Published in final edited form as:

Am J Med Genet B Neuropsychiatr Genet. 2017 December ; 174(8): 779–785. doi:10.1002/ajmg.b.32583.

The Clinical Features of Alcohol Use Disorders in Biological and Step-Fathers That Predict Risk for Alcohol Use Disorders in Offspring

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Abstract

Background—Given that Alcohol Use Disorder (AUD) is clinically heterogeneous, can we, in a large epidemiological sample using public registries, identify clinical features of AUD cases in biological and step-fathers that index, respectively, genetic and familial-environmental risk for AUD in their offspring?

Methods—From all father-offspring pairs where the father had AUD and the offspring was born 1960–1990, we identified not-lived-with (NLW) biological fathers (n=38,376) and step-father pairs (n=9,711). The relationship between clinical and historical features of the father's AUD and risk for AUD in offspring was assessed by linear hazard regression.

Results—Age at first registration for AUD and recurrence of AUD registration were significantly stronger predictors of risk for AUD in the offspring of NLW fathers than in step-fathers. By contrast, number of AUD registrations in NLW fathers and step-fathers were equally predictive of risk for AUD in offspring. However, while the number of step-father AUD registrations that occurred when he was living with them significantly predicted risk for AUD in his step-children, the number of registrations that occurred when not residing with his step-children was unassociated with their AUD risk.

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Where was the work performed: Analyses – Malmö Sweden; Writing - Richmond USA and Malmö Sweden.

Conflicts of Interest: None of the authors have any conflicts of interest to declare.

Ethical Standards: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. We secured ethical approval for this study from the Regional Ethical Review Board of Lund University (No. 2008/409).

Conclusions—In an epidemiological sample, we could meaningfully differentiate between features of AUD in fathers that indexed genetic risk which was transmitted to biological offspring (early age at onset and recurrence) versus indexed environmental risk (registrations while rearing) which increased risk in step-children.

Keywords

alcohol use disorder; genetic risk; step-fathers; rearing effects; number of registrations

In both adoption (Kendler et al., 2015a) and adoption-like designs (Kendler et al., 2015b), we and others (Cadoret et al., 1987; Cloninger et al., 1981) have shown that risk for Alcohol Use Disorders (AUD) is transmitted across generations via both genetic and rearing effects. In this report, we follow up on these findings by inquiring whether there are specific clinical and historical features of AUD that predict the cross-generational transmission of AUD from parent to child. In particular, we ask whether these features are mediated genetically versus environmentally. We accomplish this by comparing the risk of AUD in offspring as a function of the clinical features of AUD in biological fathers who have not resided with their offspring, termed “not-lived-with” (NLW) fathers (who only share genes but not rearing environment with their offspring), and step-fathers (who only share rearing environment but not genes with their offspring). We are particularly interested in determining the degree to which the features of AUD that predict genetic transmission of risk are similar or distinct from those which predict risk arising from their impact on the familial environment.

A prior twin study has shown individual symptoms of AUD are influenced by diverse genetic risk factors (Kendler et al., 2012), raising the possibility that different AUD symptoms in parents may predict risk for AUD in offspring. Furthermore, AUD severity in the parent may impact AUD risk in the offspring: in a sample of Danish men, severity of parental AUD was positively associated with risk in their sons (Goodwin et al., 1974). Given a heritability estimate for AUD of 0.49 (Verhulst et al., 2015) and the adoption studies described above, it is clear that environmental factors also contribute substantially to AUD risk. However, the extent to which clinical and historical features of AUD in the non-biological parent might impact on the risk of AUD in the offspring has been less well-characterized.

Potentially informative clinical features of parental AUD include age at onset, severity, and recurrence. Such features have been identified as characteristic of AUD typologies (Babor et al., 1992; Cloninger et al., 1981), and may be indicative of familial risk more broadly (Kendler et al., 2016; McGue et al., 1992; Nowak-Gottl et al., 2001; Sullivan et al., 2000). In the current study, which relies upon Swedish national registries of medical, crime, and pharmacy records, age of onset is operationalized as the first age at which an individual first received an AUD-related registration. Severity is measured by total number of lifetime AUD registrations. Recurrence is defined here as more than one AUD registration within a 3-year time frame. Finally, the heterogeneity of AUD presentation may contribute to distinct consequences of drinking, e.g., drinking and driving arrests vs. liver disease. In the current analyses, we can detect such variation by determining the origin of each individual’s AUD registration (i.e. from the criminal vs. medical registry).

We present here our efforts to clarify whether the clinical AUD features described above, observed in Swedish fathers, are predictive of AUD risk in their offspring, and whether that risk is conferred via genetic liability or environmental exposure. The source of risk is evaluated by testing whether the offspring's relationship to the affected parent – biological (NLW) father vs. step-father – is differentially associated with outcome. Clarification of these processes may improve risk assessment and, consequently, efforts to identify effective targets for prevention or intervention.

METHODS

We collected information on individuals from Swedish population-based registers with national coverage, and the registers were linked using each person's unique identification number. In order to preserve confidentiality this ID number was replaced by a serial number. The following sources were used to create our database: The Multi-Generation Register, providing information on family relations; the Swedish Hospital Discharge Register, containing all hospitalizations for all Swedish inhabitants from 1969–2011; the Swedish Prescribed Drug Register, containing all prescriptions in Sweden picked up by patients from 2005 to 2010; the Outpatient Care Register, containing information from all outpatient clinics from 2001 to 2010; the Swedish Crime Register included national complete data on all convictions from 1973–2011, the Swedish suspicion register included national complete data on all individuals strongly suspected of crime from 1998–2011; the Swedish Mortality Register, containing causes of death; and the Population and Housing Censuses that provided information on household and geographical status in 1960, 1965, 1970, 1975, 1980, and 1985. Geographical status was defined as Small Areas for Market Statistics (SAMS) that are small geographical units defined by Statistics Sweden, the Swedish government-owned statistics bureau. We secured ethical approval for this study from the Regional Ethical Review Board of Lund University (No. 2008/409).

Definitions of Alcohol use disorder

Alcohol use disorder (AUD) was defined by ICD codes for main and secondary diagnoses from Swedish medical registries for the following diagnoses: ICD9: alcohol-related psychiatric disorders (291), alcohol dependence (303), alcohol abuse (305A), alcohol-related polyneuropathy (357F), alcohol-related cardiomyopathy (425F), alcohol-related gastritis (535D), alcoholic fatty liver, alcohol hepatitis, alcoholic cirrhosis, unspecified liver damage caused by alcohol (571A-D), toxic effects of alcohol (980), alcoholism (V79B); ICD10: alcohol related psychiatric and behavioral disorders (F10, excluding acute alcohol intoxication: F10.0), rehabilitation of a person with alcohol abuse (Z50.2), guidance and medical advice to a person with alcohol abuse (Z71.4), alcohol-related pseudo-Cushing syndrome (E24.4), alcohol-related degeneration of the nervous system and brain (G31.2), alcohol-related polyneuropathy (G62.1), alcohol-related myopathy (G72.1), alcohol-related cardiomyopathy (I42.6), alcohol-related gastritis (K29.2), liver diseases caused by alcohol (K70.0–K70.9), acute pancreatitis caused by alcohol (K85.2), chronic pancreatitis caused by alcohol (K86.0), treatment of pregnant alcoholic woman (O35.4), toxic effects of alcohol (T51.0–T51.9), and based on Anatomical Therapeutic Chemical (ATC) codes in the Prescribed Drug Register: disulfiram (N07BB01), acamprosate (N07BB03), or naltrexone

(N07BB04). Additionally, we identified individuals with at least two convictions of drunk driving (law 1951:649) or drunk in charge of maritime vessel (law 1994:1009) in the Crime register insuring that we did not count arrests in the suspicion register that described the same event contained in the conviction register.

Sample

The database was created by selecting all unique father-offspring pairs where the offspring was born in Sweden between 1960 and 1990. From this database, we defined two types of pairs: a) not-lived-with (NLW) father-child pairs in which the offspring never resided in the same household or SAMS as the biological father, and b) step-father pairs in which the offspring did not reside the entire time from ages 0–15 with their biological father and from age 0–15, resided for at least 10 years with an adult who was i) male, ii) 18–50 years older than the offspring and iii) with whom they were not biologically related. From the database, we also retrieved information on the biological mother of the offspring. The NLW father pairs and step-father pairs were defined so that the relationship within the pairs maximally resembled that seen between an adoptee and, respectively, his or her biological and adoptive parents.

In order to define the two types of pairs, we relied on data from the above registries, whose availability varied over time. From 1960 to 1985, household ID and geographical status from the Population and Housing Census were available every 5th year. The household ID includes all individuals living in the same dwelling. From 1986 and onwards (every year) we used the Family ID and geographical status from the Total Population Register. The Family ID is defined by individuals that are related or married and who are registered at the same property (a person can only be part of one family). Furthermore, adults who are registered at the same property and have common children, but are not married, are registered in the same family. For the step-parent sample this ascertainment means that, during the period 1986 and onwards, for a proband living with his/her mother, we capture the step-father if he is either married with the mother to the proband and/or having a common child together with the mother of the proband.

Statistical Methods

We looked at the interactions between four clinical features of the AUD registration in the NLW father or step-father: 1) age at first registration (AFR); 2) recurrence (defined as 1 additional registration for AUD within 3 years of first registration); 3) number of registrations; 4) type of registration and type of pair (NLW father pair vs Step-father pair) to predict AUD in offspring on the other. We included offspring sex and AUD in the biological mother as covariates. Thus, where father's AFR was the focal risk factor, our model was as follows:

$$\text{AUD}_{\text{offspring}} \sim \text{AFR} + \text{pair_type} + \text{AUD}_{\text{mother}} + \text{sex} + (\text{AFR} \times \text{pair_type})$$

We utilized Aalen's linear hazard regression (Martinussen and Scheike, 2006; Scheike and Zhang, 2011) to investigate all pairs from age 15 in offspring until (a) year of first registration of AUD, (b) death/emigration or (c) end of follow-up (year 2011), whichever

came first. As we used Aalen's linear hazards model, the results from the models will be interpreted at the additive scale as the excess number of cases. In all models, we investigated the proportionality assumption. The key variable in each model was the interaction term between the clinical feature and type of pair.

In the first analysis, we focused on age at onset, defined as AFR in father. In the model, we investigated the linear effects of age at onset and the interaction with type of pair. In the second analysis, we focused on the number of AUD registrations in father and the interaction with type of pair. In the third analysis, we examined a binary variable – recurrence – assessed by the presence or absence of at least one AUD registration within three years of the proband's first registration. In the fourth analysis, we focused on the type of AUD registration in the proband. We categorized the registrations into three groups: (1) medical (the Swedish Hospital Discharge Register, the Out-patient Care Register); (2) criminal (the Swedish Crime Register and the Swedish Suspicion Register); and (3) prescription (the Swedish Prescribed Drug Register). In the models, we used the criminal register as the reference group. We investigated the interaction between medical registration and type of pair, and the interaction between prescription registration and type of pair. The statistical analyses were performed using SAS 9.3 (SAS Institute, 2011) and R Version 3.1.3 (R Development Core Team, 2014).

RESULTS

Key descriptive statistics of our sample are presented in table I. We have approximately 4 times as many father-offspring combinations from not-lived-with fathers with AUD as with step-fathers with AUD. The prevalence of AUD is higher in the offspring of the NLW fathers versus step-fathers. Compared to the NLW fathers with AUD, the step-fathers with AUD have fewer total registrations, are first registered at a slightly later age and were less likely to be detected in the pharmacy registry.

As seen in table II, early age at first registration in the NLW father or step-father significantly predicted risk for AUD in offspring, as did having AUD in a NLW father versus a step-father, having a mother with AUD, and being male. An early age at first registration was a significantly stronger predictor of AUD risk in the offspring of NLW fathers than step-fathers. As seen in figure 1, the difference between a father first registered for AUD at age 20 compared to at age 60 would produce 32 more cases per 10,000 person years in the offspring of NLW father and 12.3 more cases in the offspring of step-father. We then examined, with the same covariates, recurrence of AUD. As with early age at onset, recurrence was a significantly stronger predictor of AUD risk in the offspring of NLW fathers than of the step-fathers.

We next examined, with the same covariates, the total number of lifetime paternal AUD registrations (table II). This significantly predicted risk for AUD in offspring but the magnitude of the association did not differ for offspring of NLW fathers and step-fathers with AUD. We then examined AUD registrations for the step-father that occurred when he was versus was not cohabiting with his offspring. When he was living with his offspring (which accounted for 16% of his total registrations), the number of AUD registrations

significantly predicted risk for AUD in his step-children (HR=1.03, 95% CIs 1.01–1.05). However, the number of registrations that occurred when not residing with his step-children was unassociated with their AUD risk (HR=1.00, 0.99–1.01).

Finally, we examined the impact of source of AUD registration in fathers on risk for AUD in offspring. Compared to the criminal register as a reference, risk for AUD in offspring was unassociated with medical registration but was significantly lower in those ascertained through the pharmacy registry. The impact of these sources of registration did not differ significantly on risk for AUD in the offspring of the NLW fathers and step-fathers.

DISCUSSION

The goal of this paper was to determine if the clinical features of AUD that conveyed risk to children of affected fathers differed when the source of parent-child transmission was limited to genetic effects (in NLW fathers) or rearing effects (in step-fathers). Early age at first registration in fathers was associated with increased risk for AUD in their offspring. This association was much stronger between affected NLW fathers and their biological offspring than between affected step-fathers and their step-children. These results, in accord with earlier family studies (Buydens-Branch et al., 1989; Hill et al., 2000; Hill and Yuan, 1999) and one prior twin study (McGue et al., 1992), suggest that, like many other common psychiatric and biomedical conditions (Heston et al., 1981; Marenberg et al., 1994; McGue et al., 1992; Steele, 2002), early age at onset for AUD is associated with increased genetic risk. Early age at onset does appear to predict those paternal characteristics that transmit AUD environmentally from parent to offspring but this effect was considerably weaker than that seen for genetic transmission (figure 1). In accord with our findings, in disorders as diverse as venous thrombosis and major depression, recurrence is an index of elevated genetic risk (Kendler et al., 2007; Nowak-Gottl et al., 2001; Sullivan et al., 2000). Our results with regard to recurrence also echo earlier findings from Cloninger et al. who, in an adoption design found that the more heritable form of AUD, which they called type 2 alcoholism, was characterized by recurrent alcohol-related social and legal problems (Sigvardsson et al., 1996).

Number of paternal registrations for AUD predicted risk for AUD in offspring but we saw no significant difference in the strength of this relationship for NLW fathers and step-fathers. These results would suggest that number of registrations reflects to a similar extent, genetic risk factors for AUD and parental characteristics that impact on the rearing environment in such a way as to increase AUD risk. We were, in follow-up analyses of the step-fathers, able to further examine the nature of this environmental effect. Registrations of the step-father that occurred while he was living with his step-children were associated with an increase in their risk for AUD but those that occurred at other times were unrelated. These findings suggest that the disruption in step-father behavior associated with active AUD along with the associated marital and family dysfunction was a major part of the mechanism of parent-offspring environmental transmission of risk to AUD. Our results are consistent both with findings from our prior adoption study of AUD in Sweden where we found that disruptions in parent-offspring bond – as reflected by divorce or death of the adoptive parents – were associated with increased rates of AUD in the adoptees (Kendler et al., 2015a) and with an

extensive literature from intact families in which active alcohol abuse in the parents is strongly correlated with a range of stress exposures in their offspring (i.e., (Collins and Messerschmidt, 1993; Dube et al., 2001)).

Finally, compared to ascertainment in the criminal registry, we found no difference in risk to offspring for medical registration and a reduced risk for pharmacy registration. The latter finding is consistent with what we found in our within-generation analyses but the former was not (Kendler et al., 2016). The pharmacy registry differs from the medical and crime registries in that it arises when individuals fill prescriptions for drug treatment of AUD and in the Swedish context detects a form of AUD that is somewhat less familial than that seen from cases ascertained through the criminal and medical registers. Neither of these variables differed in their impact on risk for AUD in the offspring of NLW fathers versus step-fathers suggesting a similar impact of genetic and rearing effects.

Limitations

These results should be interpreted in the context of four potentially important methodological limitations. First, this study was confined to one Scandinavian country, and we cannot be certain that our findings would generalize to other cultural and ethnic groups. However, Sweden has become increasingly diverse over time; today, 17% of the population is born abroad. Second, subjects with AUD were ascertained from medical, legal and pharmacy records. Contrary to standard epidemiological surveys, this approach has the advantage of ascertaining cases independent of subject cooperation or accurate recall and reporting. However, despite the advantage of eliminating self-report bias, this method surely produces both false negative and false positive diagnoses. While there is no large population based interview study of AUD in Sweden, one conducted in neighboring Norway (Kringlen et al., 2001) found that lifetime prevalences for alcohol dependence and the broader diagnosis of AUD (abuse + dependence) using DSM-III-R criteria (American Psychiatric Association, 1987) were, respectively, 8.8 and 22.7%. These results suggest that, compared to DSM-III-R criteria, our registry based assessments of AUD (met by 4.3% of the general population) are likely to contain more false negative than false positive diagnoses. However, the use of registrations diagnoses is more likely to capture the most severe cases, i.e., those cases that are most clinically relevant.

Third, we did not systematically explore differences in transmission of risk from NLW and step-fathers to their sons versus daughters. Rates of AUD in the daughters were, as expected, less than half that seen for sons: from NLW fathers 6.4 vs. 14.5% and from step-fathers 4.6 vs. 12.4%. We were therefore not well powered to detect sex differences.

Fourth, we were only able to assess age at onset of AUD indirectly through age at first registration. The time-period between the true onset of AUD and first detection by our methods surely varies. We might generally expect this increased variability to attenuate rather than exaggerate the association with risk of illness in offspring. Similarly, our measure of recurrence, a second registration within three years of the first, is imperfect. An individual might have recurrent episodes of AUD that went undetected by our three registries. Again, the imperfection of this measure is more likely to bias downward (rather than upward) the observed association with risk of AUD in offspring.

Conclusions

Within the broad clinical features of AUD, it is possible to assess, in epidemiological samples, clinical features that usefully index the genetic liability to AUD and those parental features that increase risk of AUD in offspring via environmental exposure. Severity, in the form of early age at onset and recurrence, appears to index genetic liability while active AUD imparts environmental risk. The pathogenicity conferred environmentally by a step-father with AUD was confirmed by our finding that registrations occurring during co-habitation with a step-child increased that child's AUD risk, while registrations occurring outside that time frame did not. Our findings point to the complexity of the cross-generational transmission of risk to AUD and suggest that some clinical features of AUD may better index genetic and others environmental aspects of that risk.

Acknowledgments

Disclosures and Acknowledgements: This project was supported by the grant R01AA023534 from the National Institute of Alcohol Abuse and Alcoholism, the Swedish Research Council (K2012-70X-15428-08-3), the Swedish Research Council for Health, Working Life and Welfare (In Swedish: Forte; Reg.nr: 2013-1836), the Swedish Research Council (2012-2378; 2014-10134) and FORTE (2014-0804) as well as ALF funding from Region Skåne awarded.

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Figure 1.
The difference in risk for Alcohol Use Disorder as a function of the age of the father at first registration in both not-lived-with father and step-father father-offspring pairs

Table I

Descriptive Statistics of Fathers with Alcohol Use Disorders from Not-Lived-With and Step-Father Families *

	Not-lived- With	Step
N (unique combinations father/offspring)	38,376	9,711
AUD (offspring)	4,047 (10.6%)	832 (8.5%)
Mean age of onset (Father)	37 (13)	43 (15)
Mean number of registrations (Father)	9.7 (18.0)	5.4 (9.5)
Crime Register (Father)	46%	37%
Medical Register (Father)	78%	73%
Prescription Register (Father)	46%	19%

* 1,352 offspring are included in both not-lived with and stepfather-offspring pairs.

Table II

Prediction of Risk of AUD in Offspring of Step and Not-Lived- With Fathers with AUD as a function of the Father's Age at First Registration

	Regression Coefficient	Robust SE	z	P-value
Age at First Registration				
Paternal age at first AUD registration	-0.000073	0.000006	-11.3	0
Step- vs Not-lived-with Father	-0.000934	0.000159	-5.9	0
Interaction	0.000041	0.000012	3.2	0.0012
AUD in Mother	0.004582	0.000326	14.1	0
Gender (M vs F)	0.004327	0.000146	30.0	0
Number of Registrations				
Number of paternal AUD registrations	0.000017	0.000005	3.4	0.0001
Step- vs Not-lived-with Father	-0.001231	0.000193	-6.4	0
Interaction	0.000003	0.000019	0.2	0.85
AUD Mother	0.004717	0.000321	14.7	0
Gender (M vs F)	0.004319	0.000143	30.1	0
Recurrence				
Recurrence	0.000605	0.000181	3.34	0.0008
Step- vs Not-lived-with Father	-0.000889	0.000214	-4.15	<0.0001
Interaction	-0.000907	0.000330	-2.75	0.0060
AUD Mother	0.004748	0.000320	14.82	<0.0001
Sex (M vs F)	0.004347	0.000146	29.86	<0.0001
Form of Registration				
Medical register	0.000047	0.000210	0.23	0.82
Prescription Register	-0.000961	0.000260	-3.70	0.0002
Step- vs Not-lived-with Father	-0.001477	0.000336	-4.39	0
Interaction for medical register	0.000218	0.000371	0.59	0.56
Interaction for prescription register	0.000540	0.000457	1.18	0.24
AUD Mother	0.004717	0.000321	14.7	0
Gender (M vs F)	0.004323	0.000143	30.1	0