HHS Public Access

Author manuscript

Behav Genet. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

Behav Genet. 2016 November ; 46(6): 735–741. doi:10.1007/s10519-016-9801-7.

A Bivariate Genetic Analysis of Drug Abuse ascertained through medical and criminal registries in Swedish Twins, Siblings and Half-Siblings

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Abstract

Objective—Using Swedish nationwide registry data, the authors investigated the correlation of genetic and environmental risk factors in the etiology of drug abuse as ascertained from medical and criminal registries by modeling twin and sibling data.

Methods—Medical drug abuse was defined using public inpatient and outpatient records, while criminal drug abuse was ascertained through legal records. Twin, full and half sibling pairs were obtained from the national twin and genealogical registers. Information about sibling pair residence within the same household was obtained from Statistics Sweden. Standard bivariate genetic structural equation modeling was applied to the population-based data on drug abuse ascertained through medical and crime registries, using OpenMx.

Results—Analyses of all possible pairs of twins (MZ: N=4,482; DZ: N=9,838 pairs), full- (N=1,278,086) and half-siblings (paternal: N=7,767; maternal N=70,553) who grew up together suggested that factors explaining familial resemblance for drug abuse as defined through medical or criminal registries were mostly the same. Results showed substantial heritability and moderate contributions of shared environmental factors to drug abuse; both were higher in males versus females, and higher for drug abuse ascertained through criminal than medical records. Because of the low prevalence of both assessments of drug abuse, having access to population data was crucial to obtain stable estimates.

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Conclusions—Using objective registry data, the authors found that drug abuse - whether ascertained through medical versus criminal records - was highly heritable. Furthermore, shared environmental factors contributed significantly to the liability of drug abuse. Genetic and shared environmental risk factors for these two forms of drug abuse were highly correlated.

Keywords

drug abuse; twins; siblings and half-siblings

INTRODUCTION

Drug abuse (DA) remains a serious public health problem. According to the 2014 World Drug Report of the United Nations Office on Drugs and Crime, between 3.5 and 7% of the world's population aged 15 to 64 used an illicit drug in 2012. Approximately 0.6% of the population can be categorized as problem drug users (1). In the US, the lifetime prevalence of drug use disorder (drug abuse or dependence) has been estimated at 10.3% (2). In Sweden, 9% of high school students report lifetime use of cannabis and 4% of other illicit drugs (3), while in neighboring Norway, the lifetime prevalence of drug abuse and dependence is 4.4% (4). DA is associated with significant impairment across the lifespan, both in terms of poor family functioning, lost productivity and increased morbidity and mortality (5–7).

Twin and adoption population-based studies have consistently shown a significant genetic component to DA liability (8, 9)(8, 9), with a more modest shared environmental contribution. We have been studying DA in Sweden with cases ascertained through medical, criminal, and to a lesser extent, prescription drug registries. Registration for DA from these various sources is substantially but imperfectly correlated (8). Using twin and sibling data, we found that heritability estimates for DA were similar to those from prior twin studies that utilized personal interviews (10). These results, and other studies of DA from the Swedish registry (8, 11, 12), implicitly assumed that risk factors for DA ascertained through medical and criminal records are highly similar. In this paper, we test the validity of that assumption.

Our aims are to evaluate whether the genetic and environmental risk factors for DA ascertained through medical or criminal records are quantitatively similar (i.e., whether the estimates of heritability are nearly the same) and qualitatively similar (i.e., do the same genetic or environmental factors contribute to both). We also examine these questions separately in males and females.

METHODS

Subjects

The phenotypic data analyzed here were generated through linking comprehensive register and health care data from multiple nationwide Swedish sources using the unique individual Swedish 10-digit personal identification number assigned at birth for all residents. Details of the databases and descriptions of the populations are in the data supplement to the online edition of this article. Pairs of monozygotic (MZ) and dizygotic (DZ) twins, full siblings

(FS) and half siblings, both maternal (MH) and paternal (PH), were included if their age difference was <10 years and if they had cohabited for at least 10 years prior to age 16. To avoid substantial right or left censoring, we excluded all sibling/twin pairs in which: 1) one or both siblings/twins in the pair was born before 1950 or after 1993; 2) one or both siblings/twins had died before 1973; and 3) one or both siblings/twins died before the age of 15. Zygosity in the twin registry was assigned using standard self-report items from mailed questionnaires which, when validated against biological markers, were 95–99% accurate.

Measures

For the purposes of this report, we focused on DA as ascertained from in-patient or out-patient medical registries (DAM), and DA as ascertained from the crime registry (DAC). As relatively few cases were ascertained from other registries, we were not able to include those in our analyses. DAM was identified in the Swedish medical registries by ICD codes (ICD8: Drug dependence (304); ICD9: Drug psychoses (292) and Drug dependence (304); ICD10: Mental and behavioral disorders due to psychoactive substance use (F10–F19), except those due to alcohol (F10) or tobacco (F17)). DAC was identified through the Suspicion register by codes 3070, 5010, 5011, and 5012, which reflect crimes related to DA; and 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).

Statistical Analyses

Structural equation modeling was used to model the contributions of genetic and environmental factors to the liability of DA, assuming an underlying threshold model (13). Based on our results from previous univariate analyses (Kendler et al. 2014), we tested models including additive genetic (A), shared (C) and unique (E) environmental factors, as estimates of the special twin environment were not statistically significant. Shared (or between-family) environmental effects make family members relatively more similar, whereas unique (or within-family) environmental factors are specific to individuals within a family and contribute to differences between family members. A correlated factors model was used to estimate how much of the genetic and environmental factors are shared or unique between the two types of assessment for DA. We tested both quantitative and qualitative sex differences in the sources of individual differences in DA. We started with a model ('hom') that constrained the A, C and E sources of variance to be equal across males and females. In a second model ('qn'), each of the three sources of (co)variance was estimated freely in both sexes, while constraining the correlations between the latent factors across sex (14, 15), which is a test of quantitative sex differences in proportions of variance. A third model allowed an additional sex-specific component for either males or females for either A and C, to test whether different genetic or shared environmental factors influence DA in males and females, which we refer to as qualitative sex differences. The estimates for the common and sex-specific genetic (or shared environmental) components can be used to estimate the correlations between the factors across males and females, typically referred to as rg (or rc). Even though we potentially have information from multiple comparisons of same-sex and opposite-sex pairs (DZ twins, full siblings, half siblings), we estimate the sex-specific component in alternative models (either estimating male sex-specific genetic (Ams,

model ‘qlAms’) or shared environmental (Cms, model ‘qlCms’) or female sex-specific genetic (Afs, model ‘qlAfs’) or shared environmental (Cfs, model ‘qlCfs’) factors). We then use likelihood ratio tests and Akaike’s Information Criterion to determine the best fitting model. In each of these models, we estimated separate thresholds for i) males and females, ii) same sex twins, iii) siblings and opposite sex twins, and iv) half siblings. As zygosity is required to model data of the same sex twins, inclusion of same sex twins required participation in the Swedish Twin Registry (16)(16) leading to reduced prevalence for DA, as observed in previous analyses, because DA was weakly and inversely associated with the probability of a twin returning the zygosity questionnaire (10).

The analyses were complicated due to the low prevalence of at least one of the two phenotypes (less than 1% of the population affected for DAM in males and both DAM and DAC in females) despite the large sample sizes due to the complete population-based nature of the data. A number of alternate strategies were employed to increase the confidence of the results. Due to the low prevalence of DA, some of the cells in the pairwise contingency tables for same sex DZ twin pairs had zero frequency. Thus, we opted to include full and half siblings in addition to twins to have additional information to identify genetic versus shared environmental sources of variance. As we have access to the population data, we included all possible pairs rather than performing a pedigree-like analysis to avoid computational issues dealing with multidimensional integration. However, this led to including over 5 million records in the analyses with twins, sibs and half sibs, which required special handling with respect to the precision of the optimization.[1] Finally, due to the instability of the results, we fitted a series of models with a range of acceptable starting values for the A and C parameters and selected the model with the lowest −2 log-likelihood as the best fitting model. Instead of using constraints to scale the variance of the binary phenotypes, we fixed the diagonal E parameters (to 1) and standardized the resulting parameter estimates. Constraints were however required for identification of the heterogeneity models. As a result, standard errors could not be calculated. A new optimizer, CSOLNP, was developed as part of the OpenMx open source project; it resulted in improvements in overall model fit as well as more stable solutions (Zahery et al. in preparation). Scripts for the analyses were written for OpenMx (17, 18) and are available upon request.

RESULTS

Descriptive Statistics

Table 1 shows sample sizes and lifetime prevalence rates by sex, type of relationship and separately for same sex and opposite sex pairs in Table 1. Note that the youngest cohorts – individuals born before 1993 – may not have passed completely through the risk period for DA. The total sample included 4,482 pairs of monozygotic twins (MZ), 9,838 pairs of dizygotic twins (DZ), 1,278,086 pairs of reared-together full siblings, 7,767 pairs of reared-together paternal half siblings and 70,553 pairs of reared-together maternal half siblings. The population prevalence for DAM ascertained from medical (in-patient and out-patient)

[1]We used the arguments mvnMaxPointsC=500000, mvnAbsEps=1e-5 and mvnRelEps=0 in mxOption

registries was 1.5% for males and 1.0% for females, representing 22,830 male and 14,427 female cases respectively. Correspondingly, the prevalence rates for DAC from criminal registries were 6.0% and 1.5% with 83,849 male and 17,998 female cases. Two trends are noteworthy. First, prevalence rates for ascertainment from medical sources were similar for males and females, while males were much more likely to be ascertained through crime registries than females. Second, rates for half-siblings appeared to be two to three times as large as those for twins and full siblings. Maximum likelihood estimates of correlations for the various relative types are presented in Table 2, separately for males, females, and opposite sex pairs. Within-person correlations for DAM and DAC ranged between .63 and .86 suggesting substantial phenotypic overlap. Of the twin/sibling correlations, those for same-sex DZ pairs appeared somewhat unstable, primarily due to the low prevalence of DAM. Since opposite-sex DZ correlations were similar to the corresponding opposite-sex full sibling (FS) correlations, we estimated correlations for DZ and FS pairs combined and MH and PH pairs combined. Within-trait MZ correlations were higher than within-trait DZ/FS correlations, which were higher than within-trait PH/MH correlations. Furthermore, DZ/FS correlations were greater than half the MZ correlations, and similarly PH/MH correlations were greater than half the corresponding DZ/FS correlations. Opposite-sex correlations were lower than both sets of same-sex correlations. These observations are broadly consistent with contributions of additive genetic and shared environmental factors, as well as potentially sex limitation. Cross-twin cross-trait correlations showed a similar pattern by relative type albeit somewhat lower, suggesting that primarily additive genetic and shared environmental contributions are shared between the two phenotypes.

Bivariate Genetic Analysis

Table 3 presents goodness-of-fit statistics from fitting standard bivariate ACE models to the binary DAM and DAC data. Parameter estimates are shown in table 4. When fitting models to data of twins, full siblings and half siblings, the gender heterogeneity tests showed significant qualitative and quantitative sex differences, suggesting that the different sources of variance contribute to DA in males and females with a different orders of magnitude. The best fitting sex limitation model included male-specific genetic factors, in addition to the gender-common genetic factors which were estimated separately for males and females. The variance component estimates for DAM in males were: additive genetic, 59%; shared environment 13%; and unique environmental influences including measurement error, 28%. For females these estimates were respectively 52%, 7% and 41%. For DAC, these estimates were, respectively, 66%, 20% and 15% for males and 59%, 15% and 26% for females. With respect to the etiological overlap (see table 4 also), we found that genetic factors were substantially shared between DAM and DAC in both males (62% for genetic factors in common with females, and 76% for male-specific genetic factors) and females (59%), whilst shared environmental factors were completely shared in both sexes and specific environmental were moderately shared (40% and 38% respectively for males and females). In addition to the quantitative sex differences in the proportions of variance and covariance, qualitative differences were observed such that genetic factors contributing to DAM and DAC only partly overlapped in males and females. Estimates of the genetic correlations across sex were .82 for DAM and .39 for DAC, suggesting that mostly the same genetic

factors contributed to DAM in males and females and that mostly different genetic factors contributed to DAC in both sexes.

Several results are noteworthy: the roles of genes and environment in DAM and DAC and the amount of overlap between them. The combined data yielded very similar estimates of heritability of DAM (59–66%) and DAC (52–59%); those for males (>~60%) were slightly higher than for females (>~55%). Estimates of shared environmental contributions were consistently lower than those of genetic factors. Furthermore, these C factors also explained a larger proportion of the variance for DAC (15–20%) than DAM (7–13%) and for males compared to females. Unique environmental contributions were substantially larger for DAM than DAC, and also for females compared to males. Turning to sharing of risk factors across DAM and DAC, these analyses suggested that most of the genetic (61–76%) and the shared environmental (100%) variance of DAC was shared with DAM, whilst the unique environmental factors (including measurement error) are primarily specific to source of ascertainment.

DISCUSSION

We set out to answer whether the same or different genetic and/or environmental risk factors contribute to DA as ascertained through medical and criminal registries in males and females. We draw five main conclusions from these analyses. First, the lifetime prevalence of drug abuse as ascertained from medical records was similar for males and females (1.5% versus 1%) whilst estimates based on criminal records indicated a four-fold higher prevalence for males compared to females (6% versus 1.5%) for DA.

Second, estimates of heritability from analyses including twins, sibs, and half sibs were .59 for DAM and .66 for DAC in males. Corresponding estimates for females were .52 for DAM and .59 for DAC. These estimates are mostly consistent with those from twin analyses of DA ascertained from either medical, criminal or prescription drug registries (10), primarily with respect to the relative magnitude of the genetic and environmental influences. Of note is the slightly higher heritability estimates for DAC than DAM.

Third, estimates for the role of shared environmental factors from the current analyses are broadly consistent with those from the previous twin analysis, and these factors accounted for a moderate proportion of variance. Based on the most complete analysis including twins, sibs and half sibs, shared environmental factors contributed a greater proportion of the variance for DAC compared to DAM (.20 versus .13 in males, .15 versus .07 in females), and also for males compared to females. Noteworthy is that the current estimates are smaller than those from the previous twin analysis (10) in males but larger than those in females. Consistent with our hypotheses, shared environmental factors explained a greater amount of variance for DAC than DAM. However, contrary to our hypothesis regarding heritability, genetic factors also explained a greater amount of variance for DAC than DAM. This appears to be primarily due to a larger proportion of the variance in liability to DAM accounted for by specific environmental factors, which include measurement error.

Fourth, concerning the main aim of the paper regarding the overlap of genetic and environmental factors contributing to variance in DAM and DAC, factors accounting for familial resemblance (A & C) were predominantly shared between DAM and DAC. Less than half of the variance accounted for by specific environmental factors was shared across the two assessments of DA. Again, based on the analysis of the full twin/sibling sample, it appears that the same shared environmental factors contribute to DAM and DAC, while more than half of the genetic factors that contribute to DAM also influence DAC. Given the substantial overlap of both genetic and shared environmental risk factors for DAM and DAC, analyses using a combined measure may be valid.

Fifth, results are somewhat inconsistent with respect to sex differences. In prior twin analyses, heritability estimates for DA in males were lower than those for females whilst in the current analyses, heritability estimates of both DAM and DAC were higher for males than for females. This might be a result of having greater power to detect shared environmental influences in females with the inclusion of large samples of siblings. Sex differences were also noted in the overlap of risk factors for DAM and DAC, with results from twin/sibling analyses showing significant qualitative sex differences. The genetic correlation across sex was higher for DAM than for DAC.

In summary, this study showed substantial heritability for liability to drug abuse, as ascertained through medical or criminal records, as well as a moderate shared environmental contribution. Genetic and shared environmental risk factors for both forms of drug abuse appear to be primarily shared.

Limitations

This study should be interpreted in the context of at least four potential limitations. First, we have found that the degree of familial resemblance in siblings and half siblings changes as a function of the age difference between the siblings or half siblings and the years lived together prior to age 16 for twins, siblings and half-siblings (10, 19). We did not take these factors into account due to the low prevalence of the two phenotypes and resulting issues with optimization. Second, these same optimization issues, together with the variable sibship sizes, made it impractical to obtain confidence intervals for the parameter estimates. However, given that we are using complete population data, the precision of the estimates cannot be improved. Third, even though other Swedish registries, such as the prescription registry, contain data on drug abuse, the time frame during which those data are available is different from those of the medical and crime registries, which prevented their inclusion in the current analyses. We note also that inpatient and outpatient medical databases had to be combined to obtain manageable prevalence rates for drug abuse ascertained through medical records. Finally, it was a feature of this population that rates of DA were considerably higher in half-siblings than in full-siblings. Preliminary analyses (details not reported here) suggest that this likely arises because externalizing disorders like DA are considerably more common in the biological parents of half- than of full-siblings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: National Institutes of Health (DA030005, DA025109, DA018673, DA024304). Competing interests: none. All authors reviewed and approved the final manuscript before its submission.

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Appendix 1: Prevalence rates for DAM & DAC in twins, full and half siblings

	DAM (Medical)			DAC (Crime)		
	0	**1**	**prevalence**	**0**	**1**	**prevalence**
same sex KZ	15252	120	0.0078	15099	273	0.0178
same sex UZ	16699	203	0.0120	16229	673	0.0398
same sex	31951	323	0.0100	31328	946	0.0293
opposite sex	13112	156	0.0118	12866	402	0.0303
same sex UZ + OS	29811	359	0.0119	29095	1075	0.0356
ALL TWINS	45063	479	0.0105	44194	1348	0.0296
sibs of twins	16283	221	0.0134	15982	522	0.0316
full sibs	1757649	21568	0.0121	1719843	59374	0.0334
ALL SIBS	1773932	21789	0.0121	1735825	59896	0.0334
half sibs paternal	14982	472	0.0305	14351	1103	0.0714
half sibs maternal	130496	4498	0.0333	125274	9720	0.0720
ALL HALFSIBS	145478	4970	0.0330	139625	10823	0.0719
ALL	1964473	27238	0.0137	1919644	72067	0.0362

Table 1

Estimates of lifetime prevalence of drug abuse ascertained from medical (DAM) and criminal (DAC) records, by sex and same-sex versus opposite-sex status and relationship type

	N pairs	Diagnosed with DAM N (%)	Diagnosed with DAC N (%)	N pairs	Diagnosed with DAM N (%)	Diagnosed with DAC N (%)
	males			**females**		
MZ	2048	26 (0.6)	121 (3.0)	2434	44 (0.9)	40 (0.8)
DZ	1547	23 (0.7)	94 (3.1)	1657	27 (0.8)	18 (0.5)
FS	337915	9907 (1.5)	38342 (6.0)	301601	5889 (1.0)	7287 (1.2)
HP	2222	166 (3.9)	483 (12.2)	1593	69 (2.2)	97 (3.1)
HM	17808	1460 (4.3)	4067 (12.9)	17175	920 (2.8)	1088 (3.3)
	males in opposite sex pairs			**females in opposite sex pairs**		
DZ	6634	93 (1.4)	321 (5.1)	6634	63 (1.0)	81 (1.2)
FS	638570	9514 (1.5)	35956 (6.0)	638570	6342 (1.0)	8053 (1.3)
HP	3952	148 (3.9)	420 (11.9)	3952	98 (2.5)	119 (3.1)
HM	35570	1493 (4.4)	4045 (12.8)	35570	975 (2.8)	1215 (3.5)

MZ: monozygotic twins, DZ: dizygotic twins, FS: full siblings, HP: paternal half-siblings, HM: maternal half-siblings

Table 2

Maximum Likelihood Correlations (and standard errors) by drug abuse ascertained from medical (DAM) and criminal (DAC) records, by sex and relationship type.

		MZ	DZ/FS	PH/MH
males	**DAM1-DAC1**	0.86 (0.06)	0.78 (0.00)	0.78 (0.01)
	DAM2-DAC2	0.63 (0.10)	0.79 (0.00)	0.80 (0.01)
	DAM1-DAM2	0.69 (0.12)	0.43 (0.01)	0.27 (0.03)
	DAC1-DAC2	0.85 (0.04)	0.53 (0.00)	0.35 (0.02)
	DAM1-DAC2	0.67 (0.10)	0.40 (0.01)	0.26 (0.02)
	DAC1-DAM2	0.62 (0.10)	0.42 (0.01)	0.26 (0.02)
females	**DAM1-DAC1**	0.81 (0.06)	0.73 (0.01)	0.75 (0.02)
	DAM2-DAC2	0.63 (0.13)	0.73 (0.01)	0.75 (0.02)
	DAM1-DAM2	0.53 (0.13)	0.34 (0.01)	0.24 (0.04)
	DAC1-DAC2	0.77 (0.08)	0.45 (0.01)	0.31 (0.03)
	DAM1-DAC2	0.58 (0.13)	0.31 (0.01)	0.22 (0.04)
	DAC1-DAM2	0.42 (0.15)	0.33 (0.01)	0.22 (0.04)
opposite sex	**DAM1-DAC1**		0.78 (0.00)	0.80 (0.01)
	DAM2-DAC2		0.74 (0.00)	0.77 (0.01)
	DAM1-DAM2		0.31 (0.01)	0.18 (0.02)
	DAC1-DAC2		0.35 (0.01)	0.27 (0.02)
	DAM1-DAC2		0.32 (0.01)	0.21 (0.02)
	DAC1-DAM2		0.25 (0.01)	0.21 (0.02)

Table 3

Goodness-of-fit statistics for bivariate heterogeneity models fitted to drug abuse ascertained from medical (DAM) and criminal (DAC) records, in designs including twins, full siblings and half siblings.

model	os	ns	ep	df	−2ll	AIC
hom	5482904	1370726	19	5482885	1097748.2	−9868021.8
qn	5482907	1370726	26	5482881	1096939.8	−9868822.2
qlAms	5482907	1370726	29	5482878	1096890.7	**−9868865.3**
qlAfs	5482907	1370726	29	5482878	1096918.0	−9868838.0
qlCms	5482907	1370726	29	5482878	1096909.8	−9868846.3
qlCfs	5482907	1370726	29	5482878	1096912.7	−9868843.4

os: number of observed statistics; ns: number of pairs; ep: number of estimated parameters; df: degrees of freedom; −2ll: minus twice the log-likelihood of the data; AIC: Akaike's Information Criterion
hom: homogeneity model: no qualitative or quantitative sex differences in ACE sources of variance; qn: quantitative sex differences in ACE sources of variance; ql: qualitative and quantitative sex differences in ACE sources of variance, with either sex-specific genetic factors in males (Ams) or females (Afs), or sex-specific shared environmental factors in males (Cms) or females (Cfs)

Table 4

Estimates of proportions of variance and covariance accounted for by additive genetic, shared and unique environmental sources for drug abuse ascertained from medical (DAM) and criminal (DAC) records, in designs including twins, full siblings and half siblings.

	Amc+Ams=Am	Cm	Em	Af	Cf	Ef	rgmf
DAM	0.35+0.24 = 0.59	0.13	0.28	0.52	0.07	0.41	0.82
DAC	0.21+0.45 = 0.66	0.20	0.15	0.59	0.15	0.26	0.39
DAM-DAC covariance	0.62/0.76	1.00	0.40	0.61	1.00	0.38	

Amc: gender-common additive genetic contributon in males; Ams: male-specific additive genetic contribution, Am: additive genetic contribution in males, Af: additive genetic contribution in females, Cm: shared environmental contribution in males, Cf: shared environmental contribution in females, Em: unique environmental contribution in males, Ef: unique environmental contribution in females, rgmf: genetic correlation across males and females