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Evidence for a Gender-Specific Decline in the Rate of Schizophrenia in Rural Ireland over a 50-Year Period

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The issue of whether the incidence rate of schizophrenia may have declined over recent decades has generated considerable controversy. This study sought to ascertain and interview all patients who satisfied contemporary diagnostic criteria for schizophrenia within a defined and unusually homogeneous region of rural Ireland having a total population of 25 178 people; morbid risk for schizophrenia was then examined by quinquennia of birth from 1920–24 to 1965–69. Morbid risk appeared essentially constant for persons born between 1920 and 1939 but fell by 37% for those born between 1940 and 1969, the fall being considerably more prominent in females (−56%) than in males (−19%). Attention is focused on sexual dimorphism in cerebral development and on temporal changes in endogenous or exogenous factors that influence the rate of occurrence of schizophrenia in females.

Virtually all known diseases show variation in rate of occurrence, both temporally and geographically, and it remains a guiding principle of epidemiology that specification of such variation usually provides important clues to the origin and nature of a given disorder (Dawber *et al*, 1951; Dawber, 1980; Kleinbaum *et al*, 1982). However, it is recognised increasingly that in the temporal domain the epidemiology of schizophrenia is poorly understood (Hafner, 1987). There is contemporary opinion (Torrey, 1989) that were schizophrenia not to show variation, then this would be unique in the epidemiology of a major disease; yet there has been surprisingly little in the way of systematic investigation into these fundamental aspects of such a serious public health problem.

There has been debate (Hare, 1983; Jeste *et al*, 1985; Stromgren, 1987) over whether schizophrenia might be a disease of relatively recent origin; it has been argued that schizophrenia was little recognised before the 19th century, and attained a putative zenith in the early 20th century. Subsequently, several studies have suggested, or have been interpreted as suggesting, that the rate of schizophrenia in a number of countries may have declined over recent decades (Eagles & Whalley, 1985; Parker *et al*, 1985; Munk-Jorgensen, 1986; Munk-Jorgensen & Jorgensen, 1986; Joyce, 1987; Eagles *et al*, 1988; Der *et al*, 1990). However, many of these studies are compromised potentially by a number of methodological confounds (Crow, 1990; Graham, 1990; Manderscheid *et al*, 1990; Prince & Phelan, 1990), most seriously their reliance on retrospective hospital admission/contact data over periods during which both psychiatric health-care provision and diagnostic practice have undergone considerable revision. To clarify these important issues, it has been argued that it would be necessary to ". . . study schizophrenia diagnosed with consistent criteria in all individuals from a defined population who contacted psychiatrists as patients over the relevant three decades (1950–1980)" (Der *et al*,1990) and a similar approach has been advocated by Eagles (1991). We report here the results of such a study of schizophrenia in a rural Irish population of unusual homogeneity, in relation to patients born over a 50-year period.

Method

The initial requirement for the study was the ascertainment of all living persons having an address within a specified region who satisfy contemporary diagnostic criteria for schizophrenia; such a database was available to us through a previously completed study of geographical variations in the prevalence of schizophrenia (Youssef *et al*, 1991). In outline, the study region was essentially the eastern half of County Cavan, a north-eastern border county of the Republic of Ireland. This predominantly rural county has a substantially agricultural economy with little major industry, and the total population of the study region is 25 178 people (13 161 men and 12 017 women); during this century, emigration has resulted in the population of the study region falling slowly but steadily in an essentially linear manner, both in men (mean rate of decrease, −679 men per quinquennium; $r = -0.98$, $P < 0.001$) and in women (mean rate of decrease, −639 women per quinquennium; $r = -0.97$, $P < 0.001$), on the basis of 13 censuses between 1901 and 1986 (Central Statistics Office, 1987).

Briefly, and as described recently in detail (Youssef *et al*, 1991), between November 1987 and October 1988 the in-patient records of the psychiatric hospital (St Davnet's), which provides both in-patient care and an out-patient service to the study region under the strict catchment area

policy of the North Eastern Health Board, were reviewed to identify those patients potentially suffering from a psychotic/schizophrenia-like illness and who were admitted from an eligible home address. Additionally, using the records of the local community care service, and with the help of the extensive personal knowledge of the community psychiatric nursing service, a field investigator having long-standing familiarity with the study region sought to identify all cases of psychotic/schizophrenia-like illness living in the community at an eligible home address. All these suspected cases ($n = 123$), whether they were in-patients or living in the community, were interviewed personally in the hospital, at an out-patient clinic, or in their own home. On the basis of these interviews and all available clinical records, 83 patients (48 men and 35 women) were found to satisfy DSM-III-R criteria (American Psychiatric Association, 1987) for schizophrenia; they encompassed the entire spectrum of the illness, from chronically hospitalised in-patients through to out-patients who had been functioning at a high level in the community for various periods without current psychotic symptoms or prominent residual deficits while receiving treatment with neuroleptics. Their mean age (s.d.) was 52.7 (15.7) years (range 21–85) and their mean duration of illness was 23.7 (15.0) years (range 0.5–56), with age at onset defined by age at first contact with a psychiatric service. All patients were native Irish, of whom 79 (95%) were born in County Cavan; for 76 patients (92%), their study address was known also to be within the district electoral division in which their parents resided at the time of the patient's birth.

Morbid risk analysis

Secular trends in morbid risk for schizophrenia were explored initially by quinquennia of birth. An important element of the study was to examine any such trends for temporal relationships to changes in those factors currently hypothesised to be of aetiological relevance to schizophrenia that could be obtained from general population statistics; as such information has been available only since 1922, with earlier data including what is now Northern Ireland within the UK, the primary focus is on the 68 patients (40 men and 28 women) born in quinquennia from 1920–24 up to 1965–69, that is aged between 18 and 67 years. There were also 11 patients (six men and five women) born in the decade 1910–19, that is aged between 68 and 77 years, and four patients (two men and two women) born in the decade 1900–09, that is aged between 78 and 87 years; because of the potentially extreme influence of mortality on apparent morbid risk among such modest numbers of elderly patients, and as the published county population statistics pool together everyone aged 85 years and above, these patients are not considered further.

Morbid risk for schizophrenia was determined by adjusting for the period of risk through which each individual had lived; thus, the number of patients born in each indicated period was divided by the number of persons in the study region born similarly, with this denominator being corrected downwards to the number of risk-lives-exposed (*Bezugsziffern,* BZ) from cummulative age-at-onset distributions for this patient population according to the method of Stromgren (1935) (see also Alda *et al* (1989) and Appendix 1); morbid risk was expressed as the number of cases per 1000 risk-lives-exposed with its standard error, which was computed using the BZ as the sample size (Gottesman & Shields, 1982). Differences in morbid risk between specified periods were analysed as the relative risk/risk ratio, with determination of associated two-tailed 95% confidence intervals (Gardner & Altman, 1989). Changes in morbid risk were compared with national trends in early neonatal mortality (number of deaths at ages under one week), neonatal mortality (deaths at ages under four weeks), and infant mortality (deaths at ages under one year) obtained as rates per 1000 live births from annual population statistics (Central Statistics Office, 1922–69). Comparisons were made also with trends in the 19 individual causes of infant mortality included in these annual national statistics; because the classification and thus the enumeration of causes of infant mortality was revised fundamentally in 1952, it was possible to obtain comparable data on all causes individually only from 1922 to 1951.

Results

Trends in morbid risk

The 83 cases of schizophrenia identified within this total population of 17 873 persons aged 15 years or above indicated an overall prevalence rate of 4.6 per 1000 (Youssef *et al*, 1991). For all subjects born over the primary study period of 1920–69, 68 cases of schizophrenia were identified among a BZ of 10 263; thus morbid risk for schizophrenia was 6.6 (s.e. 0.8) per 1000 risk-lives-exposed. On analysing these data by quinquennia (Fig. 1(a)), morbid risk for schizophrenia was essentially constant for persons born in each of the four quinquennia from 1920 to 1939, varying only within the range 7.3–8.8; morbid risk among all persons born over this 20-year period was 8.3 (s.e. 1.3). Morbid risk among persons born in each of the six quinquennia from 1940 to 1969 was considerably lower, falling prominently for births in 1940–44 and less so for births thereafter within the range 4.0–5.9; morbid risk among all persons born over this 30-year period was 5.2 (s.e. 1.0). Relative risk for persons born between 1940 and 1969 compared with those born between 1920 and 1939 was 0.63 (95% confidence interval, 0.39–1.02), that is a fall in morbid risk of −37% ($P = 0.06$) between these two periods.

Data for males and females were then analysed independently (Table 1), using gender-specific age-at-onset distributions, for each of the two distinct periods of birth apparent in Fig. 1. There was no significant change in morbid risk for schizophrenia (−19%) among men when those born between 1940 and 1969 were compared with those born between 1920 and 1939 (relative risk, 0.81; 95% confidence interval, 0.43–1.49). Conversely, there was a prominent fall (−56%, $P = 0.04$) in morbid risk among women when those born in these same periods were compared (relative risk, 0.44; 95% confidence interval, 0.20–0.97).

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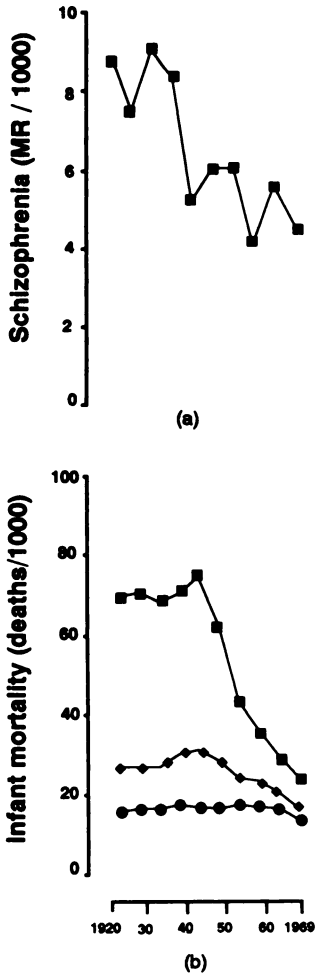

Fig. 1 (a) Morbid risk for schizophrenia, as number of cases per 1000 risk-lives-exposed, for quinquennia of birth from 1920 to 1969. (b) Infant (■), neonatal (◆), and early neonatal (●) mortality as number of deaths per 1000 live births for these same quinquennia.

Relationship to neonatal and infant mortality

Change in morbid risk for schizophrenia by quinquennia from 1920 to 1969 (Fig. 1(a)) was compared with changes in early neonatal, neonatal, and infant mortality rates over the triennium 1922–24 and quinquennia from 1925 to 1969 (Fig. 1(b)). Early neonatal mortality was essentially constant from 1922 to 1964 (mean, 15.8; range, 14.9–16.7) before falling to 12.5 in 1965–69; conversely, although neonatal mortality was essentially constant from 1922 to 1934 (mean, 25.8; range, 25.7–26.0), it rose to 30.4 in 1940–44 before declining steadily to 15.5 between 1945 and 1969. Although infant mortality was essentially constant from 1922 to 1939 (mean, 69.1; range, 67.5–70.3), it rose to 74.3 in 1940–44 before falling prominently to 23.2 between 1945 and 1969. Thus, the evident fall in morbid risk for schizophrenia, which began in 1940–45, preceded by one quinquennium the decline in infant mortality; there was little temporal relationship between changes in morbid risk for schizophrenia and either neonatal or early neonatal mortality over this same time period.

Table 1
Morbid risk for schizophrenia among men and women by period of birth

Period of birth	No. of patients	BZ[1]	Morbid risk[2]	Change in morbid risk
Men				
1920–39	20	2552	7.8 (1.8)	-
1940–69	20	3167	6.3 (1.4)	−19%
Women				
1920–39	19	2167	8.8 (2.0)	-
1940–69	9	2341	3.8 (1.3)	−56%*

1. BZ denotes *Bezugsziffern*, the total number of risk-lives-exposed.
2. Morbid risk per 1000 risk-lives-exposed (s.e.).
* Significant fall in morbid risk, $P = 0.04$.

From 1922 to 1944, baseline infant mortality in males (mean, 77.2; range, 74.7–82.6) was greater than that in females (mean, 61.5; range, 58.7–65.4); however, the rates of decline in infant mortality thereafter through 1965–69 (males, −67% to 25.5; females, −66% to 20.8) were entirely comparable. Separate examination of each of the 19 individual causes of infant mortality enumerated from 1922–51 (measles, scarlet fever, whooping cough, diphtheria, influenza, tuberculosis of the nervous system, tuberculosis of the intestines and peritoneum, other tuberculosis diseases, syphilis, meningitis, convulsions, bronchitis, pneumonia, diarrhoea and enteritis, congenital malformations, congenital debility, premature birth, injury at birth, other diseases peculiar to infancy) failed to reveal any patterns of change therein that exhibited greater temporal contiguity with the pattern of change in morbid risk for schizophrenia.

Discussion

The interpretation of these data is clearly predicated on the completeness of case ascertainment. However, as considered recently in detail in the context of geographical variations in prevalence (Youssef *et al*, 1991), the study shows some robustness in the face of potential causes of incompleteness, such as patient leakage across catchment area boundaries or attendance at private psychiatric hospitals in Dublin; there is evidence (Nielsen & Nielsen, 1977; Torrey, 1987) that the present 'key informant' strategy, when applied as it was here in a rural area over a period of time, can identify almost all cases of schizophrenia and thus produce results very similar to those obtained by direct, census approaches. Furthermore, the present overall prevalence rate of 4.6 per 1000 of population aged 15 years or above is within the middle one-third of the range documented in 70

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prevalence studies world-wide (Torrey, 1987) and is very similar to that obtained in the most recent comparable study conducted in Ireland (3.9 per 1000 of population aged 15 years or above; Ni Nuallain *et al*, 1990). Thus, although the number of cases considered here is considerably smaller than in previous studies, which have relied solely on psychiatric health service data, the present approach may be less vulnerable to those potentially serious artefacts that might arise through changes in health-care provision and diagnostic practice; evident limitations in terms of sample size are thus offset by the advantages of diagnostic consistency within a rural population of unusual socio-economic and ethnic homogeneity. However, the extent to which the present findings might generalise to populations elsewhere is unclear.

The essentially constant morbid risk for schizophrenia among persons born in the four quinquennia from 1920 to 1939 is virtually identical to the traditional and widely espoused value of 8 per 1000 risk-lives-exposed that derives from a number of early, classical studies (Gottesman & Shields, 1982). Thereafter, our data indicate a decline in morbid risk among persons born since 1940; consistent with this, those recent studies that have noted an apparent fall in incidence on the basis of first admission to hospital or other health service data did so on the basis of patient contacts over variable periods within the general limits of the mid-1960s to the mid-1980s, that is among persons born two decades previously, from the 1940s to the 1960s. There was a trend towards some subsequent slowing in the rate of decline, towards a stable morbid risk of 4–5, but long-term, follow-up work within the study region would be necessary to clarify this important issue. The ethnic homogeneity of the study region reduces the likelihood of any basis for these phenomena in the immigration or emigration of differentially vulnerable ethnic groups (Castle *et al*, 1991; Harrison *et al*, 1991).

Decline in morbid risk for schizophrenia appeared to occur primarily in females. Preferential emigration or suicide among women either with or predestined to develop schizophrenia cannot be excluded but, on sociological grounds, seems an unlikely eventuality, and the modest rate of fall in population of the study region over the century through emigration has been indistinguishably slow and linear in *both* sexes (see Method) with no evidence among either for any discontinuity in this population trend around 1940 (Central Statistics Office, 1987). The commonly reported older age at onset among women (Goldstein & Tsuang, 1990) would result in younger females having lived through a shorter period of risk for onset than their male counterparts and therefore could potentially generate results in the direction of those reported here. However, such a major artefact is unlikely for the following reasons:

(a) in the present population, mean age at onset was only 3.0 years older in women
(b) any such artefact would result in morbid risk appearing to fall more prominently the later the period of birth, when in fact the opposite profile was noted (i.e. the greatest fall was among persons born in 1940–44, with the rate of fall appearing to decline among those born thereafter)
(c) the greatest fall in morbid risk thus related to persons aged 44–48 years at the time of the study; as men and women aged, say, 46 had lived through 94% and 91% of overall risk, respectively, such an artefact could account only for a small fraction of the substantial fall in morbid risk for those born in 1940–44.

Curiously, 52.3% of the present population is male when females constitute >50% of the population in most western countries, including Ireland as a whole; however, this phenomenon has been recorded for the study County in each of 13 censuses between 1901 and 1986 (Central Statistics Office, 1987), and hence would not appear to relate to a finding that concerns women born since 1940.

Thus, these data complement and extend the substantial body of evidence (Goldstein & Tsuang, 1990; Castle & Murray, 1991; Waddington & Weller, 1992) that men and women with schizophrenia appear to differ in a variety of respects, including other epidemiological characteristics, premorbid functioning, clinical presentation, and course of illness. The temporal changes that we have identified suggest that what was once an illness of similar incidence between the sexes may now be more common in males; in the only comparable study, on the Danish island of Bornholm, the prevalence of schizophrenia in 1935 was similar in men and women, but in 1983 it was higher in males because of a selective diminution of female cases (Stromgren, 1987). Thus, recent formulations of schizophrenia being generally more common in men than in women (Castle & Murray, 1991) appear incomplete; on the basis of the present data, this may not have been always so, and might reflect a preferential decline in incidence among women.

Secular trends in disease incidence over decades classically suggest change(s) in endogenous or environmental factor(s) of aetiological significance (Dawber *et al*, 1951; Dawber, 1980; Kleinbaum *et al*, 1982; Midgard *et al*, 1991); for schizophrenia, current theory would focus on the foetal period, as elaborated

in the neurodevelopmental hypothesis (Murray & Lewis, 1987; Weinberger, 1987; Waddington, 1993). Indeed, in relation to the present sex differences, it is notable that both maternal influenza and maternal dietary insufficiency during pregnancy appear to be a much greater risk factor for subsequent schizophrenia in *females* than in males (O'Callaghan *et al*, 1991*a*; Susser & Lin, 1992). In a recent report of falling hospital first admissions for schizophrenia since the mid-1960s (i.e. primarily for patients born since the 1940s), early neonatal mortality, a putative indirect index of foetal and neonatal well-being, was noted to have fallen since 1940; on this basis, it was suggested that better maternal nutrition, decreased infectious disease, or improved prenatal care could have reduced unspecified neurodevelopmental impairment(s) that might predispose to schizophrenia (Murray *et al*, 1990), but the present data indicate these issues to be more complex.

We could not identify any relationship between changes in morbid risk for schizophrenia and early neonatal mortality in this population, although there appeared to be some qualitative relationship with changes in infant mortality. However, on detailed examination, the decline in morbid risk for schizophrenia preceded rather than paralleled or followed that in infant mortality, and there was no sex difference therein. Nevertheless, there remained a strong visual impression of some relationship between them (Fig. 1), and perhaps specific causal factors for infant mortality might exert other, initially less-serious consequences *in utero*; thus, consideration of infant mortality rate as a whole might obscure a more congruent association between one or more *individual* causes of infant death and morbid risk for schizophrenia. However, no such association was evident for any of the 19 causes of infant death that were enumerated over the relevant period, including six that are of direct or indirect relevance to various contemporary aetiological perspectives of schizophrenia: congenital debility (Lewis, 1989; McNeil, 1991); congenital malformations (Green *et al*, 1989; O'Callaghan *et al*, 1991*b*); convulsions (Roberts *et al*, 1990); influenza (Mednick *et al*, 1988; O'Callaghan *et al*, 1991*a*); measles and meningitis (Torrey *et al*, 1988; King & Cooper, 1989). If there is some association between changes in morbid risk for schizophrenia and causes of infant mortality, as Fig. 1 might imply, it is not straightforward and the available data do not allow us to specify its nature; furthermore, no other aspects of the present data support *directly* the involvement of such processes.

The notion that the incidence of such a major public health problem may have declined over recent decades has engendered much alarm lest it distract from research efforts to treat and prevent schizophrenia (Manderscheid *et al*, 1990) and be abused as an excuse to reduce funds urgently needed for patient care (Hafner & Gattaz, 1991). On the contrary, we find the rate of occurrence of schizophrenia in males to have changed little and to remain an enduring problem, while, conversely, the apparent decline in rate of occurrence primarily in females may contain an important clue to aetiology. These data might be reconciled by focusing attention on sexual dimorphism in neurodevelopment and seeking to clarify endogenous and exogenous factors by which such processes are regulated, and which might vary comparably in time.

Appendix 1

To adjust for the period of risk through which each individual has lived, morbid risk is determined as $\Sigma_i d_i / \Sigma_i w_i n_i$, where d_i is the number of those affected and n_i the total number of subjects at age i; w_i denotes the weighting for each age, derived as a cumulative frequency from the age-at-onset distribution for the population (see Stromgren, 1935; Alda *et al*, 1989).

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