a partial sample.[11]

ANALYSIS

We used a goodness-of-fit χ^2 test for the 2×12 to compare the distribution of birth between deficit and nondeficit subjects. As previous studies showed a summer increase, the data suggested the effect was restricted to a difference in June and July; the odds of June/July birth were calculated for each sample, and a pooled estimate was produced in 2 stages: first by study design (samples of convenience, prevalence samples, and study samples approximating incidence) and second by pooling all available estimates. Because of a lack of data, a time-series analysis was not possible.

Along with the odds ratio for summer birth (June/July birth) and its standard error, a heterogeneity test was performed to assess differences among the studies. Meta-analytic estimates were calculated using a fixed-effects model, and each estimate was entered in the calculation. A sensitivity analysis was also performed in which we omitted each study in turn. We attempted to minimize publication bias by including all available studies, including unpublished data; however, it is still possible that studies reporting an association have been more likely to be published, leading to publication bias. Analyses were performed using Stata version 7.0.[30]

RESULTS

A total of 1594 subjects were included in the 9 studies (407 in the samples of convenience, 331 in the prevalence samples, and 856 in the incidence samples).

The birth distribution of the samples of convenience studies is presented in **Figure 1**. For these studies, the goodness-of-fit test was not statistically significant ($\chi^2_{11}=18.05$, $P=.08$). The test for heterogeneity in these studies approached significance ($\chi^2_2=5.53$, $P<.06$). For June/July birth, the pooled estimate was not statistically significant (odds ratio, 1.59; 95% confidence interval, 0.93-2.74).

The birth distribution for the population-based prevalence studies is presented in **Figure 2**. For these studies, the goodness-of-fit test was statistically significant ($\chi^2_{11}=60.9$, $P<.001$). The test for heterogeneity was not significant ($\chi^2_1=0.23$, $P<.63$), allowing the pooling of the samples. The pooled odds ratio for June/July birth from these 2 studies was 1.64 (95% confidence interval, 1.04-2.59).

The birth distribution for the population-based samples approximating incidence is presented in **Figure 3**. For these studies, the goodness-of-fit test was statistically significant ($\chi^2_{11}=42.95$, $P<.001$). The test for heterogeneity was not significant ($\chi^2_4=1.43$, $P<.84$), allowing for the calculation of a pooled estimate; for June/July birth, this estimate was statistically significant (odds ratio, 1.95; 95% confidence interval, 1.31-2.91).

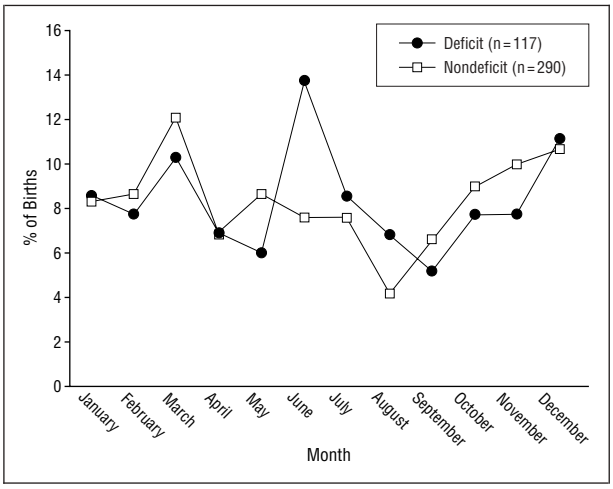

Figure 1. Monthly birth distribution in subjects with deficit and nondeficit schizophrenia in 3 northern hemisphere samples of convenience.

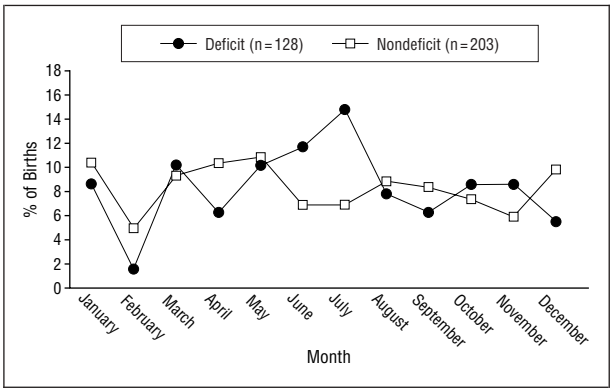

Figure 2. Monthly birth distribution in subjects with deficit and nondeficit schizophrenia in 2 northern hemisphere prevalence samples.

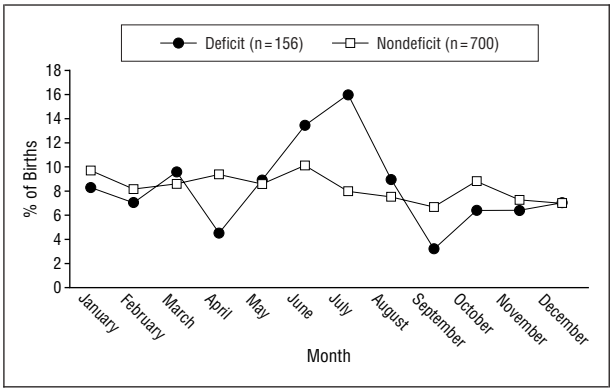

Figure 3. Monthly birth distribution in subjects with deficit and nondeficit schizophrenia in 5 northern hemisphere incidence samples.

The sensitivity analysis for all the studies combined, with the pooled estimate after omission of each study, showed a consistent pattern of association; that is, no single study, when omitted, rendered the association nonsignificant (data not shown). The pooled odds ratio estimate for June/July birth, including all studies independent of study design, was statistically significant (odds ratio, 1.93; 95% confidence interval, 1.46-2.55) (**Figure 4**).

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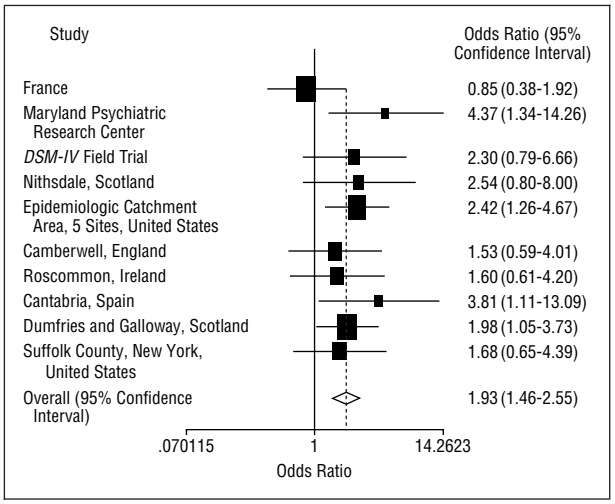

Figure 4. Odds of June/July birth. In order, the studies are based on 3 samples of convenience (*DSM-IV* Field Trial, Maryland Psychiatric Research Center outpatients, and French multicenter study), 2 population-based prevalence samples (Epidemiological Catchment Area and Nithsdale), and 5 population-based studies of incidence cases or cases that approximated incidence samples (Camberwell, Roscommon, Dumfries and Galloway, Cantabria, and Suffolk County). Size of the box is proportional to the number of subjects in the study.

COMMENT

This pooled analysis of data from 6 countries in the northern hemisphere showed a significant association between deficit schizophrenia and summer birth. A similar pattern was found in studies of samples of convenience, population-based prevalence samples, and population-based samples that approximated incidence. Information on month of birth only, as opposed to day of birth, was available across studies, and our analyses found an increase in June/July. However, it is likely that a more seasonal pattern would have been apparent with more detailed information. In future studies of season of birth, it would be useful to define the period of risk as June and July, if information on month of birth only is available.

Three different methods for categorizing patients into deficit and nondeficit groups were used: administration of the SDS, medical record review, and the PDS. There was also variation in the diagnostic criteria for schizophrenia. However, any misclassifications or misdiagnoses due to this variance in methods should bias these studies toward a failure to find an association. The consistency of the pattern across all of these data sets supports the existence of the association that we found.

All of the studies included in our analyses were conducted in the northern hemisphere. An unpublished multicenter prevalence study by McGrath and colleagues from Australia failed to show an association between deficit schizophrenia and summer birth. These data are difficult to interpret because the winter birth effect size is larger in sites further away from the equator[31] and the latitude of these Australian sites is approximately 28° to 32° south. In contrast, the approximate latitudes for the northern hemisphere sites we included in the present analysis range from 41° to 55°. A study of deficit/nondeficit births from higher latitudes in the southern hemisphere would be of considerable interest.

Although survival bias (survival in the usual sense as well as survival as a case) can lead to different results in incidence vs prevalence studies, the similarity in results between the prevalence studies and the studies approximating incidence suggests survival bias did not have a substantial impact on the association between summer birth and deficit schizophrenia. In future studies of the summer birth effect, population-based prevalence studies appear likely to yield results that are not distorted by survival bias. The overlap between the Nithsdale study and the Dumfries and Galloway study was a limitation of our analysis, but this overlap was small, and examination of both samples gave us an opportunity to examine the season of birth effect size in overlapping populations with prevalence vs incidence sampling.

From the present data, it is not possible to conclude whether the association between deficit schizophrenia and summer birth reflects an increase in summer birth in the deficit group compared with the general population or a decrease in summer birth in the nondeficit group. However, publications on these prevalence studies have provided data that suggest the deficit group has an increase in summer births compared with the general population.[7,14] Because schizophrenia as a whole is associated with winter birth and the smaller deficit group is robustly associated with summer birth, the nondeficit group appears to be abnormal as well. The finding of a summer birth excess in deficit schizophrenia does not contradict the winter birth excess[1] because the deficit group represents a relatively small percentage (15%-20% of first episode patients) of schizophrenia. The winter birth effect is probably stronger than previously thought because both deficit and nondeficit cases have been included in previous studies of the winter birth effect, but the winter birth effect appears to apply exclusively to nondeficit patients. It is important to note that even with an association with summer birth, only a minority of patients with deficit schizophrenia is born in June/July. An age-incidence bias, which was proposed as an explanation for the winter birth effect but was subsequently refuted,[32] would not account for an association with birth in the middle of the year.

Our results support the concept of a double dissociation in deficit vs nondeficit schizophrenia and the risk factor of season of birth, with the deficit group associated with summer birth and the nondeficit group with winter birth. This difference strongly suggests differences in etiology between the 2 groups. Data on family history and the prevalence of Borna disease virus seropositivity provide other evidence for etiological differences.[8,16,33] Seasonal variations in infectious agents,[1] sunlight exposure and vitamin D,[34] and the availability of nutrients[3] have been proposed as possible explanations for the seasonality of births in schizophrenia. However, to date, no specific agent has been identified. Nonetheless, summer birth may be a useful variable in studies of gene-environment interactions. More generally, etiological studies of schizophrenia would benefit from making the deficit/nondeficit categorization whenever possible.

This epidemiological analysis adds to the evidence of clinical and neurobiological differences between deficit

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and nondeficit patients.[4,5,11,29,35-44] As we have argued elsewhere, this evidence, taken together, is consistent with the proposition that deficit schizophrenia is a separate disease within the syndrome of schizophrenia.[9]

Submitted for Publication: October 25, 2002; final revision received April 21, 2004; accepted April 26, 2004.
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Funding/Support: This study was supported in part by grants MH44801 (Dr Bromet), MH41953 (Dr Kendler), MH40279 (Dr Carpenter), and MH60487 (Dr Messias) from the National Institutes of Health, Rockville, Md.
Acknowledgments: James Tonascia, PhD, Department of Biostatistics, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Md, and Robert McMahon, PhD, Maryland Psychiatric Research Center, Baltimore, both provided statistical consultation.

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