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The risk of offspring developing substance use disorders when exposed to one versus two parent(s) with alcohol use disorder: A nationwide, register-based cohort study

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ABSTRACT

Aim: Few population-based, family studies have examined associations between exposure to one vs. two parent(s) with alcohol use disorder (AUD) and the risk of offspring developing substance use disorder (SUD). Moreover, these studies have focused solely on the development of AUD, and not SUD, in offspring. The purpose of this study was to investigate whether exposure to one vs. two parent(s) with AUD increases the risk of offspring developing SUD.

Methods: A population-based, cohort study was conducted in which offspring born in Denmark between 1983 and 1989 were followed through national registries until 2011. Register-based data were obtained from the: Psychiatric Central Research Register, National Patient Registry, Civil Registration System, Fertility Database, and Cause of Death Register. Adjusted hazard ratios were calculated using multivariate Cox-regression models.

Findings: A total of 398,881 offspring were included in this study. Of these, 3.9% had at least one parent with AUD. Parental AUD was significantly associated with the development of SUD in offspring. Having one parent with AUD was linked to a 1.44-fold increased risk (95% CL, 1.29–1.61), while having two parents with AUD was linked to a 2.29-fold increased risk (95% CI, 1.64–3.20). No significant differences were found in relation to either parental or offspring gender.

Conclusions: Exposure to parental AUD is linked to an increased risk of offspring developing SUD. This risk is additive for offspring exposed to double parental AUD. The findings have important implications for clinical assessment and intervention strategies, as well as the management of offspring exposed to parental AUD.

1. Introduction

Alcohol use disorders (AUD) are a serious and widespread public health problem in Europe. The mean prevalence of AUD in the general population is 7.5%, although large variations across countries have been noted (WHO, 2014). In Denmark, approximately 17% of the adult population is believed to have AUD (Hansen et al., 2011). As a consequence, the risk of growing up in a family where one or even two parent(s) suffer from AUD is elevated.

Parental AUD tends to aggregate in families, and may be transmitted to offspring through genetic and environmental influences (McGue, 1994; Merikangas, 1990; Verhulst et al., 2015). Both twin and adoption studies show that AUD has a heritability rate of 50% and that general environmental effects exert a modest influence (Verhulst et al., 2015). Despite this apparently modest

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environmental effect, there is evidence to suggest that direct exposure to alcoholic environments through parents (e.g. parental modeling of drinking, alcohol-specific parenting style) may represent a major risk factor for the development of AUD in offspring (Christoffersen and Soothill, 2003; Finan et al., 2015; Handley and Chassin, 2013; Hawkins et al., 1992; Latendresse et al., 2008; Stone et al., 2012). In addition to the twin- and adoption studies, as well as studies on specific environmental risk factors, several family studies report that offspring exposed to parental AUD are at risk of developing AUD, as well as other SUD's (Christoffersen and Soothill, 2003; Hill et al., 2011; Marmorstein et al., 2009; Merikangas et al., 1998; Nurnberger et al., 2004; Sørensen et al., 2011). Hence, one would expect that exposure to double parental AUD should result in an additive effect of influences that further increase the risk of offspring developing addictive behaviour. However, little attention has been devoted to examining the specific associations between exposure to single vs. double parental AUD and the risk of offspring developing AUD. Furthermore, the few family studies found in this area focused solely on the transmission of AUD (Lieb et al., 2002; Yoon et al., 2013), and not SUD, which comprises several addictive disorders. Addictive disorders do not necessarily manifest themselves through the same drug of choice in offspring as they do in parents (Hill et al., 2011; Kendler et al., 2003; Krueger et al., 2002; Nurnberger et al., 2004; Tsuang et al., 2001; Young et al., 2006), whereby an extended association between parental AUD and SUD in offspring is possible. Indeed, AUD-AUD studies illustrate that offspring have an additive risk of developing AUD when exposed to either single or double parental AUD (Lieb et al., 2002; Yoon et al., 2013).

In considering the available evidence, we hypothesized that the number of AUD parents (one vs. two parents) is predictive of whether offspring have an additive risk of developing SUD. Given that SUD comprises several addictive disorders, and thus constitutes a broader outcome measure than AUD, we expect offspring to have an even greater additive risk of developing SUD.

The aim of this study was to investigate whether exposure to one vs. two parent(s) with AUD is associated with an increased risk of SUD developing in offspring.

2. Method

2.1. Data and subjects

Danish national registries offer unique opportunities for researchers to conduct population-based studies on the effects of various exposures. The authors performed a cohort study using Danish, collected, longitudinal register data from the: Psychiatric Central Research Register (covering psychiatric hospitalisations) (Mors et al., 2011), Danish National Patient Registry (covering somatic hospitalisations) (Lynge et al., 2011), Fertility database (Blenstrup and Knudsen, 2011), Cause of Death Register (Helweg-Larsen, 2011), and Civil Registration System (Pedersen, 2011). Data from the different registries were linked using Denmark's unique civil registration number, a personal identification number assigned to all Danish residents since 1968 (Pedersen, 2011).

Individuals born during the period 1983–1989 were followed from birth or immigration until the end of the study period (December 31st, 2011), death, emigration, or examined outcome. Individuals who immigrated back to Denmark were not re-included in the study. This cohort was selected in order to analyse a relatively young population in present time, and to secure perfect linkage to parents. A link to biological or legal parents was established through the Civil Registration System and the Birth Registry. Denmark provides free public health care to all citizens regardless of their income.

2.2. Outcome

The outcome in this study was SUD, which also covered AUD, in offspring, i.e. adolescents and young adults. In Denmark, individuals are diagnosed with SUD using the 8th or 10th revision of the International Classification of Diseases (ICD) when in contact with a psychiatric or somatic hospital (Organization, 1992). An SUD diagnosis is made on the basis of a medical examination adhering to the ICD criteria. The 9th version (ICD-9) was never implemented in Denmark. Records of either a main or sub-diagnosis of SUD (covering harmful use or dependence of alcohol, opioids, cannabis, sedatives, hypnotics, cocaine, other stimulants, hallucinogens, volatile solvents and multiple drug use) were obtained from the Psychiatric Central Research Register and the Danish National Patient Registry (the specific ICD-8 and ICD-10 codes are listed in Appendix A1). The date of the first recorded SUD diagnosis in offspring was chosen as the date for the outcome.

2.3. Exposure

The exposure in this study was parental AUD, defined as parents recorded as having received a diagnosis of harmful use or dependence of alcohol in the Psychiatric Central Research Registry or the Danish National Patient Registry (listed in Appendix A1). The date of the first recorded AUD diagnosis in parents was chosen as the date for the exposure.

In order to assess for a dose-response relationship (additive risk), a covariate with the following categories was created: I) no parent with AUD (baseline), II) one parent with AUD, and III) both parents with AUD.

2.4. Analyses

Survival analysis was applied to estimate the risk of offspring developing SUD as a function of age. Probability estimates for the development of SUD in relation to age of offspring and associated confidence intervals were expressed as Kaplan Meier curves.

Cox proportional hazard models were used to estimate the effect of parental AUD on the risk of offspring developing SUD. The time-unit was age measured as days. Effects were examined in both crude (unadjusted) and adjusted models covering both offspring-related and parent-related confounders. Hazard ratios (HR), that is, the ratio of the rate at which individuals in the examined groups experienced outcome events, as well as the corresponding p-value and 95% confidence intervals (CI), were obtained. All analyses were stratified by year of birth. The Cox proportional hazard models assume a proportional (constant) hazard ratio across time. Thus, we tested the proportionality for parental AUD by examining time-dependent covariates of parental alcohol abuse. Proportionality was fulfilled for maternal and paternal AUD, as well as the joined maternal and/or paternal alcohol abuse factor.

Offspring-related confounders included gender, psychiatric diagnoses other than SUD (schizophrenia, schizotypal, and delusional disorders/affective disorders/neurotic, stress-related, and somatoform disorders/disorders of adult personality and behaviour) (listed in Appendix A1), as well as numerous contacts to a psychiatric hospital (defined as three or more contacts and used as a proxy for illness severity).

Parent-related confounders included psychiatric diagnoses other than SUD (schizophrenia, schizotypal, and delusional disorders/affective disorders/neurotic, stress-related, and somatoform disorders/disorders of adult personality and behaviour), numerous contacts to a psychiatric hospital (defined as three or more contacts and used as an indicator of illness severity), parental death, as well as level of parental income (high/medium/low/missing).