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Changes in the diagnosed incidence of early onset schizophrenia over four decades

Okkels N, Vernal DL, Jensen SOW, McGrath JJ, Nielsen RE. Changes in the diagnosed incidence of early onset schizophrenia over four decades.

Objective: To explore changes in the diagnosed incidence of early onset schizophrenia (EOS) from 1971 to 2010.
Method: Examination of incidence rates of schizophrenia in patients under 18 years of age, using a nationwide, population-based, mental health register.
Results: The age-standardized incidence rate (IR) of EOS in the period 1971–2010 was 3.17 (95% CI: 3.16, 3.18) per 100 000 person years in the age group 0–18 years, and 9.10 (95% CI: 9.00, 9.21) in the age group 12–18 years. In the period 1971–1993, the age-standardized IR of EOS was 1.80 (95% CI: 1.79, 1.82) per 100 000 person years in the age group 0–18 years, and 5.02 (95% CI: 4.92, 5.11) in the age group 12–18 years. In the period 1994–2010, the age-standardized IR of EOS was 5.15 (95% CI: 5.10, 5.20) per 100 000 person years in the age group 0–18 years, and 15.73 (95% CI: 15.22, 16.22) in the age group 12–18 years. The IR was higher for males than females in the periods 1971–1993 and 1971–2010, but in the period 1994–2010 the IR was higher for females than males.
Conclusion: In recent years, the diagnosed incidence of EOS has increased and the usual male excess has disappeared. The changes in IR could be a result of changes in the diagnostic system, increased awareness of early psychosis or a reflection of actual underlying incidence of the disorder.

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Key words: incidence; schizophrenia; epidemiology

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Significant outcomes

- In the period 1971-2010, the diagnosed incidence of early onset schizophrenia was 3.17 per 100 000 person years.
- The diagnosed incidence of early onset schizophrenia has increased in recent years.
- The usual male excess found in schizophrenia epidemiology is less apparent in recent years in those with early onset schizophrenia.

Limitations

- Register-based studies may miss individuals who do not have contact with mental health services.
- The validity of early onset schizophrenia diagnoses based on mental health register has not been tested.
- The reasons behind the changes in diagnosed incidence of early onset schizophrenia cannot be determined in this study.

Introduction

The age at onset of schizophrenia varies, but most are diagnosed in late adolescence or early adulthood (1). The proportion of patients diagnosed

Please also see editorial comment by Kelly K. Anderson (Acta Psychiatr Scand 2013;127:9–10).

before the age of 18 years, known as early onset schizophrenia (EOS), is less than five per cent of all first diagnoses of schizophrenia (2–4). The incidence of EOS is of interest for several reasons. First, studies suggest that those with EOS have prominent delays in speech, language and motor development, poorer general psychopathology and poorer long-term outcome compared with adult onset schizophrenia (5). As a consequence of this, there has been considerable interest in optimizing the early identification of psychosis (6, 7) and in the development of specialized services for treatment of psychosis in teenagers and young adults (7–9). Second, there is a need to monitor secular changes in incidence rates of psychoses, in order to evaluate how the increased attention to early psychosis impacts on limited health resources (10, 11). Third, from an epidemiological perspective, changes in incidence rates can provide important clues to underlying etiological factors (12).

Changes in incidence of schizophrenia have been studied extensively, but mostly in adults (13–19). The studies report both increases and decreases in incidence (16–18, 20–23). Studies on patients diagnosed before the age of 18 years are sparse. Current Danish data show an increase in the incidence of hospitalization of EOS in the time period 1994–2006 (3). To our knowledge, no other large-scale studies have been conducted on the incidence of EOS over longer time periods.

Aims of the study

To investigate the incidence of schizophrenia in the age group 0 to 18 years from 1971 to 2010.

Material and methods

Design

We conducted a register-based study of EOS covering the period from January 1st 1971 to December 31st 2010. All incidence measures described are incidences of diagnosed disorder, implying that an unknown proportion of persons fulfilling the diagnostic criteria were not diagnosed and therefore not included. The term 'incidence' is used as a substitute for 'diagnosed incidence' throughout the paper.

Sample

Cases were selected from the Danish Psychiatric Central Research Register (DPCRR), which includes data from all admissions to psychiatric hospitals in Denmark since 1969 (24, 25). However, before 1995 only inpatients were registered. In child- and adolescent psychiatry, in-patient admissions refer to overnight stays as well as daily hospital visits over an extended period. Our study covers nearly all schizophrenia diagnoses as schizophrenia is a severe mental illness, which is most often cared for in an inpatient hospital setting, as defined above (24). Few private clinics and no private hospitals with overnight inpatient facilities were available during the study period (26). The DCPRR covers the entire Danish population, that is, both those born in the country and immigrants.

The study population consisted of all patients diagnosed with an ICD-8 schizophrenia diagnosis (295) before the age of 18 in the period from 1971 throughout 1993 or an ICD-10 schizophrenia diagnosis (F20) in the period from 1994 throughout 2010. The ICD-9 was not introduced in Denmark. To examine the relative proportions of schizophrenia *vs* all psychiatric diagnoses, we used ICD-8 diagnoses (290–315) in the period 1971 throughout 1993 or ICD-10 diagnoses (F00–F99) in the period 1994 throughout 2010. As to investigate the incidence of schizophrenia, only the first schizophrenia diagnosis in the DCPRR was utilized. Cases were not followed in the registries for subsequent diagnoses.

Diagnoses registered from emergency room visits were excluded as no investigation of the validity of these diagnoses have been conducted, and the validity is considered low if no in- or outpatient treatment has occurred. Prescription data were not used to validate case diagnosis, as data were not available for the entire study period.

Statistical analysis

Descriptive analyses were performed using the Student's *T*-test, *Z*-test, and two-sample test of proportions.

Age standardization of data was performed to account for changes in the age composition of the population during the study period. The principle is to apply the age-specific incidence rates from each year of our study population to the age distribution of a standard population. WHO recommends basing the standardization on the average age composition of the populations compared in the period (27, 28). Data on the age composition of the Danish population are available through Statistics Denmark.

Incidence rates (IR) were calculated as the number of incident cases divided by the total number of people in the population of same age that year. As

the average population size per year is approximately equal to person-time, we have used the term 'per 100 000 person years'. Incidence rates were age-standardized as described previously.

Incidence rate ratios (IRR) were calculated for different time periods as the IR of EOS divided by all IR of all psychiatric cases.

All calculations of IR and IRRs were repeated with data stratified by sex. Statistical analyses were performed with STATA (29).

To reduce the risk of Type I errors, a correction was applied to the standard p-value of 0.05, and $P < 0.01$ was selected as a reasonable significance criterion.

The data were provided at the group level and anonymously, in keeping with guidelines for epidemiological research required by the Danish Data Protection Agency and the National Board of Health. No ethical research committee approval was needed, as data were obtained from registers for statistical purposes only.

Results

A total of 1536 persons diagnosed with schizophrenia before the age of 18 years between 1971 and 2010 were identified in the DPCRR. Of these, 54% were men (male/female ratio = 1.2 : 1) ($P < 0.001$). The mean age at diagnosis was 15.8, median 16.0, interquartile range (IQR) 15.7–16.1 years, with men (mean 15.8, median 15.8, IQR 15.6–16.2) and women (mean 15.8, median 15.8, IQR 15.6–16.2) being diagnosed at the same age in the entire study period ($P > 0.999$). A total of 517 persons were diagnosed in the time period 1971–1993 (ICD-8), with 65% men and 35% women ($P < 0.001$). Mean age at diagnosis was 16.1, median 16.1, IQR 15.8–16.3 years, with men (mean 16.0, median 15.9, IQR 15.8–16.3) and women (mean 16.3, median 16.3, IQR 16.0–16.4) being diagnosed at the same age ($P = 0.347$). A total of 1019 persons were diagnosed between 1994 and 2010 (ICD-10), with 48% men and 52% women ($P = 0.071$). The mean age at diagnosis was 15.7, median 15.7, IQR 15.6–16.0 years, with no significant age difference between men (mean 15.7, median 15.7 years, IQR 15.5–16.0) and women (mean 15.7, median 15.7, IQR 15.5–16.0), $P > 0.999$. The mean age at diagnosis was significantly higher for patients diagnosed in the period 1971–1993 compared to 1994–2010, $P < 0.001$. Changes in sex distribution of schizophrenia diagnosis over time is presented in Fig. 1.

The mean age-standardized IR of EOS from 1971 to 2010 was 3.17 (95% CI: 3.16, 3.18) per 100 000 person years. The mean age-standardized IR of EOS from 1971 to 1993 was 1.80 (95% CI: 1.79, 1.82) per 100 000 person years and the mean age-standardized IR of EOS from 1994 to 2010 was 5.15 (95% CI: 5.10, 5.20) per 100 000 person years. Comparing the two time periods, the difference was 3.34 (95% CI: 3.29, 3.40). Age at diagnosis for each sex is presented in Fig. 2.

The mean age-standardized IR of EOS in the age group 12 to 18 years of age from 1971 to 2010 was 9.10 (95% CI: 9.00, 9.21) per 100 000 person years. The mean age-standardized IR of EOS in the age group 12 to 18 years of age from 1971 to 1993 was 5.02 (95% CI: 4.92, 5.11) per 100 000 person years compared with 15.73 (95% CI: 15.22, 16.22) per 100 000 person years in the period 1994 to 2010. Comparing the two time periods, the difference was 10.72 (95% CI: 10.22, 11.21). Data on IR are presented in Table 1.

The age-standardized IRR, i.e. the proportion of EOS diagnoses of all psychiatric child and adolescent diagnoses, from 1971 to 2010, was 0.016 (95% CI: 0.015, 0.017). Men had a significantly lower IRR than women, diff = 0.002 (95% CI: 0.002, 0.002). The age-standardized IRR from 1971 to 1993 was 0.034 (95% CI: 0.031, 0.037). Men had a significantly higher IRR than women, diff = 0.013 (95% CI: 0.011, 0.015). The age-standardized IRR between EOS and all psychiatric diagnoses from 1994 to 2010 was 0.013 (95% CI: 0.012, 0.014). Men had a significantly lower IRR than women, diff = 0.005 (95% CI: 0.004, 0.005). The IRRs were significantly higher for patients diagnosed in the period 1971–1993 compared to 1994–2010, diff = 0.021 (95% CI: 0.019, 0.024). This was also true for men (diff = 0.029, $P < 0.001$) and women (diff = 0.012, $P < 0.001$) divided.

Discussion

We found that the overall IR of EOS was lower in the period 1971–1993 compared to 1994–2010 both for

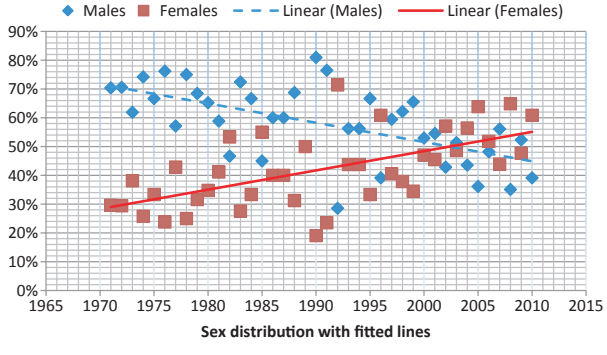

Fig. 1. Changes in sex distribution of schizophrenia diagnosis over time.

Table 1. Changes in demography and incidence rates of schizophrenia and all psychiatric diagnosis before the age of 18 years

	Incidence rate 0–18 years (per 100 000 person years)				Count of cases (0–18 years)					Age at diagnosis			
Period	Sx_{IR} (95% CI)	$Sx_{IR\ (male)}$ (95% CI)	$Sx_{IR\ (female)}$ (95% CI)	$P_{(male–female)}$	$n_{sx\ (male)}$	$n_{all\ (male)}$	$n_{sx\ (female)}$	$n_{all\ (female)}$	$P_{sx\ (male–female)}$	Age_{Sx}, mean; median (IQR)	$Age_{Sx\ male}$, Mean; Median (IQR)	$Age_{Sx\ female}$, Mean; Median (IQR)	$P_{(male–female)}$
1971–2010	3.17 (3.16–3.18)	3.34 (3.31–3.37)	2.99 (2.96–3.01)	<0.001	829 (54%)	24.815.799	707 (46%)	23.649.073	<0.001	15.8; 16.0 (15.7–16.1)	15.8; 15.8 (15.6–16.2)	15.8; 15.8 (15.6–16.2)	> 0.999
1971–1993	1.80 (1.79–1.82)	2.28 (2.25–2.31)	1.30 (1.28–1.32)	<0.001	335 (65%)	14.669.995	182 (35%)	13.998.226	<0.001	16.1; 16.1 (15.9–16.3)	16.0; 15.9 (15.8–16.3)	16.3; 16.3 (16.0–16.4)	0.347
1994–2010	5.15 (5.10–5.20)	4.87 (4.78–4.96)	5.44 (5.33–5.55)	<0.001	494 (48%)	10.145.804	525 (52%)	9.650.847	0.071	15.7; 15.7 (15.6–16.0)	15.7; 15.7 (15.5–16.0)	15.7; 15.7 (15.5–16.0)	> 0.999

	Incidence rate 12–18 years (per 100 000 person years)				Count of cases (12–18 years)				
Period	Sx_{IR} (95% CI)	$Sx_{IR\ (male)}$ (95% CI)	$Sx_{IR\ (female)}$ (95% CI)	$P_{(male–female)}$	$n_{sx\ (male)}$	$n_{all\ (male)}$	$n_{sx\ (female)}$	$n_{all\ (female)}$	P_{sx} (male–female)
1971–2010	9.10 (9.00–9.21)	9.52 (9.30–9.74)	8.66 (8.45–8.87)	<0.001	811 (54%)	8.516.365	703 (46%)	8.116.520	<0.001
1971–1993	5.02 (4.92–5.11)	6.34 (6.11–6.58)	3.62 (3.48–3.76)	<0.001	334 (65%)	5.266.584	182 (35%)	5.022.825	<0.001
1994–2010	15.73 (15.22–16.22)	14.68 (13.79–15.56)	16.84 (15.78–17.91)	<0.001	477 (48%)	3.249.781	521 (52%)	3.093.695	0.074

	$IRR_{Sx\,/\,All}$ (95% CI)	$IRR_{Sx\,/\,All\ (male)}$ (95% CI)	$IRR_{Sx\,/\,All\ (female)}$ (95% CI)	$P_{(male–female)}$
1971–2010	0.016 (0.015–0.017)	0.015 (0.014–0.016)	0.017 (0.016–0.019)	<0.001
1971–1993	0.034 (0.031–0.037)	0.040 (0.036–0.040)	0.027 (0.023–0.031)	<0.001
1994–2010	0.013 (0.012–0.014)	0.011 (0.010–0.012)	0.015 (0.014–0.017)	<0.001

IR, incidence rate; IRR, incidence rate ratio; IQR, Interquartile range (25–75% percentile).

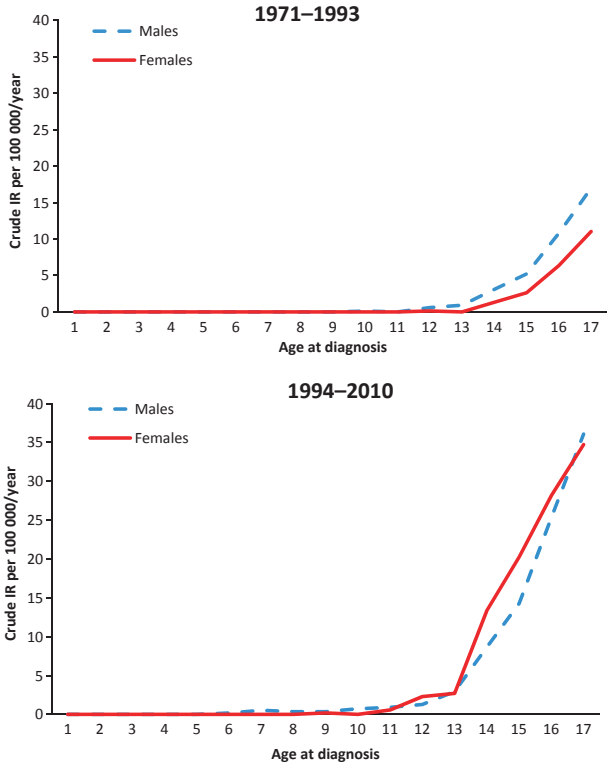

Fig. 2. Crude incidence rates at age of diagnosis.

men and women in the age groups 0–18 years and 12–18 years. The latter age group was computed because the main portion of incident EOS is within this age group. To our knowledge, there exist no clear consensus on what age the risk of schizophrenia begins, i.e. which age group should be used for calculation of IR in EOS. In the period from 1971 to 1993, men had a significantly higher IR of EOS than women, contrary to 1994–2010 where women had a significantly higher IR of EOS than men. Finally, EOS patients were diagnosed at a significantly lower age in the period 1994–2010 compared to 1971–1993, but this difference was not significant when divided into men and women.

The IRRs show that EOS made up a larger proportion of all diagnoses in the time period 1971–1993 compared to 1994–2010, both for men and women. A similar change in age-specific first-admission rates for schizophrenia and other psychotic disorders is reported in Canton Zurich, Switzerland, in the age group 15–19 years (30).

There are several possible explanations for the changes in incidence of EOS and all psychiatric diagnoses. From 1970 to 1990, a change in organizational structure of treatment facilities took place (15). In adult psychiatry, the number of psychiatric beds was reduced by 50% from mid 1970s to 1990 without sufficient supplementary extension of community psychiatric service or any other in- or outpatient treatment facility (17), thus decreasing or delaying the possibility of getting a psychiatric evaluation. Child and adolescent psychiatry as a psychiatric speciality was established in 1994. Before this, child psychiatry did not routinely include treatment of adolescents, which took place in both adult and child psychiatric wards, depending on the hospital. Data from The National Board of Health show a decrease of 33% in beds allocated to children and adolescents from 1980 to 1986, but by 1995, the number resembles that from 1980. Since 1990 the number of beds in child and adolescent psychiatry has increased. Thus, a decrease in the number of psychiatric beds could lead to a decrease in the number of psychiatric diagnoses. A study from Finland found a decrease in incidence of schizophrenia after a decrease in psychiatric beds (22). A similar decrease in incidence was found in a Danish survey from 1987 (16), examining first-admission adult patients to psychiatric institutions 1970–1980. One explanation proposed was an increased use of differential diagnosis as first-admission diagnosis for patients later to be diagnosed with schizophrenia, i.e. a tendency to avoid the diagnosis of schizophrenia. Other studies utilizing data from DCPRR have shown a tendency to withhold the schizophrenia diagnosis until patients had been ill for a longer time period, with negative symptoms, and with a confirmed poor prognosis (31). The delay in diagnosis could be even more prolonged in child and adolescent psychiatry because of the rarity of the disorder, resulting in a proportion of patients passing the age of 18 years, thereby causing a lower incidence of EOS. This explanation is supported by the higher average age at EOS diagnosis in the time period 1971–1993 compared to 1994–2010, suggesting a possible delay in diagnosis in the former compared to the latter. The greater focus on psychosis and psychosis risk could have caused the decline in age at schizophrenia diagnosis (32, 33).

In Denmark, the ICD-10 replaced the ICD-8 in 1994. No studies of ICD-8 to ICD-10 reliability of EOS have been conducted. A single study of case vignettes on adult psychiatric diagnoses from ICD-8 to ICD-10 reported no reliability problems regarding the schizophrenia diagnosis (34).

The incidence of EOS is higher in the period 1994–2010 compared to 1971–1993. It is possible that the ICD change induced a surge of re-diagnosing patients from one category to another, predominantly toward schizophrenia. If this is true, part of the increase in incidence is caused by bias in monitoring, although re-diagnosis in child and adolescent psychiatry is probably minor compared with adult psychiatry. Tsuchiya and

Munk-Jorgensen have argued against the ICD change as an explanation (15). In 2002, they documented that the increase in incidence of adult schizophrenia started before the replacement of ICD-8 by ICD-10 (15).

Men were predominately diagnosed with EOS throughout the study, 1971–2010, but the male to female ratio changed during the two study periods, with a clear male dominance in the 1971–1993 ratio. In contrast, there was no difference between the sexes in the period 1994–2010. The equilibrium between number of male and female patients in 1994–2010 is in contrast to the male dominance in adult schizophrenia diagnosis (35). No larger epidemiological studies of schizophrenia diagnosis before the age of 18 years have been performed, and therefore, no reports of male to female ratios are available for comparison. The other large Danish register study of EOS includes patients up to 21 years of age and shows similar results of no difference in male to female ratios before the age of 18 years, but with a greater proportion of males diagnosed after the age of 18 years (3).

Table 1 shows that the incidence of schizophrenia and all psychiatric diagnoses does not increase proportionally. This trend is markedly more evident for men compared with women. Overall, the changes in IRR could perhaps be attributed to more focus on child and adolescent psychiatric disorders. For example, the introduction of Aspergers syndrome and modification of the criteria of hyperkinetic disorder in ICD-10 in 1994 in Denmark, could have caused the more severe disorders, such as schizophrenia, to be diagnosed proportionally less often (36). Of great importance related to the proportion of EOS is the inclusion of outpatient incident diagnoses from 1995 in DPCRR. This might have caused a slight increasing IR of EOS, but has the greatest effect on disorders commonly treated on outpatient basis.

It has been suggested that cannabis misuse (37–40) and changes in misuse patterns during the last decades (41) could affect incidence of schizophrenia. The change in misuse of cannabis could perhaps explain the lower age at diagnosis in 1994–2010. However, data on misuse would suggest men being diagnosed earlier than women (42), but this was not implied in our findings.

Lastly, actual fluctuations in the relative number of patients developing schizophrenia or other psychiatric disorders before the age of 18 years within the four decades investigated in the study could be a possible explanation for our findings.

The study has some important limitations. (i) The validity of the EOS diagnosis has not been examined in the DPCRR, neither has the reliability of the EOS diagnosis from ICD-8 to ICD-10. (ii) All reported incidences are solely diagnosed incidences, thus individuals without contact to the psychiatric system were not included. Schizophrenia is a severe mental illness, which is most often cared for in an inpatient hospital setting, but patients diagnosed solely as outpatients before 1995, are not in the register. (iii) In calculating IR, we used the number of persons in each age group for each time period as a proxy of person-time, as data on date of diagnosis and date of birthday were unavailable.

In conclusion, we found a general increase in schizophrenia and all psychiatric disorders diagnosed before the age of 18 years over the study period of four decades. There was a change in sex distribution of EOS from an initial male dominance to an even distribution. The increase was probably caused by a combination of factors, for example, changes in diagnostic system, changes in organizational structure, drug abuse or more focus on child and adolescent psychiatric disorders in diagnostic practice. Last, but not least, our findings could be explained by a true increase in the number of persons developing psychiatric disorders.

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Declaration of interests

J. J. McGrath has received research support from Eli Lilly and Janssen. R. E. Nielsen has received research grants from H. Lundbeck for clinical trials, received speaking fees from Bristol-Myers Squibb, Astra Zeneca, Janssen & Cilag, Lundbeck and has acted as advisor to Astra Zeneca. N. Okkels, D. L. Vernal and S. O. W. Jensen have nothing to declare.

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