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The Contribution of Parental Alcohol Use Disorders and Other Psychiatric Illness to the Risk of Alcohol Use Disorders in the Offspring

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Abstract

Background—Few population based studies have investigated associations between parental history of alcoholism and the risk of alcoholism in offspring. The aim was to investigate in a large cohort the risk of Alcohol Use Disorders (AUD) in the offspring of parents with or without AUD and with or without hospitalisation for other psychiatric disorder (OPD).

Methods—Longitudinal birth cohort study of 7177 men and women born in Copenhagen between October 1959 and December 1961. Cases of AUD were identified in three Danish health registers and cases of OPD in the Danish Psychiatric Central Register. Offspring registration with AUD was analyzed in relation to parental registration with AUD and OPD. Covariates were offspring gender and parental social status.

Results—Both maternal and paternal registration with AUD significantly predicted offspring risk of AUD (odds ratios 1.96; 95% CI 1.42-2.71 and 1.99; 95% CI 1.54-2.68, respectively). The association between maternal, but not paternal, OPD and offspring AUD was also significant (odds ratios 1.46; 95% CI 1.15-1.86 and 1.26; 95% CI 0.95-1.66, respectively). Other predictors were male gender and parental social status. A significant interaction was observed between paternal AUD and offspring gender on offspring AUD, and stratified analyses showed particularly strong associations of both paternal and maternal AUD with offspring AUD in female cohort members.

Conclusions—Parental AUD was associated with an increased risk of offspring AUD independent of other significant predictors, such as gender, parental social status and parental psychiatric hospitalisation with other diagnoses. Furthermore, this association appeared to be stronger among female than male offspring. The results suggest that inherited factors related to

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alcoholism are at least as important in determining the risk of alcoholism among daughters as among sons.

Keywords

Alcohol use disorder; alcohol abuse; family history; parental risk; cohort study

Introduction

Alcohol dependence has long been recognised to aggregate in families (Bierut et al.,1998; Merikangas et al., 1998; Nurnberger et al., 2004). A genetic component in alcoholism is supported by twin studies (Heath et al., 1997; Nelson et al., 2004; Prescott et al., 1997; Xian et al., 2008) as well as adoption studies (Cloninger et al., 1981; Goodwin et al. 1973, Goodwin et al., 1974; King et al., 2009).

The lifetime risk of alcoholism is lower in women than in men, but few studies have examined the risk of alcoholism in sons and daughters conditional on an alcohol-related diagnosis in either parent. An adoption study of 913 Swedish women showed a 3-fold increase in alcohol abuse among adopted daughters of alcoholic biological mothers (Bohman et al., 1981). In support of the hypothesis that genetic factors contribute to the aetiology of alcoholism in women as well as in men, a population-based twin study in women found heritability estimates in the range of 50 to 60% (Kendler et al., 1992). A recent study of the association between early weaning and risk of alcoholism suggested that the risk of alcoholism in offspring of mothers who had been hospitalised with an alcohol-related diagnosis may be higher than the risk in offspring of fathers with an alcohol-related diagnosis (Sorensen et al., 2006).

To identify markers of future alcoholism, researchers have often used a prospective, high-risk research paradigm by following sons of alcoholic fathers (Goodwin et al., 1999, Goodwin et al., 1994; Schuckit, 1991) or offspring-of-twins designs. The latter studies focus on genetic and environmental factors underlying relationships between parental and offspring risk of alcoholism (Jacob et al., 2003; Slutske et al., 2008) or associations between parental alcoholism and offspring behavioural disorders (Haber et al., 2005; Knopik et al, 2009). However, to examine risk factors for alcoholism in the general population, it is necessary to employ a broader population-based approach. In recent years, data on risk factors for substance abuse have emerged from large birth cohort studies such as the Mater University Study of Pregnancy (MUSP) (Alati et al., 2005), the Copenhagen Metropolit Study (Osler et al., 2006) and the Copenhagen Perinatal Cohort (Brennan et al., 2002). Such studies are well suited to estimate offspring risk of alcoholism conditional on parental history of alcoholism.

We undertook the present study based on the Copenhagen Perinatal Cohort to examine the associations between a parental history of alcoholism and the risk of alcoholism in offspring. Additionally, we addressed the questions of whether other mental disorders in the parents are associated with offspring alcoholism, and whether there are gender differences in the association between parental alcoholism and the risk of alcoholism in the offspring.

Materials and Methods

Sample

The Copenhagen Perinatal Cohort comprises 9125 individuals delivered by 8949 women from October 1959 to December 1961 at the Copenhagen University Hospital, Rigshospitalet. The mothers were mainly residents in Copenhagen, but some non-residents

were admitted on obstetrical indications (Zachau-Christiansen & Ross, 1975). A total of 8400 infants survived the first month after birth. Personal identification numbers, which are required to obtain information from Danish health registers, were available for 7459 parent-child pairs. From this sample second born twins and siblings were excluded, resulting in a study sample comprising 7177 cohort members (3627 men and 3550 women) and their parents. The mean age of the mothers when they gave birth was 26 years and the mean age of the fathers was 30 years.

Alcohol use disorder

Information on alcohol use disorders (AUD) was obtained from three registers. *The Danish Psychiatric Central Register* contains data on all admissions to Danish psychiatric inpatient facilities. It has been computerized since April 1, 1969, and since 1995 outpatients have also been registered (Munk-Jorgensen & Mortensen, 1997). Parents and offspring were followed in the register until May 7, 2007. *The Danish National Hospital Register* was established in 1977 and included all admissions to somatic hospital departments in Denmark until 1994, when it was expanded to also include outpatient and emergency room contacts (Andersen et al., 1999). Parents and offspring were followed in the register until April 24, 2007. In both these registers diagnoses were classified according to the *International Classification of Diseases, 8th Revision* (ICD-8) until 1994, when the ICD-10 was introduced. *The WINALCO-database* (Becker, 2004) contains records of individuals treated for alcohol problems at an outpatient clinic covering the greater Copenhagen and Frederiksberg municipalities since 1954 (Becker, 2004). Parents and offspring were followed in the register until October 7, 2008.

Individuals identified in the *WINALCO-database* were considered to have AUD. The following diagnoses from the two hospital registers were included in the AUD category: ICD-8 diagnoses 303.09, 303.19, 303.20, 303.28, 303.29, 303.91, and 303.99 and ICD-10 diagnoses F10.1, F10.2, F10.3, F10.4, F10.6, and F10.7.

Other psychiatric disorder

In the Danish Psychiatric Central Register parents who had been admitted to psychiatric departments with any other diagnosis than AUD were identified. All non-AUD diagnoses were classified as other psychiatric disorder (OPD).Thus, this broad category included all categories of mental disorder except AUD.

Other potential risk factors

Gender of the cohort member and parental social status when the cohort members were 1 year old were included as covariates. The 1-8 point parental social status index was based on information about breadwinner's occupation, breadwinner's education, type of income, and quality of housing (Zachau-Christiansen & Ross, 1975). Data on parental social status were missing for 1318 cohort members (18.4%): when parental social status was included in statistical models, the overall mean was substituted for missing values, and a dummy variable indicating missing values was included.

Statistical analysis

Initial analyses explored associations between the proportion of cohort offspring who had developed AUD and each potential risk factor. Logistic regression was used in preliminary multivariate analyses to evaluate the linearity of the relationship between parental social status and offspring AUD and to investigate possible interactions between maternal and

paternal AUD with respect to offspring risk of AUD. These interactions were not significant in multivariate analyses.

Three primary analytical models will be presented: **Model 1** examined the unadjusted association with offspring AUD of offspring gender, parental AUD, parental OPD, and parental social status. **Model 2** included offspring gender and parental social status in four analyses that evaluated the adjusted association with offspring AUD of each parental risk factor (maternal AUD, paternal AUD, maternal OPD, and paternal OPD). **Model 3** included the four parental diagnostic categories and, in addition, adjusted for gender and social status. Secondary analyses based on model 3 tested for potential interactions between offspring gender and parental AUD and OPD with respect to offspring risk of AUD. Significant interaction effects were further examined in separate analyses stratified by gender.

Results

In the study population of 7177 offspring cohort members, 466 (6.5%) had been registered with AUD at some time in their life, 321 men (8.9%) and 145 women (4.1%). A total of 5953 cohort members (83.0%) had no parents registered with AUD. Eight hundred and one cohort members had a father registered with AUD and 321 had a mother registered with AUD. There were 102 cohort members with both parents registered with AUD.

Table 1 shows the distribution of paternal and maternal AUD and OPD. The table indicates a considerable overlap between parental registration with AUD and OPD. Of the fathers with AUD, 45.5% also had lifetime registration with OPD, while this was the case for 68.6% of the mothers.

Table 2 shows the number of cases with AUD and the cumulative risk until middle age of the offspring, conditional on father's or mother's registration with 1) AUD without OPD, 2) AUD plus OPD, 3) OPD without AUD and 4) no registration. Maternal AUD and OPD were associated with increased risk of offspring AUD in both male and female offspring. A similar pattern was observed for paternal AUD and OPD, except for paternal OPD without AUD which was not associated with increased risk of AUD in female offspring.

Table 3 (model 1) shows significant predictive effects of offspring gender, parental social status and all four parental diagnostic categories in unadjusted analyses. The column for model 2 shows significant effects of all parental diagnostic categories when adjusted for offspring gender and parental social status. The column for model 3 shows the results of including all variables in the same model. Model 3 shows significant predictive effects of maternal AUD (odds ratio 1.96 with 95% CI 2.23-6.34), paternal AUD (odds ratio 1.99 with 95% CI 1.54-2.58), and maternal OPD (odds ratio 1.46 with 95% CI 1.15-1.86). The effect of paternal OPD registration was weaker and non-significant in this multivariate model, while the effects of both offspring gender and parental social status were clearly significant.

In the study sample, there were 186 adopted children, and an analysis was conducted based on a reduced sample without these children. This analysis showed essentially the same results as those presented in table 3.

There were 1122 individuals with only one parent diagnosed with AUD, while 102 individuals had two parents (a cross-tabulation of maternal and paternal AUD showed statistically significant evidence of assortative mating). A model including parental OPD, gender and social status showed that the risk associated with having AUD in one parent was 2.18 (95% CI 1.72 – 2.76), while the risk associated with having two parents with AUD was 3.06 (95% CI 1.79-5.22).

We further analysed the interaction of offspring gender with the following independent variables: maternal AUD, paternal AUD, maternal OPD, and paternal OPD in models that, in addition to offspring gender and parental social status, included all four parental diagnostic categories. With respect to offspring AUD, the interaction between paternal AUD and offspring gender was significant ($p = 0.02$), while the interaction between offspring gender and maternal AUD was approaching significance ($p = 0.07$). Table 4 shows regression analyses of AUD stratified by gender. Among the 3627 men, both maternal and paternal AUD was associated with significantly increased risk (odds ratios 1.65-1.66), but these effects were stronger among the 3550 females (odds ratios 2.53-2.73). Thus, the data suggest a relatively stronger effect of parental AUD in females compared with males. The interactions between offspring gender and parental OPD were not significant, but table 4 also shows higher odds ratios for parental OPD for female offspring.

Separate analyses showed no significant interactions between parental AUD and OPD with respect to offspring AUD (neither in analyses of the full sample nor in analyses stratified by offspring gender). This was further investigated in an analysis based on a reduced sample that only included offspring of parents without OPD ($n = 5282$). In this analysis, the risks associated with parental AUD were slightly higher than those obtained for model 3 in table 3. In a model including gender and parental social status, the risks were 2.25 (95% CI 1.22-4.14) and 2.32 (95% CI 1.63-3.30) for maternal and paternal AUD, respectively.

Discussion

A diagnosis of Alcohol Use Disorder (AUD) in a parent was associated with a twofold elevated risk of AUD in the offspring. Maternal psychiatric hospitalisation with another mental disorder (OPD) was also associated with an elevated risk. In addition, the results suggest that the association between parental AUD and offspring risk of AUD may be stronger in females than in males; a finding which could have important implications for alcoholism research and treatment. Furthermore, male gender and parental social status were both independent predictors of offspring AUD in this sample.

Our findings support previous reports that implicate familial contributions from both biological parents as a risk factor for the development of alcoholism in the offspring. Our estimate of the risk associated with a parental history of AUD is close to the result of a large family study that used standardised diagnostic procedures and case finding methods unrelated to psychiatric treatment (Nurnberger et al., 2004).

It is a methodological advantage of our study that both genders were followed until they were about 45 years of age, and that our analyses took into account parental social status during upbringing. Controlling for parental social status slightly attenuated the risk estimates associated with parental AUD, and the results of the adjusted analyses indicate that both parental registration with AUD and parental social status are significant and independent predictors of AUD in offspring. Our results should be interpreted in the light of results from a recent Danish cohort study that identified deprived social circumstances during childhood as independent markers of substance abuse in adult life (Osler et al., 2006).

Prenatal alcohol exposure is a risk factor for alcoholism (Baer et al., 2003), and it is a limitation that data on maternal alcohol consumption during pregnancy were not available. However, alcohol consumption among women was quite rare in Denmark when the cohort was established and thus not registered systematically (Zachau-Cristiansen and Ross, 1975) Despite the ability to control for parental social status, it is a potential limitation that the study had relatively limited covariate control pertaining to other factors that confer an

increased risk of alcoholism, for instance parental loss (Kendler et al., 2002) or deprived circumstances during childhood (Osler et al., 2006).

An important limitation of the study is the fact that AUD and OPD diagnoses were register based, and that not all AUD cases will lead to registration. In this study AUD was defined both by hospitalisation with alcohol-related diagnoses and by being registered in an outpatient alcohol clinic. Post hoc analyses showed that the association between offspring and paternal AUD was strongest for registration in the WINALCO database, followed by diagnosis in the Danish Psychiatric Central Register and the Danish National Hospital Register, while the association for maternal AUD was marginally stronger for the psychiatric register than for the outpatient clinic. The relatively weak associations for the Danish National Hospital Register diagnoses may reflect substantial noise in clinical diagnoses of AUD in somatic departments.

Psychiatric Illness in the Parents

Parental OPD also significantly predicted offspring AUD in our sample. This relationship was mainly attributable to a contribution from the mother, as the rates of OPD in fathers without AUD were very low. These results suggest that familial contributions toward offspring risk of alcoholism may not be limited to familial alcoholism, but may also be the result of other psychiatric illness in the family. It is possible that the effect of parental OPD is mediated through an effect on risk of offspring mental disorders associated with increased risk of AUD. Such disorders may not only include attention deficit hyperactivity disorder (Knopik et al., 2009) and conduct disorder (Haber al., 2005), but also depression and anxiety disorders (Flensborg-Madsen et al., 2009). Support for this interpretation was obtained in an analysis that included offspring OPD as predictor. Offspring OPD was associated with an odds ratio of 13, and the effects of parental OPD became nonsignificant, while the effects of parental AUD remained significant. It is also possible that alcoholism played a role in some hospital admissions of parental OPD without being reflected in the clinical diagnoses. Parental OPD also included abuse of other substances than alcohol, but this diagnosis was relatively rare and did not independently predict offspring AUD in a supplementary analysis.

Table 1 shows a stronger association between offspring AUD and OPD in mothers than in fathers, but in the fully adjusted model, the risk of AUD was similar for offspring with maternal AUD and offspring with paternal AUD, while analyses adjusting only for offspring gender and parental social status showed a higher risk associated with maternal AUD. Thus, the present data cannot conclusively define the relative role of mother's vs. father's AUD on offspring AUD.

Gender Difference in Offspring Risk of AUD

In contrast to previous studies of risk factors for alcoholism, this prospective study also investigated the risk of AUD in offspring of both female and male patients with AUD. The results in Table 4 suggest that a stronger association may be present between parental alcoholism and alcoholism in female offspring than in male offspring. A large scale twin study did not find a significant gender difference in genetic variance in AUD (Heath et al., 1997), but a stronger effect of maternal AUD on female than male offspring may be explained by assuming that social learning and identification with the mother play a stronger role in the development of female offspring. However, this would not explain why the effect of a father with AUD also appears to be stronger in women than in men. It may indeed be argued that a stronger effect of parental AUD on female offspring is inconsistent with a previous family study (Lieb et al., 2002) as well as previous Danish adoption studies which failed to identify a genetic component in women (Goodwin et al, 1973, Goodwin et al., 1977, Goodwin et al, 1974). This inconsistency may largely be attributable to the low

prevalence of alcoholism among Danish women in this historical timeframe which severely limited the statistical power in the well-known adoption studies. Thus, it is possible that previous studies underestimated the contribution of genetic inheritance of alcoholism risk in females. The drinking habits of Danish women have changed dramatically during the three decades since the adoption studies were conducted. Thus, it may now be assumed that most Danish women are frequently exposed to alcohol, and since environmental exposure is more uniform, genetic liability may be more evident.

A gender difference in offspring AUD severity might explain the apparently stronger associations with parental AUD in females. However, among all AUD cases almost the same proportion of males and females had an AUD diagnosis from the Danish Central Psychiatric Register (64% and 67%, respectively), and to the extent that admission to psychiatric departments reflects AUD severity, the data do not suggest gender differences.

Conclusion

In this 45-year prospective longitudinal study, parental history of psychiatric hospitalisation with an alcohol-related diagnosis (AUD) was associated with an increased risk of AUD in the offspring, independent of gender, parental social status, and parental psychiatric hospitalisation with other diagnoses. These effects appeared to be stronger in female than in male offspring. The risk of offspring AUD was also increased by a diagnosis of any other psychiatric disorder in the parents. The findings suggest that the familial transmission of alcoholism may be closely related to the transmission of psychiatric illness in general and may influence females to a larger degree than males.

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Table 1

Distribution of cohort members according to parental history of registration with AUD and OPD[1].

		Paternal AUD		Maternal AUD	
		Yes	**No**	**Yes**	**No**
Parental OPD registration	Yes	411 (5.7)	428 (6.0)	290 (4.0)	971 (13.5)
	No	492 (6.9)	5846 (81.4)	133 (1.9)	5783 (80.6)
Total		903 (12.6)	6274 (87.4)	423 (5.9)	6754 (94.1)

[1]AUD = alcohol use disorder, OPD = other psychiatric disorders

Table 2

Number and percentage (with 95% confidence intervals) of cases with AUD in offspring conditional on parental registration with AUD and OPD.

	Males		Females	
	Cases/n[1]	% and 95% CI	Cases/n	% and 95% CI
Maternal registration				
AUD without OPD	10 / 67	14.9 (7.4-25.7)	6 / 66	9.1 (3.4-18.7)
AUD and OPD	26 / 147	17.7 (11.9-24.8)	21 / 143	14.7 (9.3-21.6)
OPD without AUD	57 / 488	11.6 (9.0-14.9)	27 / 483	5.6 (3.7-8.0)
No maternal registration	228 / 2925	7.8 (6.8-8.8)	91 / 2858	3.2 (2.6-3.9)
Paternal registration				
AUD without OPD	36 / 230	15.7 (11.2-21.0)	21 / 262	8.0 (5.0-12.0)
AUD and OPD	33 / 203	16.3 (11.5-22.1)	29 / 208	13.9 (9.5-19.4)
OPD without AUD	23 / 212	10.8 (7.0-15.8)	7 / 216	3.2 (1.3-6.6)
No paternal registration	229 / 2982	7.7 (6.7-8.7)	88 / 2864	3.1 (2.5-3.8)
Both parents AUD	9 / 55	16.3 (7.8-28.8)	12 / 47	25.5 (13.9-40.3)

[1] n refers to the number of offspring with a mother or a father with this particular combination of AUD and OPD.

Table 3

Odds ratios, with 95% confidence intervals, for AUD in offspring according to parental AUD, parental psychiatric registration, offspring gender and parental social status.

Independent variables	Odds ratio with 95% CI		
	Model 1[1]	Model 2[2]	Model 3[3]
Maternal registration with AUD	2.76 (2.07-3.67)	2.69 (2.01-3.60)	1.96 (1.42-2.71)
Paternal registration with AUD	2.59 (2.08-3.23)	2.36 (1.88-2.96)	1.99 (1.54-2.58)
Maternal registration with OPD	1.93 (1.56-2.39)	1.84 (1.48-2.28)	1.46 (1.15-1.86)
Paternal registration with OPD	1.96 (1.54-2.50)	1.84 (1.44-2.35)	1.26 (0.95-1.66)
Male gender of cohort member	2.28 (1.86-2.79)	2.32-2.36	2.37 (1.93-2.90)
Social Status: Linear effect	0.80 (0.75-0.85)	0.80-0.82	0.83 (0.78-0.89)

[1] Unadjusted associations.

[2] Models for each of the four parental diagnoses adjusting for gender and parental social status (linear effect). For gender and social status the range of odds ratios for the four models is shown.

[3] Model included the four parental diagnostic categories, gender and social status (linear effect).

Table 4

Gender stratified analysis showing odds ratios, with 95% confidence intervals, for psychiatric hospitalisation with AUD in offspring according to parental psychiatric registration with AUD and OPD[1].

	Odds ratio with 95% CI	
Parental registration	**AUD in males**	**AUD in females**
Maternal registration with AUD	1.65 (1.09-2.52)	2.53 (1.52-4.21)
Paternal registration with AUD	1.66 (1.19-2.32)	2.73 (1.80-4.13)
Maternal registration with OPD	1.37 (1.02-1.84)	1.70 (1.13-2.55)
Paternal registration with OPD	1.20 (0.84-1.71)	1.36 (0.86-2.15)
Social Status: Linear effect	0.83 (0.76-0.90)	0.83 (0.74-0.94)

[1] Each model included the four parental diagnostic categories and social status (linear effect).