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Parental alcohol use disorder with and without other mental disorders and offspring alcohol use disorder

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ABSTRACT

Objective: To examine the association between parental alcohol use disorder (AUD) with and without other mental disorders and offspring AUD.

Methods: Using data from Danish nationwide registers, we identified 15,477 offspring with parental AUD and 154,392 reference individuals from the general population. Parental AUD was defined as registration for AUD treatment. Parental mental disorders were identified in medical registers and comprised psychotic, mood, anxiety, personality, drug use, and other non-alcohol-related mental disorders. AUD in offspring was identified from medical, pharmacy, treatment, and causes of death registers. Hazard ratios (HRs) of AUD were estimated using Cox regression models.

Results: AUD in one or both parents was associated with higher risks of AUD in offspring compared with reference individuals. Paternal AUD plus other mental disorder (HR = 2.27, 95% CI: 2.10–2.45) and paternal AUD alone (HR = 2.21, 95% CI: 2.08–2.37) were associated with higher offspring AUD risk. Similarly, maternal AUD plus other mental disorder (HR = 3.02, 95% CI: 2.66–3.43) and maternal AUD alone (HR = 2.57 95% CI: 2.20–3.01) were associated with higher offspring AUD risk.

Conclusions: Offspring with parental AUD are at increased risk of AUD irrespective of exposure to other parental mental disorders.

KEY WORDS

alcohol drinking, alcoholism, mental disorders, cohort studies, epidemiology

SIGNIFICANT OUTCOMES

- Offspring of parents with AUD were at higher risk of AUD compared with offspring from the reference population.
- We did not find support for the hypothesis that other mental disorders in fathers or mothers with AUD were associated with higher risks of AUD in the offspring compared with offspring of fathers or mothers with AUD only.

LIMITATIONS

- Offspring AUD was based on multiple data sources, and the assessment was therefore partly based on administrative data that are not equivalent to AUD diagnoses based on diagnostic criteria.
- The temporal directionality of AUD and other mental disorders in parents was not considered, and it therefore remains unknown whether temporality affected risk of offspring AUD.

INTRODUCTION

Alcohol use disorders (AUDs) are among the most common mental disorders worldwide (1, 2). In Europe, the overall prevalence is 7.5%, with considerable variations across countries (3). Research has established that AUD aggregates in families (4). An extensive body of evidence from twin (5, 6), adoption (6-8), and family studies (9-11) has demonstrated that parental AUD is a strong risk factor for offspring AUD. Moreover, parental alcohol drinking and parental AUD have been associated with drinking behavior (12, 13), positive alcohol expectancies (14), drinking at an early age (15, 16), frequent drinking (9), and alcohol-related problems (17).

Some issues still warrant consideration in the association between parental AUD and offspring AUD, including the role of other mental disorders in parents. It has long been acknowledged that AUD is highly comorbid with common and severe mental disorders including psychotic, mood, anxiety,

personality, and substance use disorders (18-21). More than half of individuals with AUD have a comorbid mental disorder, which is a much higher prevalence than in the general population (22). Research has confirmed that individuals with AUD and other mental disorders have more severe symptoms, higher risk of relapse, more frequent physical health problems, and are more treatment-resistant (23-25). However, few studies have systematically investigated the role of other parental mental disorders in the relationship between parental AUD and offspring AUD, and the results are inconsistent. Findings from cross-sectional studies have shown higher risks of AUD among individuals with parental AUD and other mental disorders than among individuals with parental AUD only (26, 27). (30)Conversely, results from a prospective register-based birth-cohort study showed no interactions between parental AUD and other psychiatric disorders with respect to the risk of offspring AUD (10). This study was limited, however, by only using an overall measure of mental disorders in parents. To the best of our knowledge, no cohort studies have investigated the association between parental AUD and offspring AUD looking separately at offspring of parents with and without specific mental disorders. As Danish nationwide registers have high coverage and contain detailed information (28), they are useful for investigating this particular issue.

Aims of the study

In this large register-based cohort study, we investigated the association between parental AUD with or without other mental disorders and AUD in the offspring. Other parental mental disorders were assessed (i) as an overall measure and (ii) separately as psychotic disorder, mood disorder, anxiety disorder, personality disorder, drug use disorder, and other non-alcohol-related mental disorders.

MATERIAL AND METHODS

Design

We conducted a cohort study based on the offspring of members of the Copenhagen Alcohol Cohort (COPAC) and a reference population of randomly selected individuals from the general Danish

population. Information was obtained from registers with national coverage and linked using each study participant's unique personal identification number (PIN). The PIN is a ten-digit number assigned to every Danish citizen at birth. It is used consecutively across all Danish registers, thus enabling linkage between registers (29).

Data sources for the study were the COPAC database and seven national registers. COPAC contains information on individuals attending alcohol treatment from 1954–2009 at five outpatient clinics located in somatic hospitals covering the greater Copenhagen area. A diagnosis of the alcohol use disorder was based on the International Classification of Diseases Revision 8 (ICD-8) (until 1993) or Revision 10 (ICD-10) (since 1994) at time of treatment enrollment (30). The registers used were the Danish Civil Registration System, providing information on family relations, sex, date of birth, emigration status, and vital status from 1968 onwards (31); the National Registry of Alcohol Treatment, containing information on publicly financed alcohol treatment from 2006 onward; the Danish National Patient Register, containing information on admissions to non-psychiatric hospital departments from 1977 onwards (32); the Danish Psychiatric Central Research Register, providing information on psychiatric admissions to mental hospitals and psychiatric departments from 1969 onwards (33); the Danish National Prescription Registry, providing information on prescription drugs dispensed for Danish citizens at Danish pharmacies from 1991 onwards (34); the Danish Register of Causes of Death, containing dates and causes of death from 1970 onwards (35); and the Population's Education Register, providing data on highest achieved education from 1981 onwards (36) (Table S1).

Participants

From COPAC, we included 27,844 individuals with a diagnosis of AUD (ICD-8: 3030–3032, ICD-10: F101–F104 including all sub-levels). According to the Danish Civil Registration System, 16,106 (58%) were registered as parents to a total of 30,318 offspring. Offspring were included in this study if

they: 1) were born in Denmark in 1953 or later (i.e. were <15 years when the PIN was introduced); 2) were at least 15 years at end of follow-up; 3) were registered with a living address in Denmark at their 15th birthday; 4) had two parents with a valid PIN; and 5) had at least one parent registered in COPAC prior to their 15th birthday (n=15,585). A reference population was constructed by applying criteria 1–4 to all individuals registered in the Danish Civil Registration System; individuals were excluded if they had at least one parent registered in COPAC. We randomly sampled ten reference individuals per individual with parental AUD, using incidence density sampling with replacement and matching on sex, birth date (± one year), and living area (municipality) at 15th birthday. Next, we excluded individuals registered with AUD before their 15th birthday to ensure that no offspring had the outcome of interest preceding baseline. The final cohort consisted of 15,477 individuals with parental AUD and 154,392 reference individuals (Figure S1).

Measures

Predictors

Parental mental disorders (other than AUD) were defined as registration within the Danish National Patient Register or the Danish Psychiatric Central Research Register with any non-alcohol-related mental disorder (excluding ICD-8: 3030–3032, ICD-10: F101–F104, including all sub-levels) before the study participant's 15th birthday. Six diagnostic categories inspired by Flensborg-Madsen, Knop (37) were applied: 1) psychotic disorders (ICD-8: 295, 297, 298.1-9, 299, ICD-10: F20-29), 2) mood disorders (ICD-8: 296, 3004, 2980, ICD-10: F30-39), 3) anxiety disorders (ICD-8: 3000, 3002, 3003, ICD-10: F40-43), 4) personality disorders (ICD-8: 301, 30019, 30069, 30079, 30089, 30099, ICD-10: F60-F69), 5) drug use disorders (ICD-8: 304, ICD-10: F11-19 — except F17) and 6) all other non-alcohol-related mental disorders (diagnoses not belonging in any of the above categories). Time of onset of each mental disorder was defined as the date of first registration (inpatient, outpatient, or emergency department).

Outcome

Offspring AUD was based on at least one of the following: 1) registration in the National Registry of Alcohol Treatment; 2) redemption of at least one prescription of Disulfiram, Calcium carbamide, Acamprosate, Naltrexone, or Nalmefene (Anatomical Therapeutic Chemical Classification System (ATC) code: N07BB) in the Danish National Prescription Registry; 3) registration in COPAC; 4) diagnosis of AUD (ICD-8: 29109, 29119, 29129, 29139, 29199, 3030-3032, 30390, 30391, 30399, 57109, 57110, 5770, 57710, 57719, ICD-10: F10, G312, G621, G721, I426, K292, K70, K860, including all sub-levels) as main or secondary diagnosis in the Danish National Patient Register or in 5) the Danish Psychiatric Central Research Register; or 6) as underlying or supplementary cause of death in the Danish Register of Causes of Death. Time of onset of AUD was defined as the first registration in one of the above-mentioned registers.

Analyses

Using a Cox regression model, we estimated hazard ratios (HRs) with 95% confidence intervals (95% CIs) for AUD, with calendar dates as the time scale. Follow-up time started on the study participant's 15th birthday and ended at time of onset of AUD, death by other causes than AUD (n=3,325), loss to follow-up (n=5,665; 97.5% due to immigration, 2.5% due to disappearance), or end of follow-up (10th March 2018) (n=148,884), whichever occurred first. In total, 3,749,028 (median 21.5, standard deviation [SD] 12.9) person-years at risk were observed. A Chi-squared test showed a statistically significant different association between paternal and maternal AUD on offspring AUD ($P < 0.000$), thus all analyses were stratified by parental sex. All analyses were adjusted for offspring sex, birth date, and living area (matching criteria), and the fully adjusted analyses were further adjusted for father's year of birth, mother's year of birth, and family education level defined as the highest achieved educational level by either parent (*basic/secondary, vocational, short, medium, high*, or *unknown*). Robust estimations of standard error which allowed for the possibility of intragroup correlations were used, and we defined a group as the individual with parental AUD together with

the corresponding reference individuals. The proportional hazards assumption was inspected by graphical assessment of log-log plots, and the assumption was met. Chi-squared tests and t-tests were performed to test for differences in population characteristics. Chi-squared test was used to test differences regarding offspring sex and which parent had AUD. Likelihood ratio test was used to test a model including interaction between parental AUD and other mental disorder against a model without interaction. In supplementary analyses, the likelihood ratio test was used to test a model including interaction between parental AUD and offspring sex against a model without interaction. Age-specific cumulative lifetime incidence rates of AUD were estimated with the Kaplan-Meier method. Sensitivity analyses were conducted where offspring AUD was restricted to registration in an alcohol treatment register (criteria 1-3 for *AUD in offspring*). SAS Software 9.4 was used for data management, and STATA/IC 15 was used for analyses. The significance level was set to a p-value of 0.05 (two-sided).

Ethics approval

The study was approved by the Danish Data Protection Agency (2012-58-0004; AHH-2015-018, I-Suite no: 03676). Because the study did not require any contact with the participants, no written informed consent was required according to Danish law.

RESULTS

Table 1 presents some characteristics of the study population. Family education level, father's year of birth, and mother's year of birth differed significantly between offspring of parents with AUD and the reference population.

AUD in offspring by AUD in parents

Among offspring of parents with AUD, 2,251 (incidence rate [IR] = 7.0 per 1,000 person-years) developed AUD compared with 9,744 (IR = 2.8 per 1,000 person-years) reference individuals. Table 2 shows the hazard ratios (HRs) of AUD in offspring according to parental AUD. Parental AUD was associated with a HR of 2.28 (95% confidence interval [95% CI] 2.18–2.39) compared with reference individuals. Compared with the reference population, AUD in both parents was associated with more than threefold HRs of AUD. Having a mother with AUD, as opposed to a father with AUD, was associated with a higher HR for offspring AUD ($P < 0.000$). No sex differences were observed in offspring risk of AUD (Table S2).

AUD in offspring by other mental disorders in parents

Table 3 shows that offspring of fathers and mothers with a non-alcohol-related mental disorder had higher HRs of AUD when compared with offspring of fathers and mothers without a non-alcohol-related mental disorder. Offspring of fathers who had a mental disorder in the 'other' category were at higher risk of AUD when compared with offspring of fathers who did not have a mental disorder in the "other" category. Likewise, maternal registration with a mental disorder in the "other" category and maternal drug use disorder were associated with higher HRs of offspring AUD.

AUD in offspring by AUD with and without other mental disorders in parents

The HRs for AUD were 2.27 (95% CI 2.10–2.46) for offspring of fathers who had AUD plus other mental disorders, 2.21 (95% CI 2.07–2.36) for offspring of fathers who had AUD only, and 1.68 (95% CI 1.55–1.83) for reference individuals of fathers with mental disorders when compared with reference individuals of fathers without any mental disorder (Table 4). Compared with reference

individuals of mothers without any mental disorder, HRs for AUD were 3.02 (95% CI 2.66–3.43) for offspring of mothers who had AUD plus other mental disorders, 2.57 (95% CI 2.20–3.01) for offspring of mothers who had AUD only, and 1.51 (95% CI 1.30–1.76) for reference individuals of mothers with mental disorders.

The Kaplan-Meier estimator showed that, at all ages, lowest AUD incidences were observed in reference offspring of fathers and mothers without any other mental disorder. From approximately 25 and 20 years of age, the highest incidences of AUD were found among offspring of fathers and mothers with AUD – irrespective of whether the parent had other mental disorders (Figure S2).

HRs for AUD were higher among offspring of fathers and mothers who had AUD regardless of whether the AUD was comorbid with psychotic disorder, mood disorder, anxiety disorder, personality disorder, drug use disorder, or a disorder in the "other" category when compared with individuals from the reference population who had a father or mother without the given mental disorder (Table 5). Offspring of fathers with AUD and mood disorder had a lower risk for AUD than offspring of fathers with AUD and no mood disorder. HR for AUD was also lower in offspring of fathers who had AUD and anxiety disorder than in offspring of fathers who had AUD without anxiety disorder. The HRs for AUD were higher for individuals from the reference population who had a father with mood disorder, anxiety disorder, personality disorder, drug use disorder, or those in the "other" category compared with offspring of fathers without the given mental disorders. Among offspring of mothers with AUD, the adjusted HRs for AUD did not differ according to whether the mother had any of the examined mental disorders. Reference individuals of mothers who had drug use disorder or a disorder in the "other" category had higher HRs of AUD compared with offspring in the reference population of mothers without the given mental disorders.

Sensitivity analysis

Additional analyses showed a higher risk (HR = 2.71; 95% CI 2.55–2.88) for offspring AUD when we restricted offspring AUD to registration in an alcohol treatment register. With this definition, HRs for AUD were 2.82 (95% CI 2.56–3.11) for offspring of fathers who had AUD with other mental disorders, and 2.52 (HR = 2.31–2.74) for offspring of fathers who had AUD only (χ^2 = 1, degrees of freedom [df] = 3.59, *P* = 0.058). HRs for AUD were 3.55 (95% CI 3.01–4.20) among offspring of mothers with AUD and other mental disorders, and 3.17 (95% CI 2.57–3.90) among offspring of mothers with AUD only (χ^2 = 1, df = 0.92, *P* = 0.338) (not shown).

DISCUSSION

In this nationwide register-based cohort study of 15,477 offspring of parents with AUD and 154,392 reference individuals from the general Danish population, we found a more than two-fold higher risk for AUD in offspring of parents with AUD when compared with individuals from the general population. Maternal AUD was associated with a higher risk of offspring AUD than was paternal AUD. We found no evidence for higher HRs for AUD in offspring of fathers and mothers who had AUD comorbid with other mental disorders, either when assessed as an overall measure or as six types of mental disorders, when compared with offspring of fathers and mothers with AUD only. Modestly elevated relative risks for AUD were found in the reference population if the parent had a non-alcohol-related mental disorder.

(12, 45)

Our finding of higher HRs of AUD in offspring of parents with AUD corresponds well with results from other register-based cohort studies on parental AUD and offspring risk of AUD or substance use disorder (which includes AUD) (10, 38). Elevated risks of AUD among offspring of parents with AUD may be explained by genetic heritability and environmental factors (6). The higher risk of AUD among offspring with maternal AUD compared to paternal AUD may be because offspring more

often live with their mother than their father, even when the mother has AUD (39). Moreover, maternal AUD is associated with a less cohesive and organized family environment which negatively affects family functioning (40).

(46)Our finding that risks of AUD were similar among offspring of parents with AUD and other mental disorder compared with offspring of parents with AUD only may be due to various mechanisms. Compared to families with AUD only, it is likely that families with AUD and other mental disorders are more easily recognized by health professionals and the authorities, leading to the necessary arrangements to be taken in relation to the children. Moreover, because families with parental AUD are more likely than other families to be characterized by high levels of conflict (41, 42), aggression, and violence (43, 44) as well as inadequate parenting (45, 46), children of parents with AUD may suffer so many adverse consequences that the presence of other mental disorders in the parents does not impose further negative impacts. This may especially be the case in clinical populations due to more severe AUD among these individuals (21, 47). Our results are in line with those reported in a prospective register-based birth-cohort study from Denmark, where separate effects of parental AUD and other mental disorders on offspring AUD risk were found but without an interaction between parental AUD and other mental disorders in relation to offspring AUD. In contrast, Ohannessian, Hesselbrock (27) observed that adolescents of alcohol-dependent parents with comorbid mental disorders were at higher risk for developing psychopathology, including alcohol dependence, than adolescents of parents with alcohol dependence only. Moreover, Jung, Goldstein (26) showed markedly higher risks of AUD in individuals with a family history of AUD co-occurring with drug use disorder, depression, anxiety disorder, or antisocial behavior compared with individuals with a family history of AUD without any of the mental disorders. Family history was defined as parents and grandparents, however, with no distinction between family members.Jung, Goldstein (28) Additionally, the divergent findings in relation to our study may be a result of differences in study design, study participants, assessment of AUD and comorbid mental disorders,

and examination of different mental disorders. In sum, these heterogeneous characteristics make it difficult to compare results across studies.

Against our expectations, we observed lower HRs of AUD in offspring of fathers who had AUD and mood or anxiety disorder than in offspring of fathers who had AUD without mood or anxiety disorder. It is possible that pathways of protective factors against the development of AUD exist when a father has both AUD and mood or anxiety disorder. For instance, different patterns of concurrent or sequential mental disorder comorbidity might be present, so that neither the father's AUD nor the mental disorder interfered strongly with the environment in which the offspring grew up. Additionally, molecular genetic data support a causal influence of major depressive disorder (MDD) on alcohol dependence (48). The self-medication hypothesis could thus be consistent with our observations in that the father's AUD would be "caused" by his MDD. Some offspring with paternal MDD and AUD do not necessarily develop MDD themselves – or they could develop MDD and AUD later in life than could be observed in our study. Maternal AUD plus mood or anxiety disorder was not associated with lower risk of offspring AUD compared with maternal AUD only – however, offspring risk of AUD was more than two-fold regardless of whether the mother had AUD only or AUD with mood or anxiety disorder. Maternal AUD has been found to be associated with graver consequences for offspring than paternal AUD (39, 49-51), (45)which may partly explain why maternal and paternal AUD with or without mood or anxiety disorder affect offspring differently.
We observed modestly elevated risks for AUD among offspring in the reference population of fathers and mothers with other mental disorders. It is possible that offspring of parents with, for example, schizophrenia or major depressive disorder mainly carry higher liabilities for these specific disorders, and to a lesser extent for AUD (52).

The major strengths of this study include the large study population consisting of both men and women, the long study period with a median of 22 years of follow-up, and the use of prospective

data from several nationwide registers with continuously updated information. Inclusion of the whole spectrum of ICD-8 and ICD-10 mental disorders allowed us to examine other mental disorders as an overall measure and also as specific mental disorders.

Some limitations of this study should be noted. First, offspring AUD was based on registration in at least one of six registers. Despite the comprehensiveness of this approach, identification of AUD cases required that the offspring had at least one AUD-related contact to a somatic or psychiatric department or had been prescribed medication for AUD. While this approach most likely identified the severe cases of AUD, milder cases might not have been identified. Moreover, the assessment was partly based on administrative data that are not equivalent to AUD diagnoses based on diagnostic criteria. As individuals treated for AUD differ from untreated individuals (21, 47), we therefore expect that offspring classified as having AUD in this study covered a broad spectrum of AUD severity. However, research shows that only 30-50% of individuals with AUD enter treatment over lifetime (53, 54) and often several years after the onset of first AUD symptoms (54, 55). Therefore, by applying a broad definition of offspring AUD, we identified some cases of offspring AUD which would not have been identified if AUD was based solely on alcohol treatment registers. Additionally, we did not consider the temporal directionality of AUD and other mental disorders in parents, and how this might have affected risk of offspring AUD. Empirical studies report conflicting results in relation to the temporal order (18, 22). Some explanations have been proposed regarding the nature and temporal ordering of AUD and other mental disorders, but as the etiology of AUD and other mental disorders is complex and consists of several genetic, psychological, and social factors, several mechanisms might be true. Last, we cannot exclude that residual confounding may have influenced our results to some degree. For instance, one important confounder may be whether the offspring lived together with the parent with AUD. A recent study showed that offspring of parents with AUD are more likely to live with their mother than their father, regardless of whether it is the mother who has AUD (39). This may explain why higher risk of AUD was found

among offspring of mothers with AUD than fathers with AUD. However, while a recent large study showed that boys and girls living with their parent with alcohol problems had higher risks of early intoxication debut age, and girls had higher weekly alcohol consumption, no association was found between living with the parent with alcohol problems and abstention and frequent binge drinking in either boys or girls (12).

In conclusion, offspring of parents with AUD had higher risks of developing AUD compared with individuals from the general Danish population. Our findings did not reveal any additional risk of AUD in offspring of fathers or mothers with AUD plus other mental disorders than in offspring of fathers or mothers with AUD alone. This suggests that, irrespective of other parental mental disorders, offspring of parents with AUD are high-risk individuals for AUD who require targeted preventive efforts. Further investigations are still needed to clarify the mechanisms by which other mental disorders in parents might affect the association between parental AUD and offspring AUD. More knowledge could provide important information for clinicians and others working with individuals with AUD and their families, especially in settings of family-based prevention and treatment programs.

Authors' contributions

Holst, C: conceptualized the study, acquired the data, conducted the data analysis and interpreted the data, drafted the article, and approved the final version.

Tolstrup, JS: conceptualized the study, participated in the data analysis, interpretation of data, and in drafting of the article, and approved the final version.

Sørensen, HJ: conceptualized the study, participated in the data analysis, interpretation of data and in drafting of the article, and approved the final version.

Pisinger, VSC: participated in the data analysis and interpretation of data, revised the article, and approved the final version.

Becker, U: conceptualized the study, acquired the data, participated in the data analysis, interpretation of data, and in drafting of the article, and approved the final version.

All authors provided substantial contributions, and the corresponding author attests that all listed authors meet authorship criteria, and that no others meeting the criteria have been omitted. CH is the guarantor.

REFERENCES

1. Rehm J, Anderson P, Barry J, Dimitrov P, Elekes Z, Feijao F, et al. Prevalence of and potential influencing factors for alcohol dependence in Europe. Eur Addict Res. 2015;21(1):6-18.
2. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. The Lancet. 2013;382(9904):1575-86.
3. World Health Organization. Global status report on alcohol and health 2014. World Health Organization; 2014.
4. Cotton NS. The familial incidence of alcoholism: a review. J Stud Alcohol. 1979;40(1):89-116.
5. Kendler KS, PirouziFard M, Lonn S, Edwards AC, Maes HH, Lichtenstein P, et al. A National Swedish Twin-Sibling Study of Alcohol Use Disorders. Twin Res Hum Genet. 2016;19(5):430-7.
6. Verhulst B, Neale MC, Kendler KS. The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. Psychol Med. 2015;45(5):1061-72.
7. Kendler KS, Ji J, Edwards AC, Ohlsson H, Sundquist J, Sundquist K. An extended Swedish national adoption study of alcohol use disorder. JAMA Psychiatry. 2015;72(3):211-8.
8. Yoon G, Westermeyer J, Warwick M, Kuskowski MA. Substance use disorders and adoption: findings from a national sample. PLoS One. 2012;7(11):e49655.
9. Lieb R, Merikangas KR, Hofler M, Pfister H, Isensee B, Wittchen HU. Parental alcohol use disorders and alcohol use and disorders in offspring: a community study. Psychol Med. 2002;32(1):63-78.
10. Sørensen HJ, Manzardo AM, Knop J, Penick EC, Madarasz W, Nickel EJ, et al. The contribution of parental alcohol use disorders and other psychiatric illness to the risk of alcohol use disorders in the offspring. Alcohol Clin Exp Res. 2011;35(7):1315-20.
11. Yoon G, Westermeyer J, Kuskowski MA, Nesheim L. Impact of the number of parents with alcohol use disorder on alcohol use disorder in offspring: a population-based study. J Clin Psychiatry. 2013;74(8):795-801.
12. Pisinger VS, Holst CA, Bendtsen P, Becker U, Tolstrup JS. Perceived parental alcohol problems and drinking patterns in youth: A cross-sectional study of 69,030 secondary education students in Denmark. Prev Med. 2017.
13. Rossow I, Keating P, Felix L, McCambridge J. Does parental drinking influence children's drinking? A systematic review of prospective cohort studies. Addiction. 2016;111(2):204-17.
14. Handley ED, Chassin L. Intergenerational transmission of alcohol expectancies in a high-risk sample. J Stud Alcohol Drugs. 2009;70(5):675-82.

15. Grant JD, Waldron M, Sartor CE, Scherrer JF, Duncan AE, McCutcheon VV, et al. Parental separation and offspring alcohol involvement: Findings from offspring of alcoholic and drug dependent twin fathers. Alcohol Clin Exp Res. 2015;39(7):1166-73.
16. Lee SH, Lee BC, Kim JW, Yi JS, Choi IG. Association between alcoholism family history and alcohol screening scores among alcohol-dependent patients. Clin Psychopharmacol Neurosci. 2013;11(2):89-95.
17. Norstrom T, Rossow I. Alcohol consumption as a risk factor for suicidal behavior: A systematic review of associations at the individual and at the population level. Arch Suicide Res. 2016;20(4):489-506.
18. Flensborg-Madsen T, Mortensen EL, Knop J, Becker U, Sher L, Gronbaek M. Comorbidity and temporal ordering of alcohol use disorders and other psychiatric disorders: results from a Danish register-based study. Compr Psychiatry. 2009;50(4):307-14.
19. Grant BF, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, et al. Epidemiology of DSM-5 alcohol use disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA Psychiatry. 2015;72(8):757-66.
20. Lai HM, Cleary M, Sitharthan T, Hunt GE. Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990-2014: A systematic review and meta-analysis. Drug Alcohol Depend. 2015;154:1-13.
21. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA. 1990;264(19):2511-8.
22. Kessler RC, Crum RM, Warner LA, Nelson CB, Schulenberg J, Anthony JC. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. Arch Gen Psychiatry. 1997;54(4):313-21.
23. Archie S, Gyomorey K. First episode psychosis, substance abuse and prognosis: a systematic review. Curr Psychiatry Rep. 2009;5(3):153-63.
24. Najt P, Fusar-Poli P, Brambilla P. Co-occurring mental and substance abuse disorders: a review on the potential predictors and clinical outcomes. Psychiatry Res. 2011;186(2-3):159-64.
25. Schmidt LM, Hesse M, Lykke J. The impact of substance use disorders on the course of schizophrenia—a 15-year follow-up study: dual diagnosis over 15 years. Schizophr Res. 2011;130(1):228-33.
26. Jung J, Goldstein RB, Grant BF. Association of respondent psychiatric comorbidity with family history of comorbidity: Results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. Compr Psychiatry. 2016;71:49-56.
27. Ohannessian CM, Hesselbrock VM, Kramer J, Kuperman S, Bucholz KK, Schuckit MA, et al. The relationship between parental alcoholism and adolescent psychopathology: A systematic examination of parental comorbid psychopathology. J Abnorm Child Psychol. 2004;32(5):519-33.
28. Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: Structure, access, legislation, and archiving. 2011;39(7_suppl):12-6.
29. Pedersen CB. The Danish Civil Registration System. Scand J Public Health. 2011;39(7 Suppl):22-5.
30. Becker U. Documentation of patient admission in the Alcohol-unit Hvidovre Hospital, WINALCO - a clinical database [Danish]: Alkoholenheden, Hvidovre Hospital; 2004.
31. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014;29(8):541-9.
32. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449-90.
33. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. Scand J Public Health. 2011;39(7 Suppl):54-7.

34. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. Int J Epidemiol. 2017;46(3):798-f.
35. Helweg-Larsen K. The Danish Register of Causes of Death. Scand J Public Health. 2011;39(7 Suppl):26-9.
36. Jensen VM, Rasmussen AW. Danish Education Registers. Scand J Public Health. 2011;39(7 Suppl):91-4.
37. Flensborg-Madsen T, Knop J, Mortensen EL, Becker U, Sher L, Gronbaek M. Alcohol use disorders increase the risk of completed suicide--irrespective of other psychiatric disorders. A longitudinal cohort study. Psychiatry Res. 2009;167(1-2):123-30.
38. Mellentin AI, Brink M, Andersen L, Erlangsen A, Stenager E, Bjerregaard LB, et al. 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. J Psychiatr Res. 2016;80:52-8.
39. Long EC, Lonn SL, Sundquist J, Sundquist K, Kendler KS. The role of parent and offspring sex on risk for externalizing psychopathology in offspring with parental alcohol use disorder: a national Swedish study. Soc Psychiatry Psychiatr Epidemiol. 2018.
40. Jester JM, Jacobson SW, Sokol RJ, Tuttle BS, Jacobson JL. The influence of maternal drinking and drug use on the quality of the home environment of school-aged children. Alcohol Clin Exp Res. 2000;24(8):1187-97.
41. Griffin ML, Amodeo M, Fassler I, Ellis MA, Clay C. Mediating factors for the long-term effects of parental alcoholism in women: the contribution of other childhood stresses and resources. Am J Addict. 2005;14(1):18-34.
42. Rounsaville D, O'Farrell TJ, Andreas JB, Murphy CM, Murphy MM. Children's exposure to parental conflict after father's treatment for alcoholism. Addict Behav. 2014;39(7):1168-71.
43. Ellis DA, Zucker RA, Fitzgerald HE. The role of family influences in development and risk. Alcohol Health Res World. 1997;21(3):218-26.
44. Anda RF, Whitfield CL, Felitti VJ, Chapman D, Edwards VJ, Dube SR, et al. Adverse Childhood Experiences, Alcoholic Parents, and Later Risk of Alcoholism and Depression. 2002;53(8):1001-9.
45. Arria AM, Mericle AA, Meyers K, Winters KC. Parental substance use impairment, parenting and substance use disorder risk. J Subst Abuse Treat. 2012;43(1):114-22.
46. Mayes LC, Truman SD. Substance Abuse and Parenting. In: Bornstein MH, editor. Handbook of parenting. 4. 2 ed. Mahwah, NJ: Erlbaum; 2002. p. 329-60.
47. Di Sclafani V, Finn P, Fein G. Treatment-naive active alcoholics have greater psychiatric comorbidity than normal controls but less than treated abstinent alcoholics. Drug Alcohol Depend. 2008;98(1-2):115-22.
48. Polimanti R, Peterson RE, Ong JS, Macgregor S, Edwards A, Clarke T-K, et al. Evidence of causal effect of major depression on alcohol dependence: Findings from the Psychiatric Genomics Consortium. bioRxiv 412098. 2018.
49. Rognmo K, Torvik FA, Ask H, Roysamb E, Tambs K. Paternal and maternal alcohol abuse and offspring mental distress in the general population: the Nord-Trondelag health study. BMC Public Health. 2012;12:448.
50. Chassin L, Pitts SC, DeLucia C, Todd M. A longitudinal study of children of alcoholics: predicting young adult substance use disorders, anxiety, and depression. J Abnorm Psychol. 1999;108(1):106-19.
51. Christoffersen MN, Soothill K. The long-term consequences of parental alcohol abuse: a cohort study of children in Denmark. J Subst Abuse Treat. 2003;25(2):107-16.
52. Rasic D, Hajek T, Alda M, Uher R. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: a meta-analysis of family high-risk studies. Schizophr Bull. 2014;40(1):28-38.

53. Blanco C, Iza M, Rodríguez-Fernández JM, Baca-García E, Wang S, Olfson M. Probability and predictors of treatment-seeking for substance use disorders in the US. Drug Alcohol Depend. 2015;149:136-44.
54. Chapman C, Slade T, Hunt C, Teesson M. Delay to first treatment contact for alcohol use disorder. Drug Alcohol Depend. 2015;147:116-21.
55. Wang PS, Angermeyer M, Borges G, Bruffaerts R, Tat Chiu W, G DEG, et al. Delay and failure in treatment seeking after first onset of mental disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry. 2007;6(3):177-85.

TABLES

Table 1. Characteristics of the study population

	AUD offspring	Reference population	P
Number, n	15,477	154,392	
Men, n (%)	8,022 (51.8)	80,025 (51.8)	
Year of birth, n (%)			
1959 or earlier	890 (5.8)	9,003 (5.8)	
1960-1969	4,233 (27.4)	42,145 (27.3)	
1970-1979	3,911 (25.3)	39,040 (25.3)	
1980-1989	3,004 (19.4)	29,962 (19.4)	
1990 or after	3,439 (22.2)	34,242 (22.2)	
Age at parents' alcohol treatment start, n (%)			
Before birth	3,117 (20.1)	NA	
0-4 years	3,619 (23.4)	NA	
5-9 years	4,340 (28.0)	NA	
10-14 years	4,401 (28.4)	NA	
Family educational level, n (%)			
Basic or secondary	6,361 (41.1)	34,546 (22.4)	0.000[a]
Vocational	5,607 (36.2)	62,095 (40.2)	
Short	386 (2.5)	6,504 (4.2)	
Medium	1,959 (12.7)	25,837 (16.7)	
High	782 (5.1)	17,766 (11.5)	
Unknown	382 (2.5)	7,644 (5.0)	
Father's year of birth, median (5^{th}-95^{th} percentile)	1946 (1926-1967)	1947 (1924-1968)	0.037[b]
Mother's year of birth, median (5^{th}-95^{th} percentile)	1950 (1931-1970)	1949 (1929-1970)	0.000[b]

Not applicable (NA)
[a] χ^2 test
[b] t test

Table 2. Numbers and hazard ratios (95% confidence intervals) of AUD in offspring by AUD in parents

	Number	AUD cases	Incidence rate per 1,000 person-years	Basic adjusted HR (95% CI)[a]	Fully adjusted HR (95% CI)[b]	P
Reference population	154,392	9,744	2.8	1 (reference)	1 (reference)	
AUD offspring	15,477	2,251	7.0	2.49 (2.38-2.61)	2.28 (2.18-2.39)	
Men	8,022	1,524	9.4	2.53 (2.39-2.68)	2.31 (2.18-2.45)	0.466[c]
Women	7,455	727	4.5	2.42 (2.23-2.63)	2.24 (2.06-2.43)	
Parent(s) with AUD						
Father	12,344	1,729	6.5	2.34 (2.23-2.47)	2.16 (2.05-2.27)	0.000[d]
Mother	2,658	426	8.6	2.97 (2.69-3.27)	2.76 (2.51-3.05)	
Both	475	96	11.5	3.89 (3.17-4.78)	3.35 (2.72-4.12)	

[a] Adjusted for matching criteria (sex, date of birth, and living area)
[b] Adjusted for [a], family educational level, father's year of birth, and mother's year of birth
[c] χ^2 AUD in men = AUD in women
[d] χ^2 Paternal AUD = Maternal AUD

Table 3. Numbers and hazard ratios (95% confidence intervals) of AUD in offspring by other mental disorders in father and mother

	Father			Mother		
	Number/AUD cases[a] (N=140,702)	Basic adjusted HR (95% CI)[b]	Fully adjusted HR (95% CI)[c]	Number[d]/AUD cases (N=34,380)	Basic adjusted HR (95% CI)[b]	Fully adjusted HR (95% CI)[c]
Any other mental disorders in parent	12,696/1,366	1.37 (1.28-1.47)	1.33 (1.24-1.42)	4,499/522	2.07 (1.86-2.29)	1.95 (1.76-2.16)
Type of other mental disorder in parent						
Psychotic[d]	1,706/168	1.08 (0.92-1.27)	1.06 (0.90-1.24)	530/59	1.12 (0.85-1.49)	1.12 (0.85-1.49)
Mood[d]	3,433/291	1.00 (0.88-1.14)	1.03 (0.91-1.17)	1,485/138	1.02 (0.83-1.26)	1.03 (0.84-1.27)
Anxiety[d]	3,027/185	1.07 (0.91-1.25)	1.05 (0.90-1.23)	1,499/119	1.26 (1.02-1.56)	1.23 (1.00-1.52)
Personality[c]	5,570/737	1.08 (0.98-1.19)	1.08 (0.98-1.19)	1,911/264	1.20 (0.99-1.45)	1.18 (0.98-1.42)
Drug[c]	2,992/371	1.17 (1.03-1.32)	1.14 (1.00-1.29)	1,009/184	1.78 (1.45-2.18)	1.71 (1.40-2.09)
Other[c]	4,811/584	1.31 (1.18-1.44)	1.27 (1.15-1.41)	1,916/266	1.56 (1.32-1.85)	1.50 (1.27-1.77)

[a] *Type of other mental disorder in parent* does not add up to *Any other mental disorders in parent*, as parents can be registered with more than one type of mental disorder
[b] Adjusted for matching criteria (sex, date of birth, and living area), AUD in father and mother
[c] Adjusted for [b], family educational level, father's year of birth, and mother's year of birth
[d] Adjusted for [b,c] and other types of other mental disorders in parent

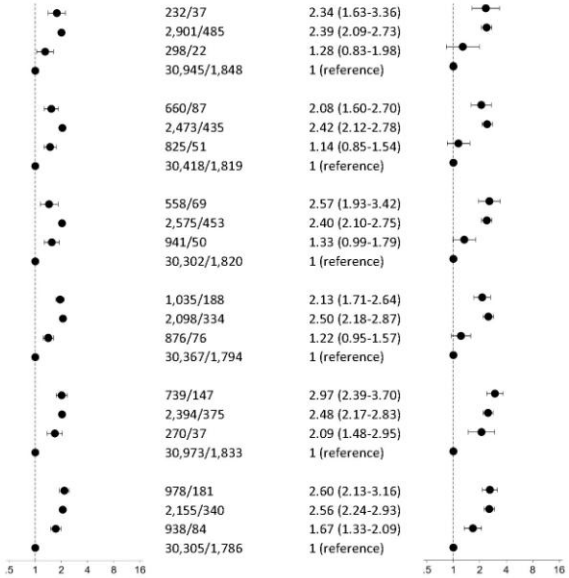
Table 4. Numbers and hazard ratios (95% confidence intervals) of AUD in offspring by AUD with or without other mental disorders in father and mother

	Other mental disorders in parent[c]	Father			Mother		
		Number/AUD cases	Basic adjusted HR (95% CI)[a]	Fully adjusted HR (95% CI)[b]	Number/AUD cases	Basic adjusted HR (95% CI)[a]	Fully adjusted HR (95% CI)[b]
AUD offspring	Yes	5,762/773	2.47 (2.29-2.67)	2.27 (2.10-2.46)	1,901/328	3.24 (2.86-3.68)	3.02 (2.66-3.43)
AUD offspring	No	7,057/1,052	2.40 (2.25-2.56)	2.21 (2.07-2.36)	1,232/194	2.80 (2.40-3.28)	2.57 (2.20-3.01)
Reference population	Yes	6,934/593	1.76 (1.63-1.93)	1.68 (1.55-1.83)	2,598/194	1.59 (1.36-1.85)	1.51 (1.30-1.76)
Reference population	No	120,949/7,571	1 (reference)	1 (reference)	28,645/1,676	1 (reference)	1 (reference)

[a] Adjusted for matching criteria (sex, date of birth, and living area) and AUD in co-parent
[b] Adjusted for [a], family educational level, father's year of birth, and mother's year of birth
[c] Psychotic disorder, mood disorder, anxiety disorder, personality disorder, drug use disorder, or other mental disorder

Table 5. Numbers and hazard ratios (95% confidence intervals) of AUD in offspring by AUD and type of other mental disorders in father and mother

	Type of other mental disorder in parent	Father		Mother	
		Number/AUD cases	Fully adjusted HR (95% CI)[a,b]	Number/ AUD cases	Fully adjusted HR (95% CI)[a,b]
	Psychotic				
AUD offspring	Yes	667/84	1.77 (1.41-2.22)	232/37	2.34 (1.63-3.36)
AUD offspring	No	12,152/1,741	2.00 (1.88-2.13)	2,901/485	2.39 (2.09-2.73)
Reference population	Yes	1,039/84	1.30 (1.04-1.62)	298/22	1.28 (0.83-1.98)
Reference population	No	126,844/8,080	1 (reference)	30,945/1,848	1 (reference)
	Mood				
AUD offspring	Yes	1,512/135	1.53 (1.27-1.84)	660/87	2.08 (1.60-2.70)
AUD offspring	No	11,307/1,690	2.05 (1.93-2.18)	2,473/435	2.42 (2.12-2.78)
Reference population	Yes	1,921/156	1.48 (1.26-1.75)	825/51	1.14 (0.85-1.54)
Reference population	No	125,962/8,008	1 (reference)	30,418/1,819	1 (reference)
	Anxiety				
AUD offspring	Yes	1,182/77	1.44 (1.14-1.83)	558/69	2.57 (1.93-3.42)
AUD offspring	No	11,637/1,748	2.03 (1.91-2.16)	2,575/453	2.40 (2.10-2.75)
Reference population	Yes	1,845/108	1.55 (1.27-1.89)	941/50	1.33 (0.99-1.79)
Reference population	No	126,038/8,056	1 (reference)	30,302/1,820	1 (reference)
	Personality				
AUD offspring	Yes	3,244/503	1.93 (1.73-2.16)	1,035/188	2.13 (1.71-2.64)
AUD offspring	No	9,575/1,322	2.08 (1.96-2.21)	2,098/334	2.50 (2.18-2.87)
Reference population	Yes	2,326/234	1.41 (1.23-1.62)	876/76	1.22 (0.95-1.57)
Reference population	No	125,557/7,930	1 (reference)	30,367/1,794	1 (reference)
	Drug use				
AUD offspring	Yes	2,001/267	2.01 (1.74-2.33)	739/147	2.97 (2.39-3.70)
AUD offspring	No	10,818/1,558	2.03 (1.91-2.16)	2,394/375	2.48 (2.17-2.83)
Reference population	Yes	991/104	1.68 (1.37-2.05)	270/37	2.09 (1.48-2.95)
Reference population	No	126,892/8,060	1 (reference)	30,973/1,833	1 (reference)
	Other				
AUD offspring	Yes	2,437/355	2.16 (1.90-2.45)	978/181	2.60 (2.13-3.16)
AUD offspring	No	10,382/1,470	2.07 (1.95-2.21)	2,155/340	2.56 (2.24-2.93)
Reference population	Yes	2,374/229	1.72 (1.50-1.97)	938/84	1.67 (1.33-2.09)
Reference population	No	125,509/7,935	1 (reference)	30,305/1,786	1 (reference)



[a] Adjusted for matching criteria (sex, date of birth, and living area) and AUD in co-parent; [b] Adjusted for [a], family educational level, father's year of birth, and mother's year of birth