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Different Characteristics and Heritabilities of Alcohol Use Disorder Classes: A Population-Based Swedish Study

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Abstract

Aims: The aims of the present study are to identify alcohol use disorder (AUD) classes among a population-based Swedish sample, determine if these classes differ by variables known to be associated with AUD and determine whether some AUD classes have stronger genetic influences than others.

Methods: A latent class analysis (LCA), based on types of registrations, was conducted on Swedish individuals with an AUD registration born between 1960 and 1990 (N = 184,770). These classes were then validated using demographics; patterns of comorbidity with drug abuse, psychiatric disorders and criminal behavior; and neighborhood-level factors, i.e. peer AUD and neighborhood deprivation. The degree of genetic and environmental influence was also investigated.

Results: The best-fit LCA had four classes: (a) outpatient/prescription, characterized by a mix of outpatient medical and prescription registrations, (b) low-frequency inpatient, characterized entirely by inpatient medical registrations, with the majority of individuals having one AUD registration, (c) high-frequency mixed, characterized by a mix of all four registration types, with the majority having four or more registrations and (d) crime, characterized almost entirely by criminal registrations. The highest heritability for both males and females was found for Class 3 (61% and 65%, respectively) and the lowest for Class 1 (20% for both), with shared environmental influences accounting for 10% or less of the variance in all Classes.

Conclusions: Using comprehensive, nationwide registry data, we showed evidence for four distinct, meaningful classes of AUD with varying degrees of heritability.

INTRODUCTION

Alcohol use disorder (AUD) is defined as 'a problematic pattern of alcohol use leading to clinically significant impairment or distress,' such as recurrent use in hazardous situations and recurrent use despite psychological or physical problems (American Psychiatric Association, 2013). The heterogeneity of AUD has long been recognized, with the last five decades of research efforts attempting to identify the number and characteristics of the subtypes needed to capture this heterogeneity (e.g. see (Babor, 1996; Hesselbrock and Hesselbrock, 2006) for reviews). One of the earliest typologies was proposed by Jellinek, who identified five subtypes of AUD based on reasons for drinking, type of dependence (e.g. physical or psychological) and resulting consequences (Jellinek, 1960; Litten *et al*., 2015). Following this, two commonly cited typologies were developed that each identified two subtypes of AUD: Cloninger's Type I/Type II typology (Cloninger *et al*., 1996) and Babor's Type A/Type B (Babor *et al*., 1992).

Attempts to replicate these two typologies have mostly relied on more sophisticated statistical methods, such as cluster analysis and latent class analysis (LCA). These attempts have resulted in the identification of three (Johnson *et al*., 1996; Kendler *et al*., 2015; Sintov *et al*., 2010), four (Bucholz *et al*., 1996; Casey *et al*., 2013; Del Boca and Hesselbrock, 1996; Lesch *et al*., 1988; Lesch *et al*., 1990), or five subtypes (Cardoso *et al*., 2005; Kendler *et al*., 1998; Moss *et al*., 2007). Some of the most recent LCAs of DSM-5 AUD have resulted in two classes (less and more severe symptoms) (Rinker and Neighbors, 2015) and three classes (mild, moderate and severe symptoms) (Swift *et al*., 2016). Accordingly, although evidence exists that AUD is heterogeneous, the number and characteristics of AUD classes needed to capture this heterogeneity are not yet established. It is also unclear if AUD classes differ meaningfully by variables known to be highly correlated with AUD, such as age, drug abuse, criminal behavior, psychiatric disorders (Compton *et al*., 2005; Grant *et al*., 2015) and neighborhood-level factors (e.g. peer AUD; neighborhood deprivation (Burk *et al*., 2012; Karriker-Jaffe *et al*., 2018; Sher *et al*., 2005)).

Further, despite the literature showing that some of the AUD classes originally proposed are more strongly influenced by genetic factors, such as Cloninger's Type II (Cloninger *et al*., 1996) and Babor's Type B (Babor *et al*., 1992), there has been limited research investigating it. While the few early studies that have been conducted showed some evidence for heterogeneity in the pattern of AUD inheritance (Dick *et al*., 2007; Pickens *et al*., 1991), we are not aware of any recent efforts to investigate the heritability of different AUD classes with adequate sample sizes. Investigating the degree of genetic influence not only will help to elucidate the nature of the heterogeneity of AUD, but it will also facilitate molecular genetic studies by showing that different classes may have different heritabilities and potentially distinct risk loci.

The aims of the present study are therefore to: (a) investigate AUD classes among a population-based Swedish sample using LCA; (b) determine if these classes differ by variables known to be highly correlated with AUD; and (c) investigate the degree of genetic influence on AUD classes. This study has critical advantages over other studies, including the use of a nationwide, population-based sample and use of objective registry data that is not subject to recall and response biases, as opposed to most prior studies that have used self-reported data. To our knowledge, this is also the largest and most comprehensive LCA of AUD to date, which will increase the precision and reliability of the results.

METHODS

Sample

We analyzed information on individuals from Swedish population-based registers with national coverage. These registers were linked using each person's unique identification number replaced by a serial number to preserve confidentiality. We secured ethical approval for this study from the Regional Ethical Review Board of Lund University. The database for the LCA was created by selecting all individuals born between 1960 and 1990 and registered with AUD between 1975 and 2014 ($N = 184{,}770$).

Measures

Based on information from the Swedish population-based registers, we created the following four dichotomous variables for registration type: registration for AUD in the prescription register (registration in the Prescribed Drug Register or not), criminal registration for AUD (registration in the Crime Register and/or the Suspicion Register or not), inpatient medical registration for AUD (registration in the Hospital Discharge Register), and outpatient/primary health care registration for AUD (registration in the Outpatient Register/Primary Health Care register or not). In addition, we summarized the number of times each individual was registered in any register. In order not to double-count registrations, we allowed for a 90-day period after each registration (within each type of register) in which a new registration was not counted. We created three groups based on this variable: (a) individuals registered once, (b) two to three times, and (c) four times or more.

AUD was identified in the following Swedish medical registries: the Swedish Hospital Discharge Register (national coverage for 1987–2012 and partial coverage for 1969–1986); and the Outpatient Care Register (national coverage for 2001–2012). We also used a new Primary Care Registry (coverage for 1998–2016; exact coverage years vary slightly by county), which included individual-level information on diagnoses from visits to primary health care centers in 15 of Sweden's 21 counties (Sundquist *et al*., 2017). The following diagnostic codes from the International Classification of Diseases (ICD) were used: ICD 8: 571A, 291,303, 980; ICD 9: V79B, 305A, 357F, 571A-D, 425F, 535D, 291, 303, 980; ICD 10: E244, G312, G621, G721, I426, K292, K70, K852, K860, O354, T51, and F10. AUD was also collected from the Crime Register (codes 3005 and 3201 reflect driving under the influence convictions); the Suspicion Register (codes 0004 and 0005; only those individuals with at least two alcohol-related crimes or suspicion of crimes from both Crime Register and Suspicion Register were included); and the Prescribed Drug Register by the drugs disulfiram (Anatomical Therapeutic Chemical (ATC) Classification System N07BB01), acamprosate (N07BB03), and naltrexone (N07BB04).

We used the following nine measures for external validators (i.e., covariates): year of birth, sex, education, age at first registration with AUD, drug abuse, psychiatric disorders, non-drug abuse-related criminal behavior, peer AUD at age 15, and neighborhood deprivation at age 15. Education was categorized into two groups: low (<9 years in school) and high (>9 years in school).

Drug abuse was identified in the Swedish medical and mortality registries by the following ICD codes: ICD8, ICD9 (292 and 304), and ICD10 (F10-F19). Drug abuse was also collected from the Crime Register (references to laws covering narcotics—law 1968: 64, paragraph 1, point 6 and drug-related driving offenses—law 1951:649, paragraph 4, subsection 2 and paragraph 4A, subsection 2); the Suspicion Register (codes 3070, 5010, 5011 and

5012, which reflect crimes related to drug abuse); and the Prescribed Drug Register (excluding those suffering from cancer) among those who had retrieved (on average) more than four defined daily doses a day for 12 months from either of Hypnotics and Sedatives (ATC) Classification System N05C and N05BA) or Opioids (ATC: N02A).

Psychiatric disorders were identified by registration in the Swedish medical registers with the following ICD codes: ICD10 codes: F00-F99, ICD8, 9: 290–319, (i.e. organic psychotic conditions, other psychoses, neurotic disorders, personality disorders, and intellectual disabilities). Codes used for drug abuse and AUD were excluded. Criminal behavior was identified by registration in the Swedish Crime Register using all available criminal conviction types (i.e. violent crime, property crime, and white-collar crime). Convictions for minor crimes like traffic infractions were excluded.

Peer AUD was calculated using geographical areas called Small Areas for Market Statistics (SAMS) that were defined by Statistics Sweden. There are approximately 9,200 SAMS throughout Sweden, with an average population of 1000. AUD was defined during the entire follow up period. The peer AUD measure was calculated at proband age 15 and based on the proportion of future AUD in the SAMS area of individuals in an 11-year interval around the age of the proband. For example, for a proband born in 1980, we measured the proportion of future AUD of individuals born between 1975 and 1985 residing in that SAMS in 1995. For more details of the peer AUD measure, see Kendler *et al.* (2014).

The neighborhood deprivation variable was created for each of the SAMS based on registry data for all residents aged 25–64 years in the neighborhood in which the proband resided at age 15. The SES composite contained: the proportion of residents with low education (<9 years), the proportion of residents with low household income (less than half the median income), the proportion of unemployed residents, and the proportion of individuals on financial assistance (Winkleby *et al.*, 2007). The SES composite was kept as a continuous variable, with the SD score ranging between −3 and 11, with higher values indicating greater levels of neighborhood deprivation.

Statistical analyses

LCA was used to identify homogeneous AUD classes based on different types of observed variables. We entered four dichotomous variables for each registration type (prescription, crime, inpatient, and outpatient/primary health care) and the three categories for the numbers of registrations into the LCA (1, 2–3, and 4 or more). The number of latent classes indicated by the observed variables was determined by comparing model fit statistics between nested models. Improvement in model fit is indicated by smaller values of the log-likelihood, Akaike's Information Criterion (AIC), and entropy values close to 1.0. However, as the number of classes is influenced by the number of observed variables, both empirical (improved model fit) and theoretical (model interpretability) aspects were considered. Individual subjects were then assigned class membership based on the likelihood of their particular response profile. The LCA was performed using PROC LCA in SAS v. 9.4 (Lanza *et al.*, 2011; Lanza *et al.*, 2007).

We then included the nine covariates (year of birth, sex, education, age at first registration with AUD, drug abuse, psychiatric disorders, criminal behavior, peer AUD, and neighborhood deprivation) to determine whether there were important differences across LCA classes. Chi-squared analyses were used to compare categorical variables and one-way ANOVA was used for continuous variables.

In a further attempt to validate the LCA, we selected from the Swedish Twin registry all twin pairs with birth years from 1960 to 1990 with known zygosity, and from the Swedish Multi-Generation Registry all Swedish-born full- and half-sibling (FS and HS) pairs, born between 1960 and 1990 and within 5 years of each other. We also required that both siblings in the pair were alive at the age of 15. We assessed, using the Swedish national census and total population registries, the cohabitation status of the twins, FS and HS pairs as the proportion of possible years lived in the same household until the oldest turned 16. We included pairs reared together, defined as living together for 80% of the possible years and pairs not reared together, defined as living together for no more than 20% of the possible years. We linked this database to assigned class membership data from the LCA, treating those in other classes as unaffected.

Tetrachoric correlations (i.e., correlations of liability for binary traits) were first estimated to determine the similarity between the twins and siblings on class membership (Pearson, 1900). Then, structural equation modeling was used to model the contributions of genetic and environmental factors to the liability of the four different classes from the LCA. In the models, we assumed a liability threshold model with three sources of liability: additive genetic (A), shared environment (C), and unique environment (E). The ACE model assumes that monozygotic (MZ) twins share all of their genes, dizygotic (DZ) twins share half of their genes, FS share half and HS a quarter of their genes identical by descent. The shared environment (C) equaled 1 for pairs reared together and 0 pairs not reared together. From this model, we can determine the parameter estimates for the contributions of A, C and E.

RESULTS

Descriptive statistics (Table 1)

Of the 184,770 individuals identified as having an AUD during the period 1975–2014, the majority was male (71.0%), was registered from medical sources (42.6% inpatient; 45.3% outpatient), and had one registration (45.8%). More than half also had comorbid psychiatric disorders (64.8%) and criminal behavior (51.5%), with property crime having the highest frequency.

Fit indices (Table 2)

Using the chosen variables, we had sufficient degrees of freedom to fit up to a six-class model. The fit indices continued to improve with an increasing number of classes, except for the entropy index. However, the most substantial drop in AIC was observed when going from a model with three classes to a model with four classes. Including more than four classes resulted only in one class (i.e. "High-Frequency Mixed") continuing to be divided into smaller classes that were difficult to distinguish from each other. Accordingly, the four-class solution was selected as the best-fitting and moved forward for further analysis.

Assignment probabilities (Table 3)

Class 1 had a class membership probability of 23.0% and contained individuals registered through prescription and outpatient sources. While the majority had one registration (69.4%), there was still a substantial amount that had two or three registrations (30.6%). None had four or more registrations. We termed this class 'outpatient/prescription.'

Class 2 had the lowest class membership probability, consisting of 18.3% of the sample and contained individuals registered from inpatient sources only. Most of these individuals had one registration (91.3%) and only 8.7% had 2–3 registrations. None had four or more. We termed this class the 'low-frequency inpatient' class.

Table 1. Descriptive statistics of individuals with an alcohol registration born between 1960 and 1990 ($N = 184,770$)

Demographics	
Year of birth, mean	1973
Men	131,276 (71.0)
Age at first registration, mean (SD)	29.5 (10.6)
Low education	46,989 (25.4)
Comorbidities	
Drug abuse	65,356 (35.4)
Psychiatric disorders	119,802 (64.8)
Criminal behavior	93,309 (51.5)
Violent crime	53,470 (28.9)
Property crime	75,139 (40.7)
White-collar crime	37,618 (20.4)
Registration source	
Prescription	59,849 (32.4)
Crime	65,222 (35.3)
Medical, Inpatient	78,750 (42.6)
Medical, Outpatient	83,630 (45.3)
Number of registrations	
1	84,659 (45.8)
2–3	47,986 (26.0)
4 or more	52,125 (28.2)
Neighborhood factors	
Peer AUD at age 15, mean (SD)	4.0% (2.8)
Neighborhood deprivation at age 15, mean (SD)	0.05 (1.5)

Note. If not otherwise indicated, numbers are count (%).

Table 2. Model fit indices

Number of latent classes	Log-likelihood	AIC	Entropy	df
2	−672603.90	272023.87	1.00	34
3	−610786.27	148402.62	0.88	27
4	−575646.81	78137.69	0.93	20
5	−569752.19	66362.45	0.89	13
6	−562284.22	51440.52	0.96	6

Class 3 had the highest class membership probability (34.8%). Individuals in the class were registered for AUD through a mixture of prescription, crime, inpatient and outpatient registries, with the majority coming from outpatient sources. All of these individuals had two or more registrations; hence, we labeled this class the 'high frequency mixed.'

Class 4 had the second-highest class membership probability (23.9%). These individuals were registered primarily from the criminal registry, with a small amount registered from inpatient (6.8%) and prescription sources (2.9%). Most of these individuals had one registration (55.1%), while 29.0% had 2–3 registrations and 15.9% had four or more. We refer to this class as the 'crime' class.

Posterior probabilities

The mean posterior probabilities of class membership for classes 1–4 were 89%, 99%, 98% and 97%, respectively.

Comparison of covariates

Table 4 compares individuals assigned to these classes across the nine covariates. The first row shows the number of individuals assigned to each class. The differences between the classes were all highly significant. There was a 5-year difference for the mean year of birth, with the oldest class being Class 3, and the youngest class being Class 1. Class 4 had the highest percentage of men (91.6%). Class 1 had the lowest rate of low education (i.e., was the most educated at 20.0%), but was fairly equivalent to Class 2 (20.8%). Class 4 had the highest rate of low education (i.e., was the least educated at 30.9%), but was similar to the rate of Class 3 (29.6%). There was a 12-year age span across classes in mean age at first registration, with Class 2 being the youngest and Class 1 being the oldest.

Rates of drug abuse were similar for Classes 1 and 2 and for Classes 3 and 4. However, the rate of drug abuse for Classes 1 and 2 was roughly half of that for Classes 3 and 4. Rates of psychiatric disorders varied dramatically between the classes, with Class 4 having the lowest rate and Class 3 having the highest. Rates of criminal behavior were unsurprisingly highest in Class 4, the crime class, with property crime having the highest rate, and were lowest in Class 1. Regarding the neighborhood-level factors, Class 1 had the lowest mean level of peer AUD, while Class 3 had the highest. Class 4 by far had the highest level of neighborhood deprivation and Class 2 had the lowest.

Tetrachoric correlations and parameter estimates from the ACE model

The tetrachoric twin correlations and parameter estimates from the ACE model are shown in Table 5.

Male–male pair correlations. We showed the strongest evidence of genetic influence for Classes 3 and 4, with the MZ correlation being much higher than the DZ correlation. For Class 3, the DZ correlation was also just greater than half than the DZ correlation, suggesting shared environmental influences may also be important, albeit minimally. For Class 4, the DZ correlation was not greater than half of the MZ correlation, although the full siblings reared together was, suggesting a possible shared environmental influence of minor importance. The correlations for the HS for these two classes were the lowest, but were higher for the HS reared together versus apart, also suggesting a very modest shared environmental influence. The MZ and DZ correlations for Class 2 were roughly equal, suggesting that both genetic and environmental effects are influential. However, the correlation for the full siblings reared apart was the highest, suggesting a somewhat stronger genetic influence. Finally, for Class 1, the MZ correlation could not be estimated, but the DZ correlation was the highest, followed by the correlation for the full siblings reared apart and then the full siblings reared together, suggesting a shared environmental influence.

Female–female pair correlations. There were only concordant pairs in Class 4 for the full siblings reared together and the HS reared apart, both showing modest correlations. A correlation could therefore not be estimated for the other pair types, making inferences difficult to draw. For Class 3, the MZ correlation was higher than the DZ correlation, suggesting a strong genetic influence, but the DZ correlation was greater than half of the MZ correlation, also suggesting a shared environmental influence. The correlations for the full siblings reared together and apart were comparable, whereas the correlation for the HS reared together was higher than for the HS reared apart, further implicating shared environmental influences. For Class 2, there were no DZ concordant pairs, but similar to the male–male pairs, the correlation for the full siblings reared apart was the highest, suggesting a strong genetic influence. For Class 1, the MZ and DZ correlations were more similar, although the MZ correlation was slightly higher. Further, the correlation for the full siblings reared

Table 3. Assignment probabilities by class

	Class 1: Outpatient/prescription	Class 2: Low frequency inpatient	Class 3: High frequency mixed	Class 4: Crime
Class membership probabilities	23.0%	18.3%	34.8%	23.9%
Item response probabilities				
Prescription	45.9	0	60.8	2.9
Crime	0	0	32.7	100
Medical, Inpatient	0	100	65.3	6.8
Medical, Outpatient	66.7	0	86.0	0
Number of registrations				
1	69.4	91.3	0	55.1
2 or 3	30.6	8.7	29.9	29.0
4 or more	0	0	70.2	15.9

Table 4. Comparison of covariates across classes

	Class 1: Outpatient/prescription	Class 2: Low frequency inpatient	Class 3: High frequency mixed	Class 4: Crime	*P*-value
Class prevalence, *n* (%)	47,886 (25.9)	34,202 (18.5)	58,543 (31.7)	44,139 (23.9)	
Demographics					
Year of birth, mean	1975	1973	1971	1973	<0.0001
Men (%)	61.9	57.4	71.0	91.6	
Low education, %	20.0	20.8	29.6	30.9	<0.0001
Age at first registration, mean	35.5	23.1	31.0	25.7	<0.0001
Comorbidities					
Drug abuse, %	24.8	20.9	48.5	40.7	<0.0001
Psychiatric disorders, %	67.7	64.3	80.1	41.9	<0.0001
Criminal behavior, %	33.8	37.2	58.9	67.8	<0.0001
Violent crime	16.5	17.8	37.0	40.5	<0.0001
Property crime	24.6	28.7	48.5	56.9	<0.0001
White-collar crime	8.8	11.5	24.9	33.7	<0.0001
Neighborhood factors					
Peer AUD at age 15, mean	3.4	4.2	4.4	3.8	<0.0001
Neighborhood deprivation at age 15, mean	−0.04	−0.07	0.04	0.40	<0.0001

together was lower than the full siblings reared apart, and the correlations for the full siblings reared apart were approximately equal to the HS reared together. Taken together, this pattern of correlations suggests a mix of genetic and shared environmental influences for Class 1.

Opposite sex pair correlations. For Class 4, the correlation was highest for the DZ pairs and decreased as genetic relatedness decreased, suggesting a strong genetic influence. For Classes 2 and 3, the correlation for the full siblings reared apart was the highest (albeit not substantially higher than the correlations for the other pair types), implicating the role of shared environmental influences for these classes. The correlations for Class 1 were all mostly negligible.

Parameter estimates from the ACE model. For males, the heritabilities were highest for Class 3 and 4 (61% and 60%, respectively), with the variance accounted for by shared environmental influences being essentially 0% for both. The next highest heritability was found in Class 2 (33%) and then Class 1 (20%), with the variance accounted for by shared environmental influences also being 0% for both. Upon inspection of the confidence intervals for the heritability estimates, there is substantial overlap between Classes 1 and 2 and between Classes 3 and 4, indicating that Classes 1 and 2 are not significantly different and Classes 3 and 4 are not significantly different.

For females, the heritability was highest in Class 3 (65%), followed by Class 2 (38%) and Class 4 (34%) and then Class 1 (20%). Shared environmental influences also accounted for essentially none of the variance in females in all Classes except for Class 1, where it accounted for 10%. The confidence intervals for the heritability estimates of Classes 1, 2 and 4 were all overlapping, while there is not much overlap with the confidence intervals for Class 3, suggesting Class 3 is different from the others.

DISCUSSION

The aims of the present study were to identify AUD classes among a population-based Swedish sample, determine if these classes differ by other variables available to us, and investigate the degree of genetic and environmental influence on AUD classes. Four meaningful and distinct classes of AUD were identified that were characterized by frequency and source of registrations. Class 3, the high frequency mixed class, was particularly distinctive. This class was notable for having the highest percentage of individuals with four or more AUD registrations, the highest class prevalence, the highest rates of comorbid drug abuse and psychiatric disorders, one of the highest rates of criminal behavior, the highest rate of peer AUD, and having the oldest individuals. These high rates of AUD registrations and

Table 5. Tetrachoric twin correlations, prevalence and parameter estimates from full ACE model among MZ twins, DZ twins, FS and HS

Tetrachoric correlations				
	Class 1: Outpatient/prescription	Class 2: Low-frequency inpatient	Class 3: High-frequency mixed	Class 4: Crime
Male–Male Pairs				
MZ ($n = 2,685$)				
Correlation (SE)	–	0.288 (0.192)	0.649 (0.084)	0.720 (0.078)
Prevalence, %	1.1	0.8	1.3	1.0
DZ ($n = 2,327$)				
Correlation (SE)	0.359 (0.133)	0.219 (0.191)	0.359 (0.120)	0.197 (0.189)
Prevalence, %	1.5	1.1	1.8	1.2
FS, reared together ($n = 307,008$)				
Correlation (SE)	0.137 (0.016)	0.154 (0.020)	0.351 (0.010)	0.339 (0.011)
Prevalence, %	1.4	1.0	1.8	1.7
FS, reared apart ($n = 6,761$)				
Correlation (SE)	0.208 (0.110)	0.359 (0.096)	0.335 (0.064)	0.387 (0.050)
Prevalence, %	1.1	1.0	2.2	3.0
HS, reared together ($n = 12,411$)				
Correlation (SE)	0.007 (0.064)	0.117 (0.068)	0.201 (0.038)	0.251 (0.037)
Prevalence, %	2.5	1.9	4.2	4.1
HS, reared apart ($n = 19,497$)				
Correlation (SE)	0.000 (0.053)	0.100 (0.053)	0.142 (0.029)	0.120 (0.031)
Prevalence, %	2.4	2.0	4.9	4.6
Female-Female Pairs				
MZ ($n = 3,233$)				
Correlation (SE)	0.481 (0.128)	0.327 (0.191)	0.697 (0.083)	–
Prevalence, %	0.8	0.7	0.9	0.1
DZ ($n = 2,600$)				
Correlation (SE)	0.373 (0.152)	–	0.477 (0.153)	–
Prevalence, %	1.0	0.8	0.8	0.0
FS, reared together ($n = 273,296$)				
Correlation (SE)	0.179 (0.021)	0.186 (0.023)	0.316 (0.019)	0.226 (0.060)
Prevalence, %	0.9	0.8	0.8	0.2
FS, reared apart ($n = 5,672$)				
Correlation (SE)	0.225 (0.171)	0.401 (0.119)	0.364 (0.098)	–
Prevalence, %	0.6	0.7	1.1	0.2
HS, reared together ($n = 11,782$)				
Correlation (SE)	0.244 (0.063)	0.081 (0.080)	0.278 (0.060)	–
Prevalence, %	1.7	1.7	1.7	0.4
HS, reared apart ($n = 17,694$)				
Correlation (SE)	0.031 (0.068)	0.102 (0.061)	0.161 (0.050)	0.206 (0.011)
Prevalence, %	1.7	1.7	2.1	0.5
Opposite Sex Pairs				
DZ ($n = 7,718$)				
Correlation (SE)	0.012 (0.145)	0.190 (0.125)	0.276 (0.075)	0.448 (0.120)
Prevalence, %	1.2/1.0	1.0/0.8	2.3/1.3	1.8/0.2
FS, reared together ($n = 575,347$)				
Correlation (SE)	0.139 (0.013)	0.133 (0.016)	0.261 (0.011)	0.241 (0.019)
Prevalence, %	1.4/0.9	1.0/0.7	1.8/0.8	1.7/0.2
FS, reared apart ($n = 12,739$)				
Correlation (SE)	0.085 (0.110)	0.248 (0.093)	0.346 (0.055)	0.212 (0.108)
Prevalence, %	1.5/0.7	0.9/0.7	2.4/1.1	3.4/0.2
HS, reared together ($n = 23,958$)				
Correlation (SE)	0.097 (0.047)	–	0.132 (0.038)	0.158 (0.064)
Prevalence, %	2.5/1.7	1.8/1.7	4.2/1.8	4.1/0.4

continued

Table 5. Continued

HS, reared apart (n = 36,521)				
Correlation (SE)	0.034 (0.041)	0.060 (0.042)	0.141 (0.028)	0.051 (0.050)
Prevalence, %	2.7/1.6	2.0/1.8	4.8/2.1	4.5/0.5

Parameter estimates from Ace model (95% CI)

	Class 1: Outpatient/prescription	Class 2: Low-frequency inpatient	Class 3: High-frequency mixed	Class 4: Crime
a^2_m	0.20 (0.00, 0.31)	0.33 (0.18, 0.40)	0.61 (0.48, 0.73)	0.60 (0.47, 0.71)
c^2_m	0.03 (0.00, 0.11)	0.00 (0.00, 0.00)	0.05 (0.00, 0.11)	0.04 (0.00, 0.11)
e^2_m	0.77 (0.69, 0.87)	0.67 (0.60, 0.75)	0.34 (0.27, 0.41)	0.35 (0.29, 0.42)
a^2_f	0.20 (0.01, 0.42)	0.38 (0.19, 0.46)	0.65 (0.59, 0.71)	0.34 (0.08, 0.63)
c^2_f	0.10 (0.00, 0.19)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.05 (0.00, 0.24)
e^2_f	0.70 (0.59, 0.81)	0.62 (0.54, 0.72)	0.35 (0.29, 0.41)	0.61 (0.37, 0.77)

comorbidities suggest this class may be the most severely affected by AUD and related comorbidity.

Class 2, the low-frequency inpatient, was notable for having 100% of the AUD registrations come from inpatient sources, having more than 90% of its members with one registration, having the lowest composition of men, and a high rate of comorbid psychiatric disorders, but the lowest rate of drug abuse. This suggests that the AUD registration source may have been largely driven by treatment at inpatient psychiatric facilities.

Class 1, the outpatient/prescription class, was characterized entirely by prescription and outpatient registration sources, was the most educated and was the youngest class, but had the oldest age of first registration. Finally, Class 4, the crime class, had the highest rate of registrations from crime sources, had the highest composition of men, was the least educated, had the youngest age at first registration, had the highest rate of criminal behavior but the lowest rate of comorbid psychiatric disorders, and had the highest level of neighborhood deprivation.

These results show similarities as well as differences with a similar LCA of AUD among Swedish adoptees and offspring of not lived with parents and stepparents (Kendler *et al*., 2015). Kendler *et al*. (2015) used a smaller and more select sample and found 3 classes rather than 4. Their Class 1 was characterized by having the highest composition of females and high rates of psychiatric disorders, which is roughly comparable to our Class 2, as it also had the highest composition of females and a high rate of psychiatric disorders (but not the highest). Their Class 2 was characterized by mild severity, which is difficult to compare to our Classes. Although our Class 2 had the highest percentage of individuals with only one AUD registration, they did not have the lowest rates of other comorbidities. Finally, their Class 3 was characterized by having a high composition of males and high rates of drug abuse and crime, which is similar to our Class 4 and consistent with an externalizing spectrum.

In a broader context, our results are consistent with the long-standing notion that AUD is a heterogeneous disorder (Babor, 1996; Hesselbrock and Hesselbrock, 2006). However, it is difficult to compare our specific findings with previous typological and LCA studies because of differences in the variables examined and methods used. For example, Lesch and colleagues (Lesch *et al*., 1988; Lesch *et al*., 1990) differentiated classes of AUD based on biochemical and neurophysiological patterns, while Bucholz *et al*. (1996) and Casey *et al*. (2013) both relied on diagnostic criteria (DSM-III-R and DSM-5, respectively) and based their classes on severity gradients (i.e. non-problem drinkers to severely affected).

Despite this, a common theme across the results of previous studies and the results of the present study is that there appears to be an underlying severity gradient for AUD. However, the characteristics underlying the remaining heterogeneity are less clearly established and there is no consensus on which variables should be used to classify this heterogeneity. While our results show evidence for four distinct classes, including a severely affected class (Class 3), future research could more thoroughly examine the heterogeneity by including additional variables (i.e., other than AUD diagnostic criteria) and rely on sophisticated statistical techniques, such as LCA.

Regarding the genetic and environmental effects, an inspection of the tetrachoric correlations for the male pairs shows strong genetic influences for Classes 3 and 4, while both genetic and environmental influences appear to be important for Classes 1 and 2. For females, both genetic and environmental influences appear to influence the liability for membership in Classes 1, 2 and 3, with genes playing a possible stronger role in Class 2.

The ACE model fitting results show the highest heritability for both males and females in Class 3 (61% and 65%, respectively) and the lowest for Class 1 (20% for both), with shared environmental influences accounting for 10% or less of variance in all Classes. For males, however, the heritability for Class 4 was almost as high as it was for Class 3 at 60%.

These results are perfectly consistent with the limited extant research. For example, Class 3 appeared to be the most severely affected class, had the highest rate of comorbid drug abuse, and had strong genetic influences This is consistent with Dick *et al*.'s (Dick *et al*., 2007) study showing that AUD with comorbid drug dependence is a particularly severe form of AUD and has higher genetic contributions to risk. Further, Class 4 is consistent with Cloninger's Type II typology, as they both primarily affect males, have an early age of onset, are associated with criminal behavior, and are largely influenced by genetic factors. Despite this, more research needed to further explore heterogeneity in the patterns of inheritance of AUD classes.

Understanding the heterogeneity of AUD has critical implications for intervention and treatment, as this knowledge can promote the advancement of personalized treatment for AUD (Litten *et al*., 2015). For example, understanding there is a mildly affected class and a more severely affected class may allow clinicians to modify the level of intervention accordingly (Rinker and Neighbors, 2015). Likewise, understanding that there is a subtype of AUD that co-occurs with other psychiatric disorders can lead to the development

of complementary treatments that target both disorders (Litten *et al*., 2015). As more knowledge is gained about the precise nature of the heterogeneity of AUD, clinicians will be able to more precisely tailor specific treatment approaches to AUD patients.

LIMITATIONS

These results should be considered within the context of three limitations. First, our sample consisted of Swedish individuals only. It is uncertain if our results will generalize to other populations. However, the findings are likely to be generalizable to other industrialized countries with similar AUD patterns.

Second, we relied on medical, legal, and pharmacy registry data for our AUD measure. While this method has the advantage of not being subject to recall biases, it can produce false negatives and positives. For example, it is likely that registries detect more severe cases of AUD, while people with less severe AUD would not be detected. Although the extent to which this occurred could not be estimated, a previous study using the same registry data showed high concordance rates for registration across the different ascertainment sources, providing support for our AUD measures (Kendler *et al*., 2015).

Third, LCA assumes local independence (i.e. the independence of all relevant variables within classes). This assumption is unlikely to have been fully met in this sample.

CONCLUSIONS

Using a population-based, nationwide Swedish sample, we showed evidence for four meaningful and distinct classes of AUD that were characterized by the frequency and source of registrations, with varying degrees of heritability. The highest heritability for both males and females was found for Class 3 (High-Frequency Mixed) and the lowest for Class 1 (Outpatient/Prescription). Understanding the heterogeneity of AUD can inform classification, prevention, and treatment where, for instance, certain classes would need targeting of antisocial behavior and others would need specific treatment for psychiatric comorbidities.

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CONFLICT OF INTEREST STATEMENT

None declared.

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