Childhood ADHD and Conduct Disorder as Independent Predictors of Male Alcohol Dependence at Age 40*

JOACHIM KNOP, M.D.,[†] ELIZABETH C. PENICK, PH.D.,[†] ELIZABETH J. NICKEL, M.A.,[†] ERIK L. MORTENSEN, CAND. PSYCH.,
MARGARET A. SULLIVAN, PH.D.,[†] SYED MURTAZA, M.D.,[†] PER JENSEN, M.D., ANN M. MANZARDO, PH.D.,[†]
AND WILLIAM F. GABRIELLI, JR., M.D., PH.D.[†]

Institute of Preventive Medicine, Center for Health and Society, Copenhagen University Hospital, Oster Sogade 18, 1 floor, DK-1357 Copenhagen K, Denmark

ABSTRACT. Objective: The Danish Longitudinal Study on Alcoholism was designed to identify antecedent predictors of adult male alcoholism. The influence of premorbid behaviors consistent with childhood conduct disorder (CD) and attention-deficit/hyperactivity disorder (ADHD) on the development of alcohol misuse was examined. **Method:** Subjects were selected from a Danish birth cohort (9,125), which included 223 sons of alcoholic fathers (high risk) and 106 matched sons of nonalcoholic fathers (low risk). These subjects have been studied systematically over the past 40 years. They were evaluated in their teens ($n = 238$), later as adults at age 30 ($n = 241$), and more recently at age 40 ($n = 202$). At 19-year/20-year follow-ups, an ADHD scale was derived from teacher ratings and a CD scale was derived from a social worker interview. At 30-year and 40-year follow-ups, a psychiatrist used structured interviews

and criteria from the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, to quantify lifetime alcoholism severity and to diagnose alcohol-use disorder. Of the original subjects, 110 had complete data for the two childhood measures and the adult alcoholism outcomes. **Results:** In this smaller subsample, paternal risk did not predict adult alcohol dependence. Subjects who were above a median split on both the ADHD and the CD scales were more than six times more likely to develop alcohol dependence than subjects who scored below the median on both. Although the two childhood measures were correlated, a multiple regression showed that each independently predicted a measure of lifetime alcoholism severity. **Conclusions:** ADHD comorbid with CD was the strongest predictor of later alcohol dependence. (*J. Stud. Alcohol Drugs* 70: 169-177, 2009)

THE Danish Longitudinal Study on Alcoholism (Goodwin et al., 1994) has examined two groups of males for 40 years: (1) high-risk sons of fathers diagnosed and treated for alcoholism and (2) low-risk sons of fathers with no official record of being treated for alcoholism. The high-risk research paradigm was adopted because evidence from family, twin, and adoption studies indicates that biological sons of alcoholic fathers have a significantly increased risk of developing alcoholism themselves, even when father and son are raised apart (Goodwin et al., 1973). The high-risk paradigm provided an opportunity to identify premorbid antecedent influences possibly responsible for the appearance, course,

and remission of alcoholism over the lifetime of the subjects. Information gathered about the subjects begins at birth and extends until age 40 (Knop et al., 1984, 2003, 2004, 2007). A major focus of the initial phase of this longitudinal study singled out behavioral signs of maladjustment in childhood as potential markers for problem drinking in adulthood (Knop et al., 1989; Pollock et al., 1990). When the subjects were approximately ages 15 to 17, school teachers rated the high-risk male teens as showing more inattentive, impulsive, and restless classroom behaviors than low-risk subjects (Knop et al., 1985). In addition, when directly asked, high-risk teens reported more antisocial acts than low-risk teens (Knop et al., 2003). Such observations have been reported by others, especially for boys (Masten et al., 2008). Investigators who have compared children of alcoholic and nonalcoholic parents typically find more impulsivity and emotional deregulation among the offspring of alcoholics (Sher, 1991; Zucker et al., 2008). These differences between high-risk and low-risk offspring have been noted even at very early ages. Such differences, beginning well before the onset of alcoholism, suggest that genetically predisposed subjects are more likely to demonstrate a pattern of maladjustment similar to that seen among children diagnosed with conduct disorder (CD) and attention-deficit/hyperactivity disorder (ADHD). Thus, behavioral deregulation or neurobehavioral disinhibition (Tarter et al., 2003) may underlie the manifestation of both childhood disorders and function as a more powerful endophenotype than either of the two disorders separately.

Received: May 29, 2008. Revision: September 15, 2008.

*This research was supported by Danish Medical Research Council grant 990 2952; Augustinus Foundation grant 01-203; Forsikring and Pension grant 1.0.1.8-012; Eli and Egon Larsen Foundation grant 26670002; and National Institute on Alcohol Abuse and Alcoholism grants R01-03448, R01-08176, R21-AA13374, and K01AA015935-01A2. Portions of the results in this article were presented at the poster session of the annual meetings of the American Psychiatric Association in 1995 by Margaret Sullivan and in 2005 by Syed Murtaza.

[†]Correspondence may be sent to Joachim Knop at the above address or via email at: jk@ipm.regionh.dk. Elizabeth C. Penick, Elizabeth J. Nickel, Margaret A. Sullivan, Ann M. Manzardo, and William F. Gabrielli, Jr., are with the Department of Psychiatry and Behavioral Sciences, University of Kansas Medical Center, Kansas City, KS. Syed Murtaza is with the Counseling Center, Manassas, VA.

A large body of evidence, both retrospective and prospective, suggests that the development of alcoholic drinking is often preceded by problematic behaviors associated with either or both of these two "externalizing" childhood disorders. CD, especially, has long been considered a risk factor for the development of substance-use disorders (Bukstein et al., 1989; Flory and Lynam, 2003; Forrest, 1994; Harford and Muthén, 2000; Hesselbrock et al., 1985; Robins and Regier, 1991; Schuckit et al., 2008; Tarter et al., 1985). For example, increasing use of alcohol over a 6-year period was predicted by the presence of CD in a prospective study of adolescent boys by White et al. (2001). Using data collected from a large collaborative study on 54 alcohol-dependent adolescents, Kuperman et al. (2001) found that—among disruptive behavioral diagnoses—CD, in particular, led to the use of substances that predicted alcohol dependence. In our 30-year follow-up of subjects in the birth cohort featured in this study, we found that boys who would develop alcohol dependence later in life reported significantly more antisocial acts than those who would not develop alcohol dependence (Knop et al., 2003). In a recent review of antisocial behavior, Taylor et al. (2006) conclude that, after antisocial personality disorder (ASPD), the diagnosis of childhood CD most strongly predicted substance-use disorder.

The results of studies focused on ADHD as a precursor to substance-use disorders are more variable (Flory and Lynam, 2003). Many early studies indicated a relationship between minimal brain dysfunction/childhood hyperactivity and later alcoholism (Biederman et al., 1995; Cadoret et al., 1980; Kessler et al., 2006; Tarter et al., 1977, 1985; Wilens et al., 1997). Mannuzza et al. (1993, 1998), in a 17-year prospective study of the adult psychiatric outcomes of hyperactive boys, reported that a continuation of ADHD symptoms into adulthood was associated both with the development of ASPD and a substance-use disorder, especially those substance-use disorders that involved illicit drugs. Murphy and Barkley (1996) compared adults diagnosed with and without ADHD in childhood and found higher rates of socially disruptive behaviors and substance abuse/dependence among the ADHD group. In an 8-year follow-up, Molina et al. (2007) studied adolescents and young adults diagnosed in childhood with ADHD and compared them with an age-matched control group. They reported age-specific results. Heavy drinking and alcoholism symptoms were elevated among ADHD subjects ages 15 to 17, compared with controls; ADHD plus CD subjects obtained the highest levels of alcoholism symptoms. Among young adults (ages 18-25), Molina et al. found that only ADHD subjects who were also diagnosed with ASPD showed significantly more heavy drinking and alcoholism symptoms than age-matched controls and probands without ASPD. Additional studies suggest that, when ADHD is not coupled with CD, ADHD alone is typically not predictive of later substance abuse/dependence (Disney et al., 1999; Ferguson et al., 1993). In a recent pro-

spective study of externalizing childhood disorders and adult alcoholism, Schuckit et al. (2008) concluded that CD was a strong predictor of substance-use problems, whereas ADHD alone was not significantly related. However, his sample of ADHD and CD subjects was relatively small. A comprehensive review of the relationships between ADHD, CD, and substance abuse by Flory and Lynam (2003) concluded that ADHD seemed to interact with CD in some manner to produce the highest risk for substance abuse than either alone.

At present, the *relative* contribution of CD and ADHD to the prediction of later alcohol abuse/dependence is not clear. CD is now regarded as a potent predictor of substance-use disorder later in life. The contribution of ADHD as a predictor, in contrast, is less clear, possibly because both ADHD and CD are often seen in the same child. Some studies report a significant association between ADHD in childhood and alcoholism later in life, even when CD is controlled. Other studies fail to find a significant relationship between childhood ADHD alone and alcoholism. The current study attempted to tease apart the relative contribution of the two childhood disorders in predicting the development of an alcohol-use disorder later in life using an approximation of the ADHD and CD diagnoses. The study was designed to evaluate the presence of ADHD and CD, both alone and in combination, on the development of alcoholism by age 40 in sons of alcoholic and nonalcoholic fathers. If, in fact, both childhood disorders predict adult alcoholism equally well, that result would strongly support the likelihood of a broad, underlying trait reflective of behavioral dysregulation. This trait could be regarded as a potentially powerful endophenotype for alcoholism. If, however, each disorder contributes uniquely to the development of adult alcoholism, then something more than a single trait is probably involved.

Method

Original sample

Subjects were selected from a large population-based cohort of babies born in the Department of Obstetrics at Rigshospitalet in Copenhagen, from October 1959 to December 1961. The birth cohort included 9,125 consecutive deliveries. All living babies were part of an extensive perinatal study focused on pregnancy and birth complications (Villumsen, 1970; Zachau-Christiansen and Ross, 1975). Data collection included measures obtained during pregnancy, delivery, at age 5 days, and at age 1 year. The birth records identified 8,440 biological fathers. When the subjects were approximately age 17, all of the fathers were searched in (1) the Danish Psychiatric Register, where information is stored for all admissions to a Danish psychiatric treatment facility (Munk-Jørgensen and Mortensen, 1997) and (2) in the files of the Municipal Alcohol Clinics in Copenhagen (Becker, 2004). From these two sources, 448 biological fathers were identified as having been treated for alcoholism at some point in their lives. Their

255 sons became eligible as subjects for the high-risk group. Of these high-risk boys, 223 were available for the study (32 were excluded because of perinatal death or family emigration). For every two high-risk boys, a single control subject was selected from the remaining pool whose fathers were not treated for alcoholism ($n = 106$). They were matched to the high-risk group according to age, mother's age, parity number, father's socioeconomic status, and their parents' marital status. Daughters were not included in this prospective study because the lifetime prevalence of female alcoholism at that time was so much lower than that for males. More details of the sample selection and procedures can be found in other publications (Knop et al., 1985, 1989).

Study follow-ups

At age 19-20 years, 204 subjects were interviewed at either the subject's home or at the Institute for Preventive Medicine. They were administered structured interviews by a psychologist and a social worker, as well as many other procedures. Also included was an 85-item School Teacher Questionnaire (Knop et al., 1985) completed by the subjects' primary teacher ($n = 144$; high risk = 95, low risk = 49). None of the subjects in their late teens were categorized by investigators as having an alcohol-use disorder (Knop et al., 1985; Schulsinger et al., 1986). Moreover, the alcohol consumption pattern of the subjects in their late teens resembled that of the general Danish male population in 1979 of the same age (Vilstrup and Nielsen, 1979).

When subjects were approximately age 30, they completed a series of clinical interviews and psychometric tests. Instruments used at 30 years were almost identical to those used in the 40-year follow-up 10 years later. Information about the 30-year and 40-year follow-ups are described in greater detail elsewhere (Goodwin et al., 1994; Knop et al., 2003).

A total of 241 subjects of the original 329 (73%) participated in the 30-year follow-up, and 202 subjects of the original sample (61%) participated in the 40-year follow-up (mean [SD] age = 40.3 [0.80] years). The initial 2:1 ratio between high-risk to low-risk subjects was maintained at both follow-ups; participation in 30-year and 40-year follow-ups was not associated with risk status. Twenty-one subjects had died by the time the 40-year follow-up was completed (Knop et al., 2004).

The present study used two drinking outcome measures obtained at either the 30-year or 40-year follow-ups. Two hundred sixty of the original 329 subjects (79%) completed either one or both of the 30-year and 40-year follow-ups. Information for the three premorbid predictors—(1) risk status, (2) childhood ADHD, and (3) childhood CD—and the two alcoholism-outcome measures was available on only 110 subjects, largely because completed School Teacher Questionnaires were obtained for less than half of the origi-

nal sample. The initial 2:1 ratio of high-risk to low-risk subjects was again maintained in this smaller subset (low-risk subjects = 37 [34%] vs high-risk subjects = 73 [66%]). No major differences were found between the 110 subjects in this study with a School Teacher Questionnaire and the other participants in 19-year/20-year follow-ups without a School Teacher Questionnaire (e.g., education status, mother's marital status, or any psychiatric treatment for the subject or his parents).

Procedure, instruments, and data sources

Subjects were invited to participate in all phases of the study by a letter that included a description of the research procedures and approval from the Danish Ethical Research Committee. The letter requested permission from the subjects for their participation in the study.

Premorbid measures

Childhood ADHD Scale. This instrument was based on teacher report: The School Teacher Questionnaire contains 85 items designed to represent behavioral, emotional, and educational traits observed in the classroom (Baker and Mednick, 1984). Each trait or item was rated by the teacher on a 4-point scale that ranged from definitely present to definitely not present. This questionnaire was sent to the primary teacher of each subject in the original study when the participants were approximately age 16. The teachers' responses were used to create the childhood ADHD Scale. The School Teacher Questionnaire reflected classroom behaviors and achievement when the subjects were approximately middle-school age. To construct the childhood ADHD Scale, the content of the 85-item School Teacher Questionnaire was first reviewed by a child psychologist (M.A.S.; Sullivan et al., 1999), who selected 22 items reflective of ADHD as defined in the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R; American Psychiatric Association, 1987). These rationally selected, criterion-based items were listed on a form and given to four board-certified child psychiatrists at the Kansas University Medical Center who were asked to rate each item on a scale that ranged from 1 = least characteristic of ADHD to 5 = most characteristic of ADHD. The final items selected for the childhood ADHD Scale were all assigned ratings of 4 or 5 by *all* four child psychiatrists. This procedure resulted in 12 consensually agreed-on items with a Cronbach's $\alpha = .92$. The childhood ADHD Scale items included the following 12 items: (1) has difficulty concentrating on cognitive tasks, (2) performs schoolwork carelessly, (3) has a poor attention span, (4) produces sloppy work products, (5) needs structure in learning situations, (6) cannot work on one activity very long, (7) is easily distracted, (8) talks out before ideas are formed, (9) acts impulsively, (10) fidgets and moves around in seat, (11) is energetic, and (12) gives up easily on problems.

One hundred ten subjects who participated in either 30-year or 40-year follow-ups had a derived childhood ADHD Scale total score that ranged from 12 to 48 (mean = 27.0 [9.87]). The childhood ADHD Scale was significantly predictive of the Conners Adult ADHD Rating Scales (CAARS; Conners et al., 1999) given at age 40, indicating strong predictive validity ($r = .30, p < .01$ for the CAARS ADHD Index).

Childhood Conduct Disorder Scale. This scale was based on information obtained by the study social worker at the 19-year/20-year follow-ups. When the subjects were first interviewed in their late teens, several questions were focused on antisocial activities consistent with the symptomatic criteria used to make a diagnosis of CD in the DSM-III-R. These items were selected to represent the premorbid Conduct Disorder Scale. The items and the scoring included the following: any contact with juvenile authorities (coded 0 = no, 1 = yes), any contact with juvenile probation officer (0 = no, 1 = yes), any trouble with school teachers and authorities (0 = never, 1 = occasionally, 2 = often), any contact with police (0 = never, 1 = once, 2 = twice, 3 = ≥ 3 times), ever detained after school (0 = never, 1 = occasionally, 2 = often), ever truant from school (0 = never, 1 = occasionally, 2 = often), and ever hit someone in a fight (0 = never, 1 = once, 2 = often).

The total scores of the derived childhood Conduct Disorder Scale ranged from 0 to 13. The mean total score for all 200 subjects interviewed as a teen was 4.8 (3.11); the median was 3.8. Cronbach's α was calculated at .69, reflecting adequate internal consistency. The total score on the childhood Conduct Disorder Scale was significantly correlated with the DSM-III-R diagnosis of ASPD on the structured diagnostic interview (Psychiatric Diagnostic Interview; PDI) at the 30-year/40-year follow-ups ($r = .46, p < .0001$). The derived childhood ADHD Scale and the derived childhood Conduct Disorder Scale were significantly correlated with each other, as one would expect ($r = .36, p < .0001$).

Drinking outcome measures obtained at age 30 or 40

The lifetime Alcoholism Severity Scale (mean = 4.0 [4.09], range: 0-26) is based on the alcoholism module of the PDI (Othmer et al., 1989, 2000). The PDI is a structured, multidimensional, criterion-referenced diagnostic interview that was designed to assess the lifetime prevalence of 18 syndromes, including alcohol abuse/dependence, ADHD, and ASPD. Its validity and reliability are well documented (Powell et al., 1985; Weller et al., 1985). Two different versions of the PDI were used in this study. At the 30-year follow-up, the PDI-R, based on DSM-III-R criteria, was administered. At the 40-year follow-up examination, the PDI-IV (Othmer et al., 2000)—based on DSM-IV (American Psychiatric Association, 1994) criteria—was used. Only items common to both editions of the PDI were used to generate the 26-item, lifetime Alcoholism Severity Scale that reviews all of the

major clinical characteristics and sequelae of alcohol abuse/dependence. This continuous measure of lifetime alcoholism severity was used as one of the two drinking outcome measures. The scale has been used in several studies; its reliability and validity are good to excellent.

DSM-III-R diagnosis of alcohol abuse/dependence was based on the judgment of a senior psychiatrist (J.K.). After the psychiatrist interviewer completed the structured interviews, he recorded up to six lifetime DSM-III-R diagnoses to characterize the psychiatric history of the subjects. The DSM-III-R criteria were used at both 30-year and 40-year follow-ups to ensure diagnostic consistency. The presence of lifetime alcohol abuse or alcohol dependence was recorded for each subject who participated in the 30-year or 40-year follow-up. Any diagnosis of DSM-III-R alcohol dependence served as the second of two drinking outcome measures. The correlation between the lifetime Alcoholism Severity Scale score and the DSM-III-R diagnosis of alcohol dependence was $r = .85, p < .0001$ (Knop et al., 2003).

Statistical analyses

Chi-square tests were used to analyze differences in proportion between high-risk and low-risk groups and to compute relative risk ratios with confidence intervals. The relative risk ratios indicate the incidence of adult alcohol dependence in subjects with either childhood risk factor, compared with subjects without the risk factor. The presence of each risk factor was represented by high scores above the median on each scale. Conversely, the absence of the risk factor was represented by scores below the median on each scale. The GLM (General Linear Model) procedure was used to compare means for continuous data. A standard multiple regression was performed to determine the size of the overall relationship between risk status, childhood ADHD, and childhood CD in predicting the Alcoholism Severity Scale Score (R^2) and to determine how much of the relationship is contributed uniquely by each predictor (sr^2). All statistical procedures were performed using SAS, Version 9.1.3 (SAS Institute, Inc., Cary, NC).

Results

Risk status

In the full follow-up study, father's alcoholism, as indicated by treatment history in archival data, significantly predicted alcohol dependence in their sons years later (high risk = 31% vs low risk = 16%; $p < .03$). However, as shown in Table 1 for this smaller subsample of 110 subjects, paternal alcoholism history was not significantly associated with lifetime alcohol dependence (high risk = 26% vs low risk = 16%; $p = .25$).

TABLE 1. Predictive relationships between risk, childhood attention-deficit/hyperactivity disorder (ADHD) and childhood conduct disorder on lifetime alcoholism severity and adult alcohol dependence, at age 30 and/or 40 years ($n = 110$)

Variable	Alcoholism severity Mean (SD)	p^a	No alcohol dependence % or mean (SD)	Alcohol dependence % or mean (SD)	p^a
Predictors					
Risk ^b					
High	4.4 (4.38)	.20	74%	26%	.25
Low	3.3 (3.61)		84%	16%	
ADHD Scale ^c					
Continuous (range: 12-48)			25.8 (9.4)	32.3 (10.1)	.003
Above median	5.3 (4.53)	.0001	68%	32%	.01
Below median	2.5 (2.82)		88%	12%	
Conduct Disorder Scale ^d					
Continuous (range: 0-13)			3.9 (2.6)	6.9 (3.1)	.0001
Above median	6.1 (4.70)	.0001	58%	42%	.0001
Below median	2.5 (2.81)		91%	9%	
Alcoholism Severity Scale ^e (range: 0-26)			2.1 (1.65)	10.5 (2.99)	.0001

Notes: **Bold** indicates statistical significance. ^a p values based on the General Linear Model procedure for continuous measures and the chi-square test for categorical measures (SAS Version 9.1); ^bhigh risk defined as treated alcoholism in the biological father; ^cchildhood ADHD derived from School Teacher's Questionnaire; ^dchildhood Conduct Disorder Scale derived from interview at age 19/20; ^eAlcoholism Severity Scale derived from the Psychiatric Diagnostic Interview alcoholism module.

Childhood predictors

Both the childhood ADHD Scale provided by school teachers and the childhood Conduct Disorder Scale obtained from the subjects in their teens were strongly associated with the two measures of alcoholic drinking at ages 30 and 40 (Table 1). DSM-III-R alcohol dependence was highly associated with ADHD as measured dichotomously by a median split or as a continuous score. Alcohol dependence was also highly associated with the measure of childhood CD as measured dichotomously (median split) or continuously. Similarly, the childhood ADHD Scale and the childhood Conduct Disorder Scale were significantly associated with the continuous measure of lifetime alcoholism severity. Subjects above the median on the school teacher childhood ADHD Scale reported twice as many lifetime alcoholism symptoms as adults than subjects below the median on the childhood ADHD Scale. The effect was even more dramatic for the teen Conduct Disorder Scale. Subjects above the median reported significantly more lifetime alcoholism symptoms as adults than subjects below the median. Table 1 also shows that the mean number of lifetime alcoholism symptoms was almost five times higher for the alcohol-dependent subjects than for the non-alcohol-dependent subjects, indicating strong agreement between the two measures of alcoholic drinking.

Combining risk and the two childhood predictors

Table 2 presents the results of a standard multiple regression procedure that was used to examine the relative

strength of the relationships between risk, the two premorbid childhood predictors, and lifetime alcoholism severity. The R^2 of .23 was highly significant ($p < .0001$), indicating that the model explained 23% of the variance (unadjusted). Paternal risk did not predict lifetime alcoholism severity in the smaller subsample. Both premorbid childhood measures predicted lifetime alcoholism severity. Childhood ADHD uniquely accounted for 4% (sr^2) of the explained variance, and the childhood Conduct Disorder Scale accounted uniquely for 10% of the variance. The shared variance was 9%. The intercorrelations shown in Table 2 indicate that the childhood ADHD Scale and the childhood Conduct Disorder Scale were significantly associated with each other despite the fact that these two measures were derived from very different sources at different times in the subject's lives. The results of the multiple regression are shown graphically in Figure 1.

Figure 2 illustrates the relative risk of developing adult alcohol dependence using the group of subjects scoring below the median split on both the childhood ADHD Scale and the childhood Conduct Disorder Scale as the reference group. Subjects scoring high on the childhood ADHD Scale were 1.6 times more likely to develop alcohol dependence than subjects with low scores on both the childhood ADHD Scale and the Conduct Disorder Scale, which was not a significant increase. Subjects scoring above the median on the childhood Conduct Disorder Scale were 3.6 times more likely to develop later alcohol dependence than subjects low on both scales, which was also not significant. However, subjects scoring high on both childhood scales were significantly more

TABLE 2. Correlations and standard multiple regression of childhood attention-deficit/hyperactivity disorder (ADHD) characteristics and conduct disorder characteristics on development of later adult alcoholism severity, controlling for risk status ($n = 110$)

	Risk status ^a	Childhood ADHD ^b	Conduct disorder ^c	Adult alcoholism severity ^d	<i>B</i>	<i>sr</i> ² (unique)
Risk status	—	.18	.08	.12	0.45	.002
Childhood ADHD	—	—	.37 [§]	.35 [§]	1.77*	.04
Conduct disorder	—	—	—	.43 [§]	2.88 [‡]	.10
Intercept					-3.53	
$R^2 = .23^§$						
Adjusted $R^2 = .21$						
Unique variability: .142						
Shared variability: .088						

Notes: ^aHigh risk (son of alcoholic father) versus low risk (son of nonalcoholic father); ^bhigh versus low scores on childhood ADHD Scale (median split); ^chigh versus low scores on Conduct Disorder Scale (median split); ^drepresented by number of alcoholism symptoms endorsed on the Psychiatric Diagnostic Interview alcoholism module (0-20).

* $p < .05$; [‡] $p < .001$; [§] $p < .0001$.

likely to develop alcohol dependence than those subjects who scored below the median on both childhood scales. Subjects scoring above the median on both the childhood ADHD and the childhood Conduct Disorder Scale were more than six times more likely to develop later alcohol dependence than subjects who scored below the median on both.

Discussion

This longitudinal study found that premorbid measures that approximate childhood ADHD and CD independently predicted lifetime alcoholic drinking years later. The combination of ADHD and CD was an especially strong predictor

of alcohol dependence. Familial risk, assessed by fathers' treated alcoholism, played a less substantial role in predicting the development of alcoholic drinking than the two childhood behavioral predictors. This result is consistent with that of Knop et al. (2003), who concluded that the predictive power of paternal risk paled beside more specific neurodevelopment measures, such as birth weight and impulse dyscontrol. In that article, we suggested that familial risk probably serves as a broad surrogate or proxy for multiple endophenotypes that are more directly and specifically associated with the development of alcoholism.

The significant relationships found between childhood ADHD, childhood CD, and problem drinking later in life are

FIGURE 1. Percentage of variance explained by conduct disorder, risk, and attention-deficit/hyperactivity disorder (ADHD) for number of lifetime alcoholism symptoms at 30-year/40-year outcome ($N = 110$). Dis = disorder; unexpl. = unexplained; sr^2 = unique variance. Total percent explained variance = 23%. Model: $F = 10.77$, $p < .0001$; $R^2 = .23$. Risk: $t = 0.6$, $p < .53$; $sr^2 = .005$. ADHD: $t = 2.3$, $p < .02$; $sr^2 = .04$. Conduct disorder: $t = 3.8$, $p < .0002$; $sr^2 = .10$.

FIGURE 2. Relative risk for 30-year/40-year alcohol dependence as a function of attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (CD). **ADHD relative risk = 1.6**, confidence interval (CI): 0.3-7.3; **CD relative risk = 3.6**, CI: 0.8-15.5; **both ADHD and CD relative risk = 6.3**, CI: 2.0-19.7. The relative risk estimates compare subjects with scores above the median on the measure(s) with subjects obtaining scores below the median on both measures (NEITHER) as a reference category.

not unique to this study. Both prospective and retrospective studies have demonstrated a strong relationship between these two childhood disorders and later alcohol misuse when the two are allowed to co-exist naturally (Flory and Lynam, 2003; Schuckit et al., 2008; Tarter et al., 2003; Zucker et al., 2008). Our current study examined how childhood ADHD and childhood CD predicts later adult alcoholic drinking. A unique feature of the study is the duration of the adult follow-up and the fact that the subjects were selected from a large birth cohort. Most prospective alcoholism studies that involve these two childhood disorders do not extend into middle age, and most begin with treatment samples that are far from representative of an entire population. Moreover, this is one of the few prospective studies that independently assessed childhood ADHD and CD in the same group of subjects at approximately the same period of time with vastly different methods that allowed a distinction to be made between the predictive influence of the two on the development of alcoholism. Despite the positive correlation between childhood ADHD and CD, the multiple regression analysis showed that both independently predicted lifetime alcoholic severity. The two conditions in combination appeared to be markers for an even greater risk for alcoholic drinking than either condition alone. The combination of childhood ADHD and childhood CD appears to indicate an especially ominous risk for developing alcohol dependence, at least among males. The fact that only males were included is a major limitation of this study. We do not know if these findings for boys will generalize to girls, although we suspect they will.

Child and adolescent mental health professionals disagree about the specific role that ADHD and CD play in alcoholic drinking. For example, Flory and Lynam (2003) believe that both childhood onset disorders reflect a central deficit responsible for the impulse dyscontrol that is associated with alcoholic drinking. Schuckit et al. (2008), in contrast, suggest that only CD in childhood conveys a unique risk for developing alcoholism later in life. Our findings support the conclusions of Flory and Lynam: Both of the two "externalizing" childhood disorders seem to be uniquely associated with problem drinking years later, even though CD is stronger. The presence of both childhood ADHD and CD together appears to strongly predict the severity of later alcoholic drinking. Like Lynam (1996), our findings suggest that it may be especially useful to subtype young people given the diagnosis of ADHD or CD for the purpose of applying specific, targeted interventions designed to prevent or minimize future alcohol abuse. For example, young people with ADHD who also show significant antisocial behaviors and young people with CD who also show significant symptoms of ADHD might be offered preventive services to help them resist impulsive reactions and learn to use alcohol wisely. Targeted interventions tailored to focus on childhood antisocial acts that are coupled with restless hyperactivity may prove more effective in preventing alcohol misuse in the future than indiscriminate, broad-based, school programs that focus on large, unselected groups of children.

This suggestion is consistent with another finding from the Danish Longitudinal Study on Alcoholism (Penick,

2006): Most premorbid measures that successfully predicted alcoholic drinking, including paternal alcoholism, failed to predict who would stop severe problem drinking and who would continue. We were surprised by this result because we expected that premorbid measures associated with the development of alcohol dependence would also predict the course of alcoholism once it began. That did not occur. We then returned to our large pool of premorbid measures that extended back to the birth of the subjects and searched for measures that predicted both the development of alcoholism and the failure to remit. Such measures, we thought, might represent especially strong endophenotypes for alcoholism. The most powerful set of premorbid measures that predicted both the onset and continuation of alcoholic drinking reflected the inability to control impulsive acts; that is, traits strongly associated with both ADHD and CD. A secondary set of premorbid measures that predicted the onset and continuation of alcoholic drinking reflected mild cognitive impairment, especially in those measures associated with concentration and freedom from distractibility that are more common in children with ADHD or CD. These findings support Tarter's suggestion that a disturbance in executive cognitive function is one component of the neurobehavioral disinhibition that underlies the vulnerability for alcoholism (Tarter et al., 2003). Thus, impulse deregulation and mild cognitive deficiencies may represent potential endophenotypes for alcoholism. In an especially succinct review of ADHD and CD, Thapar et al. (2006) note that the strong relationship between ADHD and CD could be the result of three factors: (1) common genetic factors that each share, (2) a combined synergism between currently unknown unique genetic factors associated with each condition, or (3) a stepwise biological diathesis between ADHD as the primary and necessary condition out of which CD arises for reasons that are unknown. Thapar et al. note "surprisingly little is known about what factors predict, mediate and moderate the link between ADHD and antisocial behavior..." (2006, p. 9). Our results support the final two hypotheses of Thapar and colleagues that suggest the two childhood disorders each contribute a unique risk to the development of alcoholism later in life. In a large, carefully constructed, molecular genetic study involving variations in the catechol-*O*-methyltransferase gene that influences the modulation of dopamine levels in the prefrontal cortex that is essential for executive functioning, Caspi et al. (2008) report that ADHD children with CD differed from those without antisocial traits and that "antisocial behavior was conditional on an ADHD diagnosis" (p. 209). Clearly, the search for the molecular underpinnings of ADHD, CD, and alcoholism is just beginning. Our studies suggest that an important starting place to understand the molecular genetics of alcoholism would focus on that set of behavioral precursors that are common to both ADHD and CD/ASPD among family history-positive individuals.

Acknowledgment

We thank the Danish men who agreed to participate in this study for their time and efforts.

References

- AMERICAN PSYCHIATRIC ASSOCIATION. Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R), Washington, DC, 1987.
- AMERICAN PSYCHIATRIC ASSOCIATION. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), Washington, DC, 1994.
- BAKER, R.L. AND MEDNICK, B.R. Influences on Human Development: A Longitudinal Perspective, Boston, MA: Kluwer-Nijhoff, 1984.
- BECKER, U. Documentation of Patient Admission in the Alcohol-Unit Hvidovre Hospital, Winalco: A Clinical Database (Danish). Copenhagen, Denmark: Alcoholenheden, Hvidovre Hospital, 2004.
- BIEDERMAN, J., WILENS, T., MICK, E., MILBERGER, S., SPENCER, T.J., AND FARAONE, S.V. Psychoactive substance use disorders in adults with attention deficit hyperactivity disorder (ADHD): Effects of ADHD and psychiatric comorbidity. *Amer. J. Psychiat.* **152**: 1652-1658, 1995.
- BUKSTEIN, O.G., BRENT, D.A., AND KAMINER, Y. Comorbidity of substance abuse and other psychiatric disorders in adolescents. *Amer. J. Psychiat.* **146**: 1131-1141, 1989.
- CADORET, R.J., CAIN, C.A., AND GROVE, W.M. Development of alcoholism in adoptees raised apart from alcoholic biologic relatives. *Arch. Gen. Psychiat.* **37**: 561-563, 1980.
- CASPI, A., LANGLEY, K., MILNE, B., MOFFITT, T.E., O'DONOVAN, M., OWEN, M.J., TOMAS, M.P., POULTON, R., RUTTER, M., TAYLOR, A., WILLIAMS, B., AND THAPAR, A. A replicated molecular genetic basis for subtyping antisocial behavior in children with attention-deficit/hyperactivity disorder. *Arch. Gen. Psychiat.* **65**: 203-210, 2008.
- CONNERS, C.K., ERHARDT, D., AND SPARROW, E. Connors' Adult ADHD Rating Scales (CAARS), North Tonawanda, NY: Multi-Health Systems, 1999.
- DISNEY, E.R., ELKINS, I.J., MCGUE, M., AND IACONO, W.G. Effects of ADHD, conduct disorder, and gender on substance use and abuse in adolescence. *Amer. J. Psychiat.* **156**: 1515-1521, 1999.
- FERGUSON, D.M., LYNSEY, M.T., AND HORWOOD, L.J. Conduct problems and attention deficit behaviour in middle childhood and cannabis use by age 15. *Aust. New Zeal. J. Psychiat.* **27**: 673-682, 1993.
- FLORY, K. AND LYNAM, D.R. The relation between attention deficit hyperactivity disorder and substance abuse: What role does conduct disorder play? *Clin. Child Fam. Psychol. Rev.* **6**: 1-16, 2003.
- FORREST, G.G. Chemical Dependency and Antisocial Personality Disorder: Psychotherapy and Assessment Strategies, New York: Haworth Press, 1994.
- GOODWIN, D.W., KNOP, J., JENSEN, P., GABRIELLI, W.F., JR., SCHULSINGER, F., AND PENICK, E.C. Thirty-year follow-up of men at high risk for alcoholism. *Ann. N.Y. Acad. Sci.* **708**: 97-101, 1994.
- GOODWIN, D.W., SCHULSINGER, F., HERMANSSEN, L., GUZE, S.B., AND WINOKUR, G. Alcohol problems in adoptees raised apart from alcoholic biological parents. *Arch. Gen. Psychiat.* **28**: 238-243, 1973.
- HARFORD, T.C. AND MUTHÉN, B.O. Adolescent and young adult antisocial behavior and adult alcohol use disorders: A fourteen-year prospective follow-up in a national survey. *J. Stud. Alcohol* **61**: 524-528, 2000.
- HELSELBROCK, V.M., HESSELBROCK, M.N., AND STABENAU, J.R. Alcoholism in men patients subtyped by family history and antisocial personality. *J. Stud. Alcohol* **46**: 59-64, 1985.
- KESSLER, R.C., ADLER, L., BARKLEY, R., BIEDERMAN, J., CONNERS, C.K., DEMLER, O., FARAONE, S.V., GREENHILL, L.L., HOWES, M.J., SECNIK, K., SPENCER, T., USTUN, T.B., WALTERS, E.E., AND ZASLAVSKY, A.M. The prevalence and correlates of adult ADHD in the United States: Results from the National Comorbidity Survey Replication. *Amer. J. Psychiat.* **163**: 716-723, 2006.

- KNOP, J., GOODWIN, D., TEASDALE, T.W., MIKKELSEN, U., AND SCHULSINGER, F. A Danish Prospective Study of Young Males at High Risk for Alcoholism. In: GOODWIN, D.W., VAN DUSEN, K.T., AND MEDNICK, S.A. (Eds.) *Longitudinal Research in Alcoholism*, Boston, MA: Kluwer-Nijhoff, 1984, pp. 107-124.
- KNOP, J., PENICK, E.C., JENSEN, P., NICKEL, E.J., GABRIELLI, W.F., MEDNICK, S.A., AND SCHULSINGER, F. Risk factors that predicted problem drinking in Danish men at age thirty. *J. Stud. Alcohol* **64**: 745-755, 2003.
- KNOP, J., PENICK, E.C., MORTENSEN, E.L., NICKEL, E.J., GABRIELLI, W.F., JENSEN, P., AND MEDNICK, S.A. Prediction of mortality at age 40 in Danish males at high and low risk for alcoholism. *Acta Psychiat. Scand.* **110**: 476-482, 2004.
- KNOP, J., PENICK, E.C., NICKEL, E.J., MEDNICK, S.A., JENSEN, P., MANZARDO, A.M., AND GABRIELLI, W.F. Paternal alcoholism predicts the occurrence but not the remission of alcoholic drinking: A 40-year follow up. *Acta Psychiat. Scand.* **116**: 386-393, 2007.
- KNOP, J., TEASDALE, T.W., GOODWIN, D.W., POLLOCK, V., AND SCHULSINGER, F. Premorbid characteristics in high risk and low risk individuals for developing alcoholism. In: KIIANMA, K., TABAKOFF, B., AND SAITO, T. (Eds.) *Genetic Aspects of Alcoholism*, Helsinki, Finland: Finnish Foundation for Alcohol Studies, Vol. 37, 1989, pp. 117-126.
- KNOP, J., TEASDALE, T.W., SCHULSINGER, F., AND GOODWIN, D.W. A prospective study of young men at high risk for alcoholism: School behavior and achievement. *J. Stud. Alcohol* **46**: 273-278, 1985.
- KUPERMAN, S., SCHLOSSER, S.S., KRAMER, J.R., BUCHOLZ, K., HESSELBROCK, V., REICH, T., AND REICH, W. Developmental sequence from disruptive behavior diagnosis to adolescent alcohol dependence. *Amer. J. Psychiat.* **158**: 2022-2026, 2001.
- LYNAM, D.R. Early identification of chronic offenders: Who is the fledgling psychopath? *Psychol. Bull.* **120**: 209-234, 1996.
- MANNUZZA, S., KLEIN, R.G., BESSLER, A., MALLOY, P., AND LAPADULA, M. Adult outcome of hyperactive boys: Educational achievement, occupational rank and psychiatric status. *Arch. Gen. Psychiat.* **50**: 565-576, 1993.
- MANNUZZA, S., KLEIN, R.G., BESSLER, A., MALLOY, P., AND LAPADULA, M. Adult psychiatric status of hyperactive boys grown up. *Amer. J. Psychiat.* **155**: 493-498, 1998.
- MASTEN, A.S., FADEN, V.B., ZUCKER, R.A., AND SPEAR, L.P. Underage drinking: A developmental framework. *Pediatrics* **121** (Suppl. No. 4): S235-S251, 2008.
- MOLINA, B.S.G., PELHAM, W.E., GNAGY, E.M., THOMPSON, A.L., AND MARSHAL, M.P. Attention-deficit/hyperactivity disorder risk for heavy drinking and alcohol use disorder is age specific. *Alcsm Clin. Exp. Res.* **31**: 643-654, 2007.
- MUNK-JØRGENSEN, P. AND MORTENSEN, P.B. The Danish Psychiatric Central Register. *Dan. Med. Bull.* **44**: 82-84, 1997.
- MURPHY, K. AND BARKLEY, R.A. Attention deficit hyperactivity disorder adults: Comorbidities and adaptive impairments. *Comprehen. Psychiat.* **37**: 393-401, 1996.
- OTHMER, E., PENICK, E.C., POWELL, B.J., READ, M.R., AND OTHMER, S.C. *Psychiatric Diagnostic Interview-Revised*, Los Angeles, CA: Western Psychological Services, 1989.
- OTHMER, E., PENICK, E.C., POWELL, B.J., READ, M.R., AND OTHMER, S.C. *Psychiatric Diagnostic Interview IV*, Los Angeles, CA: Western Psychiatric Services, 2000.
- PENICK, E.C. The Danish Longitudinal Study on Alcoholism: A Forty-Year Work in Progress, Invited presentation, Lubin Speakers' Series, December 2006, Kansas City, MO: Department of Psychology, University of Missouri, 2006.
- POLLOCK, V.E., BRIERE, J., SCHNEIDER, L., KNOP, J., MEDNICK, S.A., AND GOODWIN, D.W. Childhood antecedents of antisocial behavior: Parental alcoholism and physical abusiveness. *Amer. J. Psychiat.* **147**: 1290-1293, 1990.
- POWELL, B.J., PENICK, E.C., AND OTHMER, E. The discriminate validity of the Psychiatric Diagnostic Interview. *J. Clin. Psychiat.* **46**: 320-322, 1985.
- ROBINS, L.N. AND REGIER, D.A. (Eds.) *Psychiatric Disorders in America: The Epidemiologic Catchment Area Study*, New York. Free Press, 1991.
- SCHUCKIT, M.A., SMITH, T.L., PIERSON, J., TRIM, R., AND DANKO, G.P. Externalizing disorders in the offspring from the San Diego prospective study of alcoholism. *J. Psychiat. Res.* **42**: 644-652, 2008.
- SCHULSINGER, F., KNOP, J., GOODWIN, D.W., TEASDALE, T.W., AND MIKKELSEN, U.M. A prospective study of young men at high risk for alcoholism: Social and psychological characteristics. *Arch. Gen. Psychiat.* **43**: 755-760, 1986.
- SHER, K.J. *Children of Alcoholics: A Critical Appraisal of Theory and Research*, Chicago, IL: Univ. of Chicago Press, 1991.
- SULLIVAN, M.A., CHIBBER, S., PENICK, E.C., NICKEL, E.J., GOODWIN, D.W., KNOP, J., AND JENSEN, P. ADHD and ASPD as independent predictors of male alcoholism at age 30. Poster presented at the 151st Annual Meeting of the American Psychiatric Association, Washington, DC, May 1999.
- TARTER, R.E., ALTERMAN, A.I., AND EDWARDS, K.L. Vulnerability to alcoholism in men: A behavior-genetic perspective. *J. Stud. Alcohol* **46**: 329-356, 1985.
- TARTER, R.E., KIRISCI, L., MEZZICH, A., CORNELIUS, J.R., PAJER, K., VANYUKOV, M., GARDNER, W., BLACKSON, T., AND CLARK, D. Neurobehavioral disinhibition in childhood predicts early age at onset of substance use disorder. *Amer. J. Psychiat.* **160**: 1078-1085, 2003.
- TARTER, R.E., MCBRIDE, H., BUONPANE, N., AND SCHNEIDER, D.U. Differentiation of alcoholics: Childhood history of minimal brain dysfunction, family history, drinking pattern. *Arch. Gen. Psychiat.* **34**: 761-768, 1977.
- TAYLOR, J. AND LANG, A.R. Psychopathy and substance use disorders. In: PATRICK, C.J. (Ed.) *Handbook of the Psychopathy*, New York: Guilford Press, 2006, pp. 495-511.
- THAPAR, A., VAN DEN BREE, M., FOWLER, T., LANGLEY, K., AND WHITTINGER, N. Predictors of antisocial behavior in children with attention deficit hyperactivity disorder. *Europ. Child Adolesc. Psychiat.* **15**: 118-125, 2006.
- VILLUMSEN, A.L. *Environmental Factors in Congenital Malformations: A Prospective Study of 9,006 Human Pregnancies*, Kobenhavn, Denmark: F.A.D.L.'s Forlag, 1970.
- VILSTRUP, H. AND NIELSEN, P.E. Distribution of alcohol consumption in the Danish population in 1979 (Danish). *Ugeskr. Laeg* **143**: 1047-1052, 1981.
- WELLER, R.A., PENICK, E.C., OTHMER, E., RICE, A.S., POWELL, B.J., AND KENT, T.A. Agreement between two structured psychiatric diagnostic interviews: DIS and the PDI. *Comprehen. Psychiat.* **26**: 157-163, 1985.
- WHITE, H.R., XIE, M., THOMPSON, W., LOEBER, R., AND STOUTHAMER-LOEBER, M. Psychopathology as a predictor of adolescent drug use trajectories. *Psychol. Addict. Behav.* **15**: 210-218, 2001.
- WILENS, T.E., BIEDERMAN, J., MICK, E., FARAONE, S.V., AND SPENCER, T. Attention deficit hyperactivity disorder (ADHD) is associated with early onset substance use disorders. *J. Nerv. Ment. Dis.* **185**: 475-482, 1997.
- ZACHAU-CHRISTIANSEN, B., AND ROSS, E.M. *Babies: Human Development During the First Year*, Hoboken, NJ: John Wiley & Sons, 1975.
- ZUCKER, R.A., DONOVAN, J.E., MASTEN, A.S., MATTSO, M.E., AND MOSS, H.B. Early developmental processes and the continuity of risk for underage drinking and problem drinking. *Pediatrics* **121** (Suppl. No. 4): S252-S272, 2008.