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Age and Birth Cohort Effects on Rates of Alcohol Dependence

John P. Rice, Rosalind J. Neuman, Nancy L. Saccone, Jonathan Corbett, Nanette Rochberg, Victor Hesselbrock, Kathleen K. Bucholz, Peter McGuffin, and Theodore Reich

Background: Epidemiological studies of traits such as alcohol dependence and depression have often found lifetime rates in younger individuals exceeding those found in older individuals. This suggests additional influences of birth cohort or period effects so that individuals in later-born cohorts have an increased lifetime risk.

Methods: Data from the Collaborative Study on the Genetics of Alcoholism were used to investigate secular trends for alcoholism and related conditions and to examine risk predictors while taking the cohort effect into account. We used data on 4099 interviewed parents and siblings of alcohol-dependent subjects and 1054 members of control families. We used survival analysis techniques and the Cox proportional hazards regression model to estimate the relative risk for demographic covariates. We used the relative sample to predict risk in the sibling of the proband and family history information to determine whether there was a bias when deceased individuals were excluded from analysis.

Results: In the control sample, we observed a 1.8% lifetime rate of DSM-III-R alcohol dependence in women born before 1940, as contrasted to a 13% rate in women born after 1960, and a 15% lifetime rate in men born before 1940, contrasted with a 28% rate in men born after 1960. As expected, lifetime rates in relatives were increased when compared with controls. Highly significant risk ratios (RR) were observed for gender (RR, 2.3), cohort of birth (RR, 1.5 over a decade), daily smoking (RR, 2.0), heavy smoking (RR, 3.0), and comorbid diagnoses of antisocial personality (RR, 2.2) and depression (RR, 1.6). Analysis of the family history data indicated higher rates of alcohol dependence in relatives who were deceased compared to those who were living.

Conclusions: Marked cohort differences were observed and may reflect real changes over time, or artifacts of memory recall, differential mortality, or public awareness. The analysis of all relatives (living or deceased) indicates that associated mortality may, in part, explain the secular trends seen when analyses are restricted to living, personally interviewed individuals.

Key Words: Alcohol Dependence, Birth Cohort, Family Studies, Comorbidity.

TEMPORAL (OR SECULAR) trends, variations in rates of illness over time, are well established for many medical conditions, including the major mental illnesses. Most disorders, such as Alzheimer's disease (Bachman et al., 1992) and type II diabetes (Scheen, 1997), have an age effect in that the rate of illness increases as a birth cohort of individuals becomes older. Family studies traditionally compare the lifetime morbid risk in the population with that in classes of relatives of affected individuals (Slater and Cowie, 1971), whereas age-specific rates are usually reported in nonfamily studies. However, this conceptualization becomes problematic when rates in younger individuals already exceed lifetime morbid risks in older individuals.

One can consider (birth) cohort effects, where rates of illness at each age are influenced by factors that act differently depending on the cohort of birth. The size of one's birth cohort (e.g., the "baby boomers") provides an example. In a birth cohort effect, rates depend on the year of birth, whereas in a period effect, the calendar year, which cuts across different cohorts at different ages, is the key determinant. Events such as war, radiation exposure (e.g., the Three Mile Island accident), or drug availability in the late 1960s are examples of period effects. Note that such effects typically interact with age. For example, drug availability might have had a significant effect on those who were young in the 1960s but a minimal effect on those who were middle-aged. Although it is possible to conceptually distinguish age, cohort, and period effects (Fienberg and Mason, 1979), they are mathematically confounded in a linear relationship. For instance, if one knows that a person was aged 20 years in 1980, one knows that he or she was

From the Washington University School of Medicine (JPR, RJN, NLS, JC, NR, KKB, TR), St. Louis, Missouri; the University of Connecticut School of Medicine (VH), Farmington, Connecticut; and the Institute of Psychiatry(PM), Kings College, London, United Kingdom.

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Reprint requests: John P. Rice, PhD, Department of Psychiatry, Washington University School of Medicine, 660 S. Euclid Ave., Campus Box 8134, St. Louis, MO 63110; Fax: 314-286-2577; E-mail: john@zork.wustl.edu.

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born in 1960. In general, given any two values, the third can be determined. Thus, if all three quantities are independent variables in a linear model, the parameters of the model cannot be estimated. That is, for any observed data, there are multiple combinations of the three effects that would describe the same data. Although statistical analysis alone cannot decide between alternative models, other criteria, such as parsimony, may be used.

Several studies of major depression in the mid 1980s reported strong secular trends [the Epidemiologic Catchment Area (ECA) Study, Robins et al. (1984); the Collaborative Depression Study, Klerman et al. (1985); and the Camberwell Registry Study, Sturt et al. (1984)]; the frequency of lifetime depression was lowest in older cohorts and progressed upward in more recent cohorts. Klerman et al. (1985) discussed several possible methodological artifacts: subject recall, increased public awareness, differential mortality, and the possibility that more recent generations are more "psychologically minded."

Prominent secular trends for alcohol abuse/dependence were reported in the ECA sample (Robins et al., 1984). Data from the St. Louis site yielded lifetime rates for subjects in the following age groups: 18 to 24 years, 17%; 25 to 44 years, 21%; 45 to 64 years, 11.7%; and ≥65 years, 7.2%. It is striking that younger subjects have higher risks than do older subjects even though the former have been at risk for shorter periods.

Grant et al. (1994) report 1-year prevalence estimates from the large-scale National Longitudinal Alcohol Epidemiologic Survey (NLAES), based on face-to-face interviews of 42,862 respondents. They noted overall estimated prevalences for DSM-IV alcohol abuse (alcohol dependence) of 6.54% (3.18%) in individuals aged 18 to 29 years, 3.02% (1.64%) in individuals 30 to 44 years, 1.35% (1.09%) in individuals 45 to 64 years, and 0.25% (0.21%) in individuals ≥65 years, with lower rates in women compared with men and blacks compared with nonblacks. Note, moreover, that the 1-year prevalence is in some sense a composite of age, period, and birth cohort effects for age of onset, and age effects were associated with having active symptoms within the past 12 months.

Kessler et al. (1994) reported similar effects for a lifetime prevalence of any substance use disorder in the National Comorbidity Study. Finally, Kandel et al. (1997) reported a decrease in the "conditional prevalence of last year dependence," with overall rates of 8.1, 5.8, 4.6, and 2.9% in individuals aged 18 to 25 years, 26 to 34 years, 35 to 49 years, and ≥50 years, respectively, in the National Household Survey on Drug Abuse. Their rates are conditioned on subjects' having consumed some alcohol in the last year. These epidemiological studies of the general population (ECA, NLAES, and National Comorbidity Study and National Household Survey on Drug Abuse) all report large cohort effects, although they differ in terms of how they report their rates by birth cohort (lifetime versus 1-year conditional prevalence) and the diagnostic criteria used.

Lifetime population prevalences from the ECA study in St. Louis have since been used further in comparisons with the lifetime prevalence of alcoholism in relatives of alcoholics (Reich et al., 1988). In this study described by Reich et al., a sample of alcoholics was ascertained from St. Louis–area psychiatric hospitals and a local parole office. Probands and first-degree relatives were interviewed. Results showed that there seemed to have been secular trends in the familial transmission of alcohol dependence. More recently born relatives of alcoholics had a higher risk for alcoholism and earlier ages of onset than older relatives, with the disorder seeming to be more transmissible in younger cohorts. Evidence indicated that this trend of increased risk was not due simply to artifacts of ascertainment, diagnosis, recall, or differential mortality. Furthermore, comparison with general population rates indicated that although risk was increased in younger cohorts in general, the increase was most pronounced in individuals who had a family history of alcoholism (e.g., children of alcoholic probands). Interestingly, the degree of familial transmission was found to be greater than would be expected under a model of polygenic transmission alone, suggesting that the familial transmission was due to both genetic and nongenetic (e.g., cultural) factors. Another finding of interest was that in more recent cohorts, differences between male and female familial rates of alcoholism were decreased.

In this study, we used data from the Collaborative Study on the Genetics of Alcoholism (COGA) to examine these issues in families ascertained at random and in families ascertained through a DSM-III-R alcohol-dependent proband.

MATERIALS AND METHODS

Subjects

COGA is a multisite study in which data from both case and control families have been collected. Initial assessments were performed from 1991 to 1998, with 90% of individuals assessed from 1992 to 1996. Case families were ascertained through an alcoholic proband in a treatment program (Reich et al., 1998). All first-degree relatives of the proband, as well as the proband's coparent spouse, were interviewed. Probands had to meet the following criteria: (1) fulfilled requirements for both DSM-III-R alcohol dependence and Feighner definite alcoholism; (2) had at least two first-degree relatives living within the catchment area of one of the COGA centers; (3) were free of non–alcohol-related life-threatening illnesses; and (4) neither injected illicit substances within 6 months of admission nor reported more than 30 injections in their lifetime. In our analyses, we used 4099 parents and siblings (aged 18 years or older) of probands (1729 men and 2370 women) in 1044 families. We refer to this sample as the relative sample.

A smaller group of control families was ascertained. A random sample of individuals from health maintenance organizations, dental clinics, and automobile driving records was selected. This individual could be either a parent or sibling in a nuclear family with both parents and a total of four siblings (aged 7 years or older) available. These families were chosen without regard to a diagnosis of alcohol dependence, and, as a result, some control families contain alcoholics. In our analysis, we used 1054 individuals (aged 18 years or older) who were in 232 control families (509 men and 545 women). We refer to this sample as the control sample. There

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may be some bias in rates estimated from this control sample because families who do not have insurance, go to dental clinics, or drive are underrepresented. Moreover, because the prevalence of DSM-IV alcohol dependence is lower than that of DSM-III-R, direct comparison of rates of alcohol dependence with other samples, such as NLAES, would be problematic.

A third sample used in our analyses consists of all parents and siblings over age 17, whether dead or alive and whether interviewed or not. Because of the type of analysis performed, we restricted this sample to those born before 1970. This sample consists of 6159 individuals (3022 men and 3137 women) in 1174 families and is referred to as the family history sample.

Phenotypic Assessment

Each relative was administered the Semi-Structured Assessment for the Genetics of Alcoholism (Bucholz et al., 1994, 1995; Hesselbrock et al., 1999), which was designed to assess the physical, psychological, and social manifestations of alcoholism and related disorders, and the Family History Assessment Module (FHAM) (Rice et al., 1995), which makes six specific DSM-III-R diagnoses (alcoholism, drug dependence, depression, mania, schizophrenia, and antisocial personality) of relatives by history. The interviews were administered by trained raters and included questions on alcohol, tobacco, and drug use and other DSM-III-R disorders.

Statistical Methods

Survival analytic techniques—specifically, the Kaplan-Meier estimator of the survival function and the nonparametric Cox proportional hazards model of the Cox regression model (Kalbfleisch and Prentice, 1980)—were used in these analysis. The Kaplan-Meier estimates (implemented in SAS's PROC LIFETEST; SAS Institute, Cary, NC) of the survival distribution of age at the onset of alcohol dependence stratified on birth cohort allowed us to evaluate the proportionality assumption required for the validity of the Cox model. The Cox model (implemented in SAS's PROC PHREG) was used to assess the effect of covariates on time to the onset of DSM-III-R alcohol dependence.

In a preliminary analysis, the Kaplan-Meier estimator of the survival function was used to test for the proportionality assumption required for the validity of the Cox model stratified by gender and relative versus control sample. Briefly, if T is the random variable "time to DSM-III-R alcohol dependence" and f(t) and F(t) are the density and distribution functions for T, respectively, then the survival function S(t) and hazard function $\lambda(t)$ are given by

$$S(t) = 1 - F(t) = \text{Prob}(T > t),$$

$$\lambda(t) = f(t)/S(t) = \text{Prob}(t < T < t + dt | T \geq t).$$

For a set of covariates $X' = (X_1, \ldots, X_n)$, the Cox model assumes that there is a set of regression coefficients $\beta' = (\beta_1, \ldots, \beta_n)$, so that the hazard function $\lambda(t:X)$ for an individual with covariate values X is given by

$$\lambda(t:X) = \lambda_0(t)\exp(X'\beta),$$

where $\lambda_0(t)$ is an arbitrary and unspecified baseline hazard function. Under these assumptions, the curves given by $h(t) = \log(-\log(S(t)))$ are parallel.

We examined the number of subjects born in seven birth-year intervals (1910–1919, 1920–1929, 1930–1939, 1940–1949,1950–1959, 1960–1969, and 1970–1979). There were insufficient numbers of individuals in the 1910 to 1919 interval, especially in the control sample. Subjects who were at least age 18 in 1991 (when the interviews began) had to be born before 1974, so the number of subjects in the 1970 to 1979 interval was approximately half that of the number in the 1960 to 1969 interval. Moreover, censoring was quite pronounced in this seventh interval, and the survival curves would be quite unstable due to a very small number of subjects in this interval who were interviewed at the end of the intake period. For analysis, we used a set of five birth cohorts, as indicated in Table 1. PROC LIFETEST (SAS) was used to examine whether the curves h(t) were parallel within each age class. This was done separately within the relative and control samples according to their gender.

Table 1. Percentage (*n*) of DSM-III-R Alcohol Dependence by Gender and Birth Cohort

	Controls		Relatives[a]	
Birth cohort	Male	Female	Male	Female
1910–1929	0.0 (17)	0.0 (12)	35.5 (242)	4.5 (290)
1930–1939	18.8 (64)	2.3 (44)	43.0 (270)	16.9 (409)
1940–1949	23.2 (120)	4.4 (136)	51.1 (215)	22.0 (363)
1950–1959	30.6 (49)	6.4 (78)	60.0 (485)	30.3 (636)
1960–1979	28.2 (259)	13.1 (275)	55.5 (517)	30.8 (672)
Overall	25.3 (509)	8.8 (545)	51.5 (1729)	23.7 (2370)

[a] Parents and siblings of probands.

Order of Analyses

We first used survival analysis techniques to examine the relationship between the time to onset of alcohol dependence and birth cohort and gender in each sample separately. Second, we used the Cox proportional hazards regression model to test for the effect (or relative risk) of birth cohort, gender, and group (i.e., relative versus control sample) on the hazard of alcohol dependence. Third, this time using only the relative sample, the Cox proportional hazard model was again used to determine the effect of covariates measured on the parents, the alcoholic proband in the family, and the sibling covariates to predict the hazard of alcohol dependence in the sibling. The last analysis used only the family history information obtained from the proband on his or her first-degree relatives, including deceased relatives. Logistic regression was performed.

RESULTS

In a prior analysis, tests were conducted for differences among parent, sibling, and child generations because these lifetime risks may differ, and we wished to test whether a "relationship to proband" covariate was necessary. The hypothesis that the hazard was the same for each generation when controlling for age cohort ($\chi^2_2 = 4.2$; $p < 0.25$) was accepted. Concerned about possible transmission effects and because offspring tended to be censored earlier in the youngest age group, we removed offspring from these analyses.

The lifetime prevalences of DSM-III-R alcohol dependence for controls and parents and sibling of probands are given in Table 1. Note the strong effect of birth cohort on DSM-III-R alcohol dependence. As expected, men have higher rates than women, and relatives of probands have higher rates than controls.

The Kaplan-Meier survival curves $S_i(t)$ are displayed in Fig. 1. Their corresponding curves $\log(-\log(S_i(t)))$ were visually compared and found to be parallel within the five birth cohorts, indicating that the data were consistent with an age effect together with a birth cohort effect and not requiring an additional period effect. Four dummy variables were created that corresponded to the five age strata. We tested an ordinal classification for the age strata versus this categorical one defined by four dummy variables. The ordinal scale was accepted ($\chi^2_3 = 5.0$; $p < 0.25$). The final model contained three variables: gender [risk ratio (RR),

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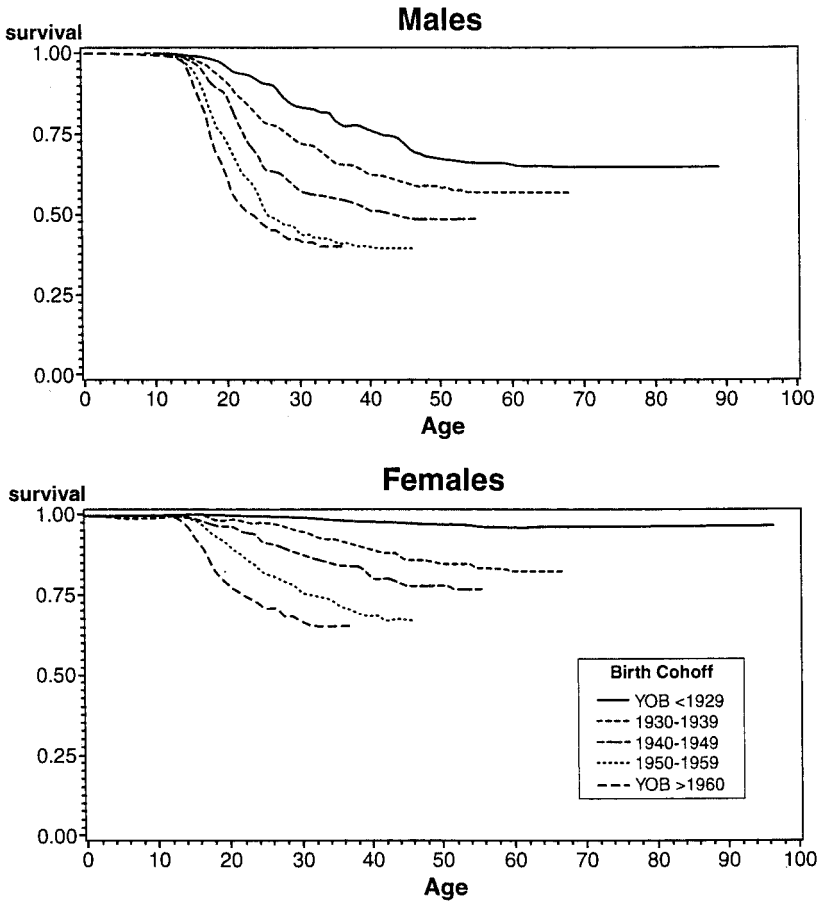

Fig. 1. Survival curves for male and female relatives of alcoholic probands stratified by five birth cohorts. The curves indicate the percentage of nonalcoholics by age. YOB, year of birth.

2.74], relative versus control (RR, 2.35), and effect of birth cohort (RR, 1.55). Note that the relative risk associated with a two-step change in the age grouping was $1.55 \times 1.55 = 2.40$ (Table 2). All further analyses included these variables as a baseline model for comparison.

Leaving gender, birth cohort, and group (relative or control) in the model, we tested for effects due to race and education with the Cox proportional hazards model. Blacks (non-Hispanic) were found to have a lower relative risk than whites ($p < 0.0001$). The racial category "other" did not differ from the "whites" category. Table 2 shows a gradient of risk for level of education, with high school dropouts having the highest RR (RR, 2.83; $p < 0.0001$).

Our third analysis used the Cox proportional hazard model to examine the time to onset of DSM-III-R alcohol dependence in the siblings of the proband in the relative sample. Covariates included in this model are displayed in Table 3. A series of univariate analyses was performed in which a model with gender, birth cohort, and each variable of Table 3 was compared with a model with gender and birth cohort alone.

The proband's gender and age of onset were significant predictors of risk to a sibling, with an earlier age of onset imparting a greater risk to the relative ($p < 0.0001$); relatives of a female proband were at greater risk than those of a male proband. A (history) diagnosis of alcohol dependence in the father was a significant predictor ($p < 0.0001$), whereas the mother's alcohol dependence was not ($p = 0.3$). Comorbid conditions (smoking, conduct disorder, antisocial personality disorder, and depression) in an individual's sibling were all highly significant predictors ($p < 0.0001$) of alcohol dependence in that individual.

All covariates were then entered into a stepwise multivariate analysis to examine relative risks. The multivariate results are given in Table 4. The individual predictors in Table 3 were potentially correlated, whereas in a multivariate setting we assessed the risk, controlling for other variables present in the model.

Heavy smoking (smoking at least one pack a day for 6 months or more) and daily smoking were both significant predictors of alcohol dependence in the siblings. The variables were coded so that the RR for heavy smoking compared with nonsmoking was $2.162 \times 1.372 = 2.966$. The relative risks shown in Table 4 for the multivariate model were typically less than those in Table 3; this reflects the correlations between the predictor variables. In the multivariate case, the effect of any single variable was adjusted for all the others. Note, also, that the two proband variables (gender and age of onset) were marginally significant. All other variables were significant at the 0.0001 level, and we expect these results would remain significant even if corrections were made for the number of statistical tests and

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Table 2. Risk Ratios for Demographic Covariates With the Cox Regression Model[a]

Covariates	Risk ratio	χ^2	*p* Value	*n*
Gender				
Male	2.74	444.1 (1)	<0.0001	2574
Female	1.00			3337
Birth cohort				
1960–1979	5.77	424.1 (1)	<0.0001	2306
1950–1959	3.72			1410
1940–1949	2.40			846
1930–1939	1.55			788
1910–1929	1.00			561
Group				
Relatives	2.35	116.5 (1)	<0.0001	4857
Controls	1.0			1054
Race[b]				
Black	0.66	36.3 (1)	<0.0001	927
Other	0.93	0.8 (1)	0.36	510
White	1.00			4470
Education[c]				
High school dropout	2.83	90.1 (1)	<0.0001	1105
High school	1.85	32.0 (1)	<0.0001	1615
Some college	1.63	19.4 (1)	<0.0001	1317
In college	1.96	27.0 (1)	<0.0001	540
4 years of college	1.59	15.1 (1)	<0.0001	704
Graduate school	1.0			521

[a] All models include gender, birth cohort, and group.
[b] Race was unknown for four individuals.
[c] A total of 107 individuals were still in high school; two unknowns were omitted.

the sample dependence due to the use of multiple siblings from a single family.

We next examined the proportion of DSM-III-R alcohol dependence in relatives by using family history information. Because the original version of the FHAM did not record the age of onset, survival analysis could not be used. Moreover, use of multiple family reports, although more valid (Rice et al., 1995), may introduce a bias because more reports would come from families in which more relatives were personally interviewed (and, thus, living). Accordingly, analyses were restricted to the FHAM administered to the proband in each family. These proportions are given in Table 5, in which noninterviewed relatives are broken down by those who were dead or alive at the time the FHAM was administered. With the exception of women in the 1910 to 1929 cohort, the family history rate of alcohol dependence in the interviewed relatives in Table 5 was lower than the corresponding rate from the Semi-Structured Assessment for the Genetics of Alcoholism direct interview (Table 1).

For our final analyses, we performed a logistic regression, regressing FHAM/DSM-III-R alcohol dependence on the predictor variables gender, birth cohort, whether the relative was alive or dead, and whether he or she had a personal interview. To reduce the effect of censoring from this analysis, data from the cohort born after 1960 were omitted. The baseline cohort was chosen to be those born in 1910 to 1929. That is, three dummy variables were created; this cohort was coded as 0 on all three variables, and each of the other cohorts was coded 1 on its indicator variable. The results are given in Table 6.

Table 3. Results of Univariate Cox Regression Analysis[a]: Risk to a Sibling of an Affected Proband

Covariate	Risk ratio	χ^2	*p* Value	*n*
Proband				
Age of onset	0.976	20.5	<0.0001	
Male gender	0.785	13.0	0.0003	2104
Parents[b]				
Father alcohol dependent	1.667	71.0	<0.001	1057
Mother alcohol dependent[c]	1.261	4.8	0.03	208
Sibling				
Daily tobacco use	2.972	202.3	<0.0001	1755
Heavy smoking	2.389	200.7	<0.0001	972
Conduct disorder	2.489	156.0	<0.0001	380
ASP diagnosis	3.23	197.5	<0.0001	229
Depression	2.015	128.5	<0.0001	1008

ASP, antisocial personality.
[a] The relative's gender and birth cohort are included in each comparison.
[b] Alcohol dependency status of both parents simultaneously included in model.
[c] Not significant once multiple testing and nonindependence of sibling sample were considered.

Table 4. Multivariate Predictors of Risk to a Sibling of a Proband

Covariate	Risk ratio	χ^2	*p* Value
Gender	2.338	164.8	<0.0001
Birth cohort	1.523	94.7	<0.0001
Daily smoking (at least 6 months)	2.162	74.5	<0.0001
Heavy smoking	1.372	19.1	<0.0001
Antisocial personality	2.186	80.7	<0.0001
Depression	1.562	48.6	<0.0001
Father's alcoholism	1.404	29.5	<0.0001
Proband's gender[a]	0.832	5.7	<0.025
Proband's age of onset[a]	0.986	6.8	<0.01

[a] Not significant once multiple testing and nonindependence of sibling sample were considered.

The highest odds ratio of 4.2 was found for gender, with men having the highest odds. Those who were deceased showed a significantly higher rate (odds ratio, 2.0) in all but one cohort group. Among living relatives, there was not a significant effect of being interviewed. There were not significant cohort differences among the cohorts born in 1910 to 1929, 1930 to 1939, or 1940 to 1949. There were differences for the 1950 to 1959 cohort, especially in men. However, the overall effect of the history data was not nearly as dramatic as that in the interview data, with the higher rates in dead individuals making the overall rates comparable across cohorts.

DISCUSSION

As noted in the figure and tables, cohort of birth was of major significance in the direct interview rates of alcohol dependence. It was less prominent in the family history rates, but it is not clear whether (1) older individuals underreport their alcohol problems, (2) younger individuals overreport problems that would not lead to a diagnosis if assessed later in life, or (3) history information is less valid and a complex set of biases diminishes the true cohort differences seen in the interview data. Perhaps longitudinal assessment can help resolve this. It is striking that family

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Table 5. Percentage (*n*) of DSM-III-R Alcohol Dependence in Relatives by Family History

Birth cohort	Men				Women			
		Not interviewed				Not interviewed		
	Interviewed	Alive	Dead	Overall	Interviewed	Alive	Dead	Overall
1910–1929	33.8 (240)	30.9 (97)	45.8 (177)	37.4 (514)	6.9 (292)	8.4 (95)	27.8 (72)	10.5 (459)
1930–1939	34.5 (267)	40.1 (147)	63.0 (54)	39.5 (468)	9.6 (406)	7.7 (104)	41.2 (17)	10.3 (527)
1940–1949	34.6 (217)	30.7 (163)	35.5 (31)	33.1 (471)	12.4 (362)	15.0 (113)	18.8 (16)	13.2 (491)
1950–1959	40.9 (484)	39.3 (346)	29.3 (41)	39.7 (871)	14.2 (633)	12.3 (228)	21.4 (14)	13.0 (875)
1960–1969	33.8 (515)	37.8 (315)	39.1 (23)	35.4 (853)	14.3 (672)	13.0 (216)	60.0 (5)	14.2 (893)

Table 6. Logistic Analysis of Family History Diagnosis[a]

Covariate	Odds ratio	χ^2	*p* Value
Gender	4.2	334.3	<0.0001
Cohort 1930–1939	1.2	3.6	0.06
Cohort 1940–1949	1.2	2.0	0.16
Cohort 1950–1959	1.5	14.0	<0.001
Deceased	2.0	37.7	<0.0001
Not interviewed	1.0	0.0	0.95

[a] Proband report only.

history rates are higher in the deceased relatives, so the rates in all relatives show diminished cohort differences compared with only those relatives who were interviewed. An additional analysis (not shown) indicated that this was not due to comorbid cigarette smoking.

The total numbers in Table 5 give interesting information on response rates. Of all available living first-degree relatives, 75.8% of women and 61.7% of men were interviewed. The greater participation of women in family studies is usually observed. With the family history report, there seem to be comparable rates of alcohol dependence in the interviewed and the living, noninterviewed individuals. In contrast, the deceased men and women showed rates of 45% and 29%, respectively. This would indicate that lifetime rates based on living individuals might be underestimates. Moreover, because the rates of death range from 34.4% in the oldest male birth cohort to 2.7% in the youngest and from 15.7 to 0.5% in women, the resulting bias is related to birth cohort.

As noted in the introduction, there is no statistical way to disentangle age, birth cohort, and period effects. Our first step in analysis was to stratify the sample in terms of the five birth cohorts depicted in Fig. 1 and to visually inspect for proportionality of the hazard functions for each stratum. This is an assumption needed for the application of the Cox proportional hazards model. The groups displayed proportionality; this is in contrast to results for major depression (Lavori et al., 1987). We would expect a period effect to influence the hazard function at a different age in each birth cohort, so that there would be nonproportionality. We interpret this to mean that age and birth cohort effects are sufficient to explain the data; however, other combinations of all three effects would be possible. One obvious source of a birth cohort effect is the differential mortality of alcohol-dependent individuals. This would seem like a birth cohort effect when only living individuals are used in analysis. Tables 5 and 6 indicate that this may be one significant factor that partially explains the data. However, this conclusion must be tempered by the possibility that the alcoholic condition of a deceased relative made the diagnosis more likely to be known to family members.

Whatever the source of the observed birth cohort differences, they must be considered when analyzing family data. For example, the rates of alcohol dependence in mothers of probands must be compared with the rates in the appropriate female birth cohort; otherwise, it is possible that a negative correlation may result from comparison to young controls. The traditional age-correction methods using lifetime morbid risk would give spurious results. For example, mothers of alcohol-dependent probands born between 1930 and 1939 show a rate of alcohol dependence of 16.9%, a 7-fold increase compared with control women from the same birth cohort. However, there was only a modest increase compared with the uncorrected rate in female controls in the 1960 to 1979 birth cohort. If inappropriate age groups were used, it is possible that an analysis might conclude that alcohol dependence was nonfamilial. Similarly, birth cohort must be considered in the analysis of any covariate that itself may vary with birth cohort.

The previous analyses treat the observations as statistically independent. In fact, the interviewed individuals are members of 1044 case families and 232 control families. This type of cluster sampling will give consistent estimates of parameters such as relative risk, but it will deflate their level of significance. Bull et al. (2001) have used simulation methods to examine design effects to give recommendations for estimating sample sizes when comparing family data with those of a simple sample of individuals. The worst-case scenario for our data would seem to be a design effect of 2.0. In this case, the χ^2 values in the tables would have to be divided by 2 to account for the dependence in the observations. Accordingly, the variables "mother alcohol dependent" in Table 3 and "proband's gender" and "proband's age of onset" in Table 6 should not be viewed as significant.

Finally, it should be noted that such secular changes in one generation cannot be due simply to genetic changes in the population (e.g., changes in gene frequencies), but must reflect environmental changes. However, this does not mean that genes are not involved or that the magnitude of genetic influences has necessarily changed. There may have been a mean shift in susceptibility due to changes in the frequencies of environmental risk factors that increase the

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prevalence of alcohol dependence, but the variability within a birth cohort is controlled by the same set of genes before and after these changes. Follow-up data in families may ultimately be needed to verify these trends in more recently born cohorts. The samples of relatives and controls in COGA are currently undergoing a 5-year reassessment that may prove useful in understanding these trends.

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