Genetic and environmental influences on illicit drug use and tobacco use across birth cohorts

KENNETH S. KENDLER1,2, CHARLES GARDNER1, KRISTEN C. JACOBSON1, MICHAEL C. NEALE1,2,3 AND CAROL A. PRESCOTT1,3

1 Virginia Institute for Psychiatry and Behavioral Genetics and Departments of Psychiatry; 2 Human Genetics; and 3 Psychology, Medical College of Virginia Commonwealth University, Richmond, VA, USA

ABSTRACT

Background. The prevalence of use of many psychoactive substances has changed considerably in recent years. While genetic factors impact on overall risk for substance use, we know little about whether the etiological importance of these factors differs across birth cohorts. One theory, which postulates that heritability of deviant traits increases in permissive environments, predicts a positive relationship across cohorts between prevalence and heritability of substance use.

Method. The lifetime history of use of tobacco, cannabis, cocaine, sedatives and stimulants were assessed in 4826 twins from male–male and female–female pairs born in Virginia from 1934 to 1974. Using empirical methods based on prevalence by birth year, these twins were divided into three cohorts for each substance (e.g. for cannabis 1934–1953, 1954–1968 and 1969–1974). Structural equation modeling was performed using the Mx software package.

Results. Prevalence rates for psychoactive substance use differed substantially across cohorts, most markedly for cocaine, sedatives and stimulants, which were highest in the 1958–1963 cohort. However, for all substances, the best-fit model constrained estimates of the etiological role of genetic and environmental risk factors to be equal across both sex and cohort.

Conclusions. We found no evidence in this sample for any systematic relationship between heritability and prevalence of psychoactive substance use—which should be a rough index of drug availability and/or acceptability. This sample had reasonable power to detect large changes in heritability across cohorts and at least moderate power to detect relatively small changes.

INTRODUCTION

Genetic studies in man commonly assume that the impact of genetic factors is the same across diverse environments. However, a large body of evidence suggests that many aspects of the environment can modify genetic effects in many organisms including humans (Boerwinkle & Hallman, 1993). Typically, such studies of genotype–environment interaction examine the impact of genetic factors on the response to discrete environmental risk factors such as industrial toxins (Perera, 1997), head trauma (Jordan et al. 1997), tobacco smoke (Khaw & Barrett-Connor, 1986), diet (Tikkanen et al. 1990), or stressful life events (Kendler et al. 1995).

Examining changes in heritability across birth cohorts is an alternative approach to the study of gene–environment interaction. Such analyses plausibly assume that short-term changes in the magnitude of genetic effects in human populations reflect changing environmental exposures. Few risk factors have changed as dramatically in frequency in Western populations in the 20th century as the use of certain
licit and illicit psychoactive drugs (Substance Abuse and Mental Health Services Administration, 1996).

Three particularly plausible hypotheses can be articulated about the relationship between the prevalence and heritability of substance use: positive correlation, negative correlation and no correlation.

The ‘positive correlation hypothesis’ predicts that the heritability of drug use will be low when availability and use are low and will increase as the drug becomes more accessible. An individual’s genetic liability to substance use will be unexpressed if no opportunity to use the substance ever arises. Therefore, when drug availability is low, the genetic variance in the population for substance use will be expressed in only the small subset of the total population for whom the drug was accessible. The positive correlation hypothesis is part of a more general perspective that predicts that the heritability of traits will increase as the environment becomes more permissive of the expression of that trait (Kendler, 2001).

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 strongly correlated with use.

The ‘no correlation hypothesis’ predicts no substantial relationship between heritability and prevalence of substance use. This pattern could arise because, given a certain degree of availability, individual differences in drug use are relatively immutable characteristics of human populations such that individuals predisposed to use will find a way to obtain the substance. Alternatively, several different processes might be at work influencing the complex inter-relationship between heritability and frequency of drug use the net effects of which are to obscure any consistent association.

Although more complex nonlinear models are also possible, in this report, we focus on evaluating the positive, negative and no correlation hypotheses by examining both the prevalence and heritability of use of one licit (tobacco) and four illicit (cannabis, cocaine, sedatives and stimulants) psychoactive substances in a large sample of male–male and female–female twin pairs born in Virginia over a 40-year period from 1934 to 1974.

METHOD

Sample and assessment procedures

The twins in this study derive from the population-based Virginia Twin Registry (Kendler & Prescott, 1999). Female–female (FF) twin pairs, from birth years 1934–1974, became eligible if both members previously responded to a mailed questionnaire in 1987–1988, the response rate to which was 64%. They have been approached for four subsequent waves of personal interviews from 1988 to 1997, with cooperation rates ranging from 85% to 92%. The male–male and male–female (MMMF) twin pairs, covering the birth years 1940–1974 were ascertained in a separate study – with an initial cooperation rate of 72.4% – and have been approached for two waves of interviews from 1993 until 1998. Zygosity was determined by a combination of standard questions (Eaves et al. 1989), photographs and DNA analysis (Spence et al. 1988; Kendler & Prescott, 1999; Kendler et al. 2000a).

The mean (s.d.) ages of the FF and MMMF samples at their final interview were, respectively, 36.6 (8.1) and 36.8 (9.1) years. Interviewers had a master’s degree in a mental health-related field or a bachelor’s degree in this area plus 2 years of clinical experience. At each wave, members of a twin pair were interviewed by different interviewers who were blind to clinical information about the co-twin. In this report, we examine only same-sex twin pairs and will, therefore, refer to male–male pairs as the MM sample.

During the second wave of interviews of the MM sample and the third and fourth interview waves for the FF sample, lifetime use was assessed separately for a range of both licit and illicit psychoactive substances including tobacco, cannabis, cocaine, sedatives, and non-cocaine stimulants using an adaptation of the SCID interview (Spitzer et al. 1987). For the illicit substances which could be legally obtained, we emphasized that we were interested solely in non-medical use defined as use (i) without a
doctor's prescription, (ii) in greater amounts than prescribed, (iii) more often than prescribed or (iv) for any other reason than a doctor said they should be taken. This study is based on complete information from a total of 4826 twins (2909 males and 1917 females).

**Analytical methods**

Drug use cohorts were defined empirically using piecewise logistic regression. For cannabis, cocaine, sedatives and stimulants, the first cohort was defined by increasing use across birth years. The second cohort was defined as a period of relatively stable use, with the function of prevalence across birth years being fairly flat. The third cohort was defined by declining prevalence across years. For tobacco, there was an initial period of decline in use, followed by a relatively flat period, followed by another period of decline in the youngest cohort. The cohort boundaries were chosen so as to maximize $-2$ times the likelihood for the piecewise logistic regression.


We use a standard liability-threshold model to estimate the genetic and environmental contributions to twin resemblance for substance use. For a categorical trait such as lifetime use, the estimates reflect resemblance of twins in a pair for their liability to use the substance (Falconer, 1965). Liability is assumed to be continuous and normally distributed in the population, with individuals who exceed a theoretical threshold expressing the trait.

Individual differences in liability are assumed to arise from three sources: Additive genetic ('A'), from genes whose allelic effects combine additively; common environment ('C') includes all sources shared by members of a twin pair, including family environment, social class, schools; and specific environment ('E') includes all remaining environmental factors not shared within a twin pair plus measurement error. MZ twins within a pair resemble one another because they share all of their A and C components, while DZ twins share (on average) half of their A and all of their C components.

Our modeling was performed using the Mx software package by maximum-likelihood analysis of raw ordinal data (Neale et al. 1999) including both single twins and members of complete pairs. Such analyses do not directly provide an overall test of goodness of fit of the model. However, it is possible to obtain tests of relative fit by comparing a baseline model with various submodels. Twice the difference in log-likelihood between this baseline model and the submodel yields a statistic that is (under certain regularity conditions) asymptotically distributed as $\chi^2$ with degrees of freedom equal to the difference in the number of parameters in the two models.

Alternative models are evaluated by comparing the difference in their $\chi^2$’s 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 significantly worse fit. We operationalize parsimony by using Akaike’s information criteria (AIC) statistic (Akaike, 1987), calculated as: $\chi^2 - 2 \text{df}$. In these analyses, our baseline model allowed separate parameter estimates both across cohorts and sexes. We then evaluated the relative fit of three submodels where we constrained parameters to equality in sexes but not cohorts, cohorts but not sexes and both sexes and cohorts. Thresholds were allowed to vary both across sex and across cohort.

**RESULTS**

The lifetime prevalence of tobacco, cannabis, cocaine, sedative and stimulant use as a function of both sex and birth cohort are seen in Table 1. For tobacco, a modest monotonic relationship was seen with use declining in younger cohorts. For the illicit substances, by contrast, use was, by design, highest in cohort 2 and usually but
not always lowest in cohort 1. The proportional changes in prevalence across cohorts were substantial for all substances. Males consistently reported higher rates of drug use than did females.

Table 1 also contains the tetrachoric correlations for liability to substance use by sex and cohort. While a few differences across cohorts are notable (e.g. in females in cohort 3 the high DZ correlation for stimulants use and the low MZ correlation for sedative use), there was no overall trend consistent with that predicted by the positive or negative correlation models. For example, the ‘positive correlation’ model would predict that the differences in the correlation for drug use in MZ and DZ twins would be greatest in the cohort with highest prevalence and least in the cohort with the lowest prevalence.

The results of model fitting (outlined in Table 2) were straightforward and the same for all five substances. In each substance, the AIC of the model was substantially improved when either parameter estimates were constrained across sexes or constrained across cohorts. For all substances, the best-fit model was the simplest which assumed the same parameter estimates in male and females and in cohorts 1, 2 and 3.

Parameter estimates for the best-fitting models are presented in Table 3. Heritability estimates are substantial for all substances with contributions of the family environment for cannabis and stimulants.
The goal of this study was to test three *a priori* hypotheses about the nature of the relationship, within historical cohorts, between the heritability and the prevalence of psychoactive substance use. Although rationales could be developed to predict that prevalence and heritability of substance use ought to have a significant positive or a significant negative correlation across cohorts, neither hypothesis received support in these analyses. For all substances examined, our results were most consistent with the hypothesis that prevalence and heritability of psychoactive substance use across cohorts had ‘no correlation’.

We are aware of five prior studies that presented results addressing the relationship between psychoactive substance use or misuse and heritability across cohorts. All of these studies examined alcohol or tobacco. In the most relevant study, regular tobacco use was examined in male and female reared-together and reared-apart twins in Sweden from three cohorts spanning the birth years 1910–1958 (Kendler et al. 2000b). In males, prevalence and heritability of tobacco use was stable across cohorts. In females, by contrast, consistent with the ‘positive correlation’ hypothesis, prevalence increased substantially over time as did heritability. In male Swedish twins, prevalence and heritability of alcohol abuse, as defined by Temperance Board registration, was examined for four birth cohorts covering the years 1910–1949 (Kendler et al. 1997). Neither prevalence nor heritability changed significantly over this time period. In the Finnish twin cohort, average monthly alcohol consumption was assessed by self-report questionnaire on two occasions in two cohorts born, respectively, in 1932–1950 and 1951–1957 (Kaprio et al. 1991). Although level of consumption was similar across the cohorts, heritability of alcohol consumption was substantially higher in the younger cohort. Smoking initiation across three age groups was examined in Australian and Swedish samples (Bierut et al. 1999) with a tendency for declining heritability in more recent cohorts in females and no change in males (Bierut et al. 1999). In a large, elderly volunteer twin sample, Prescott et al. found no evidence for differences in patterns of twin resemblance for alcohol abuse in those aged ≤74 and 75+ (Prescott et al. 1994). In aggregate, this modest literature presents no compelling overall pattern of cohort changes in the heritability of use of alcohol and tobacco.

While we were unable to duplicate the prior results for tobacco use in Swedish females (Kendler et al. 2000b), our findings cannot be viewed as a robust non-replication. While the Swedish females showed quite dramatic increases in prevalence of tobacco use across cohorts (from 18% to 52%), over the years of our study, a quite modest decrease was seen in rates of tobacco use in females (from 46% to 36%).

A critical question in the interpretation of any ‘negative’ study is the power to detect the expected effects. While exhaustive power analyses are beyond the scope of this report, we examined two relevant models, both of which assumed, across cohorts, equal sample size, a constant prevalence of substance use of 20% and a constant value for $c^2$ (shared environment) of 0.20. The first simulation assumed values for $a^2$ (heritability) and $e^2$ (individual-specific environment) across the three cohorts of 0.20/0.60, 0.40/0.40 and 0.60/0.20 while the

<table>
<thead>
<tr>
<th>Substance</th>
<th>$a^2$ Estimate</th>
<th>95% CI</th>
<th>$c^2$ Estimate</th>
<th>95% CI</th>
<th>$e^2$ Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>0.79</td>
<td>0.59–0.85</td>
<td>0.02</td>
<td>0.00–0.21</td>
<td>0.19</td>
<td>0.15–0.23</td>
</tr>
<tr>
<td>Cannabis</td>
<td>0.41</td>
<td>0.19–0.63</td>
<td>0.29</td>
<td>0.09–0.48</td>
<td>0.30</td>
<td>0.25–0.36</td>
</tr>
<tr>
<td>Cocaine</td>
<td>0.70</td>
<td>0.41–0.77</td>
<td>0.00</td>
<td>0.00–0.00</td>
<td>0.30</td>
<td>0.23–0.37</td>
</tr>
<tr>
<td>Sedatives</td>
<td>0.63</td>
<td>0.35–0.72</td>
<td>0.00</td>
<td>0.00–0.24</td>
<td>0.37</td>
<td>0.28–0.48</td>
</tr>
<tr>
<td>Stimulants</td>
<td>0.42</td>
<td>0.11–0.69</td>
<td>0.20</td>
<td>0.00–0.46</td>
<td>0.38</td>
<td>0.30–0.47</td>
</tr>
</tbody>
</table>

CI, Confidence interval.

$a^2$, Additive genetic effects; $c^2$, shared environmental effects; $e^2$, individual-specific environmental effects.
second simulation assumed that these values were \(0.30/0.50\), \(0.40/0.40\) and \(0.50/0.30\). We could reject models which constrained the parameters to equality across the three cohorts 99.4% of the time for the first simulation and 64.3% for the second simulation. (While shifting prevalence rates would have more realistically mimicked the expected findings, they would have little effect on the power to detect differences in heritability across cohorts (Neale et al. 1994). Since these analytical models have no inherent ordering, these results would not differ if the order of the cohorts were changed.) These results suggest that our sample had reasonable power to detect large changes in heritability across cohorts and at least moderate power to detect smaller changes.

In addition to the findings with tobacco use in females in Sweden (Kendler et al. 1999b), several other studies examining a range of phenotypes including age at sexual intercourse (Dunne et al. 1997), educational attainment (Heath et al. 1985; Lichtenstein et al. 1992) and disinhibited behavior (Boomsma et al. 1999) have found higher trait heritabilities in more permissive environments. Our results, which found no such trend, may reflect the complexity of the relationship between heritable human traits and drug use. For example, with respect to substance use, individuals are not simply passive recipients of permissive or restrictive environments. Rather individuals can actively seek out drugs they desire and develop peer relationships that can encourage drug use and provide easy access (Kandel, 1985).

While not the major focus of this paper, we found that for all the psychoactive substances involved, the best-fit model assumed the same magnitude of the genetic and environmental effects in males and females. We are aware of only a single study that has previously examined this question (van den Bree et al. 1998). In a sample of 188 twin pairs ascertained through alcohol and drug abuse treatment facilities, van den Bree et al. reported results of full (or ACE) models separately for drug use in MM and FF pairs. For sedatives and cocaine, heritability estimates were quite a bit higher in males than in females. For cannabis the reverse pattern was seen while for stimulants, the heritability estimates were nearly the same in the two sexes.

We have previously published the results of twin modeling for substance use separately for the FF pairs (Kendler & Prescott, 1998a, b; Kendler et al. 1999a, c) and MM pairs (Kendler et al. 2000a) in this sample. As would be expected, the estimates of the etiological role of genetic and shared environmental factors for this combined sample are generally within the range of those we reported previously. Our results suggest that genetic factors play a strong role in influencing the use of psychoactive substances. Shared environmental factors also appear to be of importance for at least some substances, most notably cannabis.

In summary, in a large population-based twin sample of men and women, we were unable to find evidence that changing availability and/or acceptability of drug consumption — as indexed by rates of substance use — produced changes in the heritability. These results suggest that the heritability of substance use may be a relatively stable characteristic of human populations and not highly variable as a result of changing patterns of drug accessibility and consumption.

Limitations

These analyses should be interpreted in the context of five potentially important methodological limitations. First, we had, in this sample, no direct measure of drug availability and so had to assume that prevalence of use was a useful proxy of availability. An ongoing follow-up in MM twin pairs is collecting detailed data on drug availability.

Second, because we defined our cohorts by patterns of use, we may not have obtained optimal power. Therefore, we repeated all the analyses using birth cohorts that were selected to equalize across the cohorts the number of twins reporting substance use. For cannabis, this resulted in the following cohort definitions: 1934–1956, 1957–1964 and 1965–1974. For all the remaining substances, the following cohort definitions worked well: 1934–1957, 1958–1963 and 1965–1974. The results were the same as those reported above, finding no evidence for significant differences in sources of liability to substance use across cohorts or across genders.

Third, our cohorts may differ meaningfully in the proportion of the risk period completed for substance initiation. We examined this using
life-table analysis. While cohort 3 (the youngest cohort) had significantly more remaining risk than cohorts 1 and 2 for all the substances examined, the magnitude of the difference was quite small, because the age at onset of drug use was generally so young. For example, for cannabis and cocaine use, the mean remaining risks for the three cohorts were as follows: cohort 1 (0.004 and 0.001); cohort 2 (0.004 and 0.004) and cohort 3 (0.026 and 0.013).

Fourth, these analyses relied solely on retrospective reports of substance use. We have previously shown that these reports had quite high test–retest reliability (Kendler et al. 1999a, 2000a). In a total of 323 randomly selected twins interviewed twice on average 4.4 weeks apart, we found that the level of agreement for substance use was unrelated to the age of the respondent. It is unlikely that our results were substantially biased by differing levels of reliability of reporting across cohorts.

Finally, our approach to twin analysis assumed that MZ and DZ pairs were equally similar in the etiologically relevant aspects of their shared environment. We have previously examined this ‘equal environment assumption’ with respect to substance use in this sample (Kendler & Prescott, 1998a, b; Kendler et al. 1999a, c, 2000a) and found no consistent evidence to suggest that it is invalid.

ACKNOWLEDGMENTS

This work was supported by NIH grants DA11287, MH/AA/DA49492, and AA-00236. We thank Dr Linda Corey for assistance with the ascertainment of twins from the Virginia Twin Registry, now part of the Mid-Atlantic Twin Registry (MATR), directed by Dr Judy Silberg. The MATR has received support from the National Institutes of Health, the Carman Trust and the WM Keck, John Templeton and Robert Wood Johnson Foundations. Patsy Waring, Frank Butera, Sarah Waltz, Barbara Brooke and Lisa Halberstadt supervised data collection. Indrani Ray and Steven Aggen provided database management.

DECLARATION OF INTEREST

None.

REFERENCES


