Reproductive fitness in familial schizophrenia¹

Anne S. Bassett^a, Alison Bury^a, Kathleen A. Hodgkinson^a, and William G. Honer^b

^aDepartment of Psychiatry, University of Toronto and Schizophrenia Research Program, Queen Street Mental Health Centre, 1001 Queen Street West, Toronto, Ontario M6J 1H4, Canada

^bDepartment of Psychiatry, University of British Columbia, 2660 Oak Street, Vancouver, B.C. V6H 3Z6, Canada

Abstract

Background—Reproductive fitness is an important factor in understanding inheritance in genetic disorders. The purpose of this study was to determine whether fitness is reduced in familial schizophrenia (FS) and if fitness in siblings differs from the norm.

Method—The number of offspring in 36 subjects with RDC schizophrenia or schizoaffective disorder (SZ) and their 101 siblings from large FS families was compared with age-adjusted census figures.

Results—Fitness in the SZ group was significantly reduced: 23% of expected in males and 51% of expected in females. Fitness of unaffected siblings was within census expectations. However, female siblings with schizophrenia spectrum features had increased fitness over census norms. Reduced fitness was correlated with low marital rates, poor functioning and positive symptoms.

Conclusions—These results indicate that reduced fitness is an important genetic force in FS and is likely inherent to the illness. Sex differences are important and would need to be considered when examining maternal and paternal transmission of schizophrenia. The results support a proposed high mutation rate for schizophrenia, consistent with a dynamic mutation mechanism.

Keywords

Schizophrenia; Fitness; Fertility; Sex differences; Schizophrenia spectrum; Mutation rate

1. Introduction

Schizophrenia has a high heritability (Kendler and Diehl, 1993) and a relatively constant prevalence in the general population (Jablensky, 1988), suggesting that forces involved in natural selection will affect the illness (Vogel and Motulsky, 1986). A model involving negative selection (reduced reproductive fitness of affected individuals having a schizophrenia genotype) balanced by a high rate of new mutations has been proposed for schizophrenia to maintain the disease in the population (Book, 1953b; Penrose, 1956). This model predicts that in familial forms of schizophrenia, in which maximal effects of selection

¹Presented in part at the Vth International Congress on Schizophrenia Research, Warm Springs, Virginia, April 8–12, 1995.

Correspondence to: Anne S. Bassett.

are likely, empirical evidence for reduced reproductive fitness should be found. Although there is strong evidence for decreased reproductive fitness in unselected samples of schizophrenia (Haverkamp et al., 1982), surprisingly fitness has not previously been examined in familial schizophrenia. A finding of reduced fitness in familial schizophrenia would be of particular interest given a recent finding of anticipation (worsening severity and decreased age at onset across generations) (Bassett and Honer, 1994). Anticipation is associated in other neuro-psychiatric disorders with unstable mutations (Sutherland and Richards, 1995), suggesting that an unstable mutation may underlie schizophrenia (Bassett and Honer, 1994; Morris et al., 1995; O'Donovan et al., 1995) and could provide a plausible mechanism for a high mutation rate.

The issue of possible sex differences in fitness also requires examination in a familial sample. There is some evidence, from both older (Erlenmeyer-Kimling et al., 1980; Odegaard, 1980) and more recent (Hilger et al., 1983; Nanko and Moridaira, 1993; Fananas and Bertranpetit, 1995; Ward et al., 1995) studies, that fitness in schizophrenia is lower in men than in women. Differential expression depending on parental origin of disease genes, or imprinting, may be important in psychiatric illnesses (Flint, 1992). Imprinting has not been established to date in familial schizophrenia (Sharma et al., 1993; Asherson et al., 1994; Bassett and Honer, 1994), however sex differences in fitness may obscure the observation of imprinting effects (Howeler et al., 1989; de Die-Smulders et al., 1994).

An alternative mechanism to high mutation rate for maintaining the prevalence of schizophrenia is positive selection: increased reproductivity of unaffected or mildly affected gene carriers (Erlenmeyer-Kimling and Paradowski, 1966). This theory has generally not been supported by studies of siblings of schizophrenic subjects (Erlenmeyer-Kimling, 1978; Gottesman and Shields, 1982; Haverkamp et al., 1982). Relatively few studies have been done, however and none has assessed siblings for diagnoses such as schizophrenia spectrum conditions that are most likely to be associated with gene carrier status.

Many older studies of reproductive fitness had methodological flaws involving the assessment of fitness and the comparison to norms (Haverkamp et al., 1982). Some studies report only 'marital fertility', the number of offspring of married individuals (Haverkamp et al., 1982; Lane et al., 1995). Reproductive fitness of all individuals regardless of marital status is the only measure relevant to genetics and the issue of selection (Erlenmeyer-Kimling et al., 1980). In addition, few studies of schizophrenia have used norms that controlled for the age of the sample (Haverkamp et al., 1982) and some have used small control samples which can introduce errors (Reed, 1959).

The current study investigated reproductive fitness in a rural Canadian sample comprised of individuals with familial schizophrenia and their siblings. Three principal hypotheses were tested: (1) that the fitness of adults with familial schizophrenia would be less than that of their siblings who did not have the disorder and less than that of age-matched census norms, (2) that fitness would be especially reduced in affected males and (3) that siblings' fitness would be equal to local census expectations, that is, would provide evidence for neither positive nor negative selection. Secondary hypotheses of clinical interest were that lower

fitness would be associated with single marital status, poor functioning, more severe positive and negative symptoms and younger age at onset.

2. Method

2.1. Sample

Subjects were members of nine extended non-consanguineous families participating in a genetic linkage study of familial schizophrenia. Local psychiatrists identified prospective pedigrees segregating schizophrenia. Families were selected for large size, availability of two or more generations of adults and apparent unilineal inheritance of schizophrenia, compatible with autosomal dominant transmission. Bilineal families, with evidence from family or collateral history of schizophrenia or other non-affective psychotic disorders on both sides, were excluded. Further details of the original ascertainment and assessment for the linkage study are described elsewhere (Bassett et al., 1993).

As previously outlined (Bassett and Honer, 1994), sibling sets (siblines) in three generations were determined by taking subjects only from the affected side of each family. For the current study, only those siblines having one or more individuals affected with schizophrenia or schizoaffective disorder and one or more full siblings who did not have these illnesses were studied. Consistent with the effects of anticipation, this criterion resulted in all subjects coming from the index or parental generations.

Of the 149 subjects in 18 affected siblines meeting initial criteria, 12 were excluded from the analyses. The nine parents of the principal proband siblines were excluded because families were ascertained partly on the basis of large sibships. Two subjects had not attained the age of 20, considered a minimum age likely to have offspring. One subject had severe mental retardation. The remaining 137 subjects from 18 siblines formed the sample for the current study.

Diagnoses of psychotic illness were made based on information from direct interview by a psychiatrist (Bassett et al., 1993), medical records and/or collateral information collected from three or more family members using the Family History-Research Diagnostic Criteria (FH-RDC) method (Andreasen et al., 1977). Diagnostic folders containing the family history and, if present, medical records and interview data, were reviewed independently by two psychiatrists (ASB and WGH); one of whom (WGH) was blind to the pedigree structures. A consensus lifetime Research Diagnostic Criteria (RDC) diagnosis and age at first hospitalization for psychotic illnesses were determined. Schizophrenia and schizoaffective disorder were approximately equivalent in severity in the current sample (Bassett et al., 1993) and were considered together in the current study. Subjects with unspecified functional psychosis ($n = 6$) and those having definite RDC schizotypal features ($n = 14$) were considered to have schizophrenia spectrum conditions. A subset of subjects directly interviewed as part of the linkage study had additional data available on functioning and severity of symptoms (Bassett et al., 1993). Global Assessment of Functioning (GAF; DSM-III-R) (American Psychiatric Association, 1987) scores and Positive and Negative Symptoms Scale (PANSS) ratings of positive and negative symptoms (Kay et al., 1989) were available for 87 subjects.

Data on the number of children born to subjects, all of whom had attained the age of 20 or older, were collected in the direct interviews and/or through collateral information from family history supplemented by genealogical records. Offspring who were products of multiple births (two sets of twins) were included each as individuals; stillbirths ($n = 3$) were excluded. Whether subjects were ever married, which included common-law arrangements of one year or more, was also recorded.

2.2. Population data

Genetic fitness is usually measured by the mean number of offspring born to individuals surviving to maturity in relation to a norm derived from local census figures, with corrections to match the age of the sample examined (Reed, 1959; Murphy, 1978). General population rates of offspring of women were available for the local area from Statistics Canada (Statistics Canada, 1993) from the 1991 census, arrayed in 5-year birth cohorts. The 1991 Canadian census had the advantage of documenting all offspring, not just legitimate offspring as had been the case in previous censuses. Comparison of fitness for comparable birth cohorts did not differ significantly from the 1961 census indicating that there was no significant change due to women dying during this 30-year period; therefore only the 1991 census was used.

Two adjustments were necessary to make sample and census data as comparable as possible. First, census data on offspring is collected only from women but the sample had approximately equal numbers of men and women. Although census data are considered valid for assessing male fitness because most women are married and there are similar numbers of each sex (Reed, 1959) in the general population, men begin reproducing 3 years later than women (Crow, 1993). The current age of males in the sample was therefore adjusted by subtracting 3 years. Second, the age distribution of the sample differed from that of the census. Therefore, original census figures for the number of women in each age cohort were adjusted to be consistent with the sample proportions, thereby controlling for changing trends in family size. Within each age cohort, the mean number of offspring that were calculated using age-adjusted data, was checked to ensure values were the same as published census means (Statistics Canada, 1993).

2.3. Analyses

Data were examined principally on two groups of siblings. The affected sibling group ($n = 36$) was made up of subjects with schizophrenia ($n = 26$) and schizoaffective disorder ($n = 10$: mainly schizophrenic, $n = 7$; mainly affective or other, $n = 3$); their 101 siblings comprised the sibling group. The groups were examined to assess reproductive fitness compared to age-adjusted census rates. T-tests were used to compare mean number of offspring between the sibling groups. Both groups were compared to the general population using a z -test. Relative fitness (Haldane, 1935; Reed, 1959) was also calculated. When there are no age differences between the comparison samples, relative fitness is a simple ratio of mean numbers of offspring compared to the general population mean; the latter therefore has a relative fitness set at 1.0. The χ^2 statistic was used for childlessness and other categorical variables. Census figures were used to determine the expected values in the χ^2 analyses. To examine the distribution of family size, both groups were compared to the general

population on categorical ratings of the number of children (childless, 1–3, 4 or more) using a *z*-test of proportions (Hays, 1988).

If reproduction was merely delayed rather than absent in subjects, age-corrected comparisons may not reveal this. To assess whether the same results held for individuals with completed fertility, i.e., who were likely to be through the reproductive period (Haldane, 1935; Reed, 1959), as for younger individuals, two birth cohorts were derived. Census and sample subjects age 45 years and over were placed in one cohort and those under age 45 years in another. The interaction of three different parameters, birth cohort, sex and marital status, on reproductive fitness in the entire sample was examined using one-way analysis of variance (ANOVA). For relevant subsamples of subjects, a Pearson correlation was used to examine the association of fitness with age of onset (using actual age of first hospitalization), GAF and positive and negative symptoms. All tests of significance were two-tailed.

3. Results

Clinical characteristics of the sample and census data are presented in Table 1. Mean ages of the affected subjects and their siblings, adjusted for males as described in the Methods, were approximately the same ($t = 0.17$, $df = 135$, $p = 0.86$). Both groups had similar proportions of subjects greater than age 45 ($\chi^2 = 0.058$, $df = 1$, $p = 0.81$), who could be assumed to have completed their reproductive period. There were no significant age differences between males and females in either group (data not shown). Marital rates were lower in the affected group as compared to either the siblings ($\chi^2 = 19.87$, $df = 1$, $p < 0.0001$) or the census population (see Table 1). Siblings did not differ from census expectations (see Table 1).

3.1. Reproductive fitness

Reproductive fitness results are shown in Tables 2 and 3. Mean reproductive fitness of affected subjects was significantly less than that for siblings ($t = 4.15$, corrected for unequal variances, $df = 93.4$, $p = 0.0001$) and general population expectations (see Table 2). Fitness of the sibling group was not elevated; mean fitness was actually somewhat lower than expected but did not differ significantly from the population mean. As expected, these results changed when the nine parents of proband sibships were added back into the sample (siblings $n = 108$, mean = 2.78, SD = 3.14, $z = 2.10$, $p = 0.036$), although results for affected subjects remained the same ($n = 38$, mean = 1.24, SD = 2.88, $z = -3.84$, $p = 0.0001$).

Individuals in the sibling group with schizophrenia spectrum features, broadly defined as subjects with two or more RDC schizotypal traits, might be expected to be at higher risk of carrying a gene for schizophrenia. If positive selection were a significant factor these would be the individuals with increased fitness. However, subjects in the sibling group who had these schizophrenia spectrum features ($n = 20$, mean = 2.55, SD = 2.95) did not have a significantly greater mean fitness than those without spectrum conditions ($n = 81$, mean = 2.15, SD = 2.13; $t = -0.57$, corrected for unequal variances, $df = 24.1$, $p = 0.57$).

Analyses were also performed to examine the distribution of family size. There were significantly increased rates of childlessness and fewer small families (one to three

offspring) in both affected and sibling groups compared with general population expectations (see Table 3). There was not a greater than expected proportion of siblings having large numbers of children (four or more).

3.2. Sex and schizophrenia spectrum effects

For the study sample (affected and sibling groups combined), an analysis of variance indicated that there was a significant effect of sex on mean numbers of offspring ($F = 4.84$, $df = 1$, $p = 0.030$). There was no interaction between affected status and sex ($F = 0.0$, $df = 1$, $p = 0.96$), consistent with data from both affected and sibling groups indicating that males had fewer children than females (Table 2). In the affected group age at onset was not significantly different between males and females (mean = 23.81, SD = 5.69; mean = 25.23, SD = 7.78, respectively; $t = -0.61$, $p = 0.54$, $df = 32$).

To determine whether the unexpected sex differences in fitness in the sibling group were related to spectrum features, the subgroup with schizophrenia spectrum conditions ($n = 20$) was examined separately from the remaining unaffected siblings ($n = 81$), revealing interesting results. The mean number of offspring was virtually identical in the unaffected sibling subgroup for males ($n = 41$, mean = 2.17, SD = 2.16) and females ($n = 40$, mean = 2.13, SD = 2.14) ($t = 0.096$, $df = 79$, $p = 0.92$). Results for both sexes were not significantly different from census expectations (males $z = -0.79$, $p = 0.22$; females $z = -0.93$, $p = 0.18$), reflected by relative fitness of 0.90 and 0.89 for males and females, respectively. The spectrum subgroup on the other hand showed significant sex differences on mean number of children: males $n = 11$, mean = 0.82 (SD = 1.25), females $n = 9$, mean = 4.67 (SD = 3.08) ($t = -3.52$, $df = 10.2$, $p = 0.006$, corrected for unequal variances), with relative fitness of 0.34 and 1.95, respectively. While intriguing, these results should be viewed with caution since the spectrum subgroup was small and older than the unaffected sibling subgroup (mean ages 51.25 years (SD = 17.40) and 41.67 years (SD = 11.57), respectively; $t = -2.34$, $df = 23.3$, $p = 0.03$, corrected for unequal variances).

3.3. Cohort effects

As expected from a decreasing birth rate in the general population and an older cohort likely to be past reproductive age, there was a significant cohort effect ($F = 18.4$, $df = 1$, $p = 0.0001$). However, there was no interaction between cohort and affected status ($F = 1.67$, $df = 1$, $p = 0.20$). Dividing the sample into two cohorts did not change z -score results for reproductive fitness for affected and sibling groups (data not shown). These results suggest that the reduced fitness of schizophrenia was not limited to either remote or recent decades and results were similar for those with presumed completed fertility (age 45 and older) and those in childbearing years.

3.4. Correlates of reduced fitness

An analysis of variance revealed a significant effect in the sample of marital status on mean numbers of offspring ($F = 20.04$, $df = 1$, $p = 0.0001$). Absence of an interaction between affected status and marital status ($F = 1.52$, $df = 1$, $p = 0.22$), however, indicated that the effect of marital status on fitness was the same for both sample groups. In the affected group ($n = 34$), early age at onset ($r = -0.10$, $p = 0.56$) was not correlated with reduced fitness.

Fitness was also examined in a subsample of 27 affected subjects and 60 siblings with respect to three other clinical parameters. Positive symptoms ($r = -0.30$, $p = 0.004$) and global functioning ($r = 0.23$, $p = 0.03$) were significantly correlated with fitness but negative symptoms ($r = -0.13$, $p = 0.23$) were not.

4. Discussion

This study has provided empirical evidence that reproductive fitness is decreased in familial schizophrenia, suggesting that negative selection is an important force in schizophrenia. These results, together with those from previous studies (Erlenmeyer-Kimling et al., 1980; Haverkamp et al., 1982), support the validity across time and locale of reduced fitness in the illness. Also consistent with others' findings (Erlenmeyer-Kimling et al., 1980; Hilger et al., 1983; Nanko and Moridaira, 1993; Fananas and Bertranpetit, 1995; Ward et al., 1995), male subjects with schizophrenia had lower fitness than females. There was no evidence supporting positive selection in siblings taken as a group and clearly no increased fitness in brothers. However, contrary to expectations there was some evidence suggesting increased fitness which was limited to a small subsample of sisters at high risk of being gene carriers. Clinically, reduced fitness was correlated with decreased likelihood of marriage, poorer functioning and more severe positive symptoms; negative symptoms were not correlated. Age at onset in affected individuals was not correlated with fitness, consistent with results from other groups (Essen-Moller, 1959; Ward et al., 1995).

4.1. Advantages and limitations

The current study has a number of advantages that differentiate it from previous investigations. First, the sample is well characterized and contains both patients with schizophrenia and their siblings, with approximately equal numbers of each sex, allowing examination of sex differences. A unique advantage over any previously reported study is the ability to examine a subgroup of individuals at increased risk of being gene carriers to better test the hypothesis of positive selection. Most importantly, a familial sample has an enhanced probability of examining only one or few schizophrenia genotypes and should therefore optimally demonstrate effects of selection forces.

Second, a contemporary local census was carefully adjusted to match the age distribution of the sample, including an adjustment to make sample males more comparable for comparison with census data collected only from women. Relatively few previous studies have used detailed age corrections (Haverkamp et al., 1982). Age matching is a critical component of any fitness investigation since fitness varies directly with age through childbearing years. As well, trends in birth control availability and changing societal expectations in recent years provide additional reasons for careful age matching of census values.

A familial sample has limitations, however. Sample sizes were relatively small compared to previous institutional samples (Haverkamp et al., 1982). Results may not be generalizable to all forms of schizophrenia, but are consistent with previous research. Large sibships were selected, possibly increasing expectations of subjects to have large families. This would have worked against findings of reduced fitness, but could have uniquely influenced female siblings with spectrum traits. Conversely, having two or more individuals per family affected

with schizophrenia could increase the likelihood of ‘social selection’: voluntary limiting of family size (Yokoyama, 1983). This may have contributed to the non-significantly reduced fitness in unaffected siblings, results similar to 0.91 relative fitness found in a survey of sisters (Buck et al., 1975).

4.2. Clinical implications

The consistency of results in the current study and throughout this century (Kallmann, 1938; Book, 1953a; Essen-Moller, 1959; Lindelius, 1970; Slater et al, 1971; Bleuler, 1978; Vogel, 1979; Erlenmeyer-Kimling et al., 1980; Odegard, 1980; Ward et al., 1995) suggests that reduced fitness is an inherent feature of schizophrenia. In contrast to manic depression which has relatively preserved reproductive fitness (Erlenmeyer-Kimling, 1978; Lane et al., 1995), high rates of single marital status and childlessness are common in schizophrenia. Similar reduced fitness was found in younger and older subjects, indicating the finding is not merely due to delayed reproduction. Treatment venue (institution or community), medications and social conditions appear to have a relatively limited effect on fitness (Ward et al., 1995). Poor general functioning and positive symptoms may limit the ability of patients and some siblings, to marry and reproduce. Future improvements in treatment could ameliorate these disabilities, suggesting reproductive fitness should be monitored in longitudinal studies.

Also clinically important is the effect of fitness on estimating morbidity risks to relatives (Risch, 1983; Kendler and MacLean, 1989). Recurrence risk estimates generally have assumed no sex differences and normal fitness for all siblings. Results of the current study suggest possible changes in published risks may be warranted.

4.3. Selection effects and sex differences

Results of the present study support negative selection as an important force in familial schizophrenia. The lower fitness of affected men compared with women, is similar to sex differences seen in other genetic disorders. Interestingly, these include several neuropsychiatric diseases caused by dynamic mutations: myotonic dystrophy (Howeler et al., 1989; de Die-Smulders et al., 1994), fragile X syndrome (Fryns, 1986; Loesch and Hay, 1988), Huntington disease in some studies (Mastromauro et al., 1989) and spinocerebellar ataxia type 1 (Jodice et al., 1994). The common mechanism for reduced fitness in these disorders appears to be low marital rates.

Due to differential fitness effects, women with schizophrenia or spectrum conditions have a two to six times greater risk of transmitting a schizophrenia gene than affected men, suggesting schizophrenia may die out more quickly in families where most affected individuals are men. The results also suggest caution when investigating sex differences in transmission (imprinting effects) since these could be masked by fitness effects. This could explain observed higher rates of maternal transmission from grandparental to parental generations in familial schizophrenia (Bassett and Honer, 1994).

Some mildly affected female gene carriers may have increased fitness (positive selection). This phenomenon has been observed in myotonic dystrophy (Howeler et al., 1989), Huntington disease (Mastromauro et al., 1989) and fragile X syndrome (Fryns, 1986; Loesch

and Hay, 1988). As in these other conditions, increased fitness in women with schizophrenia spectrum features may be due to possible hormonal disturbances involving ovarian function or the hypothalamic-pituitary-adrenal axis, vulnerability to prolific mates, poor judgment or decreased intellect (Fryns, 1986; Loesch and Hay, 1988). This area warrants further study. Whatever the cause, observed positive selection appears to involve relatively few gene carriers, not enough to offset the loss of disease alleles through the majority of (affected) gene carriers who have significantly reduced fitness.

4.4. New mutations and a proposed mutational model

Given the clear evidence for reduced fitness in schizophrenia, including familial schizophrenia, the possibility that a high mutation rate maintains genetic equilibrium requires re-examination. Book (1953a) and Penrose (1956) hypothesized mutation rates for schizophrenia higher than any known for genetic diseases at the time (1.5×10^{-3} to 4×10^{-4}). Book speculated that it was “not at all unlikely that man possesses a number of unstable, i.e., highly mutable genes”. The recent demonstration of anticipation in schizophrenia has suggested trinucleotide repeat expansion or unstable DNA as a possible genetic mechanism for schizophrenia that would be compatible with the mutation rates proposed by Book and Penrose (Bassett and Honer, 1994). Alternatively, polygenic inheritance, involving dozens of independent gene loci each mutating at relatively low rates could be acting to replenish gene losses from reduced fitness (Erlenmeyer-Kimling and Paradowski, 1966). However, a model involving a few loci (Risch, 1990) and a high mutation rate is a more parsimonious and testable possibility. Guided by new molecular mechanisms being uncovered in human genetics and a recently proposed three-stage process suggested for myotonic dystrophy (Carey et al., 1994), the authors propose an updated conceptual model for new mutations in schizophrenia.

Stage one would be preferential transmission in the general population of an at-risk chromosome, from which mutations are more likely to occur and that may show sex differences (Carey et al., 1994). This process is called meiotic drive or segregation distortion. Stage two would be a mutation, at a rate of 1/20 000 to 1/1000, resulting in expansion of a trinucleotide repeat sequence to a potentially unstable level with minimal or no resulting behavioural expression. This second stage would be most comparable to traditional concepts of mutation and would be consistent with rates proposed for schizophrenia (Book, 1953a; Penrose, 1956). The final stage, in a subsequent generation, would be further expansion of the trinucleotide repeat sequence, occurring at a rate of 1/1000 to 1/2 and resulting in a dynamically unstable gene with phenotypic expression ranging from mild to severe.

The proposed model provides a mechanism accounting for the persistence of mutable genes despite a significant biological disadvantage (reduced fitness) associated with their full expression (Carey et al., 1994). The model is consistent with recent evidence of trinucleotide repeat sequences associated with schizophrenia (Morris et al., 1995; O'Donovan et al., 1995). In addition, the model predicts high variability of repeated DNA sequences in a normal range which would be compatible with an evolutionary explanation of psychosis (Crow, 1995). Identification of a specific gene for schizophrenia is required to test the

proposed model and examine its relationship to fitness, natural selection, disease prevalence and human evolution. For the immediate future, however, further studies of fitness in families with familial schizophrenia are needed. These should clarify the sex differences in schizophrenia and related disorders and resultant effects of fitness on imprinting, thereby providing insights into fundamental genetic mechanisms in schizophrenia.

Acknowledgments

This work was supported in part by grants from the Medical Research Council of Canada, Ontario Mental Health Foundation and Ian Douglas Bebensee Foundation. The authors thank the families for their cooperation, J. McAlduff, R.N., for invaluable assistance and Dr. Joseph Berg for his critique and suggestions.

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Table 1

Characteristics of sibling groups and age-adjusted general population

Group	Age		45 Years old				Ever married	
	Age ^a (years)							
	Range	Mean	SD	n	%	n	%	
Affected (<i>n</i> = 36)	18–73	43.14	10.63	14	38.9	19	52.8	
Siblings (<i>n</i> = 101)	20–81	43.56	13.39	37	36.7	89	88.1	
Age-adjusted census ^c (<i>n</i> = 45 668)	<i>d</i>	43.32 ^d	12.58	17 003	37.2	40 373	88.4	
	</							

^a Age of affected subjects and siblings was recorded at time of assessment in 1994 or at death (*n* = 14). Ages of male subjects were adjusted by subtracting 3 years. Census age was as at 1991.

^b χ^2 analyses were performed using census figures as expected values.

^c Census figures were adjusted to match the age distribution of the sample.

^d Age range of census was from 20 to over 70 years old. To calculate the overall mean, the mid-point for each 5-year age cohort was used; the over 70 category was estimated to have a mean age of 75.

Table 2

Reproductive fitness of a familial schizophrenia sample

Group	Number of offspring			Analysis ^a		Relative fitness
	Range	Mean	SD	z-score ^b	P	
Affected siblings						
Total (<i>n</i> = 36)	0–6	0.81	1.53	–5.10	< 0.0001	0.37 ^c
Males (<i>n</i> = 22)	0–5	0.54	1.26	–4.65	< 0.0001	0.23
Females (<i>n</i> = 14)	0–6	1.21	1.85	–2.37	0.02	0.51
Siblings						
Total (<i>n</i> = 101)	0–9	2.23	2.31	–0.38	0.71	0.93
Males (<i>n</i> = 52)	0–9	1.88	2.06	–1.98	0.05	0.79
Females (<i>n</i> = 49)	0–8	2.59	2.51	0.72	0.47	1.08
Age-adjusted census	<i>d</i>	2.40 ^d	1.87	–	–	1

^aAnalyses were performed using the overall population mean calculated from age-adjusted census figures.

^bValues less than –1.96 or greater than 1.96 are significant for $\alpha = 0.05$.

^cCorrected for sex distribution differences (uncorrected value = 0.34), using a mean fitness of 0.88 derived from the unweighted mean for males (0.54) and females (1.21) (Reed, 1959).

^dThe census gave figures for individuals with 0, 1, 2, 3, 4, 5, and 6 or more offspring. To calculate the overall mean, the 6 or more category was estimated to have a mean of 7 children.

Table 3

Distribution of family sizes

Group	Childless			1–3 offspring			4 offspring		
	n	%	z-test ^a	n	%	z-test ^a	n	%	z-test ^a
Affected siblings(<i>n</i> = 36)	25	69.44	127.03, <i>p</i> < 0.0001	8	22.22	37.17, <i>p</i> < 0.0001	3	8.33	9.25, <i>p</i> < 0.0001
Siblings (<i>n</i> = 101)	32	31.68	38.08, <i>p</i> < 0.0001	45	44.55	25.89, <i>p</i> < 0.0001	24	23.76	0.29, <i>p</i> = 0.77
Age-adjusted census(<i>n</i> = 45 668)	8610	18.90	–	26 728	58.50	–	10 330	22.60	–

^a Z test of a single proportion comparing sample values to the census-based expectations.