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Illicit psychoactive substance use, abuse and dependence in a population-based sample of Norwegian twins

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Abstract

Background—Prior population-based twin studies from two Anglophonic countries with relatively high rates of drug use – the USA and Australia – suggest that genetic factors contribute substantially to individual differences in the use, abuse and dependence of illicit psychoactive substances. Would these results replicate in Norway, a Nordic country with a low prevalence of illicit drug use?

Method—Lifetime use, abuse and dependence of five illicit drug categories (cannabis, stimulants, opiates, cocaine and psychedelics) were assessed at personal interview in 1386 complete young adult twin pairs ascertained from the Norwegian Institute of Public Health Twin Panel. Twin model fitting was performed using the Mx statistical package on three phenotypes: any lifetime use, endorsement of at least one DSM-IV symptom of abuse or dependence, and meeting DSM-IV criteria for abuse or dependence.

Results—Significant lifetime use of illicit substances (defined as use 10 or more times) was reported by only 6.4% of the sample. Meaningful analyses were possible for use of any substance and each of the five substances individually, but for symptoms or a diagnosis of abuse/dependence meaningful analyses were possible only for any substance and cannabis. Full twin models uniformly found twin resemblance to be due largely or entirely to genetic factors. Best-fit models for all analyses included only genetic and individual-specific environmental effects with heritability estimates ranging from 58% to 81%.

Conclusion—In accord with prior results from the USA and Australia, genetic factors appear to play an important role in the etiology of use and abuse/dependence of illicit drugs in Norway.

INTRODUCTION

Illicit psychoactive substance use, abuse and dependence are major public health problems. Understanding the sources of differences in risk is important in helping to develop effective approaches to prevention and treatment. Substantial evidence suggests that the liability to psychoactive substance use disorder (PSUD) aggregates in families (Rounsaville *et al*.

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DECLARATION OF INTEREST
None.

1991;Bierut *et al*. 1998;Merikangas *et al*. 1998). Both twin (Grove *et al*. 1990;Tsuang *et al*. 1996;Kendler & Prescott, 1998;van den Bree *et al*. 1998;Kendler *et al*. 2000*a*) and adoption studies (Cadoret *et al*. 1986,1995,1996) suggest that part of this familial aggregation results from genetic factors.

One of the most valuable sources of information about individual differences in liability to PSUD has been population-based twin studies, which allow the study of drug use and misuse independent of treatment history. However, all population-based twin studies of PSUD to date have been performed in either the USA (Tsuang *et al*. 1996;Kendler & Prescott, 1998;Kendler *et al*. 2000*a*) or Australia (Lynskey *et al*. 2002) – two countries with relatively high rates of illicit drug use. Given the wide cultural differences in attitude toward drug use and substantial variation in drug availability between countries, it is important to determine whether the findings from twin studies of PSUD would differ in countries with rates of drug use differing from those seen in the USA and Australia. For example, several different predictions are possible about the association between the availability of illicit drugs – reflected by the prevalence of their use – and the heritability of drug use (see below; Kendler *et al*. 2005). In this report, we examine illicit drug use and misuse in a population-based sample of personally interviewed twins from Norway, a country with relatively low levels of drug use and abuse/dependence (Kringlen *et al*. 2001).

METHOD

Sample and assessment

Data for these analyses come from the Norwegian Institute of Public Health Twin Panel (NIPHTP; Harris *et al*. 2002). Twins were identified through information contained in the Norwegian National Medical Birth Registry, established 1 January 1967, which receives mandatory notification of all live births. The current panel includes 15 370 like- and unlike-sexed twins born from 1967 to 1979. Thus far, two questionnaire studies have been conducted: one in 1992 (twins born 1967–1974) and another in 1998 (twins born 1967–1979). Altogether, 12 700 twins received the second questionnaire, and 8045 responded after one reminder (response rate 63%). The sample included 3334 pairs and 1377 single responders.

Data for the present report derive from an interview study of axis I and axis II psychiatric disorders begun in 1999. Participants were recruited among 3153 complete pairs who, in the second questionnaire, agreed to participate in the interview study, and 68 pairs who were drawn directly from the NIPHTP. Of these 3221 eligible pairs, 0.8% were unwilling or unable to participate, and in 16.2% of pairs only one twin agreed to the interview. After two contacts requesting participation, 38.2% did not respond. The reasons for non-cooperation were largely absence of response, with much smaller percentages due to unknown address or refusal. Approval was received from The Norwegian Data Inspectorate and the Regional Ethical Committee, and written informed consent was obtained from all participants after complete description of the study. Altogether, 2801 twins (44% of those eligible) were interviewed.

The data for this report came from the Norwegian version of the computerized Munich-Composite International Diagnostic Interview (M-CIDI; Wittchen & Pfister, 1997), a comprehensive structured interview for the assessment of DSM-IV axis I diagnoses (APA, 1994) and ICD-10 diagnoses. The CIDI was initially developed by the World Health Organization (WHO) and the former United States Alcohol, Drug Abuse and Mental Health Administration, and has been shown to have good test–retest and inter-rater reliability (Wittchen, 1994;Wittchen *et al*. 1998;Rubio-Stipec *et al*. 1999). Both the paper-and-pencil version of CIDI and the computerized version identical to the one we used in this investigation have been used for previous studies in Norway (Kringlen *et al*. 2001;Landheim *et al*. 2003).

Interviewers were mostly psychology students in the final part of their studies and psychiatric nurses. They were trained in a standardized program by teachers certified by the WHO and were supervised closely during data collection. Interviews were carried out between June 1999 and May 2004, and were largely conducted face to face. For practical reasons, 231 interviews (8.3%) were conducted over the telephone. Each twin in a pair was interviewed by different interviewers.

DSM-IV (APA, 1994) diagnoses were generated automatically by the data program and stored in a data file. Responses relating to individual DSM-IV criteria were also stored for analyses. Of those interviewed, 36.5% were male and the mean (S.D.) age was 28.2 (3.9).

Zygosity diagnosis

Zygosity was initially determined by questionnaire items that previously have been shown to categorize correctly more than 97% of the cases in another Norwegian twin cohort (Harris *et al*. 2002). Twenty-four microsatellite markers were then genotyped on a subsample of 676 of the 1061 like-sex pairs in the sample. Results from these markers were used as dependent variables in a discriminant analysis with the above-mentioned questionnaire items as independent variables. Seventeen of the 676 pairs with DNA information (2.51%) were found to be misclassified by the questionnaire data and were corrected. Thus, the total number of expected misclassified pairs could be estimated as 2.51% of the 385 unlike-sex pairs with only questionnaire-based zygosity, that is 9.7 pairs. This figure corresponds to a misclassification ratio of 0.69% for the total sample, including unlike-sex twins.

Statistical methods

We use a standard liability-threshold model to estimate the genetic and environmental contributions to twin resemblance for substance use and PSUD. For a categorical characteristic, such as lifetime use, resemblance in twin pairs is assessed by a tetrachoric correlation (or correlation in liability) (Falconer, 1965). Liability is assumed to be continuous and normally distributed in the population, with individuals who exceed a theoretical threshold expressing the disorder.

Individual differences in liability are assumed to arise from three sources: additive genetic (‘A’), that is from genes whose allelic effects combine additively; common environment (‘C’), which includes all sources shared by members of a twin pair, including family environment, social class and schools; and specific environment (‘E’), which includes all remaining environmental factors not shared within a twin pair plus measurement error. Monozygotic (MZ) twins within a pair resemble one another because they share all of their A and C components, while dizygotic (DZ) pairs share (on average) half of their A and all of their C. While it is possible to include non-additive genetic effects such as dominance or epistasis, they are not considered here because they have not been implicated in prior studies of PSUD and our power to detect such effects is very low (Neale *et al*. 1994).

Model fitting was performed with using the Mx statistical package (Neale *et al*. 1999). Alternative models are evaluated by comparing the difference in their χ^2 values relative to the difference in their degrees of freedom (df). According to the principle of parsimony, models with fewer parameters are preferable if they do not provide a significantly worse fit. We operationalize the optimal balance between goodness of fit and parsimony by using Akaike’s information criterion (AIC; Akaike, 1987), calculated as: χ^2–2 df.

Traditional twin models assume that MZ and DZ twins are equally correlated in their exposure to trait-relevant environments. We tested the validity of this ‘equal environment assumption’ by constructing two variables that reflected, respectively, similarity of childhood and adult

environments. The similarity of childhood environment was indexed by two items that assessed the years that the twins were in the same class at school and the years the twins lived in the same residence. The similarity of adult environment was indexed by three items that inquired about the frequency of in-person and telephone contact during the past year and the distance between their current residences. Using logistic regression, we tested the equal environment assumption by predicting twin concordance from the mean of the twins' report on environmental similarity controlling for zygosity.

RESULTS

Usable information on psychoactive substance use, abuse and dependence was available for both members of 1386 pairs and 11 single twins. The zygosity distribution of the complete pairs was: 220 male–male MZ, 117 male–male DZ, 448 female–female MZ, 263 female–female DZ and 338 male–female DZ.

We attempted to predict twin concordance for the 10 traits depicted in Table 1 from our measures of childhood and adult environmental similarity. Of these 20 tests, three were significant at the 5% level, a pattern that does not differ significantly from chance expectation (Feild & Armenakis, 1974). These results are consistent with prior studies of the equal environment assumption in studies of PSUD (Kendler & Prescott, 1998;Kendler *et al*. 2000*a*;Lynskey *et al*. 2002).

Entry criteria for the CIDI PSUD section required lifetime use of illicit substances 10 or more times – which we term 'significant use'. Thus, all of our results presented here are among individuals who screened positive for significant use. Table 1 shows that significant use of illicit substances was relatively uncommon, being reported by only 6.4% of subjects. Table 1 also reports twin resemblance for the drug use-related phenotypes assessed in this study. Resemblance for significant substance use was much higher in MZ twins (+0.80) than in DZ pairs (+0.16).

Any DSM-IV symptom of abuse or dependence with any substance was reported by 3.5% of the sample. The tetrachoric correlation for any symptom was substantially greater in MZ (+0.81) than in DZ pairs (+0.04). Full criteria for abuse or dependence of any substance were met by only 1.9% of the sample. Resemblance for a diagnosis of PSUD was much greater in MZ (+0.69) than in DZ pairs (+0.23).

Sufficient data were available to examine use, and symptoms or a diagnosis of abuse or dependence, only for cannabis. As seen in Table 1, the results closely paralleled those seen for any substance.

For stimulants, opiates, cocaine and psychedelics, prevalence rates were so low that we could only meaningfully examine lifetime use (Table 1). The prevalence of any use (among those with significant use) ranged from 0.9% for opiates to 2.7% for stimulants. Resemblance for lifetime use was for all substances higher in MZ than in DZ pairs.

Table 2 depicts our model fitting results. Notably, for all substance use and abuse categories that we examined, we could, with considerable confidence, reject an 'E-only' model. Thus, we have evidence for the familial aggregation, within Norwegian twin pairs, of the tendency to use and abuse psychoactive substances. For all substance use and abuse categories, the AE model provided the best fit. For all the analyses, except for opiate and cocaine use, the CE model could be rejected with considerable statistical confidence. However, for opiate and cocaine use, the fit for the AE model was only slightly superior to that found for the CE model.

Parameter estimates and 95% confidence intervals (CIs) for the full (or ACE) model and the best-fit model are presented in Table 3. The estimated heritabilities in both the full and best-fit models are relatively high, exceeding 0.65 for all variables except opiate and cocaine use. The CIs for many of these estimates are relatively wide, reflecting the low accuracy of parameter estimation.

Because of the rarity of the drug use and PSUD in this sample, these analyses were all conducted assuming no sex-dependent thresholds and no sex-dependent genetic and environmental parameters. However, of the 10 PSUD traits we examined, males had higher prevalence rates for all of them except opiate use. This difference reached statistical significance for any significant use [odds ratio (OR) 1.56, $\chi^2 = 8.16$, df=1, p=0.004], any diagnosis of abuse/dependence (OR 2.27, $\chi^2 = 8.41$, df=1, p=0.004), cannabis use (OR 1.56, $\chi^2 = 8.00$, df=1, p=0.005), cannabis abuse/dependence (OR 2.56, χ^2=9.45, df=1, p=0.002), and any psychedelic use (OR 1.96, χ^2=6.05, df=1, p=0.01). Therefore, for these five PSUD-related traits, we fitted twin models that allowed for both sex-dependent thresholds and parameters. In each case, the best AIC was obtained when the parameters were constrained to equality across the sexes and the thresholds permitted to differ in males and females. All parameter estimates from these models were within ± 0.02 of those presented in Table 3.

DISCUSSION

The aim of this study was to examine the role of genetic and environmental factors in the etiology of the use and misuse of illicit psychoactive substances in Norway. These results are of particular interest because parallel findings have, until now, been available only from two Anglophonic countries with similar cultures and high rates of psychoactive substance use. Because heritability estimates are properties of populations and not traits or disorders (Kendler, 2005), it is of interest to see whether prior evidence of substantial heritabilities for substance use and misuse could be replicated in a Nordic country with considerably lower levels of PSUD.

The prevalence for lifetime drug abuse or dependence in our population-based twin sample (1.9%) is substantially lower than the 3.4% estimated from a prior epidemiologic study in Norway (Kringlen *et al*. 2001), which is in turn much lower than the 11.9% lifetime prevalence estimates from the United States National Comorbidity Study (Kessler *et al.* 1994). However, while our sample was drawn from over all of Norway, the epidemiologic sample of Kringlen *et al*. (2001) came only from Oslo. Prior evidence suggests considerably higher illicit drug use in the major urban centers in Norway (Oslo, Bergen and Trondheim) than in the remaining more rural parts of the country (Hammer & Vaglum, 1990). Evidence for low rates of drug use in Norway is available from other sources. According to the European School Survey Project on Alcohol and Other Drugs (Hibell *et al*. 2000), in 1999, 16-year-old students in Norway reported rates of lifetime use of cannabis and amphetamine of, respectively, 9% and 2%. Parallel figures in 1999 from tenth-grade students in the USA (who are typically 16 years old) from the Monitoring the Future Project (Johnston *et al*. 2006) are, respectively, 24% and 16%.

Our ability to address questions of interest was limited by the particularly low prevalence rates we observed for substance use. In prior population-based twin studies, shared environmental effects have commonly been seen for substance initiation (Kendler & Prescott, 1998;Kendler *et al*. 2000*a*;Lynskey *et al*. 2002). In these analyses, we saw only hints of such effects and only in the full models for opiate and cocaine use. Whether there is true population difference in the sources of variance for drug initiation will need to await further research.

Estimates of the heritability of diagnoses or symptoms of abuse and dependence for any substance and cannabis were high – in the range of 0.68–0.78. These results are similar to those found previously in the Virginia Twin sample, where estimates for the heritability for cannabis

abuse and dependence were, respectively, 0.72 and 0.62 in females (Kendler & Prescott, 1998) and 0.76 and 0.58 in males (Kendler *et al*. 2000*a*). However, heritability estimates for cannabis misuse are higher in this Norwegian sample than those reported in the Australian (0.45 for cannabis dependence) (Lynskey *et al.* 2002) or US Vietnam Era twin registries (0.33 for cannabis abuse or dependence) (Tsuang *et al*. 1996).

We outlined previously two particularly plausible hypotheses about the relationship between the prevalence and heritability of substance use: positive correlation and negative correlation (Kendler *et al.* 2005). The positive correlation hypothesis predicts that the heritability of drug use will be low when availability and use are low because the genetic liability to use will remain unexpressed in a large proportion of the population who have not come into contact with the substance. The negative correlation hypothesis predicts that heritability of drug use will be high when a drug is difficult to obtain but will become lower as the drug becomes more widely available. This pattern might arise if high levels of heritable 'risk-taking' traits are needed to seek out and use a rare and potentially stigmatized drug. However, as that drug becomes more widely available and its use becomes acceptable, deviant personality traits would no longer be needed to use the substance.

We are aware of only one study providing strong support for the positive correlation hypothesis, where, in Swedish women, both prevalence and heritability of regular tobacco use increased dramatically in successive cohorts born from 1910 to 1958 (Kendler *et al*. 2000*b*). We recently examined changes in the heritability of use of a wide range of illicit substances in the Virginia Twin Registry (Kendler *et al.* 2005), and despite substantial changes in the prevalence of use, we were unable to find evidence for changing heritability. Results of the present study are particularly inconsistent with the positive correlation hypothesis, which would have predicted low levels of heritability of drug use in Norway given the low rates of use. Clearly, we understand relatively little about the relationship between heritability and availability and acceptability of psychoactive substances across populations.

Limitations

These findings should be interpreted in the context of four potential methodologic limitations. First, as noted above, these analyses had modest power and because of low prevalence, we were unable to examine abuse and dependence for most individual drug classes. Our ability to detect shared environmental, non-additive genetic and sex-dependent effects for the PSUD variable we did examine were also likely to be quite limited.

Second, PSUD is inherently a conditional process. The consumption of a significant amount of a substance must precede the development of dependence. While methods have been developed for incorporating this conditionality in twin models (Kendler *et al*. 1999), the low prevalence of PSUD in this sample made the application of such methods impractical.

Third, substantial attrition was observed in this sample from the birth registry through three waves of contact consisting of two questionnaires and a personal interview. We report detailed analyses of the predictors of non-response across waves elsewhere (Harris *et al*. in preparation). In brief, cooperation was strongly and consistently predicted by female sex, monozygosity, older age, and higher educational status, but not by psychiatric symptoms or psychoactive drug use. While we had no measures of illicit drug use prior to the personal interview, measures of current smoking and alcohol intake from the first and second questionnaires did not significantly predict, respectively, return of the second questionnaire and participation in the personal interview. Furthermore, measures of antisocial personality traits assessed at the second questionnaire did not predict cooperation at interview. While we cannot be certain that our sample was representative with respect to illicit psychoactive drug use and abuse/dependence, these results suggest that a substantial bias is unlikely.

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Table 1

Prevalence and tetrachoric correlations (with standard errors) for use of illicit psychoactive substances, symptoms of abuse/dependence and the diagnosis of abuse or dependence in Norwegian twins

			Tetrachoric correlation			
			MZ		DZ	
Substance	**Phenotype**	**Prevalence (%)**	***r***	**S.E.**	***r***	**S.E.**
Any	Significant use	6.4	0.80	0.06	0.16	0.13
	Symptoms of abuse/ dependence	3.5	0.81	0.07	0.04	0.20
	Abuse or dependence	1.9	0.69	0.24	0.14	0.23
Cannabis	Use	6.3	0.78	0.06	0.17	0.13
	Symptoms of abuse/ dependence	2.9	0.78	0.08	0.11	0.21
	Abuse or dependence	1.6	0.77	0.12	0.31	0.23
Stimulants	Use	2.7	0.78	0.08	0.33	0.18
Opiates	Use	0.9	0.78	0.14	0.57	0.23
Cocaine	Use	1.8	0.59	0.15	0.35	0.23
Psychedelics	Use	2.0	0.83	0.08	0.30	0.22

Significant use means lifetime use of illicit substances 10 or more times; *r*, tetrachoric correlation; S.E., standard error.

Table 2

Model-fitting results for substance use, symptoms of abuse/dependence and the diagnosis of abuse or dependence

		Model fit from the ACE model					
		AE		CE		E	
Substance	Phenotype	$\Delta\chi^{2}{}_{1}$	AIC	$\Delta\chi_{1}{}^{2}$	AIC	$\Delta\chi^{2}{}_{2}$	AIC
Any	Significant use	0.00	−2.00*	20.02	18.02	74.25	70.25
	Symptoms of abuse/ dependence	0.00	−2.00*	12.33	10.33	43.89	39.89
	Abuse or dependence	0.00	−2.00*	3.35	1.35	14.01	10.01
Cannabis	Use	0.00	−2.00*	18.23	16.23	69.38	65.38
	Symptoms of abuse/ dependence	0.00	−2.00*	8.81	6.81	33.32	31.32
	Abuse or dependence	0.00	−2.00*	4.21	2.21	17.63	13.63
Stimulants	Use	0.00	−2.00*	5.61	3.61	38.05	34.05
Opiates	Use	0.42	−1.58*	0.71	−1.29	16.02	12.02
Cocaine	Use	0.07	−1.93*	0.67	−1.33	12.03	8.03
Psychedelics	Use	0.00	−2.00*	5.88	3.88	37.70	33.70

* Best-fit model.

Significant use means lifetime use of illicit substances 10 or more times.

$\Delta\chi1^{2}$, change in χ^{2} with one degree of freedom; $\Delta\chi2^{2}$ change in χ^{2} with two degrees of freedom; AIC, Akaike's information criterion; A, additive genetic effects; C, common or shared environment; E, unique or individual specific environment.

Table 3

Parameter estimates (95% confidence intervals) for full and best-fit models for use of illicit psychoactive substances, symptoms of abuse/dependence and the diagnosis of abuse or dependence

Substance	Phenotype	Full			Best-fit	
		A	C	E	A	E
Any	Significant use	0.77 (0.54–0.87)	0.00 (0.00–0.19)	0.23 (0.13–0.36)	0.77 (0.64–0.87)	0.23 (0.13–0.36)
	Symptoms of abuse/dependence	0.77 (0.45–0.89)	0.00 (0.00–0.27)	0.23 (0.11–0.42)	0.77 (0.58–0.89)	0.23 (0.11–0.42)
	Abuse or dependence	0.68 (0.00–0.88)	0.00 (0.00–0.56)	0.32 (0.12–0.65)	0.68 (0.35–0.88)	0.32 (0.12–0.65)
Cannabis	Significant use	0.76 (0.51–0.86)	0.00 (0.00–0.20)	0.24 (0.14–0.39)	0.76 (0.61–0.86)	0.24 (0.14–0.39)
	Symptoms of abuse/dependence	0.75 (0.34–0.89)	0.00 (0.00–0.34)	0.25 (0.11–0.47)	0.75 (0.53–0.89)	0.25 (0.11–0.47)
	Abuse or dependence	0.77 (0.05–0.94)	0.00 (0.00–0.56)	0.23 (0.07–0.55)	0.77 (0.46–0.93)	0.23 (0.07–0.54)
Stimulants	Use	0.76 (0.14–0.89)	0.00 (0.00–0.54)	0.24 (0.11–0.44)	0.76 (0.56–0.89)	0.24 (0.11–0.44)
Opiates	Use	0.44 (0.00–0.94)	0.33 (0.00–0.85)	0.23 (0.05–0.60)	0.79 (0.45–0.95)	0.21 (0.05–0.55)
Cocaine	Use	0.44 (0.00–0.80)	0.13 (0.00–0.69)	0.43 (0.19–0.76)	0.58 (0.27–0.80)	0.42 (0.20–0.73)
Psychedelics	Use	0.81 (0.17–0.93)	0.00 (0.00–0.57)	0.19 (0.07–0.40)	0.81 (0.61–0.93)	0.19 (0.07–0.39)