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Familial transmission of externalizing syndromes in extended Swedish families

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Abstract

Risk for criminal behavior (CB), alcohol use disorder (AUD), and drug abuse (DA) are known to be familial. We know less about their transmission across three generations. We examined 844,109 probands born in Sweden 1980–1990, their parents, aunts/uncles, and grandparents for registration in population-based registers for CB, AUD, and DA. Mean tetrachoric relative-proband correlations (95% CIs) were highest for DA (+0.24, 0.24–0.25), followed by CB (+0.23, 0.22–0.23) and AUD (+0.17, 0.16–0.17). AUD and CB were relatively stably transmitted across generations, while DA resemblance among relatives was stronger in the younger generations. For all three syndromes, male-male transmission was modestly stronger than female–female. Cross-sex transmission was significantly weaker than same-sex transmission for DA and CB but not AUD. Risk to probands with only an affected grandparent or aunt/uncle were increased 50–60% for CB and AUD, and 70–100% for DA. Parallel figures for affected parents only and parents + grandparent or aunt/uncle were 2–3-fold and 4–5-fold for CB and AUD, and 4–5-fold and 6–7-fold for DA. CB, AUD, and DA are all substantially familial in the Swedish population with the transmission across three generations stable for CB and AUD but not DA. Modest quantitative sex effects are seen in the familial transmission of CB, AUD, and DA, and qualitative sex effects for CB and DA. Risk prediction in offspring is orderly with affection status in grandparental and avuncular relationships adding appreciably to that from the parental generation.

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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).

CONFLICTS OF INTEREST

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

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Keywords

alcohol use disorder; crime; drug abuse; familial transmission; grandparents; parents; sex

1 | INTRODUCTION

Criminal behavior (CB), Alcohol Use Disorder (AUD), and Drug Abuse (DA) are all strongly transmitted within families (Besemer, 2012; Cotton, 1979; Merikangas et al., 1998). Twin and adoption studies suggest that while a substantial proportion of this transmission of these syndromes results from genetic factors, familial environmental effects also contribute (Kendler et al., 2012, 2014; Kendler, Ji, et al., 2015; Kendler, Lonn, et al., 2016; Verhulst, Neale, & Kendler, 2015). A limitation of the systematic studies of the familial transmission of AUD and DA is that they have almost exclusively examined only nuclear families—looking at resemblance of twins or siblings, or more rarely parents and children. Only with CB is there a substantial literature exploring the transmission across three generations (Besemer, 2012; Besemer, Axelsson, Sarnecki, 2016; Junger, Greene, Schipper, Hesper, & Estourgie, 2013; Putkonen, Ryyanen, Eronen, & Tihiainen, 2007; van de Weijer, Bijleveld, & Blokland, 2014). Avuncular relationships—between uncles/aunts and their nieces and nephews—have been even more infrequently examined because such data is rarely available.

In this paper, we report a national Swedish study of transmission of the three major externalizing syndromes of CB, AUD, and DA from grandparents, aunts/uncles and parents to offspring, whom we term *probands*. We address the following three topics. First, how stable are the patterns of familial resemblance across generations and do these patterns differ across the three syndromes? This is of interest because in Sweden, during the time period covered in this report, there have been changes in the availability of alcoholic beverages (Castberger, Hibell, & Olsson O., 1994; Gustafsson & Ramstedt, 2011; Norstrom & Ramstedt, 2006) and in rates of DA (Giordano et al., 2013). Second, do we see sex-specific effects in the familial transmission of these externalizing syndromes? We are interested in two kinds of effects. The first is quantitative: Do correlations for these disorders differ in male–male versus female–female pairs of relatives? The second is qualitative: Are the correlations observed in opposite-sex pairs of relatives different than would be expected from the same-sex pairs, thereby suggesting that the familial factors that predispose to these disorders are not identical in males and females?

Our third goal is to elucidate the pattern of empirical risk figures for CB, AUD, and DA in the offspring generation as a function of risk for these syndromes in grandparents, aunts/uncles, and parents. For example, controlling for affection status of the parents, how much is the proband risk altered by affected grandparents or aunts/uncles? Results for AUD in grandparents and parents in a subset of these families have been presented previously (Kendler, Ohlsson, Sundquist, & Sundquist, 2017).

2 | 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, this ID number was replaced by a serial number. We secured ethical approval for this study from the Regional Ethical Review Board of Lund University (No. 2008/409).

From the Multigenerational register, we selected all individuals born in Sweden between 1980 and 1990 who still resided in Sweden at age 15 ($N = 1,034,344$). We randomly selected one male and one female proband from each set of full siblings. Furthermore, we included information on parents, grandparents, aunts and uncles, and for certain analyses, great-aunts, and great-uncles to the proband. To be included, we required that the relative was residing in Sweden in 1980. In situations where the proband had more than one maternal aunt, we selected one such individual to be included in the database and then did the same for maternal uncle, paternal aunt, and paternal uncle. Of the 844,109 probands from unique families 0.13% had none of the 10 possible relatives (2 parents, 4 grandparents, and 2 paternal aunts/uncles, and 2 maternal aunts/uncles) registered in the database; 88.7% had 5 or more and 11.2 % had all 10 relatives registered.

The three externalizing syndromes ascertained from official registries and used as outcomes in the analyses were DA, AUD, and CB. The following registers were used to create the three outcome variables: Swedish Hospital Discharge Register, containing hospitalizations for all Swedish inhabitants from 1964 to 2012; Swedish Prescribed Drug Register, containing all prescriptions in Sweden picked up by patients from 2005 to 2012; Outpatient Care Register, containing information from outpatient clinics from 2001 to 2012; Swedish Crime Register, containing national data on all convictions from 1973 to 2012; Swedish Suspicion Register, containing national data on all individuals strongly suspected of crime from 1998 to 2012; Swedish Mortality Register, containing all causes of death.

DA was identified in the Swedish Medical and Mortality Registries by ICD codes (ICD8: Drug dependence (304); ICD9: Drug psychoses (292) and Drug dependence (304), Nondependent abuse of drugs (305; excluding 305.0); ICD10: Mental and behavioral disorders due to psychoactive substance use (F10–F19), except those due to alcohol (F10) or tobacco (F17)); in the Suspicion Register by codes 3070, 5010, 5011, and 5012, that reflect crimes related to DA; and in the Crime Register by references to laws covering narcotics (law 1968:64, paragraph 1, point 6) and drug-related driving offences (law 1951:649, paragraph 4, subsection 2 and paragraph 4A, subsection 2). DA was identified in individuals (excluding those suffering from cancer) in the Prescribed Drug Register who had retrieved (in average) more than four defined daily doses a day for 12 months from either of Hypnotics and Sedatives (Anatomical Therapeutic Chemical [ATC] Classification System N05C and N05BA) or Opioids (ATC: N02A).

CB was identified by registration in the Swedish Crime Register which excluded convictions for minor crimes like traffic infractions. We assessed CB using the following criminal conviction types during the entire follow up period: (aggravated) assault, illegal threats, intimidation and illegal coercion, threats or violence against a police officer, (aggravated) robbery, murder, manslaughter or filicide, kidnapping, arson, sexual crimes (excluding prostitution and the buying of sexual services but including child pornography), fraud, forgery and dishonesty, and embezzlement, theft, vandalism, vandalism causing danger to the public and trespassing.

AUD was defined by ICD codes for main and secondary diagnoses from Swedish Medical Registries for the following diagnoses: ICD9: 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 woman (O35.4), toxic effects of alcohol (T51.0–T51.9), and based on Anatomical Therapeutic Chemical (ATC) codes in the Prescribed Drug Register: disulfiram (N07BB01), acamprosate (N07BB03), or naltrexone (N07BB04). Additionally, we identified individuals with at least two convictions of drunk driving (law 1951:649) or drunk in charge of maritime vessel (law 1994:1009) in the Crime Register. We used the Cause of Death Register to obtain data on alcohol-associated death and used the same codes as above.

To study the transmission of the three major externalizing syndromes of CB, AUD, and DA from grandparents, aunts/uncles, and parents to probands, we first calculated unadjusted tetrachoric correlations between all included relatives. In the next step, we equated all correlations between the proband and his/her relatives. We compared the combined correlations across phenotypes using the Olkin-Pratt (OP) meta-analytical approach (Schulze, 2004). In the next models, we calculated an overall correlation first between parents and proband, followed by an overall correlation between grandparents and proband, and finally an overall correlation between aunts/uncles and proband. Additionally, we included an overall correlation for great aunts/uncles to proband. 33% of the probands had at least one great aunt/uncle in the registers who were alive in 1980. Thereafter, we constrained the model to one combined correlation for maternal and paternal relatives. Our test for qualitative sex effects was to calculate the geometric mean of the correlations in male–male and female–female proband-relative pairs (the expected correlation in opposite-sex pairs if all the familial factors were identical across sexes) and determine if the observed correlation in opposite sex pairs differed significantly from that expectation.

In our final analyses, using logistic regression, we estimated the association between CB (AUD, DA) in maternal and paternal grandparents on the one hand and CB (AUD, DA) in proband on the other, while controlling for CB (AUD, DA) in the intervening parent (the father for paternal grandparents the mother for maternal grandparents). The same approach was then used for maternal and paternal aunts and uncles.

The correlation analyses were performed using the Mplus software (Muthén & Muthén, 2015). The Mplus software uses all data that is available to estimate the model using full

information maximum likelihood. Each parameter is estimated directly without first filling in missing data values for each individual.

3 | RESULTS

3.1 | Descriptive statistics

Our probands ($n = 844,109$) were born in Sweden between 1980 and 1990 and still resided there at age 15. Table 1 depicts their mean year of birth, prevalence of CB, AUD, and DA, and mean age at registration as well as those of their grandparents, maternal, and paternal aunts/uncles and parents. We see consistently higher rates of CB, AUD, and DA in males than females. The mean ages at first registration during the study period was considerably higher in grand-parents than parents which in turn were higher than in offspring. This is because the years of available information about CB, AUD, and DA registration in Sweden were from 1973 to 2012. This means we could only ascertain CB, AUD, and DA 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.

3.2 | Descriptive findings: Familial resemblance in grandparents, biological aunts/uncles, parents and probands

We quantify familial resemblance using the tetrachoric correlations because of its ease of interpretation and its relative insensitivity to different base-rates (Babchishin & Helmus, 2016). Tables 2–4 show the tetrachoric correlations for, respectively, CB, AUD, and DA across and within three generations. Results for male and female probands are given below and above the diagonal. We describe the major results for CB in detail and then summarize findings for AUD and DA. For CB, first, spousal correlations are high, ranging from +0.34–0.44. Second, parent-offspring correlations, which include proband and their parents, parents and grandparents, and aunts/uncles and grandparents are similar, ranging from +0.27 to +0.35. Third, sibling relationships seen between the parents and their siblings (aunts/uncles to the proband) range from +0.30 to +0.41. Fourth, grandparent-proband relationships are also comparable ranging from +0.13 to +0.19. Fifth, avuncular correlations (aunt/uncle-proband) are slightly greater than grandparent-proband ranging between +0.17 and +0.22. Finally, there is a general trend for correlations involving male probands to be higher than those involving female probands.

Results for AUD (Table 3) were broadly similar to those found for CB, although on average modestly lower. The correlations between grandparents and the proband and aunts/uncles and the proband were quite similar. Spousal correlations were stable across generations. Somewhat higher correlations were seen from grandparents and aunts/uncles with male than with female probands.

Results from DA (Table 4) differed in several ways from those seen for CB and AUD. First, correlations were higher than those seen for CB and especially AUD. Second, spousal correlations were not stable across time, and were nearly twice as high in the parental as in the grandparental generation. Third, correlations with the proband were appreciably higher for aunts/uncles than with grandparents. Fourth, parent-offspring correlations were higher

from parents to the proband (+0.33 to +0.36) than from grandparents to parents and aunts/uncles (+0.22 to +0.31).

3.3 | Analysis of overall patterns of familial transmission

We calculated the mean tetrachoric correlation between the proband and his/her parents, grandparents and maternal and paternal aunts and uncles. This equaled (with 95% CIs) +0.23 (0.22–0.23) for CB, +0.17 (0.16–0.17) for AUD and +0.24 (0.24–0.25) for DA. These correlations all differed significantly from one other ($p < 0.0001$). Of these three syndromes, DA is the most and AUD the least familial.

We then examined the overall pattern of familial resemblance—as mean relative-proband correlations—across our classes of relatives adding great-aunts and uncles so that we included examples of first, second and third-degree ancestral relationships (Table 5). We have three comparisons of interest: (i) first versus second degree relationships in the direct line of descent (parents versus grandparents); (ii) second versus third degree relationship in collateral line of descent (aunts/uncles vs. great aunts/uncles); and (iii) second degree relationships in direct and collateral line of descent (grandparents versus aunts/uncles). For CB, the mean correlation in parents is slightly less than twice that seen in grand-parents and aunts/uncle correlations are almost exactly twice that seen in great aunts/uncles. Aunts/uncles are modestly more highly correlated with the proband than are grandparents. For AUD, parents are slightly more than twice as correlated as grandparents. In our two groups of second-degree relationships, we see a slightly higher correlation in aunts/uncles versus grandparents. The correlation in great aunts/uncles is almost exactly half that seen in aunts/uncles. For DA, the pattern is quite different. The mean correlation in parents is three times that seen in grandparents, and aunts/uncle correlations are more than twice that seen in great aunts/uncles. Aunts/uncles are much more closely correlated with probands than are grandparents.

3.4 | Effects of sex on patterns of familial transmission

We examined, for the three externalizing syndromes, the mean correlations between all male and female relatives and male and female probands (Table 6). Male to male transmission was significantly but modestly stronger than female to female transmission for CB, AUD, and DA. The cross-sex transmission was significantly lower than expected for CB and DA, indicating the presence of qualitative sex effects. For AUD, by contrast, the observed cross-sex transmission did not differ significantly from expectation.

3.5 | Empirical risk prediction

We predicted risk for CB, AUD, and DA in probands as a function of a history of the same syndrome in each of the four grandparents, their maternal and paternal aunts and uncles and the intervening parent (that is, the father for paternal grandparents and aunts/uncles and mother for maternal grandparents and aunts/uncles). We review in detail the results for prediction of CB and then more briefly for AUD and DA. The top rows in Table 7 show the absolute prevalences and odds ratio for CB in four groups of probands: those with (i) an unaffected parent and grandparent; (ii) an affected parent and unaffected grandparent; (iii) an unaffected parent and affected grandparent; and (iv) both an affected parent and grandparent.

For fathers and paternal grandparents, and mothers and maternal grandparents, the results are orderly and similar. Compared to the first lowest risk group, having only an affected grandparent increased risk for CB around 50% while having only an affected parent increased risk by 150–200%. Having both an affected parent and grandparent produced a 300–350% increase in risk. The top row of Table 8 shows the results for fathers and paternal aunts/uncles, and mothers and maternal aunts/uncles. The findings are similar to that seen for grandparents. Having only an affected aunt/uncle increases proband risk for CB around 50% while having both an affected aunt/uncle and parent (from the same side of the family) carried a substantially greater risk than only an affected parent.

The pattern of results for AUD with both grandparents/parents (Table 5) and aunts/uncles/parents (Table 8) are both quite similar to each other and resemble rather closely those seen for CB. For DA, by contrast, the ORs are higher. For example, having only affected aunt/uncle approximately doubles risk and having an affected parent and grandparent increases risk about 500%.

3.6 | Potential bias due to censoring of age at onset distribution of first registration

The differences in the mean age of registration across generations raises concerns about the validity of our findings. Given the years of availability of information on CB, AUD, and DA, affected grandparents typically are registered in mid to late adult life while their grandchildren were registered in early adult life. The left and right truncations of the age at registration distributions of these externalizing syndromes across generations could plausibly substantially distort our results.

We first examined this question by taking a broad parental cohort born 1931–1960 and their offspring where we have relatively good ascertainment across ages in both generations. In that sample, the cross-generational correlations for CB, AUD, and DA were (along with their SE), respectively, 0.26 (0.00), 0.25 (0.00), and 0.31 (0.00). We then imposed an arbitrary censoring that simulated the real censoring by eliminating the 25% youngest ages at registration in the parental generation and the 25% oldest in the offspring generation. If an individual's only registration was in that time-period, they would be excluded in the sample. But if they were also registered when older, then, as in our real sample, they would remain in the sample. Similarly, someone in the offspring generation only ascertained when old would be missed while one registered in the registry both younger and older would be detected.

The cross-generational correlations for CB, AUD, and DA changed quite modestly to, respectively, 0.27 (0.00), 0.25 (0.00), and 0.31 (0.00). If we increased the proportion of onsets censored to 35% in both groups, the cross-generational correlations for CB, AUD, and DA changed a bit more to, respectively, 0.26 (0.00), 0.23 (0.00), and 0.30 (0.00). We then simulated a reduced left truncation in the parental generation (sampling parental birth years 1945–1960) and reduced right truncation in the offspring generation (sampling parental birth years 1931–1950). These produced, respectively, the following estimates for cross-generational correlations for CB (0.28 [0.00] and 0.26 [0.00]), AUD (0.26 [0.00] and 0.24 [0.00]), and DA (0.33 [0.00] and 0.25 [0.00]). Overall, these analyses suggest that the censoring of the ascertainment of cases by the years of availability of the key registries is unlikely to markedly bias our estimates of familial aggregation.

4 | DISCUSSION

We sought to address three inter-related questions regarding the familial transmission of three major externalizing syndromes (CB, AUD, and DA) from grandparents, aunts/uncles, and parents to offspring (whom we here call probands). We examine these questions in turn. We first explored the stability of the patterns of transmission over three generations. For CB and AUD, the general patterns were stable and orderly with small fluctuations. Spousal correlations were broadly similar across generations. For both disorders, the correlations in first and second degree relatives in the direct line of descent and second and third degree relatives in collateral lines were relatively close to a 2:1 ratio. This was not the case for DA for three sets of findings suggested something changing across the generations. Spousal correlations were much higher in recent generations. The parent-proband correlations were three times larger than the grandparent-proband and the aunt/uncle-proband correlations were quite a bit more than twice as great as those seen for the great aunt/uncles.

What might be the source of these differences? We suspect that that these results are largely driven by the increasing prevalence for severe DA in Sweden over the years of this study (Giordano et al., 2013; Kaye & Weltzin, 1991) which may in turn be associated with increased drug availability and “normalization” of illicit drug use in Sweden over recent decades (Szmitman, 2008). This permits individuals at lower liability to experiment with illicit drugs with some probability of then progressing to DA. These findings could, of course, arise from changes in ascertainment including the addition in recent years of new forms of detection, for example, the Pharmacy Registry. However, arguing against this explanation is that these same registries were used to ascertain AUD which demonstrated no such shifts. Indeed, we saw no clear effects of the gradual albeit modest increase in per capita alcohol intake in Sweden in the second half of the 20th century associated with a gradual shift in intake from spirits to beer and wine (Kaye & Weltzin, 1991; Leifman, 2001) nor the changes in alcohol policies associated with Sweden's entry into the European union in 1995 (Holder, 2000).

We next explored potential sex differences in familial transmission. First, we found that the mean relative-proband correlations were significantly higher for male–male than for female–female pairs for CB, AUD, and DA. The differences were not large but suggest modest quantitative sex effects in the familial transmission of these syndromes, that is, these disorders are somewhat more familial in males than females. Second, we examined the average resemblance among opposite sex relatives and found that they were significantly lower than expectation for CB and DA but not AUD. While the differences were quite modest, they suggest qualitative sex effects of these syndromes—that the familial factors influencing males and females for CB and DA are not entirely identical. It is difficult to directly compare our findings with those in the literature as our methods are dissimilar from nearly all prior studies and our large sample size gives us great power to detect modest differences. Furthermore, a number of studies, especially of CB, utilize ORs to quantify familial resemblance (Auty, Farrington, & Coid, 2015; Farrington, Barnes, & Lambert, 1996). These studies often show higher ORs for female-female pairs where CB in females is much rarer than in males. But these findings could result from the base-rate sensitivity of

ORs where for the same correlation of liability ORs are greater the rarer the trait (Kraemer, 2004, 2006).

We review a few relevant prior studies to put our findings in context. A recent meta-analysis of twin and adoption studies of AUD found no evidence for quantitative or qualitative sex effects (Verhulst et al., 2015). A review of family studies of AUD noted that in the three studies that addressed this question, none found sex differences in familial transmission (Merikangas, 1990). An older meta-analysis on antisocial behavior found significantly higher heritability in females and evidence for qualitative effects in their entire sample but when they restricted their studies to those that included both males and females in the same study, these effects disappeared (Rhee & Waldman, 2002). In a study of the famous Cambridge Study in Delinquent Development using tetrachoric correlations, Rowe and Farrington (1997) found evidence for sex-specific transmission of CB both within sibling and parent-offspring pairs. However, Besemer et al. (2016) in a study of CB in the three generations of the Stockholm Life Course Project did not find strong support for stronger inter-generational transmission in same versus opposite-sex pairs. One relatively large population based twin study of DA found no differences in level of heritability in male–male versus female–female pairs (Kendler, Prescott, Myers, & Neale, 2003).

On average, male–male correlations in our three generation families will more often involve father-offspring transmissions than will the female–female correlations. While others have noted the absence of a specific study of non-paternity rates in Sweden (Magnusson & Rasmussen, 2002), rates in most Western countries vary between 2% and 5% (Sykes & Irven, 2000). We simulated the effects of non-paternity on father-offspring correlations for CB, AUD, and DA. They declined between 1.4% and 2% given 2% non-paternity, and 4.1–4.5% given 5% non-paternity. These results are modest but suggest that we have slightly underestimated the impact of quantitative sex effects on familial transmission, as non-paternity should attenuate the male-male correlations more than the female-female correlations.

The final aim of our paper was to explore the empirical risk figures for CB, AUD, and DA in the offspring generation as a function of risk in grandparents, aunts/uncles, and parents. These results were orderly with broadly similar patterns across the three externalizing syndromes. For each disorder, risk was significant and modest for an affected grandparent or aunt/uncle, considerably higher given an affected parent but highest for those individuals with both an affected parent and an affected aunt/uncle or grandparent.

As we noted, considerable prior efforts have been made to characterize the genetic-epidemiology of our three syndromes (Besemer, 2012; Cotton, 1979; Kendler et al., 2012, 2014; Kendler, Ji, et al., 2015; Kendler, Lonn, et al., 2016; Merikangas et al., 1998; Verhulst et al., 2015). What does this inquiry add? We would suggest four points. First, both CB and AUD demonstrate a stable pattern of familial transmission across three generations which speaks to a robustness of these transmission patterns. Second, however, this pattern was not stable for DA. Changes in access or social attitudes can, if strong enough, shift patterns of familial resemblance over time. Third, albeit subtle, with large sample sizes and a variety of kinds of relationships, we detected modest sex effects in familial transmission including

stronger aggregation for all three syndromes in males and qualitative sex effects in CB and DA. Finally, the orderly and roughly additive effects on proband risk of the parental, avuncular, and grand-parental affection status for CB and AUD also speaks to the stability of the cross-generational transmission of these syndromes.

It is important to note that our descriptive analyses are unable to determine the sources of the familial aggregation of CB, AUD, and DA. We have studied this question for each of these syndromes previously in the Swedish population. In both twin (Kendler, Maes, et al., 2015; Kendler, Maes, Sundquist, Ohlsson, & Sundquist, 2013; Kendler, PirouziFard, et al., 2016) and adoption (Kendler et al., 2012, 2014; Kendler, Ji, et al., 2015; Kendler, Ohlsson, et al., 2015), we found evidence for both genetic and shared environmental effects, although genetic effects were always somewhat and often substantially stronger. These results are broadly congruent with our findings in that the kind of additive polygenic transmission assumed in these twin studies would predict a decline of 50% in the correlation in relatives with each degree of separation—such as first to second and second to third degree relationships (Falconer, 1989). This is the pattern seen rather clearly in CB and AUD, although not, possibly for reasons noted above, for DA.

4.1 | Limitations

These results should be interpreted in the context of four potentially important methodological limitations. First, ascertaining cases of CB, AUD, and DA from registry data has important advantages, especially being independent of subject cooperation and accurate recall and reporting for syndromes that are often both illegal and socially stigmatizing. However, it also has significant limitations. In Sweden, as in virtually all other countries, most crimes are not officially reported or do not result in a conviction. Therefore, we are likely studying in our registry data the more severe end of the spectrum of criminal activities (Swedish National Council for Crime Prevention, 2008). For DA and AUD, there are surely false negatives for individuals who abuse substances but avoid medical or police attention. The validity of our detection of these syndromes is best supported by evidence that detection across our multiple registries are highly inter-correlated. The mean OR for case detection of DA across our five relevant registries was 52 (Kendler et al., 2012) and for AUD across four registries was 33 (Kendler, Ji, et al., 2015).

Second, we cannot be certain that registration for these disorders in criminal or medical settings were entirely independent of family history. It is therefore possible that resemblance across relatives is upwardly biased. Such biases would be expected, however, to operate considerably more strongly across close than more distant relationships. The orderliness of the overall patterns of resemblance across three degrees of relationship for CB and AUD make it unlikely, in our view, that our findings are seriously distorted by biases in the probability of registration as a function of family history. In addition, such a bias is probably more likely to occur when relatives live at the same address.

Third, registration for CB, DA, or AUD was not available for a long enough time-period in Sweden for us to sample each generation at comparable ages. Therefore, compared to the parental generation where we had the most complete ascertainment, we had to detect these syndromes at older ages in the grand-parental and younger ages in the proband generation.

We conducted simulations reported above that suggest that this approach was unlikely to produce large biases in our estimates of familial transmission. But we cannot rule out the possibility that our findings are, in fact, seriously distorted.

Fourth, individuals with our syndromes of interest have increased mortality rates (Kendler, Ohlsson, Sundquist, & Sundquist, 2016; Kendler, Ohlsson, Sundquist, & Sundquist, 2017). Could this produce biases in the observed correlations in relatives? We explored the impact by changing the inclusion criteria for year of death from 1980 to 1970, thereby relaxing the differential mortality effect. Of the 36 correlations between CB, AUD, and DA in probands and their two parents and four grandparents, 24 were unchanged to 2 significant places and 12 changed only ± 0.01 . These analyses provide tentative evidence that excess mortality rates among affected individuals are unlikely to substantially distort patterns of familial aggregation.

5 | CONCLUSIONS

Using three generation data, we found that CB, AUD, and DA are all substantially familial in the Swedish population. The familial transmission across these three generations was generally stable for CB and AUD. For DA, by contrast, familial resemblance increased in the younger generations. Quantitative sex effects were seen in the familial transmission of CB, AUD, and DA all showing modestly stronger familial aggregation in males than females. Qualitative sex effects, also modest, were found CB and DA each suggesting some familial factors that are not shared across the sexes. Risk prediction in the proband was quite orderly with affection status in grandparental and avuncular relationships adding appreciably to the predictive effects from the parental generation.

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TABLE 1

Sample size and prevalence and mean age at first registration for criminal behavior (CB), alcohol use disorder (AUD), and drug abuse (DA) in relatives of probands born 1980–1990

	Prevalence				Mean age at first registration			
	N	CB	AUD	DA	Mean YoB	CB	AUD	DA
Males								
Proband	434,111	13.2	3.0	8.3	1985	18.0	21.7	21.3
Father	422,732	20.9	7.7	3.0	1954	26.8	42.7	41.6
Mother	426,862	7.1	3.3	2.2	1957	27.9	41.1	41.9
Grandfather (P)	329,414	6.3	6.6	0.6	1924	51.2	56.5	62.8
Grandmother (P)	363,976	3.0	2.2	0.8	1927	52.7	56.1	65.4
Grandfather (M)	345,993	7.5	7.6	0.7	1927	49.0	54.8	60.0
Grandmother (M)	375,933	3.5	2.6	0.9	1930	49.9	54.2	62.7
Aunt (P)	212,200	5.2	3.1	1.8	1954	29.2	42.8	44.0
Uncle (P)	217,023	18.6	7.9	2.9	1954	25.8	42.1	40.0
Aunt (M)	213,800	6.0	3.2	2.0	1957	27.4	40.7	41.3
Uncle (M)	226,337	20.4	8.0	3.3	1957	24.4	40.4	38.7
Females								
Proband	410,853	6.6	2.1	3.2	1985	17.5	20.9	21.0
Father	400,008	20.9	7.7	3.0	1954	26.8	42.8	41.7
Mother	403,722	7.1	3.3	2.1	1957	27.9	41.0	41.9
Grandfather (P)	311,561	6.3	6.6	0.6	1924	51.4	56.5	63.1

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	Prevalence				Mean age at first registration			
	N	CB	AUD	DA	Mean	YoB	CB	DA
Grandmother (P)	344,180	3.0	2.2	0.8	1927		52.6	65.0
Grandfather (M)	327,146	7.5	7.6	0.8	1927		49.0	60.2
Grandmother (M)	355,500	3.5	2.6	0.9	1930		49.8	63.0
Aunt (P)	201,081	5.2	3.1	1.8	1954		29.2	43.5
Uncle (P)	205,170	18.7	7.8	2.9	1954		25.9	39.9
Aunt (M)	201,434	5.9	3.2	1.9	1957		27.3	41.6
Uncle (M)	213,686	20.5	8.0	3.3	1957		24.4	38.8

TABLE 2

Tetrachoric correlations and standard errors of resemblance for registration for criminal behavior in male and female probands (below and above the diagonal, respectively) and their parents, grandparents, aunts, and uncles

	Proband	Father	Mother	Grandfather (P)	Grandmother (P)	Grandfather (M)	Grandmother (M)	Aunt (P)	Uncle (P)	Aunt (M)	Uncle (M)
Proband		0.27 (0.00)	0.29 (0.00)	0.13 (0.01)	0.14 (0.01)	0.15 (0.01)	0.15 (0.01)	0.13 (0.01)	0.15 (0.01)	0.16 (0.01)	0.16 (0.01)
Father	0.34 (0.00)		0.43 (0.00)	0.34 (0.00)	0.30 (0.01)	0.23 (0.00)	0.20 (0.01)	0.30 (0.01)	0.41 (0.00)	0.23 (0.01)	0.25 (0.00)
Mother	0.33 (0.00)	0.44 (0.00)		0.21 (0.01)	0.20 (0.01)	0.30 (0.01)	0.33 (0.01)	0.21 (0.01)	0.23 (0.01)	0.35 (0.01)	0.31 (0.01)
Grandfather (P)	0.17 (0.01)	0.34 (0.01)	0.21 (0.02)		0.34 (0.01)	0.15 (0.01)	0.12 (0.01)	0.30 (0.01)	0.33 (0.01)	0.13 (0.01)	0.13 (0.01)
Grandmother (P)	0.16 (0.01)	0.30 (0.01)	0.20 (0.02)	0.35 (0.01)		0.13 (0.01)	0.14 (0.01)	0.32 (0.01)	0.30 (0.01)	0.12 (0.01)	0.11 (0.01)
Grandfather (M)	0.19 (0.01)	0.24 (0.01)	0.31 (0.01)	0.16 (0.01)	0.14 (0.01)		0.36 (0.01)	0.14 (0.01)	0.14 (0.01)	0.31 (0.01)	0.34 (0.01)
Grandmother (M)	0.17 (0.01)	0.22 (0.01)	0.33 (0.01)	0.14 (0.01)	0.14 (0.01)	0.37 (0.01)		0.12 (0.01)	0.14 (0.01)	0.31 (0.01)	0.30 (0.01)
Aunt (P)	0.17 (0.01)	0.30 (0.01)	0.21 (0.01)	0.29 (0.01)	0.31 (0.01)	0.13 (0.01)	0.12 (0.01)		0.31 (0.01)	0.13 (0.01)	0.14 (0.01)
Uncle (P)	0.20 (0.00)	0.40 (0.01)	0.24 (0.01)	0.32 (0.01)	0.29 (0.01)	0.16 (0.01)	0.13 (0.01)	0.30 (0.01)		0.15 (0.01)	0.16 (0.01)
Aunt (M)	0.19 (0.01)	0.23 (0.01)	0.35 (0.01)	0.13 (0.01)	0.13 (0.01)	0.30 (0.01)	0.31 (0.01)	0.11 (0.01)	0.16 (0.02)		0.30 (0.01)
Uncle (M)	0.22 (0.00)	0.25 (0.01)	0.31 (0.01)	0.14 (0.01)	0.11 (0.01)	0.35 (0.01)	0.29 (0.01)	0.12 (0.01)	0.16 (0.01)	0.31 (0.01)	

TABLE 3

Tetrachoric correlations and standard errors of resemblance for registration for alcohol use disorder in male and female probands (below and above the diagonal, respectively) and their parents, grandparents, aunts, and uncles

	Proband	Father	Mother	Grandfather (P)	Grandmother (P)	Grandfather (M)	Grandmother (M)	Aunt (P)	Uncle (P)	Aunt (M)	Uncle (M)
Proband		0.23 (0.01)	0.24 (0.01)	0.09 (0.01)	0.12 (0.01)	0.12 (0.01)	0.11 (0.01)	0.07 (0.01)	0.12 (0.01)	0.10 (0.01)	0.10 (0.01)
Father	0.28 (0.01)		0.32 (0.01)	0.27 (0.01)	0.24 (0.02)	0.13 (0.01)	0.14 (0.01)	0.25 (0.01)	0.30 (0.01)	0.14 (0.01)	0.14 (0.01)
Mother	0.27 (0.01)	0.32 (0.01)		0.11 (0.01)	0.12 (0.01)	0.24 (0.01)	0.28 (0.01)	0.11 (0.01)	0.11 (0.01)	0.29 (0.01)	0.25 (0.01)
Grandfather (P)	0.13 (0.01)	0.26 (0.01)	0.12 (0.01)		0.31 (0.01)	0.10 (0.01)	0.10 (0.01)	0.24 (0.01)	0.26 (0.01)	0.07 (0.01)	0.07 (0.01)
Grandmother (P)	0.11 (0.02)	0.24 (0.01)	0.10 (0.02)	0.31 (0.01)		0.08 (0.01)	0.10 (0.01)	0.27 (0.01)	0.24 (0.01)	0.06 (0.02)	0.05 (0.02)
Grandfather (M)	0.13 (0.01)	0.14 (0.01)	0.25 (0.01)	0.09 (0.01)	0.09 (0.01)		0.31 (0.01)	0.05 (0.01)	0.06 (0.01)	0.22 (0.01)	0.26 (0.01)
Grandmother (M)	0.14 (0.02)	0.14 (0.01)	0.28 (0.01)	0.10 (0.01)	0.10 (0.01)	0.32 (0.01)		0.06 (0.01)	0.06 (0.01)	0.27 (0.01)	0.27 (0.01)
Aunt (P)	0.12 (0.01)	0.24 (0.01)	0.13 (0.01)	0.25 (0.01)	0.27 (0.01)	0.06 (0.01)	0.06 (0.01)		0.23 (0.01)	0.04 (0.02)	0.05 (0.01)
Uncle (P)	0.13 (0.01)	0.30 (0.01)	0.11 (0.01)	0.25 (0.01)	0.24 (0.01)	0.08 (0.01)	0.06 (0.01)	0.23 (0.01)		0.07 (0.01)	0.08 (0.02)
Aunt (M)	0.14 (0.01)	0.14 (0.01)	0.30 (0.01)	0.08 (0.01)	0.08 (0.01)	0.24 (0.01)	0.27 (0.01)	0.07 (0.02)	0.07 (0.01)		0.25 (0.01)
Uncle (M)	0.15 (0.01)	0.14 (0.01)	0.27 (0.01)	0.07 (0.01)	0.07 (0.01)	0.27 (0.01)	0.24 (0.01)	0.06 (0.01)	0.07 (0.01)	0.26 (0.01)	

TABLE 4

Tetrachoric correlations and standard errors of resemblance for registration for drug abuse (DA) in male and female probands (below and above the diagonal, respectively) and their parents, grandparents, aunts, and uncles

	Proband	Father	Mother	Grandfather (P)	Grandmother (P)	Grandfather (M)	Grandmother (M)	Aunt (P)	Uncle (P)	Aunt (M)	Uncle (M)
Proband		0.33 (0.01)	0.36 (0.01)	0.13 (0.02)	0.10 (0.02)	0.11 (0.02)	0.13 (0.01)	0.14 (0.01)	0.17 (0.01)	0.16 (0.01)	0.17 (0.01)
Father	0.37 (0.01)		0.48 (0.01)	0.25 (0.01)	0.25 (0.01)	0.16 (0.01)	0.16 (0.01)	0.29 (0.01)	0.44 (0.01)	0.23 (0.01)	0.24 (0.01)
Mother	0.33 (0.01)	0.48 (0.01)		0.11 (0.02)	0.15 (0.02)	0.23 (0.01)	0.30 (0.01)	0.17 (0.02)	0.22 (0.01)	0.35 (0.01)	0.31 (0.01)
Grandfather (P)	0.11 (0.01)	0.25 (0.01)	0.11 (0.02)		0.23 (0.02)	0.04 (0.03)	0.11 (0.03)	0.21 (0.02)	0.28 (0.02)	0.09 (0.03)	0.03 (0.03)
Grandmother (P)	0.09 (0.01)	0.21 (0.01)	0.13 (0.02)	0.21 (0.02)		0.09 (0.03)	0.11 (0.02)	0.28 (0.02)	0.26 (0.02)	0.09 (0.02)	0.07 (0.02)
Grandfather (M)	0.11 (0.01)	0.19 (0.01)	0.23 (0.01)	0.07 (0.03)	0.07 (0.03)		0.23 (0.02)	0.05 (0.03)	0.08 (0.02)	0.26 (0.02)	0.26 (0.02)
Grandmother (M)	0.12 (0.01)	0.19 (0.01)	0.28 (0.01)	0.04 (0.03)	0.05 (0.02)	0.24 (0.02)		0.06 (0.02)	0.09 (0.02)	0.28 (0.02)	0.21 (0.02)
Aunt (P)	0.14 (0.01)	0.30 (0.01)	0.18 (0.01)	0.22 (0.02)	0.29 (0.02)	0.12 (0.02)	0.05 (0.02)		0.31 (0.02)	0.07 (0.03)	0.11 (0.02)
Uncle (P)	0.22 (0.01)	0.43 (0.01)	0.25 (0.01)	0.25 (0.02)	0.25 (0.02)	0.11 (0.02)	0.07 (0.02)	0.32 (0.02)		0.12 (0.02)	0.16 (0.02)
Aunt (M)	0.18 (0.01)	0.24 (0.01)	0.37 (0.01)	0.06 (0.03)	0.06 (0.03)	0.26 (0.02)	0.29 (0.02)	0.10 (0.02)	0.10 (0.02)		0.31 (0.02)
Uncle (M)	0.21 (0.01)	0.24 (0.01)	0.32 (0.01)	0.09 (0.02)	0.08 (0.02)	0.29 (0.02)	0.22 (0.02)	0.11 (0.02)	0.16 (0.02)	0.33 (0.01)	

TABLE 5

Tetrachoric correlations for criminal behavior (CB), alcohol use disorder (AUD), and drug abuse (DA) in four groups of relatives and the offspring generation

Degree of relationship	Tetrachoric correlations (SEs) ORs (95% CIs)		
	Criminal behavior	Alcohol use disorder	Drug abuse
Parents			
1st	0.308 (0.304; 0.312)	0.259 (0.252; 0.266)	0.339 (0.332; 0.346)
Aunts/uncles			
2nd	0.183 (0.178; 0.187)	0.121 (0.113; 0.129)	0.180 (0.173; 0.188)
Grandparents			
2nd	0.163 (0.158; 0.167)	0.120 (0.113; 0.126)	0.110 (0.101; 0.119)
Great aunts/uncles			
3rd	0.091 (0.083; 0.098)	0.055 (0.044; 0.066)	0.084 (0.071; 0.098)

TABLE 6

Mean tetrachoric correlations between the proband and male and female relatives for criminal behavior (CB), alcohol use disorder (AUD), and drug abuse (DA)^a

Syndrome	Mean correlation (95% CIs)			Difference between correlations			
	Female to female transmission	Male to male transmission	Cross-Sex transmission expected	Cross-sex transmission observed	F–F vs. M–M	F–F vs. CS	M–M vs. CS
Criminal Bbehavior	0.202 (0.196; 0.209)	0.253 (0.249; 0.257)	0.226	0.213 (0.210; 0.217)	<0.0001	0.003	<0.0001
Alcohol use disorder	0.152 (0.141; 0.162)	0.184 (0.177; 0.191)	0.167	0.161 (0.154; 0.167)	<0.0001	0.162	<0.0001
Drug abuse	0.241 (0.231; 0.252)	0.270 (0.262; 0.277)	0.255	0.227 (0.221; 0.234)	<0.0001	0.025	<0.0001

^aIncludes parents, grandparents, and aunts/uncles.

TABLE 7

Risk for criminal behavior (CB), alcohol use disorder (AUD), and drug abuse (DA) in probands as a function of the affection status of grandparents and parents

Status	Parent status	Grand-parents	Intervening parent	% in proband	Odds ratio (95% CI)	Grand-parents	Intervening parent	% in proband	Odds ratio (95% CI)
Grandfather-Grandmother									
No CB	No CB	Paternal	Father	7.1	Ref	Maternal	Mother	8.2	Ref
CB	CB			16.9	2.67 (2.62; 2.73)			21.1	2.99 (2.90; 3.08)
CB	No CB			10.0	1.47 (1.41; 1.53)			13.0	1.68 (1.63; 1.72)
CB	CB			21.9	3.71 (3.58; 3.84)			29.0	4.58 (4.38; 4.78)
Grandfather-Grandmother									
No AUD	No AUD	Paternal	Father	2.1	Ref	Maternal	Mother	2.2	Ref
AUD	AUD			5.9	2.99 (2.85; 3.14)			6.9	3.30 (3.09; 3.52)
AUD	No AU			3.2	1.56 (1.47; 1.65)			3.6	1.68 (1.60; 1.77)
AUD	AUD			8.0	4.12 (3.80; 4.47)			9.5	4.72 (4.28; 5.20)
Grandfather-Grandmother									
No DA	No DA	Paternal	Father	4.8	Ref	Maternal	Mother	5.1	Ref
DA	DA			19.4	4.74 (4.54; 4.94)			19.6	4.55 (4.35; 4.76)
DA	No DA			7.1	1.50 (1.37; 1.64)			8.3	1.69 (1.57; 1.82)
DA	DA			25.4	6.70 (5.71; 7.86)			24.3	5.98 (5.11; 6.99)

Risk for criminal behavior (CB), alcohol use disorder (AUD), and drug abuse (DA) in probands as a function of the affection status of uncles/aunts and parents

TABLE 8

Status	Parent Status	Aunt/Uncle	Intervening Parent	% in Proband	Odds Ratio (95% CI)	Aunt/Uncle	Intervening parent	% in proband	Odds ratio (95% CI)
Aunt-Uncle									
No CB	No CB	Paternal	Father	7.0	Ref	Maternal	Mother	8.0	Ref
	CB			16.1	2.54 (2.45; 2.64)			18.9	2.69 (2.53; 2.86)
CB	No CB			9.8	1.44 (1.38; 1.50)			12.8	1.69 (1.64; 1.75)
	CB			21.9	3.71 (3.57; 3.86)			29.0	4.74 (4.50; 5.00)
Aunt-Uncle									
No AUD	No AUD	Paternal	Father	2.1	Ref	Maternal	Mother	2.3	Ref
	AUD			6.1	3.04 (2.81; 3.28)			7.2	3.32 (2.98; 3.70)
AUD	No AUD			3.4	1.64 (1.51; 1.78)			3.7	1.64 (1.52; 1.77)
	AUD			7.7	3.94 (3.52; 4.42)			9.9	4.72 (4.07; 5.47)
Aunt-Uncle									
No DA	No DA	Paternal	Father	4.8	Ref	Maternal	Mother	5.0	Ref
	DA			18.6	4.53 (4.21; 4.87)			18.3	4.26 (3.91; 4.64)
DA	No DA			9.0	1.96 (1.82; 2.11)			9.7	2.04 (1.91; 2.18)
	DA			26.3	7.02 (6.21; 7.93)			28.0	7.40 (6.42; 8.52)