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Clinical Features of Registry-Ascertained Alcohol Use Disorders that Reflect Familial Risk

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Abstract

Background—Alcohol Use Disorder (AUD) is clinically heterogeneous. Using a large epidemiological sample ascertained via public registries, is it possible to identify clinical and historical features of AUD that reflect familial risk?

Methods—Using registration in national medical, legal or pharmacy registries, we identified four kinds of relative pairs ($n=683,223$) starting with a proband with AUD: cousins, half-siblings, full-siblings and monozygotic cotwins. Using linear hazard regression, we examined the interaction between five clinical/historical features of AUD in the proband and risk for AUD in these relatives.

Results—Increased risk for AUD in relatives was predicted by the proband's early age at first registration, total number of registrations, recurrence, history of drug abuse and ascertainment in the medical versus the legal or pharmacy registry. In multivariate models, age at first registration, number of registrations, recurrence and history of drug abuse remained significant and in aggregate strongly predicted the risk for AUD in relatives. The risk for AUD in siblings of AUD probands in the highest decile of genetic risk predicted by these four indices was more than twice as great as that predicted in siblings of probands in the lowest risk decile.

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Contributors

The authors all contributed substantially to the writing and editing of the present paper. KSK planned the study, directed the analyses and wrote the initial draft of the paper. HO conducted all the statistical analyses. JS and KS oversaw the access to the Swedish registry data. JS, KS, ACE and KJKJ all helped in the final writing of the paper. All authors have approved the final version of the article.

Conflict of Interest

The authors have no conflicts of interest.

Conclusions—In an epidemiological sample, familial risk for AUD can be assessed by simple clinical and historical variables.

Keywords

alcohol use disorder; familial risk; age at onset; number of registrations

1. INTRODUCTION

Alcohol use disorder (AUD), a syndrome strongly influenced by familial/genetic factors (Cotton, 1979; Verhulst et al., 2015), is clinically heterogeneous. For both research and clinical purposes, it is useful to determine whether readily available clinical or historical information about affected individuals reflect their underlying familial vulnerability to AUD. In both neuropsychiatric and medical disorders, age at onset (AAO) is frequently inversely related with level of familial risk (Heston et al., 1981; Marenberg et al., 1994; McGue et al., 1992; Steele, 2002). In disorders as diverse as venous thrombosis and major depression, recurrence is an index of elevated familial risk (Kendler et al., 2007a; Nowak-Gottl et al., 2001; Sullivan et al., 2000).

Here, in a study of AUD in Sweden, we use publicly available information (Kendler et al., 2015) to identify subjects through medical, criminal, and pharmacy records, and examine whether age at first registration (AFR) for AUD, total number of AUD episodes (as reflected in lifetime number of registrations), recurrence (defined as 1 additional registrations for AUD within 3 years of first registration), a history of registration for drug abuse (DA) and mode of ascertainment predict risk for AUD in four classes of relatives: cousins, half-siblings, full-siblings and monozygotic (MZ) cotwins. We also examine whether individuals ascertained in the medical registry because of diagnoses of AUD versus diagnoses of alcohol-related medical problems differ in their average familial risk. This question is of interest because we cannot assume that individuals who are registered for AUD because of legal difficulties, medical problems or the receipt of drugs treatment of AUD all have the same level of familial risk. This report reflects an extension of a prior paper from our group asking what clinical features of probands with drug abuse in Sweden predict familial risk (Kendler et al., 2014).

We predict that early age at onset, total number of AUD episodes, recurrence in the proband and a history of DA will predict risk for AUD in relatives, and that the strength of this prediction will be related to the degree of familial relationship (with the strongest relationships expected for MZ cotwins, followed by siblings, half-siblings, and, finally, cousins). Although objective, these indices are all imperfect as they are measured from patterns of registration for AUD rather than episodes of illness as might be obtained directly from an interview-based survey.

Due to lack of prior studies, we did not begin this study with clear predictions about the relationship between familial risk and source of ascertainment for AUD across registries or within the medical registry.

2. METHODS

We collected information on individuals from Swedish registers with national population 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. We secured ethical approval for this study from the Regional Ethical Review Board of Lund University. The following sources were used to create our database: The Multi-Generation Register (Ekbom, 2011) and the Swedish twin register (Lichtenstein et al., 2006), providing information on family relations; the Swedish Hospital Discharge Register (Socialstyrelsen, 2016b), containing all hospitalizations for all Swedish inhabitants from 1987–2011 and with partial data between 1969–1986; 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 (2016), including national data on all convictions from 1973–2011; the Swedish suspicion register, including national data on all individuals suspected of crime from 1998–2011; and the Swedish Mortality Register (Socialstyrelsen, 2016a), containing causes of death.

2.1 Identification of Alcohol Use Disorder

Alcohol use disorder (AUD) was defined in the medical registries by International Classification of Disease (ICD) codes for the following main and secondary diagnoses: ICD8 and 9: alcohol-related psychiatric disorders (291), alcohol dependence (303), unspecified liver damage caused by alcohol (571A–D), toxic effects of alcohol (980); ICD9: alcohol abuse (305A), alcohol-related polyneuropathy (357F), alcohol-related cardiomyopathy (425F), alcohol-related gastritis (535D), alcoholic fatty liver, alcohol hepatitis, alcoholic cirrhosis, 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). In the Prescribed Drug Register, AUD was based on the following Anatomical Therapeutic Chemical (ATC) codes: disulfiram (N07BB01), acamprosate (N07BB03), or naltrexone (N07BB04). Additionally, in the Crime registries, we identified individuals with at least two arrests or convictions of drunk driving (law 1951:649) or drunk in charge of maritime vessel (law 1994:1009) to insure that we did not count arrests in the suspicion register that described the same event contained in the conviction register. Thus, for this report we defined lifetime AUD as the presence of one or more registrations in the medical, criminal or pharmacy registries using the above definitions. We could not exclude cases from the Crime registry driving under the influence of drugs. Each registration was dated, allowing us to calculate the age at first registration for all subjects. We also tallied the total number of lifetime registrations.

2.2 Sample

The dataset was created by double-entering all cousin, half-sibling, full-sibling, and MZ twin pairs in the Swedish population where both individuals in the pair were born between 1950 and 1980, and still residing in Sweden at age 15. As noted below, our models for AUD began measuring AUD from age 10. Furthermore, we required that the first individual (the proband) in the pair was registered as having AUD. That is, all probands in our sample had been registered for AUD. In concordant pairs where both were registered as AUD, each would be treated once as a proband. In the database, each pair was assigned their degree of genetic resemblance (1 for MZ twins; 0.5 for full-siblings; 0.25 for half-siblings; 0.125 for cousins). The number of pairs of each type can be seen in Table 1. As outlined in detail elsewhere (Kendler et al., 2012), DA was assessed from relevant registrations in the Hospital Discharge Register, the Swedish Crime Register and the Swedish Prescribed Drug Register.

2.3 Statistical Methods

As we wanted to know whether new cases of AUD will be produced when individuals are “exposed” to higher familial resemblance as well as the clinical feature of interest beyond what would be expected from the impact of the familial resemblance and the clinical feature of interest on their own, we utilized Aalen’s linear hazard regression model (Kendler and Gardner, 2010; Martinussen and Scheike, 2006; Scheike and Zhang, 2011). Because we used this model, results will be interpreted at the additive scale as the excess number of case. In Aalen’s linear hazard regression model the intensity function is governed by the covariates as well as the past events through a linear regression. Estimation of Aalen’s nonparametric regression coefficients is performed via weighted least squares. We investigated all pairs of relatives from age 10 until (a) year of first registration of AUD in the relative, (b) death/emigration in the relative or (c) end of follow-up (year 2011), whichever came first. We looked at interactions between five clinical features of the AUD registration in the proband [(1) age at first registration; (2) number of registrations; (3) recurrence, (4) history of DA and (5) type of registration] and risk for AUD in classes of relatives ranked by degree of familial relationship. As we have previously found in our data, relatives are significantly more similar in their history of AUD if they are closer (versus more distant) in age (Kendler et al, unpublished observations). Therefore, we controlled for the absolute age difference between the proband and the relative in all models. For full siblings each extra year between siblings decrease the odds of AUD in sibling by 4%. As there could be several pairs from the same cluster of relatives, we used robust standard errors to take into account their non-independence. In all models we checked whether the regression coefficients varied over time. However, in no cases were there substantial changes to our results. The key predictor variables in the models were the interaction terms between the clinical feature and familial resemblance.

In the first analysis, we focused on age at onset, defined as AFR in the proband. In the model we investigated the linear effects of age at onset and the interactions with familial resemblance. The quadratic term was not significant ($p=0.39$) and therefore was not included in the final model. In the second analysis, we focused on lifetime AUD registrations in the proband defined as the total number of independent times the person has been registered in the medical, criminal or pharmacy registries meeting the criteria outlined above. We

investigated both the linear and quadratic effects of the number of AUD registrations and their interactions with familial resemblance. The quadratic term was not significant ($p=0.25$) and therefore was not included in the final model.

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. The fourth analysis also involved a binary variable – a lifetime history of DA. In the fifth 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 Outpatient 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 familial resemblance, as well as the interaction between prescription registration and familial resemblance. We also estimated a model including all clinical features and their interactions with familial resemblance simultaneously.

In the final analysis, we translated registration into a continuous variable based on the relative size of the interaction term between the contrasts and the nature of familial relationship (1= medical registration, 2=prescription registration, and 3=criminal registration). As a proband could appear in several different types of registers, we selected the register in which the proband was first registered for the contrasts. The statistical analyses were performed using SAS 9.3 (SAS Institute, 2011) and the R-package 3.1.3 (R Development Core Team, 2014).

3. RESULTS

3.1 Nature of the Sample

The key descriptive features of the sample used in this report, which includes a total of 684,223 relative pairs, are outlined in Table 1. The lifetime prevalence for AUD in Swedes born 1950–1980 was 4.3%. As expected, the frequency of AUD in the co-relative of our proband with AUD was increased above this baseline and greater the closer the familial relationship: cousins 6.5%, half-siblings 12.9%, full-siblings 14.6%, and MZ cotwins 34.0%. Across all groups, probands and affected relatives were most commonly detected in the medical registry. The average age at first AUD registration was in the late 20s to early 30s and the median number of registrations was 2 (across all groups).

3.2 Age at Onset and Relationship with Familial Risk

We first modeled risk as a linear hazard function for all relatives examined together. For each year increase in AFR for AUD in the proband, the absolute risk for AUD in relatives decreased by 0.22 cases per 10,000 person-years ($z=18.7$, $p<0.0001$). Then, as seen in Table 2, we included in our model the linear effects of AFR for AUD, familial relationship between the pair, and their interaction, controlling for age difference of the proband and relative. In this model, AFR no longer had a significant main effect, but we saw a strong main effect for familial relationship, and a robust interaction between AFR and familial

relationship. As seen in Figure 1, the magnitude of the decline in risk in the co-relative as a function of increasing AFR in the proband is strongly related to the degree of familial relationship of the relative pair. That is, it is strongest in MZ twins and declines in magnitude to siblings to half-siblings to cousins. (To help interpret these figures, the baseline incidence rate of AUD per 10,000 person years varied across our groups as follows: population - 12.88, cousins - 13.43, half-siblings - 25.51, siblings - 13.99 and MZ twins - 9.84). Of note, while the differences in increased risk across different relationships is very large when AFR for AUD is under 20, these differences become much smaller when AFR exceeds age 40.

3.3 Number of Alcohol Use Disorder Registrations and Relationship with Familial Risk

Across all relatives, each additional registration for AUD in the proband was associated with an absolute risk increase in relatives of 0.257 cases per 10,000 person-years ($z=20.9$, $p<0.0001$). As seen in Table 2, we next modeled risk as a linear function of the number of AUD registrations, age differences between proband and relative, familial relationship, and interaction between familial relationship in the relative pair with number of registrations. We saw a modest main effect for number of registrations, a robust main effect for familial relationship and a highly significant interaction between the two. As seen in Figure 2, the increase in number of new cases of AUD in relatives with increasing numbers of registrations in the proband is greater in close relationships (i.e. MZ twins) than in more distant relationships (i.e., cousins). These differences, however, are more modest than those seen with AFR.

3.4 Recurrence of Alcohol Use Disorder Registration and Relationship with Familial Risk

Across all relatives, recurrence of AUD in the proband was associated with an absolute risk increase in relatives of 4.63 cases per 10,000 person-years ($z=14.38$, $p<0.0001$). We then examined the effect of recurrence along with age differences between proband and relative, familial relationship, and interaction between familial relationship in the relative pair with recurrence (table 2). We saw a modest non-significant main effect for recurrence, a robust main effect for familial relationship and a highly significant interaction between the two. As seen in figure 3, the increase in number of new cases of AUD in relatives with recurrence was considerably stronger in close relationships (MZ twins and siblings) than in more distant relationships.

3.5 A history of Drug Abuse (DA) and Relationship with Familial Risk

Across all relatives, a history of DA in the proband was associated with an absolute risk increase in relatives of 9.91 cases per 10,000 person-years ($z=31.10$, $p<0.0001$). We then examined the effect of a DA history along with age differences between proband and relative, familial relationship, and interaction between familial relationship in the relative pair with a proband history of DA (table 2). We saw a non-significant main effect for a history of DA, a quite strong main effect for familial relationship and a highly significant interaction between the two. As seen in figure 4, the increase in number of new cases of AUD in relatives with DA in the proband was much stronger in close relationships (MZ twins and siblings) than in more distant relationships.

3.6 Source of Alcohol Use Disorder Ascertainment and Relationship with Familial Risk

Across all relatives, appearance of the proband in the medical register is associated with 0.52 more cases per 10,000 person years compared to appearance in the criminal register ($z=1.6$, $p=0.06$). The corresponding figure for the prescription versus criminal register is 2.52 fewer cases ($z=9.1$, $p<0.0001$). Table 2 presents the model where we compare risk in relatives as a function of source of AUD registration, again with the reference group being the criminal register. We see significant interactions between both contrasts and the nature of the familial relationship. The interaction is positive for the medical register meaning that proband registration in the medical versus crime register is associated with an increase in the number of AUD cases in relatives, this effect being stronger in closer than more distant relatives. The interaction for the prescription register is negative meaning that the opposite pattern is seen. Proband registration in the prescription versus crime register is associated with a decrease in the number of AUD cases in relatives, this effect being stronger in closer than in more distant relatives.

3.7 Diagnoses of AUD versus Alcohol-related Medical Conditions in the Medical Registry

When we compared types of diagnoses in the medical register, we found that, across all relatives, proband registration for an actual diagnosis of AUD was associated with 6.4 more cases per 10,000 person years in relatives compared to proband registration for an alcohol-related medical condition ($z=21.1$, $p<0.0001$). A highly significant interaction was seen between familial relationship and AUD diagnosis versus an alcohol-related medical condition ($z=17.3$, $p<0.0001$; full model available upon request). That is, the increase in risk among relatives of those with an AUD diagnosis versus an alcohol-related medical condition was much greater in close relatives (MZ twins and siblings) than in more distant relatives (cousins).

3.8 All Five Indices of Familial Risk for Alcohol Use Disorder in a Single Model

Table 3 presents the results of z-score transformations of the five indices of familial risk as predictors of risk for AUD in relatives. Four of the five indices continued to have a statistically robust interaction with level of familial relatedness (AFR, number of registrations, recurrence and a history of DA). As assessed by the z-score of the interaction, when jointly analyzed, a history of DA is the most powerful index of familial risk ($z=15.5$) followed by AFR ($z=15.0$), recurrence ($z=8.5$) and number of registrations ($z=7.3$). Type of register ran a distant fifth ($z=0.5$).

Finally, we aggregated the z-scores for the five clinical features and constructed one summary measure. We then divided this summary measure into 10 equally-sized groups and performed a logistic regression analysis using the summary measure to predict AUD in the each relative group. The difference in risk for AUD in the close relatives of AUD probands (MZ co-twins and siblings) classified as being at low versus high familial risk was quite substantial. As seen in Figure 5, the predicted risk for AUD in the MZ co-twin and siblings of an AUD individual ranked in the lowest, fifth and highest deciles of familial risk were 20.2, 38.1 and 55.7%, and 11.5, 16.7 and 22.1%, respectively. The differences in more distant relatives were more modest, with predicted risk for AUD in half-siblings and cousins

of probands in the lowest, fifth and highest deciles of familial risk of, respectively, 12.6, 15.3 and 17.7%, and 5.6, 6.9 and 8.0%.

4. DISCUSSION

4.1 Predictive Effects

The goal of this report was to determine whether five clinical features of AUD ascertained through official registries were related to familial risk as assessed by the prevalence of AUD in cousins, half-siblings, full-siblings, and MZ cotwins in a Swedish national sample. Risk of AUD in relatives was predicted by the proband's early AFR, higher numbers of AUD registrations, recurrence, history of DA and by type of registration. As would be expected if these measures indexed familial risk, this association varied as a function of the nature of the relationship of the relative pair. It was strongest in MZ pairs, intermediate in full-siblings, weaker in half-siblings, and weakest in first cousins. Within the medical register, we found that a diagnosis of AUD predicted a higher risk of AUD in relatives than did a diagnosis of one or more alcohol-related medical conditions. Finally, when put into a multivariate model, four of the five predictors (AFR, number of registrations, recurrence and history of DA) significantly interacted with the degree of familial relationship. Overall, a DA history was the most powerful predictor of familial risk, followed by AFR, recurrence and number of registrations, with the source of registration being the weakest predictor.

There are precedents for our finding that AFR is inversely related to familial risk for AUD. Several prior family studies have noted an association between early age at onset of AUD and risk for AUD in relatives (Buydens-Branch et al., 1989; Hill et al., 2000; Hill and Yuan, 1999). In a twin study, McGue et al. noted a substantially higher estimated heritability for AUD in early-versus late-onset cases (McGué et al., 1992) and Prescott and Kendler noted that age at onset of drinking is associated with genetic risk for AUD (Prescott and Kendler, 1999). Our finding of a positive association between total number of AUD registrations and recurrence with risk for AUD in relatives is anticipated by earlier findings of Cloninger et al. showing recurrent alcohol-related social and legal problems were characteristic of type 2 alcoholism, the more heritable form in his typology (Sigvardsson et al., 1996). That a history of DA in an AUD proband would reflect higher familial risk is consistent with a series of prior, including one conducted in Sweden, showing substantial sharing of familial/genetic risk factors for AUD and DA (Kendler et al., 2007b; Kendler et al., 2011, 2016).

We wondered whether familial risk for AUD would differ for individuals with medical complications of AUD compared to those only diagnosed with AUD in the medical register. Higher levels of alcohol consumption might, on average, be needed to observe alcohol-related medical complications than to merit solely a diagnosis of AUD, and therefore might be related to greater familial risk. Furthermore, our choice of medically related disorders was narrow, only including categories clearly described in ICD as being associated with excess alcohol consumption. However, we did not find support for this. Registration for AUD was more strongly related to familial risk than registration for alcohol-related complications.

It is of interest to compare our findings with those obtained from a similar study of drug abuse ascertained from Swedish registers (Kendler et al., 2014). As we see for AUD, risk for drug abuse in relatives was strongly indexed by AFR and number of registrations, with effects stronger in more closely-related classes of relatives. However, for drug abuse, a substantially higher risk in relatives was associated with criminal versus medical registration. For AUD, the opposite effect was seen. These results suggest that familial factors more strongly drive criminal registration for drug abuse than they do for AUD. This is likely a result of the differences between drug abuse, which is by definition illegal, and legalized alcohol consumption.

4.2 Limitations

These results should be interpreted in the context of six 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. Among European countries, Sweden shares with Finland and Russia a distinctive drinking pattern characterized by large quantities consumed per occasion and a high degree of intoxication-oriented drinking (Leifman, 2002). Second, subjects with AUD were ascertained from medical, legal and pharmacy records. Unlike traditional epidemiological surveys, this approach has the advantage of ascertaining cases independent of subject cooperation or accurate recall and reporting. However, 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 was conducted in neighboring Norway (Kringlen et al., 2001) and 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 population) are likely to contain many more false negative than false positive diagnoses.

Third, we were only able to assess age at onset of AUD indirectly through AFR. The time period between the true onset of AUD and first detection by our methods is undoubtedly variable. We might expect this increased variability to attenuate rather than exaggerate the association with risk of illness in relatives, particularly because it is highly likely the true onset of problematic alcohol use and AUD were earlier than the AFR recorded in these three data sources. 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 methods. Again, the imperfection of this measure is more likely to bias downward the observed association with risk of AUD in relatives.

Fourth, the medical discharge registry was less complete in the years 1969–1986 than later. To examine the possible effects of this, we looked at differences in our key results for our sample divided into two birth cohorts: 1950–1965 and 1966–1980. No significant differences were seen in the effect of medical versus crime registration or recurrence. For AFR, the effect on risk of AUD in relatives was stronger in the older cohort while for number of registrations the effect was stronger in the younger cohort.

Fifth, there is evidence for cohort changes in patterns of alcohol consumption in Sweden over the years of this study (Ahacic et al., 2012). We therefore repeated all of our main analyses adding as a control variable year at birth. Changes were very modest involving at most alterations in the third significant place of our regression estimates.

Finally, our statistical models did not formally account for possible differences between the four kinds of relative pairs according to gender concordance (i.e., male-male, male-female, female-male, and female-female). We therefore re-ran all models including these pairs and found that the changes in key parameters were very modest. For example, the key regression coefficient ($AFR \times \text{familial risk}$) changed from -0.000125 (from table 1) to -0.000129 when controlling for the four kinds of pairs of relatives. These results suggest that our original estimates ignoring gender concordance in pairs of relatives were relatively accurate.

4.3 Conclusions

In a large registry-based sample of the Swedish population, we identified five relatively simple clinical or historical features of AUD that reflected the familial risk to AUD, especially when summed into an aggregate measure. Individuals who were first registered at a young age, had many registrations, had comorbidity with DA, had a recurrence of AUD soon after onset and/or had medical registration for their AUD were at particularly high familial risk. These results suggest at least some features of the heterogeneity of the AUD syndrome can be meaningfully indexed by simple clinical measures obtained from epidemiological samples. These methods could easily be adapted to be used in standard clinical settings where these indices could be assessed during a routine history taking. Our results also have implications for gene-finding efforts if the goal is to identify AUD probands for analysis who have, on average, high familial liability.

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None

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Highlights

In a large epidemiological sample, we identified clinical features of Alcohol Use Disorder (AUD) cases that index familial risk.

Early age at onset, number of registrations and recurrence predicted risk for AUD in relatives.

This prediction was stronger for more closely related relatives consistent with these indexing genetic risk.

Combining these indices, the highest decile of familial risk predicted risk for AUD in siblings 60% greater than that seen in the lowest decile.

FIGURE 1.

The predicted Excess Number of Cases of Alcohol use disorder per 10,000 Person Years in Monozygotic Cotwins, full-siblings, half-siblings and cousins of Proband's with Alcohol use disorder as a Function of the Proband's Age at First Registration for Alcohol use disorder.

FIGURE 2.

The predicted Excess Number of Cases of Alcohol use disorder per 10,000 Person Years in Monozygotic Cotwins, full-siblings, half-siblings and cousins of Proband's with Alcohol use disorder as a Function of the Number of the Proband's Registrations for Alcohol use disorder.

FIGURE 3.

Predicted results from the Linear Hazard Model presented in full in table 2. This figure depicts the predicted Excess Number of Cases of Alcohol use disorder per 10,000 Person Years in Monozygotic Cotwins, full-siblings, half-siblings and cousins of Probands with Alcohol use disorder as a Function of the Proband's History of Recurrence.

FIGURE 4.

Predicted results from the Linear Hazard Model presented in full in table 2. This figure depicts the predicted Excess Number of Cases of Alcohol use disorder per 10,000 Person Years in Monozygotic Cotwins, full-siblings, half-siblings and cousins of Proband's with Alcohol use disorder as a Function of the Proband's History of Drug Abuse (DA).

FIGURE 5.

Predict risk for Alcohol Use Disorder as calculated by logistic regression in Monozygotic Cotwins, full-siblings, half-siblings and cousins of Proband's with Alcohol Use Disorder as a Function of the Proband's Aggregate Familial Risk Estimated from the Model presented in full in table 3. The z-scores for the 5 clinical features were aggregated into one summary measure and divided into 10 equally sized groups. The figure depicts the predicted probability of AUD in relatives for the 10 groups.

TABLE 1**Characteristics of the Sample Studied**

	Cousins	Half-siblings	Siblings	MZ Twins
Number of Proband-Relative Pairs	385,245	91,771	205,766	441
Number of Relatives with AUD	25,151 (6.5 %)	11,842 (12.9%)	30,048 (14.6%)	150 (34.0%)
Proband Age at first registration (SD)	28.2 (10.1)	29.3 (11.0)	31.4 (11.8)	33.7 (11.9)
Number of registrations (P)	5.1 (11.1)	6.5 (14.4)	6.4 (13.5)	5.9 (11.3)
Number of Crime registrations (P)	0.9 (2.2)	1.2 (2.8)	1.0 (2.3)	0.6 (2.8)
Number of Medical registrations (P)	3.0 (8.4)	4.1 (11.7)	4.2 (11.2)	4.3 (10.1)
Number of registrations from Prescription registry (P)	1.2 (5.9)	1.2 (6.9)	1.2 (6.1)	1.0 (3.0)
Mean Year of Birth (SD) (P)	1967 (6.8)	1963 (7.8)	1962 (7.5)	1962 (8.8)
Mean Year of Birth (SD) (R)	1968 (5.8)	1965 (8.1)	1962 (7.5)	1962 (8.8)
Medical Register (P) *	260,417 (68%)	63,231 (69%)	143,730 (70%)	355 (81%)
Medical Register (R) *	16,674 (66%)	8,163 (69%)	21,502 (72%)	128 (85%)
Criminal Register (P) *	142,521 (37%)	38,362 (42%)	77,980 (38%)	105 (24%)
Criminal Register (R) *	10,509 (42%)	5,326 (45%)	13,198 (25%)	43 (29%)
Prescription Register (P) *	101,463 (26%)	22,066 (24%)	53,802 (26%)	128 (29%)
Prescription Register (R) *	6,233 (25%)	2,795 (24%)	7,448 (25%)	47 31%)

* The number and proportion of probands (P) and relatives (R) that were registered for AUD in the three registries. These sum to more than one because individuals could be entered into more than one registry.

TABLE 2

Results of Linear Hazard Models Predicting Risk of Alcohol Use Disorder in Relatives as a Function of the Linear Effect of the Proband's Age at First Registration, Number of Registrations, Recurrence and Type of Registration, the Familial Relationship between Proband and Relative, Age Differences and the Interaction between these Five Clinical Features and Familial Relationship

Clinical Feature	Beta Coefficient	Robust SE	z-value	P-value
Age at First Registration				
Age at First Registration (AFR) for AUD (centered at mean)	0.000002	0.000001	1.2	0.23
Familial Relationship	0.005750	0.000127	45.1	<0.0001
Age difference in Relative Pair	-0.000012	0.000003	-4.2	<0.0001
AFR*Familial Relationship	-0.000125	0.000007	-17.9	<0.0001
Number of registrations				
Number of registrations	-0.000004	0.000002	-2.3	0.02
Familial Relationship	0.004620	0.000116	39.6	<0.0001
Age difference in Relative Pair	-0.000012	0.000003	-4.1	<0.0001
Number of registrations*Familial Relationship	0.000094	0.000007	12.0	<0.0001
Recurrence				
Recurrence	-0.000061	0.000052	-1.2	0.241
Familial Resemblance	0.004708	0.000116	40.6	<0.0001
Age difference	-0.000014	0.000003	-5.0	<0.0001
Recurrence * Familial Resemblance	0.001783	0.000193	9.2	<0.0001
Drug Abuse (DA)				
DA	-0.000032	0.000056	-0.57	0.56
Familial Relationship	0.004145	0.000127	45.7	<0.0001
Age difference in Relative Pair	-0.000013	0.000003	-4.6	<0.0001
DA *Familial Relationship	0.004428	0.000216	20.5	<0.0001
Type of Registration[#]				
Medical Register	-0.000264	0.000047	-5.6	<0.0001
Prescription register	-0.000144	0.000048	-2.9	<0.0001
Familial Relationship	0.004638	0.000173	26.8	<0.0001
Age difference in Relative Pair	-0.000012	0.000003	-4.1	<0.0001
Medical Register * Familial Relationship	0.001036	0.000168	6.2	<0.0001
Prescription Register * Familial Relationship	-0.000427	0.000174	-2.5	0.01

[#] the type of Registration of the Proband is coded 1= Medical, 2= Prescription, 3=Crime.

TABLE 3

Results of a Linear Hazard Model Predicting Risk of Alcohol Use Disorder in Relatives as a Function of z-transformed Scores for the Source of Registration of the Proband (coded 1= Medical, 2= Prescription, 3=Crime), Age at First AUD Registration, Number of Registrations, Recurrence and Drug Abuse, Familial Relationship between Proband and Relative, Age Differences and the Interaction between Source of Registration, Age at Registration, Recurrence and Number of Registrations and the Familial Relationship

	Beta Coefficient	Robust SE	Z	P
Age at registration	−0.0000033	0.0000023	−1.45	0.148
Type of registration	0.00012	0.000028	4.35	0.000
Number of registrations	−0.0000050	0.0000022	−2.28	0.023
Recurrence	−0.00014	0.000058	−2.81	0.004
Drug Abuse	0.000013	0.000058	0.23	0.813
Age difference	−0.000013	0.0000028	−4.61	0.000
Familial Resemblance	0.0036	0.0000028	17.49	0.000
Age at registration* Familial Resemblance	0.00011	0.0000074	14.98	0.000
Number of registrations * Familial Resemblance	0.000058	0.0000079	7.28	0.000
Type of register * Familial Resemblance	0.000052	0.000098	0.52	0.598
Recurrence * Familial Resemblance	0.0015	0.00018	8.52	0.000
Drug Abuse*Familial Resemblance	0.0034	0.00022	15.46	0.000