Disentangling the Complex Association Between Childhood Sexual Abuse and Alcohol-Related Problems: A Review of Methodological Issues and Approaches*

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ABSTRACT. This review describes and evaluates methodological approaches aimed at unraveling the association between childhood sexual abuse (CSA) and later misuse of alcohol, which is complicated by the significant overlap between factors that elevate risk for CSA exposure and those that increase risk for problem alcohol use. We critique methods used to distinguish direct effects of CSA events on alcohol-related outcomes from the effects of risk factors frequently present in families in which CSA exposure occurs (e.g., parental alcohol-related problems). These methods include measurement and adjustment for potentially confounding factors and the use of co-twin designs. The findings across methodological approaches provide support for a CSA-specific risk for alcohol misuse, despite the significant contribution of family background factors to overall risk, but much work remains to be done before a comprehensive model for this association can be proposed. Additional directions for research, including the incorporation of measured genes and the use of longitudinal designs, are proposed to further efforts to model the pathways from CSA to alcohol-related problems. (*J. Stud. Alcohol Drugs* **69:** 718-727, 2008)

CHILDHOOD SEXUAL ABUSE (CSA) is highly prevalent in the general population (approximately 4% in men and 20% in women; Fergusson et al., 1996b; Vogeltanz et al., 1999; Walker et al., 2004) and has been linked to increased risks for a range of psychiatric and health outcomes (Fergusson et al., 1996a; Kendler et al., 2000; Molnar et al., 2001). Although these risks span multiple domains, the focus of the current article is on the risk it poses for alcohol-related problems, which are far-reaching in their impact. In addition to the impairment that stems from misuse of alcohol, individuals with CSA histories who drink at problem levels are at elevated risk for sexual revictimization (Coid et al., 2001; Messman-Moore and Long, 2003) and are more likely to engage in sexual practices that increase risk for HIV infection (Bensley et al., 2000; NIMH Multisite Prevention Trial Group, 2001). The number of investigations focused on CSA and alcohol-use disorders (AUDs) has grown in the last 2 decades, and as evidence for the association between CSA and problem alcohol use has accumulated, the complexity of the relationship has become increasingly apparent. As a consequence, a wider range of approaches has developed to identify factors that increase CSA-associated risk and to delineate the pathways from CSA to AUDs.

The aim of the present review is to highlight the utility of two methodological approaches for disentangling the contribution of risk factors common to CSA and problem alcohol use in determining the risk attributable specifically to CSA events. The first is to measure and adjust for factors that may confound the relationship between CSA and alcohol-related problems, and the second is to make use of co-twin designs to control for genetic and shared environmental contributions to alcohol-related outcomes. To underscore the contribution of these two approaches, we begin by addressing potential confounding factors that need to be considered in this line of research. Most crucial among these is the overlap in the constellation of risk factors associated with CSA exposure with those that predict alcohol-related problems, but also included are possible biases in findings derived from clinical versus community-based samples.

Elevated risk for alcohol-related problems among individuals who have experienced CSA is well documented in clinical populations (Simpson and Miller, 2002). History of CSA has been associated with earlier age at initiation of alcohol use, a greater number of alcohol-related problems, and earlier age at onset of AUDs in individuals presenting for alcohol treatment (Brems et al., 2004; Moncrieff et al., 1996; Zlotnick et al., 2006). More rapid relapse rates following treatment have been reported as well for individuals exposed to CSA (Greenfield et al., 2002; Walitzer and Dearing,

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2006). Evidence for the link between CSA and alcohol-use outcomes is even more striking among adolescents with alcohol abuse or dependence. Clark and colleagues (1997), for example, reported that, compared with subjects recruited from the community, adolescents receiving treatment for AUDs were 18-21 times more likely to have sexual abuse histories. However, whether the same association would be found among adolescents in the general population who meet criteria for AUDs is unclear. Individuals seeking treatment typically have more severe manifestations of alcohol misuse than those who do not present for treatment (Bucholz et al., 1994), and these referral biases limit the generalizability of results from studies of clinical samples.

It is important then to examine findings from investigations of CSA and problem alcohol use in samples representative of the general population, the majority of which, in fact, parallel those derived from the clinical literature. Early initiation of alcohol consumption (Dube et al., 2006; Edgardh and Ormstad, 2000) and heavy episodic drinking (Hussey et al., 2006; Luster and Small, 1997) have been tied to CSA history in community samples. Numerous population-based studies have documented elevated rates of alcohol-related problems (Galaif et al., 2001; Kendler et al., 2000; MacMillan et al., 2001; Pedersen and Skrondal, 1996; Spak et al., 1998; Wilsnack et al., 1997), including the onset of AUDs in late adolescence and young adulthood (Fergusson et al., 1996a; Kilpatrick et al., 2000) among individuals who have experienced CSA. For example, in a longitudinal community-based study conducted by Silverman et al. (1996), women with histories of CSA were significantly more likely to meet AUD criteria at age 21 than were women who had not been exposed to CSA (prevalence rates of 43.5% and 7.9%, respectively). A report based on respondents 15-54 years of age from the National Comorbidity Study (Molnar et al., 2001) produced similar findings: individuals with histories of CSA had elevated rates of alcohol dependence (AD). Taken together, these studies provide crucial evidence that the association of alcohol-related problems with CSA is not unique to the subset of drinkers who present for treatment.

Risk Factors Common to CSA and Alcohol-Related Problems

CSA frequently occurs in the context of multiple risk factors for psychopathology and alcohol-related problems. An investigation by Dong et al. (2003) revealed that individuals who experienced CSA had 2-3 times higher likelihood of exposure to additional adverse childhood experiences, such as emotional neglect or parental separation, than those without histories of CSA. Physical abuse, violence between parents, and frequent conflict in the home have been associated with CSA history in several studies (Fergusson et al. 1996b; Fleming, 1997; Mullen et al., 1993; Silverman et al., 1996).

Parental alcohol-related problems have received a significant amount of attention in this line of research, owing to their clear potential for directly affecting offspring alcohol-use outcomes. The literature on children of alcoholics documents the clustering in these high-risk families of nonalcohol-specific risk factors for offspring alcohol-related problems, including numerous indicators of an unstable home environment also linked to risk for CSA. Among these are high levels of conflict and disorganization in the family, marital distress, and low cohesion among family members (Hussong and Chassin, 1997; Jacob and Leonard, 1994; Reich et al., 1988; West and Prinz, 1987). In such an overall dysfunctional environment, parents are less likely to provide the support and monitoring that serve as protective factors against exposure to CSA and other adverse events. It comes as no surprise then that parental AUDs and CSA have consistently been linked in the literature. Higher rates of parental AUDs have been found among individuals with CSA histories (Anda et al., 2002; Fergusson et al., 1996b). Elevations in likelihood of CSA exposure in offspring of parents with AUDs have also been reported (Dube et al., 2001; Sher et al., 1997). The potential for alcohol-related problems in parents to contribute to offspring alcohol-use outcomes both indirectly—that is, via common risk factors—and through direct routes, including genetic transmission of risk, poses significant challenges for mapping the channels CSA-specific risk travels.

Conceptualizing the pathway from CSA to alcohol-related problems as a direct one, possibly resulting from attempts at regulating abuse-related negative affect through alcohol consumption, is intuitively appealing and common in the clinical literature. The temporal progression, with CSA preceding onset of alcohol use in the majority of cases, further promotes the notion of a direct causal pathway. However, as indicated in the above summary of common risk factors, there may be an indirect relationship in which both CSA and problem alcohol use result from shared risk factors, such as poor parental supervision (Walsh et al., 2003) or parental psychopathology, including AUDs (Fergusson et al., 1996b; Vogeltanz et al., 1999; Walsh et al., 2003). Two primary methodological approaches used to tease apart indirect influences of risk factors that typically co-occur with both CSA and alcohol-use problems from those effects specific to CSA are outlined below.

Methodological Approaches to Studying the Link Between CSA and Alcohol-Use Outcomes

Epidemiological studies using measured covariates

A number of investigations seeking to clarify the nature of the relationship between CSA and alcohol-use outcomes have measured and adjusted for the influences of other

relevant familial risk factors. For example, Fergusson and colleagues (1996a) examined CSA in relation to psychiatric disorders, including AUDs, in a study of 1,019 18-year-olds who had reported on familial risk factors such as parental psychopathology, family conflict, and parental substance abuse, in earlier waves of data collection. Their analyses adjusting for these and other potential confounders revealed that CSA remained a significant predictor of AUDs, with odds ratios of 3.2 (contact abuse with no intercourse) and 2.7 (abuse involving intercourse). A similar approach was used by Kilpatrick et al. (2000) in their investigation of CSA and past-year substance abuse/dependence in a national probability sample of 12- to 17-year-olds. After accounting for family history of alcohol-related problems, familial drug-use problems, and sociodemographic factors, CSA was associated with an odds ratio of 2.4 for the development of alcohol abuse or dependence.

Studies conducted with samples representing an older and broader age range have led to similar conclusions. Miller and colleagues' investigation (1993), for example, was based on a sample of 472 women ranging in age from 18 to 45 years, who were recruited from both treatment settings and the community. After adjusting for parental alcohol-related problems and treatment condition in addition to demographic factors, CSA remained a significant predictor of participants' alcohol-related problems. A total of 5,877 respondents to the National Comorbidity Study (all individuals from 15 to 24 years of age and a random sampling from the remaining respondents ages 25-54 years) comprised the sample in Molnar and colleagues' investigation (2001) of CSA and a range of psychiatric disorders, including AD. Similar to the approach taken in the previously cited studies, the authors included in the statistical models demographic indicators and measured covariates known to be associated with alcohol-use outcomes, specifically, race, age cohort, maternal and paternal physical or verbal abuse toward respondent, parent-to-parent verbal or physical abuse, maternal psychopathology, paternal psychopathology, maternal and paternal substance-use problems and antisocial behavior, and parental divorce. Elevations in rates of AD were apparent, although more modest than in other studies, after accounting for all of these risk factors. For females, the odds ratio was 1.5 and for males 1.7 (Molnar et al., 2001). Using a sample of 1,411 female twins ages 17-55 years, Kendler et al. (2000) examined the degree to which CSA predicted AD (among other substance use and psychiatric outcomes) after adjusting for a broad range of indicators of family functioning, as reported by parents. Even after accounting for parental education, parental psychopathology, quality of the mother's and father's relationship, the family's socioeconomic status, parental discipline practices, offspring separation from parents, church attendance, and level of conflict in the family, CSA remained a robust predictor of AD, with an odds ratio of 2.9.

With few exceptions (e.g., Widom et al.'s [1995] matched control-group study based on court records of child abuse), carefully controlled epidemiological studies provide evidence of a link between CSA and later alcohol misuse that does not disappear after adjusting for shared risk factors. This consistency in findings is especially striking given the variations from study to study in the measurement of CSA and the relative instability of abuse reports (Fergusson et al., 2000). Interviews tend to produce higher rates of reporting than surveys, as do behavior-specific inquiries, when compared with assessment methods requiring respondents to identify these events as sexual abuse, such as asking "Have you ever been sexually abused?" (Martin et al., 1993; Simpson and Miller, 2002). Accurate measurement of CSA remains a challenging task but, importantly, estimates of its association with psychiatric outcomes do not appear to be altered by errors in reporting of abuse history (Fergusson et al., 2000) or to vary systematically with quality of research designs (Simpson and Miller, 2002).

The application of this methodological approach has contributed tremendously to the goal of distinguishing direct from indirect effects of CSA on alcohol-related behaviors, but there are several limitations to using this strategy. Because of the extensive number of possible confounds in the relationship between CSA and alcohol-use outcomes, a range of psychiatric and psychosocial factors need to be assessed and included as measured covariates. Omission of crucial factors or errors in measurement of potential confounders may result in the misattribution of risk to CSA rather than to another source. On the other hand, the inclusion of a large number of covariates can compromise statistical power, which is decreased even further when possible interactions between risk factors are modeled.

Co-twin designs

Co-twin designs have evolved as an alternative approach to the use of measured covariates because they offer the means to adjust for all aspects of the environment that are shared between members of twin pairs—in addition to genetic contributions to alcohol-use outcomes. The nature of the risk factors that jointly influence CSA exposure and alcohol-related outcomes (e.g., parental psychopathology and familial conflict) are such that they would be expected to impact members of a twin pair similarly. Thus, the utility of statistically controlling for these environmental contributors to alcohol-use outcomes is clear. The importance of adjusting for genetic influences on alcohol-related problems is based on an extensive literature demonstrating the heritability of a variety of alcohol-use outcomes. The most widely studied is AD, which has an estimated heritability of 50%-60% (Reed et al., 1996; True et al., 1996; van den Bree et al., 1998). Long established as having genetic origins in men (Hrubec and Omenn, 1981; Romanov et al., 1991), AD is

now well documented as a heritable disorder in women as well (Heath et al., 1997; Kendler et al., 1994; Knopik et al., 2004; Prescott et al., 1999). Recent findings from this rapidly growing area of research suggest the importance of adjusting for heritable influences to alcohol-related behaviors across stages of use. Genetic contributions to initiation of alcohol use (Hopfer et al., 2003), problem drinking (Rhee et al., 2003), and the rate of progression between stages of AD development (Liu et al., 2004; Sartor et al., 2008) have all been reported in the literature.

Several methods employing twin pairs have been used to investigate the extent to which genetic and environmental risk for AUDs is modified by exposure to CSA. One of the most straightforward techniques is to examine whether the twin pair correlation for AUDs is modified by one twin's exposure to CSA and, further, whether this association differs by zygosity (monozygotic [MZ] vs dizygotic [DZ] status). Incorporation of data from co-twins creates the opportunity to statistically control for genetic and environmental factors shared by members of a twin pair. In this approach, the contribution of such factors as parental history of problem drinking is accounted for by the research design and thus ruled out as a possible source of distinction between CSA-exposed and nonexposed individuals. Recent work from our group illustrates this strategy. In a sample of 3,536 female twins, we examined CSA history in relation to two major transitions in the course of AD development: onset of first alcohol use and transition time from consumption of first alcoholic drink to onset of AD. CSA status was entered into the analyses after co-twin AD status, zygosity, and an interaction term reflecting zygosity by co-twin AD status, which provided an estimate of the degree to which familial risk may be attributed to genetic versus environmental factors. Our results revealed that, after adjusting for potential confounders through co-twin AD status, the risk conferred by CSA for rapid transition in AD development was apparent only among the earliest initiates of alcohol use and was specific to the onset of first alcohol consumption (Sartor et al., 2007), thus suggesting that the association with CSA is not universal across alcohol-related behaviors.

The discordant twin design, by contrast, draws on a unique subset of twin pairs: those who are discordant for exposure to the risk factor of interest, in this case, CSA. Instead of statistically adjusting for the co-twin's status on the outcome (e.g., AUD diagnosis), the discordant twin design uses twin pairs who differ on exposure to CSA, such that the unexposed co-twin serves as a matched control for the exposed twin. The method is a simple extension of matched-pair conditional (or fixed effects) logistic regression, in which, along with matching for age and gender (by default, identical in same-sex twin pairs) and shared environment, there is graded matching (100% in MZ and 50% in DZ pairs) for genetic background. (See Kendler et al. [1993] for an overview of conclusions that can be drawn using the co-twin control method.)

Figure 1 illustrates the association between CSA exposure and risk for subsequent AUDs under three possible models. The solid black bar in the figure represents the association between CSA exposure and AUDs in individuals from a randomly selected population of unrelated individuals. Clearly, there is evidence that CSA exposure is associated with an increased relative risk for AUDs. Now, consider the white (MZ) bars. These bars represent the relative risk ratios for AUDs expected in the unexposed twin of MZ twin pairs discordant for CSA. If the association between CSA and AUDs were entirely a result of factors that jointly contribute to exposure to CSA and AUDs, then we would expect there to be no additional risk for AUDs in MZ twins exposed to CSA when compared with their unexposed counterparts. Because they are completely matched for genetic and shared environmental influences with their exposed MZ twins, the relative risk of the unexposed twins would equal that of individuals in the general population who have experienced CSA. On the other hand, if the association between CSA and AUDs were a direct causal one, then we would expect no elevation in risk for unexposed MZ twins. Finally, if the association between CSA and AUDs were attributable to a combination of CSA-specific risk factors with risk common to CSA exposure and alcohol-related problems, then we would expect that unexposed MZ twins in discordant pairs would be at elevated risk for developing AUDs but that their risk would be lower than that of individuals who have experienced CSA.

Findings from discordant twin studies suggest that CSA poses risk for alcohol-related problems above and beyond risk attributable to family background factors known to contribute both to CSA exposure and to alcohol-use outcomes. Nelson and colleagues (2006), for example, investigated CSA in relation to alcohol- and drug-use outcomes by conducting conditional logistic regression analyses that estimated risk in CSA-positive versus CSA-negative members of twin pairs. Their results revealed an elevation in risk for AD among twins who had experienced sexual abuse (odds ratio = 1.6; Nelson et al., 2006). Kendler et al. (2000) also studied twins discordant for CSA to characterize the relationship between CSA and psychiatric outcomes, including AD. The ratios reflecting the number of cases in which the exposed twin developed AD to the number of cases in which the unexposed twin developed AD were calculated and produced an odds ratio of 2.8. Dinwiddie and colleagues (2000) examined CSA history and psychopathological outcomes in a large twin sample (n = 5,995) by calculating matched-pair odds ratios for same-sex twin pairs in which one twin reported CSA exposure and the other did not. These authors found an elevated risk for AD in women and men (odds ratios of 2.8 and 1.9, respectively) among CSA-exposed twins. Some of these same studies have also produced evidence for the role of risk factors common to CSA exposure and alcohol-related

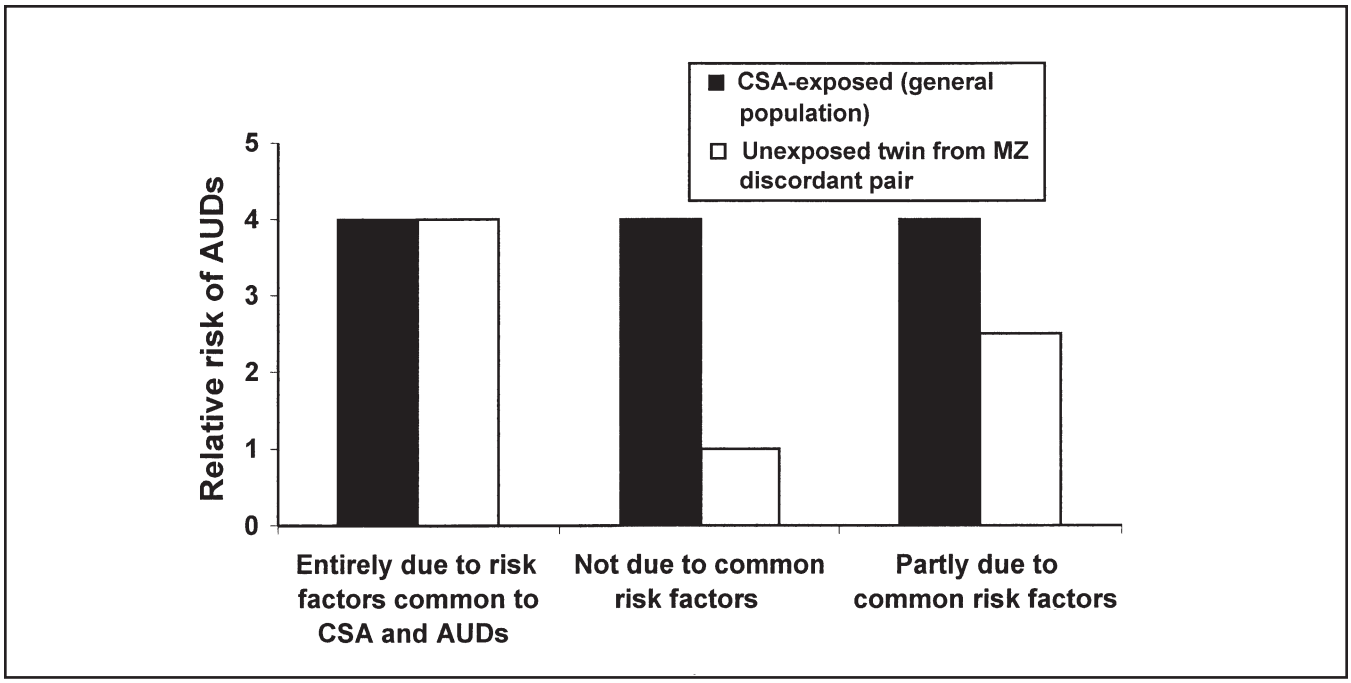

FIGURE 1. Three possible models of the association between childhood sexual abuse (CSA) and relative risk of alcohol-use disorder (AUD). Black bars = risk of AUD for a CSA-exposed individual in the general population. White bars = risk of AUD in the unexposed monozygotic (MZ) twin from an MZ discordant pair.

problems in shaping outcomes. Dinwiddie et al. (2000), for example, noted that the odds ratios based only on discordant pairs were lower than those calculated with the full sample (2.5 vs 2.8 for females and 1.0 vs 1.9 for males), indicating that additional family background factors contributed to the development of AD. Similarly, in their 2002 study, Nelson et al. reported that, although risk for AD was significantly higher in CSA-positive versus CSA-negative members of discordant twin pairs, the contribution of risk factors such as maternal and paternal alcohol-related problems, parental conflict, physical abuse, and neglect was also evident.

In sum, conclusions from studies employing co-twin methodology coincide with those derived from general population-based studies using measured covariates. Familial risk factors, such as parental AUDs and family conflict, contribute to AUDs, but CSA confers additional risk that is not fully accounted for by these factors.

Future Directions

The constellation of risk factors that characterize family environments where children are vulnerable to CSA exposure—and its considerable overlap with the adversities to which offspring of parents with AUDs are likely to be exposed—creates significant challenges for developing a comprehensive model for the pathway (or pathways) from CSA to the manifestation of alcohol-related problems. The two methodologies described above represent important steps toward reaching this goal, but much work remains to be done. The weight of the evidence suggests that CSA-associated risk for alcohol-related problems is attenuated but not fully explained by common risk factors, yet describing the association as a "direct path" may be overstating the implications of findings in the current literature. Furthermore, the meaning of such a direct path cannot be fully understood until the underlying mechanisms that link CSA to problem alcohol use are more clearly articulated. Twin-based studies, much like investigations using measured covariates, cannot completely address the challenges of this line of research. Although powerful tools for accounting for familial risk, they do not control for confounding factors that are unique to members of a twin pair. The impact of an individual-specific environmental risk factor that precedes and increases likelihood of exposure to CSA and that influences alcohol-use outcomes (e.g., early association with deviant peers and their families) would not be detectable using the basic co-twin design. To detect such an effect, measured covariates would need to be added to the co-twin design, thereby posing the same challenge described earlier: including a comprehensive group of relevant risk factors while maintaining statistical power. Discordant twin studies present an additional concern. Given the high concordance rates of CSA in twin pairs (Dinwiddie et al., 2000; Kendler et al., 2000), CSA exposure in only one member of a twin pair may reflect an atypical sexual abuse history, calling into question the generalizability of findings. In addition, the logistical problem of limited

accessibility to twin registries is exacerbated by the relative rarity of twin pairs discordant for CSA.

As no single method addresses all issues inherent in this line of research, it is crucial that findings derived from a range of available methodological approaches be integrated to develop explanatory models of the biological and psychosocial processes that account for the relationship between CSA and problem alcohol use. Such models will also prove useful for exploring CSA in relation to problem use of other substances, as evidence continues to build for the association of CSA with smoking-related (Anda et al., 1999; Hussey et al., 2006; Plant et al., 2004) and illicit drug-use outcomes (Boden et al., 2006; Lynskey et al., 2006; MacMillan et al., 2001; Thompson et al., 2002). Toward this end, we propose three additional directions for research.

Investigating gene by environment effects

First, gene by environment interaction (G × E) models can be used to investigate the association between CSA and AUDs without the potential problem of inflated heritability estimates that can result from the misattribution of G × E effects to genetic sources in classical twin models. Specifically, G × E models can assess whether the association between AUDs and polymorphisms in candidate genes varies with exposure to CSA and whether genes mediate the association between CSA and subsequent alcohol-related problems. This approach was used to examine antisocial behavior in a seminal study by Caspi et al. (2002), in which they found that the monoamine oxidase A (MAOA) gene and childhood maltreatment independently and interactively predicted conduct disorder in boys. Covault and colleagues (2007) recently applied this methodology to the study of negative life events and drinking behaviors in college students by incorporating genotypic data, specifically, allele length in the functional polymorphism 5-HTTLPR (in the serotonin transporter gene) into their design. The results revealed significant interaction effects between genotype and exposure to multiple negative life events in predicting alcohol-use outcomes. Elevations in quantity and frequency of alcohol use were evident in individuals homozygous for the short allele, but not among those homozygous for the long allele, when exposed to multiple stressful events (Covault et al., 2007). Tests of the effect of measured genotypic vulnerability on the increased risk for AUDs in individuals exposed to CSA may reveal a similar susceptibility group.

Exploring possible changes in the CSA-alcohol association over the course of use

Second, to capture the association between CSA and the developmental course of alcohol-related problems, it is crucial to assess variability in the association between CSA status and alcohol-use outcomes across stages of use and to examine mechanisms driving those changes. Whether the association between CSA and alcohol-related behaviors is stable across drinking course or, as we found in our study of CSA and stages of alcohol use (Sartor et al., 2007), most pronounced in early stages (exerting primarily a proximal influence) has only rarely been investigated. Continuity in the relationship of CSA history with alcohol-use outcomes may reflect the stable influence of risk factors common to CSA exposure and alcohol-related problems or sequelae of CSA exposure (e.g., a decreased ability to regulate negative affect). Conversely, continuity (or discontinuity) in the association may be the product of cumulative risk, that is, a chain of events (e.g., early initiation, additional exposures to sexual assault) resulting from a combination of genetic and environmental liabilities. Retrospective accounts of these events (including their temporal sequence) are susceptible to errors in reporting. In addition to the lower accuracy of reporting inherent in retrospective versus prospective assessments that results from degradation in memory over time, there is a possibility that events occurring between the time of alcohol-use initiation and the time of assessment (e.g., recounting sexual abuse and/or alcohol-use history in treatment) may lead to biases in reporting. Such inaccuracies in reporting can be reduced significantly in prospective studies. Thus, characterizing potential variability in CSA-related risk across the course of alcohol use necessitates the considerable investment of resources involved in conducting longitudinal investigations, but the goals such studies can achieve are crucial ones. Identifying those junctures in the pathway to AUDs where outcomes are most malleable is an essential task to decrease the susceptibility to alcohol-related problems in individuals who have experienced CSA.

Examining the potential contribution of CSA-related modification in gene expression

Third, our review of genetically informative studies has focused on the effects of latent and measured genotype on alcohol-related outcomes and the increased sensitivity to these genetic underpinnings via exposure to a potent stressor, CSA. Revealing research in animal paradigms suggests that stress can modify gene expression through epigenetic modification (Kaffman and Meaney, 2007; Szyf et al., 2007; Weaver et al., 2004a,b). Weaver et al. (2004a,b) have repeatedly demonstrated that rat pups reared by mothers low in licking-grooming and arch-back nursing (LG-ABN), behaviors considered representative of maternal care, show increased methylation in the promoter region of the gene encoding the glucocorticoid receptor. Importantly, these researchers have also demonstrated that cross-fostering, that is, provision of maternal care from a high LG-ABN foster mother to a pup born to a low LG-ABN mother, can reverse methylation-induced gene silencing. Although studies of this nature are challenging within the human paradigm (see

Kaffman and Meaney, 2007), it is noteworthy that, in the twin design, epigenetic variation may not be captured by the measure of genetic relatedness but instead remain in the measure of individual-specific environment. Therefore, it is possible that variations in alcohol-related outcomes in a pair of MZ twins who are discordant for exposure to chronic stress (e.g., CSA) may be the consequence of large scale epigenetic change (Ptak and Petronis, 2008). Identification of gene networks that can be modified by CSA exposure and examination of the effect of the consequent epigenetic change on risk for alcohol-related problems (through the study of MZ twin pairs discordant for CSA) may eventually lead to the development of therapeutics for epigenetic misregulation attributable to CSA.

In humans, the most widely studied aspects of stress-responsivity are through its action on hypothalamic-pituitary-adrenal (HPA-axis) modulation. The corticotrophin-releasing hormone, encoded by the CRH gene, mediates and modulates stress responsivity via HPA mechanism. Several animal models of ethanol intake have demonstrated an association between CRH and alcohol ingestion (see Kiefer and Wiedemann, 2004, and Orozco-Cabal et al., 2006, for reviews). Reduced CRH activity, which can result from chronic stress exposure, is associated with an increased craving for alcohol and a high probability of relapse following abstinence, suggesting a synergy between prolonged exposure to stress and modified genotypic control of ethanol intake. Regulatory regions of genes constituting the HPA-axis (such as CRH) may therefore be susceptible to epigenetic modification and may serve as potential candidates for fine-mapping in MZ twins discordant for CSA.

These avenues for research highlight two crucial aspects of the relationship between CSA and alcohol-related behaviors. First, the impact of exposure to CSA is potent: both biology and behavior are vulnerable to its effects. Second, the pathway from CSA to alcohol misuse involves a complex cascade of events that may include cyclical modifications of genotypic sensitivity (via G × E interactions) and gene expression (via epigenetic programming), as well as such psychosocial processes as the onset of psychiatric conditions (e.g., depression and post-traumatic stress disorder) following exposure to CSA that, in turn, increase risk for the development of AUDs (Moncrieff and Farmer, 1998; Wilsnack et al., 1997). A comprehensive etiological model for the association between CSA and problem alcohol use cannot yet be proposed, but pursuing the major lines of research outlined here will move us closer to that goal.

The Need for Careful Interpretation of Findings

Despite substantial empirical evidence tying alcohol-related (and other substance-use and psychiatric) outcomes to CSA and the utility of methodological designs that account for the contribution of common risk factors in delineating pathways from CSA to AUDs, such approaches are underrepresented in the extant literature. Underuse of the strategies described above may stem in part from hesitation among some investigators to conduct research whose findings could be misinterpreted to imply that there are not, in fact, significant implications for the health and well-being of individuals subjected to sexual abuse. Take for example a study that finds the impact of CSA on AUDs is largely mediated through familial risk factors that contribute both to likelihood of exposure to CSA and to elevated risk for AUDs (e.g., poor parental monitoring). Results could be misconstrued as suggesting that sexual abuse is not associated with alcohol abuse and dependence when, in fact, such findings would imply that those individuals who experience sexual abuse are likely to come from environments where they are exposed to *multiple* risk factors that elevate their chances of developing alcohol-use problems.

The potential for such a misinterpretation is greater still in genetically informative studies whose results may implicate a heritable component to risk for CSA exposure. We do not posit that genes influence risk for CSA, primarily because the literature does not support this assertion, but also because this statement is misleading. Setting aside for the moment the stigmatizing effects of attributing biological predisposition to CSA exposure, it is unlikely that there are genetic influences that act solely and directly to make an individual more or less vulnerable to exposure to childhood maltreatment. However, there are several mechanisms by which genetic liability influences exposure to CSA. For example, genes that jointly influence risk for antisocial behavior and AUDs (Kendler et al., 2003; Krueger et al., 2002) may contribute to CSA exposure, especially in cases where the perpetrator is related to the individual subjected to the abuse. In this instance, the perpetrator, whose abusive behavior is correlated with his/her antisociality, transmits some of this genetic risk to the child, who in turn suffers the double "hit" of inherited risk and CSA exposure. (For similar examples, see Kim-Cohen et al., 2006.) The limiting concern in this research is the sensitivity surrounding the discussion of biology and CSA exposure because it may be misunderstood as attributing a causal burden on the individual experiencing the abuse (i.e., one is predisposed to CSA). Furthermore, although not unique to genetically informative research, the potential for findings to be misinterpreted in deterministic rather than probabilistic terms is high in genetic studies. The message that an AUD (or, for that matter, any psychiatric disorder) is by no means an inevitable consequence of experiencing CSA, but simply a more likely outcome in this population, is an important one to emphasize (Collishaw et al., 2007; Lynskey and Fergusson, 1997). Through carefully constructed research, and open, thoughtful dialogue, investigators may begin to disentangle the complex mechanisms, including genetically informative routes, through which CSA is intertwined with alcohol-related outcomes. Thus,

rather than minimizing the sequelae of CSA or suggesting that a predetermined biological mechanism drives CSA risk, investigations of this nature can lead to the identification of modifiable factors that confer risk for alcohol-related problems.

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