Do Premorbid Predictors of Alcohol Dependence Also Predict the Failure to Recover From Alcoholism?*

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ABSTRACT. Objective: In a search for viable endophenotypes of alcoholism, this longitudinal study attempted to identify premorbid predictors of alcohol dependence that also predicted the course of alcoholism.

Method: The 202 male subjects who completed a 40-year follow-up were originally selected from a Danish birth cohort ($N = 9,182$). Two thirds of the subjects were high-risk biological sons of treated alcoholics. A large number of measures (361) were obtained at different periods before any subject had developed an alcohol-use disorder. At age 40, a psychiatrist provided mutually exclusive lifetime diagnoses of alcohol abuse or alcohol dependence that were characterized as currently active or currently in remission according to Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, course specifiers. **Results:** The majority of subjects with a diagnosis of alcohol abuse were in remission

at age 40 compared with those with a diagnosis of alcohol dependence (88% vs. 58%). Treatment did not predict remission. Fourteen of the 18 predictors of remission that also predicted dependence were submitted to an exploratory factor analysis (varimax). Two premorbid dimensions were identified: cognitive efficiency and early behavioral dyscontrol in childhood. Both factors predicted the failure to remit (low cognitive efficiency and high behavioral dyscontrol) even when lifetime alcoholism severity was controlled. **Conclusions:** This 4-decade study found a striking disconnect between measures that predicted alcohol dependence and measures that predicted remission from alcohol dependence. Reduced cognitive efficiency and increased behavioral dyscontrol may be basic to gaining a fuller understanding of the etiology of alcoholism. (*J. Stud. Alcohol Drugs*, 71, 685-694, 2010)

IN THE LAST 60 YEARS, prospective longitudinal studies have attempted to identify the premorbid antecedents of the alcohol-use disorders, especially alcohol dependence, by examining subjects before drinking problems began and following them into adulthood (Goodwin et al., 1994; Hill et al., 2000; Knop et al., 2003; Trim et al., 2010; Vaillant, 1995, 2003; Zucker, 2006). The number of premorbid research domains that have been investigated is quite large and range from genetic, family history, and developmental domains through personality, social, and behavioral domains, to cultural and social context domains. These longitudinal studies have produced lists of replicated risk factors that are thought to function as premorbid predictors or markers of alcoholism. Among the best established of these premorbid

risk factors are family history of alcoholism; male gender; behavioral deviance of all sorts in early childhood, especially that associated with impulsivity; unstable family environment; lower social class; high “innate” tolerance to the effects of alcohol; early age at onset of problem drinking; and peer pressure.

It is frequently assumed that risk factors known to increase the probability of developing an alcohol-use disorder are the same as those that interfere with or impede the recovery from alcoholic drinking. Despite the seemingly reasonable assumption that premorbid risk factors also predict the course of alcoholism, the empirical proof for its validity is lacking. Virtually no evidence exists to indicate that specific premorbid factors, operating before the initiation of problem drinking, are related to remission or the failure to stop drinking. Research focused on the correlates of remission has largely ignored the possible “hidden” long-term effects of premorbid influences on the success or failure to stop problematic drinking. Efforts to identify factors associated with remission from maladaptive drinking have focused almost exclusively on psychosocial and contextual variables that reflect the “social capital” accrued by an individual over time (Granfield and Cloud, 2001; Moos and Moos, 2003, 2006; Tucker, 2003). The focus on psychosocial and contextual influences as predictors of remission is puzzling because most measures of social capital such as family support, employment, or social networks are themselves directly affected by excessive alcohol consumption. The focus on

Received: October 2, 2009. Revision: March 10, 2010.

*This research was supported by National Institute on Alcohol Abuse and Alcoholism grants R01-03448, R01-08176, R21-AA13374, and K01-AA015933; Danish Medical Research Council grant 990 2952; Augustinus Foundation grant 01-203; Forsikring and Pension grant 1.0.1.8-012; and Eli and Egon Larsen Foundation grant 26670002. Parts of this study were presented to the 158th Annual Meeting of the American Psychiatric Association, Atlanta, GA, May 2005.

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psychosocial and contextual correlates of remission is also puzzling because identified predictors of remission from alcoholism account for relatively little of the outcome variance (Cunningham et al., 2000; Dawson et al., 2006; Klingemann, 2001; Moos and Moos, 2007). Lifetime alcoholism severity continues to serve as the strongest and most reliable predictor of the future drinking of an individual with an alcohol-use disorder (Moos and Moos, 2007).

Longitudinal studies have shown that the course of alcoholic drinking varies considerably among individuals who have the diagnosis of an alcohol-use disorder (Manzardo et al., 2008; Polich et al., 1981; Vaillant, 1995, 2003). The pronounced waxing and waning of maladaptive drinking over time by most individuals with an alcohol-use disorder is striking among those who receive treatment for their drinking problem as well as those who do not (Bischof et al., 2001; Cunningham et al., 2000; Klingemann, 2001; Moos and Moos, 2007; Sobell et al., 1996, 2000; Tucker, 2003; White, 2006). Contemporary research indicates that a substantial number of alcoholic drinkers manage to stop drinking or to stop problematic drinking on their own without assistance (Dawson et al., 2005, 2006; Klingemann, 2001; Moos and Moos, 2003, 2006; Russell et al., 2001; Walters, 2000). It is important to understand mechanisms associated with the long-term course of problem drinking. Such information is not only essential to the rational allocation of resources for treatment and prevention but is also important to the identification of etiological factors that directly influence the most virulent forms of alcoholic drinking.

This article hypothesizes that presently unidentified biological influences, present from birth and interacting with premorbid environmental factors, play a major role in the remission from alcoholic drinking. We assume that such unidentified factors exert their influence directly on the course of alcoholic drinking, independent of their effect on alcoholism severity. Among many chronic medical disorders, interacting genetic and premorbid psychosocial factors are known to affect both the manifestation of an illness as well as its course over time, regardless of treatment. Thus, obesity, partially determined by inheritance and influenced by myriad environmental factors, not only serves as a risk factor for diabetes but also predicts a poorer diabetic outcome, no matter what treatment is offered. The current study was designed to examine the hypothesis that variables that predict the development of alcoholic drinking are likely to predict the failure to recover from alcoholic drinking as well. We reasoned that premorbid measures that successfully predict *both* the development and course of the problem drinking would reflect powerful premorbid endophenotypes for alcoholism. Identification of endophenotypes, regarded as partially under genetic control, is generally regarded as a first step in guiding research toward a more complete understanding of the fundamental nature and etiology of complex diseases such as alcoholism (Gottesman and Gould, 2003).

The Danish Longitudinal Study of Alcoholism is a prospective, high-risk study that has focused on two groups of boys/men: high-risk sons of treated alcoholic fathers and low-risk sons of fathers who were never formally treated for alcoholism (Goodwin et al., 1994; Knop, 1985; Knop et al., 1985, 2003). The subjects were drawn from a large birth cohort that has been systematically studied for over 40 years. Initial studies were focused on premorbid differences between high-risk and low-risk subjects before any had developed an alcohol problem (Knop et al., 1985, 2003; Schulsinger et al., 1986). Later studies examined the extent to which premorbid high-risk and low-risk differences predicted an alcohol-use disorder. Approximately 30% of these high-risk/low-risk differences actually predicted subjects who would later develop alcohol dependence (Knop et al., 2007). In the current study, a three-step empirical strategy was used to search for endophenotypes of alcohol dependence. First, we identified from a diverse pool of premorbid measures, those measures that predicted lifetime alcohol dependence. Second, we determined which of the premorbid measures that predicted alcohol dependence also predicted its remission. Third, premorbid measures that predicted both alcohol dependence and its remission were submitted to a factor analysis. Any premorbid dimension emerging from the factor analysis was regarded as an especially strong representation of an endophenotype for alcoholic drinking.

Method

Subjects

A total of 202 subjects completed the 40-year follow-up phase of this longitudinal study that initially included 329 subjects. As noted in Figure 1, the original sample was selected from a large ($N = 9,182$) Copenhagen birth cohort formed to investigate the causes of birth defects and anomalies (Zachau-Christiansen, 1972; Zachau-Christiansen and Ross, 1975). Extensive information was gathered on each baby before birth, at birth, and 1 year later. When the subjects were approximately 16 years old, their fathers were searched in two Danish archival sources for a diagnosis of alcoholism: the Central Psychiatric Register (Byrne et al., 2005; Munk-Jørgensen and Mortensen, 1997) and the local Municipal Alcoholism Treatment Clinics operating in Copenhagen. Two hundred twenty-three high-risk sons of alcoholics were available for study. Data from matched pairs of high-risk sons were used to select 106 sons of non-alcoholic fathers, the low-risk group, in a 2 to 1 ratio. Sons were the focus of this longitudinal study because the lifetime prevalence of alcoholism was much lower among women in Denmark at the time. Information about the subjects was available from five different periods: perinatal phase, school-age phase, age 18-20 years, age 30 years, and age 40 years. A detailed description of the subject selection and

FIGURE 1. Study timeline for the Danish Longitudinal Study of Alcoholism. HR = high risk (sons of treated alcoholics); LR = low risk (matched sons of nonalcoholics). ^aTwenty-one of the original 329 subjects were deceased by the 40-year follow-up.

procedures used at the different phases of the study can be found elsewhere (Goodwin et al., 1994; Knop, 1985; Knop et al., 2003; Schulsinger et al., 1986).

By the 40-year follow-up, 21 of the original 329 subjects were dead (Knop et al., 2004). Risk status was not related to premature death. The 202 surviving subjects who participated in the 40-year follow-up represented two thirds of the original sample. The 2:1 ratio between high-risk and low-risk subjects was maintained, $\chi^2(1) = 0.50$, $p = .48$. The average age of the subjects who participated in the 40-year follow-up was 40.4 years ($SD = 0.81$); 69% were married or cohabiting; 13% were separated/widowed; and 84% were employed at the time of the interview. Approximately 76% of the subjects were classified in the lowest two social strata. The surviving 106 nonparticipants did not differ from the 202 participants according to age, risk status, family social class, or the level of education achieved at age 19. The amount of beer, wine, and distilled spirits consumed at age 19 did not distinguish 40-year nonparticipants from participants; the reported incidence of illegal acts, fighting, arguing, lost work, and traffic accidents when drinking also did not distinguish participants from nonparticipants. A search of both the Central Psychiatric Register and local alcoholism clinics at the 40-year follow-up indicated that an equal number of the surviving study nonparticipants (12%) and participants (7%) had ever been assigned an alcoholism diagnosis ($p = .16$).

Premorbid screening measures

A total of 361 measures were screened for their association with alcohol dependence. All but four of these measures

were collected *before* any subject had developed an alcohol-use disorder. Four of the “premorbid” measures collected at the 30- and/or 40-year follow-ups specifically referenced the subject’s childhood and were included among the premorbid measures after passing several validity checks. The premorbid screening measures included 45 measures from the perinatal phase; 87 measures from the early school-age phase; 176 variables from interviews completed by a physician, a social worker, and a psychologist at the late-adolescent follow-up phase; as well as 33 measures from a neuropsychological test battery and 15 from an alcohol challenge test also obtained at the late-adolescent follow-up. These premorbid measures were previously used to compare high-risk and low-risk subjects, the results of which have been reported elsewhere (Drejer et al., 1985; Knop, 1985; Pollock et al., 1983, 1986; Volavka et al., 1996).

Adult outcome measures

At both the 30-year and 40-year follow-ups, two structured interviews (the Psychosocial Interview [Knop et al., 2003] and the Psychiatric Diagnostic Interview–Revised [PDI-R; Othmer et al., 1989]) were administered by the psychiatrist interviewer, and several rating scales were completed by the subject and the interviewer.

The Psychosocial Interview is a 264-item, precoded, structured interview that examined family history of psychiatric disorder (including alcoholism), ratings of early childhood experiences, treatment for medical and psychiatric disorders, a thorough history of drinking and its sequelae, and current sociodemographic information (Knop et al.,

2003). The retrospective Childhood Deviance Scale reflects the adult subjects' self-ratings of 12 behaviors enacted during development to age 18, and contains internalizing and externalizing behavioral traits associated with hyperactivity, restlessness, aggression, shyness, withdrawal, and depression. The Childhood Deviance Scale correlated significantly with comparable items collected 10 or 20 years earlier, such as the Childhood Conduct Disorder Scale ($r = .56, p < .0001$) and the School Teacher Questionnaire Behavioral Summary Score ($r = .37, p < .0001$) (Knop et al., 2009). The Psychosocial Interview also collected extensive data about the quantity and frequency of the consumption of beer, wine, and distilled spirits in the recent past and included the 32-item Alcoholism Severity Scale used in other studies by our group (Penick et al., 1987; Powell et al., 1992) to evaluate the major symptoms of alcoholic drinking both in the past year and over the subject's lifetime.

The second interview administered at the 30-year follow-up was the PDI-R (Othmer, et al., 1989). At the 40-year follow-up, a later version of the Psychiatric Diagnostic Interview was administered (PDI-IV, Othmer et al., 2000). The PDI-IV is a descriptive, criterion-referenced, structured diagnostic interview that uses simply worded and extensively tested questions to systematically review 20 basic DSM-IV psychiatric syndromes (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; American Psychiatric Association, 1994) that include alcohol abuse and dependence. Age at onset as well as age at last problem for each positive syndrome is also recorded. For this study, all of the symptomatic alcoholism questions ($N = 26$) were asked of all subjects, an implementation that resulted in a dimensional lifetime alcoholism score as well as a categorical designation of alcohol abuse and alcohol dependence. The PDI-IV diagnosis of antisocial personality disorder requires multiple antisocial offenses before age 15 years, which is consistent with a childhood conduct disorder diagnosis. The diagnosis of antisocial personality disorder on the PDI was significantly associated with the Conduct Disorder Scale, which consisted of a list of antisocial activities reviewed when the subjects were in their late teens. The mean Conduct Disorder Scale score obtained in late adolescence for subjects later diagnosed with antisocial personality disorder was significantly higher than for subjects without antisocial personality disorder (8.5 vs. 4.2, $p < .0001$).

Procedure

If the subject agreed to participate in the study, written informed consent was obtained and the study psychiatrist administered a series of structured interviews, rating scales, and questionnaires, as previously described. The study was approved by both the Danish Scientific Ethics Research Committee and the institutional review board of the University of Kansas Medical Center.

When the clinical interviewer had completed the struc-

tured interviews and ratings, he formulated one or more DSM, Third Edition, Revised (DSM-III-R; American Psychiatric Association, 1987), lifetime diagnoses. The DSM-III-R diagnostic criteria were employed to maintain continuity with the 30-year follow-up that was completed before the DSM-IV was published (in 1994). The psychiatrist was free to provide up to six separate DSM-III-R diagnoses for each subject. If one or more of the diagnoses assigned to a subject was a substance-use disorder diagnosis, the psychiatrist interviewer then applied the DSM-III-R course specifier that defines "full remission." The interviewer was blind to the subjects' original risk status.

Alcohol-abuse/dependence diagnoses. The mutually exclusive DSM-III-R lifetime diagnoses of either alcohol abuse or alcohol dependence at age 40 served as the first major outcome variables. These diagnoses were provided by the study psychiatrist (J.K.) after he had completed the two clinically detailed, structured interviews.

Remission from alcohol abuse/dependence. The DSM-III-R course specifier for full remission was used by the study psychiatrist for all subjects who satisfied criteria for lifetime alcohol abuse or alcohol dependence. Full remission is defined in the DSM-III-R as a minimum of at least 6 months with "either no use of the substance, or some use of the substance and no symptoms of dependence" (American Psychiatric Association, 1987, p. 168). It stipulates no use of alcohol or no pathological use of alcohol during the previous 6-month period.

Data reduction and analyses

Information obtained at each phase of the study has been stored in an integrated SAS database (SAS Institute Inc., Cary, NC) that encompasses 28 different research protocols. The data-reduction strategy (a) eliminated the electrophysiological variables that have been reported elsewhere (Volavka et al., 1996) and (b) eliminated many perinatal and 19- to 20-year measures because of insufficient variance, exceptionally high intercorrelations, and excessive missing data. This winnowing process resulted in a total of 361 premorbid variables that represented all phases of the study and all study domains except electrophysiological. The 361 selected variables were subjected to two independent univariate comparisons in a sequential strategy. First, measures from all domains that significantly differentiated ($p < .05$) subjects who did and did not satisfy a DSM-III-R lifetime diagnosis of alcohol dependence by age 40 were identified. Second, those measures that distinguished alcohol dependence were then used to compare alcohol-dependent subjects who were or were not in remission at the 40-year follow-up. Any premorbid variable that did not predict the occurrence of lifetime alcohol dependence *and* also distinguish the remission status of the alcohol-dependent subjects was eliminated from further analyses, with one exception. An intelligence test (Borge Priens Prove) administered by

the Danish military draft board (Mortensen et al., 1989), obtained when the subjects signed up for this obligatory service in their late teens or early 20s, was also included in this final set of variables despite the fact that the military IQ did not significantly distinguish subjects who would become alcohol-dependent later in life ($p = .53$). The military IQ was included because risk was significantly associated with many measures in the neuropsychological test battery administered premorbidly (Drejer et al., 1985) and because general measures of intellectual functioning correlate strongly with a great number of social and behavioral outcomes (Batty et al., 2007; Gottfredson, 1998). Premorbid items that predicted both alcohol dependence and remission status were examined in a correlation matrix for redundancy and other features. A final list of 14 premorbid markers was entered into a principal component exploratory factor analysis.

All statistical analyses were performed using SAS Version 9.1.3. Chi-square tests were applied to categorical data and the general linear model procedure was used for continuous data. Factor analysis was performed using the principal component method of factor analysis with raw scores as input and with varimax rotation. After inspecting the resulting eigenvalues, a two-factor solution was imposed (NFACT = 2). Standardized factor scores were then calculated for each individual on each of the two factors. Logistic regression analysis was used to model the relationship between the two premorbid factor scores and a measure of alcoholism severity as explanatory variables to predict the probability of the failure to remit from alcohol dependence. Logistic regression was performed using PROC LOGISTIC (SAS Institute) with no sequential model specified.

Results

Alcohol abuse and alcohol dependence at age 40

Forty-two percent ($n = 85$) of the 202 men who completed the 40-year follow-up developed an alcohol-use disorder at some point in their lives. Sixteen percent of the sample ($n = 33$) developed alcohol abuse, and 26% ($n = 52$) developed alcohol dependence. On the 32-item Alcoholism Severity Scale, subjects with an alcohol-use disorder endorsed an average of 11.4 ($SD = 5.56$) lifetime alcoholism symptoms compared with subjects with no alcohol-use disorder, who endorsed an average of 2.4 ($SD = 1.04$) symptoms ($p < .0001$). High-risk subjects were significantly more likely than low-risk subjects to develop alcohol dependence (31% vs. 18%, $p < .03$). However, the development of alcohol abuse was not related to risk status (Knop et al., 2003).

Remission from alcohol abuse and dependence

As shown in Table 1, the majority of men with any lifetime alcohol-use disorder (69%) were in remission at

TABLE 1. Remission status at age 40 of Danish men with a lifetime DSM-III-R diagnosis of alcohol dependence ($n = 52$) or alcohol abuse ($n = 33$)

DSM-III-R diagnosis	In remission ^a		Nonremission		p^b
	n	%	n	%	
Alcohol abuse	29	88	4	12	.004
Alcohol dependence	30	58	22	42	
Alcohol abuse/dependence	59	69	26	31	

Notes: DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. ^aRemission is based on the DSM-III-R definition (p. 168). Full remission: "During the past 6 months, either no use of the substance, or use of the substance with no symptoms of dependence." The DSM-III-R designation of "partial remission" was not used because of the small number of subjects in this category. ^bSignificantly more of the subjects with alcohol abuse were in remission at the 40-year follow-up compared with those subjects given a lifetime diagnosis of alcohol dependence, $\chi^2(1) = 8.66, p < .004$.

the 40-year follow-up. The remission rate for subjects with alcohol abuse was 88%, which is significantly higher than the 58% remission rate for subjects diagnosed with alcohol dependence ($p < .004$).

Risk status was not associated with remission from either alcohol dependence or alcohol abuse (Knop et al., 2007). On the lifetime Alcoholism Severity Scale, subjects with alcohol abuse in remission did not differ from those not in remission (6.2 vs. 5.5, $p = .53$). In contrast, alcohol-dependent subjects in remission at the 40-year follow-up endorsed significantly fewer lifetime alcoholism symptoms on the Alcohol Severity Scale ($M = 12.8, SD = 4.15$) than currently active alcohol-dependent subjects ($M = 17.5, SD = 2.79, p < .0001$). The failure to remit from alcohol dependence, but not abuse, was associated with greater lifetime alcoholism severity. The reported duration of alcoholic drinking was more than twice as long for the nonremitted alcohol-dependent subjects than for remitted alcohol-dependent subjects ($M = 18.7$ years, $SD = 5.84$ vs. $M = 8.6$ years, $SD = 7.11, p < .0001$).

Among the 40-year follow-up subjects in this study who were assigned a lifetime diagnosis of alcohol abuse, the vast majority (97%) reported drinking some alcohol during the month before the follow-up interview. Alcohol-abuse subjects in remission did not differ from nonremitted alcohol-abuse subjects according to whether they drank any alcohol in the previous month ($p = .71$). However, the *amount* of pure alcohol consumed in the month before the 40-year follow-up interview did significantly distinguish the alcohol-abuse remitters ($M = 1.0$ g, $SD = 0.82$) from alcohol-abuse nonremitters ($M = 3.9$ g, $SD = 0.49, p < .0001$). Similarly, 87% of the 40-year follow-up subjects in the remitted alcohol-dependence group reported having at least one drink in the month before the follow-up interview compared with 91% of the subjects in the nonremitted alcohol-dependence group, a difference that was not significant ($p = .64$). Nevertheless, the *amount* of pure alcohol consumed in the month before follow-up was significantly higher ($p < .0001$) in the nonremitted alcohol-dependence group ($M = 4.9$ g, $SD =$

TABLE 2. Eighteen premorbid predictors of alcohol dependence that also predicted remission status at the 40-year follow-up ($n = 52$)

Premorbid measure	In remission <i>M (SD)</i> or % yes	Nonremission <i>M (SD)</i> or % yes	<i>p</i>
No. of mother's pregnancies	2.0 (1.13)	2.7 (1.62)	.08
One-year neurological scale, 0-18	0.17 (0.46)	1.0 (1.66)	.01
Rated too energetic by teacher, 1-4 ^a	2.5 (1.13)	3.4 (0.81)	.04
CNS abnormality identified by a school M.D. ^a	55%	26%	.06
"Other" medical problem by study M.D. ^a	9%	38%	.04
Housing problems in childhood	5%	24%	.07
Had a special teacher	0%	17%	.04
Saw a probation officer ^a	5%	24%	.06
Treated for a nervous problem	5%	25%	.07
Reports illegal acts when drinking, 1-3	0.19 (0.51)	1.06 (1.18)	.005
Clinician judgment irresponsibility	14%	44%	.04
Seven-item conduct disorder scale, 0-13	5.6 (2.58)	7.8 (3.39)	.03
WAIS Digit Span SS	10.4 (2.13)	8.1 (3.09)	.01
Serial 7's backwards, sec.	48.3 (19.76)	68.9 (40.34)	.05
Word fluency animals	19.19 (3.23)	16.5 (3.58)	.02
BPP Military IQ	98.9 (14.01)	90.4 (13.61)	.05
Adult rating of childhood deviance, 0-4	1.3 (0.3)	1.5 (0.3)	.03
Adult ASP/conduct disorder	34%	70%	.01

Notes: **Bold** indicates statistical significance at $p < .10$. CNS = central nervous system; M.D. = medical doctor; WAIS = Wechsler Adult Intelligence Scale; SS = scaled score; sec. = second; BPP = Borge Priens Prode, Danish Military IQ; ASP = antisocial personality. ^aItems eliminated from the factor analysis.

2.97) than in the remitted alcohol-dependence group ($M = 1.1$ g, $SD = 1.24$).

The mean duration of abstinence or nonproblem drinking among the alcohol-dependent subjects in remission was 11.1 years ($SD = 6.95$); the median remission duration was 11.6 years. Fifty-nine percent of the alcohol-dependent subjects in remission reported no problem drinking for 10 or more years, and another 21% reported no problem drinking for 5-9 years. More than 86% of the alcohol-dependent subjects in remission reported no symptoms associated with excessive drinking during the 2-year period preceding the 40-year follow-up.

Was treatment for alcoholism related to who would and would not remit?

Only 12% of the subjects with a lifetime diagnosis of alcohol abuse received some form of treatment for their drinking; all of these subjects were in remission at the 40-year follow-up. In contrast, 62% of the alcohol-dependent subjects reported receiving some kind of treatment for their drinking; 47% of the remitted alcohol-dependent subjects received treatment for their drinking compared with 82% of the nonremitted subjects, $\chi^2(1) = 8.7$, $p < .003$. These results indicate that treatment for a drinking problem was more strongly associated with the failure to remit.

Premorbid measures that predicted both alcohol dependence and remission

Table 2 lists 18 measures of the 361 tested that were significantly related ($p < .10$) to both alcohol dependence

and the failure to recover. Most notable is that only 17% of the 109 premorbid measures that were associated with the development of alcohol dependence also predicted its course by age 40. The measures that were associated with both dependence and its course were drawn from all phases of the study. Of the 18 variables associated with both the onset and remission of alcohol dependence, 4 were eliminated for various technical reasons, such as redundancy and a smaller n .

The remaining 14 variables were submitted to an exploratory principal component factor analysis. The Scree Test identified three factors with eigenvalues greater than 1.0 that accounted for 88% of the variance. The smallest eigenvalue at 1.2 was considered quite weak and not interpretable. The varimax rotation was restricted to two factors ($NFACT = 2$) that accounted for 73% of the explained variance. Table 3 presents the results of the factor analysis of premorbid items associated with both the development of alcohol dependence and the failure to recover by age 40. The first and largest premorbid factor, accounting for 49% of the variance, appeared strongly associated with behavioral dyscontrol, pathological disinhibition, or antisocial tendencies reported by the subjects and their teachers in their late teens.

The second premorbid factor, accounting for 24% of the variance, appeared to reflect cognitive efficiency, indicative of the ability to concentrate and focus normally. The correlation between Behavioral Dyscontrol (Factor I) and Intellectual/Cognitive Efficiency (Factor II) was $-.28$, indicating a moderate negative overlap between the two identified dimensions (i.e., greater behavioral dyscontrol was associated with poorer cognitive efficiency). The results of the factor analysis provided the opportunity to construct two premorbid standardized factor scores for each alcohol-dependent

TABLE 3. Varimax factor solution of premorbid measures that distinguished both alcohol dependence and its remission after 40 years ($n = 202$)^a

Premorbid measures	Factor I Behavioral dyscontrol	Factor II Cognitive efficiency
Conduct Disorder Scale (19/20 year)	.752	—
Rating of child deviance (30/40 year)	.681	—
Antisocial personality disorder	.644	—
Treated for nervous problem (19/20 year)	.603	—
Teacher rating irresponsible	.592	—
Illegal acts when drunk (19/20 year)	.547	—
Saw a special teacher (19/20 year)	.372	—
WAIS Digit Span (19/20 year)	—	.821
Military IQ (≥ 20 year)	—	.702
Word fluency (19/20 year)	—	—
Housing problem (19/20 year)	—	—
1-year neurological (perinatal) ^b	—	-.409
No. of prior pregnancies (perinatal) ^b	—	-.451
Serial 7s backwards (19/20 year) ^b	—	-.836
Eigenvalue	3.60	1.75
Variance, %	49%	24%

Notes: Values less than 0.3 not shown. ^aNFACT = 2; ^bhigher score = poorer performance.

participant. As expected, alcohol-dependent subjects who failed to recover obtained significantly higher factor scores on the premorbid behavioral dyscontrol scale ($p < .01$) and significantly lower factor scores on the premorbid cognitive efficiency scale ($p < .01$) than remitted subjects (see Table 4).

The final question addressed by these data was the extent to which the two identified premorbid factor dimensions predicted the failure to remit from alcohol dependence even when lifetime alcoholism severity was statistically controlled. Table 4 presents the results of a logistic regression that examined the extent to which the failure to recover from alcohol dependence was predicted by the Behavioral Dyscontrol Scale and the Cognitive Efficiency Scale independent of lifetime alcoholism severity. The regression model was significant, likelihood ratio $\chi^2(3) = 32.55$, $p < .0001$, indicating good predictability. As noted, the two, factor-analytically derived premorbid scores independently predicted the failure to remit, even when lifetime alcoholism severity was controlled. Each additional point on the Behavioral Dyscontrol Factor Scale was associated with a 3.1 times increase in the likelihood of *not* recovering from alcohol dependence. In contrast, each additional point on the Cognitive Efficiency

Factor Scale was associated with a small decrease in the likelihood of not recovering from alcohol dependence.

Discussion

This 40-year, high-risk longitudinal study adopted a systematic, three-step strategy to discover possible endophenotypes of alcohol dependence from a very large database that extended across the lives of individual subjects. We found that the majority of the premorbid measures that predicted the development of alcohol dependence failed to predict the course of alcoholic drinking once it began. A total of 361 premorbid variables were selected for testing from multiple domains, provided by multiple observers, beginning at birth. We expected that a majority of the premorbid measures that predicted the development of alcohol dependence would also correlate with the failure to recover. We found, in fact, that premorbid measures associated with the development of alcohol dependence infrequently predicted recovery from alcoholic drinking by age 40. Treatment for a drinking problem did not predict which subjects would recover from alcohol dependence; instead, more frequent treatment was significantly related to nonremission. Individuals assigned

TABLE 4. Regression of lifetime alcoholism severity and two premorbid factor scores (behavioral dyscontrol and cognitive efficiency) on failure to remit from alcohol dependence at age 40 ($n = 52$)^a

Variable	Remitted <i>M</i> (<i>SD</i>)	Nonremitted <i>M</i> (<i>SD</i>)	Wald χ^2	<i>p</i>	OR	[95% CI]
Lifetime alcoholism severity ^b	12.8 (4.1)	17.5 (2.8)***	6.58	.01	1.4	[1.1, 1.8]
Behavioral dyscontrol (FACT I) ^c	-0.38 (.72)	0.52 (1.0)**	5.82	.02	3.1	[1.2, 7.6]
Cognitive efficiency (FACT II) ^c	0.35 (.63)	-0.48 (1.2)**	5.18	.02	0.27	[0.1, 0.8]

Model likelihood ratio $\chi^2(3) = 32.55$, $p < .0001$

Notes: OR = odds ratio; CI = confidence interval. ^aRaw scores used as input; ^brange = 0-32, higher scores indicate greater severity; ^cstandardized factor scores ($M = 0.0$, $SD = 1.0$).

Analysis of variance: ** $p < .01$; *** $p < .001$.

the diagnosis of alcohol abuse were more likely to be in remission at age 40 than those assigned a diagnosis of alcohol dependence, not an unexpected finding (Vaillant, 1995). The majority of subjects in both the alcohol-abuse and alcohol-dependence groups reported drinking some alcohol in the month before the 40-year follow-up, regardless of remission status. Nevertheless, subjects in remission drank significantly less alcohol in the prior month than subjects who continued to drink with problems. This was true for both alcohol-abusing and alcohol-dependent subjects. Duration of problem drinking and lifetime alcoholism severity was significantly greater for alcohol-dependent subjects who failed to remit. Alcoholism severity was not related to remission among the alcohol-abuse subjects.

Regarded as "proxies" of putative endophenotypes for alcoholism, the 18 premorbid measures that predicted both alcohol dependence and its continuation were quite heterogeneous with respect to the period during which they were collected and the measurement domain they represented. The premorbid predictors of the failure to recover included a virus in the mother during her pregnancy; the number of previous pregnancies (more in non-remitted subjects); housing conditions around birth (poorer in nonremitted subjects); performances on some tests of cognition (lower in nonremitted subjects); and a large number of impulsive, deviant social behaviors occurring in multiple settings (greater deviant behavior in non-remitted subjects). A factor analysis of 14 premorbid predictors of both alcohol dependence and its remission revealed two major dimensions: One reflected cognitive efficiency and the other reflected behavioral dyscontrol or behavioral disinhibition. Alcohol-dependent subjects who failed to achieve remission by age 40 obtained lower premorbid factor scores on the Cognitive Efficiency Scale and higher premorbid factor scores on the Behavioral Dyscontrol Scale. The relationship between the two premorbid factor scales and failure to recover was maintained even when lifetime alcoholism severity was statistically controlled. The premorbid Behavioral Dyscontrol Scale was most strongly predictive of the failure to remit by age 40. Boys from larger families with fewer financial resources who were most restless, impulsive, likely to break rules, and unhappy with themselves had the greatest difficulty recovering from alcohol dependence once it began, even when the severity of their alcoholic drinking was taken into account. The association between behavioral dyscontrol in childhood and the development of alcohol dependence has been reported frequently in both retrospective and prospective studies (De Wit, 2008; Zucker, et al., 2009) beginning as early as 1966 with Lee Robins's classic *Deviant Children Grown Up*. The items loading on the Behavioral Dyscontrol Factor closely resemble the behavioral characteristics associated with Type A alcoholism described by Babor et al. (1992), Type II alcoholism identified by Cloninger et al. (1996), and one of the four alcoholisms proposed by Zucker (1987).

The relationship between certain neuropsychological test performances and remission was not surprising. More than a decade ago, Gottfredson (1998) concluded that "general intelligence" played a major role in how individuals recover from any long-lasting tragedy or affliction, whether a medical illness or personal setback. Jessor et al. (1991) proposed a general theory of deviance that included cognitive deficits. Alcohol-dependent subjects with a history of antisocial traits and cognitive difficulties were less likely to recover "naturally."

A question these data cannot address is this: How specific are premorbid characteristics of cognitive efficiency and increased behavioral dyscontrol to recovery from alcoholism? Premorbid cognitive limitations and poor behavioral control may predict the failure to recover from most, if not all, psychiatric disorders, not just alcoholism. Nevertheless, that reduced cognitive efficiency and increased behavioral dyscontrol predicted *both* the manifestation of alcohol dependence as well as its long-term course suggests that they are likely to play a crucial role in understanding the causes of this disorder and discovering more effective forms of treatments. Genes and environmental influences that are causally linked to poor behavioral control and reduced cognitive efficiency in childhood are likely to be directly related to the development of alcoholism and its course over time. Behavioral disinhibition and cognitive inefficiency would seem to function as common final pathways to the manifestation of the most malignant form of alcoholism, at least in boys.

One of the most interesting challenges presented by our findings is why so many of the premorbid measures that successfully predicted alcohol dependence failed to predict remission status. We appreciate George Vaillant's summary of his 60-year study of alcoholic drinkers that nicely mirrors the results of this study. Vaillant proposed: "The skills it takes to fall into a hole are very different from the skills that it takes to climb out" (G.E. Vaillant, personal communication, Autumn, 2004). The disconnect between premorbid predictors of alcohol dependence and premorbid predictors of the failure to remit may be simply because the processes that "turn on" alcoholism are quite different from the processes that turn it off. Genetic or epigenetic factors may be more influential to the development of alcohol dependence, whereas psychosocial and environmental influences may indeed be more important to the recovery from alcohol dependence, whether or not any formal treatment is involved. More studies are needed to pin down the role of premorbid factors in the course of alcoholic drinking.

The strengths of this study include the long duration of follow-up, the inclusion of perinatal measures not commonly available to longitudinal investigations, and the cultural and biological homogeneity of the subjects in the sample. The two major limitations of this study are that it (a) deals only with men and (b) contains a relatively small number of

subjects in the two remission groups. An increase in power could have resulted in the selection of a different set of items that predict both alcohol dependence and its failure to remit. However, we doubt that the basic conclusions of the study would differ if the number of subjects in the remitted and nonremitted groups was increased. The sustained consistency and direction of the results of the study were remarkable. Although not always reaching statistical significance, in more than 97% of the premorbid item comparisons, those subjects who would become alcohol dependent were found in the least favorable or most disadvantaged category, clearly not a chance finding. Moreover, of the 18 measures found to distinguish those subjects who would become alcohol dependent and fail to remit, 17 indicated greater deviance or disadvantage for those who would not recover. For these reasons, we believe that the two identified premorbid dimensions are likely to reflect true endophenotypes that serve as important precursors to the development of and the recovery from alcoholism. We suggest that these data, when combined with findings from other longitudinal studies of alcoholism, support the hypothesis that traits associated with poor behavioral control and reduced cognitive efficiency represent proxies or markers of alcoholism (Dick and Agrawl, 2008; Mayfield, et al., 2008). These suggestions mirror modern theorizing about the neurobiology of addiction (Fillmore, 2003; Zahr and Sullivan, 2008). Contemporary neurobiological theories of substance misuse implicate unspecified deficits in the dopamine reward system and the inhibitory control system of the brain involving cortico-basal ganglia-thalamocortical pathways (Goldstein and Volkow, 2002; Koob and LeMoal, 2006). Such an expansive brain system, incorporating both cortical and subcortical structures, would suggest that alcoholic drinking and its course are related to an underlying biology associated with early deficiencies in cognition and behavioral control.

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