An Extended Swedish National Adoption Study of Alcohol Use Disorder

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IMPORTANCE Alcohol use disorder (AUD) runs strongly in families. It is unclear to what extent the cross-generational transmission of AUD results from genetic vs environmental factors.

OBJECTIVE To determine to what extent genetic and environmental factors contribute to the risk for AUD.

DESIGN, SETTING, AND PARTICIPANTS Follow-up in 8 public data registers of adoptees, their biological and adoptive relatives, and offspring and parents from stepfamilies and not-lived-with families in Sweden. In this cohort study, subtypes of AUD were assessed by latent class analysis. A total of 18 115 adoptees (born 1950-1993) and 171 989 and 107 696 offspring of not-lived-with parents and stepparents, respectively (born 1960-1993).

MAIN OUTCOMES AND MEASURES Alcohol use disorder recorded in medical, legal, or pharmacy registry records.

RESULTS Alcohol use disorder in adoptees was significantly predicted by AUD in biological parents (odds ratio, 1.46; 95% CI, 1.29-1.66) and siblings (odds ratio, 1.94; 95% CI, 1.55-2.44) as well as adoptive parents (odds ratio, 1.40; 95% CI, 1.09-1.80). Genetic and environmental risk indices created from biological and adoptive relatives acted additively on adoptee AUD liability. Results from biological and adoptive relatives were replicated and extended from examinations of, respectively, not-lived-with parents and stepparents. Multivariate models in these families showed that AUD in offspring was significantly predicted by AUD, drug abuse, psychiatric illness, and crime in not-lived-with parents and by AUD, drug abuse, crime, and premature death in stepparents. Latent class analyses of adoptees and offspring of not-lived-with parents with AUDs revealed 3 AUD classes characterized by (1) female preponderance and high rates of psychiatric illness, (2) mild nonrecurrent symptoms, and (3) early-onset recurrence, drug abuse, and crime. These classes had distinct genetic signatures in the patterns of risk for various disorders in their not-lived-with parents and striking differences in the rates of recorded mood disorders.

CONCLUSIONS AND RELEVANCE Parent-offspring transmission of AUD results from both genetic and environmental factors. Genetic risk for AUD reflects both a specific liability to AUD and to other externalizing disorders. Environmental risk reflects features of both parental psychopathology and other aspects of the rearing environment. Alcohol use disorder is a heterogeneous syndrome and meaningful subtypes emerged from latent class analysis, which were validated by patterns of disorders in biological parents and specific psychiatric comorbidities. The general population contains informative family constellations that can complement more traditional adoption designs in clarifying the sources of parent-offspring resemblance.
Alcohol use disorder (AUD) is strongly familial. While twin studies have shown that genetic factors contribute substantially to familial aggregation of AUD,\textsuperscript{2-8} their results were less consistent regarding familial-environmental effects. Some twin studies suggested modest or substantial familial-environmental influences on AUD risk\textsuperscript{2-5} while other reports found no evidence for such effects.\textsuperscript{6-8} Furthermore, traditional twin studies examined influences on the resemblance of individuals in the same generation. We know less about genes and environment contributions to cross-generational transmission of AUD.

The adoption design is a common approach to disentangle genetic and environmental sources of parent-offspring resemblance. Of the 3 major adoption studies of AUD, the Danish studies did not explore familial-environmental effects (eg, the study by Goodwin et al\textsuperscript{9}). In other publications from US adoption samples, Cadoret and Gath\textsuperscript{10} and Cutrona and colleagues\textsuperscript{11} reported a range of findings of the familial-environmental effects from no direct impact on the risk for AUD in adoptees to significant effects of “alcohol problems in adoptive family” in males only.\textsuperscript{12,13}

The Stockholm Adoption Study showed that placement experiences and socioeconomic status of the adoptive father impacted AUD risk but the magnitude of this impact varied as a function of both genetic risk and AUD subtype.\textsuperscript{14,15} Men with a genetic diathesis toward mild or severe—but not moderate—AUD had poorer outcomes when exposed to adverse postnatal environments. Most, but not all, of these results were replicated in an independent sample.\textsuperscript{16}

Outside of adoptions, other family constellations can assist in disentangling the nature of parent-offspring transmission. Biological parents beget offspring with whom they never live. Stepparents raise children who are genetically unrelated to them. In this report, we expand the traditional adoption design to include these additional informative families termed not-lived-with (NLW) families and stepfamilies, respectively.

We examined 6 questions in a nationwide Swedish sample. First, with a greater sample size than previously available, can we clarify the degree to which cross-generational transmission of AUD results from genetic vs environmental effects? Second, do conditions other than AUD in biological parents predict adoptee risk for AUD? Third, do other disorders in the adoptive parents or features of the adoptive home predict adoptee AUD? Fourth, do findings from NLW families and stepfamilies replicate those seen in the adoption sample? Fifth, can we replicate prior evidence for gene-by-environment interaction in AUD? Finally, given the long-standing view that AUD is etiologically heterogeneous, can we replicate prior typologies of AUD using latent class analysis and validate the resulting subtypes with the pattern of disorders in biological parents?

**Methods**

We linked the following registers and health care data from multiple nationwide sources:

1. The Swedish Hospital Discharge Register included all hospitalizations for all people in Sweden from 1964 through 2010. Every record has the main discharge diagnosis and 8 secondary diagnoses.
2. The Swedish Prescribed Drug Register included all prescriptions in Sweden from July 1, 2005, through December 31, 2010. It is complete because all prescriptions are registered at the National Board of Health and Welfare.
4. The Total Population Registry included annual data on education and marital status from 1990 to 2009.
5. The Multi-Generation Register provided information on family relationships from 1932 to 2009 including all adoptions and adoptive and biological parents and siblings.
6. The Outpatient Care Register included information from all outpatient clinics in Sweden from 2001 to 2010.
7. The Primary Health Care Register included outpatient care data on diagnoses and time for diagnoses from 2001 to 2007 for around 1 million patients from Stockholm and middle Sweden.
8. The Swedish Crime and Suspicion Register included national complete data on all convictions, including those for AUD, from 1973 to 2011.

Linking was based on the unique individual Swedish 10-digit personal identification number that is nearly 100% complete and is assigned at birth for all Swedish residents for his or her lifetime. This number was replaced by a serial number to guarantee confidentiality for all individuals. The study was approved by the ethics committee of Lund University in Malmö, Sweden; patient consent was waived.

**Study Sample**

We examined 3 study groups: (1) adoptees, (2) offspring not living with 1 parent, and (3) offspring living with a stepparent. Adoptees were selected if individuals were born from 1950 to 1993 and information on both adoptive and at least 1 biological parent was available. Individuals adopted by biological relatives or an adoptive parent living with a biological parent were excluded. The age at formal adoption was recorded from 1991 onward. For individuals adopted before 1991, we estimated age at adoption by age at first cohabitation with adoptive parents (AFCAP) from census data including individual addresses. Census data were available every 5 years; therefore, the AFCAP represents an upper limit of true age at adoption.

The National Censuses Registry included information on household serial number for each individual. Each household and each family has its own respective serial number. A household implies that the person or group of persons were registered in the same municipality and lived in the same dwelling. The Total Population Registry included family information, which consists of a maximum of 2 generations where people have relationships with each other and are registered on the same property. For years in which we did not have exact information, we approximated the household and geographical status with the information from the closest year. The study sample of offspring not living with a parent refers to those...
individuals who never lived with 1 of their biological parents in the same household or the same community (eAppendix 1 in the Supplement). Because household serial number was recorded from 1960 onward, we identified only those offspring not living with parents from 1960 to 1993.

Offspring living with a stepparent did not reside with the relevant biological parent (father or mother) from ages 0 to 15 years and resided for at least 10 years with an adult who was (1) the same sex as the missing parent, (2) 18 to 50 years older than the offspring, and (3) with whom they were not biologically related. We identified only those offspring living with a stepparent from 1960 to 1993.

Our definitions of AUD and the genetic and environmental risk factors used in our adoption and NLW analyses are outlined in eAppendix 1 and eAppendix 2 in the Supplement.

Statistical Methods
Because our outcome variable, AUD, is dichotomous, we used logistic regression and modeled AUD as a function of genetic and environmental risk factors. We sought to determine whether genetic and environmental risk factors interacted in the etiology of AUD and we have previously argued that the scale of raw probabilities is appropriate for such analyses.17 Therefore, for these analyses, we used PROC GENMOD in SAS18 with the identity link and specified the variance to be binomial. We specified the effects of the explanatory variables (and the interaction term) to be additive on the scale of probabilities. All P values are reported 2-tailed. For our latent class methods, see eAppendix 3 in the Supplement.

Results
Adoption Analyses
The general characteristics of our adoptive sample are outlined in Table 1. In the 18 115 adoptees, the prevalence of AUD was 9.4%. Compared with adoptive parents, biological parents had much higher rates of AUD, crime, drug abuse (DA), and psychiatric illness. Similar differences were seen between the adoptive and biological full- and half-siblings.

Table 2 provides basic information on the 1702 adoptees with AUD. A total of 73% were males. Males had an earlier mean age at registration and more registrations and higher rates of criminal registration. These 1702 cases had the following registrations: hospital discharge (n = 860), crime (n = 795), outpatient (n = 600), prescription (n = 527), and primary health care (n = 138). The validity of our AUD diagnosis was supported by high rates of coascertainment across registries (mean odds ratio [OR], 32.7; eTable 1 in the Supplement).

In our main adoption analyses, focusing first on the univariate analyses, AUD in adoptees was significantly associated with AUD, DA, psychiatric illness, crime, maternal divorce, low education level, and young age in biological parents and AUD and DA in biological siblings (Table 3). In multivari-
In the univariate analyses, AUD was significantly predicted by a history of AUD, crime, divorce or death, and low education level in biological parents and siblings, divorce, low education level, and young age in biological parents remained significant.

In univariate analyses, AUD was significantly predicted by a history of AUD, crime, divorce or death, and low education level of adoptive parents and AUD and hospitalization in adoptive siblings (Table 3). In multivariate analyses, AUD, crime, and death in adoptive parents and hospitalization in adoptive siblings remained significantly predictive.

From the multivariate analyses, we constructed genetic and environmental aggregate risk indices divided into deciles. The correlation of the genetic and environmental risk scores, which reflects assortative placement, was statistically significant but small (+0.07; *P* < .01).

We predicted risk for AUD in adoptees from these indices: sex, AFCAP, and age (Table 4). The aggregate effects of genetic factors on the risk for AUD in adoptees were approximately twice as strong as the familial-environmental factors. In the final model, the effect of AFCAP was not significant. On the scale of raw probabilities, we then tested for an interaction effect between our genetic and environmental risk indices. As seen in eTable 2 in the Supplement, no interaction was seen. For further details on this analysis, see eAppendix 3 in the Supplement.

**NLW Families**

We identified 171,989 offspring of NLW parents, 94% of whom were fathers. Table 5 depicts the predictors of AUD risk from biological father and mother from the adoptive sample and the fathers and mothers in both the paternal and maternal NLW families. An NLW parent could influence the risk for AUD in an outcome directly through genetic transmission or through assortative mating to a spouse who would contribute genes and rearing environment for the offspring. The tetrachoric correlation for AUD in parents in NLW families was +0.17 (*P* < .001), indicating modest assortment. Therefore, we present in Table 5 the results for NLW families (and the comparison biological parents of adoptees) for both mothers and fathers together so multivariate models control for assortative mating.

In the univariate analyses, AUD in the offspring was significantly predicted by AUD, DA, psychiatric illness, and crime in the NLW father. In the multivariate analyses, controlling for the impact of the mother, NLW paternal AUD, DA, and crime remained significant risk factors. The format of Table 5 permits a direct comparison of results from the NLW fathers and the biological fathers in the adoptive sample. Focusing on the multivariate results, AUD and crime were more predictive of offspring AUD risk in the NLW than the biological fathers (Table 5).

Univariate analyses showed that AUD, DA, psychiatric illness, and crime in the NLW mother significantly predicted AUD risk in offspring and AUD, DA, and crime remained significant in the multivariate analyses controlling for impact of the father. In the multivariate analyses, AUD was a stronger risk factor in biological than NLW mothers while the reverse was seen for DA and crime (Table 5).
Stepfamilies

We identified 107,696 offspring reared by stepparents, 86% of whom were stepfathers. The correlation for AUD in the step-parents and biological parents was small (+0.11). To be conservative, we presented parallel univariate and multivariate results for the adoptive and stepfamilies including both the biological and stepparents or adoptive parents (Table 6). In univariate analyses, the risk for AUD in offspring was significantly increased by a history of AUD, DA, crime, and psychiatric illness in the stepparent. These results were broadly comparable with those seen between the adoptive parents and adoptees. In the multivariate analyses in both the adoptive and stepfamilies, only AUD and crime in the step/adoptive parents remained significantly associated with AUD in the offspring, with the associations being stronger in the adoptive families (Table 6).

In additional analyses, the univariate ORs between offspring AUD and low education level and death in the adoptive parents and stepparents were very similar (low education: OR, 0.81; 95% CI, 0.72-0.92 and OR, 0.78; 95% CI, 0.74-0.82, respectively, and parental death: OR, 1.42; 95% CI, 1.21-1.67 and OR, 1.43; 95% CI, 1.10-1.85, respectively). In multivariate analyses, including all the parental phenotypes examined in Table 6, the results were very similar for parental death in the adoptive (OR, 1.45; 95% CI, 1.23-1.71) and stepparent (OR, 1.44; 95% CI, 1.36-1.53) families while low education level was more strongly predictive of offspring AUD risk in the stepparent (OR, 0.83; 95% CI, 0.79-0.86) than the adoptive families (OR, 0.95; 95% CI, 0.86-1.06).

Latent Class Analysis

We fitted latent class models to data from the adoptees with an AUD registration (n = 1702) on their sex and 6 binary variables relevant to AUD: criminal conviction, recurrerence, early age at onset, DA, alcohol-associated medical disorder, and psy-
chiatric illness. The 3-class model provided a good fit to the data (eTable 3 in the Supplement) and was readily interpretable. Table 7 shows the frequency and item response probabilities for the 3-class solution. The frequency of all variables differed significantly across classes. Class 1 had by far the highest proportion of females and cases with a psychiatric diagnosis. Class 2 had low overall endorsements and appeared to represent largely mild cases. Class 3 was characterized by the lowest proportion of females and the highest proportion of crime, recurrence, early age at onset, and DA. We then applied a 3-class latent class analysis solution on the AUD cases of crime, recurrence, early age at onset, and DA. We then applied a 3-class latent class analysis solution on the AUD cases from the NLW families (n = 14,488), the results of which, also provided a 3-class latent class analysis solution on the AUD cases from the NLW families (n = 14,488), the results of which, also shown in Table 7, rather closely resembled those seen in the smaller adoptee sample.

**Validation of the Latent Classes**
To validate these latent AUD classes, we first looked at their mode of ascertainment and the specific recorded psychiatric diagnoses (eTable 4 in the Supplement). In both the adoptees and offspring of the NLW families, members of class 1 were the most likely to have been identified through medical registries and class 3 through criminal registries, and members of class 1 were more likely to receive all of the specific psychiatric disorders examined. Class 2 had very low rates of all psychiatric illnesses. The results were particularly striking for mood disorders. While 50% to 55% of class 1 members received a mood disorder diagnosis, the parallel figures for classes 2 and 3 were around 2% and 20%, respectively.

Next, we examined the association between class assignment in the offspring and key features of the biological mothers and fathers in the larger and more statistically powerful NLW families (eTable 5 in the Supplement). In both NLW mothers and fathers, class 3 was associated with the highest rates of parental AUD, DA, crime, and low educational attainment. The NLW mothers of class 1 AUD offspring had the highest rates of psychiatric illness. The parents of offspring with class 2 AUD had the lowest rates of all the traits examined. Broadly similar results were seen in the biological parents in our adoption sample.

**Discussion**

**Questions Addressed**
We addressed 6 questions. First, consistent with prior adoption studies, the risk for AUD was increased in the adopted-away offspring of biological parents with AUD. We expanded on these results showing the risk for AUD was also increased in biological siblings of the adoptee and, to our knowledge, we demonstrated for the first time that the risk for AUD in adoptees was significantly increased by AUD in adoptive parents. Parent-offspring transmission of AUD results from both genetic and environmental factors.

Second, congruent with prior studies suggesting that AUD is part of an externalizing genetic spectrum, risk for AUD in adoptees was significantly increased by a history of crime and DA in biological parents.

Third, in addition to AUD in adoptive parents, AUD in adoptees was significantly predicted by a criminal history, low parental education level, and adoptive parental divorce and death. These results are consistent with prior Swedish findings that AUD in adoptees is predicted by low occupational status in the adoptive father. Controlling for an adoptive parental history of AUD, adoptee AUD was still significantly predicted by adoptive parental crime and death. These results are consistent with a prior twin-family study, which showed that the pathway from parental loss in childhood to risk for AUD in offspring was largely environmental in nature.

Fourth, we expanded on the traditional adoption design to more typical family relationships, assuming that NLW and stepparents would, like biological and adoptive parents from a classic adoption design, reflect genetic and familial-environmental sources of parent-offspring resemblance, respectively. Results with the NLW parents broadly replicated those seen with biological parents but with greater statistical power. In multivariate analyses, we were able to see that a history of DA in NLW fathers and crime in NLW fathers and mothers independently predicted the risk for offspring AUD. Results from the stepparents also broadly replicated findings from

**Table 7. Frequency and Item Response Probabilities for Latent Class Analysis of Alcohol Use Disorder in Adoptees**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adoptees</th>
<th>Offspring of Not-Lived-With Parent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Class 1</td>
<td>Class 2</td>
</tr>
<tr>
<td>Frequency, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>30.3</td>
<td>45.6</td>
</tr>
<tr>
<td>Crime (&gt;75th percentile)</td>
<td>0.03</td>
<td>0.07</td>
</tr>
<tr>
<td>Recurrence (&gt;75th percentile)</td>
<td>0.33</td>
<td>0.09</td>
</tr>
<tr>
<td>Early age at onset (≤25th percentile)</td>
<td>0.05</td>
<td>0.27</td>
</tr>
<tr>
<td>Drug abuse</td>
<td>0.35</td>
<td>0.01</td>
</tr>
<tr>
<td>Alcohol-associated medical disorder</td>
<td>0.19</td>
<td>0.08</td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>0.84</td>
<td>0.18</td>
</tr>
</tbody>
</table>

* Numbers in bold are for the class with the highest response probability.
adoptive parents. In multivariate analyses, stepparental AUD, crime, low education level, and premature death all significantly predicted the risk for AUD in the stepchild.

Fifth, 2 prior adoption samples$^{11,14}$ found that genetic risk from biological parents and features of the rearing environment statistically interacted in predicting adoptee risk for all cases of AUD$^{14}$ or in a subset.$^{14}$ Despite our substantially greater sample size, we did not replicate these findings. Using a conservative statistical approach that examined interactions based on risk differences rather than risk ratios,$^{17}$ genetic and environmental risk factors for AUD added together.

Finally, a long historical tradition has suggested that AUD is clinically or etiologically heterogeneous.$^{14,23,24}$ A latent class analysis of AUD cases in adoptees identified 3 classes. The second class reflected mild cases of what might be termed alcohol abuse. The first and third classes substantially resemble types identified in prior typologies.$^{14,24}$ Our classes 2 and 3 are reminiscent of Babor’s type A and B alcoholics, respectively.$^{2,4}$ The former (class 2 and type A) is generally less severely affected, with modest psychiatric comorbidity. The latter (class 3 and type B) is associated with early onset, greater severity, and poorer medical outcomes. Parallels to the typologies of Cloninger et al$^{4,23}$ are also evident: our class 3 and type II of Cloninger et al both had early onsets and a severe course. Women are more likely to belong to our class 1, similar to type I of Cloninger et al.$^{25}$ The adoptive types replicated well in the much larger sample of AUD offspring from NLW parents.

These typologies predicted the source of ascertainment for the individuals with AUD and the patterns of specific psychiatric comorbidities. These AUD classes also had distinct genetic risk signatures reflecting phenotypes in their biological parents. Biological parents of class 3 AUD offspring stood out as having the highest rates of AUD, DA, crime, and low educational attainment. Biological mothers of AUD class 1 offspring had the highest rates of psychiatric illness. This is also congruent with the findings of Cloninger et al$^{14}$: biological fathers of adopted type II cases were more likely to have a history of severe alcohol abuse and criminality.

Limitations
These results should be interpreted in the context of 3 potentially important method limitations. First, we detected individuals with AUD from medical, legal, and pharmacy records. While this method has the advantage of not requiring accurate respondent recall or reporting, it produces both false-negative (individuals with AUD who escaped registration) and false-positive diagnoses (individuals detected who were not truly disordered). We cannot precisely estimate these biases.

Given that the population prevalence of AUD using our method (6%-10% over most of the birth years examined in this study) is lower than estimates from most epidemiologic surveys including one from nearby Norway,$^{26,27}$ cases in our sample were likely, on average, to be more severely ill than those detected in population-based interview studies. Similarly, because the current analyses were limited to the Swedish population, we cannot be certain that the results generalize to other populations or races/ethnicities. The validity of our definition of AUD is supported by the high rates of concordance for registration across our difference-ascertainment methods (eTable 1 in the Supplement).

Second, nonrandom placement of adoptees can bias adoption studies. Prior studies of Swedish adoptions noted modest selective placement (eg, +0.14 correlation in educational attainment between biological and adoptive parents).$^{28,29}$ Our indices of genetic and environmental risk for AUD were also intercorrelated (+0.07) but the magnitude was too modest to substantially influence our findings.

Third, AUD has been studied previously in Swedish adoptive samples.$^{14,16}$ However, there is no overlap between these studies, which sampled adoptees born from 1930 through 1949 and the current study that began with adoptees born from 1950 through 1993.

Conclusions
Using a national epidemiologic sample and a definition of AUD based on registration in medical, legal, and pharmacy records, we found, using a traditional adoption design, that AUDs were strongly transmitted from parents to offspring. Offspring risk for AUD was also independently predicted by DA and crime in the biological parents, supporting prior evidence that, from a genetic perspective, AUDs are part of an externalizing spectrum. We also found strong evidence for both direct and indirect environmental transmission. That is, AUD in adoptees was predicted both by AUD in adoptive parents and by other measures of potential adversity in the adoptive home such as parental death and low socioeconomic status. Despite a large sample, we found that genetic and environmental risk factors for AUD combined additively. These adoption results were replicated in an expanded adoption design wherein results from NLW parents and stepparents approximated those seen with biological and adoptive parents, respectively. Finally, we identified subtypes of AUD, which resemble prior typologies. These classes were validated by showing specific and expected relationships with different disorders in biological parents.
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REFERENCES