Effects of Premature Birth on the Risk for Alcoholism Appear to Be Greater in Males Than Females*

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ABSTRACT. Objective: A large Danish birth cohort was used to test the independent and joint effects of perinatal measures associated with premature birth as predictors of the development of alcoholism in male and female subjects. **Method:** Subjects were born at the Copenhagen University Hospital between 1959 and 1961 (N = 9,125). A comprehensive series of measures was obtained for each of the 8,109 surviving and eligible infants before birth, during birth, shortly after birth, and at 1 year. The adult alcoholism outcome was defined as any ICD-10 F10 diagnosis (*Mental and behavioral disorders due to alcohol use*) or an equivalent ICD-8 diagnosis found in the Danish Psychiatric Central Research Register or the Municipal Alcohol Clinics of Copenhagen by 2007. **Results:** Multiple perinatal markers of premature birth independently predicted the development of an alcoholism diagnosis in male (n = 310) but not female (n = 138) subjects. Logistic regression modeling with a global prematurity score, adjusted for social status, maternal smoking, and gender, indicated a significant association of prematurity score for males ($p < .02$), but not females ($p = .51$), on the risk of developing an alcohol use disorder. **Conclusions:** The results suggest that neurodevelopmental sequelae of premature birth are associated with gender-specific effects on the development of alcoholism in the male baby: small, premature, or growth-delayed male babies appear to be selectively vulnerable to alcoholic drinking years later. The findings implicate neurodevelopmental influences in alcoholism pathophysiology in males and suggest the possibility of distinct, gender-specific pathways in the etiology of severe problem drinking. (*J. Stud. Alcohol Drugs, 72,* 390–398, 2011)

PREMATURE BIRTH and very low birth weight are associated with increased rates of a variety of health problems later in life, including cardiovascular and respiratory disease in adulthood and possibly an increased risk for diabetes (Doyle, 2008; Doyle and Anderson, 2010). Premature babies are also at an increased risk of neurological and cognitive impairment; moreover, the sequelae associated with prematurity may increase the likelihood of psychiatric disorders (Anderson et al., 2004; Botting et al., 1997; Chaimay et al., 2006; Indredavik et al., 2004; Johnson, 2007; Lindström et al., 2009; Stjernqvist and Svenningsen, 1999). Severe neurodevelopmental syndromes such as periventricular leukomalacia and cerebral palsy are more common among preterm infants and can result in marked cognitive disabilities. Preterm infants reportedly experience increased psychiatric symptoms of anxiety and depression during childhood and adolescence (Botting et al., 1997; Indredavik et al., 2004; Stjernqvist and Svenningsen, 1999). Preterm infants also have increased rates of psychiatric hospitalization in adolescence and young adulthood (Hack, 2006; Lindström et al., 2009). Premature birth is strongly associated with the appearance of impulse control behavioral disorders such as attention deficit hyperactivity disorder and childhood conduct disorder (Anderson et al., 2004; Botting et al., 1997; Johnson, 2007), which are established risk factors for the development of alcoholism and substance use problems later in life (Crews and Boettiger, 2009; Giancola and Moss, 1998; Knop et al., 2009).

Although such findings implicate prematurity as a possible risk factor for alcoholism, a predictive relationship between preterm birth and alcohol or substance use problems in adulthood has not been firmly established (Bjerager et al., 1995; Cooke, 2004; Hack et al., 2002; Lindström et al., 2009). Longitudinal follow-up studies focused on adolescents and young adults have failed to identify a consistent change in alcohol consumption or the rates of alcohol use

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disorders among individuals who were born prematurely (Bjerager et al., 1995; Cooke, 2004; Hack et al., 2002; Lindström et al., 2009). Research extending beyond adolescence and the age of risk for developing an alcohol use disorder is needed to rule out an association between premature birth and alcohol/substance use problems later in life.

The 40-year, high-risk Danish Longitudinal Study on Alcoholism, involving a selective sample of only males, identified several perinatal neurodevelopmental markers that predicted the development of alcoholism in adulthood (Manzardo et al., 2005). These markers represent biological characteristics associated with premature birth, such as low birth weight and delayed achievement of developmental motor milestones in walking and standing (Berkowitz, 1981). Perinatal developmental delays observed in this birth cohort were also associated with abnormal muscle strength and muscle tone at age 20 years, suggesting a robust and long-lasting association between perinatal variables and adult development (Manzardo, 2006; Manzardo and Penick, 2006).

The present study builds on the results of the all-male Danish Longitudinal Study on Alcoholism to test the hypothesis that neurodevelopmental deficits acquired during the perinatal period are precursors of alcoholism in both male and female babies. The study includes data from the entire birth cohort of 9,125 male and female babies. The current study permits a direct comparison of the association between perinatal measures and adult alcoholism without any exclusions. Because of the size of this birth cohort and the availability of archival information over the lifetime of the subjects, we were able to determine whether the previously reported relationship between prematurity and alcoholic drinking was upheld for both boys and girls.

Method

Subject population

The study sample consisted of male and female subjects obtained from a large Danish birth cohort of 9,125 consecutive deliveries (more than 20 weeks gestation) from 1959 through 1961 (Villumsen, 1970; Zachau-Christiansen, 1972). All births took place in the maternity ward of the State University Hospital (Rigshospitalet) in Copenhagen, Denmark. The sample population contains an overrepresentation of mothers from a slightly lower social class and a predominantly urban environment. Subject mothers also possessed a modestly increased risk of pregnancy and birth complications (Baker and Mednick, 1984). Of the original 9,125 babies enrolled in the cohort, 728 died in the first year and therefore were excluded from follow-up. Another 288 subjects did not have personal identification numbers and therefore could not be linked to the Danish Psychiatric Central Research Register or other Danish archival sources. These subjects are presumed to have died or emigrated from Denmark as children.

Perinatal measures

Information obtained before, during, and shortly after birth includes indices of the social and medical status of the mother during pregnancy, complications during pregnancy and birth, and birth weight and the infant's condition at birth (Villumsen, 1970; Zachau-Christiansen, 1972). Two neonatal examinations were carried out (Day 1 and Day 5), and a 1-year postnatal examination was performed that included development and diet during the first year of life and ratings of the general physical condition of the child at 1 year of age. Full neurological and motor development evaluations were performed at birth and 1 year of age. A priori scales constructed by the original study investigators were also available that reflected the neurological development of babies at birth. The perinatal file provides more than 2,000 variables on each subject. Despite the amount of detailed information collected about the mothers and babies in this perinatal cohort, no information was collected about the mother's alcohol consumption either before or during pregnancy. For this study, after examining the intercorrelations among a large number of perinatal measures, six variables were selected to reflect biological correlates of premature birth (Berkowitz, 1981; Berkowitz et al., 1982), and five measures were selected to control for extraneous influences known to be associated with premature birth (Berkowitz et al., 1982). Because of limitations of computer capacity at the time of the original study (1959–1961), the perinatal data were not always recorded as discrete numerical values and were, on occasion, coded categorically as ordinal levels or categorical ranges. In some instances, it was possible only to approximate a mean value for a tested variable.

Prematurity measures

Prematurity score. A derived, a priori, summary prematurity score was constructed by the original team of investigators from the perinatal cohort study (Villumsen, 1970; Zachau-Christiansen, 1972). This score combines data from birth stage and birth weight with a subjective global impression of maturity by the examining pediatrician to provide a weighted measure of prematurity. The weighted global prematurity score was constructed as a Likert scale ranging from 0 to 4, with 0 indicating no prematurity. The overall distribution of the global prematurity score was highly skewed toward 0, or normal, with a mean (*SD*) of 0.79 (1.05).

Clinical impressions. Clinical impressions of size, based on the baby's gestational age, were recorded for the infant subjects 5 days after birth. The level of maturity was desig-

nated as premature, mature, or postmature according to the judgment of the examining pediatrician (Villumsen, 1970, Zachau-Christiansen, 1972). Categorical analysis combined the mature and postmature groups (n = 6,681) and compared them with the premature group (n = 1,377).

Birth stage. The gestational age at the time of delivery, in weeks, was recorded in levels: 1 = less than 28 weeks, 2 = 28–29 weeks, 3 = 30–31 weeks, 4 = 32–33 weeks, 5 = 34–35 weeks, 6 = 36–37 weeks, 7 = 38–39 weeks, 8 = 40–41 weeks, 9 = 42–43 weeks, 10 = 44–45 weeks, and 11 = more than 45 weeks. The frequency data as coded approximate a normal distribution with a mean (*SD*) of 7.30 (1.32), which approximates 38.3 weeks (9.5 months). Categorical analyses divided subjects into two groups: premature (Levels 1–6 = <38 weeks; n = 1,252) and full term (Levels 7–11 = ≥38 weeks; n = 5,268), based on Centers for Disease Control and Prevention (2010) guidelines, which define premature birth as a birth stage less than 38 weeks.

Birth weight. The weights of the newborn subjects (in grams) were also recorded as levels: 1 = less than 1,000 g, 2 = 1,000–1,500 g, 3 = 1,501–2,000 g, 4 = 2,001–2,500 g, 5 = 2,501–3,000 g, 6 = 3,001–3,500 g, 7 = 3,501–4,000 g, 8 = 4,001–4,500 g, 9 = 4,501–5,000 g, and 10 = more than 5,000 g, with a mean (*SD*) level of 5.8 (1.25), which approximates 2,800 g (6.2 lb). Categorical analyses divided subjects into lower birth weight (Levels 1–4 = ≤2,500 g, n = 1,046) and higher birth weight (Levels 5–10 = >2,500 g, n = 7,082) groups.

Birth length. The lengths of the newborn subjects (in centimeters) were recorded as levels in a semicontinuous fashion: 1 = less than 40 cm, 2 = 40–44 cm, 3 = 45–47 cm, 4 = 48–49 cm, 5 = 50–51 cm, 6 = 52–54 cm, 7 = 55–59 cm, 8 = 60 cm or more. The frequency data approximate a normal distribution with a mean (*SD*) of 5.07 (1.15), which approximates 50 cm, or about 20 inches.

Head circumference. The head circumference (in centimeters) of each newborn subject was recorded as levels in a semicontinuous fashion: 2 = 30 cm, 3 = 31 cm, 4 = 32 cm, 5 = 33 cm, 6 = 34 cm, 7 = 35 cm, 8 = 36 cm, 9 = 37 cm, 10 = 38 cm, 11 = 39 cm or more. The frequency scale approximates a normal distribution with a mean (*SD*) of 6.0 (1.53), or 34 cm (13 inches). There are no readily available normative data regarding the head circumference of Danish infants in this historical timeframe. This scale was used to divide subjects into two groups reflecting the lower one third and upper two thirds of the population distribution: small head circumference (<34 cm, levels 1–5, n = 2,805) and normal head circumference (≥34 cm, Levels 6–11, n = 4,988).

Walking measure. This 1-year walking measure was derived from the mother's report of the age at which subjects could walk with support and the age at which subjects could walk without support. The single derived variable for walking was categorized according to the number of subjects achieving the benchmark at or before 11 months of age (n = 7,062, 87.09%) and the number who achieved it at 12 months of age or older (n = 1,047, 12.31%).

Possible confounding measures that were controlled

Infant gender. The sample population consisted of 4,114 (51%) males and 3,995 (49%) females. Duplicate sources within the perinatal database were cross-checked against the Danish Central Person Register to ensure accuracy in gender designations.

Maternal age at pregnancy. Younger mothers have been shown to have an increased risk of premature birth. The age of the mother at the time of the birth was recorded as a continuous measure in years. The mean (*SD*) age of the mother at the birth of the subject was 25.3 (6.5) years.

Parental social status at 1 year. Lower socioeconomic status and social standing have been associated with an increased risk of both premature birth (Morgen et al., 2008) and the development of substance use disorders (Dohrenwend et al., 1992). Data about parental social status were obtained from an interview with the mother when the child was 1 year old. The 1- to 9-point Social Status Scale was based on the breadwinner's occupation, education, type of income, and quality of housing (Villumsen, 1970; Zachau-Christiansen, 1972). The distribution of the sample population is slightly skewed toward the lower social class, with a mean (*SD*) level of 4.0 (1.85).

Maternal smoking status in the third trimester. Maternal smoking during pregnancy has been associated with an increased risk of both premature birth (McElrath et al., 2008; Morgen et al., 2008) and the development of alcohol and substance use problems in exposed offspring (Button et al., 2007; Morgen et al., 2008). Additionally, smoking in pregnancy is correlated with maternal psychiatric disorders, including alcoholism and an increased likelihood of alcohol consumption during pregnancy (Knopik et al., 2005; Lasser et al., 2000). The smoking status of subjects' mothers in the third trimester was coded in a dichotomous fashion as "yes" (smoking) or "no" (not smoking). The total sample contained 4,158 (52.5%) mothers who were self-reported smokers and 3,761 (47.5%) mothers who were nonsmokers in the third trimester. Smoking in the third trimester was also highly correlated with smoking throughout the course of the entire pregnancy.

Maternal weight increase in pregnancy. Weight gain during pregnancy is a measure of the growth and maturity of the fetus. The change in weight (in kilograms) of the subjects' mothers over the course of the pregnancy was recorded in a semicontinuous fashion as levels: 1 = less than 6 kg; 2 = 6–8 kg; 3 = 9–10 kg; 4 = 11–12 kg; 5 = 13–15 kg; 6 = 16 kg or greater. The frequency data approximate a normal distribution with a mean (*SD*) of 3.87 (1.58), which approximates 9.8 kg (21.6 lb).

Adult outcome measure

Lifetime alcoholism diagnoses. Psychiatric outcomes at age 45–47 years were obtained from a comprehensive search of two archival resources in 2007. The Danish Psychiatric Central Research Register included diagnoses recorded for all admissions to a Danish psychiatric hospital or unit (since 1969) over the lifetime of the subjects (Munk-Jorgensen and Mortensen, 1997). In addition, records at the Municipal Alcohol Clinics of Copenhagen (WINALKO) were searched. The WINALKO database contains records of individuals treated for alcohol problems at an outpatient clinic covering the greater Copenhagen and Frederiksberg municipalities since 1954 (Becker, 2004). Over the period surveyed, hospital diagnoses in Denmark were based on the International Classification of Diseases, Revision 8 (ICD-8), until 1994, when the ICD-10 system was adopted (Denmark never formally adopted the ICD-9 system). Only ICD-10 categories (F10.00–F10.99, Mental and behavioral disorders due to use of alcohol) or comparable ICD-8 categories (291.0–291.9; 303.0–303.9) were examined. A single ICD-10 F10 or equivalent ICD-8 code in the Danish Psychiatric Central Research Register or any listing in the municipal alcohol clinic database was sufficient to fulfill criteria for the diagnosis of alcoholism.

Data analysis

Statistical analyses were performed using SAS software Version 9.2 (SAS Institute Inc., Cary, NC). Univariate analyses were performed on each individual perinatal variable for male and female subjects with and without an alcoholism diagnosis. A correlation matrix was generated to assess the degree of colinearity between perinatal variables for the entire sample. The Pearson's chi-square test of independence was used to examine the effect of dichotomized perinatal variables on the diagnosis of alcoholism. Analysis of variance was used to test for differences between mean values of ordinal and interval measures for subjects with and without an alcoholism diagnosis. In Figure 1, a simple linear regression line was fit to male and female groups. Logistic regression modeling was used to compare the independent and joint effects of perinatal variables on the risk of developing alcoholism. The presence of a Gender × Prematurity interaction was tested as an a priori hypothesis in these analyses. The logistic regression model was adjusted for several major confounding factors known to increase the risk of both alcoholism and premature birth: male gender (including the interaction with prematurity score), lower social class, maternal smoking, and mother's age. Adjusted odds ratios and corresponding 95% Wald confidence intervals were

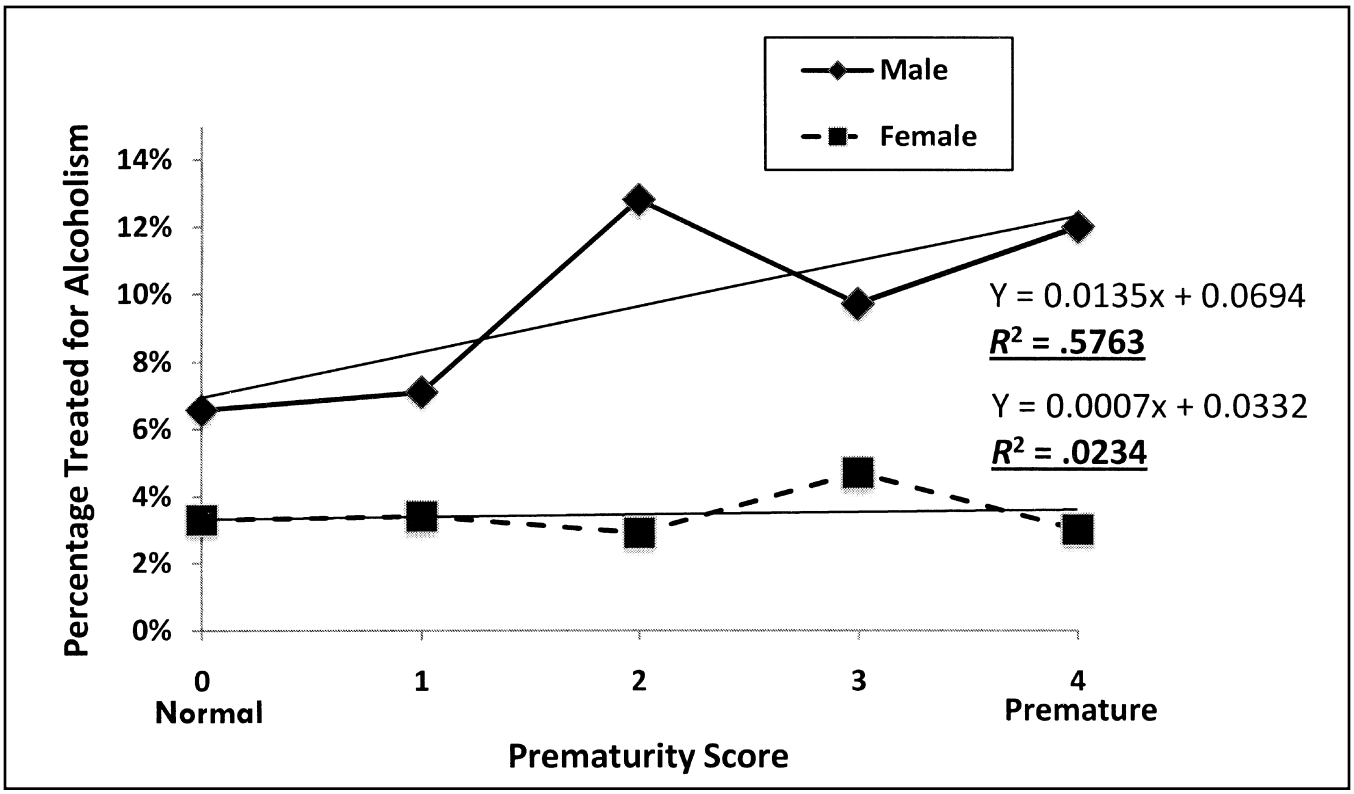

FIGURE 1. Gender effects on the relationship between prematurity and alcoholism in adulthood

TABLE 1. Bivariate associations of perinatal markers of premature birth on the risk of developing adult alcohol dependence stratified by gender

		Male			Female			Total	
Variable	(*n*)	AD (*n* = 310) Freq. (%) or *M* (*SD*)	NAD (*n* = 3,804) Freq. (%) or *M* (*SD*)	*p*	AD (*n* = 138) Freq. (%) or *M* (*SD*)	NAD (*n* = 3,857) Freq. (%) or *M* (*SD*)	*p*	Male vs. female *p*	AD vs. NAD *p*
Mother at pregnancy									
Mother's age, years	(8,108)	24.87 (6.54)	25.41 (6.56)	.1583	23.78 (5.92)	25.32 (6.50)	**.0058**	.4743	**.0083**
Weight increase, gm[a]	(4,732)	3.65 (1.58)	3.96 (1.56)	**.0123**	3.82 (1.68)	3.79 (1.58)	.8406	**.0007**	.0979
Smoking in last trimester, *n* (%) yes	(7,919)	187 (61.51%)	1,876 (50.59%)	**.0003**	96 (72.18%)	1,999 (52.97%)	**.0001**	**.0499**	**.0001**
Social status[a,b]	(6,476)	3.34 (1.61)	4.04 (1.86)	**.0001**	3.32 (1.72)	4.00 (1.85)	**.0002**	.6913	**.0001**
Baby at birth									
Prematurity score[c]	(8,109)	0.97 (1.15)	0.75 (1.05)	**.0004**	0.9 (1.2)	0.82 (1.04)	.3612	**.0089**	**.0015**
Clinical impressions[d]	(8,058)	72 (23.30%)	566 (14.97%)	**.0001**	27 (19.57%)	712 (18.59%)	.7725	**.0003**	**.0035**
Birth stage[e]	(6,519)	64 (26.34%)	585 (19.28%)	**.0079**	20 (18.02%)	582 (18.59%)	.8781	.2095	**.0258**
Birth weight, *n* (%) <2,500 g	(8,108)	60 (19.35%)	430 (11.31%)	**.0001**	22 (15.94%)	534 (13.84.%)	.4843	**.0071**	**.0004**
Birth length[a,f]	(8,096)	4.99 (1.32)	5.25 (1.14)	**.0001**	4.80 (1.19)	4.91 (1.12)	.2940	**.0001**	**.0089**
Head circumference, *n* (%) <33 cm	(7,794)	56 (18.98%)	416 (11.34%)	**.0001**	32 (24.06%)	728 (19.70%)	.2152	**.0001**	**.0056**
Baby at 1 year									
Unable to walk with support, *n* (%)	(8,109)	57 (18.39%)	476 (12.51%)	**.0031**	24 (17.39%)	491 (12.70%)	.1084	.9309	**.0008**

Notes: Alcohol dependence outcomes reflect lifetime diagnoses. Dichotomous variables were analyzed using Pearson's chi-square test of independence. Ordinal/interval measures were analyzed using analysis of variance. **Bold** indicates statistical significance. AD = alcohol dependent; NAD = non-alcohol dependent; freq. = frequency. [a]Variables are coded in levels; outcomes show the mean level; [b]social status was determined the Social Status Scale, with 1 indicating the lowest and 9 indicating the highest social status; [c]prematurity was based on a Likert-type scale with 0 representing no prematurity and 4 representing the highest level of prematurity; [d]designation of infant size as "premature" or "mature" was determined by the examining pediatrician; [e]proportion of infants born above and below 38 weeks; [f]1 = less than 40 cm, 8 = 60 cm or more (see *Birth length* in the Method section for scoring details).

presented based on the final model. This model was assessed using the Hosmer–Lemeshow goodness-of-fit test.

Results

Of the 8,109 eligible subjects, 448 (5.5%), received a formal diagnosis of alcoholism at some point in their lifetime. A majority of these (74%) were males by a 3:1 ratio: 310 males and 138 females ($p > .0001$). In the total sample, all six of the perinatal measures were highly correlated with one another, yielding 36 *p* values at less than .0001 (minimum $r = .31$; data not shown). When gender was held constant, all of the perinatal variables reflecting the status of the baby at birth and 1 year predicted alcoholism in adulthood. In every comparison, the direction indicated a significantly greater degree of prematurity among those subjects who would later develop alcoholism. Adult alcoholism in the total sample was also related to smoking in the third trimester and lower social class of the parents. Male babies showed more signs of prematurity at birth than female babies, who were more likely to have mothers who smoked. Mothers of female babies also gained more weight during pregnancy than mothers of male babies. A summary of the influence of each perinatal variable on the development of alcoholism is shown in Table 1.

Striking differences emerged when the adult alcoholism outcome was considered separately by gender (Table 1). For male babies, all of the perinatal measures that reflect prematurity at birth predicted alcoholism years later. Again, the direction of deviance indicated that male babies at risk for developing alcoholism showed more anomalies at birth. In contrast, for females, none of the perinatal measures reflective of the condition of the baby at birth predicted alcoholic drinking. For both males and females, lower social class and smoking by the mother increased the risk for alcoholism. Younger age of the mother was associated with alcoholism among females, whereas failure to gain weight in pregnancy was associated with alcoholism among males.

Modeling of the effects of perinatal measures on alcoholism outcome

The strong correlations across the perinatal variables limited the number of measures that could be considered simultaneously in statistical model-building procedures. As a consequence, we chose to focus on the a priori global clinical scale created by the original study investigators, which is based on a combination of birth weight, birth stage, and clinical impressions of the newborn's immaturity. The global prematurity score was selected to serve as the index of prematurity for modeling procedures. The global prematurity score correlated at greater than the .0001 level of significance with the five remaining measures of prematurity.

Table 2. Logistic regression model predicting alcohol dependence

Explanatory measure	Adjusted OR [95% CI]	Wald χ^2 p
Smoking in the third trimester	1.49 [1.17, 1.88]	.0011
Socioeconomic status	0.81 [0.76, 0.87]	<.0001
Prematurity score, per 1-unit increase		
Among males	1.15 [1.02, 1.30]	.0193
Among females	1.06 [0.88, 1.28]	.5131

Notes: OR = odds ratio; CI = confidence interval.

As shown in Figure 1, the global prematurity score strongly predicted the risk for alcoholism among males (R^2 = .58) but not among females (R^2 = .02). Logistic regression modeling was used to consider the possible interactive effects between the global prematurity score and male gender on the risk for developing alcoholism while controlling for the effects of social class, maternal smoking, and mother's age. The effect of mother's age was not significant after these adjustments; therefore, it was removed from the final model. The final logistic regression model (Table 2) did not suffer from lack of fit (p = .8966). After adjustment for maternal smoking and social class, the global prematurity score continued to significantly predict the development of alcoholism among males (p = .0193) but not among females (p = .5131). When controlled in a similar manner, the effects of low birth weight and small head size were also significant in males, at the $p < .01$ alpha level, but not in females, whereas premature birth stage and smaller birth length showed trends ($p < .1$) toward significance in males. The results suggest a selective vulnerability of premature male babies to the development of alcoholism, a finding we have not seen previously reported.

Discussion

Perinatal neurodevelopmental factors commonly associated with premature birth significantly and independently predicted treated alcoholism in adulthood among members of a large Danish birth cohort. This relationship was found to be driven primarily by the effect of prematurity on male babies. Premature birth had no measurable effect on the risk of developing alcoholism among females. This gender-specific relationship was upheld even after controlling for social class and maternal smoking, which are strong risk factors for both premature birth and alcoholism. The findings support the hypothesis of distinct, gender-differentiated pathways for the development of the most severe form of alcoholism and specifically implicate neurodevelopmental influences in the pathophysiology of alcoholism in males. Although our conclusions appear to contradict those of Lindström et al. (2009), who did not report a relationship between premature birth and alcoholism, it should be noted that Lindström et al.'s study found that premature birth was related to a higher incidence of addictive disorders comorbid with other psychiatric illnesses in a relatively young sample.

Male vulnerability

Premature birth is associated with lower birth weight, smaller birth length, smaller head circumference, and delayed motor development. Birth weight, in particular, is considered to be a reliable measure of gestational age and thus a good reflection of or "proxy" for prematurity. A large and consistent body of literature supports an association between very low birth weight and serious neurodevelopmental impairment (Anderson et al., 2004; Aylward, 2005; Miller et al., 2005; Wilson-Costello et al., 2005). Male newborns are intrinsically vulnerable to the neurodevelopmental sequelae concomitant with premature birth (Ingemarsson, 2003). Male newborns suffer from proportionally more perinatal syndromes, such as periventricular leukomalacia and cerebral palsy, than similarly exposed female newborns. In addition, an increased incidence of childhood behavioral disorders and increased psychiatric symptomology are more commonly found among male children who were born prematurely (Anderson et al., 2004; Johnson, 2007). Although previous reports from longitudinal follow-up assessments of preterm infants have not consistently supported a direct relationship between premature birth and alcoholism, the majority of those studies were limited to the assessment of alcohol consumption in adolescence, which is a weak indicator of future alcohol disorders.

The present study shows that premature birth is associated with a statistically meaningful increase in the risk of developing alcoholism in males but not females. A linear relationship was found between a global prematurity score and the risk of being treated for alcoholism among males. The risk of being treated for alcoholism as an adult was 6% for full-term male babies compared with 14% for the most severely preterm male babies. In contrast, the risk of being treated for alcoholism among females was 3% for both premature and full-term female infants. It would appear that premature birth directly contributes to an increased likelihood of a baby boy developing an alcohol problem as an adult. Female infants, in contrast, appear to be spared the deleterious influence of premature birth on the development of alcoholism. We propose that the selective sensitivity of male babies to the sequelae of premature birth could be one explanation for the established overrepresentation of alcoholism among men. These findings cannot be accounted for by a possible gender bias that favors the identification of alcoholism in males because the rates of alcoholism among male and female subjects of this large birth cohort approximated estimates of alcoholism prevalence in epidemiological studies (Bijl et al., 1998; Obot and Room, 2005). Moreover, any selective bias against the identification of females with alcoholism should tend to obscure gender differences between prematurity and

an alcohol use disorder, which was not found in this study. We suggest that the "protective" gender effect observed in this study may be the result of an intrinsic resilience of the female brain to perinatal neurodevelopmental insult. The seeming "gender protection" also suggests that alcoholism in women may arise through a separate neuroanatomical pathway that is either not influenced by or is less influenced by perinatal injury.

Neurological targets of premature birth

At least two parallel biological mechanisms could explain the present findings. One results from direct neurological injury of the brain; the other involves adaptive, epigenetic mechanisms possibly triggered by perinatal exposure to stress hormones. It is well known that the most distinctive pattern of neuronal injury observed among preterm infants is found in the periventricular white matter where immature oligodendroglias, responsible for the production of brain myelin, appear to be uniquely sensitive to injury (Back et al., 2007; Buonocore et al., 2001; Volpe, 2001). These cortical and subcortical white matter tracts provide the neuroanatomical framework underlying brain connectivity. These tracts are especially important for the regulation of executive and other "higher order" cognitive functions. Numerous reports have implicated selective deficits in executive functioning as a vulnerability factor in the development of alcoholism (Crews and Boettiger, 2009; Giancola and Moss, 1998; Penick et al., 2010). In addition, volume deficits in subcortical gray matter have been reported in reward-related structures such as the basal ganglia, amygdala, hippocampus, and brain stem of preterm infants (Kaindl et al., 2009; Volpe, 2009). Disruption of these and other neurological systems within the perinatal timeframe could possibly influence both the perception of and response to rewarding events throughout the life of an individual and could therefore markedly elevate the vulnerability to later alcohol and substance use problems.

Adaptive responses to fetal hypoxia, lower birth weight, and perinatal stressors have also been associated with alterations in gene expression patterns by epigenetic mechanisms that are thought to elevate the risk to develop a substance use disorder (Darnaudéry and Maccari, 2008; Gheorghe et al., 2007; Meaney et al., 2007; Roth et al., 2009). Epigenetic modification of the hypothalamic–pituitary–adrenal axis in response to perinatal injury could contribute to a core dysfunction of the stress response system (Meaney et al., 2007), which then might contribute to the development of psychiatric illness, including alcoholism (Adinoff et al., 2005; Gillespie et al., 2009). It is also possible that familial contributions toward alcoholism in men may arise from or be augmented by an increased risk of premature birth among alcoholic families (Levit et al., 2009). For example, differential expression of dopamine D_1 and D_2 receptors has been implicated as a vulnerability factor for both alcoholism (Le Foll et al., 2009) and perinatal asphyxia (Kaewsuk et al., 2009), a leading cause of perinatal brain injury.

Study limitations

We know from previous studies that a large number of subjects with a significant alcohol problem will not seek treatment in their lifetime and therefore will not be identified as alcohol dependent in archival searches of treated individuals. Archival data sources from the Danish Psychiatric Central Research Register may also differentially represent subjects with comorbid psychiatric problems in addition to alcoholism. As a result, the conclusions of this study are limited to the most severely impaired alcoholism groups and may not generalize to all alcohol misusers.

The present study used perinatal measures that are known to correlate with adverse neurodevelopmental outcomes later in life but are not, themselves, direct measures of neurological integrity. Therefore, the association between the six perinatal measures selected for this study and alcoholism in adulthood cannot be definitively linked to neurological sequelae of premature birth. The observed relationship between prematurity and alcoholism may be related to other correlates of prematurity (e.g., maternal parenting) that may be the "true" causal influence. Nevertheless, we believe the most plausible explanation for the findings of this study suggest that the special biological vulnerability of the male baby to the effects of premature birth is associated with an increased risk of developing alcoholism as an adult.

The results of the present study do not consider the influence of the mothers' drinking during pregnancy. Fetal exposure to alcohol has been associated with an increased risk of both fetal growth restriction and alcoholism in the offspring (Ornoy and Ergaz, 2010). Although we do not have specific information regarding the mothers' alcohol use during pregnancy, the level of alcohol use by Danish women in general during this historical time frame is estimated to be very low. We think that it is very unlikely that mothers of male babies drank appreciably more alcohol during their pregnancy than the mothers of female babies. However, it is possible that gender differences in the teratogenic effects of fetal alcohol exposure could differentially influence the risk of developing alcoholism in males and females who are exposed (Haley et al., 2006).

Implications

Our findings suggest that the rates of the most severe forms of alcoholism may be modified by a concerted effort to reduce premature birth, especially among high-risk male babies. Modern technological advancements in neonatal care are likely to offset some or all of the acquired risk associated with prematurity. We would also expect that neurodevel-

opmental contributions to alcoholism would be especially responsive to environmental influences such as parental nurturing and healthy nutrition, which have the potential to correct or override any acquired deficits associated with premature birth. Our findings support the use of targeted interventions to improve childhood developmental outcomes as a strategy to reduce alcoholism among males. A different early intervention strategy may be needed to address alcohol problems in women.

Conclusions

The present study suggests that gender-based biological differences may exist in the origins of alcoholism. Perinatal neurodevelopmental factors, commonly associated with premature birth, independently predicted the development of alcoholism in males but not in females. The intrinsic vulnerability of male newborns to the neurodevelopmental sequelae concomitant with premature birth could represent a causal biological pathway for the development of alcoholism in males. The intrinsic resilience of the female brain toward perinatal neurodevelopmental injury may offer a protective advantage against the development of alcoholism in women. A gender-based difference in the influence of premature birth on the development of alcoholism, such as was found in this study, could contribute to the observed overrepresentation of alcoholism among men.

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