ORIGINAL ARTICLE

A Family Study of Alcohol Dependence

Coaggregation of Multiple Disorders in Relatives of Alcohol-Dependent Probands

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Background: Alcohol dependence tends to aggregate within families. We analyzed data from the family collection of the Collaborative Study on the Genetics of Alcoholism to quantify familial aggregation using several different criterion sets. We also assessed the aggregation of other psychiatric disorders in the same sample to identify areas of possible shared genetic vulnerability.

Design: Age-corrected lifetime morbid risk was estimated in adult first-degree relatives of affected probands and control subjects for selected disorders. Diagnostic data were gathered by semistructured interview (the Semi-Structured Assessment for the Genetics of Alcoholism), family history, and medical records. Rates of illness were corrected by validating interview and family history reports against senior clinicians' all sources best estimate diagnoses. Sex, ethnicity, comorbidity, cohort effects, and site of ascertainment were also taken into account.

Results: Including data from 8296 relatives of alcoholic probands and 1654 controls, we report lifetime risk rates of 28.8% and 14.4% for *DSM-IV* alcohol dependence in relatives of probands and controls, respectively; respective rates were 37.0% and 20.5% for the less stringent *DSM-III-R* alcohol dependence, 20.9% and 9.7% for any *DSM-III-R* diagnosis of nonalcohol nonnicotine substance dependence, and 8.1% and 5.2% for antisocial personality disorder. Rates of specific substance dependence were markedly increased in relatives of alcohol-dependent probands for cocaine, marijuana, opiates, sedatives, stimulants, and tobacco. Aggregation was also seen for panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, and major depression.

Conclusions: The risk of alcohol dependence in relatives of probands compared with controls is increased about 2-fold. The aggregation of antisocial personality disorder, drug dependence, anxiety disorders, and mood disorders suggests common mechanisms for these disorders and alcohol dependence within some families. These data suggest new phenotypes for molecular genetic studies and alternative strategies for studying the heterogeneity of alcohol dependence.

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ALCOHOL CONSUMPTION AND alcohol dependence are influenced by genetic factors in humans and experimental animals. The heritability of alcohol consumption is estimated at 35% to 40% in twin studies.[1-3] Twin studies of alcohol dependence have generally shown a ratio of monozygotic concordance–dizygotic concordance of about 2:1, with differences in the absolute value of the concordance related to diagnostic criteria.[4-8] A study of 133 adoptees was performed by Goodwin and Schulsinger[9]; adopted-away sons of alcoholics had an 18% rate of alcohol dependence (similar to that in sons of alcoholics raised in their biological families) and adopted-away sons of control subjects had a 5% rate of alcohol dependence. Bohman[10] studied 2324 adoptees, finding 39% alcohol dependence in sons of alcoholic fathers and 20% alcohol dependence in sons of controls; the comparable figures for daughters were 20% and 6%. Family studies were reviewed by Cotton[11] in 1979, including data on 6251 relatives of alcoholics and 4083 relatives of controls. Rates of illness in fathers in the 2 groups were 27% and 5%, respectively; respective rates in mothers were 5% and 1%.

Characteristically, women have had lower rates of alcohol dependence than men, in epidemiologic and family and twin studies.[12,13] The question arises whether risk for alcohol dependence is passed on comparably by female and male relatives in families with cases of alcohol dependence. Kaij and Dock[14] found that grandsons of alcoholics had equal risk whether

they were the son of a son of an alcoholic or the son of a daughter of an alcoholic. Likewise, Cloninger et al[15] reported as much alcohol dependence in relatives of female alcoholics as in relatives of male alcoholics. This suggests that the 2 sexes are equivalent in genetic load for alcohol dependence and that differential expression of the illness in the 2 sexes is related to nongenetic factors.

We may distinguish between comorbidity (disorders occurring together in an individual) and coaggregation (disorders occurring together in families). Certain psychiatric disorders have been reported to be more prevalent in persons with alcohol dependence compared with controls (comorbid disorders), including child conduct disorder and adult antisocial personality disorder (ASPD),[10,16] depression,[17-20] and anxiety disorders.[18,21] Other disorders have been noted in relatives (coaggregating disorders), including drug abuse or dependence,[22] somatization in female relatives,[15] and attention-deficit/hyperactivity disorder in juvenile offspring.[23]

Our goal was to perform a family study using modern diagnostic criteria and a structured assessment for multiple disorders on Axis I and ASPD on Axis II. The purpose was to identify disorders aggregating in relatives of persons with alcohol dependence and, thus, specify areas of possible shared genetic vulnerability factors. We studied 1269 probands with alcohol dependence ascertained through treatment facilities without regard to family history (a subset of high-density families were later studied for genetic linkage[12,24]). They and their relatives are compared with the relatives of 232 probands ascertained at 6 centers to represent a population control sample. In all, 8296 adult first-degree relatives of alcohol-dependent probands were compared with 1654 adult controls.

Table 1. Description of the Sample of Relatives and Controls, With a Detailed Description of Those Directly Interviewed*

Characteristic	Relatives of Alcohol-Dependent Probands	Control Sample	Total
All Subjects With Diagnostic Information†			
Sex			
Male	4083 (49.2)	815 (49.3)	**4898** (49.2)
Female	4213 (50.8)	839 (50.7)	**5052** (50.8)
Age, mean, y	47.0	43.2	46.4
Interviewed Subjects‡			
Sex			
Male	2291 (42.9)	529 (47.9)	**2820** (43.7)
Female	3052 (57.1)	576 (52.1)	**3628** (56.3)
Age, mean, y	49.0	41.2	47.7
Ethnicity			
White (non-Hispanic)	3892 (72.8)	928 (84.0)	**4820** (74.8)
African American	976 (18.3)	67 (6.1)	**1043** (16.2)
Hispanic	331 (6.2)	49 (4.4)	**380** (5.9)
Native American	53 (1.0)	10 (0.9)	**63** (1.0)
Other/unknown	39 (0.7)	25 (2.3)	**64** (1.0)
Married	2868 (53.7)	624 (56.5)	**3492** (54.2)
Education, mean, y	12.7	14.3	13.0

*Data are given as number (percentage) of each group unless otherwise indicated. Percentages may not total 100 because data may not be available for all subjects.

†The denominators for the groups are as follows: relatives, N=8296; controls, N=1654; and total, N=9950.

‡The denominators for the groups are as follows: relatives, N=5343; controls, N=1105; and total, N=6448.

METHODS

The Collaborative Study on the Genetics of Alcoholism began in 1989 with the participation of 6 centers (Indiana University School of Medicine; University of Iowa; University of Connecticut; State University of New York Health Sciences Center at Brooklyn; University of California, San Diego; and Washington University). A semistructured interview (the Semi-Structured Assessment for the Genetics of Alcoholism [SSAGA][25,26]) was designed to assess alcohol dependence by multiple criteria and other major psychiatric disorders. The study was approved by institutional review boards at each site. Probands with alcohol dependence by *DSM-III-R* criteria (American Psychiatric Association, 1987) and definite alcoholism by the criteria of Feighner et al[27] were systematically ascertained from consecutive admissions to treatment facilities and invited to participate in the study. This ascertainment method was specifically designed to support a family study. Inclusion criteria included the availability of 4 first-degree relatives, at least 2 of whom were living in the catchment area of one of the participating sites. Probands and relatives were required to be English speaking. Exclusion criteria included habitual intravenous drug use (>30 times in a lifetime or within 6 months of ascertainment), known human immunodeficiency virus–positive status, or a terminal illness not related to alcoholism. These families were designated as stage 1 and form the data set for the analyses in this report. A subset of families (designated as stage 2) contained at least 2 additional first-degree relatives with alcohol dependence; members of these families were included in analyses of genetic linkage and electrophysiological features (Rice et al[28] provide a summary). Control families were identified from various source populations, including motor vehicle registrants, dental clinic attendees, and parents of college students. Such families were required to have spouses and 3 children older than 13 years willing to participate. Because controls were selected to represent a subset of the general population, they were not excluded if they met the criteria for alcohol dependence or any other psychiatric disorder. Probands, spouses, and first-degree relatives of those aged 18 years and older were then invited to participate (children and adolescents in these families were assessed using age-appropriate instruments and will be the subject of a separate report). A comparison of demographic characteristics in the relative and control groups is shown in **Table 1**. Differences in age, sex, and ethnicity were accounted for in the multivariate analyses presented later.

Participants provided informed consent and were personally interviewed with the SSAGA and the Family History Assessment Module (FHAM). Medical records were sought for those with a history of psychiatric treatment. Certain disorders, including posttraumatic stress disorder (PTSD), nicotine dependence, and attention-deficit/hyperactivity disorder, were only assessed using a revised version of the SSAGA prepared in 1997 and, thus, the denominators for these disorders are smaller than for the other disorders. All diagnoses were assessed on a lifetime basis. Disorders judged to be organic (ie, direct effects of substance use) were not included in these analyses. Original analyses separated control probands from control relatives; later analyses combined control probands and control relatives (referred to generically as "controls" from this point on), and results were essentially the same. Interview instru-

ments and procedures were the same for relatives of alcohol-dependent probands and controls. Conference calls and continuously updated procedure manuals were used to standardize interview technique and scoring norms across sites.

Assessment folders were developed for each subject, including the interview and information from relatives and medical records, where available. A subset of subjects (1929 of 9950 subjects, or 19.4% of the sample studied herein) were diagnosed by best estimate procedures. This included all members of the stage 2 families included in the genetic linkage studies and a subset of controls. Probands with alcohol dependence were also diagnosed by best estimate procedures, but their data are not included herein because of their ascertainment as affected persons. The best estimate process involved senior clinician assessment (J.I.N., S.O., T.R., M.S., L.K., T.P., L.B., S.K., and V.H.) of all diagnostic material to assign lifetime diagnoses, blind to proband or relative status. The best estimate process was then used to validate information from the SSAGA and FHAM. Considering the best estimate as the gold standard, diagnoses based on algorithmic extraction of information from the SSAGA were classified as true positive, true negative, false positive, and false negative. These functions were used to adjust rates of diagnoses in interviewed subjects not included in the best estimate process (4324 of 9718 subjects, or 44.5%), using the following function: Total number of affected subjects = [SSAGA-positive subjects × (true positives/total positives)] + [SSAGA-negative subjects × (false negatives/total negatives)].

By using a similar procedure, information from the FHAM was validated, to assign diagnoses to subjects who did not participate in the SSAGA interview (3497 of 9718 subjects, or 36.0%). As an example, 75.9% of subjects implicated as having *DSM-III-R* alcohol dependence by 1 first-degree relative in fact were assigned that diagnosis in the best estimate process, 87.7% of subjects implicated by 2 relatives received that diagnosis by best estimate, and 93.7% of subjects implicated by 3 relatives received that diagnosis by best estimate. In this way, the results of the best estimate process were generalized to all first-degree relatives of alcohol-dependent probands and control probands.

Because the total subject group (and the group of best-estimated subjects) included many more relatives of alcoholics than controls (8296/9718), the validation of SSAGA and FHAM was differentially reflective of relationships among self-report, relatives' reports, and clinician judgment in families of an alcoholic proband. However, we have tested the premise that information from relatives is related to self-report (by SSAGA) similarly in families of alcohol-dependent probands and controls. In fact, comparison of the proportion of SSAGA-affected subjects among groups of relatives and controls separated by number of implications of illness by family members did not differ significantly for any condition used in the analysis, with a single exception: subjects with 3 or more implications of *DSM-IV* alcohol dependence by family members were more likely to be affected by SSAGA among relatives of alcohol-dependent probands (66%) than among controls (37%). Because only a few controls were in this category, correction for this difference would reduce the estimated prevalence of alcohol dependence in controls only from 14.4% to 14.0%. The diagnostic criteria are *DSM-III-R* unless otherwise noted. We have observed the standard *DSM* convention that subjects diagnosed as having substance dependence are not also diagnosed as having substance abuse, even though most would meet the symptomatic criteria for abuse as well.

Age correction was performed for 6 disorders: alcohol dependence by *DSM-III-R* and *DSM-IV*, major depression, mania, drug dependence (any diagnosis of nonalcohol nonnicotine substance dependence), and ASPD. For these disorders, data from all directly interviewed affected subjects in the data set were used to generate an age-of-onset function. The group of subjects at risk was then divided by decade, and the size of the unaffected portion of each group adjusted by the proportion of affected subjects, with onset by the median of that decade, producing the age-adjusted number of subjects at risk (a modified Stromgren procedure, as in the studies by Johnson and Leeman[29] and Gershon and colleagues[30]). The age of onset was considered to be the year that a subject met the full criteria for the disorder. For ASPD (presumed to be a continuous trait that begins, by definition, during childhood), the age of onset was considered to be the age at the time of the first symptom and, thus, age-corrected data for this group of adult subjects were identical to the raw data. We also studied Kaplan-Meier survival curves using the Cox proportional hazards regression model for these disorders (ie, alcohol dependence, major depression, mania, drug dependence, and ASPD). Rates of illness in relatives of alcohol-dependent probands were compared with rates of illness in controls using the χ^2 test. Relative risk (RR) estimates were calculated with their 95% confidence intervals (CIs).

A multivariate logistic regression model was used to account for the effects of sex, ethnicity, site of ascertainment, birth cohort, comorbidity in the proband, and comorbid alcoholism in the relative. Cohort effects were assessed by dividing relatives into groups by decade of birth. Familial effects (the effect of the variable number of first-degree relatives in families) were controlled using a random effects odds ratio method and a marginal odds ratio method.

RESULTS

Table 2 shows the prevalence of various psychiatric disorders in first-degree relatives of probands with Collaborative Study on the Genetics of Alcoholism–determined alcoholism (*DSM-III-R* alcohol dependence plus Feighner et al[27] definite alcoholism) and in the sample of controls. Many disorders seem to cluster in families with an alcohol-dependent proband, including alcohol dependence itself (by 4 criterion systems), other forms of substance dependence, ASPD, several anxiety disorders, major depression, and dysthymia. Diagnoses that did not seem to cluster in relatives include anorexia, bulimia, mania, and several forms of substance abuse, including *DSM-IV* alcohol abuse. Somatization disorder was too infrequently diagnosed for an accurate comparison. Attention-deficit/hyperactivity disorder was assessed only in those subjects interviewed after 1997, and that subgroup does not show a significant aggregation. **Table 3** corrects the raw data for all interviewed subjects, based on the SSAGA false-negative and false-positive rates (see the "Methods" section). This correction lowers the rate of *DSM-IV* alcohol abuse and increases the rate of *DSM-IV* alcohol dependence, among other changes. Versions of Tables 2 and 3 in which probands are diagnosed by *DSM-IV* or *International Classification of Diseases, 10th Revision (ICD-10)* are available at the following Web site (http://ipr.iupui.edu/coga/research.html); in general, RRs are quite comparable to those presented herein, and there is no case in which a disorder shows significant familial aggregation in one version of the table but not others. Controlling for the effect of family size did not change the pattern of familial aggregation (data not shown). Marginal odds ratios were significant for each disorder in Table 2, with $P < .05$.

Table 2. Prevalence and Relative Risk of Particular Disorders in Adult First-Degree Relatives of Probands With Alcohol Dependence Compared With Control Subjects

Disorder*	Affected Subjects	Risk Set	Incidence, %	χ^2 Value	*P* Value	Relative Risk (95% Wald CI)
ADHD†						
Controls	3	157	1.91	1.23	.27	1.96 (0.60-6.48)
Relatives	22	586	3.75			
Agoraphobia						
Controls	14	1105	1.27	2.04	.15	1.50 (0.86-2.61)
Relatives	101	5318	1.90			
Alcohol abuse						
Controls	17	1105	1.54	5.11	.02	1.78 (1.08-2.92)
Relatives	146	5342	2.73			
Alcohol abuse (*DSM-IV*)						
Controls	232	1105	21.00	0.18	.67	0.97 (0.86-1.10)
Relatives	1091	5342	20.42			
Alcohol dependence						
Controls	176	1105	15.93	120.15	<.001	2.19 (1.90-2.52)
Relatives	1865	5342	34.91			
Alcohol dependence (*DSM-IV*)						
Controls	72	1105	6.52	132.48	<.001	3.82 (3.04-4.80)
Relatives	1329	5342	24.88			
Alcohol dependence (*ICD-10*)						
Controls	43	1105	3.89	112.92	<.001	5.03 (3.74-6.78)
Relatives	1046	5342	19.58			
Alcoholism (Feighner)						
Controls	187	1105	16.92	124.62	<.001	2.16 (1.89-2.47)
Relatives	1954	5342	36.58			
Anorexia						
Controls	3	1104	0.27	0	.95	1.04 (0.30-3.59)
Relatives	15	5304	0.28			
ASPD						
Controls	36	1104	3.26	20.83	<.001	2.18 (1.56-3.06)
Relatives	379	5320	7.12			
Bulimia						
Controls	16	1104	1.45	0.16	.69	1.12 (0.66-1.89)
Relatives	86	5319	1.62			
Cocaine abuse						
Controls	1	1105	0.09	4.48	.03	8.51 (1.17-61.77)
Relatives	41	5326	0.77			
Cocaine dependence						
Controls	21	1105	1.90	61.87	<.001	5.63 (3.66-8.66)
Relatives	570	5326	10.70			
Depression (lifetime)						
Controls	169	1104	15.31	9.54	.002	1.27 (1.09-1.47)
Relatives	1032	5329	19.37			
Drug dependence§						
Controls	81	1105	7.33	96.82	<.001	2.95 (2.38-3.67)
Relatives	1154	5329	21.66			
Dysthymia						
Controls	8	1104	0.72	4.31	.04	2.15 (1.04-4.43)
Relatives	83	5326	1.56			
General anxiety†						
Controls	1	915	0.11	0.23	.63	1.71 (0.19-15.24)
Relatives	4	2146	0.19			
Mania						
Controls	5	1105	0.45	2.43	.12	2.08 (0.83-5.19)
Relatives	50	5325	0.94			
Marijuana abuse						
Controls	4	1105	0.72	6.77	.009	2.59 (1.26-5.31)
Relatives	86	5332	1.88			
Marijuana dependence						
Controls	72	1105	6.52	44.33	<.001	2.20 (1.75-2.78)
Relatives	766	5332	14.37			
OCD						
Controls	3	1104	0.27	5.24	.02	3.88 (1.22-12.36)
Relatives	56	5316	1.05			

(continued)

Table 2. Prevalence and Relative Risk of Particular Disorders in Adult First-Degree Relatives of Probands With Alcohol Dependence Compared With Control Subjects (cont)

Disorder*	Affected Subjects	Risk Set	Incidence, %	χ^2 Value	*P* Value	Relative Risk (95% Wald CI)
Opiate abuse						
Controls	1	1105	0.09	1.50	.22	3.53 (0.47-26.47)
Relatives	17	5326	0.32			
Opiate dependence						
Controls	8	1105	0.72	16.40	<.001	4.31 (2.12-8.73)
Relatives	166	5326	3.12			
Panic disorder						
Controls	17	1104	1.54	9.24	.002	2.15 (1.31-3.52)
Relatives	176	5316	3.31			
PTSD†						
Controls	13	910	1.43	16.62	<.001	3.29 (1.86-5.83)
Relatives	100	2127	4.70			
Sedative abuse						
Controls	1	1105	0.09	2.87	.09	5.60 (0.76-41.18)
Relatives	27	5326	0.51			
Sedative dependence						
Controls	5	1105	0.45	17.70	<.001	6.72 (2.77-16.33)
Relatives	162	5326	3.04			
Social phobia						
Controls	19	1104	1.72	2.48	.12	1.47 (0.91-2.36)
Relatives	134	5313	2.52			
Somatization						
Controls	1	1104	0.09	‡	.17	NA
Relatives	0	5322	0			
Stimulant abuse						
Controls	2	1105	0.18	2.27	.13	3.01 (0.72-12.59)
Relatives	29	5326	0.54			
Stimulant dependence						
Controls	9	1105	0.81	33.92	<.001	7.10 (3.67-13.73)
Relatives	308	5326	5.78			
Tobacco dependence (*DSM-IV*)†						
Controls	130	914	14.22	85.13	<.001	2.24 (1.88-2.65)
Relatives	681	2142	31.79			

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASPD, antisocial personality disorder; CI, confidence interval; *ICD-10, International Classification of Diseases, 10th Revision (ICD-10)*; NA, data not applicable; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder.
*All disorders were diagnosed by *DSM-III-R* unless otherwise indicated. Feighner indicates the criteria of Feighner et al.[27]
†Data are taken from Semi-Structured Assessment for the Genetics of Alcoholism II data only.
‡The Fisher exact test was used to obtain the *P* value.
§Any diagnosis of nonalcohol nonnicotine substance dependence.

For certain disorders, we were able to systematically include information from relatives in assigning diagnoses, because detailed information was provided in the FHAM. These included alcohol dependence, drug dependence, mania, depression, and ASPD. These data have also been age corrected. Results are presented in **Table 4**. Adjusted rates of *DSM-III-R* alcohol dependence are 37.0% and 20.5% in relatives of probands and controls, respectively (RR, 1.8; 95% CI, 1.6-2.0). Comparable figures for *DSM-IV* alcohol dependence are 28.8% and 14.4% (RR, 2.0; 95% CI, 1.8-2.3); for any form of *DSM-III-R* nonalcohol nonnicotine substance dependence, 20.9% and 9.7% (RR, 2.2; 95% CI, 1.9-2.5); for primary major depression, 19.5% and 18.0% (RR, 1.1; 95% CI, 1.0-1.2); for mania, 1.2% and 0.9% (RR, 1.3; 95% CI, 0.7-2.3); and for ASPD, 8.1% and 5.2% (RR, 1.6; 95% CI, 1.3-2.0). These prevalence figures represent the best estimate of rates of illness for the full complement of 8296 adult first-degree relatives of alcohol-dependent probands and 1654 adult controls. Relative risk estimates in siblings alone (data not shown) were generally comparable to those in all first-degree relatives; the RR for ASPD in siblings of 2.0 (95% CI, 1.5-2.7) was somewhat higher than that in first-degree relatives generally. Cox proportional hazards regression ratios for these disorders (interviewed relatives only) are 2.9 ($P<.001$) for *DSM-III-R* alcohol dependence, 3.2 ($P<.001$) for *DSM-IV* alcohol dependence, 3.2 ($P<.001$) for drug dependence, 1.1 ($P=.08$) for major depression, 1.7 ($P=.16$) for mania, and 2.5 ($P<.001$) for ASPD.

Prevalence estimates were also determined separately by sex (data not shown). Generally, similar patterns are seen in RRs for male and female relatives, with an exception being an RR of 1.8 (95% CI, 1.4-2.4) for ASPD in men compared with an RR of 1.2 (95% CI, 0.8-1.8) in women. As expected, the absolute prevalence rates in male relatives exceed those in female relatives for *DSM-III-R* alcohol dependence (48.0% vs 26.3%), *DSM-IV* alcohol dependence (37.1% vs 20.7%), drug dependence (26.0% vs 15.9%), and ASPD (11.7% vs 4.6%). Prevalence rates in female relatives exceed those in male relatives for depression (22.8% vs 16.0%). Prevalence rates for alcohol dependence for each sex are plotted by age

Table 3. Corrected Prevalence of Psychiatric Disorders in Interviewed First-Degree Relatives of Probands With Alcohol Dependence and Control Subjects*

Disorder†	Affected Subjects	Total Subjects Assessed	Prevalence, %	χ^2 Value	*P* Value	Relative Risk (95% Wald CI)
Alcohol abuse						
Controls	38	1105	3.46	0.69	.41	1.15 (0.82-1.62)
Relatives	212	5342	3.96			
Alcohol abuse (*DSM-IV*)						
Controls	124	1105	11.22	1.50	.22	1.12 (0.93-1.34)
Relatives	671	5342	12.55			
Alcohol dependence						
Controls	222	1105	20.10	90.36	<.001	1.81 (1.60-2.05)
Relatives	1947	5342	36.44			
Alcohol dependence (*DSM-IV*)						
Controls	150	1105	13.56	85.45	<.001	2.08 (1.78-2.42)
Relatives	1505	5342	28.17			
Alcohol dependence (*ICD-10*)						
Controls	119	1105	10.76	73.13	<.001	2.16 (1.81-2.58)
Relatives	1243	5342	23.26			
Alcoholism (Feighner)						
Controls	242	1105	21.88	92.74	<.001	1.77 (1.58-1.99)
Relatives	2072	5342	38.79			
ASPD						
Controls	69	1105	6.22	7.52	.006	1.41 (1.10-1.80)
Relatives	468	5342	5.79			
Cocaine abuse						
Controls	17	1105	1.51	1.21	.47	1.21 (0.73-2.01)
Relatives	99	5326	1.85			
Cocaine dependence						
Controls	40	1105	3.64	49.94	<.001	3.10 (2.26-4.24)
Relatives	597	5342	11.22			
Major depression						
Controls	188	1104	17.03	3.53	.06	1.14 (0.99-1.32)
Relatives	1039	5329	19.49			
Drug dependence‡						
Controls	106	1104	9.61	73.75	<.001	2.28 (1.89-2.75)
Relatives	1165	5320	21.85			
Mania						
Controls	10	1105	0.91	0.48	.49	1.27 (0.65-2.46)
Relatives	61	5325	1.14			
Marijuana abuse						
Controls	32	1105	2.87	0.52	.47	1.15 (0.79-1.66)
Relatives	177	5332	3.31			
Marijuana dependence						
Controls	94	1105	8.50	28.74	<.001	1.75 (1.42-2.14)
Relatives	792	5332	14.85			
OCD						
Controls	4	1105	0.36	2.37	.12	2.23 (0.80-6.21)
Relatives	43	5326	0.81			
Opiate abuse						
Controls	8	1105	0.68	0.01	.92	1.04 (0.49-2.21)
Relatives	40	5326	0.75			
Opiate dependence						
Controls	15	1105	1.34	12.14	<.001	2.53 (1.50-4.27)
Relatives	183	5326	3.43			
Panic disorder						
Controls	26	1104	2.37	4.84	.03	1.57 (1.05-2.36)
Relatives	197	5316	3.70			
Sedative abuse						
Controls	10	1105	0.86	0.11	.74	1.12 (0.57-2.19)
Relatives	54	5326	1.02			
Sedative dependence						
Controls	22	1105	2.01	9.23	.002	1.96 (1.27-3.03)
Relatives	208	5326	3.90			
Stimulant abuse						
Controls	10	1105	0.90	0.11	.74	1.12 (0.57-2.19)
Relatives	54	5326	1.02			
Stimulant dependence						
Controls	26	1105	2.34	25.02	<.001	2.73 (1.84-4.04)
Relatives	342	5325	6.42			

Abbreviations: See Table 2.
*Semi-Structured Assessment for the Genetics of Alcoholism data were corrected by the best estimate method.
†All disorders were diagnosed by *DSM-III-R* unless otherwise indicated. Feighner indicates the criteria of Feighner et al.[27]
‡Any diagnosis of nonalcohol nonnicotine substance dependence.

Table 4. Age-Corrected Prevalence of Selected Disorders in Interviewed First-Degree Relatives of Alcohol-Dependent Probands Compared With Interviewed Controls and in All First-Degree Relatives Compared With All Controls*

Disorder	Relatives			Controls			χ^2 Value	*P* Value	Relative Risk (95% Wald CI)
	Affected	At Risk	Rate	Affected	At Risk	Rate			
Interviewed Relatives									
Alcohol dependence									
DSM-III-R	1865	5189	0.36	176	1019	0.17	106.47	<.001	2.08 (1.81-2.39)
DSM-IV	1329	5142	0.26	72	992	0.07	120.03	<.001	3.56 (2.84-4.47)
Drug dependence†	1151	5279	0.22	81	1062	0.08	91.30	<.001	2.86 (2.30-3.55)
Depression	1032	4999	0.21	169	963	0.18	4.67	.03	1.18 (1.02-1.36)
Mania	50	4869	0.01	5	939	0.01	1.97	.16	1.93 (0.77-4.82)
ASPD	379	5343	0.07	36	1105	0.03	20.65	<.001	2.18 (1.56-3.05)
All Relatives									
Alcohol dependence									
DSM-III-R	2939	7943	0.37	314	1529	0.21	126.82	<.001	1.81 (1.63-2.00)
DSM-IV	2261	7862	0.29	215	1498	0.14	113.00	<.001	2.01 (1.77-2.29)
Drug dependence†	1691	8108	0.21	154	1586	0.10	93.12	<.001	2.16 (1.85-2.53)
Depression	1489	7646	0.20	263	1463	0.18	1.88	.17	1.09 (0.96-1.22)
Mania	88	7469	0.01	13	1428	0.01	0.69	.40	1.28 (0.72-2.29)
ASPD	671	8296	0.08	86	1654	0.05	16.37	<.001	1.57 (1.26-1.96)

Abbreviations: See Table 2.
*Data given are age corrected. All disorders were diagnosed by *DSM-III-R* unless otherwise indicated.
†Any diagnosis of nonalcohol nonnicotine substance dependence.

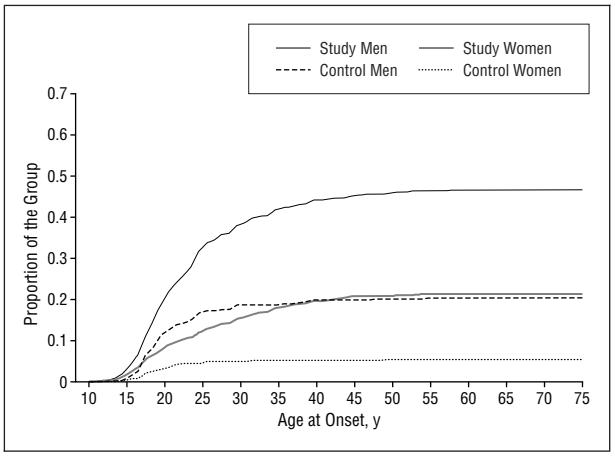

Figure 1. The development of *DSM-III-R* alcohol dependence in male and female relatives of alcohol-dependent probands and control subjects is shown. A significant effect of sex and relative vs control status (hazard ratio, 2.73; $P<.001$ [for both variables]) is seen.

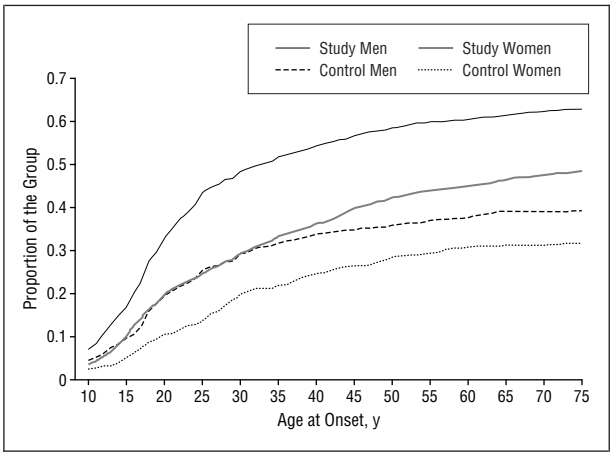

Figure 2. The development of any coaggregating *DSM-III-R* disorder (alcohol dependence, nonnicotine drug dependence, antisocial personality disorder, mood disorder, or anxiety disorder) in male and female relatives of alcohol-dependent probands and control subjects is shown. A significant effect of sex (hazard ratio, 1.55; $P<.001$) and relative vs control status (hazard ratio, 1.58; $P<.001$) is seen.

in **Figure 1**; significant effects of sex, and study vs control status, are seen. Rates of alcohol dependence in female relatives of alcohol-dependent probands are not different from rates in male controls. Prevalence rates for all coaggregating disorders are shown by sex in **Figure 2**; significant effects of sex, and study vs control status, are seen. In addition to having a higher chance of having any of the coaggregating disorders, relatives have more disorders (mean±SD, 1.3±1.2 vs 0.6±0.9 for men [Wilcoxon $z=12.6$, $P<.001$]; and mean±SD, 0.9±1.1 vs 0.4±0.7 for women [Wilcoxon $z=10.7$, $P<.001$]).

Noting the relatively high prevalence of ASPD in the control group, we examined symptom counts for antisocial behavior in relatives and controls for 29 variables (to assess whether the ASPD-diagnosed controls were as symptomatic as the ASPD-diagnosed relatives of alcohol-dependent probands). Semi-Structured Assessment for the Genetics of Alcoholism–positive relatives of probands (n=325) showed a mean±SD of 18.2%±9.2% of possible symptoms and SSAGA-positive controls (n=37) showed a mean±SD of 21.3%±8.6% of possible symptoms. Semi-Structured Assessment for the Genetics of Alcoholism–negative relatives of probands showed a mean±SD of 11.9%±3.1% of symptoms and SSAGA-negative controls showed a mean±SD of 11.0%±3.2% of symptoms. Subjects with false-negative SSAGA results (compared with best estimate results in the same person) showed 14.8%±6.5% of symptoms, whereas sub-

jects with true-negative SSAGA results showed 11.5%±3.0% of symptoms. If we make the conservative assumption that SSAGA-negative subjects with a score of 18% or more are actually false negatives (only 2.3% of true negatives have that many symptoms), the prevalence estimate of 3.6% in controls using raw data (Table 2) would increase to 5.4%; this tends to support our final estimate of 5.3% in controls.

Because cohort effects have been reported for alcoholism and depression,[28,31-33] we controlled our data for cohort effects (linear and quadratic) by dividing subjects into decade of birth (**Table 5**). We also controlled for sex, ethnicity, ascertainment site, comorbidity in probands, and comorbidity in relatives. These analyses include results for interviewed subjects only (because the estimates for all relatives include projected data). Most disorders studied continue to show aggregation with these effects accounted for, including alcohol dependence (by *DSM-III-R*, *DSM-IV*, Feighner et al,[27] and *ICD-10*), alcohol abuse (by *DSM-III-R*), all forms of substance dependence except for opiate dependence, ASPD, major depression, obsessive-compulsive disorder, panic disorder, and PTSD. Thus, these disorders are found in increased rates in relatives of alcoholic probands, independent of whether the proband has the disorder or whether the relative has comorbid alcoholism. If we rerun the analysis without controlling for comorbidity (data not shown), the categories of any anxiety disorder and opiate dependence are significantly aggregated as well, suggesting that in these cases it is a comorbid disorder (alcohol dependence plus any anxiety disorder or alcohol dependence plus opiate dependence) that is familial. The correction for comorbidity applied herein is a conservative one, testing the hypothesis that the pure form of one (noncomorbid) disorder is related to the pure form of the other. This underestimates the common genetic variance represented by familial comorbid illness, which is substantial.

Table 5. Data for Familial Aggregation of Various Disorders in Relatives of Alcohol-Dependent Probands*

Disorder	Odds Ratio (95% CI)	F Value	*P* Value
Alcohol dependence (*DSM-IV*)	6.03 (4.57-7.96)	161.20	<.001
Alcohol abuse (*DSM-IV*)	1.18 (0.98-1.42)	2.89	.09
Any anxiety disorder	1.26 (0.94-1.69)	2.32	.13
Alcohol dependence (Feighner)	4.05 (3.24-5.06)	151.44	<.001
Agoraphobia	1.07 (0.54-2.14)	0.04	.85
Alcohol dependence (*ICD-10*)	7.27 (5.24-10.08)	141.74	<.001
Alcohol dependence	3.94 (3.16-4.91)	148.78	<.001
Alcohol abuse	2.44 (1.35-4.42)	8.67	.003
ASPD	1.87 (1.20-2.92)	7.72	.006
Anorexia	4.25 (0.57-31.56)	2.00	.16
Bulimia	1.36 (0.65-2.84)	0.66	.42
Cocaine dependence	3.11 (1.83-5.30)	17.44	<.001
Cocaine abuse	3.73 (0.67-20.86)	2.25	.13
Depression	1.35 (1.09-1.67)	7.84	.005
Drug abuse	2.38 (1.74-3.24)	29.92	<.001
Dysthymia	1.76 (0.75-4.14)	1.70	.19
Marijuana dependence	2.10 (1.53-2.89)	20.73	<.001
Marijuana abuse	2.37 (1.04-5.40)	4.25	.04
Mania	1.38 (0.54-3.56)	0.45	.50
OCD	4.00 (1.13-14.20)	4.61	.03
Opiate dependence	2.45 (0.93-6.42)	3.31	.07
Panic disorder	1.90 (1.03-3.51)	4.23	.04
PTSD	2.77 (1.16-6.62)	5.31	.02
Sedative dependence	5.54 (1.62-18.93)	7.46	.006
Social phobia	1.19 (0.64-2.22)	0.30	.58
Stimulant dependence	5.17 (2.44-10.98)	18.37	<.001
Stimulant abuse	1.18 (0.24-5.86)	0.04	.84
Tobacco dependence (*DSM-IV*)	1.57 (1.17-2.12)	8.89	.003

Abbreviations: See Table 2.
*Data were controlled for sex, ethnicity, ascertainment site, cohort effect, and comorbidity. All disorders were diagnosed by *DSM-III-R* unless otherwise indicated. Feighner indicates the criteria of Feighner et al.[27]

COMMENT

Alcohol dependence diagnosed by any of 4 criterion sets is clearly familial. The risk ratio we report herein is somewhat lower than has been reported in other family studies (those reviewed by Nurnberger and Gershon[34] and Merikangas and Risch[35]). This is primarily related to our control values, which range (Table 3) from 10.76% (*ICD-10*) to 21.88% (Feighner et al[27]). Relative risk increases modestly, progressing from the more inclusive criteria of Feighner et al to the more restrictive criteria of *ICD-10*. The high rates in controls are also seen in the raw data (15.93% for *DSM-III-R* and 16.92% for Feighner et al), and are slightly increased by age correction, correction for SSAGA false negatives and false positives, and inclusion of uninterviewed relatives. Of course, these are lifetime diagnoses and quite often do not represent an active drinking problem. The best approximations we have for the true rate of *DSM-IV* alcohol dependence in controls come from the data summarized in Table 4 (14.4% in all relatives). This is comparable to the SSAGA-corrected rate of 13.56% in Table 3 (our best estimate of true prevalence in interviewed relatives only).

It may be argued that the present set of controls has been selected for health, in that the participation of spouse and children were required. However, the rate of *DSM-III-R* alcohol dependence we report in controls, based on direct interview (17.3% [Table 4]), is similar to the rate reported by Kessler et al (14.1%) in the National Comorbidity Survey.[20] Rates of major depression, drug dependence, mania, and ASPD (17.5%, 7.6%, 0.5%, and 3.3%, respectively) are also generally comparable to National Comorbidity Survey rates (17.1%, 7.5%, 1.6%, and 3.5%, respectively). The alcohol-dependent probands, with 4 participating first-degree relatives, may also be relatively healthy because they represent affected persons with some family ties. In that regard, the substantially increased rates of illness in family members are even more remarkable.

We may also ask about the true RR of alcohol dependence in relatives of alcoholic probands compared with controls. It seems that it is safe (and conservative) to estimate an RR of about 2. Higher rates are seen with *ICD-10* and *DSM-IV* criteria in Table 2, but they are decreased when best estimate procedures are used. Estimates of RR in siblings alone (the Risch λ) also give an estimate of about 2 (data not shown).

Alcohol abuse (*DSM-IV*) does not cluster in families of alcohol-dependent probands. Semi-Structured Assessment for the Genetics of Alcoholism–corrected rates are

4.0% and 3.5% for relatives of probands and controls, respectively, for the *DSM-III-R* definition of abuse, and 12.6% and 11.2%, respectively, for the *DSM-IV* definition. Cocaine abuse, opiate abuse, sedative abuse, and stimulant abuse also show no difference between familial groups in SSAGA-corrected rates. Rates of abuse are low in relation to rates of dependence. In controls, corrected data show 6-fold more subjects with *DSM-III-R* alcohol dependence than abuse; the comparable value for *DSM-IV* alcohol dependence and abuse is 1.2-fold; for cocaine, 2-fold; for marijuana, 3-fold; for opiates, 2-fold; for sedatives, 2-fold; and for stimulants, 2-fold. In relatives of alcohol-dependent probands, the values are generally higher (eg, 2-fold for *DSM-IV* and 9-fold for *DSM-III-R* alcohol dependence vs alcohol abuse). It may be that abuse is underdiagnosed using the present criteria, that dependence is overly diagnosed, or that both are true. On the other hand, it may be more accurate to think of these disorders as truly independent of each other. These issues have also been discussed by Grant and colleagues.[36-40]

In contrast to abuse, all forms of nonalcohol substance dependence show aggregation in relatives of alcoholic probands, including cocaine (RR, 3.1), marijuana (RR, 1.8), opiates (RR, 2.5), sedatives (RR, 2.0), stimulants (RR, 2.7), and tobacco (RR, 2.2). In fact, the RR for any form of drug dependence excluding tobacco is 2.3, which is equal to or greater than the RR for alcohol dependence by any definition. This is consistent with studies showing evidence for a generalized genetic predisposition to substance dependence[41-44] as well as specific factors related to alcohol dependence. Support for specific genetic factors for substance dependence other than alcohol would require probands with other forms of substance dependence (which is beyond the scope of this study).

The excess of ASPD diagnoses in relatives of alcoholic probands is consistent with many previous studies. The prevalence of ASPD in controls in this study is relatively high. Estimates in these data vary from 3.3% in interviewed relatives to 5.2% in all relatives to 6.2%, applying corrections for SSAGA false negatives and false positives. However, estimates of ASPD in relatives of alcoholic probands are consistently higher (7.1%, 8.1%, and 8.8%, respectively).

Individual anxiety disorders that remain modestly but significantly aggregated after controlling for multiple factors include obsessive-compulsive disorder, panic disorder, and PTSD. The rates of some of these disorders in relatives were determined as part of previous reports,[45,46] and do not seem substantially different in the present (expanded) data set. The excess of anxiety disorders in relatives cannot, in general, be explained by the presence of an anxiety disorder in the proband (except for the category of any anxiety disorder). Previous studies of PTSD have shown ambiguous results in the assessment of the familial relationship with alcohol dependence.[47,48]

There is a modest excess of major depression (odds ratio, 1.35) in relatives of alcoholics after controlling for multiple factors. In a separate analysis, the rate of comorbid major depression was not elevated in alcoholic probands, although the rate of secondary depression (depression in the context of heavy drinking or other organic precipitants) was elevated.[49] Secondary depression also seemed to be elevated in relatives of alcoholic probands in that study, and comorbid alcoholism and depression aggregated in families. There is no evidence for aggregation of mania in relatives of alcoholic probands (Table 4). Comorbid mania does seem to be elevated in alcoholic subjects themselves in the Collaborative Study on the Genetics of Alcoholism data set.[50] Comorbid alcoholism and mania are also more likely to appear in relatives of comorbid (alcohol-dependent and manic) probands.[50]

Attention-deficit/hyperactivity disorder[23] and bulimia[51] have been reported in some previous studies to be related to alcohol dependence. We cannot confirm a relationship in this population.

The addition of family history data on uninterviewed relatives resulted in minor adjustments in prevalence estimates (the exception being *DSM-IV* alcohol dependence in controls), suggesting that the diagnostic profile of uninterviewed relatives was fairly similar to that of the interviewed relatives.

An excess of men among subjects diagnosed as having externalizing disorders and an excess of women among those diagnosed as having depression would be expected from previous studies.

Variation in rates of illness by ascertainment site may reflect different sources for controls at different sites (eg, motor vehicle records vs dental clinics). Our multivariate analysis considered site as a confounding variable and still revealed significant coaggregation of multiple disorders.

Family studies by their nature include environmental effects, genetic-environmental interactions, and genetic effects. One complex effect is that of assortative mating, which is known to occur in families with cases of alcohol dependence.[52,53] These effects may never be completely controlled for; analysis of sibling pairs, however, eliminates the effect of multigenerational assortative mating and shows generally similar results to analysis of all first-degree relatives.

Family studies may suggest new phenotypes for genetic linkage and association studies. It would be useful to consider ASPD or the combination of ASPD and alcohol dependence as a genetic phenotype. Linkage studies of habitual smoking in this sample have been reported,[54] as have linkage studies of alcoholism and/or depression.[49] Because evidence in the present analysis suggests that anxiety disorders (specifically, panic disorder, PTSD, and any anxiety disorder) aggregate in relatives of alcoholics independent of comorbidity, it would seem useful to test anxiety as a possible alternate phenotype within families with alcohol dependence.

Another, and perhaps more general, role of family studies is to define the familial/genetic relationships between disorders. A disorder more common in relatives than controls may share specific genetic vulnerability factors with the illness in the proband. In combination with twin studies, we may think of the genetic spectrum of alcohol dependence as including not only ASPD but also multiple forms of drug dependence and some forms of depressive and anxiety disorders. This familial coaggre-

gation is distinct in origin and significance from comorbidity (multiple disorders in the same person), which may result from secondary effects of one disorder on another. Coaggregation in families is more likely to represent shared genetic variance.

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Correction

Errors in Tables. In the Original Article by Nurnberger et al titled "A Family Study of Alcohol Dependence: Coaggregation of Multiple Disorders in Relatives of Alcohol-Dependent Probands," published in the December issue of the ARCHIVES (2004;61:1246-1256), there were errors in Tables 2 and 3. In Table 2, the heading for column 4 should have read "Prevalence, %." In Table 3, under the heading "Prevalence, %," the value for ASPD in Relatives should have read 8.79. The journal regrets the error.