

Shared Genetic Vulnerability in Alcohol and Cigarette Use and Dependence

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IN BOTH CLINICAL and general community samples, high rates of smoking have consistently been found among alcoholics (Glassman et al., 1990; Istvan and Matrazzo, 1984). For example, in a sample of Australian adult twins, women with histories of regular smoking were five to six times more likely to report a history of DSM-III-R alcohol dependence, compared with female nonsmokers. A similar but somewhat smaller association was found in the men (Madden et al., 2000). Among these same adults, a positive relationship was found between the number of symptoms of DSM-III-R alcohol dependence and a history of smoking; the greater the number of symptoms of alcohol dependence reported, the more likely they were also to have previously reported a history of regular smoking (Madden et al., 2000).

There have been fewer findings published on the association between the use of alcohol and cigarettes in adolescents. However, in Dutch adolescent twins, a strong relationship was observed by Koopmans et al. (1997) between experimentation with cigarettes and alcohol in both girls (odds ratio [OR], 6.6) and boys (OR, 8.9) as young as 12 to 14 years of age, and a smaller yet substantial association was also observed in an older Dutch cohort of young adult twins 17 to 25 years of age (OR: male, 5.7; female, 4.3).

Findings from most twin and adoption studies of alcoholism, whether assessed by interview or from medical or other official records, are consistent with an important genetic influence on alcoholism in men (reviewed in Heath et al., 1997b; for recent studies, see Heath et al., 1997a; Prescott et al., 1999; True et al., 1996), and most recent studies suggest a genetic influence on alcoholism in women (Heath et al., 1997a,b; Prescott et al., 1999). There is also a growing body of twin research that suggests an important genetic influence on various aspects of cigarette smoking (including both the initiation and persistence in smoking)

and nicotine dependence in adult twins (reviewed in Heath and Madden, 1995; see also Kendler et al., 1999; True et al., 1999) and adolescent twins (Koopmans et al., 1997). An obvious question for those who are interested in the cause, prevention, and treatment of problems related to use of alcohol, therefore, is the extent to which there is a shared genetic vulnerability between alcoholism and aspects of cigarette use and nicotine dependence.

EVIDENCE FOR SHARED GENETIC VULNERABILITY BETWEEN CIGARETTE SMOKING, NICOTINE DEPENDENCE, AND ALCOHOL USE/DEPENDENCE IN ADULTS

A familial association between different lifetime measures of cigarette and alcohol consumption, that is due at least in part to genetic factors, has been observed in adult men (Swan et al., 1997) and women (Prescott and Kendler, 1995) as well as between DSM-III-R lifetime history of nicotine and alcohol dependence in men (True et al., 1996) and a lifetime history of regular cigarette use and DSM-III-R alcohol dependence in men and women (Madden et al., 2000). Most studies have failed to control for personality, sociodemographic, and psychiatric risk factors, yet because many of the identified risk factors for smoking (e.g., Glassman et al., 1990) are also risk factors for alcohol dependence (e.g., Kessler et al., 1997) and are influenced by genetic factors, this sharing of risk factors would create shared genetic risk between cigarette smoking and alcohol dependence. An exception is provided by the Madden et al. (2000) analyses of data from Australian adult male and female twins from a panel maintained by the Australian National Health and Medical Research Council. This panel was first surveyed by mailed questionnaire in 1980 to 1982, completing assessments that included a lifetime history of cigarette smoking and measures of Eysenck's personality traits (extraversion, neuroticism, tough-mindedness, and social nonconformity) as well as sociodemographic variables. These data were combined with diagnostic information on history of DSM-III-R alcohol dependence and other psychopathology (major depression and conduct disorder) obtained in a follow-up telephone interview conducted in 1992 to 1994. A significant familial association was found to remain between risk of regular smoking and DSM-III-R alcohol dependence, even after controlling for sociodemographic variables, personality, and history of psychopathology. Furthermore, because a stronger residual

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association was observed between regular smoking and co-twin's alcohol dependence in monozygotic than in dizygotic twin pairs, this suggests that a significant residual genetic variance contributes to risks of regular smoking and alcohol dependence.

FAMILIAL ASSOCIATION BETWEEN CIGARETTE SMOKING AND ALCOHOL USE/DEPENDENCE IN ADOLESCENTS

A strong familial association has also been found between experimentation (i.e., ever use) in a large genetic epidemiologic study of adolescent (12–16 years of age) and young adult twins (17–25 years of age) (Koopmans et al., 1997). These researchers suggested that shared genetic factors seemed to be more important determinants of the smoking–alcohol association in young adults than in adolescents. However, these analyses failed to adjust for censoring, i.e., the problem that adolescents were only partially through their period of risk for the onset of use of cigarettes and of alcohol; therefore, it remains unclear whether different factors account for first use of these substances in adolescence versus adulthood or, alternatively, whether the problem of censoring is masking a shared genetic predisposition in adolescents. Clarification of this issue will be of some importance in the design of future efforts to prevent the onset of smoking and alcohol use in adolescents.

SMOKING AND DIFFERENCES IN LEVEL OF RESPONSE TO ALCOHOL

Because of the close association consistently observed between the use of alcohol and tobacco from early to later stages of use and dependence, it is important that we understand mechanisms that underlie the relationship between these substances. The analyses of the Australian twin cohort suggest that shared sociodemographic and other risk factors may only partially account for this shared risk. So what may account for the substantial residual genetic correlation that remains? Evidence from cross-sectional studies of sons of alcoholics and controls (e.g., Schuckit, 1980) and prospective follow-up of these samples (e.g., Schuckit and Smith, 1996) supports the hypothesis that less intense responses to alcohol (e.g., subjective reactions or ataxia), assessed in an alcohol challenge paradigm, predict increased risk of future onset of alcohol dependence and may represent one pathway by which genetic influences on alcohol dependence may arise. In a reanalysis of alcohol challenge data obtained from 206 pairs of Australian twins in 1979 to 1981 by Martin et al. (1985) in a protocol in which no formal restrictions were placed on smoking, we found (1) an association between cigarette smoking and postalcohol intoxication that remained even when the effects of a history of heavy drinking were controlled for (Madden et al., 1995); (2) a significant genetic correlation between intoxication and regular smoking (in women at least; Madden et al., 1997); and (3) using follow-up diagnostic interview data, that level of response to alcohol (a

composite of ataxia and subjective intoxication) was strongly associated with alcohol dependence in men, with a nonsignificant trend in women (Heath et al., 1999). These findings raise the question of whether a change in subjective experiences with alcohol, altered by cigarette use, may in part account for the familial association between a history of cigarette smoking and different stages of alcohol use and dependence.

CONCLUSION

In conclusion, there is evidence of a strong familial association that is, at least in part, genetically determined, between stages in the consumption of alcohol and of cigarettes, from initial use to continued use and dependence. However, existing studies leave many important questions unanswered. For instance, it remains unclear at what stages in the progression from initial experimentation through onset of regular smoking to nicotine dependence an increased risk for problems with alcohol arise and whether factors responsible for shared genetic risk between these two substances remain consistent from early adolescence through adulthood. The extent to which shared personality, sociodemographic, and psychiatric risk factors that are heritable contribute to the shared genetic risk between alcoholism and different aspects of cigarette smoking, particularly nicotine dependence, remains to be clarified. The Australian sample analyzed by Madden et al. (2000), for example, did not complete an assessment of nicotine dependence. Limited experimental data concerning the association between level of response to alcohol and smoking history raises the possibility that cigarette smoking directly increases risk of alcohol dependence, a critical question that should be addressed in future research. If indeed there is a direct causal influence of cigarette smoking on risk of alcohol dependence, then the strong association between cigarette smoking and alcohol use during adolescence suggests a need for prevention efforts that target both substances jointly.

In the coming years, we may anticipate identification of genetic loci with important effects on risk of cigarette smoking and nicotine dependence and the determination of whether these same loci predict differences in risk of alcohol dependence. It will still be necessary, however, to identify the mechanisms by which such gene effects translate into joint increases in risk of cigarette smoking and alcohol dependence. Gene-mapping studies to identify common genetic risk factors, molecular epidemiologic studies (cf. Heath et al., 2001) that characterize their effects and interactions with other (including environmental) risk factors, and human and animal experimental studies that dissect the joint and separate effects of nicotine and alcohol (ideally, stratified by identified genetic risk factors) will play an important role in helping to improve our understanding of the co-occurrence of cigarette smoking and alcohol dependence.

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