The Genetic and Environmental Architecture of Substance Use Development from Early Adolescence into Young Adulthood:

A Longitudinal Twin Study of Comorbidity of Alcohol, Tobacco and Illicit Drugs Use

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Keywords

Substance use, alcohol use, tobacco use, illicit drugs use, comorbidity, longitudinal, adolescence, heritability, twin study
Abstract

Aims To investigate how use of alcohol, illicit drugs and tobacco come from substance specific pathways and from pathways general to all three substances through adolescents’ development.

Design Analysis of population-based survey. Adolescent twins reported alcohol use (AU), tobacco use (TU), and illicit drug use (IDU) at 3 waves (2006, 2008, 2010). Restructuring data by age allowed for variance decomposition into age and substance specific and common genetic and environmental variance components.

Setting Norway.

Participants Seven national twin birth cohorts 1988 to 1994, totaling 2340 individuals, 1483 pairs (558 monozygotic; 925 dizygotic, same and opposite sex).

Measurements 6-point Likert scores of AU, TU and IDU on items from the Monitoring the Future Study.

Findings Substance use was found to be highly heritable: a2=.73 (CI .61-.94) for AU, a2=.36 (CI .18-.52); d2=.49 (CI95 = .29-.62) for IDU and a2=.46 (CI .23-.54); d2=.05 (CI95 = .00-.07) for TU over the whole adolescence period. General substance use (GSU) was also highly heritable at each age and averaged a2=.57 (CI95= 48-.66). There was a high genetic carry-over from earlier age to later age. Genetic effects on GSU at age 12-14 were still detectable 4 years later. New substance (general and specific) genetic effects also appeared. IDU demonstrated significant nonadditive genetic effects (age 12-14). Shared environment had a small impact on AU only. There was almost no nonshared environmental carry-over from age to age, the effect probably partly due to reliability deficiency. Common genetic effects across substance and substance-specific genetic effects were observed at each age period.

Among Norwegian adolescents, there appear to be strong genetic effects on both substance specific and comorbid use of alcohol, illicit drugs and tobacco. Among Norwegian adolescents, individual differences in alcohol use can be partially explained by family background.
The Genetic and Environmental Architecture of Substance Use Development from Early Adolescence into Young Adulthood: A Longitudinal Twin Study of Comorbidity of Alcohol, Tobacco and Illicit Drugs Use

Introduction

Adolescence is the peak period for the onset of using substances. The median age of onset for alcohol and tobacco use is 16-18 years worldwide, and somewhat later for illicit drugs use like marijuana (18-19 years) and cocaine (21-24 years) (1). Low use of alcohol or tobacco are the most prevalent patterns (2). Using multiple substances, and including illicit drugs (3), is associated with different predictors and more problematic outcomes (4).

The causal mechanisms behind substance use in adolescence are still largely unknown, but genetic influences are indicated. Molecular studies have shown several genetic variants associated with substance use (individual effect sizes typically low (5, 6)) some also pointing to a more nonspecific liability for abuse and dependence across substance types (7, 8).

Genetically informative designs,(twin and extended family studies) estimating the total effect of genetic and environmental influences in complex traits, have proven very useful in studying the structures behind substance use, abuse and dependence (9). Twin studies have demonstrated heritabilities of 40-70% for alcohol and illicit drugs dependence (9, 10). The heritability of substance use, is smaller (11). Genetic sources explained about half of the variation in lifetime use of any substance in young twins (12). An additive genetic component explaining around 60% of the common liability factor across alcohol, tobacco, and cannabis dependence (13), showed moderate, correlated genetic influences at two consecutive waves into young adulthood (14). Yet, results concerning substance abuse and dependence may not apply for substance use, and underlying structures may differ in adults,
and adolescents. A few studies have reported increasing heritability estimates for substance use and abuse from adolescence to adulthood (15-17). However, there is a paucity of studies investigating the development of comorbid drugs use from early adolescence into young adulthood within genetically informative designs.

Using a population based community sample of twins followed longitudinally throughout adolescence to young adulthood answering questionnaires about recent substance use at ages 12-14, 15-17 and 18-22 years, the aim of the present study was to

1) investigate how use of alcohol, illicit drugs and tobacco come from substance specific pathways
2) investigate the role of any general liability to using these substances

Method

To investigate how – throughout adolescence – individual differences in alcohol, illicit drugs, and tobacco use depend on substance common and substance unique genetic and environmental factors, a repeated measures twin study was used. This allowed us to decompose the observed variance into latent genetic and environmental variance components (18), which is possible since twins come into two kinds: monozygotic (MZ) twins, who share 100% of their genetic variance, and dizygotic (DZ) twins, who share on average 50% of segregating genes. The use of repeated measures makes it possible to investigate stability and change in those environmental and genetic variance components across time or age.

Design Multivariate repeated measures twin design. Adolescent MZ and DZ twins (see sample description) reported Alcohol, Tobacco, and Illicit Drug use (see measures) in three waves (in 2006, 2008, 2010). For statistical analyses these data were restructured according
to age (more details below), such that the genetic and environmental variance components could be further decomposed into age specific and age common variance components.

**Participants** The sample of MZ and DZ twins was recruited as follows: Information about all multiples born in Norway between 1988 and 1994 (N=5374 multiple births, 10748 individual twins) and their parents was provided by the Norwegian Medical Birth Register. A postal invitation to participate was sent to the 4669 twin pairs who were still alive and residing in the country (elective pairs) when the study started. Of those pairs, 2486 pairs gave informed consent. Surveys were sent to total of 1393 pairs (29.8 % of the elective pairs) participated in the first wave, 1065 (22.8 %) in the second wave, and 883 (18.9 %) in the third. Based on questionnaire signed response dates, the median time span between Wave 1 and Wave 2 was 1.8 years (94.4% between 1.5-2.5 years); 2.6 years between waves 2 and 3 (99.6% between 2.0-3.0 years), and 4.4 years between waves 1 and 3 (96.7 % between 4.0 - 5.0 years). The number of pairs with a response from at least one of the twins on at least one of the measurement occasions for at least one measure of substance use was 1483 (32% of elective pairs). Of these, 558 were monozygotic and 928 were dizygotic, same and opposite sex. In 428 pairs, both twins gave valid answers on all three substance measures at all waves (complete pairs). Comparisons between the ‘complete’ and ‘incomplete’ pairs indicated lower rates of substance use for complete pairs. Further analyses on longitudinal attrition indicated that there were in general no differences in zygosity and sex distribution between the complete pairs and the pairs including those without cotwin (any pairs: complete plus incomplete pairs) for all waves (for details, see S-Table 1 in supplementary material).

Generally, the percentages of males and opposite sex pairs decreased from first to third wave. All relevant cross-sectional and longitudinal within-twin and between-twin correlations were calculated separately for the ‘complete pairs’ and ‘any pairs’. Only small differences between the corresponding correlations for these two samples were observed.
Their averages were also nearly identical (.41 versus .43). For further details on recruitment, participation, and dropout rates, see Waaktaar and Torgersen (19).

**Measures** At each wave, substance use was assessed by youth’s self-report and parents’ report using items from the Monitoring the Future study (19). For statistical analyses, we selected responses on the self-reports on the three items that asked how many times participants used (1) tobacco, (2) alcohol, and (3) illicit drugs during the past 12 months. The measurement of illicit drug use at Wave 1 (ages 12-14) was an exception; here, the twins were asked how many times they had used illicit drugs in their entire life. Response options were ‘never’ (coded 0); ‘1-2 times’ (coded 1); ‘3-5 times’ (coded 2); ‘6-9 times’ (coded 4); ‘10-19 times’ (coded 5); ‘20-39 times’ (coded 6), and ‘40 or more times’ (coded 7).

Zygosity was determined through a combination of questionnaire data on twin physical similarity and DNA secured through cheek swabs from a subsample of the participants. For details, see (19, 20).

**Statistical Analysis**

Since the data were obtained in waves rather than age, data were first restructured according to age, using 3 bins: Age 12 to 14, Age 15 to 17, and Age 18 to 22. Whenever two measures fell in the same bin, these were averaged. Descriptive statistics of the restructured data are provided in Table 1 (centrality and dispersion measures) and Supplementary material, S-Tables S3 (age bin to age bin correlations) and S4 (I and II) (twin correlations). The relationships between wave, cohort, and age bin are provided in table S-Table 5.

From the twin correlations it can be derived that phenotypic similarity of DZ twins was generally close to half that of the of MZ twins, suggesting that genetic effects on substance abuse were mainly additive (A) and environmental effects between twins.
THE GENETIC AND ENVIRONMENTAL ARCHITECTURE OF ADOLESCENTS’ SUBSTANCE USE

nonshared (E). However, for alcohol use, the DZ correlations were clearly more than half the MZ correlations, while for tobacco use and illicit drug use they tended to be less than half the MZ correlations. This suggested the presence of additional shared environmental effects (C) on alcohol use (but not on tobacco use and illicit drug use), and the possible presence of nonadditive genetic effects (D) on drug use and illicit drug use (but not on alcohol use).

To incorporate all effects, we constructed the statistical model displayed graphically in Figure 1. It describes how observed variance in the observed variables was split into substance common and substance specific variance components at each age (bin), and how those components related across age. More specifically, the model distinguishes at each age between substance common and substance specific additive genetic variance components (depicted as first order latent A factors) and substance common and substance specific nonshared environmental variance components (first order latent E factors) on which the observed variables Alcohol, Illicit Drug and Tobacco use were regressed. In addition, the Alcohol Use measures were regressed on age specific and age common environmental components (alcohol specific latent C factors), while the Tobacco and Illicit Drug Use scores were regressed on an age common and age specific nonadditive genetic variance components common to Tobacco and Illicit Drug Use (depicted as latent D factors).

Statistical overlap (correlations) among the three substance common, age specific A factors was handled by adding three latent A factors at the second order and by regressing the first order substance common A factor at a given age on (1) the second order A factor at that age, and (2) any such factors on previous ages. Statistical overlap among the three substance common, age specific E factors was modeled accordingly.

The model was implemented in R, package OpenMx (21), using Full Information Maximum Likelihood. To lower the computational burden, the observed variables were
treated as continuous. As the number of categories of the observed variables was larger than 5 this is not problematic in many cases (22). We note, however, that standard errors (of large factor loadings especially) might be underestimated (and that model comparison can therefore be problematic), for example, since the observed variables were skewed to the left. Our results should thus be interpreted with some degree of caution. However, we stress that our focus was not so much on individual parameters of the model or on coming up with a best fitting model. Rather we were interested in the (potentially different) roles of genetic and environmental sources of individual differences in a model that can be regarded as as saturated as possible.

Because qualitative and quantitative sex differences in genetic and environmental effects are rare (23), and have not been detected in earlier studies into substance use (24), we assumed such differences were not present in the present sample either. Importantly, this assumption increased the power to detect possible C and D effects substantially. Yet, per recommendation of Del Boca (25), we did allow for sex differences, namely in the observed means, so in the frequency of substance use (even though the descriptives suggested such sex differences were small and likely insignificant). This was accomplished by including sex as a covariate (definition variable in OpenMx), i.e. as a predictor of the observed variables Tobacco Use, Alcohol Use, and Illicit Drug Use.

Results

The model as described above, turned out to be empirically nonidentified, but by fixing the near-zero loading of Illicit Drug Use on the age common D factor to actually 0, this issue was solved. Figure 1 includes the standardized path coefficients (and their 95% confidence intervals) that followed.
The additive genetic pathways (Figure 1a) show that the substance common additive genetic effects present at ages 12-14 were also present at later ages, because the second order factor at age 12-14 (which is identical to the first order factor at age 12-14) significantly predicted the first order factors at ages 15-17 and 18-22. Significant new substance common additive genetic effects also emerged, at age 15-17. Substance specific additive genetic effects were generally not significant, with the exception of additive genetic effects on Alcohol Use at age 18-22. In conclusion, additive genetic effects mainly contributed to comorbidity, and to comorbid stability as well as comorbid change. Additive genetic influences do not provide a good explanation of why some individuals are inclined to use alcohol while others tobacco or illicit drugs.

The nonadditive genetic effects on Tobacco Use and Drug Use (Figure 1b) could not be dropped from the model without a significant decrease in model fit (see Supplementary material S-Table 2 for fit statistics of nested models), yet such effects must be considered limited, as the only significant effect (at $\alpha = .05$) was on Drug Use at age 12-14. From age 15-17 onwards, significant nonadditive effects were absent. Thus, if not indicating a false positive (as mentioned standard errors can be underestimated), these results suggest that in contrast to additive genetic effects, any genetic effects vanish, and quickly so.

The shared environmental pathways on Alcohol Use (Figure 1c) could not be dropped either. Only at age 17-22 there was a significant, moderate contribution (of the age common C factor). However, the sum of the age specific and age common contributions appeared significant at each age, suggesting that shared environmental effects were present throughout the whole age span, but that we lacked power to distinguish between age specific and age common effects.
From the nonshared environmental pathways (Figure 1d), we observed that substance nonshared environmental effects were largely age specific, implying that these effects contributed mainly (though not only) to change. An important distinction here is between age specific substance specific nonshared environmental effects and age specific substance common nonshared environmental effects. The former includes (and may be largely comprised of) the effects of measurement error. The latter do not include effects of measurement error and represent actual environmental effects that contribute to comorbidity. The pathways from the second order factors to the first order components show that such environmental effects did not so much explain comorbid stability, but rather comorbid changes, since the pathways from first order variables to previous second order variables were insignificant.

Summarized, the results suggest that (a) stability in comorbidity was mainly due to additive genetic effects, (b) while changes in comorbidity are mainly due to nonshared environmental effects, and (c) substance unique variance was of various sources and did not show much carry-over, perhaps except the contribution of shared environmental effects on alcohol use.

Apart from studying the pathways, and thus the qualitative roles of genetic and environmental effects in explaining stability and change, we also calculated the relative, quantitative contributions of genetic (and shared and nonshared environmental) variance to total (phenotypic) variance and covariance at each specific age and across age. These contributions (‘heritability coefficients’) are provided in Table 2. Their standard errors and confidence intervals should again be interpreted with caution. Again, the pattern in these results is more important than single heritability estimates. This pattern suggests that heritability of substance use is moderate to high, providing evidence that the genetic effects on influences on all Alcohol Use, Tobacco Use, and Drug Use were substantial throughout
the entire age span and that the same holds for the accumulated effects of all the influences that contribute to comorbid substance use.

[INSERT TABLE 2 ABOUT HERE]

Discussion

Corroborating previous findings, our model showed that comorbid substance use is moderately to highly heritable from early adolescence into young adulthood. The comorbidity factor in alcohol, tobacco, and illicit drugs use had a heritability of .57 across the age span, varying from .51 (in early adolescence), to .75 (in young adulthood). Comparable estimates were reported in the liability for comorbid alcohol, tobacco, and cannabis DSM-IV lifetime dependence symptoms in young people (13). Genetic effects across adolescence are also supported by molecular genetic studies on substance use (6) and dependence (8).

Our longitudinal design showed that genetic and environmental factors have different roles in explaining stability and change over time. Stability in comorbidity was primarily due to genetic effects, while the environmental influences on comorbidity lead to comorbid change. An earlier study on adolescents’ substance use covering a narrower age span, also found a common genetic factor accounting for stability in comorbid tobacco-, alcohol- and drugs use (24). While they reported shared environmental effects contributing substantially to comorbid continuity, in our study these were small and specific to alcohol use. We lacked power to determine whether these effects were the same shared environmental effects across development, however, our results fit with estimates reported on alcohol disorders (26).

A novel finding is that illicit drugs use was partly driven by nonadditive genetic (dominance or epistasis) influences. Clear genetic dominance effects were recently documented in molecular genetic studies of substance dependence (27), supporting the relevance of such models in twin designs. However, nonadditive genetic influences were
substance specific changes at specific ages. Within the context of the full model, they did not contribute to comorbidity or stability. After age 18 these effects had disappeared. Large-scale extended family designs are needed to explore further the relative roles of C and D modeled together.

Noteworthy, the importance of genetic effects in explaining comorbid stability does not exclude additive genetic effects (also) explain change. In fact, the additive genetic effects that lead to change in the present study merely tended to accumulate, whereas all effects of genetic dominance, shared environment and nonshared environment were idiosyncratic. Thus, some additive genetic effects do not vanish while all other effects do. Those additive genetic effects that do not vanish all contribute to comorbidity.

Finally, a highly interesting finding is that the comorbidity of adolescents’ substance use is mainly due to a common genetic liability, while genetic specificity for alcohol, drugs and tobacco become more prominent in young adulthood. This is supported in a study reporting decreasing common genetic liability and increasing substance specific genetic effects in regular smoking, alcohol intoxication and illicit drug use through adolescence (24). A longitudinal twin study of comorbid alcohol, tobacco and marijuana dependence (28) found a genetic component of around 70% in the common comorbidity factor at 17 years, deceasing to less than 50% by age 29 years. There, the nonshared environmental influence increased accordingly, explaining more of the differentiation between substances than substance specific genetic liabilities. Conversely, others have (29) reported that comorbidity of substance use in adolescents was mainly caused by common shared environmental influences, while comorbidity in young adults was caused by common genetic sources. Although results from studies throughout adolescence differ markedly on the relative importance of common and substance specific causation, maybe indicating a cultural tunneling of the expression of genetic effects on substance use, increasing differentiation
from adolescence to adulthood have also been found in other studies of externalizing symptomatology. Thus, in early adolescence, the subjective response to the different drugs differs very little across substances (30), an effect that is partly influenced by a general genetic liability across substances (31). Some (32) have reported nonspecific genetic vulnerability across substances, while others (33) have found common genetic sources as well as substance specific sources in substance use disorders in adults. Similar results have been reported in molecular genetic studies on adult lifetime substance dependence (8).

The present results bear several implications for molecular genetic studies. They demonstrate that genes are highly influential in explaining variance in substance use - not only substance abuse and dependence - throughout adolescence and early adulthood. Common and substance specific genetic sources should be investigated across age groups as potential causal agents behind both stability and change in these phenotypes.

**Strengths and Limitations**

Major advantages of the present study are the longitudinal genetically informative twin design, the population based sample, use of adolescents’ self-report on behaviors under normative and legal restrictions, and the wide age span included. Some basic assumptions inherent in the classical twin design, e.g. that the same amount of environmental variation is affecting MZ and DZ twins (equal environments), and that there is no genetic correlation between the parents (random mating) (34) were not specifically tested. Results from other studies indicate low threat on assumptions for the phenotypes studied here (35-38). As we assumed rather than tested for qualitative and quantitative sex differences in genetic and environmental effects, we cannot exclude such effects were actually present. If so, our results should be interpreted as averaged across the sexes. Above, we mentioned sex effects are rare
and have not been detected in earlier studies into substance use (24), but they may be small, so that they went undetected in previous studies due to a lack of power. In line with recommendation of Del Boca (25), we therefore advice future (large-scale) studies to (re)address possible qualitative and quantitative sex differences in any phenotype in general and in substance abuse in particular (25).

Since we were focusing on stability and change in inter-individual differences in substance use as such, initiation and progression were here taken together. Twin studies separating initiation and progress (39) may provide further insight.

Attrition may constitute a threat to representativeness. Earlier analyses indicated somewhat higher parental socioeconomic status (SES) among the participating families compared to the national mean (19). Norway is a highly egalitarian society (40), and SES-based differences in parental and young people’s health related behavior are generally small compared to other European countries (41, 42). However, further studies on more SES-diverse samples are warranted. Analyses did not indicate marked effects of systematic attrition in association between variables longitudinally.

Conclusion

Results indicate that within the Norwegian population and society individual differences in substance use (alcohol, tobacco and illicit drugs) are in large part driven by stable genetic sources. Environmental influences (including measurement error) are in large part the motor of time and/or substance specific use. Shared environmental effects are limited to alcohol use.
Acknowledgements

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Figure 1 Results of the biometric model fitting analyses
## Table 1 Descriptive statistics (95% confidence intervals between square brackets; percentages between round brackets)

<table>
<thead>
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<th>Age 12-14</th>
<th></th>
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<th>Age 18-22</th>
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<td>Tobacco</td>
<td>Alcohol</td>
<td>Illicit Drug</td>
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<td>.02</td>
<td>1.91</td>
<td>.08</td>
<td>.23</td>
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Mean values are given in [ ] for 95% confidence intervals.
### THE GENETIC AND ENVIRONMENTAL ARCHITECTURE OF ADOLESCENTS’ SUBSTANCE USE

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<th>SD</th>
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<td>.49 [.44,.51]</td>
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<td>6</td>
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<td>.09 [.08,10]</td>
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</table>

**Note:** n = number of individual observations; np = number of twin pairs; %comp; percentage complete twin pairs; MZm; Monozygotic male; MZf Monozygotic female; DZm; Dizygotic male; DZf Dizygotic female; DZo Dizygotic opposite sex; SD = Standard Deviation of the variable; min = minimum observed score on the variable; max = maximum observed score on the variable.
Table 2 Heritability coefficients (and their 95% confidence intervals) as obtained from the best fitting adjusted developmental (ADCE) model

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<th>$d^2$</th>
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<td>-</td>
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<td>-</td>
<td>.11</td>
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Figure Captions

**Figure 1**, showing the standardized path coefficients (and their 95% confidence intervals) in the adjusted developmental model. To avoid clutter the coefficients are shown separately for the additive genetic factors (panel a), nonadditive genetic factors (panel b), shared environmental factors (panel c), and (d) nonshared environmental factors (panel d) that influence Alcohol Use (alc), Drug Use (drg), and Tobacco Use (tob), at ages 12-14, 15-17, and 18-22. The path in grey represents the path coefficient that was fixed to 0. Measurement specific residual E is omitted.


and illicit drug dependence: genetics of vulnerability to drug dependence, Addiction 2015: 110: 530-537.


17. KENDLER K. S., SCHMITT E., AGGEN S. H., PRESCOTT C. A. Genetic and environmental influences on alcohol, caffeine, cannabis, and nicotine use from early adolescence to middle adulthood, Arch Gen Psychiatry 2008: 65: 674-682.


22. RHEMTULLA M., BROSSEAU-LIARD P. É., SAVALEI V. When can categorical variables be treated as continuous? A comparison of robust continuous and categorical SEM estimation methods under suboptimal conditions. , Psychological methods 2012: 17: 354.


24. BAKER J. H., MAES H. H., LARSSON H., LICHTENSTEIN P., KENDLER K. S. Sex differences and developmental stability in genetic and environmental influences on
psychoactive substance consumption from early adolescence to young adulthood,

25. DEL BOCA F. K. Addressing sex and gender inequities in scientific research and

26. VERHULST B., NEALE M. C., KENDLER K. S. The heritability of alcohol use disorders:
a meta-analysis of twin and adoption studies, Psychol Med 2015: 45: 1061-1072.

27. CHEN G., ZHANG F., XUE W., WU R., XU H., WANG K. et al. An association study
revealed substantial effects of dominance, epistasis and substance dependence co-
morbidity on alcohol dependence symptom count, Addict Biol 2016.

28. VRIEZE S. I., HICKS B. M., IACONO W. G., McGUIE M. Decline in genetic influence on
the co-occurrence of alcohol, marijuana, and nicotine dependence symptoms from age

29. KOOPMANS J. R., VAN DOORNEN L. J., BOOMSMA D. I. Association between alcohol
use and smoking in adolescent and young adult twins: a bivariate genetic analysis,

30. ZEIGER J. S., HABERSTICK B. C., CORLEY R. P., EHRINGER M. A., CROWLEY T. J.,
HEWITT J. K. et al. Subjective effects for alcohol, tobacco, and marijuana association

31. HABERSTICK B. C., ZEIGER J. S., CORLEY R. P., HOPPER C. J., STALLINGS M. C., RHEE
S. H. et al. Common and drug-specific genetic influences on subjective effects to

32. YOUNG S. E., RHEE S. H., STALLINGS M. C., CORLEY R. P., HEWITT J. K. Genetic and
environmental vulnerabilities underlying adolescent substance use and problem use:
general or specific?, Behav Genet 2006: 36: 603-615.


