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Is the decline in diagnoses of schizophrenia caused by the disappearance of a seasonal aetiological agent? An epidemiological study in England and Wales

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ABSTRACT

Background. Studies from several countries have shown a decline, in the last few decades, of the number of admissions with a diagnosis of schizophrenia. This could be due to a fall in the incidence of schizophrenia, but it also could be due to confounding factors. The hypothesis tested in the study is that the incidence of schizophrenia is actually falling because of a decrease in the presence of a seasonal aetiological agent.

Methods. The hypothesis was tested by analysing the dates of birth of the patients discharged with a diagnosis of schizophrenia from NHS hospitals in England and Wales and would be confirmed by an appropriate change in the seasonality of the births over time.

Results. Evidence of seasonality has been observed in the schizophrenic births, but with no significant change over time.

Conclusions. The fall in first admissions with a diagnosis of schizophrenia does not seem to be due to a change in the prevalence of a seasonal aetiological factor. Therefore, either there has been a reduction in incidence due to a change in a non-seasonal agent, or the incidence of schizophrenia is not changing and the fall in first admissions is due to confounding factors.

INTRODUCTION

Studies from different countries including England and Wales (de Alarcon *et al*. 1990; Der *et al*. 1990), Scotland (Eagles & Whalley, 1985; Eagles *et al*. 1988; Geddes *et al*. 1993; Kendell *et al*. 1993), Ireland (Waddington & Youssef, 1994), Denmark (Munk-Jörgensen, 1986, 1987; Munk-Jörgensen & Jörgensen, 1986; Munk-Jörgensen & Mortensen, 1992), New Zealand (Joyce, 1987) and Australia (Parker *et al*. 1985) show a decrease, in the second part of this century, of first contacts with health services that lead to a diagnosis of schizophrenia. This fall in contacts amounts, in most of the studies, to between 35 and 50%.

These results do not necessarily mean that the incidence of schizophrenia is declining because several other factors can also explain these findings: changes in diagnostic practices over time; a move towards community care; patients misreported as first contact; and benign metamorphosis of the schizophrenic illness. On the other hand, if the decrease in first contacts was really due to a decline in the incidence of schizophrenia, it would be reasonable to think that an aetiological agent has either disappeared, or is disappearing from the environment.

The 'neurodevelopmental damage hypothesis' maintains that there is an aetiological agent for schizophrenia that acts during the pre-perinatal period, which disrupts the neurodevelopment of the foetus and has a seasonal presence in the environment. The seasonal action

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of this agent would explain the widely replicated phenomenon of the winter excess of schizophrenic births (Boyd *et al.* 1986).

The hypothesis tested in this study is that the decline in first diagnoses of schizophrenia is due to a fall in the incidence of the disorder and that this is caused by the reduced prevalence of this seasonal aetiological agent. This hypothesis is tested by verifying the consistency over time of the seasonality of the schizophrenic births in a large dataset of patients discharged with a diagnosis of schizophrenia in England and Wales. The hypothesis would be confirmed if there was a suitable variation of the seasonality over time.

METHOD

Patients

The dates of births of the 24 576 discharges who have a diagnosis of schizophrenia from NHS hospitals in England and Wales over the period 1 April 1993–31 March 1994 were provided by the Department of Health and Social Security (DHSS). We restricted the sample of our study to patients born between 1938 and 1977 and to only one episode for each patient. Patients with more than one admission during this period are, therefore, represented only once. After these restrictions the sample object of the study was represented by 19 824 patients.

The control population is represented by all live births in England and Wales from 1938 to 1977 and these data were also provided by the DHSS. A control population is necessary because the distribution of live births in the general population is not homogeneous, but shows variations from month to month and from year to year. In particular, there is a large seasonal factor in the number of births across a year that must be accounted for in the analysis.

Only subjects who were born between 1938 and 1977 were considered in the study due to the fact that the numbers of live births in England and Wales prior to 1938 were recorded quarterly, not monthly.

Procedure

Details of the methodology can be found in Appendix 1. We present here a brief overview of the method. We follow the general methodology of Generalised Linear Models (GLM), see McCullagh & Nelder (1983) or Aitkin *et al.* (1989). Note that this methodology follows closely that of a similar study on schizophrenia in Takei *et al.* (1994).

The basic model, which was used in this study, assumes that in any given month the number of cases follows a Poisson distribution. This assumes that there is a small, but fixed probability, that any birth in any given month will go on to develop schizophrenia. It further asserts that the probabilities of separate births developing schizophrenia are independent. Rather than model this probability directly we model the average (mean) number of cases per birth per month as is usual in GLM methodology.

We are interested in testing if there is a seasonal effect on the mean proportion of cases born in a given month. To do this we must first remove the effects of any overall trends, once this is done we can test our statistical model for a seasonal effect. This model is shown graphically in Fig. 1. The solid line represents the prediction of the model of the number of cases per month. Notice that there is already a strong seasonal component in the model due to the large seasonality of the control population. In particular, we tested if there was a statistically significant difference between summer and winter births and if such an effect showed a significant change over time.

RESULTS

Fig. 1 shows the result of modelling the trend in the average number of cases. The crosses represent the observed number of cases of schizophrenia who were born in each month, and the solid line represents the predicted mean value, assuming no seasonal effect. Note that the clearly observed seasonal variation in the predicted mean value is due purely to the seasonal variation in the number of births per month. This model, which describes the trend, will be referred to as the null model.

Table 1 shows the effect of adding a seasonal component to the null model. It can be seen that there was a significant effect on the model ($P = 0{\cdot}03$), indicating evidence of a seasonal component in the number of cases born per month on top of that which is explained by the seasonality in the number of births. This is shown graphically in Fig. 2 where two box plots

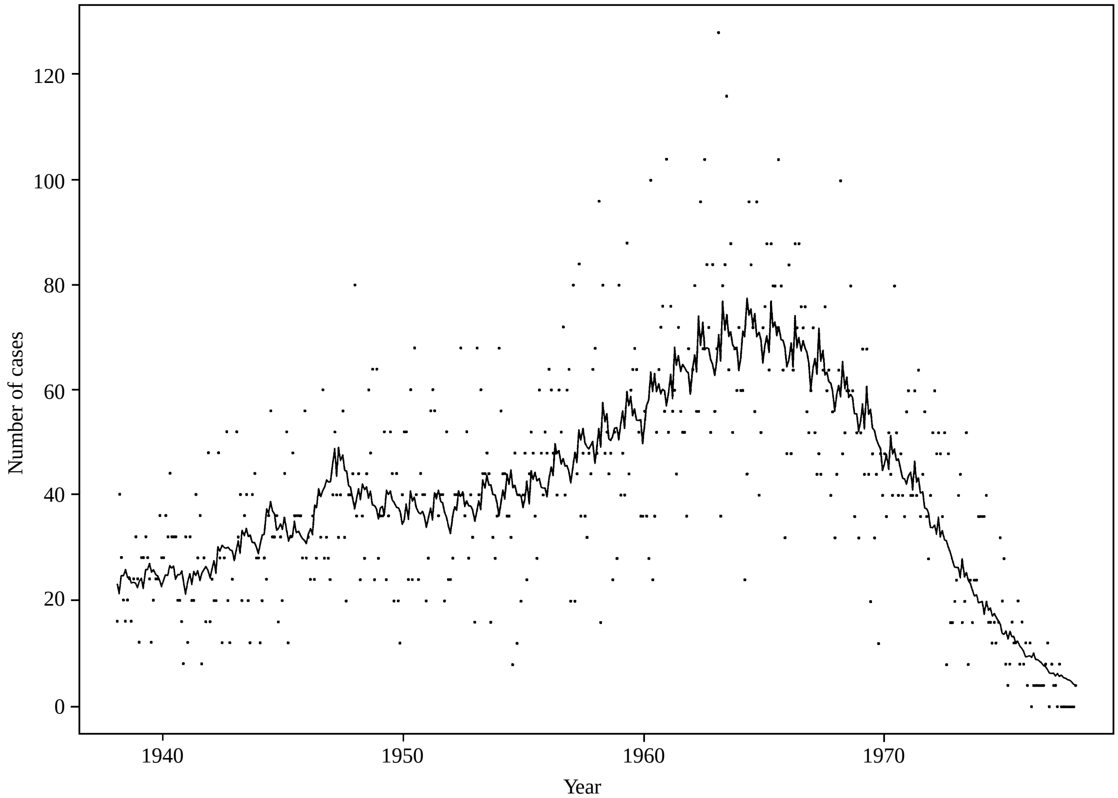

FIG. 1. Number of cases (—, model prediction; ·, observed number of cases).

Table 1. *The effect of adding a seasonal component to the null model*

Model	*P*
Null model + seasonal effect	0·03
Null model + seasonal effect + interaction	0·78

of the residuals from the model show a statistically significant difference between summer and winter. Table 1 also shows that there was no significant effect of adding a term that allows this seasonal effect to vary with time ($P = 0{\cdot}78$), indicating that this seasonal effect has not changed over the period of interest. For more details of the statistical analysis see Appendix 1.

DISCUSSION

The analysis of patients discharged with a diagnosis of schizophrenia in England and Wales over the period 1 April 1993–31 March 1994 shows that the seasonality of their birthdates has not changed significantly over time. There seems, therefore, to be no correlation between the observed decrease in first contacts with a diagnosis of schizophrenia and the hypothesized seasonal aetiological factor for schizophrenia.

A potential limitation of the study is that the patient sample is formed by prevalent cases discharged from psychiatric hospitals over a 1 year period, and not just by first admissions. Schizophrenia is a disease with heterogeneous prognosis, so that over the 1 year period patients with bad prognosis are more likely to have multiple admissions and hence they will be over-represented when compared with patients with a more benign form of illness. If seasonality is in some way related to the prognosis then there could be an artefactual effect. On the other hand, the form of sampling used can allow large enough numbers for a meaningful statistical analysis. A previous study on a Scottish sample of schizophrenic patients reached similar conclusions despite several methodological short-

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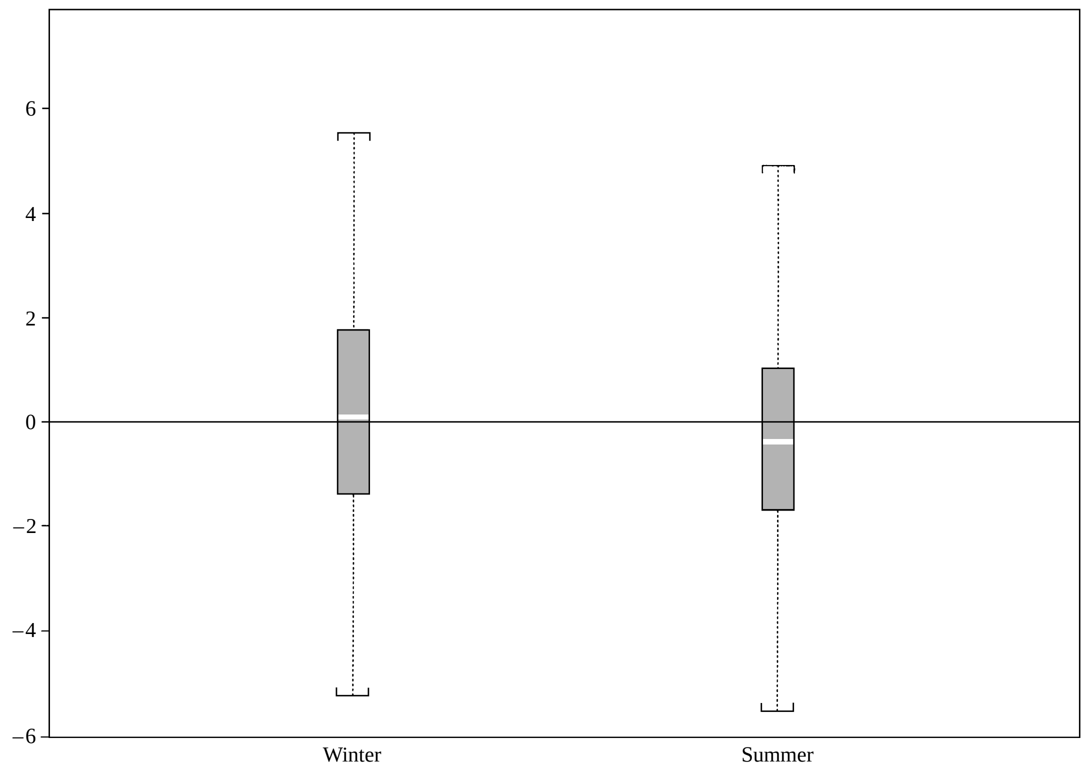

FIG. 2. Boxplot of residuals for winter and summer.

comings highlighted by the authors themselves (Eagles *et al*. 1995).

Some studies have noticed a greater fall of first contacts in females than in males (Kendell *et al*. 1993; Waddington & Youssef, 1994), others have observed the opposite (de Alarcon *et al*. 1990). The study by Eagles *et al*. (1995), mentioned above, seems to indicate sex differences in the trend of seasonality over time in schizophrenia. We felt that our sample does not allow a separate analysis by sex: in any study of seasonality the dates of births in the general population are needed as a control, and in England and Wales they are available separately by sex only from 1954. The need for the control population is due to the fact that there is a pronounced seasonality in the number of births in the general population.

The study of Castle *et al*. (1991) in Camberwell, Harrison *et al*. (1991) in Nottingham and Bamrah *et al*. (1991) in Salford have failed to detect any fall in contacts leading to a diagnosis of schizophrenia in the period between the mid-1960s and the late-1980s. These results are, as we have seen, discordant from most of the literature. One reason for this could be that the areas of these three studies have had, during the period investigated, a large increase in their Afro-Caribbean population, in which there seems to be evidence of an unexplained excess of diagnoses of schizophrenia (Harrison *et al*. 1988). Furthermore, in all these three studies the selection of the control population was far from ideal.

The consistency of the seasonal effect over time, observed in our study, does not mean that the decrease in first contacts could not be due to a decrease in the incidence of schizophrenia. In fact, it is generally accepted that the hypothesized seasonal aetiological agent accounts for only a minority of cases. There are, anyway, several other explanations for the decline in first admissions that do not involve a decrease in the incidence of schizophrenia.

Changes in diagnostic practice over time

The decrease in first admissions for schizophrenia could be due to the tendency to use stricter diagnostic criteria. New diagnostic systems were, in fact, introduced in the time period under consideration: ICD-9 (World Health Organization, 1978), DSM-III (American Psychiatric Association, 1980) and DSM-III-R (American Psychiatric Association, 1987). Kendell *et al*. (1993), for instance, found in their Scottish sample a 22% reduction of the diagnoses of schizophrenia made by hospital psychiatrists over the period 1971–1989, but when the data from the casenotes were analysed by a computer program no decline was noticed. The authors, therefore, suggest that patients who previously were diagnosed as suffering from schizophrenia are now diagnosed in a different way.

Other studies have reported results that seem to confirm this hypothesis (Dickson & Kendell, 1985; Parker *et al*. 1985; Munk-Jörgensen, 1986; Munk-Jörgensen & Jörgensen, 1986; Joyce, 1987), but the extent of the increase in other diagnoses in these studies was inadequate to explain the decrease in diagnoses of schizophrenia.

The results of the study by Der *et al*. (1990) seem to refute this hypothesis: they noticed in fact that the decrease in first diagnoses of schizophrenia was parallelled by a decrease in diagnoses of affective psychoses and neurotic disorders with an unchanged incidence of 'other psychoses'. This finding makes unlikely the hypothesis of a shift of the diagnosis from schizophrenia to these other categories. Similar conclusions have been reached in the articles by Eagles & Whalley (1985), Eagles *et al*. (1988) and Geddes *et al*. (1993).

Move towards community care

Several authors suggest that the decrease in first hospital admissions with a diagnosis of schizophrenia is caused by the movement towards community care (Prince & Phelan, 1990). The argument being that the former belief that all schizophrenics are eventually admitted to hospital (Ødegård, 1952) may no longer be true. Cooper *et al*. (1987), in their Nottingham study, found out that about 10% of first contact schizophrenics were never admitted to hospital during a 2 year period. Similar values have been found by Geddes & Kendell (1995) in a Scottish sample of schizophrenic patients.

The results in the study by Der *et al*. (1990) contradict this theory: in their sample of psychiatric patients diagnoses of schizophrenia represented, in fact, 21% of first admissions in 1952, but just 9% of the admissions in 1986. Their argument is that it is highly unlikely that patients suffering from schizophrenia could have surpassed other patients in the 'move towards the community'.

Other authors have tried to settle the controversy by using studies that included all the first contacts, therefore not just in-patients, but also day-patients and out-patients (Eagles *et al*. 1988; Munk-Jörgensen & Mortensen, 1992; Kendell *et al*. 1993). All these studies confirmed a decrease in first contacts leading to a diagnosis of schizophrenia.

Patients misreported as first contacts

Another potential source of bias has been identified by Kendell *et al*. (1993) in their Edinburgh study: they noticed how at least 59% of 'first admissions' for schizophrenia in 1971 had in reality been previously admitted in psychiatric hospitals. The same problem has been identified by Munk-Jörgensen & Mortensen (1992) in their Danish sample.

Benign metamorphosis of schizophrenia

The hypothesis is that the natural history of schizophrenia is changing towards a more favourable outcome (Hare, 1974, 1979; Zubin *et al*. 1983). Harrison & Mason (1993), after reviewing the published literature, concluded that there is no evidence for a benign metamorphosis in the natural history of schizophrenia over the last century.

CONCLUSION

From the analysis of a large sample of schizophrenic patients from England and Wales it appears that the reduction of first diagnoses of schizophrenia beginning from the mid-1960s is not due to seasonal aetiological agents. This leaves space for two other possible explanations: either the incidence of schizophrenia is declining

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because of the disappearance of a non-seasonal aetiological factor, or the incidence is not decreasing. In the last case the reduction in first contacts would be due to other factors like changes in diagnostic practices, the move towards community care, further contacts reported as first contacts, a benign metamorphosis of the natural history of schizophrenia.

APPENDIX 1

The initial model for the data was based on the assumption that the number of cases born in each month has a Poisson distribution, so the probability that there are r_t cases in month t where there are N_t births in that month is

$$\Pr(R_t = r_t) = \frac{(\lambda_t N_t)^{r_t}}{r_t!} e^{-\lambda_t N_t}.$$

The parameter λ_t is the incidence rate in month t. Since inspection of the observed incidence rate, indicts that the rate changes over time we model it by assuming that the rate follows a non-linear trend:

$$\log(\lambda_t) = \beta_0 + \beta_1 t + \beta_2 t^2 + \beta_3 t^3 + \beta_4 t^4.$$

The number of births per month, N_t, which is the control population in this study, is included in the model as an offset in accordance with McCullagh & Nelder (1983, page 206). An offset is a covariate in the model whose coefficient is constrained to be 1. The values of the free coefficients β_i were found by the method of maximum likelihood estimation. This method of Poisson regression was done using the package S-plus, further details can be found in McCullagh & Nelder (1983). The methodology also follows that of Takei *et al.* (1994) who studied the effect of influenza on the development of schizophrenia. The fit of this model is shown in Fig. 1. Notice that there is already some observable seasonal effect in the predicted value of the number of cases of schizophrenia per month. This is because we are assuming a given proportion of N_t will develop schizophrenia and N_t, itself will have a strong seasonal effect. This point makes it vital that a control population has been included in the analysis.

As in the case of Normal least squares regression investigation of the residuals after the trend is fitted contains important information about the goodness-of-fit of the model. A Poisson random variable has the property that its variance equals its mean and this property gives a natural measure of goodness-of-fit. In fact, for this data the variance of the residuals is approximately five times larger than the model predicts. This effect for a Poisson model is called 'over-dispersion', for details see McCullagh & Nelder (1983, page 198).

Table 2. *Addition of a seasonal variable: analysis of deviance*

Model	df	Deviance	Residual deviance	F	P
Null			4772·815		
$.+t$	1	7·588	4765·227	1·5410	0·2150842
$.+t^2$	1	1533·404	3231·823	311·4029	0·0000000
$.+t^3$	1	674·242	2557·581	136·9247	0·0000000
$.+t^4$	1	109·659	2447·922	22·2695	0·0000000
. + Season	1	31·864	2424·535	4·7186	0·0303336

In order to estimate parameters in an over-dispersed model, one approach is to use a pseudo-likelihood model, McCullagh & Nelder (1983, page 124). In this model rather than the variance of the Poisson model being equal to the predicted mean it is assumed to be proportional to the mean and the constant of proportionality is called the 'scale parameter'. The parameter is estimated in the fitting process, and then inference is done conditionally on the value of the scale parameter. In this paper this methodology was followed.

To test for a seasonal effect, a two factor dummy variable was fitted for 'winter' and 'summer'. Summer was defined to be the 6 months between June till November. The addition of this seasonal variable was tested for statistical significance using the method of Analysis of Deviance. The deviance is defined as twice the difference between the maximum (pseudo-) likelihood for the model which includes the monthly effect minus the maximum (pseudo-) likelihood for the null model. The result of the analysis of deviance is shown in Table 2. The notation $.+t$ etc. indicates that the covariate t has been added to the previous model. The row then gives the changes in deviance associated to this change in the model. The statistical significance is evaluated with an F test. Note that the linear term (t) has been retained in the model despite the fact that its inclusion did not reach statistical significance of 0·05. This is in accord with McCullagh & Nelder (1983, page 89) where it is recommended that lower degree polynomial terms are retained if higher ones are included. Terms were fitted in the polynomial until the deviance indicated that the improvement of fit was not statistically significant. From Table 1 it can be seen that fitting the seasonal effect has a statistically significant effect ($P = 0{\cdot}03$) on the goodness-of-fit of the model. There seems therefore to be reasonable evidence of the seasonal effect.

We then wish to test if this effect is varying over time. We fit, therefore, an interaction term of time and the seasonal effect. The analysis of deviance table for this model does not show a significant interaction ($P = 0{\cdot}780$), indicating that there is no evidence that the seasonal effect is varying over time.

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