Supplementary Online Content

Kendler KS, Ji J, Edwards AC, Ohlsson H, Sundquist J, Sundquist K. An extended Swedish national adoption study of alcohol use disorder. *JAMA Psych*. Published online January 7, 2015. doi:10.1001/jamapsychiatry.2014.2138.

eAppendix 1. Definitions

eAppendix 2. Risk Factors

eAppendix 3. Methods and Analyses

eReferences

eTable 1. Registration of Alcohol Use Disorders in Adoptees Among the Five Swedish Registers Used in this Study

eTable 2. Prediction of AUDs Among Adopted Children From the Genetic and Environmental Risk Scores and Their Interaction on the Scale of Raw Probabilities

eTable 3. Fit Indices of Latent Class Analysis of Alcohol Use Disorders in Adoptees

eTable 4. Differences Across Latent Classes in Registry Membership and Specific Psychiatric Diagnoses

eTable 5. Association With Biological Parents in Not-Lived-With Families From the Latent Class Analysis

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Definitions

Definition of Alcohol Use Disorder

Individuals with AUD were identified from a range of Swedish registries. All individuals who have been diagnosed with the following ICD codes from the Swedish hospital discharge, primary care, and outpatient care registers were included: ICD9 (V79B,305A,357F,571A,571B,571C,571D,425F,535D,291,303,980) and ICD 10 (E244,G312,G621,G721,I426,K292,K700,K701,K702,K703,K704,K705,K706,K707,K708,K709,K852,K860,O354,T510,T512,T511,T513,T514,T515,T516,T517,T518,T519, F101,F102,F103,F104,F105,F106,F107,F108,F109).

Individuals were also identified in the Crime Register by codes 3005, 3201, which reflect crimes related to alcohol abuse. In addition, we identified those who were recorded by codes 0004, 0005 from the Swedish Suspicion Register. Only those individuals with at least two alcohol-related crimes or suspicion of crimes from both Crime Register and Suspicion Register were included in our study.

In addition, we identified AUD among individuals who had retrieved disulfiram (Anatomical Therapeutic Chemical (ATC) Classification System N07BB01), acamprosate (N07BB03), and naltrexone (N07BB04) from the Prescription Registry.

Definition of Small Geographical Area

For our definition of "not-lived-with" parents, we required that the parent never reside in the same community as their offspring. For community, we used the "Small Areas for Market Statistics (SAMS)" as defined by Statistics Sweden. There are approximately 9,200 SAMS throughout Sweden and their boundaries are defined by homogeneous building types, have an average of ~1,000 inhabitants and approximate the concept of neighborhoods.

Maintenance of Confidentiality

Statistics Sweden replaced the original IDs before the registries were sent to the analytic team, ensuring that none of us had any access to identifying information.

eAppendix 2. Risk Factors

Genetic risk factors in the adoptees and offspring not living with parents

We utilized the following variables in biological parents and/or biological siblings, measured during the entire life course: AUD (defined above), hospitalization due to drug abuse, hospitalization due to psychiatric illness, and criminality (ever identified in the Swedish crime register). Drug abuse was identified in the Swedish Hospital discharge register according to the following ICD codes ICD8: 304; ICD9: 292, 304; ICD10: F11-F16, F18, F19. Psychiatric illness was identified in the Swedish Hospital discharge register according to the following ICD codes: ICD8: 295-302, 305-307, ICD9: 295-298, 300-302, 306-309, 311,312, ICD10: F20-F25, F28-F34, F38-F45, F48, F50-F54, F59-F69, F99. Among parents, at least one parent had to be defined according the above criteria. For siblings, we created a weighted score from the number of full and half siblings with the former weighted twice as much as the latter to reflect their genetic relatedness to the adoptee.

In parents, we considered educational attainment as a proxy for socioeconomic status. To control for cohort effects, we defined low and high educational attainment as below or above the 75th percentile of the distribution of years of education in the appropriate decade of birth for the entire Swedish population. We also considered divorces among biological mothers (if no biological mother or missing marital status for mother, the father's status was taken) during the entire life course. Finally, we considered the mothers age at birth. If mother's age was missing, the biological father's age was chosen.

Environmental risk factors in the adoptees and offspring with step parents

We utilized a range of variables in adoptive and step parents from first cohabitation with adoptive parents until the adoptee was aged 20 (for definition see above) to index potential environmental risk factors: AUD, hospitalization due to drug abuse, criminality, hospitalization for any medical problem and psychiatric illness, and divorce. We also considered education as a proxy for socioeconomic status, using the highest education of adoptive mother or father. We also considered age of the adoptive mother at the time of adoption.

The following variables were considered among adoptive siblings and were measured during their entire life course (for definition of variables see above): AUD, hospitalization due to drug abuse, psychiatric illness, other medical problems, and criminality. We created a score weighted according to the number of siblings.

Environmental and genetic risk factors in adoptees

We performed a logistic regression on the entire sample of 18,115 adoptees and modelled AUD as a function of numerous genetic and environmental factors associated with an increased risk for AUD. All variables linked with biological parents/siblings and associated with AUD ($p<0.10$) in univariate analyses were included in the genetic risk score. We obtained the predicted probabilities (i.e. genetic risk scores) for each adoptee and categorized them into ten groups by deciles and used these variables as continuous variables in the final analysis. The same procedure was performed for all variables linked with adoptive parents/siblings to create an environmental risk score.

Latent Class Analysis Methods

Latent class analysis was used to identify heterogeneous AUD groups based on different clinical characteristics. The following variables (dichotomous) were used in the LCA analyses: (1) sex; (2) early onset of AUD (age at onset lower than 25th percentile of the total distribution); (3) serious crime (number of committed crimes above than 75th percentile of the total distribution); (4) frequent AUD (number of identification from the above registers above than 75th percentile of the total distribution); (5) drug abuse; (6) psychiatry diseases; (7) alcohol associated medical disorder. 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 G2, Akaike's Information Criterion, the Bayesian Information Criterion 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. We used $\chi 2$ analyses to determine whether there were important differences across LCA classes in terms

of these seven validators included in the LCA. Statistical analyses were performed using PROC LCA in SAS v. 9.2 [1] [2;3].

eAppendix 3. Methods and Analyses

Latent Class Methods

Validation studies assessed whether the prevalence of specific alcohol-associated medical disorders and specific psychiatric diagnoses differed across latent classes. The alcohol-associated medical disorders queried were liver disease (ICD-10 codes K70.0-K70.9), pancreatitis (K86.0), gastritis (K29.2), and myopathy (G62.1), neuropathy (G72.1), and cardiomyopathy (I42.6) We examined diagnoses related to schizophrenia (ICD-10 codes: F20, F25), affective disorders (F30, F31, F32, F33, F34), anxiety disorders (F40, F41, F42, F43, F48), and personality disorders (F60.1, F60.2, F60.30, F60.31, F60.4, F60.5, F60.6).

Interaction Analyses

In addition to examining the interaction between the genetic and environmental risk factors in the etiology of AUD in our adoption sample on the scale of raw probabilities (using PROC GENMOD in SAS with the identity link and specified the variance to be binomial), we calculated the Relative Excess Risk due to Interaction (RERI) [4] and the 95%CI using bootstrap percentile method by logistic regression. The RERI was 0.004 (95%CI 0.001-0.009), suggesting a very modest level of positive interaction on the additive scale. We then examined the interaction with logistic regression and it was not significant: OR=0.99 (95% CI 0.99-1.00). $\times^2$=0.13, p=0.70. In our study, the OR per decile for the genetic risk score was 1.10, and for environmental risk score was 1.05. The OR expected on an additive scale would then be (1.10-1)+(1.05-1)=1.15 while the OR expected on a multiplicative scale would be 1.10x1.05=1.155. So in this instance, the expectations from these two scales of measurement are very similar – hence the very similar results. We are unable to explain the very slight evidence for a positive interaction in RERI.

eReferences

1. SAS Institute I. SAS Institute Inc, SAS ONLINE DOC Version 9.2, Cary, NC, SAS Institute Inc, 2002-2008. 2008. Cary, NC, SAS Institute, Inc.

2. *PROC LCA & PROC LTA* [Version Version 1.3.0 [Software]. University Park: The Methodology Center, Penn State, College of Health and Human Behavior; 2013.

3. Lanza ST, Dziak JJ, Huang L, Wagner A, Collins LM. *PROC LCA & PROC LTA Users' Guide (Version 1.3.0)*. University Park: The Methodology Center, Penn State, College of Health and Human Behavior, 2013.

4. Richardson DB, Kaufman JS. Estimation of the relative excess risk due to interaction and associated confidence bounds. *Am J Epidemiol* 2009;169(6):756-760.

eTable 1. Registration of Alcohol Use Disorders in Adoptees Among the Five Swedish Registers Used in this Study

	Odds ratio (95% CI)			
	Hospital discharge	Outpatient	Primary Health Care	Prescription
Crime	13.5 (11.5-16.1)	11.8 (9.7-14.3)	9.6 (6.6-14.1)	10.0 (8.1-12.3)
Hospital discharge		74.8 (61.6-90.8)	28.5 (20.2-40.3)	32.0 (26.4-38.7)
Outpatient			49.3 (34.7-70.1)	72.8 (59.2-89.5)
Primary Health Care				24.5 (17.2-34.9)

eTable 2. Prediction of AUDs Among Adopted Children From the Genetic and Environmental Risk Scores and Their Interaction on the Scale of Raw Probabilities

	Without interaction term			With interaction term		
	Beta	95%CI		Beta	95%CI	
Genetic risk score	**0.0075**	0.006	0.009	**0.0072**	0.0045	0.0099
Environmental risk score	**0.0039**	0.0024	0.0054	**0.0031**	0.0004	0.0058
Sex	**0.0788**	0.0704	0.0873	**0.0790**	0.0706	0.0874
AFCAP	0.0008	-0.001	0.0026	0.0005	-0.0013	0.0023
Birth year	**-0.0015**	-0.002	-0.0009	**-0.0019**	-0.0025	-0.0013
Interaction term(genetic*environmental risk scores)				0.0002	-0.0003	0.0007

Bold, - statistically significant.

eTable 3. Fit Indices of Latent Class Analysis of Alcohol Use Disorders in Adoptees

Model	# classes	AIC	BIC	aBIC	Entropy
1	2	574.5	656.1	608.5	0.68
2	3	235.0	406.2	333.1	0.66
3	4	277.4	446.1	347.5	0.70
4	5	192.9	453.4	329.5	0.72

eTable 4. Differences Across Latent Classes in Registry Membership and Specific Psychiatric Diagnoses

	Adoptive				Not Lived With			
	Class 1	Class 2	Class 3	p	Class 1	Class 2	Class 3	p
%								
Primary health care	11.9	5.1	8.2	0.02	9.83	3.99	5.77	<0.0001
Hospital inpatient	67.0	33.9	59.1	<0.0001	60.12	39.07	39.42	<0.0001
Hospital outpatient	51.2	22.5	36.7	<0.0001	45.74	18.33	25.62	<0.0001
Prescription	42.2	26.1	23.5	<0.0001	33.2	18.19	19.97	<0.0001
Crime	17.8	55.1	73.1	<0.0001	17.91	42.94	75.13	<0.0001
%								
Schizophrenia	4.5	0.1	5.4	0.39	5.68	0.18	3.48	<0.0001
Mood disorder	50.3	2.4	22.3	<0.0001	56.88	1.31	18.28	<0.0001
Anxiety	61.4	2.9	36.7	0.0005	69.46	1.47	28.90	<0.0001
Personality Disorder	12.8	0.4	16.1	<0.0001	17.47	0.14	11.23	<0.0001

NLW mothers and fathers are collapsed into a single group. Registry totals might exceed unity given that cases could have been identified through multiple registries. ICD codes for included alcohol-associated medical and psychiatric diagnoses are available in Appendix III.

eTable 5. Association With Biological Parents in Not-Lived-With Families From the Latent Class Analysis

	Biological father in NLW						Biological mother in NLW					
	Class 1	Class 2	Class 3	Non-AUD	Chisq* (df=2)	p	Class 1	Class 2	Class 3	Non-AUD	Chisq* (df=2)	p
AUDs	30.7	28.7	37.7	20.1	72.2	<0.0001	13.6	10.0	14.9	5.9	46.7	<0.0001
Drug abuse	11.1	9.2	14.6	6.9	55.2	<0.0001	8.5	5.6	11.1	4.0	74.0	<0.0001
Psychiatric disease	15.6	12.9	15.9	12.8	17.7	<0.0001	31.3	21.1	28.1	20.6	117.5	<0.0001
Convictions	64.2	63.7	71.8	56.9	64.2	<0.0001	30.0	27.0	40.5	21.7	163.1	<0.001
Higher Education	58.2	57.4	52.9	63.1	22.6	<0.0001	65.4	64.6	60.9	71.2	16.6	0.0002

*The chi-square test is across the three latent classes and does not include the non-AUD offspring.