Psychological Medicine (2018), **48**, 33–42. © Cambridge University Press 2017
doi:10.1017/S0033291717000794

ORIGINAL ARTICLE

Transmission of alcohol use disorder across three generations: a Swedish National Study

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Background. While risk for alcohol use disorder (AUD) is correlated in twins, siblings and parent-offspring pairs, we know little of how this syndrome is transmitted across three generations.

Method. We examined 685 172 individuals born in Sweden from 1980 to 1990 with four grandparents, and both parents alive in 1980. AUD was assessed in all these individuals from nationwide medical, criminal and pharmacy registries.

Results. AUD was stably transmitted across three generations. Parent-child and grandparent-grandchild tetrachoric correlations equaled +0.25 and +0.12, respectively. Grandchild AUD risk did not vary as a function of the sex of the parent or grandparent. However, from grandparents and parents, transmission to grandchildren was stronger in same-sex than opposite-sex pairs. Compared with a grandchild with unaffected parents and grandparents, risk for AUD with a grandparent but no parent affected, a parent but no grandparent affected or both affected increased approximately 70% and 3 and 4-fold, respectively. Grandchildren with $\geqslant 2$ grandparents affected had a 40% greater AUD risk than those with only one affected. Tetrachoric correlations for AUD between offspring and great-aunts/uncles, and aunts/uncles equaled +0.06 and +0.13, respectively.

Conclusions. The transmission of AUD in Sweden across three generations is relatively stable. An orderly pattern of resemblance is seen with correlations declining by approximately 50% between first and second, and second and third-degree relatives. While the transmission of risk from affected male and female relatives does not differ, we find consistent evidence for greater resemblance in same-sex *v.* opposite-sex across generational pairs of relatives.

Received 3 January 2017; Revised 1 March 2017; Accepted 7 March 2017; First published online 28 September 2017

Key words: Alcohol use disorder, familial transmission, grandparents, parents, sex.

Alcohol use disorder (AUD) is strongly transmitted within families (Cotton, 1979). Twin and adoption studies suggest that while most of this transmission results from the action of genetic factors, familial environmental effects also contribute (Verhulst *et al.* 2015). A limitation of the systematic studies of the familial transmission of AUD is that they have been almost entirely within one generation (e.g. twin and siblings) or across two generation designs (e.g. adoption and other parent-offspring). Indeed, in Cotton's detailed review of the 39 earlier studies on the familial incidence of alcoholism, only two (Bleuler, 1955; Lucero *et al.* 1971) – both based on quite small samples – report rates on grandparents. We uncovered one further small sample study of AUD across three generations (Kaij & Dock, 1975).

In this paper, we report a national Swedish study of transmission of AUD from grandparents to parents and parents to their offspring. We seek to address the following four major questions. First, how stable is the pattern of AUD transmission across these generations? This is of particular interest because in the time period covered in this report, changes have occurred in the availability of alcohol beverages in Sweden (Castberger *et al.* 1994; Norstrom & Ramstedt, 2006; Gustafsson & Ramstedt, 2011) and rates of drug abuse have substantially increased (Giordano *et al.* 2013).

Second, are sex-specific effects seen in the three-generational familial transmission of AUD? In particular, is there evidence for (i) differences in the risk for AUD in children and grandchildren of affected women *v.* affected men and/or (ii) greater same-sex *v.* opposite sex cross-generational transmission for AUD? Furthermore, we examine, starting with grandfathers with AUD, a test for sex-linked transmission of

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AUD by comparing the risk for AUD in the sons of their sons *v.* the sons of their daughters (Kaij & Dock, 1975). This is of potential interest because of prior evidence for sex-specific transmission of liability to AUD (Guze *et al.* 1986; Prescott *et al.* 1999).

Third, what are the empirical risk figures for AUD in the offspring generation as a function of risk for AUD in the parental and grandparental generation? In particular, how much is the risk for AUD increased in grandchildren with affected grandparents but unaffected parents? Fourth, what is the pattern of transmission for AUD to the offspring generation from four key classes of antecedent relatives: parents, aunts/uncles, grandparents, and great-aunts/great-uncles?

Methods

This study utilized several different Swedish population-based registers with national coverage, linking them using each person's unique identification number. To preserve confidentiality, their ID number was replaced by a serial number. We secured ethical approval for this study from the Regional Ethical Review Board of Lund University (No. 2008/409).

From the multigenerational register, we selected all individuals born in Sweden between 1980 and 1990 ($N = 1\,120\,469$). Furthermore, we required that the biological mother, biological father and all four biological grandparents were included in the register, and that the grandparents were alive in 1980. 2 23 080 individuals were excluded due to lack of information on all four grandparents and 212 217 due to death of one or more grandparents prior to 1980. In total we investigated 685 172 (61% of the original sample) individuals. No restrictions were made on the basis of the other relatives (e.g. aunts/uncles, and great-aunts/great-uncles) having to be alive in 1980.

AUD was defined from three sources:

(1) by ICD codes for main and secondary diagnoses from Swedish medical and Cause of Death registries (the Swedish Hospital Discharge Register, containing all hospitalizations for all Swedish inhabitants from 1973 to 2012, and the Outpatient Care Register, containing information from all outpatient clinics from 2001 to 2012; the Swedish Cause of Death Register, containing information on all deaths in Sweden from 1963 to 2012) for the following diagnoses: ICD8 and 9: alcohol-related psychiatric disorders (291), alcohol dependence (303), alcohol abuse (305A), alcohol-related polyneuropathy (357F), alcohol-related cardiomyopathy (425F), alcohol-related gastritis (535D), alcoholic fatty liver, alcohol hepatitis, alcoholic cirrhosis, unspecified liver damage caused by alcohol (571A-D), toxic effects of alcohol (980), alcoholism (V79B); ICD10: alcohol related psychiatric and behavioral disorders (F10, excluding acute alcohol intoxication: F10.0), rehabilitation of a person with alcohol abuse (Z50.2), guidance and medical advice to a person with alcohol abuse (Z71.4), alcohol-related pseudo-Cushing syndrome (E24.4), alcohol-related degeneration of the nervous system and brain (G31.2), alcohol-related polyneuropathy (G62.1), alcohol-related myopathy (G72.1), alcohol-related cardiomyopathy (I42.6), alcohol-related gastritis (K29.2), liver diseases caused by alcohol (K70.0-K70.9), acute pancreatitis caused by alcohol (K85.2), chronic pancreatitis caused by alcohol (K86.0), treatment of pregnant alcoholic women (O35.4), toxic effects of alcohol (T51.0-T51.9);
(2) by anatomical therapeutic chemical (ATC) codes in the Prescribed Drug Register (containing all prescriptions in Sweden picked-up by patients from July 2005 to 2012): disulfiram (N07BB01), acamprosate (N07BB03), or naltrexone (N07BB04);
(3) by registrations of individuals in the Swedish Crime Registers (the Swedish Crime Register included national complete data on all convictions from 1973 to 2010 and the Swedish Suspicion Register included national complete data on all individuals strongly suspected of crime from 1998 to 2010) with at least two convictions of drunk driving [suspicion code 3005, law 1951:649 (paragraph 4 and 4A)] or drunk in charge of a maritime vessel [suspicion code 3201, law 1994:1009 (chapter 20, paragraph 4 and 5)]. We ensured that we did not count arrests in the Suspicion Register that described the same event contained in the Conviction Register.

These criteria have been used in multiple prior studies of AUD in Sweden. We chose (i) medical diagnoses, which reflected both direct clinical judgment about the presence of problematic alcohol consumption, (ii) all available medical diagnoses that indicated physiological damage from excess alcohol intake, (iii) receipt of medications used specifically in the treatment of AUD and (iv) repeated alcohol-related criminal offences, which are strongly sanctioned in Sweden.

AUD was defined as a binary variable (any registration *v.* no registration). Unadjusted tetrachoric correlations and Odds Ratios (ORs) were calculated in order to study transmission of AUD. We calculated the combined correlations/ORs and the p values for the heterogeneity tests using the Olkin-Pratt (OP) meta-analytical approach (Schulze, 2004). We performed 11 statistical tests for the heterogeneity of ORs and adopt a Bonferroni corrected p value of $0.05/11 = 0.0045$ for

https://doi.org/10.1017/S0033291717000794 Published online by Cambridge University Press

significance. All statistical analyses were performed using SAS 9.3 (SAS Institute, 2011).

Results

Descriptive statistics

Our offspring cohort consisted of 685 172 individuals born in Sweden from 1980 to 1990 with all four grandparents and both parents alive in 1980. Table 1 depicts the mean year of birth, prevalence of AUD and mean age at registration of the four-grandparents, two parents and the offspring. We see the expected sex difference with higher rates of AUD in males than females. Rates of AUD in our male and female probands were, respectively, 2.79 and 1.96%, indicating that the male to female ratio for AUD is decreasing over our generations from around 3.0 in grandparents, to 2.4 in parents and 1.4 in probands. The mean age at first registration was considerably higher in grand-parents than parents, which in turn was higher than in offspring. This is because the years of available information about AUD registration in Sweden were from 1973 to 2012. This means we could only ascertain AUD in later adult life in the grand-parental generation, through most of adult life in the parental generation and only in early adult life in the offspring generation.

Patterns of familial resemblance in grandparents, parents and grandchildren

We utilize two different statistics to describe patterns of familial resemblance: tetrachoric correlations and ORs. An important advantage of the former is its relative insensitivity to changing base-rates (Babchishin & Helmus, 2016). ORs, by contrast, are more widely used in epidemiology and statistical methods permit the easy comparison of multiple ORs, something much more difficult to do with tetrachoric correlations. Table 2 shows the tetrachoric correlations and ORs for AUD across and within our three generations. Focusing on the correlations, Table 2 presents three major results. First, the spousal resemblance for AUD was relatively stable across generations with correlations of approximately +0.30 in the paternal and maternal grandparents, and in the parents. Second, the parent-offspring correlation for AUD was also stable across generations ranging from +0.24 to +0.27 between the paternal grandparents and the father, the maternal grandparents and the mother, and the mother and father and the proband. Furthermore, these correlations did not consistently vary when the parent was male or female. Third, the grandparent-grandchild resemblance was also similar across the four grandparents, ranging from +0.11 to +0.13.

Table 1. *Year of birth, prevalence of and mean age at first registration for alcohol use disorders in grandparents, parents and the offspring generation*

	Paternal grandfather	Paternal grandmother	Maternal grandfather	Maternal grandmother	Father	Mother	Offspring
Mean year of birth (S.D.)	1925 (9)	1928 (9)	1928 (9)	1931 (8)	1955 (6)	1958 (5)	1986 (3)
Prevalence	6.6%	2.1%	7.5%	2.6%	7.3%	3.0%	2.4%
Mean age at first registration (S.D.)	56.2 (13)	55.9 (13)	54.5 (13)	54.2 (13)	42.0 (12)	40.6 (12)	21.3 (5)
OR (95% CIs) from multivariate logistic model predicting offspring AUD – Model 1	1.59 (1.51–1.67)	1.74 (1.61–1.89)	1.70 (1.62–1.59)	1.79* (1.66–1.92)			
OR (95% CIs) from multivariate logistic model predicting offspring AUD – Model 2	1.37 (1.30–1.44)	1.50 (1.38–1.63)	1.52 (1.45–1.60)	1.53** (1.42–1.65)	2.59*** (2.48–2.70)	2.69 (2.54–2.85)	

*Combined OR 1.68 (1.63–1.73), Heterogeneity test $p = 0.04$.
**Combined OR 1.47 (1.43–1.51), Heterogeneity test $p = 0.02$.
***Combined OR 2.62 (2.54–2.71), Heterogeneity test $p = 0.30$.

https://doi.org/10.1017/S0033291717000794 Published online by Cambridge University Press

Table 2. *Tetrachoric correlations (with Standard Errors) and Odds Ratios (with 95% CIs) for alcohol use disorder across and within generations*

	PGF	PGM	MGF	MGM	Mother	Father	Proband
PGF		3.84 (3.63; 4.06)	1.46 (1.40; 1.52)	1.62 (1.53; 1.72)	1.69 (1.60; 1.79)	*2.79* (*2.70; 2.88*)	**1.69 (1.61; 1.78)**
PGM	0.30 (0.01)		1.51 (1.42; 1.61)	1.70 (1.54; 1.88)	1.77 (1.62; 1.94)	*2.97* (*2.81; 3.13*)	**1.95 (1.80; 2.11)**
MGF	0.09 (0.01)	0.09 (0.01)		3.75 (3.56; 3.94)	*2.80* (*2.68; 2.94*)	1.69 (1.63; 1.74)	**1.81 (1.72; 1.89)**
MGM	0.10 (0.01)	0.10 (0.01)	0.31 (0.01)		*3.77* (*3.53; 4.02*)	1.86 (1.76; 1.96)	**2.03 (1.89; 2.18)**
Mother	0.12 (0.01)	0.11 (0.01)	*0.24* (*0.00*)	*0.27* (*0.01*)		3.63 (3.48; 3.79)	*3.55* (*3.36; 3.76*)
Father	*0.26* (*0.00*)	*0.24* (*0.01*)	0.13 (0.00)	0.14 (0.01)	0.31 (0.01)		*3.06* (*2.94; 3.19*)
Proband	**0.11 (0.01)**	**0.12 (0.01)**	**0.13 (0.01)**	**0.13 (0.01)**	*0.26* (*0.01*)	*0.25* (*0.01*)	

PGF, paternal grandfather; PGM, paternal grandmother; MGF, maternal grandfather; MGM, maternal grandmother.

Parent-offspring resemblance (both grandparent to parent and parent to offspring) in italics. Grandparent grandchild resemblance in bold.

We formally tested for heterogeneity of the four grandparent-grandchild ORs (Table 1). They did not significantly differ ($p = 0.04$, Bonferroni corrected alpha level of 0.0045) and the combined OR (95% CIs) was estimated at 1.68 (1.63–1.73). We also fitted a model, which predicted risk of AUD in the grandchild from AUD in all four grandparents and both parents (Table 1). The combined OR for the grandparents was 1.47 (1.43–1.51) and did not differ across the four grandparents ($p = 0.02$). The combined OR for the parents was 2.62 (2.54–2.71) and did not differ between mother and father ($p = 0.30$). We also examined whether AUD in the four grandparents differentially predicted risk for AUD in their grandsons *v.* granddaughters. These interactions were not significant for paternal grandfathers ($p = 0.12$), paternal grandmothers ($p = 0.40$), maternal grandfathers ($p = 0.12$) and maternal grandmothers ($p = 0.21$). Testing for X-linked transmission, we found, starting with an affected grandfather, no significant difference in the risk for AUD in the sons of his sons *v.* the sons of his daughters: 4.57 and 4.78%, respectively ($p = 0.27$).

We then tested for same *v.* opposite sex transmission. In paternal grandparents, the tetrachoric correlation was significantly higher for same-sex transmission (grandfather to grandson and grandmother to granddaughter) than for opposite sex transmission (grandfather to granddaughter and grandmother to grandson): +0.14 (0.01) and 0.08 (0.01), respectively, heterogeneity $p < 0.0001$. The same pattern was seen in maternal grandparents: 0.15 (0.01) and 0.10 (0.01), respectively, heterogeneity $p < 0.0001$. In parents, same-sex transmission (father to son and mother to daughter) was significantly stronger than opposite sex transmission (father to daughter and mother to son): +0.27 (0.01) and 0.24 (0.01), respectively, heterogeneity $p < 0.0001$. A similar pattern was seen using ORs.

In Table 3, we examined in more detail the impact of risk for AUD in the offspring generation as a function of a history of AUD in each of the four grandparents and the intervening parents (that is, father for paternal grandparents and mother for maternal grandparents). Focusing, as an illustration, on paternal grandfathers, we divided all their grandchildren into four groups: (1) those where the grandfather and father were both unaffected, (2) whether the grandfather was unaffected and the father affected, (3) where the grandfather was affected and the father unaffected, and (4) where the grandfather and father were both affected with AUD. The pattern of findings was relatively similar across the four grandparental groups. On average, compared with the low risk group # 1, risk was increased about 70% if only the grandparent was affected, around 3-fold if only the parent was affected, and about 4-fold if both parent and grandparent were affected. We repeated these analyses but also considered the AUD status of the other parent (that is, for example, the mother and father along with the paternal grandfather). Results were little changed from Table 3.

We then examined the impact of the number of affected grandparents on risk for AUD in their grandchildren (Table 4). When none of the parents were affected, the risk for AUD in grandchildren was approximately 40% greater when more than one *v.* only one grandparent was registered for AUD. The result was similar when one or more parents were affected.

Resemblance in risk for AUD in the offspring generation and in four antecedent relative types

As seen in Table 5, focusing on the tetrachoric correlations, the magnitude of resemblance for liability to AUD in the offspring generation and four classes of

https://doi.org/10.1017/S0033291717000794 Published online by Cambridge University Press

Table 3. *Risk for alcohol use disorder (AUD) in grandchildren as a function of the AUD status of their parents and grandparents*

Grandparent and *N* with AUD	Grandparent AUD status	Parent AUD status	Intervening parent	% Occurrence	% AUD in Grandchild	Odds ratio (95% CI)
Paternal grandfather (*N* = 28 865)	No AUD	No AUD	Father	93.3	2.0	REF
		AUD		6.7	6.0	3.07 (2.93–3.21)
	AUD	No AUD		83.4	3.2	1.57 (1.48–1.67)
		AUD		16.6	7.2	3.74 (3.41–4.09)
Paternal grandmother (*N* = 9300)	No AUD	No AUD	Father	92.9	2.1	REF
		AUD		7.1	6.0	3.00 (2.52–3.58)
	AUD	No AUD		81.5	3.5	1.58 (1.39–1.80)
		AUD		18.5	9.1	4.17 (3.48–4.99)
Maternal grandfather (*N* = 32 425)	No AUD	No AUD	Daughter	97.4	2.1	REF
		AUD		2.6	7.1	3.50 (3.29–3.73)
	AUD	No AU		92.9	3.6	1.71 (1.63–1.80)
		AUD		7.1	9.5	4.83 (4.31–5.41)
Maternal grandmother (*N* = 11 007)	No AUD	No AUD	Daughter	97.2	2.2	REF
		AUD		2.8	7.3	3.50 (3.30–3.71)
	AUD	No AUD		90.2	4.0	1.88 (1.73–2.03)
		AUD		9.8	10.1	5.02 (4.29–5.89)
GP (*N* = 81 597)	No AUD	No AUD	–	95.2	1.8	REF
		AUD		4.8	5.4	3.09 (2.95–3.24)
	AUD	No AUD		87.8	3.1	1.71 (1.64–1.79)
		AUD		12.1	7.8	4.57 (4.32–4.84)

Table 4. *Risk for alcohol use disorder in grandchildren as a function of the number of grandparents with alcohol use disorder when one of more of their parents do and do not have alcohol use disorder*

Parents	Number of grandparents with AUD	% AUD in grandchild	Odds ratio (95% CI)
No AUD	1	2.9	REF
	>1	4.2	1.44 (1.29–1.60)
AUD	1	7.3	REF
	>1	9.8	1.37[a] (1.21–1.55)

[a] If we eliminate grandchildren with two parents with AUD (*n* = 1789), this ORs decreases slightly to 1.32 (1.14; 1.52).

Table 5. *Tetrachoric correlations and odds ratios for alcohol use disorders in four Groups of relatives and the offspring generation*

	Tetrachoric correlations (S.E.S)	ORs (95% CIs)
Parents	0.247 (0.004)	3.16 (3.06–3.27)
Grandparents	0.119 (0.003)	1.80 (1.75–1.86)
Aunts/uncles	0.131 (0.005)	1.88 (1.81–1.96)
Great aunts/uncles	0.056 (0.004)	1.30 (1.26–1.34)

antecedent relatives is rather orderly. The correlations between grandparent-offspring and aunt/uncle-offspring (both second-degree relatives) equal respectively, +0.12 and 0.13. These are nearly exactly half of that seen between parents and offspring (a first-degree relationships), which equals +0.25. Furthermore, the correlation between great-aunt/great-uncle and offspring (a third-degree relationship) equals +0.06, approximately half that seen in the two second-degree relationships and one-quarter that seen in the first-degree parent-offspring relationship.

Possible bias due to censoring of age at onset distribution

A key question in considering the validity of our three generation analyses is the large differences in the mean age of registration across the generations. Given the years of availability of information on AUD, affected grandparents had to have alcohol problems in mid to late adult life, while their grandchildren had to have problems in early adult life. Perhaps the left and right truncation of the age at registration distributions of AUD in the grandparents and grandchildren, respectively, has substantially distorted our results.

We examined this question in two ways (Table 6). First, we estimated the parent-offspring tetrachoric

https://doi.org/10.1017/S0033291717000794 Published online by Cambridge University Press

Table 6. *The impact of Censoring of age at first registration in parental and offspring generation on the observation correlation of AUD across generations*

	Parents			Offspring			Parent-offspring Tetrachoric correlation for AUD
Years of birth of parents	Mean year of birth (S.D.)	Prevalence AUD (%)	Mean age at first registration (S.D.)	Mean year of birth (S.D.)	Prevalence AUD (%)	Mean age at first registration (S.D.)	
1921–1930	1925 (3)	4.1	59.1 (10.8)	1955 (7)	5.6	42.8 (12.5)	0.23 (0.00)
1931–1940	1936 (3)	5.6	53.7 (12.4)	1963 (6)	4.6	36.8 (11.5)	0.24 (0.00)
1941–1950	1946 (3)	6.0	48.8 (12.4)	1973 (6)	3.3	29.5 (9.8)	0.25 (0.00)
1951–1960	1955 (3)	5.4	42.5 (11.8)	1983 (5)	2.8	23.2 (6.4)	0.26 (0.00)
1961–1970	1964 (2)	5.6	35.7 (10.5)	1988 (2)	3.1	20.6 (4.0)	0.24 (0.01)
1931–1960	1945 (8)	5.7	48.6 (13.0)	1973 (9)	3.5	30.9 (11.2)	0.25 (0.00)
Subset (s) censored							
Oldest quartile parents	1945 (8)	4.3	43.2 (9.8)	1973 (9)	3.5	30.9 (11.2)	0.25 (0.00)
Youngest quartile parents	1945 (8)	5.1	50.7 (11.8)	1973 (9)	3.5	30.9 (11.2)	0.24 (0.00)
Oldest quartile offspring	1945 (8)	5.7	48.6 (13.0)	1973 (9)	2.7	26.1 (7.7)	0.25 (0.00)
Youngest quartile offspring	1945 (8)	5.7	48.6 (13.0)	1973 (9)	2.8	34.3 (9.8)	0.25 (0.00)
Oldest quartile Parents + oldest quartile offspring	1945 (8)	4.3	43.2 (9.8)	1973 (9)	2.7	26.1 (7.7)	0.25 (0.00)
Oldest quartile Parents + youngest quartile offspring	1945 (8)	4.3	43.2 (9.8)	1973 (9)	2.8	34.3 (9.8)	0.26 (0.00)
Youngest quartile parents + oldest quartile offspring	1945 (8)	5.1	50.7 (11.8)	1973 (9)	2.7	26.1 (7.7)	0.25 (0.00)
Youngest quartile parents + youngest quartile offspring	1945 (8)	5.1	50.7 (11.8)	1973 (9)	2.8	34.3 (9.8)	0.24 (0.00)

Oldest quartile among Parents: 58 years and above are censored.
Youngest quartile among Parents: 39 years and below are censored.
Oldest quartile among Offspring: 40 years and above are censored.
Youngest quartile among Offspring: 22 years and below are censored.

correlation for AUD from parents born in five different decades from 1921 to 1970. As expected, we saw the mean age at registration in both generations become younger and younger in more recent cohorts. Despite these substantial shifts, the tetrachoric correlation (here chosen because of its lack of base-rate sensitivity) changed very little.

Second, we took the entire parental cohort from 1931 to 1960 and imposed arbitrary censoring by deleting the oldest and youngest quartile alternately and then together in the parent and offspring generation. As seen in Table 6, the parent-offspring tetrachoric correlation for AUD was quite stable across these various truncated samples.

Discussion

Stability of transmission

The goal of this report was to clarify the nature of the transmission of AUD across three generations in a general population Swedish cohort. We sought to address four specific questions, which we now review in turn. First, we sought to examine the stability of the familial transmission of AUD over generations. This is of interest because the time period examined (from 1973 to 2012) in Sweden included changes in the availability and pricing of alcohol in Sweden (Castberger *et al.* 1994; Norstrom & Ramstedt, 2006; Gustafsson & Ramstedt, 2011) and rising rates of drug abuse (Giordano *et al.* 2013), partly due to requirements on the Swedish authorities from the European Union to change alcohol policies and to have more open borders. While these and other factors could have perturbed the patterns of familial transmission of AUD, our results suggest they did not. Resemblance of risk for AUD between spouses and between parents and children were relatively stable across three generations. Our results are consistent with a prior twin study of AUD in Sweden using temperance board registrations (Kendler *et al.* 1997). That study found that the magnitude of genetic and environmental effects on AUD in Swedish men in four approximately equal sized cohorts born 1902–1917, 1918–1930, 1931–42, and 1943–49 were indistinguishable despite a wide range of changes in overall income and rules for alcohol access over this time period. From these results, it is possible to conclude tentatively that the broad patterns of the familial aggregation of AUD in human populations is relatively stable and not very sensitive to historical forces or alterations in laws governing alcohol access.

The validity of our conclusions about the cross-generational transmission of AUD is dependent on knowing whether our sampling of AUD cases from later adult life in the grandparental and early adult life in the offspring generation biased our results. We explored this question both by examining parent-offspring generation across five separate cohorts and by introducing artificial left and right censoring of the age at registration distributions across our cohort. In both set of analyses, the parent-offspring correlations for AUD were quite stable, suggesting that cross-generational resemblance for AUD is not highly sensitive to left and right truncations of the age at registration distribution. Thus our analyses are likely at least broadly valid.

Sex effects

Second, we examined whether transmission of AUD varied as a function of the sex of the relative. Despite our large sample sizes, we were unable to find statistical evidence that the risk for AUD differed in the children or grandchildren of men *v.* women with AUD. These results are of particular interest because a standard liability multiple threshold model would suggest that, given the lower prevalence of AUD in women, affected women with AUD would on average have a higher liability to AUD than affected men. Given the important role of familial factors in AUD, it would further be expected that the familial liability to AUD would be higher in affected women *v.* men. But that would be reflected in a higher risk of AUD in the relatives of affected women *v.* men, which we do not see. Our results, while puzzling, are consistent with prior observations in families (Cloninger *et al.* 1978; Guze *et al.* 1986), and a recent meta-analysis of twin and adoption studies (Verhulst *et al.* 2015).

The lack of significant differences in the transmission of AUD from grandfathers *v.* grandmothers and especially fathers *v.* mothers is inconsistent with high rates of non-paternity and an important contribution of intrauterine effects. Given the strong role of genetic factors in the familial transmission of AUD (Verhulst *et al.* 2015), high rates of non-paternity would depress AUD transmission from males *v.* females, which we do not observe. If intrauterine effects, especially exposure to high levels of alcohol consumed during pregnancy [which may increase risk for AUD in exposed offspring (Yates *et al.* 1998; Riley *et al.* 2011)] contributed substantially to the cross-generational transmission of AUD, then we should see stronger transmission of AUD from women than men, which we do not.

Using an old test for X-linked transmission (Kaij & Dock, 1975), starting with an affected grandfather, we found no difference in risk for AUD in the sons of his sons (none of whom share his X-chromosome) and the sons of his daughters (50% of whom share

https://doi.org/10.1017/S0033291717000794 Published online by Cambridge University Press

his X-chromosome). These results are consistent with the one previous study of this question (Kaij & Dock, 1975). Given the likely highly multifactorial genetic transmission of AUD, we can only conclude from these analyses that the hypothesis that large substantial proportion of the risk variants for AUD are located on the X-chromosome is unlikely to be true.

We then examined grandparent-grandchild and parent-child transmission for AUD within *v.* across-sexes. We found consistent evidence that transmission was higher in within-sex *v.* cross-sex pairs of relatives, supporting the hypothesis that the familial factors, which predispose to AUD, while correlated, are not identical in males and females. Our results are consistent with results of one large-scale twin study that resemblance for AUD is lower in opposite-sex *v.* same-sex relative pairs (Prescott *et al.* 1999) and an older family study (Guze *et al.* 1986), but inconsistent with results from a recent meta-analysis of twin and adoption studies of AUD (Verhulst *et al.* 2015). In an even more recent large scale twin-sibling study of AUD in Sweden we found modest evidence for sex-specific transmission (Kendler *et al.* 2016). These results, if verified, have implications for molecular genetic strategies for the study of AUD – that greater power would be found in studying individuals of the same sex – as was recently suggested in the first replicated evidence for genetic risk variants of major depression obtained in a female-only sample (CONVERGE consortium, 2015). However, our present results cannot rule out that the sex-specific transmission of AUD is due to environmental mechanisms, such as social learning (Bandura, 1986).

Grandparent-grandchild transmission of risk for AUD

Our third aim was to examine the empirical risk figures for AUD in the offspring generation as a function of grandparental and parental AUD. These results were sensible, broadly consistent with expectations and similar across the four grandparents. We found that when no parents were affected with AUD, risk for AUD in the grandchild of an affected grandparent was increased about 70%. If one parent but no grandparents were affected, the risk was approximately tripled. If both parent and grandparent were affected the risk was approximately quadrupled. The most comparable study we were able to find was published over 60 years ago by Bleuler (1955) who examined risk in a wide range of first, second and third-degree relatives of 50 probands with alcoholism. He calculated age-corrected rates of alcoholism of 13.7% in parents, 8.9% in aunts/uncles and 7.3% in grandparents. The absence of matched controls makes these figures problematic to interpret, but they suggest a pattern of findings broadly similar to those we report.

Overall pattern of resemblance with antecedent relatives

Finally, we examined the pattern of familial transmission of AUD to the offspring generation from four classes of antecedent relatives: great-aunts/uncles, grandparents, aunts/uncles, and parents. Examining tetrachoric correlations, the pattern was orderly, the correlations being almost exactly twice as great in first-degree relatives (parents) as in second-degree relatives (grandparents and aunts/uncles), which were in turn twice as great as third-degree relatives (great-aunts/uncles). While this is the pattern of resemblance predicted by additive genetic effects (Falconer, 1989), in fact our own studies of both twins and siblings (Kendler *et al.* 1997, 2016) and parent-offspring (Kendler *et al.* 2015*a*, 2015*b*) in Sweden suggest that familial environmental effects also contribute to familial transmission. One plausible interpretation of these findings is that these familial-environmental effects attenuate with more distant family relationships at a rate similar to that seen for genetic effects.

Limitations

These results should be interpreted in the context of two potentially important methodological limitations. First, as noted above, because of the years over which information on registration for AUD were available to be ascertained, our grandparental generation had to have recurrent or later onset AUD and our grandchild generation had to have early onset AUD. We explored the possible bias these selections effects might produce in some detail and our results suggest that the bias is likely to be modest. But we cannot rule out a larger effect.

Second, we detected subjects with AUD from medical, criminal and pharmacy records. This method has the major advantage of not requiring cooperation or accurate reporting. However, it cannot be expected to replicate findings from interview-based epidemiological surveys. By that standard, our approach would surely produce both false negative and false positive diagnoses. Because the population prevalence of AUD in this sample is lower than estimates from epidemiologic surveys (Kessler *et al.* 1994; Grant *et al.* 2015) including one from nearby Norway (which estimated lifetime prevalence for AUD at 13.2 and 5.2% in males and females, respectively, compared with 7.3 and 3.0% in our fathers and mothers) (Kringlen *et al.* 2001), false negative diagnoses are probably considerably more common than false positive ones. Compared with those identified in epidemiologic

https://doi.org/10.1017/S0033291717000794 Published online by Cambridge University Press

surveys, the cases of AUD that we studied are likely to be more severe. The best available validation for our definition of illness is the high rates of concordance for registration observed across our different ascertainment methods (Kendler *et al*. 2015*a*). We cannot rule out that our incomplete ascertainment distorted the pattern of familial correlations for AUD. However, our analyses presented in Table 6 are somewhat reassuring in that they show quite stable parent-offspring despite substantial shifts in prevalence rates.

Conclusions

The familial transmission of AUD is relatively stable over the last three generations in Sweden. Affected men and women transmit risk to AUD equally to their descendants. However, across both two and three generations, individuals transmit higher liability to their same-sex than to their opposite-sex descendants. We found no evidence supporting a strong X-chromosome effect on risk for AUD. Risk for AUD in the grandchild generation is influenced most strongly by parental AUD status. However, controlling for parental AUD status, grandparental AUD also impacts appreciably on risk. The correlation in risk between our offspring and four classes of ancestors (great-aunts/uncles, grandparents, aunts/uncles, and parents) is quite orderly with the correlation declining by approximately 50% moving from first, to second to third degree relatives. These results have potential implications for studies seeking to map molecular risk variants for AUD.

Acknowledgements

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

Declaration of Interest

None of the authors have any conflicts of interest to declare.

Ethical Standards

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

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