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Birth Cohort and Familial Risk of Epilepsy: The Effect of Diminished Recall in Studies of Lifetime Prevalence

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This study separated the effects of age, birth cohort, and generation (parents, siblings, and offspring) on familial risk of epilepsy. The study population comprised 9,741 parents, siblings, and offspring of 1,957 adult probands with epilepsy ascertained from 10 voluntary organizations in New York, New Jersey, Connecticut, and Massachusetts between 1985 and 1988. Semistructured telephone interviews with probands and selected family members were used to collect data on the history of epilepsy in the relatives. The risk of epilepsy increased in successive generations (cumulative incidence to age 40: parents, 1.8%; siblings, 2.9%; offspring, 5.6%) but, with the exception of one subgroup (offspring of female probands), these differences disappeared after controlling for age and birth year of the relatives. With age and relationship controlled, the risk of epilepsy increased approximately 50% for each 20 advancing years of birth. Population-based data indicate that age-specific incidence rates of epilepsy have not increased during the age and time periods investigated here; thus, the most plausible explanation for the findings is that epilepsy is underreported in persons born in earlier time periods. These results illustrate a general phenomenon of underreporting in studies of lifetime prevalence, and they caution against interpreting apparent cohort effects in such studies as evidence of secular changes in incidence. *Am J Epidemiol* 1995;141:235–41.

cohort effect; epilepsy; genetics; seizures

In several complex familial disorders, including depression (1), mania (2), and alcoholism (3), a "cohort effect" has been reported involving higher risk in more recent cohorts. Such an effect can confound the interpretation of genetic risks and testing of genetic models, because different classes of relatives generally belong to different birth cohorts, and the effect will differ among them accordingly. For example, if the mode of inheritance is autosomal dominant and if risks in recent cohorts are higher than in past ones, the risks will be higher in siblings than in parents, creating the impression of a recessive influence on susceptibility.

An apparent cohort effect in a family study, manifested as an increase in incidence over time, could arise merely from changes in disease reporting in successive birth cohorts. For example, most family studies obtain data on disease status of the relatives by interviewing probands or other informants. If, as is likely, recall is more complete for recent than for past events, disease occurring at a young age in older relatives will be underreported. This effect would be especially problematic in a disorder such as epilepsy, which can remit at a young age. Although Annegers et al. (4) noted that this is a potential problem, no previous family study of epilepsy has investigated the effect of birth cohort on familial risks.

This paper is the first of a series describing the results from the Epilepsy Family Study of Columbia University, our ongoing study of genetic influences on susceptibility to epilepsy (5). Here we consider the extent to which differences in the risks of epilepsy in the parents, siblings, and offspring of all 1,957 probands with epilepsy can be attributed to differences in birth cohort.

MATERIALS AND METHODS

Data collection

Data collection methods in the Epilepsy Family Study of Columbia University have been described in detail previously (5). Briefly, 1,957 adult (aged ≥18 years) probands with epilepsy were ascertained from 10 voluntary organizations for epilepsy through a telephone survey conducted between 1985 and 1988. The

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Abbreviations: RR, rate ratio; SE, standard error.
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participation rate for probands was 84 percent. Trained lay interviewers used semistructured telephone interviews with probands to collect personal and family history data on seizures and other disorders in parents, full and half-siblings, offspring, and spouses. For 60 percent of the probands, medical records were also obtained.

In 67 percent of the families, we were also able to interview a second family informant (the proband's mother whenever possible) about his or her own medical history and that of the proband's parents and siblings. In order to confirm and augment the seizure history, we were also able to interview 51 percent of the relatives reported to have had seizures after the age of 5 years who were currently ≥18 years old and who had not already been interviewed as second informants. The main reasons for noninterview were lack of permission from probands and difficulty in locating relatives. Only 5 percent of the relatives contacted by mail returned postcards refusing further contact, and only 4 percent of those remaining refused interview.

Eighty-seven percent of the probands were white, 55 percent had some college education, and 60 percent were women. The subjects interviewed did not differ from those who refused in sex or ethnicity, but they were more educated than those who refused. Probands ranged in age from 18 to 82 years and averaged 36 years (males, 35 years; females, 36 years).

The *final diagnosis* was based on a review of all information collected on each proband or relative (proband interview, second informant interview, direct interview, and/or medical record). Epilepsy was defined as a lifetime history of two or more unprovoked seizures (6). The proband's family history report of epilepsy in parents and siblings had excellent validity (sensitivity, 87 percent; specificity, 99 percent), using the mother's report as the gold standard (7). Seizures were classified according to the 1981 criteria of the International League against Epilepsy (8). As we have reported previously, the resulting seizure classifications were reliable (9) and valid, compared with diagnoses of physicians with expertise in epilepsy (10). Epilepsy in both probands and affected relatives was also classified by age at onset and presumed etiology, according to standardized criteria (6).

Data analysis

We used actuarial life table analysis (11) to evaluate the cumulative incidence of epilepsy in relatives (parents, full siblings, and offspring) of probands. For this purpose, we assumed that each relative was at risk of epilepsy from birth until current age or age at death (if unaffected) or age at first unprovoked seizure (if affected with epilepsy). We also used univariate and multivariate Cox proportional hazards analysis (12) to compute rate ratios (RRs) for epilepsy in relatives, according to the relationship to the proband and birth year of the relatives (coded as a continuous variable). Relatives with missing information on birth year or history of epilepsy were excluded from the analysis. Among the 10,765 first-degree relatives of all 1,957 probands, 1,024 (10 percent) were excluded (parents, 14 percent; siblings, 8 percent; offspring, 6 percent).

RESULTS

Table 1 shows the total number of relatives included in the study and the proportion reported to be affected with epilepsy by relationship to the proband and birth cohort of the relatives (≤1920, 1921–1940, 1941–1960, ≥1961). The prevalence of a history of epilepsy (unadjusted for age) was lower in parents (2.3 percent) and siblings (2.6 percent) than in offspring (4.2 percent). In parents, the prevalence increased in successive cohorts (≤1920, 1.9 percent; 1921–1940, 2.5 percent; 1941–1960, 3.2 percent). In siblings also, the prevalence was lower among those born ≤1920 (1.2 percent) than among those born in more recent cohorts (2.6 percent). In offspring, the cohort trend was reversed, with a lower prevalence among those born ≥1961 (3.8 percent) than among those born earlier.

TABLE 1. Prevalence of a history of epilepsy in first-degree relatives of probands with epilepsy ascertained from voluntary organizations from 1985 to 1988, by relationship to the proband and birth cohort of the relatives

	Total no.	Mean years at risk	No. with epilepsy	%
Parents				
≤1920	1,390	69.3 (10.8)*	26	1.9
1921–1940	1,804	57.1 (6.6)	45	2.5
1941–1960	189	44.1 (3.1)	6	3.2
≥1961	0		0	0.0
Total	3,383	61.6 (11.1)	77	2.3
Siblings				
≤1920	169	59.4 (21.1)	2	1.2
1921–1940	621	51.0 (11.6)	17	2.7
1941–1960	2,835	33.6 (7.5)	75	2.6
≥1961	1,023	21.2 (4.9)	28	2.7
Total	4,648	34.3 (13.2)	122	2.6
Offspring				
≤1920	0		0	0.0
1921–1940	19	44.3 (15.3)	3	15.8
1941–1960	337	31.4 (7.4)	17	5.0
≥1961	1,354	12.3 (7.3)	51	3.8
Total	1,710	16.4 (11.0)	71	4.2

* Numbers in parentheses, standard deviation.

Figure 1 shows the cumulative incidence of epilepsy by age in each class of relatives. The risk was lowest in parents (risk to age 40, 1.8 ± 0.2 (standard error) percent), intermediate in siblings (risk to age 40, 2.9 ± 0.3 percent), and highest in offspring (risk to age 40, 5.6 ± 0.7 percent). For all three classes of relatives combined, figure 2 shows the age-specific cumulative incidences of epilepsy, stratified by birth cohort of the relatives. The risks were lowest in relatives born ≤1920 (risk to age 40, 1.2 ± 0.3 percent) and increased in each subsequent cohort (risks to age 40 for the 1921–1940 cohort, 2.4 ± 0.3 percent; for the 1941–1960 cohort, 3.1 ± 0.3 percent; and for the ≥1961 cohort, 4.3 ± 0.5 percent).

As expected, the different relative classes had very different birth cohort distributions. For example, 41 percent of parents, 4 percent of siblings, and 0 percent of offspring were born prior to 1921, while 0 percent of parents, 22 percent of siblings, and 79 percent of offspring were born after 1960 (table 1). Also, even within the 20-year birth cohorts shown in table 1, age differences among the three classes of relatives remained (e.g., mean years-at-risk of relatives born during 1941–1960, for parents, 44.1; for siblings, 33.6; and for offspring, 31.4). To partially disentangle the effects on epilepsy risk of birth cohort and relationship to proband, we compared the risks in different relative classes within each 20-year birth cohort (figure 3). Only 16 offspring were born prior to 1941; thus, we examined the risks in offspring only in the last two birth cohorts. Within each birth cohort, the parents and siblings did not differ in reported risks of epilepsy, but the risks in offspring were higher than in parents and siblings.

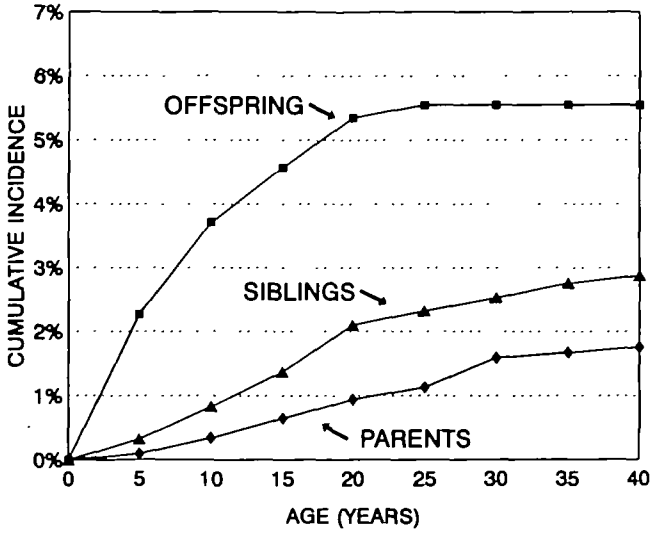

FIGURE 1. Age-specific cumulative incidence of epilepsy in parents, siblings, and offspring of probands with epilepsy ascertained from voluntary organizations from 1985 to 1988, by relationship to the proband.

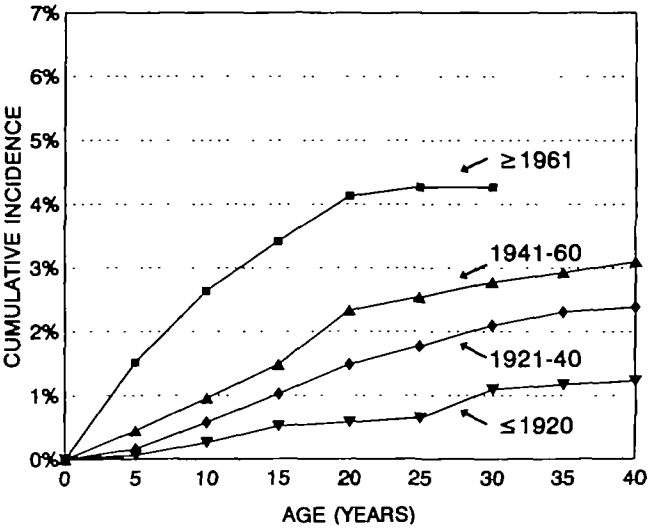

FIGURE 2. Age-specific cumulative incidence of epilepsy in parents, siblings, and offspring of probands with epilepsy ascertained from voluntary organizations from 1985 to 1988, by birth cohort of the relatives.

To explore the higher risks in offspring further, we examined the risks in the last two birth cohorts after stratifying on the sex of the proband (figure 4). The higher risk in offspring than in parents and siblings was restricted to offspring of female probands (figure 4, A and B). The risks were similar (approximately 3 percent to age 40) in every other subgroup in this analysis (parents and siblings of probands of both sexes and offspring of male probands).

Finally, we used Cox proportional hazards analysis to compute univariate and multivariate rate ratios for epilepsy in relatives according to the relationship to the proband and birth year of the relatives (table 2). Among the relatives of all probands, the univariate analysis showed that risk was significantly increased in both siblings (RR = 1.5) and offspring (RR = 4.2), compared with parents. After controlling for birth year in the multivariate analysis, the increased risk in siblings disappeared (RR = 0.9), and that in offspring was much reduced (RR = 1.8). There was a significant effect of birth year after controlling for relationship, with a 2 percent increase in age-specific incidence per year of birth (RR = 1.02; table 2). This is equivalent to an increase in incidence of approximately 50 percent for each 20 advancing years of birth (i.e., 1.02^{20} = 1.48). The significantly higher risk in offspring than in parents, after controlling for birth year, was observed in relatives of female probands (RR = 2.7) but not in relatives of male probands (RR = 0.6).

DISCUSSION

In this study we attempted to separate the effects, on familial risks of epilepsy, of three highly correlated,

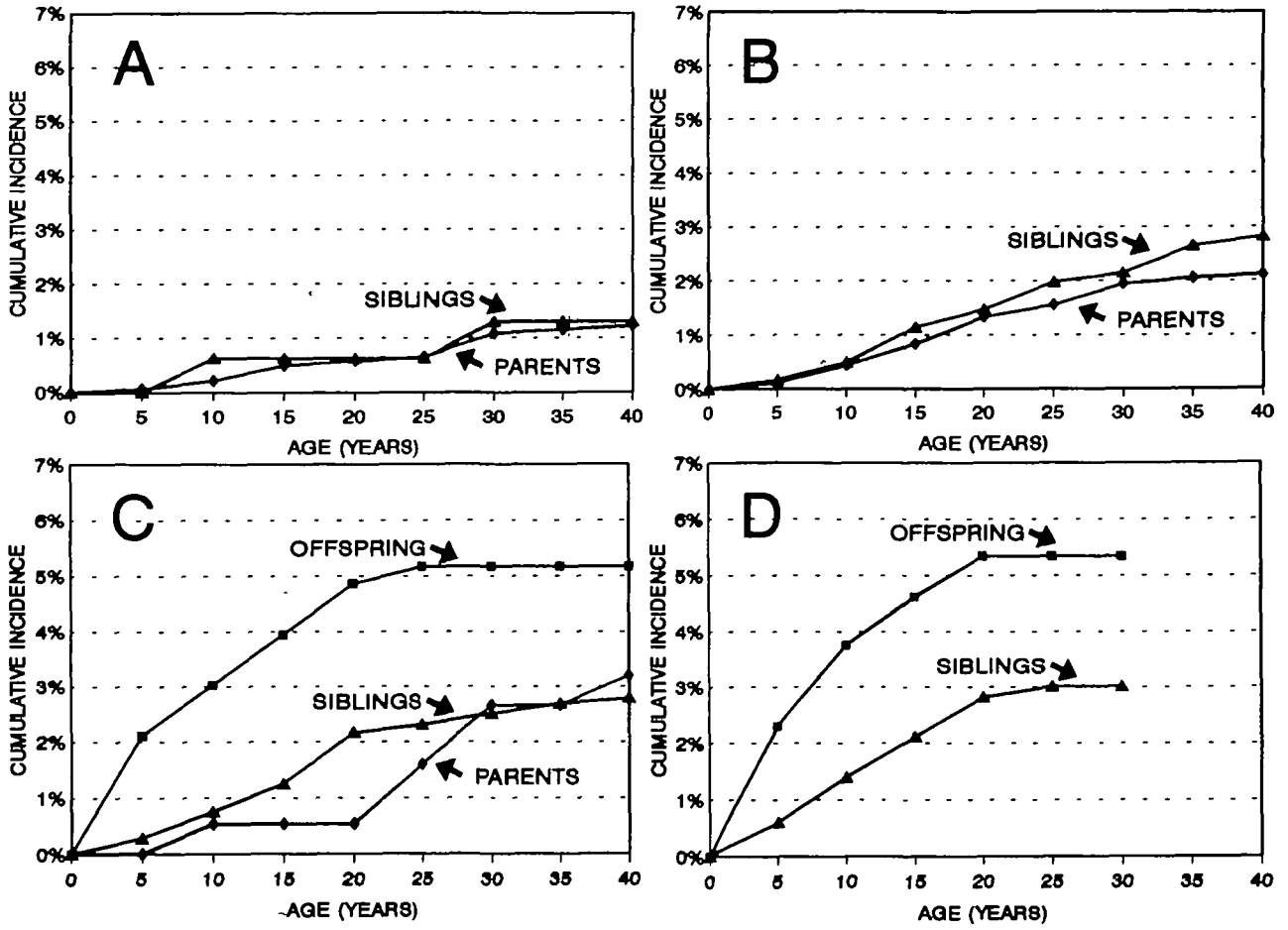

FIGURE 3. Age-specific cumulative incidence of epilepsy in relatives of probands with epilepsy ascertained from voluntary organizations from 1985 to 1988, by relationship to the proband and birth cohort of the relatives. A, relatives born ≤1920; B, relatives born 1921–1940; C, relatives born 1941–1960; D, relatives born ≥1961.

time-related variables: age, birth cohort, and generation (parents, siblings, and offspring). Initially, we observed a large difference in risk between different classes of relatives but, with the exception of one subgroup (offspring of female probands), this difference disappeared after controlling for age (by survival analysis methods) and birth cohort. As we have noted previously, the higher risk of epilepsy in offspring of female versus male probands has been observed consistently and cannot be explained by any simple genetic model (13, 14). This finding will be the subject of a subsequent paper.

With epilepsy as with any age-related disorder, "lifetime prevalence" or (more correctly) "prevalence of a history" (i.e., the proportion of individuals who have had the disorder at any time in their lives) is expected to increase with age. This pattern is reflected in offspring in table 1; the prevalence of a history of epilepsy was higher in offspring born from 1940 to 1961 (5.0 percent), who were older at the time of the study, than in those born ≥1961, who were younger (3.8 percent). However, the results in table 1 for parents and siblings are paradoxical; they indicate *lower* prevalence of a history of epilepsy in persons born in earlier cohorts (i.e., older persons) than in those born in more recent cohorts.

In order to resolve this paradox, we used survival analysis methods and a "reconstructed cohort" approach (15) to disentangle the effects of age and birth cohort on epilepsy risk. We used information on each relative's years-at-risk of developing epilepsy within each age interval to reconstruct age-specific cumulative incidences from birth until the time of the study. Then we compared relatives born during different periods in terms of their risks at comparable ages (figure 2). The results showed the expected pattern of increased risk with increasing age within each cohort but higher risks at all ages in more recent cohorts.

Many previous family studies of epilepsy have reported the same trend of increasing risk of epilepsy

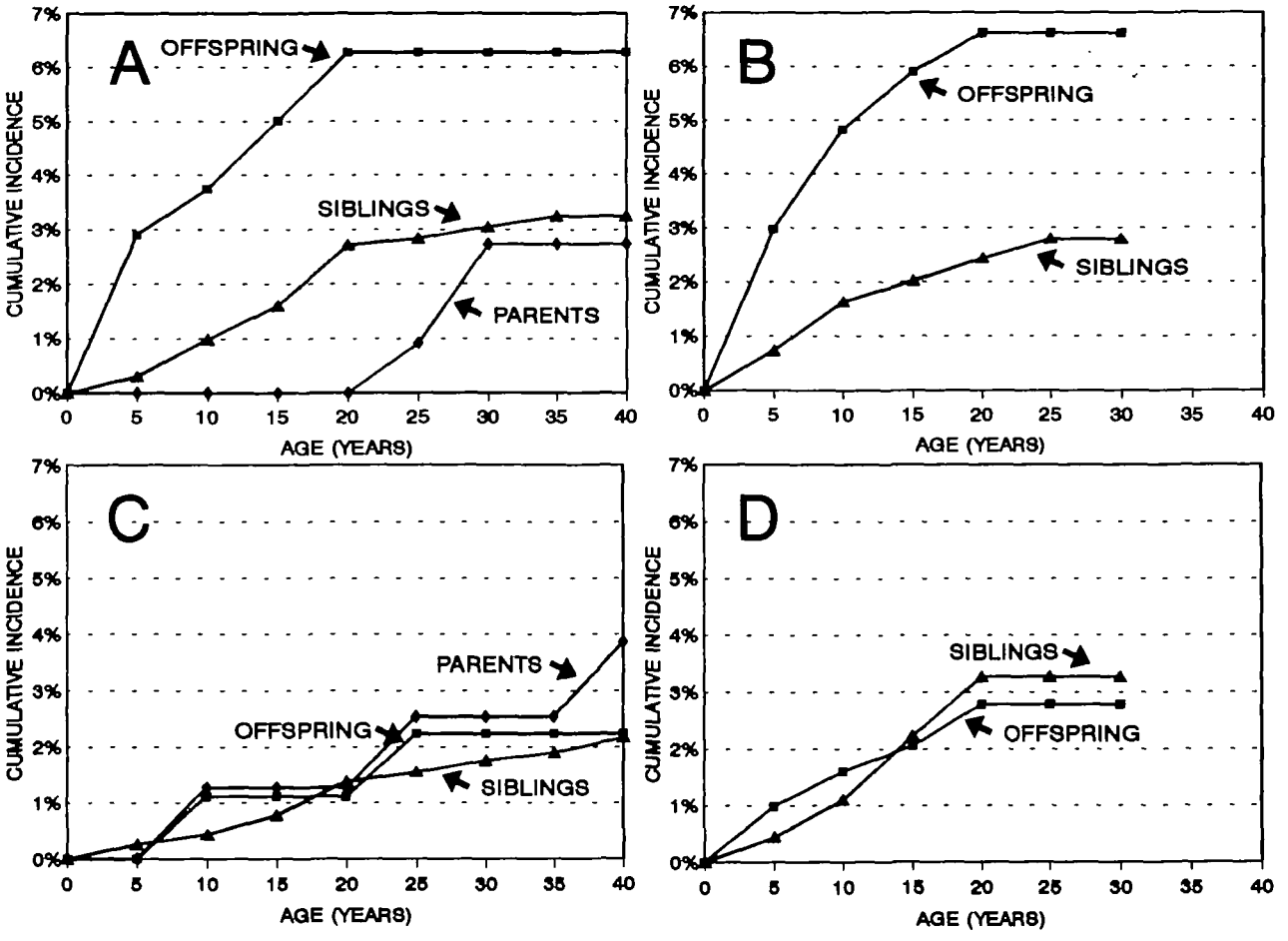

FIGURE 4. Age-specific cumulative incidence of epilepsy in relatives of probands with epilepsy ascertained from voluntary organizations from 1985 to 1988, by relationship to the proband, birth cohort of the relatives (1941–1960, ≥1961), and sex of the proband. A, relatives of female probands born 1941–1960; B, relatives of female probands born ≥1961; C, relatives of male probands born 1941–1960; D, relatives of male probands born ≥1961.

with advancing generation. Alstrom (16) reported age-adjusted risks of 1.3 percent in parents, 1.5 percent in siblings, and 3.0 percent in offspring. In a study of the families of probands with what would now be called juvenile myoclonic epilepsy, Tsuboi and Christian (17) reported age-adjusted risks of 3.3 percent in parents, 5.4 percent in siblings, and 13.6 percent in offspring. Harvald (18) and Matthes and Weber (19) both reported risks of approximately 3 percent in parents and 4 percent in siblings. Doose and Baier (20) reported a positive seizure history in 7.5 percent of parents and 10.2 percent of siblings of children with generalized minor motor epilepsies. Eisner et al. (21) did not report risks separately for different relative classes, but they noted that the prevalence of a history of epilepsy was lower in relatives who were older than 40 at the time of the study than in younger relatives.

Higher age-specific risks in more recent birth cohorts would be expected if the incidence of a disorder were increasing over time. Consequently, the cohort effects in psychiatric disorders such as depression, mania, and alcoholism (1–3) have been interpreted as evidence of increasing incidence. With all of these disorders as with epilepsy, however, the cohort effects have been observed in studies using cross-sectional designs to collect data on lifetime prevalence; i.e., individuals were interviewed about symptoms (in themselves or their relatives) that occurred at varying lengths of time in the past. This type of design introduces an unavoidable recall bias, because events that occurred at any given age will have occurred longer ago for older individuals than for younger ones. Because of this bias, in such studies it is difficult to distinguish the effects of diminished recall from genuine secular changes in incidence.

With epilepsy, we can reject the explanation of a secular change in incidence on the basis of direct evidence. Population-based data from Rochester, Min-

TABLE 2. Univariate and multivariate rate ratios for epilepsy in relatives of probands with epilepsy ascertained from voluntary organizations from 1985 to 1988, by relationship to the proband and birth year of the relatives

	No. of relatives	No. with epilepsy	% with epilepsy	Univariate		Multivariate	
				Rate ratio	95% CI*	Rate ratio	95% CI
Relatives of all probands							
Offspring	1,710	71	4.2	4.18	2.98–5.87	1.84	1.06–3.19
Siblings	4,648	122	2.6	1.52	1.13–2.04	0.89	0.59–1.34
Parents	3,383	77	2.3	1.00	Reference	1.00	Reference
Birth year				1.03	1.02–1.03	1.02	1.01–1.03
Relatives of male probands							
Offspring	566	10	1.8	2.02	0.97–4.20	0.60	0.21–1.75
Siblings	1,954	44	2.3	1.30	0.81–2.08	0.58	0.29–1.18
Parents	1,359	32	2.4	1.00	Reference	1.00	Reference
Birth year				1.02	1.01–1.03	1.03	1.01–1.05
Relatives of female probands							
Offspring	1,144	61	5.3	5.12	3.41–7.69	2.65	1.37–5.14
Siblings	2,694	78	2.9	1.69	1.16–2.47	1.10	0.66–1.83
Parents	2,024	45	2.2	1.00	Reference	1.00	Reference
Birth year				1.03	1.02–1.04	1.02	1.00–1.03

* CI, confidence interval.

nesota (22), indicate that, between 1935 and 1984, the incidence of epilepsy has *decreased* approximately 40 percent in children under age 10 and increased only in the elderly. This trend of decreasing incidence in children would lead us to expect lower, rather than higher, risks among persons born in recent time periods. (The trend of increasing incidence in the elderly does not apply to our results because we investigated risks only up to age 40.)

Recently, Giuffra and Risch (23) investigated the impact of diminished recall on lifetime prevalence of disease in successive cohorts, when data are collected in cross-sectional designs. Using simulation, they showed that annual rates of "forgetting" as low as 1–5 percent can produce apparent cohort effects. It may be impossible to avoid the effects of such diminished recall in studies using interviews to collect data, without using expensive prospective, longitudinal designs. The family studies from the Rochester-Olmsted County Record Linkage Project (e.g., references 4 and 14) surmounted this problem by using record linkage rather than interviews to collect data.

Since familial aggregation of epilepsy is well established (4, 14, 16–21), our main goal was to test the consistency of the familial distribution with various genetic models, rather than to compare risks in relatives of affected and unaffected persons. Consequently, we did not collect data on epilepsy in the families of unaffected individuals and were unable to assess underreporting by comparison of data on controls with population-based data. The cumulative incidence of epilepsy to age 40 was 1.6 percent in the general population of Rochester, Minnesota (22). Although the suitability of the Rochester population as a control series for our data is uncertain, our finding of a 3 percent risk of epilepsy to age 40 among relatives born after 1940 (figure 4) probably reflects the well-known familial aggregation of epilepsy.

The most plausible explanation for the cohort effect that we observed is that epilepsy is underreported in family members born in earlier time periods. Further, the similarity of the findings in epilepsy to those reported in psychiatric disorders suggests that the effects of underreporting may be sufficient to explain the cohort effects observed in those disorders also. In the absence of direct evidence about age-specific incidence rates, the cohort effects in studies of lifetime prevalence of a disease should not be interpreted as indicating secular changes in incidence.

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