THE SCIENCE OF PREVENTION

METHODOLOGICAL ADVANCES FROM ALCOHOL AND SUBSTANCE ABUSE RESEARCH

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BEHAVIORAL GENETIC METHODS IN PREVENTION RESEARCH: AN OVERVIEW

ANDREW C. HEATH, WENDY S. SLUTSKE, KATHLEEN K. BUCHOLZ, PAMELA A. F. MADDEN, AND NICHOLAS G. MARTIN

In this chapter, we focus on the potential contributions of behavioral genetic methods to prevention research. We use illustrations drawn primarily from research on alcoholism. However, as reviewed in a recent book on behavioral genetic methods in behavioral medicine (J. R. Turner, Cardon, & Hewitt, 1994), these same methods apply to a broad range of other disorders, including diverse topics such as obesity and eating disorders, stress, cardiovascular reactivity, smoking, and illicit drug use. We begin by reviewing the evidence for an important genetic contribution to alcoholism risk. We then provide an overview of the types of research questions that may be addressed most powerfully in a behavioral genetic framework, ex-

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panding on ideas originally summarized by Heath (1993). We examine some of the research challenges that arise in behavioral genetic research on alcoholism and other disorders. Finally, from these considerations, we draw conclusions about appropriate sampling strategies for prevention research in a behavioral genetic framework and examine their implications for other prevention and epidemiological research strategies.

THE GENETIC CONTRIBUTION TO ALCOHOLISM RISK

Adoption and twin studies using samples that have been ascertained systematically from birth or adoption records provide compelling evidence for an important genetic influence on alcoholism risk in both men and women (Heath, Slutske, & Madden, in press; McGue, 1994). (Later, we review some of the problems associated with studies using twins identified through treatment sources, which have yielded more inconsistent results; Caldwell & Gottesman, 1991; Gurling, Oppenheim, & Murray, 1984; McGue, Pickens, & Svikis, 1992; Pickens et al., 1991.) Studies of samples of male like-sex twin pairs identified from birth records, conducted in Sweden (Allgulander, Nowak, & Rice, 1991, 1992; Kaij, 1960), Finland (Koskenvuo, Langinvainio, Kaprio, Lonnqvist, & Tienari, 1984; Romanov, Kaprio, & Rose, 1991), and the United States (Hrubec & Omenn, 1981), consistently have shown a higher (albeit not always significantly higher) rate of alcoholism in monozygotic (MZ) than in dizygotic (DZ) cotwins of male alcoholics. With one exception, adoption studies conducted in Denmark (Goodwin, Schulsinger, Hermansen, Guze, & Winokur, 1973; Goodwin et al., 1974), Sweden (Bohman, Sigvardsson, & Cloninger 1981; Cloninger, Bohman, & Sigvardsson, 1981, 1985), and the United States (Cadoret, 1994; Cadoret, Cain, Troughton, & Heywood, 1985; Cadoret, Troughton, & O'Gorman, 1987) have shown higher rates of alcoholism in the adopted-away sons of alcoholic biological parents than in control adoptees; the one study that failed to indicate a difference showed abnormally high rates of alcoholism in its male control adoptees (Cadoret, 1994). This consistency of findings is especially remarkable given the diversity of assessments of alcoholism used in different studies, ranging from diagnostic interviews (Cadoret, 1994; Cadoret et al., 1985, 1987; Goodwin et al., 1973, 1974) to U.S. Veterans Administration treatment records (Hrubec & Omenn, 1981), hospital discharge codes (Allgulander et al., 1991, 1992; Koskenvuo et al., 1984; Romanov et al., 1991; True et al., 1996), annotations in adoption records (Cadoret, 1994; Cadoret et al., 1985, 1987), and registrations with the Swedish Temperance Board, a now-defunct organization that was charged with handling cases of public drunkenness and other alcohol-related problems (Cloninger et al., 1981, 1985; Kaij, 1960; Kendler, Prescott, Neale, & Pedersen, 1997).

Evidence for an important genetic influence on alcoholism in women, based on samples ascertained systematically from birth or adoption records, has been much weaker. The Danish adoption study of Goodwin, Schulsinger, Knop, and Mednick (1977) and Goodwin, Schulsinger, Knop, Mednick, and Guze (1977) showed rates of alcoholism that were no higher in adopted-away daughters of alcoholic parents than in control female adoptees, while the Swedish adoption study of Cloninger and colleagues (Bohman et al., 1981; Cloninger et al., 1985) showed a significant association between alcohol problems in female adoptees and their biological mothers, but not their biological fathers. In the United States, one study did indicate a significantly elevated risk of alcoholism in the adopted-away daughters of alcoholic parents (Cadoret et al., 1985), but a second study by the same group did not (Cutrona et al., 1994). Findings from twin studies have been similarly inconclusive. No concordant alcoholic female pairs were found in the Finnish twin study (Koskenvuo et al., 1984), whereas in the similar study of Swedish twins by Allgulander et al. (1991, 1992), although there was a trend for higher rates of alcoholism in the MZ than in the DZ twins of alcoholic parents, this was not significant (reanalyzed by Heath, Slutske, & Madden, in press). In a study of female like-sex twin pairs born in Virginia, Kendler, Heath, Neale, Kessler, and Eaves (1992) could not reject the hypothesis of no genetic influence for alcohol dependence (as defined by criteria from the revised third edition of the *Diagnostic and Statistical Manual of Mental Disorders [DSM–III–R]*, American Psychiatric Association, 1987), although significant evidence for genetic effects was found if either a broader problem-drinking measure or a more restrictive measure requiring physiological dependence (defined as *tolerance* or *withdrawal*) was used.

The weakness of this evidence for a genetic influence on alcoholism risk in women has led some to suggest that there may be a subtype of alcoholism that is predominant in women and shows only modest heritability, with strong moderation by environmental influences (Cloninger, 1987). In high-risk research on the offspring of alcoholic parents, it has also led to a much stronger focus on men than women (e.g., as reviewed by Sher, 1991). Failure to reject the null hypothesis of no genetic influence in women, however, is not convincing evidence that genetic effects are unimportant. Such a failure also may be a function of low statistical power: Given the lower base rate of alcoholism in women (Kessler et al., 1994; L. N. Robins & Regier, 1991), much larger numbers of female relatives of alcoholic individuals are needed to demonstrate a genetic effect. A more convincing demonstration would be to show that genetic factors are significantly more important in men than in women, that is, that they account for a significantly higher proportion of the total variance in alcoholism risk (i.e., have significantly higher heritability). If low statistical power is explaining the negative results in women, it should not be possible to demonstrate significantly lower heritability of alcoholism in women than

EXHIBIT 1
Nine Key Questions About the Causes of Alcoholism

1. How do genes act to increase alcoholism risk? What are the mediators—biological, sociodemographic, or behavioral—of genetic influences on alcoholism risk?
2. Are individuals at high genetic risk also more likely to be exposed to high-risk environments (gene–environment correlation)?
3. What environmental risk factors contribute to alcoholism risk?
4. Can researchers identify individual genetic loci that contribute to differences in alcoholism risk and understand their mode of action?
5. Can researchers identify alcoholic subtypes with distinct modes of inheritance or type-specific risk factors?
6. How do genetic and environmental influences vary as a function of gender, birth cohort, or culture?
7. How do genetic and environmental influences unfold through time to determine the natural history of drinking and of alcohol-related problems?
8. What vulnerability or protective factors exacerbate or reduce the risk of alcoholism in individuals at high genetic risk? How important is Genotype × Environment interaction?
9. At what levels of exposure to alcohol does genetic predisposition become important?

in men. This is indeed what we have found. When we reanalyzed data from the genetic studies that included both women and men, we found that it was not possible in any study to reject the hypothesis that there was no gender difference in the magnitude of the genetic influence on alcoholism risk (Heath, Slutske, & Madden, in press). In the absence of further contrary data, we consider it most appropriate to assume that genetic factors play no less a role in determining alcoholism risk in women than in men.

The demonstration of a significant genetic influence on alcoholism risk is often (but erroneously) viewed as an end point for behavioral genetic research; instead, it should be viewed as a beginning (Heath, 1993). In Exhibit 1, we summarize nine key questions about the causes of alcoholism. The questions focus on how genes and environment coact and interact, how their influences unfold through development, and the behavioral and biological pathways from genotype to alcoholism risk. It will become apparent that progress in answering these questions is only just beginning. Because the questions provide a framework in which the influences of genes and environment may be studied jointly, behavioral genetic methods have enormous potential for addressing such questions.

DEFINING WHO IS AT RISK

On the basis of an unpublished series of meta-analyses (summarized by Heath, 1995a), we have estimated that in individuals of European an-

cestry, genetic factors may account for as much as 60% of the total variance in alcoholism risk. (Insufficient numbers of other population groups, such as African Americans or Hispanics, have been studied using behavioral genetic methods.) Results from a telephone interview survey of approximately 6,000 adult Australian twins (Heath, Bucholz, et al., in press) yielded comparable estimates for the heritability of alcoholism, operationalized as *DSM–III–R* alcohol dependence, in both women and men. This information in itself is important for prevention efforts because it confirms that abstinence, or increased vigilance about drinking practices, is necessary for those with a family history of alcoholism.

Unfortunately, assuming that multiple genetic and environmental risk factors contribute to differences in alcoholism risk, many individuals at high genetic risk will have no affected immediate family members. For example, assuming 60% heritability of a broadly defined measure of alcohol dependence, with a lifetime prevalence of 24% in men and 6% in women, in both parental and offspring generations, and allowing for a modest degree of assortative mating (i.e., the tendency for alcoholic individuals to marry other alcoholic individuals) with a spousal correlation of .4, we can compute that slightly more than 50% of the men who become alcoholic and 38% of the women will have no parental history of alcoholism. Conversely, many of those from a high-risk genetic background would not be expected to become alcoholic. Under these same assumptions, 40% of men who have only an alcoholic father, 44% of men who have only an alcoholic mother, but 65% of men with both parents alcoholic would be expected to become alcoholic. Because of the much lower base rate assumed for women than men, corresponding proportions for women would be only 11.6%, 13.6%, and 28.4%, respectively. (These illustrative estimates were obtained under the assumption that alcoholism liability is approximately normally distributed in the general population, by integrating the quadrivariate normal distribution for a correlational structure defined by our heritability and assortative mating parameters, ignoring shared environmental causes of familial resemblance.) For women with both an alcoholic mother and maternal aunt, the risk increases to 36.5% if both parents are affected, implying that special sampling schemes may be necessary for high-risk research on women (cf. Hill, 1995).

In what ways can researchers improve identification of individuals at increased risk of alcoholism, for whom targeted prevention efforts may be appropriate? Behavioral genetic methods can play a crucial role in addressing six related questions: (a) What mediating variables can researchers identify that explain the behavioral or biological pathways by which genetic and environmental risk factors act to increase alcoholism risk; (b) are individuals at high genetic risk more likely to be exposed to high-risk environments (genotype–environment correlation); (c) what environmental factors contribute to differences in alcoholism risk; (d) what individual

genetic loci can researchers identify that contribute to differences in alcoholism risk, and what can they discover about their mode of action; (e) can researchers identify subtypes of alcoholic individuals, who may differ in their mode of inheritance or associated risk factors; and (f) how do genetic and environmental influences unfold through time to determine the natural history of drinking and of alcohol-related problems?

Mediating Variables

The search for mediating variables—in our case, variables that may intervene in the causal pathways from genotype (or environment) to alcoholism risk—has a long history in alcoholism research. Much recent pertinent work has been carried out within the framework of high-risk studies on the offspring of alcoholic parents and in epidemiological research on psychiatric comorbidity with alcoholism (see Sher, 1991, for a review of recent research). Examples may be found in Schuckit's (1984, 1985; Schuckit & Gold, 1988) alcohol challenge research demonstrating differences in objective (e.g., body sway) and subjective (e.g., self-rated intoxication) responses to alcohol between the sons of alcoholic and control parents, differences that were predictive of alcoholism rates at longitudinal follow-up (Schuckit, 1994), or in the evoked potential research of Begleiter, Porjesz, Bihari, and Kissin (1984) demonstrating P300 differences between alcohol-naive sons of alcoholic and control parents (see Polich, Pollock, & Bloom, 1994, for a recent review). In both cases, there is at least some evidence for an important genetic contribution to individual differences in these variables (Heath, Neale, Kessler, Eaves, & Kendler, 1992; Rust, 1975). Cross-sectional epidemiological studies have demonstrated strong comorbidity between alcoholism and a history of conduct disorder (Helzer & Pryzbeck, 1988), a disorder that typically has early onset and, in Australian twin data, has been found to have high heritability in both women and men (Slutske et al., 1997). Prospective studies of high-risk populations likewise have identified measures of impulsivity or behavioral undercontrol, and perhaps also of anxiety or negative affectivity, as potential mediators of alcoholism risk (Sher, 1991). Here again, the evidence for a major contribution of genetic factors to personality differences, from adoption, twin, and separated-twin studies, is strong (Eaves, Eysenck, & Martin, 1989; Loehlin, 1992). Thus, many potential mediators of genetic or environmental influences on alcoholism risk have been identified.

How can behavioral genetic methods advance this research? The demonstration in separate studies that such potential mediating variables are associated with differences in alcoholism risk and are heritable tells researchers little about how important a role they play in accounting for genetic influences on alcoholism risk. By comparing the covariances of

alcoholism and a postulated mediating variable (a) within individuals and (b) between biologically related individuals (e.g., biological parent and adopted-away offspring or MZ vs. DZ twin pairs), it becomes possible to partition the total genetic variance in alcoholism risk into variance that is associated with differences in the postulated mediating variable and a residual genetic variance. Although we cannot, except under rare conditions (Neale & Cardon, 1992), leap from such an estimate to inferences about direction of causation, we can at least obtain lower bound estimates of how much of the genetic variance in alcoholism risk remains unaccounted for. With multivariate data measured on relatives, factor models estimating separate genetic and environmental factors (Neale & Cardon, 1992) and more elaborate models for the covariance structure of genetic and environmental influences on alcoholism risk and associated variables can be tested using standard multiple-group structural equation modeling. (Intuitively, it can be seen that a comparison of covariance matrices between relatives, that is, giving the covariances of Relative A's variables with Relative B's variables, in MZ vs. DZ twin pairs or biological vs. adoptive relative pairs, permits resolution of genetic vs. shared environmental covariance structures, whereas the additional information provided by the within-persons covariance matrix, that is, giving the covariances of variables within individuals, permits estimation of the within-families environmental covariance structure of alcoholism and related variables.)

Additionally, in the case of the twin design, several issues that can be addressed only by longitudinal follow-up in conventional high-risk designs can be addressed cross-sectionally. In a conventional high-risk design, studying single offspring of alcoholic and control parents, an association between parental alcoholism and mediators measured in the offspring (e.g., cortisol and prolactin measures of response to alcohol challenge; Schuckit & Risch, 1987) may reflect a variety of nongenetic causes, including comorbidity in the offspring generation (e.g., depression induced by parental alcoholism) and cross-assortative mating (e.g., if depressed mothers marry alcoholic fathers and transmit an increased risk of depression to their offspring). Only costly long-term follow-up studies will confirm that the postulated mediators are primary predictors of differences in alcoholism risk rather than of other outcome variables. In the twin design, by contrast, nongenetic causes of such an association will produce equally elevated values of the mediating variable in MZ and in DZ cotwins of alcoholic twins, allowing such nongenetic effects to be distinguished from genetic associations.

To date, the potential of behavioral genetic methods for identifying important mediating variables remains underexploited. Most major studies of the genetics of alcoholism have not addressed the question of how genetic influences are acting. McGue (1994) reviewed some of the evidence

for the role of personality variables as mediators. In our own work, although we have not found personality variables to be important mediators, we have found results suggesting that even in populations of European ancestry there are polymorphic loci that lead to differences in alcohol preference or self-exposure and ultimately lead to differences in alcoholism risk: Even if we exclude twin pairs concordant for alcoholism (to avoid the complication of the effect of alcoholism on drinking patterns), maximum reported 24-hr consumption of alcohol is predictive of the *cotwin's* alcoholism risk and is significantly more strongly associated in MZ than DZ pairs (Heath, Slutske, et al., 1994). A rapid growth in the number of behavioral genetic publications on mediating variables is to be anticipated.

Genotype–Environment Risk Factors

The analysis of genotype–environment correlation may be viewed as a special case of the analysis of mediating variables, in which our focus is on the role of family (and potentially also friends) as mediators of differences in alcoholism risk. There are a variety of mechanisms by which individuals at high genetic risk for developing alcoholism also may come to be at high environmental risk (Eaves, Last, Martin, & Jinks, 1977; Heath, 1993; Plomin, DeFries, & Loehlin, 1977). These include the following: (a) genotype–environment autocorrelation, in which individuals at high genetic risk expose themselves to high-risk environments; (b) parent–offspring environmental influences in intact nuclear families, in which alcoholic parents both transmit genetic risk factors and create a high-risk rearing environment; (c) environmental influences by other biological relatives, such as older sibling or cotwin environmental influences; or (d) environmental influences by a spouse, partner, or peers who have correlated genetic risk because of selective mating or selective friendship (i.e., the tendency for individuals at high risk to assort with others at high risk). A variety of behavioral genetic designs may be used to resolve these various genotype–environment correlation effects, including prospective twin studies (to resolve the genotype–environment autocorrelation; Eaves et al., 1977), studies of twins and their parents or offspring or of adoptees and controls and their biological and adoptive relatives (to resolve parent–offspring and sibling environmental influences; Eaves, 1977; Fulker, 1981; Heath, Kendler, Eaves, & Markell, 1985), and studies of the spouses (or peers) of twin pairs (Heath, 1987; Heath & Eaves, 1985). As in the case of mediating variables, addressing such questions compels researchers to focus on the mechanisms by which genetic and environmental influences are transmitted rather than to be satisfied with statements about the importance of genetic factors, or of individual genetic loci, in the etiology of alcoholism.

From consideration of the issues of genotype–environment correla-

tion, we are led naturally to the view that environmental risk factors can be studied most convincingly in the context of a genetic design. An observed correlation between parental marital discord and offspring alcoholism risk, for example, may merely be a *genetic* correlation that we would have observed to be equally as strong when marital discord was studied in the biological parents and associated with alcoholism risk in their adopted-away offspring. This might occur if parental alcoholism, sociopathy, or other potentially unmeasured heritable variables are contributing to risk of parental marital discord and if genetic risk factors for these disorders are transmitted to the offspring generation, for whom they increase alcoholism risk.

In principle, one might expect adoption designs to provide the most convincing evidence for environmental influences on alcoholism risk. In practice, however, as in the case of the Stockholm Adoption Study (Cloninger et al., 1981, 1985), stringent screening criteria for adoptive parents have the consequence that most adoptees are reared in low-risk environments. As an alternative to the adoption paradigm, the study of adult MZ and DZ twin pairs and their spouses and offspring (e.g., Heath et al., 1985; Nance & Corey, 1976) offers the best prospect for studying the environmental sequelae of parental alcoholism, controlling for genetic effects. By studying parenting behaviors such as marital discord in MZ and DZ twin pairs, the extent to which such measures are genetic correlates of alcoholism (i.e., elevated in the cotwins of alcoholic twins) can be determined. Under random mating, the genetic correlation between parent and child is the same as that between parent's MZ cotwin and parent's child, so that any excess of the parent–offspring compared with the MZ cotwin–offspring correlation is indicative of an environmental influence. If these two correlations do not differ significantly, this may indicate either genetic transmission or an influence on the twins' own parenting behavior of early rearing experiences and similar family background factors shared equally by twin pairs reared in the same family; these two possibilities may be distinguished by also obtaining data on DZ twin pairs and their offspring because the hypothesis of genetic transmission, but not that of shared family background influences, predicts a significantly lower DZ cotwin–offspring correlation than the parent–offspring and MZ cotwin–offspring correlations.

Assortative mating, by creating a genetic correlation between the twin parents and their spouses, also leads to the prediction of a higher parent–offspring than MZ cotwin–offspring correlation (Eaves & Heath, 1981; Heath et al., 1985). However, by obtaining data on the spouses of MZ and DZ twin pairs, the contributions of assortative mating to the genetic correlation between spouses may be modeled and adjusted for statistically (Heath & Eaves, 1985), so that a test for parent–offspring environmental influences is still possible. In theory, such a design is much less

powerful than the classical adoption design in which, in the absence of selective placement effects, estimates of genetic and environmental influences are orthogonal (Heath et al., 1985). However, because the screening for good parenting skills that occurs in the adoption process does not apply in the twin-family design, in practice, this latter approach offers the best prospect of studying the environmental impact of parental alcoholism.

In a similar fashion, the study of twin pairs and their spouses offers the best prospect in naturalistic studies of resolving the environmental impact of a partner's drinking and related behaviors on the course of alcoholism or other psychopathology. Matched-pairs case-control comparisons of MZ twin pairs who are discordant for marriage to an alcoholic spouse, particularly when used in a prospective design, provide a test for the environmental impact of being married to an alcoholic individual. More generally, case-control comparisons of risk factor discordant pairs may prove helpful in confirming or disconfirming the postulated etiological role of an environmental risk factor, controlling for family background and (in the case of MZ pairs) for genotype. Thus, demonstration of a significant association between early sexual abuse and later alcoholism does not address the extent to which the association may reflect the influences of variables with common effects on both outcomes, such as a disrupted family environment, parental sociopathy, and so on (Dinwiddie et al., 1997). Finding that in twin pairs discordant for sexual abuse, alcoholism rates were significantly elevated in the abused twins but that in the nonabused twins, the rates did not differ from general population rates in nonabused individuals would more strongly support the hypothesis that sexual abuse is an important environmental risk factor for alcoholism. Comparison of alcoholism-discordant pairs, and pairs concordant for alcoholism but discordant for treatment, likewise permits naturalistic studies of the long-term socioeconomic, health, services use, and other outcomes of alcoholism and the extent to which these are ameliorated by treatment (True et al., 1996).

Identifying Susceptibility Loci

The term *susceptibility locus* has come to be used in genetic research on complex disorders such as alcoholism or cardiovascular disease to identify genes that contribute to differences in the risk of developing a disorder, to emphasize that there is no single "alcoholism" gene. Continuing efforts to identify such susceptibility loci in individuals of European ancestry, as well as Hispanics and African Americans, using both linkage and genetic association studies, have not yet yielded consistently replicable findings. Initial reports of a significant genetic association between the A1 allele at the DRD2 locus and alcoholism (Noble & Blum, 1991) have yielded a series of replication studies with both positive (Blum et al., 1993; Comings et al., 1991) and negative (Gelernter et al., 1991; Suarez et al., 1994; E.

Turner et al., 1992) findings. Unfortunately, such association studies have used a standard case-control methodology in which allele frequencies were compared in a series of alcoholic and control participants. Because marked differences in allele frequency at this locus (as well as many others) have been observed as a function of ethnic background (Barr & Kidd, 1993; Goldman, 1993), differences in the alcoholism rates between different ethnic groups will easily generate false-positive findings. Given the highly mixed ancestry of the U.S. population, in particular, appropriate matching of cases and controls is unlikely to be achieved. Research methods that avoid this problem are available, notably by examining DNA markers in a series of parents of alcoholic offspring and comparing the frequency of candidate alleles transmitted by the two parents to their alcoholic offspring and of the nontransmitted alleles, providing a matched-pairs comparison that controls for ethnic background (Falk & Rubinstein, 1987; Spielman, McGinnis, & Ewens, 1993). Positive associations with alcoholism obtained using such methods, however, have not yet been reported, to our knowledge.

The fact that susceptibility loci have not yet been identified in individuals of European ancestry does not, of course, imply that none exist. In individuals of Asian (e.g., Japanese, Chinese, or Korean) ancestry, the contribution of a polymorphism at the ALDH2 locus to differences in alcoholism risk is already well established. In some individuals of Asian ancestry, an allele is found at the ADLDH2 locus that leads to a flushing response, reduced alcohol consumption (Higuchi et al., 1991), and reduced alcoholism risk (for a review, see Thomasson, Crabb, & Edenberg, 1993). Unfortunately, almost all those of European, Hispanic, and African American ancestry appear to carry the "high-risk" gene.

There are several reasons for optimism about the likelihood that more susceptibility loci for alcoholism will be identified in the near future. The existence of rodent models for various aspects of drinking behavior, ranging from alcohol preference (Li, 1990) to withdrawal sensitivity (Crabbe, Belknap, & Buck, 1994), offers the prospect that genetic polymorphisms associated with these behavioral differences will be identified. The high degree of synteny between mice and humans, in particular, means that it will be possible to identify candidate chromosomal regions in humans where equivalent polymorphisms may be sought. The success of such strategies has already been demonstrated in work with mice strains selected to model hypertension (Hilbert et al., 1991) or obesity (Zhang et al., 1994).

There are, of course, no guarantees that the existing rodent models will identify key polymorphisms in human populations. However, the mapping of so-called *quantitative trait loci* (e.g., Kruglyak & Lander, 1995; Risch & Zhang, 1995), genes that contribute to variations in continuously distributed variables, also is becoming feasible in human samples, at least in the case of moderately or highly heritable traits (cf. Cardon et al., 1995).

By studying the number of alleles at a given locus (0, 1, or 2) that pairs of relatives (e.g., siblings) have inherited from common ancestors (e.g., parents), it is possible to test for an association between the degree of allele sharing at that genetic locus with the within-pairs trait variance: Significantly higher sibling correlations would be predicted for the pairs who share two alleles inherited from their two parents, intermediate correlations for those who share only one allele, and lower correlations for those who share neither allele at this locus. Although large numbers (e.g., many thousands) of sibling pairs must typically be screened for these methods to give adequate statistical power, the selection of pairs that are highly concordant for scores on the quantitative trait (e.g., both scoring above the 10th percentile) and of pairs that are highly discordant (e.g., with one in the bottom 30th percentile and the second in the top 10th percentile) means that a much reduced proportion needs to be genotyped (Eaves & Meyer, 1994; Risch & Zhang, 1995). In our own twin family studies in Virginia and Australia, self-report questionnaire measures of such quantitative risk factors as alcohol consumption level (Heath, 1995b) were obtained from more than 10,000 DZ twin and sibling pairs and trios, providing a basis for such targeted follow-up efforts.

The identification of individual genetic loci that contribute to alcoholism risk offers the eventual prospect of a much more refined analysis of the ways in which individual genetic loci and specific environmental risk factors coact. It also may offer the prospect of prevention efforts targeted at individuals identified as being at high genetic risk, although if, as in the case of the ALDH2 polymorphism in Asian populations, many such polymorphisms are found to have protective effects, this latter benefit may be more limited.

Identifying Alcoholism Subtypes

To the extent that alcoholism is a heterogeneous disorder, as has often been suggested (e.g., Babor et al., 1992; Cloninger, 1987; Jellinek, 1960), one might expect that it would be possible to uncover stronger associations between genetic or environmental risk factors and alcoholic subtypes than would be the case if all alcoholic individuals were combined. Behavioral genetic approaches clearly can be informative for this purpose. If researchers are able to demonstrate distinct coaggregation of particular alcoholism subtypes in families and to establish different modes of inheritance for different subtypes, confidence in a subtyping scheme would be greatly advanced (E. Robins & Guze, 1970). Despite various attempts to define such subtypes (e.g., Cloninger, 1987; Cloninger et al., 1981), however, none have been consistently supported by empirical data.

One approach to subtyping, which ultimately may allow joint testing of a genetic model and a model defining alcoholic subtypes (Eaves et al.,

1993), is provided by latent class analysis (LCA). LCA may be viewed as a categorical variant of factor analysis (Bartholomew, 1987). Factor analysis seeks to explain the correlations observed between a set of variables in terms of the linear effects on those variables of a small number of underlying continuously distributed latent variables or factors, and it postulates that if a sufficiently large number of factors is estimated, the residual terms for the observed variables will be statistically independent. Structural equation modeling may be used to test hypotheses about the number of factors needed to account for the observed correlations between variables and about the loadings of individual items on individual factors (i.e., whether a particular latent factor has a direct influence on a particular item). Similarly, LCA seeks to explain the associations between a set of binary or polychotomous items by the existence of a small number of mutually exclusive subject categories, or "classes," that differ in their item-endorsement probabilities; it also permits tests of hypotheses about the number of classes needed to explain the observed associations between items and about item-endorsement probabilities of individual items conditional on membership in a given class. A critical assumption of LCA is that within a class, item-endorsement probabilities are homogeneous for all class members and are statistically independent (Goodman, 1974; McCutcheon, 1987).

It might be anticipated that LCA would be an ideal technique for identifying subtypes of alcoholic individuals having different symptom profiles (cf. Cloninger, 1987). In analyses using only alcoholic symptom data, however, we have found that the classes identified appear to fall along a continuum of severity of alcohol-related problems (e.g., Bucholz et al., 1996; Heath, Bucholz, et al., 1994) rather than representing distinct subtypes. Figure 1, for example, shows results from a reanalysis (using a smaller number of alcoholic symptoms) of lifetime symptom data from a general community sample of Australian adult male twins (1,846 men who had more than minimal alcohol exposure; Heath, Bucholz, et al., 1994) for a four-class model. In addition to item-endorsement probabilities for each class, 95% confidence limits for these conditional probabilities, estimated by bootstrapping (Efron & Tibshirani, 1986), also are shown. All analyses were run using a program written by us, using the standard EM algorithm for LCA (McCutcheon, 1987). The four classes may be identified as those with no alcohol-related problems, heavy drinkers, those with moderate problems, and those with more severe problems. Prevalence estimates for these classes (equivalent to class membership probabilities) in our reanalysis were 41.4%, 40.1%, 15.2%, and 3.3%, respectively. In those labeled *heavy drinkers*, only symptoms such as "getting drunk when didn't want to," "using alcohol more than intended," tolerance, hazardous alcohol use, and alcohol-related blackouts were endorsed with a moderately high (.35–.63) probability. Only in the most severe class were symptoms such as "unable to stop or cut down on drinking" (.64) and withdrawal symp-

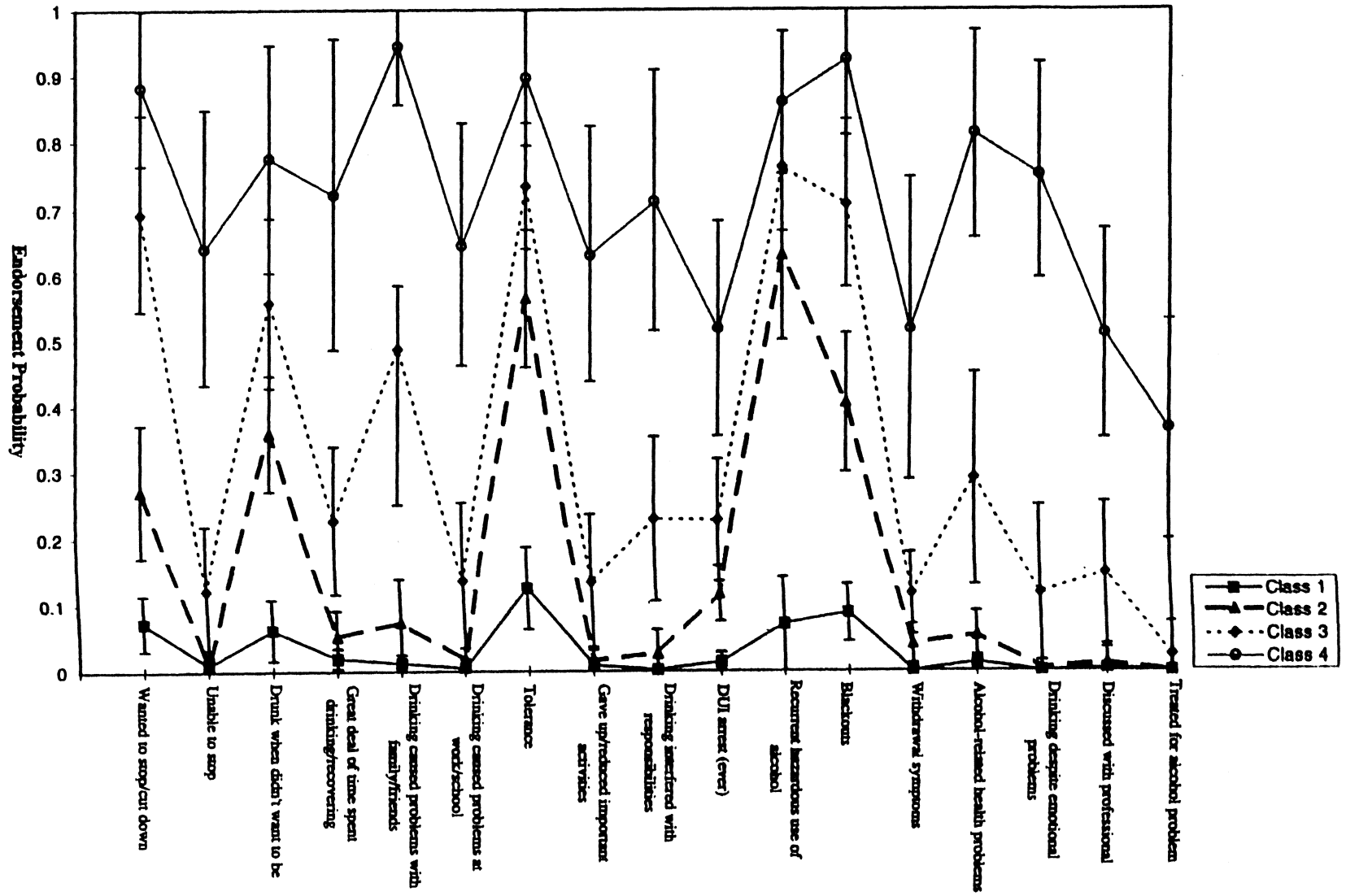

Figure 1. Symptom endorsement probabilities (and 95% confidence intervals) estimated by latent class analysis under a four-class model. Class membership probabilities are as follows: Class 1, ■, .41 (.31–.52); Class 2, ▲, .40 (.32–.49); Class 3, ◆, .15 (.07–.23); and Class 4, ○, .03 (.02–.05). Probabilities do not sum to 1 because of rounding error. DUI = driving under the influence.

toms (.52) endorsed with high probability. Endorsement probabilities for the moderate problems class were intermediate between those for the heavy drinking and severe problems classes. The analysis presented in Figure 1 ignores the fact that data were obtained on twin pairs. In principle, however, it should be possible to model jointly the causes of twin pair concordance and discordance for class membership and item-endorsement probabilities for each class (Eaves et al., 1993), although our own efforts in this regard suggest that such joint models are numerically ill-behaved, so that obtaining a global maximum-likelihood solution is a challenge.

Developmental Perspectives

Most psychiatric genetic researchers use as an outcome measure the presence or absence of a given disorder, assessed on a lifetime basis. On the basis of the results of our analyses of alcohol symptom data using LCA, however, we have come to believe that it is important to go beyond this simple lifetime approach. It is natural to question whether latent classes such as those illustrated in Figure 1 can be viewed as temporal stages in the course of alcoholism. Although this issue would be best addressed prospectively, it is possible to use retrospective reports of age of onset of individual symptoms to examine the accumulation of symptoms through time. Using an approach from event history analysis (Allison, 1984), a person–year file is created in which a separate vector of observations is created for each year of each respondent's drinking career (Nelson, Heath, & Kessler, 1997), indicating whether the respondent has reported experiencing any of the symptoms during or before that particular year of his or her life. Such data then may be used as input for an LCA, to obtain estimates of class membership and item-endorsement probabilities and to compute from these the most likely class membership for every symptom profile occurring in the data set. In this way, it becomes possible to search for risk factors that predict respondents' transitions between classes over time (Nelson et al., 1997). As others have noted (e.g., Collins et al., 1994), different risk factors may determine transitions from nonproblem use to experiencing first substance-related problems versus transitions from first to more severe problems; thus, identifying the stages in the natural history of alcohol use and abuse or dependence at which particular risk factors are operating would have important implications for prevention efforts (Nelson, Little, Heath, & Kessler, 1996).

Although these methods have not yet been applied in a genetic framework, to do so would be a necessary extension of this work. From a genetic perspective, it is natural to question whether genetic loci that influence the transition from moderate to excessive or problem drinking are the same as those that determine, for example, the probability of development of physiological dependence, as indicated by the presence of with-

drawal symptoms. The twin design permits powerful tests of autoregressive (e.g., Eaves, Long, & Heath, 1986), growth curve, and similar developmental behavioral genetic models (e.g., Meyer & Neale, 1992). Of particular importance, with longitudinal data, or quasi-longitudinal data created from retrospective data, it allows researchers to test whether there would be stage-specific genetic or environmental influences on the course of alcohol-related problems and to test how these influences covary and interact. Thus, researchers can move away from the simple "lifetime" perspective that has dominated psychiatric genetic research.

AT RISK UNDER WHAT CONDITIONS?

Neither an individual's increased genetic risk of alcoholism nor increased environmental risk implies an alcoholic destiny. However great the risk factors, those who have never been exposed to alcohol will not become alcoholic. A second broad class of interrelated questions about the etiology of alcoholism that can be powerfully addressed using behavioral genetic methods and that have obvious relevance to prevention research, concerns the conditions under which genetic and environmental risk factors lead to alcoholism: (a) How do genetic and environmental influences vary as a function of gender, birth cohort, or culture? (b) What moderator variables—vulnerability or protective factors—interact with genetic risk of alcoholism or with environmental risk factors to determine outcome? (c) At what levels of exposure to alcohol does genetic predisposition become important?

Moderating Effects of Gender, Birth Cohort, and Culture

The extension of behavioral genetic methods to allow for interactions of genetic predisposition with gender, with birth cohort, and, in cross-cultural studies, with societal norms and associated social differences is straightforward. As in most multiple-group structural equation modeling analyses (Bollen, 1989), one can compare the fit of models that constrain genetic and environmental parameters to be the same across groups with models that allow parameters to differ between groups. In the case of unlike-sex relative pairs, it may be shown that the genetic covariance between relatives will be a function of the geometric mean of the male and female genetic variances (Bulmer, 1980). As more elaborate models incorporating mediating variables are developed, hypotheses about differences in the relative importance of different causal pathways from genotype to behavioral (or biological) differences to alcoholism risk can be similarly tested. In view of the important differences in drinking patterns that exist between societies and between genders, and the changes in drinking pat-

terns that occur over time, one might anticipate that strong interaction effects would be found.

In the case of alcoholism, we commented earlier on the lack of evidence for male–female differences in the heritability of alcoholism from within-studies comparisons. The absence of a gender difference in the heritability of alcoholism does not, of course, imply equal rates of alcoholism in male and female relatives of alcoholic individuals. The gender difference in lifetime prevalence and the higher rates of alcoholism observed in male cotwins of alcoholic mothers compared with male DZ cotwins of alcoholic fathers (e.g., McGue et al., 1992) suggest that on average, women who become alcoholic are at higher genetic risk than men who become alcoholic. Results of a meta-analysis (Heath, 1995a) show a trend for reduced (rather than increased) heritability of alcoholism in Scandinavian men than in Scandinavian women and American men and women, but differences in methodology between studies, and the fact that several studies have excluded women, leave us uncertain about whether this reflects a Genotype × Culture (× Gender) interaction or is merely a consequence of methodological differences. Kendler et al. (1997) failed to find birth cohort differences in the heritability of alcoholism in an analysis of data on Swedish Temperance Board registrations in male twins; and in the same meta-analysis, we found remarkable consistency of heritability estimates across studies using different birth cohorts. To date, the evidence for interactions between genotype and gender, birth cohort, and culture is thus weak.

Genotype × Environment Interaction

Interactions of genotype with gender, birth cohort, or culture may be viewed as a special case of Genotype × Environment interaction, the moderating effect of environmental variables on genetic influences on alcoholism risk. Testing for such interactions is the most straightforward when the postulated moderating environmental variable is binary. Such a model can be tested in a multiple-group structural equation modeling (SEM) analysis, in which separate groups are created for relative pairs of a given type who are concordant nonexposed, discordant, or concordant for exposure to the moderating variable (Heath, Neale, Hewitt, Eaves, & Fulker, 1989). As in the previous examples, models are compared that constrain genetic and environmental parameters to be the same across groups and that estimate separate genetic or environmental parameters for nonexposed versus exposed conditions, with the geometric mean of the genetic or environmental variances under the two conditions being used for the covariance terms for discordant pairs. Comparison of the goodness of fit of the model constraining both genetic and environmental parameters across exposure conditions, with models that allow for differences in either genetic param-

eters (Genotype × Environment interaction) or environmental parameters (moderation of environmental risk factors), provides a likelihood ratio chi-square test for the significance of the postulated moderating effect (Heath, Neale, et al., 1989).

Reports of a significant Genotype × Environment interaction have emerged most often from the adoption study paradigm (Cadoret et al., 1985; Cloninger et al., 1981), although in a twin study of genetic influences on variation in alcohol consumption levels, we were able to demonstrate a significant interaction with marital status in women (Heath, Jardine, & Martin, 1989). Replicated examples of Genotype × Environment interaction are still wanting.

Exposure Effects on Alcoholism Vulnerability

In genetic research on substance use disorders, the task of resolving genetic influences on the level of self-exposure to alcohol, tobacco, or other drugs and genetic influences on the risk of becoming dependent for a given level of substance exposure is an important but neglected topic. Extensive twin data from both European, American, and Australian samples indicate an important genetic influence on alcohol consumption levels in general community (therefore predominantly nonalcoholic) samples (reviewed by Heath, 1995b); in addition, we noted earlier that in Asian samples, a polymorphism at the ALDH2 locus contributes to variability in drinking patterns. Researchers therefore must ask whether risk factors for substance dependence ultimately can be explained as risk factors for substance exposure or whether researchers can demonstrate genetic (or environmental) risk factors that specifically cause differences in risk of dependence among individuals with similar exposure histories. Related to this is the question of whether researchers can define "safe" drinking levels, short of complete abstinence, at which the risk to the biological relative of an alcoholic individual is not increased above general population rates, and "unsafe" levels, which, in presymptomatic individuals at high genetic risk, would indicate a need for early intervention efforts.

Behavioral genetic methods have the potential to make important contributions to such questions. To address the second question, an approach adapted from survival analysis (Lee, 1992) should be possible, in which researchers examine in biological relatives of alcoholic and random control participants the proportions of individuals who have experienced no alcohol-related problems at different levels of reported maximum alcohol consumption. One may wonder, for example, whether the difference in alcoholism rates between male and female siblings of an alcoholic male proband can be explained entirely by differences in the level of self-exposure to alcohol, implying that proportions of unaffected relatives will no longer be different when estimated conditional on level of alcohol ex-

posure. To address the first question, we have begun to develop hierarchical models that allow joint estimation of genetic effects on substance exposure, and genetic effects on risk of dependence, given the level of substance exposure (e.g., Heath & Martin, 1993).

CHALLENGES FOR BEHAVIORAL GENETIC RESEARCH ON ALCOHOLISM

From a review of the potential of behavioral genetic methods for prevention research on alcoholism, we now move to a consideration of the practical limitations and their implications for research design. To understand the issues involved, it is helpful to consider the ways in which behavioral genetic data are used to quantify genetic and environmental contributions to alcoholism risk.

Quantifying Genetic and Environmental Influences

For purposes of illustration, Table 1 shows data from the twin studies of Hrubec and Omenn (1981), Kendler et al. (1992), and McGue et al. (1992). Hrubec and Omenn and Kendler et al. used birth-record-derived twin samples that were screened for history of alcoholism. Hrubec and Omenn's data are based on a register of American like-sex male twin pairs identified from birth records from 1917 through 1927; all of the participants had served in the military during World War II or the Korean War. For this study, the diagnosis of alcoholism was derived from a search of Veterans Administration records to identify reports of alcoholism or alcoholic psychosis. The data of Kendler et al. were based on a sample of twin pairs identified from birth records for the state of Virginia from 1915 through 1968 (although most of the pairs were born after 1945) and were based on interview assessments of lifetime history of *DSM–III–R* alcohol dependence. For these two samples, numbers of concordant unaffected, discordant, and concordant affected twin pairs are presented. The data of McGue et al., by contrast, were based on a mailed questionnaire survey of alcohol problems in a sample of twin pairs ascertained because at least one twin from the pair was identified from the records of an alcohol treatment facility. We therefore report the numbers of unaffected and affected cotwins of the alcoholic twin probands.

The Hrubec and Omenn (1981) and Kendler et al. (1992) studies permit direct estimates of the prevalence of alcoholism, as defined in those studies. In the Virginia data, 8.1% of the MZ female twins and 10.2% of the DZ female twins met broadly defined criteria for lifetime history of *DSM–III–R* alcohol dependence. In the Veterans Administration twin data, only 2.6% of the MZ male and 3.1% of the DZ male twins had a

TABLE 1
Twin Data on the Familial Aggregation of Risk From U.S. Twin Studies

Twin group	Hrubec and Omenn (1981)			McGue et al. (1992)		Kendler et al. (1992)		
	Concordant unaffected	Discordant	Concordant affected	Cotwin unaffected	Cotwin affected	Concordant unaffected	Discordant	Concordant affected
MZ males	5,661	230	41	20	65			
DZ males	7,110	416	28	44	52			
MZ females				9	8	510	65	15
DZ females				14	10	361	68	11
DZ cotwin female proband				5	18			
DZ cotwin male proband				45	20			

Note. Data are recomputed from the original publications by these authors. MZ = monozygotic; DZ = dizygotic.

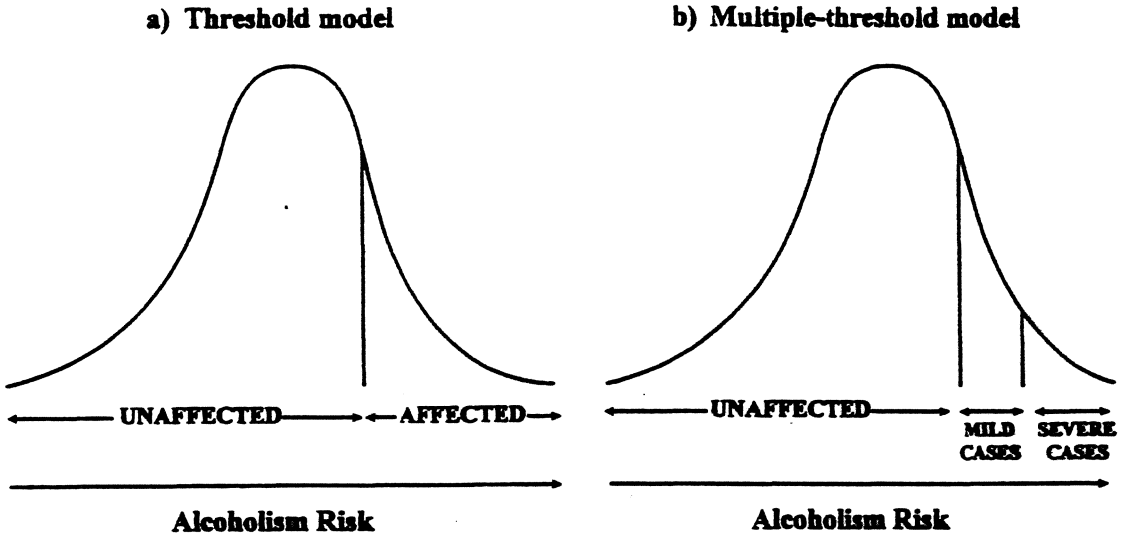

Figure 2. Threshold and multiple-threshold models relating alcoholism liability to history of alcohol dependence. Individuals with liability scores below the threshold remain unaffected, whereas others become alcohol dependent (in the case of the multiple-threshold model, either mild or severe cases, depending on how deviant are their liability scores).

Veterans Administration alcoholism diagnosis. These latter data on average include much more seriously affected individuals, as is apparent from the high rates of alcoholic cirrhosis among alcoholics in the sample (22.7%). As might be expected from the base-rate differences, there are important differences in the estimates of the rates of alcoholism in the relatives of alcoholic individuals between these two studies. In the Virginia data, 31.6% of the cotwins of female MZ alcoholic individuals versus 24.4% of the cotwins of female DZ alcoholic individuals also met criteria for a lifetime history of *DSM–III–R* alcohol dependence. Corresponding estimates of the risk ratio (i.e., the ratio of the rate of alcoholism in relatives of a given degree to the prevalence of alcoholism in the general population) were 3.9 for MZ pairs and 2.4 for DZ pairs. In Hrubec and Omenn's data, the rates of alcoholism were 26.3% for male MZ versus 11.9% for male DZ cotwins of alcoholic individuals, with risk ratios of 10.0 and 3.8, respectively. How can researchers find a metric that will allow them to pool such results from studies that have used widely different methodologies?

One approach that has long been used by geneticists (e.g., Pearson, 1900) is to work with tetrachoric or polychoric correlations (Olsson, 1979), assuming a "threshold" model (see Figure 2a). This assumes that (a) liability to alcoholism is determined by the additive effects of multiple risk factors, which may be genetic or environmental, and is (at least approximately) normally distributed in the general population and (b) the individuals who become alcoholic have liability scores that exceed some threshold value (scaled as a deviation from the mean—usually set to zero—of the liability distribution). Correlations between relatives for alcoholism liability may be estimated by maximum likelihood (Olsson,

1979). As shown in the multiple-threshold model in Figure 2b, narrower versus broader definitions of alcoholism may be represented using more versus less deviant threshold values. No direct test of these assumptions is possible in the case of binary data, although they certainly appear to be plausible for alcohol dependence. With three or more response categories, a chi-square test of the goodness of fit of the multiple-threshold model does become possible.

Table 2 shows, for a range of informative values, the proportions of concordant unaffected, discordant, and concordant affected relatives predicted for a given liability correlation between relatives and given population prevalence estimates (which may differ for first and second relatives because of gender, birth cohort, or other differences). Comparing first cases in which the prevalence is assumed to be the same in both relatives, it can be seen that the predicted rates of alcoholism in the relatives of alcoholic individuals increase as a function both of the magnitude of the liability correlation and of the prevalence of alcoholism, so that the same risk to relatives (e.g., 25%) may reflect a modest familial correlation for a highly prevalent trait (r = .15; 20% prevalence) or a much stronger correlation for a low prevalence trait (r = .6; 2.5% prevalence). The risk ratios for these two examples are much different (1.3 vs. 10.0), but the same risk ratio may likewise reflect much different degrees of familial correlation (e.g., correlations of .6, 10% prevalence vs. .3, 2.5% prevalence yield risk ratios of 3.9 and 3.8, respectively).

Table 2 also illustrates how, under the assumptions of a multiple-threshold model, the risk to relatives of more severe cases is increased relative to the risk to relatives of all alcoholic individuals (including milder cases). Suppose that a given operationalization of alcoholism identifies 30% of men but only 10% of women as having a lifetime history of alcohol dependence and the liability correlation between first-degree, unlike-sex relative pairs is .3. If this difference in prevalence reflects gender differences in thresholds for alcohol dependence, implying that compared with alcoholic men, alcoholic women must have accumulated more risk factors (i.e., they have more deviant liability scores) for alcoholism, then the predicted risk to a first-degree male relative of an alcoholic woman will be 50%, whereas the risk to a first-degree female relative of an alcoholic man will be only 16.7% (although the risk ratio is the same in each case, 1.67). Once again, even assuming the same prevalence for alcoholism (say, 30%), as defined for relatives of alcoholic individuals (e.g., assessed by a diagnostic interview), differences in the operationalization of alcoholism for alcoholic probands (identifying individuals in the top 30% vs. the top 2.5% of the liability distribution) may cause similar risk ratios to be associated with different liability correlations (e.g., correlations of .6 for the former case and .3 for the latter case both generate risk ratios of 1.9). We will see later

TABLE 2

Population Distribution of Pairs of Relatives With Both Alcoholic, Neither Alcoholic, or Only One Relative Alcoholic as a Function of Lifetime Prevalence of Alcoholism and Liability Correlation for Alcoholism of Relatives

Relative A prevalence (%)	Relative B prevalence (%)	Liability correlation	Both affected (%)	Discordant		Both unaffected (%)	Risk to relative of an alcoholic[a] (%)	Relatives' risk ratio[b] (%)
				A affected (%)	B affected (%)			
30	30	.6	17.3	12.7	12.7	57.3	57.6	1.9
		.3	12.8	17.2	17.2	52.8	42.7	1.4
		.15	10.9	19.1	19.1	50.9	36.2	1.2
30	10	.6	7.4	22.6	2.8	67.4	73.5	2.5
		.3	5.0	25.0	5.0	65.0	50.1	1.7
		.15	4.0	26.0	6.0	64.0	39.6	1.3
30	2.5	.6	2.1	27.9	0.4	69.6	85.6	2.9
		.3	1.4	28.6	1.1	68.9	57.3	1.9
		.15	1.1	28.9	1.4	68.6	43.0	1.4
20	20	.6	9.9	10.1	10.1	69.9	49.6	2.5
		.3	6.6	13.4	13.4	66.6	33.1	1.7
		.15	5.2	14.8	14.8	65.2	26.2	1.3
10	30	.6	7.4	2.7	25.0	65.0	24.5	2.5
		.3	5.0	5.0	25.1	65.0	16.7	1.7
		.15	4.0	6.0	26.0	64.0	13.2	1.3
10	10	.6	3.9	6.1	6.1	83.9	39.0	3.9
		.3	2.2	7.8	7.8	82.2	21.6	2.2
		.15	1.5	8.5	8.5	81.5	15.2	1.5
10	2.5	.6	1.4	8.6	1.1	89.9	55.7	5.6
		.3	0.7	9.3	1.8	88.2	27.3	2.7
		.15	0.4	9.6	2.1	87.9	17.4	1.7
2.5	2.5	.6	0.6	1.9	1.9	95.6	24.9	10.0
		.3	0.2	2.25	2.25	95.2	9.5	3.8
		.15	0.1	2.35	2.35	95.1	5.2	2.1

[a]Assumes that the prevalence of alcoholism as defined for an alcoholic proband is as for Relative B.

[b]Ratio of risk to the relative of a proband to prevalence in general population, assuming that prevalence of alcoholism as defined for relative is as for Relative A.

TABLE 3
Contributions of Genes and Environment to Alcoholism Liability Correlations for Different Familial Relationships

Relationship	Genes	Environment shared by family members	Nonshared environment
MZ twin pairs	1	1	0
DZ twin pairs/biological parent and nonadopted child	.5	1	0
Biological parent/adopted-away child	.5	0	0
Adoptive parent/adopted child	0	1	0
Total population variance in alcoholism liability	1	1	1

Note. MZ = monozygotic; DZ = dizygotic.

that this issue becomes especially important when one tries to interpret data from clinically ascertained twin series.

On the basis of these considerations, if the assumptions of the multiple-threshold model are at least approximately valid, it clearly is not appropriate to attempt to pool estimates of alcoholism rates in relatives, or risk ratios, across studies, as has sometimes been attempted (e.g., Merikangas, 1990). One feasible strategy would be to estimate polychoric correlations between relatives separately for each study, with their asymptotic covariance matrix (e.g., using standard statistical packages such as PRELIS; Jöreskog & Sörbom, 1993b). Models would then be fitted to these data by means of packages for structural equation modeling such as LISREL (Jöreskog & Sörbom, 1993a) in a multiple-group analysis using an asymptotic weighted least squares fitting function. This approach has the advantage that it generalizes easily to multivariate problems, where one is interested in identifying potential mediators of genetic or environmental influences on alcoholism risk. Male like-sex twin pair correlations from the study of Hrubec and Omenn (1981) were as follows: MZ male pairs, .61 ± .04, and DZ male pairs, .33 ± .04. Female like-sex pair correlations from the Kendler et al. (1992) study were .53 ± .09 and .35 ± .11 for MZ and DZ pairs, respectively.

In Table 3, we summarize the contributions of genes, shared environment, and nonshared environment to the familial correlations for alcoholism of twins and adoptees and their biological parents. The expectations were derived under a highly simplified model used in the meta-analysis of Heath (1995a). We assume that all gene action is additive, ignoring complications such as genetic dominance or epistasis (gene–gene interactions). We ignore assortative mating (i.e., the tendency for alcoholic individuals to marry other alcoholic individuals), which, if present, might inflate estimates of the genetic contribution to alcoholism risk in adoption data and of the shared environmental contribution in twin data. (These differential

effects will arise if matings of biological pairs who are both at increased genetic risk for alcoholism occur more often than would be expected by chance. In such a case, the correlation between the biological parent and the adopted-away child will reflect both genes transmitted from that parent to the child and, because of the genetic correlation between spouses induced by assortative mating, an indirect contribution via genes transmitted from the second parent. However, the genetic correlation between DZ twin pairs will be increased above the expected .5 under random mating, hence mimicking the effects of shared environmental effects in twin data.) We ignore selective placement (i.e., the tendency for individuals from a high-risk genetic background to be placed in a high-risk adoptive home) and other forms of genotype–environment correlation (as when, in intact families, a biological alcoholic parent both creates a high-risk rearing environment and passes on genes that increase alcoholism risk). We ignore Genotype × Environment interaction, which may arise if individuals differ in their vulnerability to environmental risk factors because of genetic differences or, conversely, if there are important environmental moderators of genetic risk. Thus, as a starting point, we are ignoring the complex interplay of genetic and environmental risk factors that is most relevant to prevention research on alcoholism.

When we fitted models to the Hrubec and Omenn (1981) and Kendler et al. (1992) data sets, we obtained estimates of the genetic contribution to variance in alcoholism risk (the "heritability" of alcoholism) of 63% for Hrubec and Omenn's data and 55% for the Kendler et al. data. In neither case did we find a significant shared environmental contribution to alcoholism risk. By contrast, in a reanalysis of the Stockholm Adoption Study data on temperance board registrations of Cloninger et al. (1985), we obtained a heritability estimate of only 37%, with no significant gender difference (Heath, Slutske, & Madden, in press). Reporting only these point estimates, however, could easily cause us to overestimate their precision. In epidemiology, it is accepted practice to report 95% confidence limits for odds ratios. For comparability, we have estimated the upper and lower bounds for the 95% confidence interval for these heritability estimates by finding those values of the genetic, shared environmental, and within-families environmental variances that produce a just-significant deterioration in fit of the model ($\chi^2_1 > 3.84$, $df = 1$). For the Swedish adoption data, the 95% confidence interval for the heritability estimate was 19%–56%; for the U.S. Veterans Administration twin data, it was 31%–69%; and for the Virginia twin data, it was 0–69%. Clearly, exclusive focus on point estimates of heritability can greatly mislead. From the Hrubec and Omenn (1981) and Kendler et al. (1992) twin studies, the 95% confidence intervals for the estimate of the shared environmental contribution to variance in alcoholism risk were 0–25% and 0–55%, respectively. In twin data (except when data on separated twins are available), there is a strong neg-

ative correlation between estimates of genetic and shared environmental variances. As a consequence, the 95% confidence limits are usually asymmetrical about the point estimates of these variances, as can be seen in our examples. This complication invalidates attempts to test for the significance of genetic and environmental parameters using the standard errors of those parameter estimates (e.g., Allgulander et al., 1991, 1992; Pickens et al., 1991; Romanov et al., 1991) because their sampling distribution is asymmetrical; likelihood ratio tests of the significance of dropping a genetic or shared environmental parameter from the model are more appropriate.

Clinically Ascertained Samples

The broad confidence intervals obtained for estimates of genetic and environmental parameters in the Kendler et al. (1992) and Hrubec and Omenn (1981) data sets, despite seemingly large sample sizes, reflect the low precision of these estimates for binary variables in random samples, particularly when the population prevalence is low. One noteworthy aspect of our simulations in Table 2 is the small differences in proportions of concordant unaffected relative pairs as a function of the relative pair liability correlation, particularly for low-prevalence traits. Most of the information about the magnitude of the familial correlation for alcoholism is derived from pairs with at least one alcoholic twin, as can be confirmed by statistical power calculations for genetic modeling (Neale, Eaves, & Kendler, 1996). This suggests that the research strategy of identifying alcoholic probands through treatment or other settings and conducting follow-up assessments with their relatives, as was used by McGue et al. (1992), would be an especially powerful one. Such a strategy also has been used in studies of twin series ascertained from treatment settings in London (Gurling et al., 1984), St. Louis (Caldwell & Gottesman, 1991), and, in a sample that overlapped with that used by McGue, Minnesota (Pickens et al., 1991). It also has been used with considerable success in family studies (e.g., Reich, Cloninger, Van Eerdewegh, Rice, & Mullaney, 1988) and in the adoption studies conducted by Cadoret (1994; Cadoret et al., 1985, 1987) and Goodwin et al. (1973, 1974). However, for behavioral genetic research, it is not without complications.

To estimate genetic and environmental contributions to alcoholism risk from clinically ascertained samples, researchers need to know not only the proportions of alcoholic and nonalcoholic relatives of the alcoholic probands but also two additional pieces of information: estimates of the population prevalence of alcoholism as defined for the alcoholic proband and alcoholism as defined for the relatives of the proband (as can be seen from Table 2). The researchers who have attempted to derive estimates of genetic and environmental parameters from such clinically ascertained

samples (e.g., Caldwell & Gottesman, 1991; McGue et al., 1992; Pickens et al., 1991) have most commonly assumed that these two prevalence estimates will be the same and have used estimates derived from general population surveys such as the Epidemiological Catchment Area (ECA; e.g., L. N. Robins & Regier, 1991), adjusted for the age distribution of each twin group. Unfortunately, it is by no means clear that this is a reasonable assumption. In terms of the threshold models of Figure 2, this is equivalent to assuming that Figure 2A applies, so that individuals who get into treatment for alcoholism can be viewed as a random sample of alcoholism cases in the general population, at least with respect to alcoholism liability. An alternative and perhaps more plausible assumption is that Figure 2B applies, with alcoholic individuals in treatment disproportionately representing the severe cases, whereas those in community samples are predominantly mild cases (Heath, Bucholz, et al., 1994).

As we have shown elsewhere (Heath, Slutske, & Madden, in press), these different approaches lead to different estimates for correlations between relatives for alcoholism liability. For *DSM–III–R* alcohol abuse, for example, McGue et al. (1992) used prevalence estimates of 29.8% for MZ men, 28.1% for DZ men, 9.0% for MZ women, and 9.2% for DZ women, based on ECA data. Interpolating approximate values for the prevalence estimates for men and women from unlike-sex pairs (not given by McGue et al., 1992) and using the proportions of alcoholic and nonalcoholic cotwins from Table 1, we obtained the following estimates of the twin pair tetrachoric correlations: MZ male pairs, .87; DZ male pairs, .56; MZ female pairs, .61; DZ female pairs, .65; DZ unlike-sex pairs ascertained through female probands, .69; and DZ unlike-sex pairs ascertained through male probands, .99. Comparing the like-sex MZ and DZ correlations, McGue et al. concluded that genetic factors were an important determinant of alcoholism risk in men, but not in women. However, this conclusion was not supported by the high correlations estimated for unlike-sex pairs, which, indeed, will cause any simple genetic model to fail to fit these data: If genetic effects were the predominant cause of family resemblance in men and shared environmental effects in women, we would predict a zero or low correlation between unlike-sex pairs. As reviewed by Heath, Slutske, and Madden, only approximately 1 in 5 men in the ECA survey meeting criteria for *DSM–III* alcohol abuse or dependence and 1 in 4 women reported any alcohol-related treatment contacts. If we assume that it is the "severe" cases that are being represented in treatment settings, use prevalence estimates of 6.5% and 2.44% for male and female alcoholic probands, respectively, and retain the original McGue et al. estimates for their cotwins, we obtain estimated twin correlations of .58, .35, .46, .49, .55, and .57, respectively. The two estimates of the unlike-sex DZ correlation are still both moderately high, but at least they are also now comparable in magnitude to one another.

Not surprisingly, these different assumptions about how to adjust for nonrandom sample ascertainment also have an important effect on the estimates of the heritability of alcoholism. If we follow McGue et al. (1992) and assume that treated alcoholic individuals are a random sample of all alcoholic individuals and discard data from unlike-sex twin pairs, then we obtain heritability estimates (and 95% confidence intervals) of 0% (0–47%) for women and 62% (22%–94%) for men. Under the alternative severity model, assuming a much lower prevalence value for alcoholic probands than for relatives and using data from the unlike-sex pairs, we found no significant gender difference in the heritability of alcoholism ($\chi^2_2 = 3.62$, $df = 2$, $p > .05$), obtaining a pooled heritability estimate of 18% that was nonsignificant (95% confidence limits = 0–40%). In practice, of course, neither model of the relationship between alcoholism liability and probability of getting into treatment is likely to be correct because factors such as comorbid drug abuse or other psychiatric disorders also may lead to the identification of individuals with mild alcohol problems in treatment series. For reasons such as these, our estimates of genetic and environmental parameters from treatment series will be clouded in uncertainty.

IMPLICATIONS FOR RESEARCH DESIGN

Two-Stage Sampling Schemes

In the analysis of twin and adoption data from clinically ascertained samples, researchers cannot avoid the difficulty that they do not know how to model the relationship between alcoholism liability and the probability of being represented in a treatment sample. This is not a problem if researchers are primarily interested in genetic linkage or association studies to identify individual genetic loci that contribute to alcoholism risk. However, it becomes more of a problem when researchers wish to use twins or adoptees to examine the joint action and interaction of genetic and environmental risk factors. Yet, as we have shown in Table 2, random sampling also is not an efficient strategy because it leads to inclusion of many concordant nonalcoholic relative pairs who provide minimal information about the causes of individual differences in alcoholism risk.

In response to this, we have pioneered the use of a two-stage sampling strategy in behavioral genetic research. In the first stage, brief diagnostic interviews are conducted with twin pairs and other family members. For twins, adoptees, and other rare population groups who may be spread over a large geographic area, we have found that conducting diagnostic interviews by telephone is a highly efficient strategy. For the second stage, a random sample of families and a high-risk sample selected from the remaining families on the basis of assessments made in the first stage are

identified for more extensive follow-up. The use of random and high-risk samples permits case-base comparisons (cf. Wacholder, McLaughlin, Silverman, & Mandel, 1992), and in general facilitates data analysis, compared with the sampling scheme in which high- and low-risk samples are drawn and contrasted. Because families are selected on the basis of phenotypic data assessed on the entire sample in the first stage, estimates of population parameters in analyses of the selected sample as well as random-sample Stage 2 data can be obtained using maximum-likelihood methods (e.g., Eaves, Last, Young, & Martin, 1978; Lange, Westlake, & Spence, 1976) because Stage 2 data are missing at random, in the sense used by Little and Rubin (1987) and Little and Schenker (1995).

A critical decision in the implementation of two-stage sampling schemes is the choice of criteria used for inclusion in the high-risk sample. We noted earlier that oversampling on the basis of parental alcoholism is a much more efficient strategy for identifying men at high risk for alcoholism than for identifying women at high risk. A result well-known to quantitative geneticists (e.g., Falconer, 1981), but that applies equally under most plausible environmental models, is that selection on the basis of an individual's characteristics is a much more efficient strategy for identifying individuals at high risk than selecting on characteristics of the parents, although selecting on the phenotype of a MZ cotwin will be the second most efficient strategy. Thus, because our interest is in identifying risk factors for making transitions from heavy to problem drinking, or from problem drinking to alcohol dependence, selection of a high-risk sample of heavy or problem-drinking women will be much more efficient than selecting a sample of women with a history of parental alcoholism.

Cohort-Sequential Sampling

To the extent that we take a developmental rather than a cross-sectional, or lifetime, perspective on the etiology of alcohol dependence, we are forced to adopt longitudinal research designs. Early longitudinal studies in alcoholism and related fields (e.g., McCord & McCord, 1962; Vaillant, 1983) have used the traditional strategy of identifying a cohort of individuals of the same age and following them prospectively. Such an approach would work well in an era of stable research funding, stable assessment practices, and low geographic mobility. From the early 1950s (Bell, 1953), however, the value has been recognized of a cohort-sequential sampling scheme, in which, for example, cohorts of 11-, 13-, 15-, 17-, 19-, and 21-year-olds are identified at the beginning of a study and followed prospectively (e.g., every 2 years). Such a design permits, within a 5-year research project, the years from 11 to 26 to be spanned, and, because 11-year-olds have been followed at 13 and 15, 13-year-olds at 15 and 17, and

so on, the design permits risk factors assessed in early adolescence to be related to outcomes in early adulthood.

Such designs have only recently begun to be used in behavioral genetic research (e.g., Hewitt, Eaves, Neale, & Meyer, 1988) and in alcoholism research (e.g., Duncan, Duncan, & Hops, 1994) but have enormous potential. In an era in which the continuity of research funds is uncertain and the updating of assessment approaches is as rapid (e.g., American Psychiatric Association, 1987, 1994) as might be expected under a "planned obsolescence" approach, these designs allow prospective data to be collected covering a broad range of ages while funding is still intact and assessments are still current. Because individual cohorts are followed over a relatively brief time span, problems of sample attrition are minimized. Finally, because multiple cohorts are assessed at the same age but in different years, the impact of sudden social changes (e.g., drug epidemics and declines) can be detected.

Combining a cohort-sequential design with a two-stage sampling approach, however, is not without problems. There is an implicit assumption that individuals from different cohorts can be viewed as being sampled from the same population, so that, for example, 21-year-olds sampled at the beginning of the study can be meaningfully compared with 21-year-olds taken into the study at age 17. Even if a high-risk sample is drawn on the basis of parental history of alcohol dependence, this would require that parental onset be before the age of initial assessment of the youngest cohort in the study; otherwise, cases with late parental onset would be disproportionately represented in cohorts entered into the study at older ages. Likewise, oversampling on the basis of offspring rather than parental characteristics would require that consideration be limited to behaviors with onset before the age of the youngest cohort taken into the study.

The Use of Twin Registers

Using a cohort-sequential sampling strategy raises additional challenges when researchers want to span the years from early adolescence into early adulthood, as is clearly necessary in alcoholism-related research. Researchers cannot simply recruit volunteers from schools—the most common research strategy with this age group—unless using a retrospective search of elementary school records from as many as 10 years earlier. Otherwise, researchers would miss school dropouts and would have great difficulty drawing an appropriate sample for cohorts aged 19+ at intake into a study. In research on twin pairs and other rare populations, meeting this challenge with adolescents has most usually required that individuals be identified from birth records (e.g., in the Minnesota Twin Study and our own Missouri Adolescent Twin Study) and tracked wherever they may be found.

BROADER IMPLICATIONS FOR EPIDEMIOLOGICAL AND PREVENTION RESEARCH

Although some of the research questions that we have discussed require working with special populations such as twins or adoptees, a behavioral genetic framework has more general implications for epidemiological and prevention research on alcoholism. First, a developmental perspective would appear to be important. In the recent U.S. National Comorbidity Survey (Kessler et al., 1994; Nelson et al., 1996), the median reported age of onset of most individual alcoholic symptoms was 20. Like smoking, alcoholism has increasingly become a disorder with pediatric onset, albeit with adverse sequelae occurring most frequently in later adulthood. Epidemiological surveys have most commonly focused on adult populations (L. N. Robins & Regier, 1991) or have included relatively small numbers of older adolescents because of the broad span of ages covered (Kessler et al., 1994). If our goal is to describe and understand early transitions into problem drinking and the predictors of transitions into more severe stages of alcohol-related problems, then a survey more narrowly focused on the years of adolescence and early adulthood would appear to be necessary. Researchers can start to refine hypotheses by making fuller use of retrospective data on ages of onset reported in adult surveys, but data reported by younger respondents are likely to have greater reliability and validity.

Second, alcoholism is a strongly familial disorder. In conventional survey research, in which the goal is to obtain highly precise estimates of the prevalence and incidence of a disorder, sampling is restricted to one individual per household to avoid the within-households correlations that would occur and the consequent increase in the sampling variance achievable with a given sample size if multiple individuals from the same household were sampled. If the goal is also to identify mediators and moderators of alcoholism risk, because many of these risk factors also are likely to be familial, direct interview assessment of all family members, including absentee individuals, would be preferable. The strategy of studying only one offspring per family, as in many high-risk research studies (Sher, 1991), seems indefensible because it loses the power of within-sibships comparisons. Although the statistical procedures for analyzing familial data are a little more complicated than in the case of samples of unrelated individuals, techniques such as bootstrapping (Efron & Tibshirani, 1986) greatly simplify the task of obtaining appropriately adjusted statistical tests.

Third, because alcoholism is strongly familial, there will be a relatively high proportion of uninformative low-risk families in any general community sample. A two-stage sampling strategy, in which a relatively low-cost screening interview is followed by more exhaustive follow-up of a random subsample and a subsample identified as being at high risk for

alcoholism, would be the most efficient, as is the case with more conventional behavioral genetic designs. Of special concern, not only for epidemiological and prevention studies but also for high-risk research, is the fact that the standard technique of oversampling on the basis of a paternal history of alcohol dependence (assessed by personal interview), although highly productive for studying the causes of male alcoholism, is much less efficient for studies of alcoholism in women. Oversampling families with an alcoholic female relative, or preferably two female relatives (cf. Hill, 1995), would greatly increase the numbers of disorders of those who are expected to become alcohol dependent. Oversampling on the basis of an adolescent's own drinking problems will always be more efficient than oversampling because of problems in a first-degree relative, although it raises potential reporting bias problems, as in any retrospective research.

Fourth, researchers can obtain only limited data from a single cross-sectional survey of alcohol-related behaviors. For the purposes of prevention research, identifying predictors of transitions from alcohol use to early alcohol-related problems, and from early problems to more severe alcohol-related problems, can best be achieved in a prospective design. The cohort-sequential sampling strategy that we have discussed for behavioral genetic research is equally relevant here and brings the same advantages and challenges.

Finally, given the important role that genetic factors play in determining differences in alcoholism risk, there are strong arguments for wanting to include a genetic perspective in such epidemiological or prevention research. In the context of conducting in-person interviews with family members, the additional costs of obtaining and storing blood samples for genotyping are minimal. As individual genetic markers of alcoholism risk are identified, the potential for analyses of the coaction and interaction of genetic and environmental risk factors will be enhanced greatly. Ascertaining a parallel sample of genetically informative kinships such as twin pairs and their families, assessed using a protocol identical to that used in the broader community sample, will provide much additional information about questions such as those highlighted in Exhibit 1.

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