Decline in the Incidence of Schizophrenia in Finnish Cohorts Born From 1954 to 1965

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Background: The declining incidence of schizophrenia observed in several countries is believed by many to merely reflect methodological problems in the studies performed. We report the first nationwide historical cohort study of changes in the incidence of schizophrenia, in which many of the previous methodological problems were overcome.

Methods: We used the Finnish Population Register to identify everyone born in Finland from 1954 to 1965. These persons were followed up from their 16th to their 26th birthdays, and all cases of schizophrenia (International Classification of Diseases, Eighth Revision and International Classification of Diseases, Ninth Revision code 295) that emerged were identified from the National Hospital Discharge Register, the Pension Register, and the Free Medicine Register. Persons for whom an age of onset could be defined were included in the analyses (n = 5645). We used the Poisson regression model to estimate the effects of age, sex, birth cohort, period of diagnosis, and season of birth on the incidence of schizophrenia. The relative importance of cohort and period were assessed using an age-period-cohort model.

Results: The incidence declined significantly in each successive cohort, from 0.79 to 0.53 per 1000 among males and from 0.58 to 0.41 per 1000 among females. The effects of cohort and period on the change were both significant.

Conclusions: The incidence of schizophrenia has declined in Finland. This was partly caused by confounding factors, as reflected in the significant period effect. The significant birth cohort effect suggests that the intensity or frequency of one or more risk factors for schizophrenia has decreased.

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SUBJECTS AND METHODS

COHORTS

The Population Register Center provided sex-specific, monthly numbers of births in each Finnish municipality (n = 548 between 1954 and 1965) from 1940 to 1969 as multidimensional tables, with sex and year, month, and place of birth as marginals. A large number of birth cohorts was thus formed, each consisting of males or females born in the same municipality during 1 month of a particular year. From each we obtained the number of deaths up to 1969 and the annual number of deaths from 1970 to 1991. Persons born outside Finland or of unknown birthplace were excluded from the study population.

SUBJECTS

We limited this study to persons born between 1954 and 1965 to be reliably able to identify the first admission and allow identical follow-up times for each cohort. We used 3 nationwide registers, the National Hospital Discharge Register, the Pension Register, and the Free Medicine Register, to identify all persons who had been hospitalized or who were receiving a disability pension or free antipsychotic medication because of schizophrenia. Patients with a diagnosis code of 295 according to International Classification of Diseases, Eighth Revision (ICD-8) and International Classification of Diseases, Ninth Revision (ICD-9) were accepted, which includes schizophrenia, schizophreniform disorder, and schizoaffective disorder. Data were linked using personal identification numbers, which code birthdate and sex and are unique for each person. Background demographic variables for each individual were obtained from the Population Register Center.

The Population Register Center records birthplace, residence, marital status, and first-degree relatives, and also the date of death for persons who have died since the register was established. The National Hospital Discharge Register covers all hospitals. It lists admission and discharge dates, and primary and up to 3 subsidiary diagnoses for each inpatient and day-patient stay. First admissions are not coded separately. The Pension Register includes beginning dates and the primary diagnoses for all disability pensions, and the Free Medicine Register includes the diagnoses of persons receiving free outpatient medication. The health care registers were computerized in 1968. The ICD-8 diagnostic criteria and codes were used before 1987; since then, psychiatric diagnoses have been coded according to ICD-9, applying DSM-III-R diagnostic criteria. However, schizophrenia was coded separately in the Free Medicine Register only until 1987, whereafter all psychotic disorders received the same coding. Information up to 1992 was obtained from each register.

Each person was followed up from his or her 16th through 26th birthdays. Patients born outside Finland or of unknown birthplace were excluded. Patients had to have received the first diagnosis of schizophrenia between their 16th and 26th birthdays. However, age at onset was defined as age at the beginning of the first hospitalization for any psychotic disorder (ICD-8 and ICD-9 codes 295-299), which is a closer approximation of the time of emergence of first psychotic symptoms than the age at the beginning of first hospitalization for schizophrenia. In addition, patients for whom disability pension because of schizophrenia had been granted somewhere between their 16th and 26th birthdays and who were hospitalized for any psychotic disorder at that age were also included. Age at onset for them was also defined as age at the beginning of the first hospitalization for any psychotic disorder. Persons who received the first diagnosis of schizophrenia after their 26th birthday were not included in the sample (Table 1).

Table 1. Patients With Schizophrenia Born Between 1954 and 1965, Followed Up From Their 16th to 26th Birthdays*

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Person-Years (1000)</th>
<th>Included†</th>
<th>Age at Onset &lt;16 y‡</th>
<th>Disability Pension, No Hospitalization§</th>
<th>Free Medication, No Hospitalization‖</th>
</tr>
</thead>
<tbody>
<tr>
<td>1954-1955</td>
<td>1736</td>
<td>1191</td>
<td>46</td>
<td>113</td>
<td>60</td>
</tr>
<tr>
<td>1956-1957</td>
<td>1701</td>
<td>1116</td>
<td>51</td>
<td>88</td>
<td>29</td>
</tr>
<tr>
<td>1958-1959</td>
<td>1597</td>
<td>945</td>
<td>35</td>
<td>63</td>
<td>36</td>
</tr>
<tr>
<td>1960-1961</td>
<td>1601</td>
<td>869</td>
<td>40</td>
<td>64</td>
<td>24</td>
</tr>
<tr>
<td>1962-1963</td>
<td>1602</td>
<td>788</td>
<td>44</td>
<td>51</td>
<td>20</td>
</tr>
<tr>
<td>1964-1965</td>
<td>1559</td>
<td>736</td>
<td>44</td>
<td>51</td>
<td>12</td>
</tr>
</tbody>
</table>

* Data are number of patients unless otherwise specified.
† First diagnosis of schizophrenia between 16th and 26th birthday, at least 1 hospitalization.
‡ First diagnosis of schizophrenia before 16th birthday.
§ Disability pension because of schizophrenia granted before 26th birthday, no hospitalizations.
‖ Free medication but no hospitalizations or disability pension because of schizophrenia.

years old in the first and 40 to 60 years old in the second. In etiologic research, however, changes between birth cohorts are more interesting than changes between periods. The effects of period and cohort on incidence changes can be separated using the age-period-cohort analysis method, although only one study of schizophrenia has used this.11

Finland is an ideal country to study time trends in the incidence of schizophrenia because of the existence of reliable, person-identifiable population and health care registers, a homogenous population, and a low migration rate.28 We exploited these assets to conduct the first nationwide historical cohort study of the incidence of schizophrenia among all persons born in Finland be-
We excluded patients first diagnosed with schizophrenia before their 16th birthdays, because the available follow-up time was not identical for all cohorts. These patients were identified from the registers and their numbers in each cohort compared to estimate whether their exclusion caused any bias. We also excluded patients with no hospitalizations, because a meaningful age of onset could not be defined. Their numbers allowed us to estimate the proportion of patients treated as outpatients in each cohort (Table 1).

We also identified persons who had only received a diagnosis of other nonaffective psychotic disorder (ICD-9 codes 297-299) between their 16th and 26th birthdays to assess whether any changes in the incidence of these disorders had occurred. These codes include delusional disorder, brief psychotic disorder, and psychotic disorder not otherwise specified.

STATISTICAL ANALYSIS

Age-specific incidences in each cohort and period were first calculated using exact person-years at risk for each cohort. Age refers here to age at onset as defined above, period to year of onset, and cohort to year of birth. Age, period, and cohort were each divided into 2-year intervals.

Age-period-cohort analyses aim to separate the effects of age, period, and cohort on changes in the rates of a particular disorder. The problem with such analyses is that age, period, and cohort are linearly dependent: knowing any 2 of them, the third can be calculated. Because of this, the linear effects of age, period, and cohort cannot be separated; there is no unique set of regression parameters. Different methods to overcome this nonidentifiability problem have recently been reviewed by Robertson and Boyle. Methods that estimate deviations from linearity, which are measures of curvature and are estimable, are the only ones that avoid using arbitrary constraints or making strong assumptions about the effects of age or cohort. We used one of these, the method of Clayton and Schifflers, in which a parameter called drift, representing the sum of linear period and cohort effects, is introduced to represent regular, linear trend. Drift, unlike the separate linear effects of cohort and period, is estimable. After fitting the drift term, the curvature effects of age, cohort, and period can be reliably estimated.

We used the Poisson regression model with standard Poisson assumptions. The effects of age, period, and cohort were assumed to be multiplicative. Seasonality of monthly number of births was modelled using the method of Jones et al, which allows an arbitrary shape for the seasonal effect by representing the data as a short Fourier series. Only the first harmonic was found significant, and was entered into the main model as “seasonality.” After fitting the main effects, all 2-variable interactions involving sex were tested.

Curvature effects mean that the relative risks between adjacent periods or cohorts are not identical, and are therefore expressible as contrasts between such relative risks. Clayton and Schifflers recommended the use of these contrasts, because their value is affected only by neighboring data. Thus, we estimated curvature effects by calculating the ratio of relative risks in adjacent periods. The significance of each explanatory variable, after adjusting for the effect of other variables, was assessed by comparing the full age-period model with one including all other variables except the one whose significance was tested.

The goodness of fit of the models was compared using χ² likelihood ratio tests. Analyses were performed with statistical software S-PLUS, version 3.4.

RESULTS

INCIDENCE

Incidence peaked in the 20- to 21-year age group in both sexes, and no sex differences in onset age were detected (Figure 1). Males had 31% higher incidence than females (Figure 1). Incidence declined significantly in successive cohorts, from 0.79 per 1000 among males and 0.58 per 1000 among females in the 1954 to 1955 cohort to 0.53 and 0.41 per 1000, respectively, in the 1964 to 1965 cohort (Table 2). A steady decline in incidence was observed among the 16- to 19- and 22- to 23-year-old males. Among 20- to 21-year-old males, incidence fell in the 1954 to 1959 cohorts but then rose slightly in the 1960 to 1963 cohorts, after which it declined again. In 24- to 25-year-old males, incidence rose until the 1958 to 1959 cohort, after which it declined. Among 16- to 19-year-old females, a sharp fall occurred between the 1956 to 1957 and 1958 to 1959 cohorts, while in 20- to 23-year-old females incidence actually rose slightly until the 1958 to 1959 cohort, and then declined. A steady fall in incidence was observed among 24- to 23-year-old females. The overall decline in each age group was of the same magnitude among both sexes (Table 2).

Figure 1. Age-specific incidences per 100 000 for females and males in cohorts born between 1954 and 1965 (N = 5645).
Because the data were cohort-based, the age groups were not equally represented in each period. Only the periods from 1978 to 1983 include all age groups, those aged 16 to 19 years represented by cohorts born in the 1960s and those aged 22 to 25 years by cohorts born in the 1950s. In these periods, the incidences are quite low among the 16- to 19-year-olds but still high among the 22- to 25-year-olds, thus not supporting a strong period effect (Table 3).

The number of patients who had received disability pensions because of schizophrenia before their 26th birthdays and those with free medication because of schizophrenia but without hospitalizations or disability pension decreased in successive cohorts. The number of
patients with childhood-onset schizophrenia was stable, but we lacked information concerning the youngest age groups from the 1950s cohorts (Table 1).

The proportion of patients diagnosed with schizophrenia in their first admission decreased from 77% in the first to 70% in the last cohort. The incidence of other nonaffective psychotic disorders increased from 0.13 to 0.19 per 1000 between the first and last cohorts (Table 4).

**AGE-PERIOD-COHORT MODEL**

After fitting the full age-period-cohort model, the significance of each variable was tested by omitting it and comparing the resulting model with the full model. The main effects of age, sex, period, cohort, and seasonality were all significant (Table 5). The deviances of age and sex were both very large, reflecting their considerable influence on incidence. The deviances of cohort, period, and seasonality were smaller, each of the same magnitude. There were no interactions between sex and age, period, or cohort, but a weak interaction between seasonality and sex was observed ($\chi^2 = 7.0$, $df = 2$, $P = .03$). Both females and males had a significant winter-spring excess of births, but this peaked slightly earlier (February vs March) among females and was sharper (data not shown). Relative risk for developing schizophrenia in the last cohort, compared with the first cohort, was 0.67 among males and 0.71 among females, based on parameter estimates from the model (Table 2). The cohort effect was quite consistent, curvature effects revealing only the rapidity at which the incidence declined between successive cohorts (Figure 2). The period effect was more prominent in the early 1970s and mid to late 1980s (Figure 3).

**COMMENT**

The incidence of schizophrenia in the 16- to 25-year-old groups was higher than in the World Health Organization Ten-Country Study, where incidences of the same magnitude among the 15- to 24-year-olds were observed only in a few areas and with broadly defined schizophrenia. However, previous Finnish studies have obtained similar results: the cumulative incidence of DSM-III-R schizophrenia up to age 28 years was 0.69% in the northern Finland 1966 cohort, and the incidence of all psychotic disorders in a study conducted in the 1980s varied between 0.49 and 0.88 per 1000 among the 15- to 24-year-olds. The prevalence of schizophrenia in Finland is also higher than elsewhere: 1.3% in a study based on the Present State Examination, and 1.2% in a register-based study.

Our method differed from other studies, except that from south Verona, Italy, because we examined birth cohorts, while others investigated patients admitted for the first time in a defined period. Our virtually complete ascertainment of treated patients from entire birth cohorts of 1 country was a major strength. The results suggest that the incidence of schizophrenia has declined. We found no sex differences, while others have found a greater decline in females or in males. The decline was similar to that observed in previous European studies. In accordance with the Scottish age-period-cohort analysis, the effects of period and cohort were both significant.

**COHORT-RELATED FACTORS**

The significant birth cohort effect suggests that the frequency or intensity of 1 or more risk factors involved in the etiology of schizophrenia, probably operating early in life, has decreased—or the intensity or frequency of some protective factors has increased. As no protective factors for schizophrenia are currently known, we will focus on risk factors whose intensity might have decreased. While the most important risk factors for schizophrenia are genetic, environmental factors, which may interact with genetic factors, have also been identified. Both risk factor types may change over time.

### Table 4. Incidences per 1000 of Other Nonaffective Psychotic Disorders in Cohorts Born Between 1954 and 1965

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Person-Years (1000)</th>
<th>No. of Patients</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1954-1955</td>
<td>1785</td>
<td>236</td>
<td>0.13</td>
</tr>
<tr>
<td>1956-1957</td>
<td>1757</td>
<td>250</td>
<td>0.14</td>
</tr>
<tr>
<td>1958-1959</td>
<td>1662</td>
<td>237</td>
<td>0.14</td>
</tr>
<tr>
<td>1960-1961</td>
<td>1676</td>
<td>251</td>
<td>0.15</td>
</tr>
<tr>
<td>1962-1963</td>
<td>1682</td>
<td>285</td>
<td>0.17</td>
</tr>
<tr>
<td>1964-1965</td>
<td>1646</td>
<td>318</td>
<td>0.19</td>
</tr>
</tbody>
</table>

### Table 5. The Fitted Age-Period-Cohort Model Including the Main Effects of Age, Sex, Cohort, Period, and Season of Birth, With Significance Tests for All Main Effects

<table>
<thead>
<tr>
<th>Model</th>
<th>Residual Deviance</th>
<th>df</th>
<th>Test of Significance: Effect</th>
<th>Deviance</th>
<th>df</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grand mean</td>
<td>3250</td>
<td>2159</td>
<td>...†</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Age + sex + cohort + period + seasonality</td>
<td>2412</td>
<td>2137</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Sex + cohort + period + seasonality</td>
<td>2636</td>
<td>2141</td>
<td>Age</td>
<td>283</td>
<td>4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age + cohort + period + seasonality</td>
<td>2519</td>
<td>2138</td>
<td>Sex</td>
<td>106</td>
<td>1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age + sex + period + seasonality</td>
<td>2428</td>
<td>2142</td>
<td>Cohort</td>
<td>16</td>
<td>5</td>
<td>.007</td>
</tr>
<tr>
<td>Age + sex + cohort + seasonality</td>
<td>2440</td>
<td>2147</td>
<td>Period</td>
<td>28</td>
<td>10</td>
<td>.002</td>
</tr>
<tr>
<td>Age + sex + cohort + period</td>
<td>2428</td>
<td>2139</td>
<td>Seasonality</td>
<td>16</td>
<td>2</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*By $\chi^2$ test.
†Ellipses indicate not applicable.
The Finnish population was relatively isolated for centuries. Genetic isolation may be the reason for pockets of exceptionally high prevalence of schizophrenia (3%-4%) in rural eastern and northern Finland.28 Emigration from rural to urban regions increased rapidly after World War II, and marriage between persons originating from different parts of Finland became more common. In our sample, the proportion of patients with parents born in the same municipality fell from 30% in 1954 to 23% in 1965. This may have caused the incidence to decline, if genes predisposing to schizophrenia have been enriched in some areas of Finland.

Public health care in Finland improved substantially from 1954 to 1965, reflected in drastic decreases in infant and maternal mortality and increases in hospital deliveries, from 75% to 99%.46 Because obstetric complications are a risk factor for schizophrenia,44 these improvements may have affected the incidence of schizophrenia.

Several epidemiological findings support the hypothesis of infections being involved in the etiology of schizophrenia.45 Many,46-55 although not all,56-59 studies have found that second-trimester exposure to influenza epidemics increases the risk of developing schizophrenia. If so, the fact that large influenza epidemics occurred between 1953 and 1957, while none as large occurred between 1938 and 1965, might partly explain the observed decline in the incidence. Another possibility is the elimination of poliovirus in the early 1960s: we have observed50 an increased risk of adult schizophrenia in persons exposed to poliovirus epidemics during the second trimester of fetal development.

We also have observed elsewhere that seasonality in schizophrenic births was prominent in patients born in the 1950s but decreased considerably in the 1960s (J.M.S., unpublished data, 1999). This suggests that the frequency or intensity of some seasonally varying risk factor(s) has diminished.

**PERIOD-RELATED FACTORS**

The effect of period on the incidence of schizophrenia was significant. Period effects reflect the effect of factors operating in adult life that affect several age groups simultaneously. Although they may represent real variation in exposure to risk factors, it is likely that in schizophrenia they are artifacts caused by period-related confounding factors.

Register information reliability may change over time. Registers not using personal identification numbers usually have a code for first admissions, which has been used in several previous register-based studies and found to be rather unreliable.18 We avoided this problem. The accuracy of data on psychiatric diagnoses in the Finnish Hospital Discharge Register was studied in 1986 and found to be excellent—the primary diagnosis in the register and in the hospital case notes was identical in 99% for schizophrenia and in 98% for all mental disorders.61 Furthermore, the proportion of schizophrenic patients who never receive psychiatric treatment in Finland is small. In a health survey based on a nationally representative sample of 8000 persons carried out in 1978 to 1980, 99% of persons with a psychotic disorder had received psychiatric treatment.62 The Finnish psychiatric health care system has undergone considerable changes. The number of beds in psychiatric hospitals peaked at the beginning of the 1970s, followed by a decline,63 particularly in the 1980s. Although a shift toward outpatient treatment could have occurred at the same time, the numbers of patients receiving disability pension or free medication for schizophrenia but never hos-
hospitalized did not indicate any rise in the proportion of patients treated solely as outpatients.

The reliability of diagnosis of schizophrenia in the Hospital Discharge Register has been assessed in several studies. Those comparing research diagnoses based on structured clinical interviews or all available case note information, with register diagnoses have observed that Finnish psychiatrists tend to apply a narrow definition of schizophrenia in their clinical practice, with more tendency toward false-negative than false-positive diagnoses. Nevertheless, diagnostic criteria changed in 1987, when DSM-III-R criteria were adopted for clinical use. We observed a subsequent significant increase in the incidence of other nonaffective psychotic disorders. Although the numbers were small, a diagnostic shift from schizophrenia to these diagnoses could explain some of the observed decline in schizophrenia incidence. The rise in other nonaffective psychotic disorders also reflected the increased diagnostic delay, partly caused by shorter hospital admissions in the 1980s: the proportion of schizophrenic patients who were so diagnosed in their first admission decreased from 77% in the first to 70% in the last cohort. Thus, a narrowing clinical concept of schizophrenia probably at least partially explains the observed period effect.

Changing migration patterns may cause spurious changes in incidence. Immigration to Finland was rare until the 1970s, while emigration has been much more extensive and remained in Finnish registers. It is thus impossible to correct for all the effects of migration, although we excluded persons born outside Finland. Persons from these cohorts who emigrated to Sweden may have had more psychiatric morbidity than those who stayed in Finland, but many returned if longer periods of psychiatric treatment were needed. Therefore, migration is unlikely to be a major confounding factor in the observed decline.

If the age at onset or the time lag between the onset of first symptoms and the beginning of first hospitalization change, age-specific incidences may alter without any change in the overall incidence. No increase in the age at onset was observed in this study; on the contrary, the peak of highest incidence shifted toward an earlier age. The time lag between the onset of first symptoms and first hospitalization has been assessed in studies of first-admission patients conducted quinquennially in the Helsinki area. Although the lag has varied somewhat over the years, being longest in the 1965 and 1970 cohorts, no major changes that could explain the observed decline in the incidence have occurred.

The age-period-cohort analysis method we used is widely accepted, and produces reliable estimates. However, it assesses only deviations from linearity (curvature effects) while the effects of period and cohort in steady, linear changes remain unexplained. Because of this, the effects of period and cohort we observed should not be interpreted as the total effects of cohort and period on the incidence. Nevertheless, curvature effects provide valuable information, because many changes in cohort-related factors, eg, infections, and period-related factors, eg, changes in diagnostic criteria, are abrupt in nature and should cause deviations from linear trend.

CONCLUSIONS

The age-specific incidence of schizophrenia among persons aged 16 to 25 years in Finland has decreased. A significant cohort effect was observed, suggesting that some risk factors for schizophrenia, probably operating early in life, have diminished in intensity. The effect of period was also significant and probably reflects changes in diagnostic criteria. The findings from this cohort-based study accorded with several period-based studies, thus strengthening evidence of a worldwide decline in the incidence of schizophrenia.

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