

The Behavioral Genetics of Alcoholism

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Abstract

Twin and adoption studies consistently implicate the importance of genetic influences on alcoholism risk, especially in men. Heritability estimates suggest that approximately 50% to 60% of the variability in alcoholism liability is associated with genetic factors. Although there has been progress in identifying specific genes that predispose toward alcoholism, we know relatively little about the nature of the genetic influence on alcoholism risk. We also know relatively little about how genetic factors combine with environmental factors to affect alcoholism risk. Genotype-environment interaction models posit that alcoholism occurs when individuals both inherit a vulnerability to develop alcoholism and are reared in a provocative environment. Such models hold great promise for understanding alcoholism's etiology.

Keywords

alcoholism; heritability; genotype-environment interaction

Alcoholism is a common and costly (both economically and socially) behavioral disorder. In an effort to inform prevention and intervention efforts, alcohol researchers have attempted to identify the major factors that contribute to alcoholism risk. As a consequence of these efforts, we know that alcoholism rates are higher among persons who were reared in an environment where drinking was tolerated or encouraged, among those with certain personality characteristics, among those suffering from other forms of mental illness, and, especially, among those who are biologically related to an alcoholic. Indeed, one of the most consistently implicated predictors of alcoholism risk is a positive family history, with the biological offspring of alcoholics being approximately three to five times more likely to develop alcoholism during their lifetime than the biological off-

spring of nonalcoholics (Cotton, 1979).

A positive family history can, of course, reflect shared environmental influences, common genetic effects, or both. Behavioral geneticists have used twin and adoption studies to identify the separate contributions of genetic and shared environmental factors to the familial transmission of alcoholism. In so doing, they have documented the substantial contribution of genetic factors to alcoholism risk, laid the foundation for efforts to identify genes associated with alcoholism, and helped to characterize the nature of environmental contributions.

THE GENETIC EPIDEMIOLOGY OF ALCOHOLISM

The most direct demonstration of genetic contributions to the familial transmission of alcoholism comes from adoption studies investigating rates of alcoholism among adopted ("reared-away") offspring of parents with alcoholism. Such studies have consistently shown that the reared-away sons of male alcoholics have higher rates of alcoholism than the reared-away sons of nonalcoholics (McGue, in press). The finding of genetic influences in adoption studies is further support

ed by twin studies that have compared the concordance rate for alcoholism (i.e., the rate of alcoholism in twins of alcoholics) among genetically identical, monozygotic (MZ) twins and dizygotic (DZ) twins (who share on average only 50% of their genes). There have been eight major twin studies of alcoholism in men, and in all but one of these studies the concordance rate for alcoholism was significantly greater in MZ than DZ twins (McGue, in press). The robustness of the finding of genetic influences on risk of alcoholism in men is nicely illustrated by a recent study by

Kendler, Prescott, Neale, and Pedersen (1997). In successive cohorts of nearly 9,000 Swedish male twins born from 1902 to 1949, MZ twin concordance always significantly exceeded DZ twin concordance, which in turn always significantly exceeded the prevalence of alcoholism in the total twin sample (Fig. 1).

In quantifying the strength of genetic influence, behavioral geneticists typically decompose the variance of a quantitative trait into its genetic and environmental components. A trait's heritability is the proportion of trait variance that

can be attributed to genetic factors. For a categorical trait like diagnosis of alcoholism, the heritability applies to an assumed underlying quantitative continuum (usually called liability), rather than to the categorical trait itself (Fig. 2). In other words, the members of a population have varying degrees of liability, and those individuals whose positions on the continuum of liability are above a certain threshold are alcoholics. Heritability can be estimated from a twin study. In studies of male twins, heritability estimates have ranged from 49% to 64%, indicating that from one half

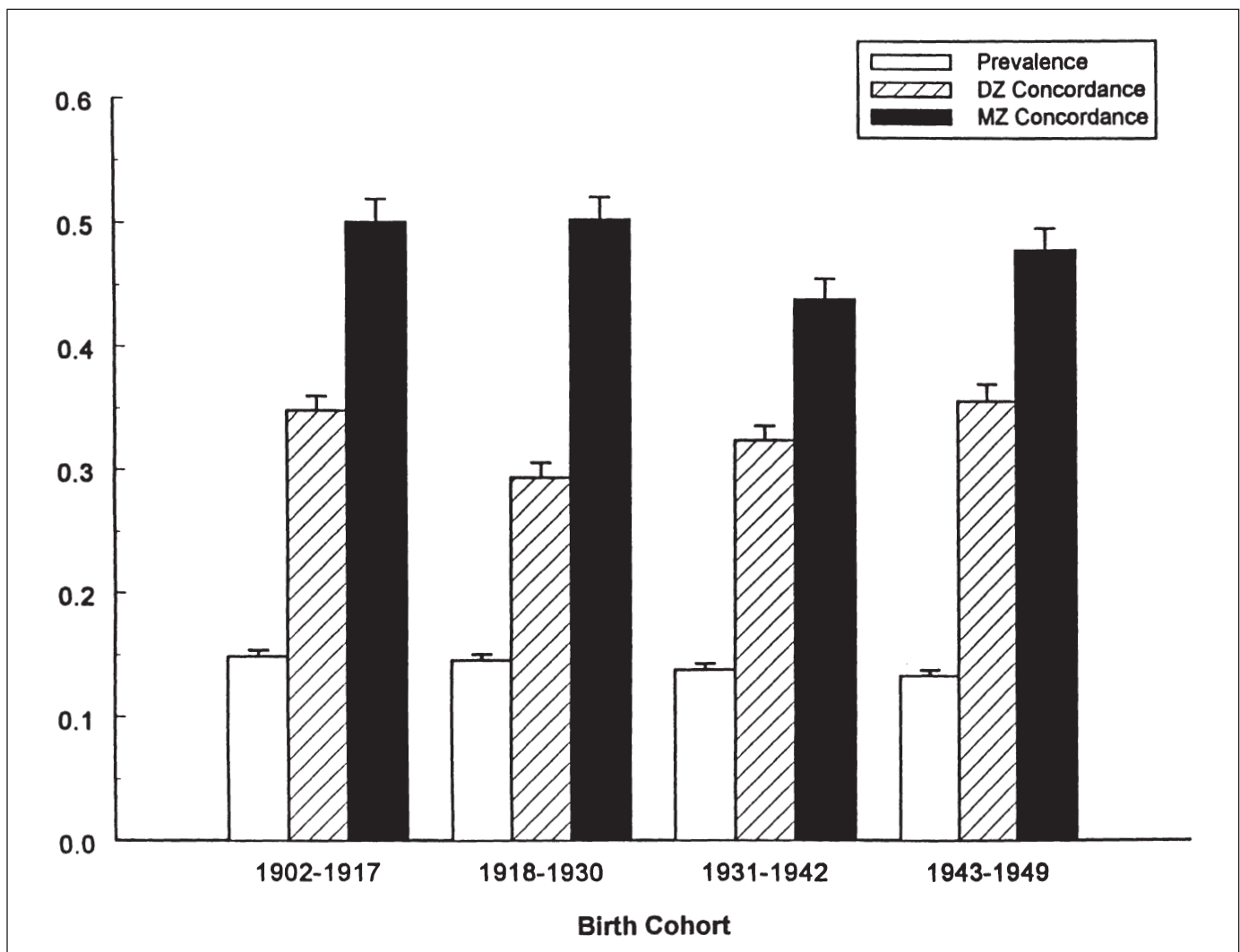


Fig. 1. Prevalence of alcoholism in twins and monozygotic (MZ) and dizygotic (DZ) twin concordance for alcoholism in a study of 8,935 pairs of Swedish male twins. Adapted from data reported by Kendler, Prescott, Neale, and Pedersen (1997). Bars demarcate 1 standard error.

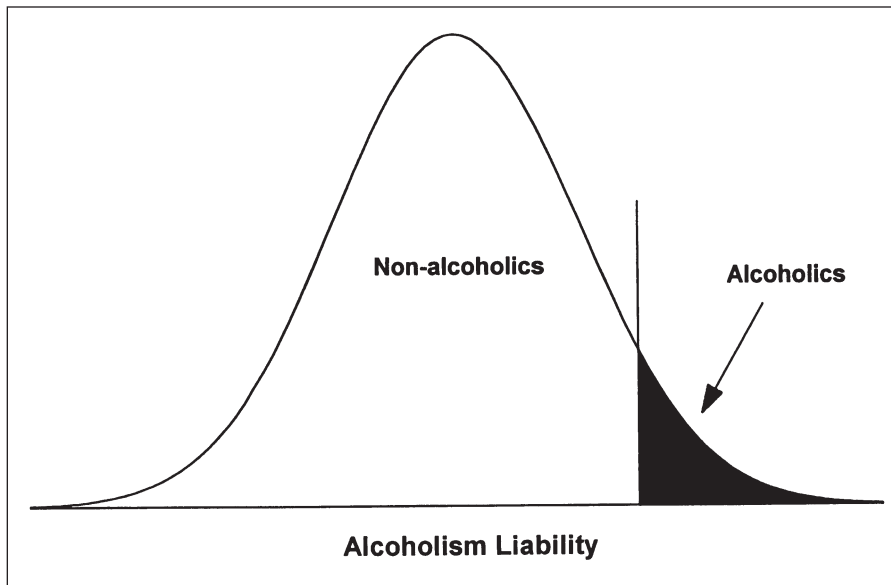


Fig. 2. The liability-threshold model of alcoholism. The categorical classification of alcoholism is assumed to be a manifestation of an underlying quantitative continuum termed liability. Heritability estimates from twin studies of alcoholism estimate the percentage of variance in the underlying liability that is associated with genetic factors.

to two thirds of the variance in alcoholism liability is associated with genetic factors.

Alcoholism is, of course, a clinically heterogeneous disorder, and a question of substantial theoretical and practical significance concerns whether there are alternative forms of alcoholism that are differentially heritable. Based on findings from the Stockholm Adoption Study, Cloninger (1987) distinguished a form of alcoholism characterized by a relatively late onset and neurotic features (designated Type I) from a form characterized by a relatively early onset and elevated levels of antisocial behavior (designated Type II). Analysis of data from male adoptees showed that although Type II alcoholism was strongly heritable (estimated heritability of 90%), Type I alcoholism was only moderately heritable (heritability estimate of less than 40%). Many of the key results from the original Stockholm Adoption Study were recently independently replicated in a second Swedish city, Gothenburg (Sigvardsson, Bohman, & Cloninger, 1996).

In contrast to studies on male alcoholics, twin and adoption studies of women have not consistently reported genetic effects on alcoholism risk. The reared-away daughters of alcoholics have not always been found to have a higher rate of problem drinking or alcoholism than the reared-away daughters of nonalcoholics, and concordance for alcoholism in female MZ twins has not consistently exceeded concordance for alcoholism in female DZ twins (McGue, in press). Although the failure to consistently observe genetic effects has led some researchers to conclude that genetic factors contribute less to the etiology of alcoholism in women than in men, the two most recent twin studies of alcoholism in women have reported heritability estimates that are comparable to those reported in studies of men (i.e., 50% and greater; Heath et al., 1997). Because these two studies are also the largest and best designed of the twin studies of alcoholism in women (the earlier studies lacked statistical power because of small sample size), the hypothesis that alcoholism is as heritable in women

as men has gained acceptance among many behavioral geneticists. Nonetheless, there are differences in the development of alcoholism in men and women (e.g., a history of childhood abuse is predictive in women but not men, age of onset is typically later in women than in men; Howard, Martin, Mail, Hilton, & Taylor, 1996), and the differential contribution of genetic factors to the etiology of alcoholism in women and men is an issue that is not completely resolved by the existing literature.

THE MOLECULAR GENETICS OF ALCOHOLISM

The familial transmission of alcoholism does not follow the classic patterns of inheritance first observed by Mendel, indicating that alcoholism is a complex disorder whose genetic effect is not due to a single gene, but rather is due to multiple contributing genes. Identifying genes contributing to complex characters has been notoriously difficult, and, not unexpectedly, early attempts to identify genes contributing to alcoholism risk generally failed to produce unambiguous or replicable results. The recent development of powerful gene-mapping methodologies as part of the Human Genome Project has, however, provided researchers with the tools needed to systematically search for genes affecting complex characters (Schork & Schork, 1998). The past 5 years have witnessed progress in identifying genes predisposing to complex disorders, including alcoholism.

One of the best examples of an association between a specific gene and human behavior comes from the study of alcoholism. Ethanol is metabolized in the liver, where it is converted to acetaldehyde by the enzyme alcohol dehydrogenase

(ADH). Acetaldehyde, in turn, is converted to acetate by the enzyme aldehyde dehydrogenase (ALDH). There is variation in the genes coding for both these enzymes. Because high levels of acetaldehyde in the blood are associated with the unpleasant effects of drinking (e.g., nausea, dizziness, headaches), variation in the genes coding for the ADH and ALDH enzymes might be expected to be associated with alcoholism risk.

Approximately one third to one half of East Asians inherit a deficiency in the form of ALDH (designated ALDH2) that metabolizes most of the ethanol in the cell (Agarwal & Goedde, 1989). Individuals with ALDH2 deficiency have a greatly diminished capacity to convert acetaldehyde to acetate. As a consequence, they are much more likely than those having functional ALDH2 to experience the dysphoric effects of drinking, and much less likely to chronically abuse alcohol to the degree needed to develop alcoholism. Consistent with this account, rates of ALDH2 deficiency are some 20 to 30 times lower among East Asian alcoholics than among East Asian nonalcoholics (e.g., Harada, Agarwal, Goedde, Tagaki, & Ishikawa, 1982).

The relationship between ALDH2 deficiency and alcoholism risk illustrates the probabilistic relationship between genes and human behavior. Some East Asians who inherit the protective ALDH2 deficiency nonetheless become alcoholic. Although metabolic factors (e.g., variation in genes coding for ADH) may help to account for differential rates of alcoholism among individuals who are ALDH2 deficient, it also appears that cultural factors can moderate the protective effect of ALDH2 deficiency. Higuchi et al. (1994) reported that the rate of ALDH2 deficiency among Japanese alcoholics increased from 2.5% in 1979 to 8.0%

in 1986 and 13.0% in 1992. This increase came during a period when per capita alcohol consumption in Japan was also increasing, suggesting that the protective effect of ALDH2 deficiency has diminished as Japanese culture has become more accepting of alcohol consumption.

In 1989, the National Institute on Alcohol Abuse and Alcoholism initiated the Collaborative Study on the Genetics of Alcoholism (COGA), a large, systematic effort to identify the genes that predispose to alcoholism. By identifying genetic markers that reliably predict the transmission of alcoholism within multigenerational alcoholic families (a strategy known as genetic linkage), COGA researchers aim to identify regions of the human genome that are likely to contain genes influencing alcoholism risk. This is the first step in a process that involves successive narrowing of the region until it is sufficiently narrow to allow the gene's DNA sequence to be determined. In 1998, COGA researchers published their initial linkage findings based on an analysis of nearly 300 genetic markers (Reich et al., 1998). Suggestive evidence for the existence of genes increasing alcoholism risk was found for Chromosomes 1 and 7, while a third region on Chromosome 4 was implicated as containing a gene (or genes) that protects against alcoholism. At the same time as the COGA findings were published, a second large-scale linkage study of alcoholism, based on a sample of Native Americans, reported suggestive evidence of the existence of a predisposing gene (or genes) on Chromosome 11 and a protective gene (or genes) on Chromosome 4 (Long et al., 1998). Although only the Chromosome 4 findings overlap, the two studies sampled different ethnic groups, and the genes that underlie alcoholism risk might reasonably be expected to vary for

groups having distinct evolutionary histories. In any case, these studies represent important initial attempts to localize the genes predisposing to alcoholism. Over the next few years, researchers will attempt to replicate these results and narrow the implicated genomic regions, as well as identify other regions of relevance to alcoholism.

THE NATURE OF ENVIRONMENTAL INFLUENCE

It is clear that genetic factors, although important, cannot alone account for individual differences in alcoholism risk. Concordance rates for alcoholism among MZ twins are uniformly, and usually substantially, less than 100%, and heritability analyses suggest that as much as half of the variance in alcoholism liability is nongenetic in origin. In characterizing the nature of nongenetic influence, behavioral geneticists have found it useful to distinguish shared environmental influences (i.e., those environmental influences that are shared by relatives who are reared together and that therefore contribute to their behavioral similarity) from nonshared environmental influences (i.e., those environmental influences that are not shared by relatives who are reared together and that are thus a source of their behavioral dissimilarity). Analyses of twin data suggest that the predominant source of nongenetic variance in alcoholism risk is attributable to nonshared rather than shared environmental factors (e.g., Heath et al., 1997). Nonetheless, alcoholism may be relatively unusual among behavioral disorders in being affected by shared family environmental effects as well.

The contribution of shared environmental factors to alcoholism risk can be established most direct-

ly by studying adoptive families, in which resemblance is environmentally, and not genetically, mediated. Most studies of adoptive families have not found an increased risk of alcoholism among the non-biologically related children of alcoholic adoptive parents (McGue, in press). One research group, however, has reported two separate studies showing that individuals reared in an adoptive family containing an alcoholic member experienced a significant increase in alcoholism risk (e.g., Cadoret, Troughton, & O'Gorman, 1987). However, a positive adoptive-family history was based on sibling as well as parental alcoholism in these two studies, but on parental alcoholism only in the studies that failed to observe a significant adoptive-family effect. It may be that sibling, rather than parental, alcoholism is the most potent family environmental influence on alcoholism.

In order to investigate parent versus sibling effects, my colleagues and I recently completed an adoption study of alcohol use and misuse among adolescents (McGue, Sharma, & Benson, 1996). Our findings were consistent with previous adoption studies indicating that parent-offspring resemblance for alcohol-related measures is genetically and not environmentally mediated: We found that parents' problem drinking was significantly correlated with adolescents' alcohol involvement for biological offspring (multiple correlation of .30, $p < .05$), but not adoptive offspring (multiple correlation of .04, n.s.).

Nonetheless, we observed significant resemblance in the alcohol involvement of adoptive sibling pairs who were not biologically related ($r = .24$, $p < .01$), suggesting that shared environmental factors accounted for approximately 25% of the variance in adolescents' alcohol use and misuse.² Moreover, the correlation between adoptive siblings was significant and sub-

stantial among like-sexed siblings who were within 2 years of age ($r = .45$), but nonsignificant among unlike-sexed siblings who differed by more than 2 years in age ($r = .01$). These findings implicate siblings as a more likely source of family environmental influence than parents. This finding is at odds with the parent-centered focus of much (non-behavioral-genetic) research aimed at identifying the environmental origins of alcoholism. By failing to consider genetic contributions, however, earlier investigators may have misinterpreted parent-offspring resemblance for alcohol measures as evidence of parental environmental influence.

THE JOINT INFLUENCE OF GENETIC AND ENVIRONMENTAL FACTORS

The diathesis-stress model that provides the conceptual framework for much psychopathology research posits the existence of an inherited predisposition (i.e., the diathesis) that manifests as psychopathology only when the individual is exposed to a provocative environment (i.e., stress). The validity of the diathesis-stress formulation in the case of alcoholism is supported not only by the research on ALDH2 deficiency reviewed earlier, but also by findings from adoption studies that indicate genetic background interacts with rearing circumstance to predict adoptees' risk of alcoholism.

The strongest evidence for genotype-environment interaction effects for alcoholism comes from the Swedish adoption studies. In the original sample of adoptees from Stockholm, the genetic and environmental backgrounds of male adoptees were classified as either high or low risk for Type I alco-

holism (i.e., the form of alcoholism that is hypothesized to be least heritable and thus most susceptible to environmental influence). A significantly elevated rate of Type I alcohol abuse was observed only among adoptees classified as high risk on both dimensions. This interaction effect was independently replicated in a sample of male adoptees from Gothenburg for severe (i.e., recurrent) Type I alcohol abuse (Fig. 3), but not for mild Type I alcohol abuse. Even though the original Stockholm findings were not completely replicated in Gothenburg, the Swedish adoption studies provide a useful illustration of how adoption studies can be used to characterize the potentiating effect of environmental factors on inherited risk.

PROSPECTS

The past 25 years of behavioral genetic research have unambiguously documented the existence of genetic influences on alcoholism risk. Nonetheless, we know relatively little about the mechanisms underlying those influences and the processes by which genetic and environmental factors combine to affect alcoholism risk. Clearly, gene identification will be a major focus of future behavioral genetic research in this area, and these efforts will benefit greatly from the progress of the Human Genome Project, as well as from research aimed at identifying the specific genetic contributions to alcohol-related measures in nonhuman animals. Although gene-identification efforts should ultimately help in explicating the physiological pathways underlying alcoholism, it is important to recognize that the effects of genes on behavior are necessarily indirect. Genetic influences are likely to be mediated by the personality characteristics, psy-

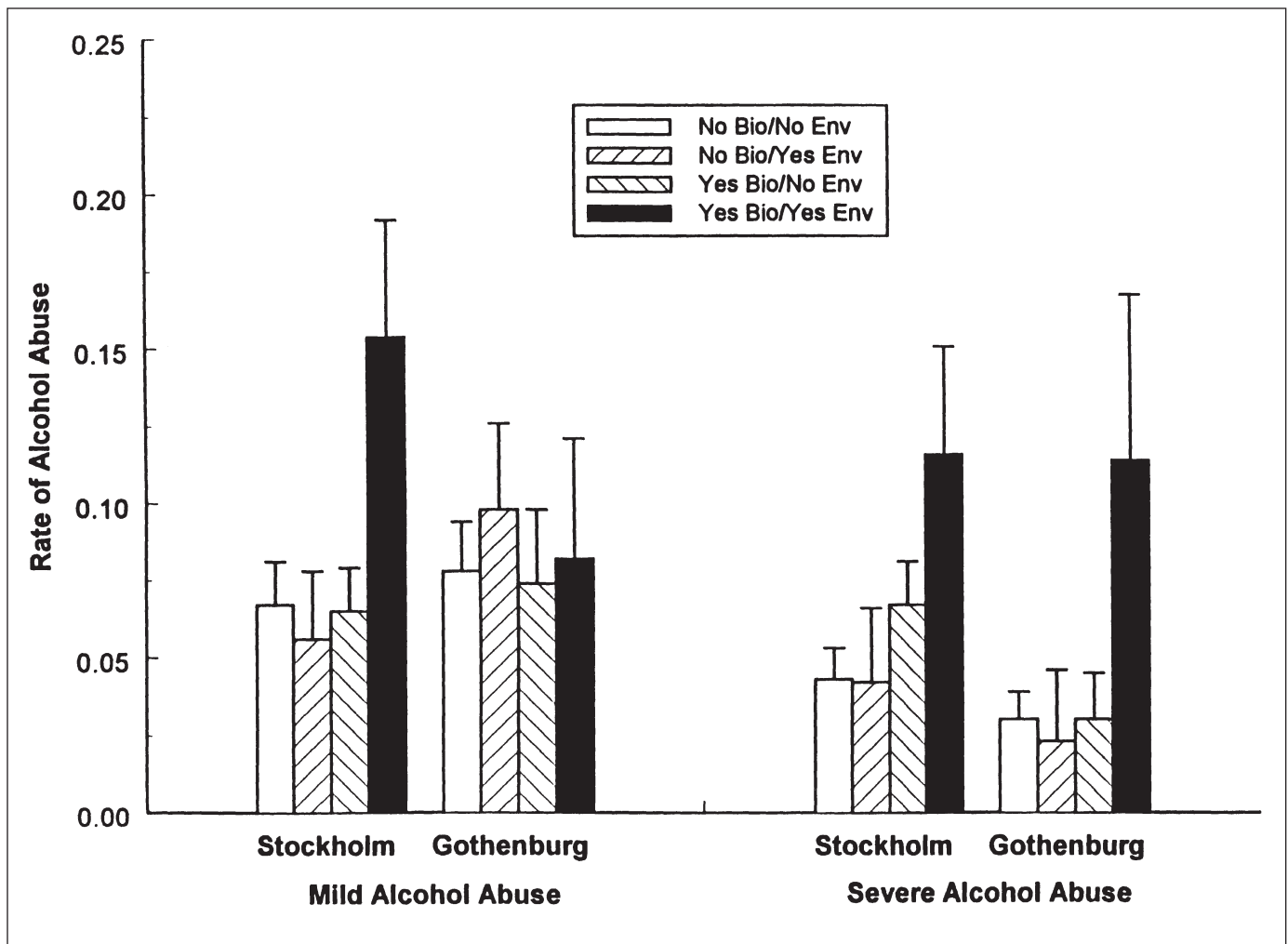


Fig. 3. Rate of Type I alcoholism in Swedish male adoptees as a function of biological and environmental background. Functions determining degree of biological and environmental risk were determined statistically in the Stockholm sample and applied independently to the Gothenburg sample. Adoptees' biological and environmental backgrounds were separately classified as either high risk (designated as "Yes Bio" and "Yes Env") or low risk (designated as "No Bio" and "No Env") for developing alcoholism. Adapted from data reported by Sigvardsson, Bohman, and Cloninger (1996). Bars demarcate 1 standard error.

chopathology, and psychophysiological markers known to be associated with alcoholism risk. Explaining how genetic factors affect alcoholism risk will ultimately require not only identifying the specific genes involved, but also determining how mediating inherited factors interact with experience to affect the etiology of alcoholism.

Recommended Reading

Begleiter, H., & Kissin, B. (1995). *The genetics of alcoholism*. New York: Oxford University Press.

McGue, M. (in press). (See References)
National Institute on Alcohol Abuse and Alcoholism. (1995). The genetics of alcoholism [Special issue]. *Alcohol Health & Research World*, 19(3).

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Notes

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2. The square of the correlation between two observed variables estimates the percentage of variance in one that is accounted for by, or predictable from, the second. We are not, however, interested in the percentage of variance for a measure (phenotype) on an individual that is predictable from knowledge of his or her sibling's phenotype, but rather, we are interested in the percentage of variance in an individual's phenotype that can be attributed to the unobserved environment shared with his or her sibling. In this case, the observed sibling correlation provides a direct estimate of the percentage of phenotypic variance attributable to the unobserved shared factor.

References

- Agarwal, D.P., & Goedde, H.W. (1989). Human aldehyde dehydrogenases: Their role in alcoholism. *Alcohol*, *6*, 517-523.
- Cadore, R.J., Troughton, E., & O'Gorman, T.W. (1987). Genetic and environmental factors in alcohol abuse and antisocial personality. *Journal of Studies on Alcohol*, *48*, 1-8.
- Cloninger, C.R. (1987). Neurogenetic adaptive mechanisms in alcoholism. *Science*, *236*, 410-416.
- Cotton, N.S. (1979). The familial incidence of alcoholism: A review. *Journal of Studies on Alcohol*, *40*, 89-116.
- Harada, S., Agarwal, D.P., Goedde, H.W., Tagaki, S., & Ishikawa, B. (1982). Possible protective role against alcoholism for aldehyde dehydrogenase isozyme deficiency in Japan. *Lancet*, *ii*, 827.
- Heath, A.C., Bucholz, K.K., Madden, P.A.F., Dinwiddie, S.H., Slutske, W.S., Bierut, L.J., Statham, D.J., Dunne, M.P., Whitfield, J.B., & Martin, N.G. (1997). Genetic and environmental contributions to alcohol dependence risk in a national twin sample: Consistency of findings in women and men. *Psychological Medicine*, *27*, 1381-1396.
- Higuchi, S., Matsushita, S., Imazeki, H., Kinoshita, T., Takagi, S., & Kono, H. (1994). Aldehyde dehydrogenase genotypes in Japanese alcoholics. *Lancet*, *343*, 741-742.
- Howard, J.M., Martin, S.E., Mail, P.D., Hilton, M.E., & Taylor, E.D. (1996). *Women and alcohol: Issues for prevention research* (Research Monograph No. 32, NIH Publication No. 96-3817). Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism.
- Kendler, K.S., Prescott, C.A., Neale, M.C., & Pedersen, N.L. (1997). Temperance Board registration for alcohol abuse in a national sample of Swedish male twins, born 1902 to 1949. *Archives of General Psychiatry*, *54*, 178-184.
- Long, J.C., Knowler, W.C., Hanson, R.L., Robin, R.W., Urbanek, M., Moore, E., Bennett, P.H., & Goldman, D. (1998). Evidence for genetic linkage to alcohol dependence on chromosomes 4 and 11 from an autosome-wide scan in an American Indian population. *American Journal of Medical Genetics (Neuropsychiatric Genetics)*, *81*, 216-221.
- McGue, M. (in press). Behavioral genetic models of alcoholism and drinking. In K.E. Leonard & H.T. Blane (Eds.), *Psychological theories of drinking and alcoholism*. New York: Guilford Press.
- McGue, M., Sharma, A., & Benson, P. (1996). Parent and sibling influences on adolescent alcohol use and misuse: Evidence from a U.S. adoption cohort. *Journal of Studies on Alcohol*, *57*, 8-18.
- Reich, T., Edenberg, H.J., Goate, A., William, J.T., Rice, J.P., Van Eerdewegh, P., Foroud, T., Hesselbrock, V., Schuckit, M.A., Bucholz, K., Porjesz, B., Li, T.K., Conneally, P.M., Nurnberger, J.I., Tischfield, J.A., Crowe, R.R., Cloninger, C.R., Wu, W., Shears, S., Carr, K., Crose, C., Willig, C., & Begleiter, H. (1998). Genome-wide search for genes affecting risk for alcohol dependence. *American Journal of Medical Genetics (Neuropsychiatric Genetics)*, *81*, 206-215.
- Schorck, N.J., & Schork, C.M. (1998). Issues and strategies in the genetic analysis of alcoholism and related addictive behaviors. *Alcohol*, *16*, 71-83.
- Sigvardsson, S., Bohman, M., & Cloninger, C.R. (1996). Replication of the Stockholm Adoption Study of alcoholism: Confirmatory cross-fostering analysis. *Archives of General Psychiatry*, *53*, 681-687.