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The British Journal of Psychiatry 1994 165: 466-473
Access the most recent version at doi:10.1192/bjp.165.4.466

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British Journal of Psychiatry (1994), **165**, 466–473

Age at Onset, Sex, and Familial Psychiatric Morbidity in Schizophrenia

Camberwell Collaborative Psychosis Study

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Background. Although a genetic component in schizophrenia is well established, it is likely that the contribution of genetic factors is not constant for all cases. Several recent studies have found that the relatives of female or early onset schizophrenic patients have an increased risk of schizophrenia, compared to relatives of male or late onset cases. These hypotheses are tested in the current study.

Method. A family study design was employed; the probands were 195 patients with functional psychosis admitted to three south London hospitals, diagnosed using Research Diagnostic Criteria (RDC), and assessed using the Present State Examination (PSE). Information on their relatives was obtained by personal interview of the mother of the proband, and from medical records. Psychiatric diagnoses were made using Family History – Research Diagnostic Criteria (FH–RDC), blind to proband information.

Results. There was a tendency for homotypia in the form of psychosis within families. The lifetime risk of schizophrenia in the first degree relatives of schizophrenic probands, and the risk of bipolar disorder in the first degree relatives of bipolar probands, were 5–10 times higher than reported population risks. Relatives of female and early onset (<22 years) schizophrenic probands had higher risk of schizophrenia than relatives of male and late onset schizophrenic probands. However, this effect was compensated in part by an excess of non-schizophrenic psychoses in the relatives of male probands.

Conclusions. These results suggest a high familial, possibly genetic, loading in female and early onset schizophrenia, but do not resolve the question of heterogeneity within schizophrenia.

The classification of the functional psychoses by Kraepelin (1896) into dementia praecox and manic–depressive psychosis was followed by the demonstration that these disorders were familial in their occurrence (Rudin, 1916; Slater, 1936). Modern studies using stringent methodology, including the systematic sampling of probands and concurrent controls, and the 'blind' assessment of relatives, have repeatedly confirmed the familial clustering of both schizophrenia and affective psychosis. For narrowly defined schizophrenia, as for bipolar affective disorder, the lifetime risk of the illness in first degree relatives of affected probands is 5 to 20 times higher than that of general population controls (Kendler, 1988; Tsuang & Faraone, 1990). Twin and adoption studies have shown that much of this familial clustering is due to genetic inheritance, for both schizophrenia (Gottesman & Shields, 1982) and affective psychosis (McGuffin & Katz, 1986).

However, a number of basic questions remain. The modes of inheritance of both schizophrenia and manic–depressive psychosis remain unclear (Baron, 1986; Tsuang & Faraone, 1990). Whether schizophrenia and affective psychosis are two distinct disorders, or are closely related in aetiology, is still debated (Crow, 1986; Taylor, 1992). Even within schizophrenia, the question of aetiological heterogeneity has been raised (Murray *et al*, 1992). Some experts suggest that the application of modern molecular genetic techniques may not disclose specific disease-predisposing genes, unless these basic questions are adequately answered (McGue & Gottesman, 1989).

Recently, it has been suggested that gender differences in schizophrenia (reviewed by Lewine, 1988) may have aetiological implications (Goldstein *et al*, 1989; Castle & Murray, 1991; Lewis, 1992). Men have an earlier onset than women (Lewine, 1981); a poorer outcome (Angermeyer *et al*, 1990); and contrary to traditional belief (Wyatt *et al*, 1988), higher population risk, according to studies by Bland *et al*, 1984; Munk-Jorgensen *et al*, 1986; NiNullain *et al*, 1987; Lee *et al*, 1990; and Iacono & Beiser, 1992. Also contrary to conventional teaching (e.g. Slater & Cowie, 1971) are recent reports of a higher risk of the illness in the relatives of female than those of male schizophrenics (Shimizu *et al*, 1987; Goldstein *et al*, 1990; Pulver *et al*, 1990).

In many diseases, such as coronary heart, diabetes mellitus and Alzheimer's dementia, age at onset has proved to be a useful indicator of aetiological

heterogeneity. Recently, Murray *et al* (1992) have suggested that early onset schizophrenia is a disorder of prenatal neurodevelopment, distinct from late onset forms, and that the abnormal neurodevelopment may be in part due to genetic defects (Jones & Murray, 1991). While Kendler *et al* (1987) concluded that there was no "strong or consistent relationship" between age at onset and familial risk in schizophrenia, after summarising the literature, McGlashan & Fenton (1991) reviewing the traditional subtypes of schizophrenia, concluded that earlier onset, non-paranoid schizophrenia was associated with higher familial risk than later onset, paranoid schizophrenia. Indeed, Kendler & MacLean (1990), after correcting for familial correlation in age at onset, found an inverse relationship between age at onset in probands and risk in siblings in a Swedish family study. Pulver *et al* (1990) also found an increase in familial risk in very early onset (before 17 years) schizophrenia, which persisted after allowing for familial correlation in age at onset by a multivariate survival analysis (Pulver & Liang, 1991).

This study was designed to investigate the inter-relationships between the genetic–epidemiological, phenomenological neuropsychological and neuro-radiological features of functional psychotic disorders (Bebbington *et al*, 1993; Jones *et al*, 1993). The wide range of variables measured enables a detailed examination of the characteristics of the probands which are associated with familial psychiatric morbidity. Here we examine whether the age at onset and sex of schizophrenic patients are related to the risk of schizophrenia in relatives in this sample.

Method

The probands were 195 patients of age 16 to 50 years, who were admitted to the Maudsley, Bethlem Royal, and Dulwich North Hospitals from 1987 to 1989 with delusions, hallucinations or thought disorder (as defined in RDC; Spitzer *et al*, 1978), but without evidence of gross organic pathology. They were screened from consecutive admissions, patients whose mothers were unavailable for interview being excluded. The probands were therefore representative of patients hospitalised for functional psychotic symptoms, subject to the constraints of the inclusion criteria. Phenomenological assessment was made using the PSE (Wing *et al*, 1974), and diagnoses were made according to RDC. Demographic and historical information, such as marital status and occupation, were also recorded. The sampling procedures for the probands, and the assessment which they underwent, have been described more fully elsewhere (Jones *et al*, 1993).

Information on relatives were obtained from three sources: the probands' mothers, the medical records of relatives with a psychiatric history, and the probands' case notes. With permission from the probands, mothers were contacted and interviewed with FH–RDC (Andreasen, 1986) and were administered a questionnaire on the probands' obstetric history and early development (Lewis & Murray, 1987). Details of psychiatric admissions of any relatives were obtained so that requests could be made to the admitting hospitals for medical records.

Two of the authors independently rated the relatives for FH–RDC diagnoses using all available sources of information, blind to information on the proband. Inter-rater reliability for the various diagnoses was assessed by kappa coefficients. A consensus diagnosis was reached, in cases of disagreement.

Indicators of age at onset obtained were: age at first contact with any psychiatric services (i.e. being assessed or treated by a psychiatrist), age at first psychotic symptoms, and age at first hospital admission for psychosis. Definition of onset as the first occurrence of psychotic symptoms is perhaps the most satisfactory, being mostly a feature of the illness rather than the psychiatric services. However, where pre-psychotic psychiatric problems are present, these may have the same aetiological basis as the later psychosis. Moreover, the onset of psychotic symptoms is often insidious, and difficult to establish reliably. We have, therefore, used age at first psychiatric contact as our measure of age at onset. In cases where age at first psychotic symptoms could be obtained, this was highly correlated with age at first psychiatric contact (Pearson correlation coefficient 0.85).

Data analyses and results

We identified 925 first degree relatives, and obtained information on 891. The demographic characteristics of the probands and first degree relatives are shown

Table 1
Characteristics of probands

Proband's RDC diagnosis	Sex of proband		Age of proband (years)	
	Male	Female	Mean	s.d.
Schizophrenia	78	23	26.24	6.08
Schizoaffective-manic	7	9	30.19	6.97
Schizoaffective-depressed	10	6	29.80	8.56
Bipolar	15	17	29.72	7.80
Unspecified functional psychosis	6	5	28.18	7.94
Depression	6	7	29.77	8.46
Others	3	3	27.67	8.19

Table 2
Characteristics of first degree relatives

Proband's RDC diagnosis	Sex of relative Male	Female	Age of relative (years) Mean	s.d.
Schizophrenia	236	231	39.07	16.87
Schizoaffective-manic	45	33	40.00	18.78
Schizoaffective-depressed	34	49	39.57	15.33
Bipolar	66	63	42.28	19.30
Unspecified functional psychosis	28	23	30.72	21.46
Depression	34	27	38.73	19.09
Others	14	8	38.28	16.66

in Tables 1 and 2 respectively. The kappa coefficients for FH–RDC diagnoses were generally high (Table 3), indicating an adequate level of inter-rater reliability. These coefficients were based on 740 first and second degree relatives for whom sufficient information was available for FH–RDC ratings.

The frequencies of FH–RDC diagnoses in first degree relatives, expressed as percentages, were tabulated against the diagnoses of the probands (Table 4). Taking into account the small sample sizes in some rows, some homotypia was evident, with the relatives of schizophrenic probands having the greatest frequency of schizophrenia (4.34%), and the relatives of bipolar probands having the greatest frequency of bipolar disorder (1.92%). The lifetime risks of schizophrenia and bipolar disorder in relatives were estimated by the method of Stromgren (1935), using age-of-onset distributions derived from Mental Health Enquiry data on 12 regions in England and Wales (Takei *et al*, 1992). Standard errors of these estimates were calculated using a normal approximation as suggested by Risch (1983). Some homotypia was again evident from the estimated lifetime risks of schizophrenia and bipolar disorder in the first degree relatives of schizophrenic and bipolar probands (Table 5).

Table 3
Inter-rater reliability of FH–RDC diagnosis in first and second-degree relatives ($n = 740$)

FH–RDC diagnosis	Number affected	Kappa
Schizophrenia	27	0.94
Schizoaffective	15	0.80
Depression	77	0.95
Bipolar disorder	8	0.85
Unspecified functional psychosis	19	0.85
Alcoholism	26	0.98
Drug abuse disorder	4	0.86
Anti-social personality	4	0.67
Senile organic brain syndrome	6	0.66
Completed suicide	9	1.0

Of the 195 probands, 101 had RDC schizophrenia. Of these, 78 were men and 23 women; with a mean age at first psychiatric contact of 20.7 years (s.d. 60), and 21.7 (s.d. 6.4) respectively. As the median age at first contact for the whole sample was 21 years, we grouped those with an age at first contact of 21 years or younger (earlier onset) and those with an age at first contact of 22 years or older (later onset).

A total of 407 first degree relatives (16 years old and above) of these 101 probands were identified. According to FH–RDC, schizophrenia was present in 14 of the 339 first degree relatives for whom adequate information was available for a rating to be made. Similarly, schizoaffective disorder, bipolar disorder and major depression were rated as present in 2, 3, and 21 relatives, respectively. FH–RDC diagnosis was made with the information from psychiatric records, in addition to information from maternal interview, in 10 cases with schizophrenia, 2 cases with schizoaffective disorder, 3 cases with bipolar disorder, and 4 cases with major depression.

The lifetime risks of schizophrenia, psychotic disorders (schizophrenia, schizoaffective and bipolar disorders, and unspecified psychosis) and affective disorders (bipolar and unipolar disorders) in these first degree relatives were estimated, for various subgroups defined by the age at onset and sex of the probands. Affective disorders were lumped together, there being too few relatives with bipolar disorders to consider separately. The method of Stromgren (1935) was used, assuming sex-specific population age-at-onset distributions derived from

Table 4
Frequencies of FH–RDC diagnoses in first degree relatives against diagnosis of proband

Proband's RDC	Number of relatives	Frequency of FH–RDC diagnosis in first degree relatives (%) Schizophrenia	Schizoaffective	Depression	Bipolar disorder	Unspecified psychosis	Alcoholism
Schizophrenia	346	4.34	0.58	6.07	0.87	1.16	2.60
Schizoaffective	129	1.55	1.55	10.08	0.78	1.55	3.10
Bipolar	104	1.92	3.85	10.58	1.92	0.96	3.85
Unspecified psychosis	44	0	0	11.36	2.33	0	0
Depression	44	2.27	0	13.64	0	0	0

Table 5
Lifetime risk estimates of FH-RDC schizophrenia and bipolar disorder in first degree relatives of schizophrenic and bipolar probands

Proband's RDC diagnosis	Estimated lifetime morbidity risk (and 95% CI) in first degree relatives	
	Schizophrenia	Bipolar disorder
Schizophrenia	7.4% (3.6-11.2)	2.1% (0-4.5)
Bipolar disorder	3.3% (0-7.9)	4.3% (0-10.3)

Mental Health Enquiry data on 12 regions in England and Wales (Takei *et al*, 1992). Confidence intervals (CI) for these estimates were obtained from 1000 bootstrap samples (see Appendix) generated by GLIM (Numerical Algorithms Group, 1985). Likewise, null hypotheses of no morbid risk difference between two groups were tested using the bootstrap samples.

The lifetime risk estimate of schizophrenia for the whole sample of 407 first degree relatives was 7.4% (95% CI, 3.7-11.4%). The lifetime risk estimate of schizophrenia (Table 6) was higher in the first degree relatives of earlier onset probands (11%) than those of later onset probands (2.3%), and higher in the first degree relatives of female probands (20.6%) than those of male probands (4%). These differences were significant at $P<0.01$. First degree relatives of earlier onset female probands had significantly higher lifetime risk of schizophrenia than those of earlier onset male probands ($P<0.01$) and those of later onset female probands ($P<0.05$). The lifetime risks of schizophrenia in first degree relatives of earlier onset male, later onset male, and later onset female probands were not significantly different, although these tests had limited power.

When all psychotic disorders were considered (Table 7), the effect of the sex of the proband was diminished. Although the estimated risk of psychotic disorders in the relatives of female probands was twice that of male probands, this difference was not statistically significant. Evidently, non-schizophrenic psychotic disorders were more common in the relatives of male than in the relatives of female probands in this sample.

The lifetime risk estimates of affective disorders were not significantly different between the first degree relatives of earlier and later onset probands, or between the first degree relatives of male and female probands (Table 8).

Table 6
Lifetime risk of FH-RDC schizophrenia in first degree relatives of RDC schizophrenic probands in relation to age at onset and sex of proband

Characteristic of proband	First degree relatives of age 16 years or above				
	Number with FH-RDC schizophrenia	Total number with information	Age corrected number (BZ)	Lifetime risk estimate (%)	95% CI interval (%)
Early onset (<22 years)	11	185	99.65	11.0	4.9, 17.9
Late onset (>21 years)	2	142	88.07	2.3	0.0, 5.8
Male	6	265	150.07	4.0	1.3, 7.7
Female	8	64	38.90	20.6	8.1, 34.9
Early onset, male	4	146	77.31	5.2	1.2, 11.5
Early onset, female	7	39	22.34	31.3	10.9, 53.1
Late onset, male	1	117	71.50	1.4	0.0, 4.5
Late onset, female	1	25	16.57	6.0	0.0, 20.9

Significant differences: early onset v. late onset, $P<0.01$; male v. female, $P<0.01$; early onset female v. early onset male, $P<0.01$; early onset female v. late onset female, $P<0.05$.

Table 7
Lifetime risk of FH-RDC psychotic disorders in first degree relatives of RDC schizophrenic probands in relation to age at onset and sex of proband

Characteristic of proband	First degree of relatives of age 16 years or above				
	Number with FH-RDC psychotic disorders	Total number with information	Age corrected number (BZ)	Lifetime risk estimate (%)	95% CI interval (%)
Early onset (<22 years)	18	185	99.65	18.1	10.5, 15.3
Late onset (>21 years)	4	142	88.07	4.5	1.1, 9.4
Male	15	265	150.07	10.0	5.3, 15.3
Female	8	64	38.90	20.6	8.1, 34.9

Significant differences: early v. late onset, $P<0.01$.
Psychotic disorders include schizophrenia, schizoaffective disorder, bipolar disorder and unspecified psychosis.

Table 8
Lifetime risk of FH-RDC affective disorders in first degree relatives of RDC schizophrenic probands in relation to age at onset and sex of proband

Characteristic of proband	First degree relatives of age 16 years or above				
	Number with FH-RDC schizophrenia	Total number with information	Age corrected number (BZ)	Lifetime risk estimate (%)	95% CI interval (%)
Early onset (< 22 years)	16	185	76.15	21.0	11.9, 31.3
Late onset (> 21 years)	8	142	69.22	11.6	4.3, 19.9
Male	21	265	115.75	18.1	11.3, 25.9
Female	3	64	30.61	9.8	0.0, 21.3

Affective disorders include bipolar disorder and major depression.

Table 9
Lifetime risk of FH-RDC schizophrenia in first degree relatives of RDC schizophrenic probands in relation to characteristics of relative

Characteristic of relative	First degree relatives of age 16 years or above				
	Number with FH-RDC schizophrenia	Total number with information	Age corrected number (BZ)	Lifetime risk estimate (%)	95% CI interval (%)
Male	6	161	101.18	5.9	1.9, 11.1
Female	8	168	87.80	9.1	3.3, 15.6
Male, parent	1	75	67.71	1.5	0.0, 4.7
Female, parent	7	82	64.08	10.9	3.2, 18.9
Male, sibling/offspring	5	86	33.46	14.9	3.0, 30.4
Female, sibling/offspring	1	86	23.72	4.2	0.0, 14.2

Significant differences: male parent v. female parent, $P<0.05$; male parent v. male sibling/offspring, $P<0.05$.

Finally, we examined the effect of the sex of the relative on the lifetime risk of schizophrenia in relatives. Overall, the lifetime risk was 5.9% in male and 9.1% in female relatives; this difference was not statistically significant (Table 9). We then considered siblings and offspring separately from parents, because the risk estimates of the former should be relatively unaffected by fertility effects, which are known to substantially reduce the apparent risk in the fathers of schizophrenics (Essen-Moller, 1955). The lowest risk was in the fathers of the probands (1.5%), consistent with a reduction in fertility in schizophrenic males. The estimated lifetime risk in brothers/sons (14.9%) was three times higher than in sisters/daughters (4.2%); this difference again was not statistically significant.

Discussion

The limitations of the study need to be considered. First, the psychiatric status of the relatives was not assessed by direct interview, but by maternal interview and examination of medical records. The sensitivity and specificity of the family history method of diagnosing schizophrenia in relatives is modest (Andreasen *et al*, 1986; Zimmerman *et al*, 1988). However, we did achieve a high level of reliability in the diagnosis of schizophrenia and other psychiatric disorders, perhaps as our diagnoses were based in many cases on hospital psychiatric records as well as maternal interviews.

A second limitation is that the sample size does not allow very precise estimates of the familial rates of psychiatric disorders, especially when the probands are divided into small subgroups. This is compounded by the low frequencies of the major psychotic disorders, so that a precise estimate requires a large sample size. The confidence intervals in this study are rather wide.

Also, our sample of probands were probably younger and more severely ill than a random sample of schizophrenics from the local community, because they were ascertained from hospital admissions, and were required to be aged less than 50 years and to have mothers available for interview. As a result, we had a very high male to female ratio (78 to 23), and a very early mean age at onset (21 years) among the schizophrenics. The generalisability of our findings to less severe and later onset forms of schizophrenia is therefore limited.

Finally, in the estimation of lifetime morbid risk, we used an age correction according to the age at onset distributions derived from Mental Health

Enquiry data, in which the diagnosis of schizophrenia is based not on RDC but on ICD-9. ICD-9 schizophrenia is a more inclusive category than RDC schizophrenia, and has a slightly later mean age at onset (Castle *et al*, 1991). The lifetime risks in this study might therefore have been slightly overestimated. However, any bias should be small, and equally applicable to all the comparison groups.

The risks of schizophrenia and manic–depressive psychosis in the relatives of our probands are comparable to the risk estimates from other family studies, both being 5–10 times above the reported risks in the general population (Kendler, 1988; Tsuang & Faraone, 1990). Although suggesting a degree of genetic overlap between schizophrenia and manic–depressive psychosis, in that the risk of schizophrenia appears to be increased in the relatives of manic–depressive probands, and vice versa, this evidence must be considered very tentative because of the imprecision of the family history method in distinguishing between different forms of psychotic illnesses.

Our results on sex differences confirm that the lifetime risk of schizophrenia is higher in the relatives of female than male probands, consistent with recent studies (Shimizu *et al*, 1987; Goldstein *et al*, 1990; Pulver *et al*, 1990). This effect requires explanation. Adopting a liability-threshold model, in which liability is determined of the combined effects of genes, family environment, and individual environment, the excess familial risk observed in female probands can be explained by (a) a smaller genetic component in males, (b) a greater family environmental component in females, or (c) a higher threshold of affection in females. The current study was not designed to resolve these alternative explanations, which are best examined by twin studies. Nevertheless, the recent reports of a lower population risk of schizophrenia in females than in males (Bland *et al*, 1984; Munk-Jorgensen *et al*, 1986; NiNullain *et al*, 1987; Lee *et al*, 1990; Iacono & Beiser, 1992; Castle *et al*, 1993) is consistent with a higher threshold in females. For example, it is possible that, for any given level of liability, females tend to have a milder illness than males, so that when the same modern, stringent diagnostic criteria are applied to men and women, the threshold is in effect set at a higher level for women than for men. The average liability of female schizophrenics would then be greater than that of male schizophrenics.

Obstetric complications, which have been implicated as a possible environmental risk factor of schizophrenia (McNeil & Kaji, 1978; Lewis & Murray, 1987; Foerster *et al*, 1991; O'Callaghan *et al*, 1992), have been reported to be more common in male than in female schizophrenics (Wilcox & Nasrallah, 1987; Pearlson *et al*, 1989; Foerster *et al*, 1991; O'Callaghan *et al*, 1992), suggesting greater individual environmental influences, and hence a relatively smaller genetic component, in male schizophrenia. In particular, an environmental factor of major effect would produce phenocopies, whose relatives would be at no greater risk to schizophrenia than the general population. An excess of male phenocopies has the interesting implication that the risk of schizophrenia in male and female relatives should be approximately equal. In this regard, our results are inconclusive; the risk in male relatives was higher than in female relatives, excluding parents, but the difference was not statistically significant.

The observed reduction in the sex difference in familial risk with a wider definition of illness in the relatives is consistent with the report of Goldstein *et al* (1990) of a significantly higher risk of schizotypal personality disorder in the relatives of male than in the relatives of female schizophrenic probands. One possible explanation is that we might have had better diagnostic information on the relatives of female than on the relatives of male probands. Another possibility is that the relationship between schizophrenia and 'schizophrenia spectrum' disorders may be tighter in males than in females. For example, certain genetic and environmental factors may predispose to both 'spectrum' disorder and schizophrenia in males, but not in females.

Our finding of an association between early onset and high familial risk suggests an overlap between the familial factors which determine age at onset and those which determine whether the illness develops. Moreover, the decreased risk of schizophrenia in relatives of later onset probands was not associated with a compensatory increase in the risk of affective illness. This does not support the notion that later onset schizophrenia is aetiologically more closely related to affective disorders (Castle & Murray, 1991). However, since the probands as a group have very early onset, they are not ideal for addressing issues concerning late onset (typically after the age of 45 years) schizophrenia.

A problem in relating age at onset in proband and risk in relatives is that, if age at onset is positively correlated between relatives, then the age range of risk may be earlier in relatives of early onset than in those of late onset probands. In other words, at any age, a relative of an earlier onset proband may have lived through a greater proportion of his or her risk period than a relative of a later onset proband. Ideally, we should have separate age corrections for the relatives of earlier and later onset probands. However, the correlation in age at onset between first

degree relatives is only modest (Kendler *et al*, 1987). In two recent studies, the correction for correlated ages at onset did not change the conclusion of the study (Kendler & MacLean, 1990; Pulver & Liang, 1991). An inverse relationship between age at onset and familial risk has been reported for many disorders of complex inheritance (Childs & Schriver, 1986). If the risk of schizophrenia is determined by several genes, it is plausible that a high 'dosage' of these genes would also cause an earlier age at onset. However, environmental determinants of age at onset must also exist, since among monozygotic twin pairs concordant for schizophrenia, about 40% have a difference in age at onset exceeding 5 years (Abe, 1969).

In conclusion, this study suggests that early onset, female schizophrenic patients have the highest familial rates of schizophrenia, and may constitute a rewarding group for genetic research. However, we have not resolved whether the excess of early onset males over early onset females is due to a greater number of male phenocopies, or a greater susceptibility of males to environmental factors which interact with the genetic predisposition to schizophrenia. The resolution of these alternative hypotheses requires further, larger, family studies.

Appendix

Bootstrap confidence limits for the Stromgren estimator of lifetime risk

The Stromgren estimator of lifetime risk, p, is asymptotically normal:

$$p \sim \text{normal}\{\pi,\ p(\Sigma W_i - p.\Sigma W_i^2)/(\Sigma W_i)^2\}$$

where π is the true lifetime risk, and W_i is the probability of an onset of the disease before the age of the i'th individual in the sample, conditional on the disease occurring sometime in that individual's lifetime (Risch, 1983). Confidence limits for π and a test (namely the *t*-test) for the difference between two π's can be constructed according to this asymptotic distribution. However, for small samples and small π's the distribution of p is not normal but skewed, with a variance greater than the asymptotic variance. A better estimate of the sampling distribution of p can be obtained by the Bootstrap method (Efron, 1979). This involves repeatedly taking random samples (of the same size as the original sample) with replacement from the original sample and calculating p for each sample. The distribution of the p's of the 'bootstrap samples' is taken as an estimate of the sampling distribution of p, so that confidence limits of p can be obtained directly. To test the significance of the difference between two πs, we take, repeatedly, a bootstrap sample from each original sample and calculate the difference between the estimated ps, to estimate the sampling distribution of the differences, From this the p-value for the null hypothesis that the true difference is 0 can be obtained.

Acknowledgements

This work was supported by training fellowships from the Wellcome Trust (PCS), the Medical Research Council (PBJ) and a project grant from the Mental Health Foundation.

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(First received September 1992, final version November 1993, accepted December 1993)