EXPLORING THE RELATION BETWEEN CIGARETTE SMOKING AND ALCOHOL HANGOVER FREQUENCY

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And hereby certify that in their opinion it is worthy of acceptance.

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ABSTRACT

Drinkers differ meaningfully in their susceptibility to hangover, and prior studies suggest individual differences in hangover proneness may be related to risk for alcohol use disorders (AUD). This project examined whether smoking behavior, a frequent concomitant of drinking, accounts for some of the variation in self-reported hangover. Data from a longitudinal familial high-risk study (N=489; 51% with a family history of alcoholism) were used to assess the association of smoking with hangover. In bivariate correlational analyses, hangover was associated with sex, positive family history status, alcohol consumption, and smoking. Cross-sectional and multilevel regression modeled self-reported hangover scores from six study waves spanning ages 18 to 30. Results revealed main effects for smoking such that smokers reported higher mean hangover. Additionally, smoking interacted with alcohol consumption; the relation between drinking and hangover was weaker among smokers than among nonsmokers. Exploration of hangover at early and late time-points among naturally occurring groups who changed smoking status reinforced these results. Analyses comparing tobacco abstainers with tobacco initiators showed a significant group by time interaction, such that those who initiated smoking reported increased hangover over time, and those who never smoked

reported decreased hangover across time. Analyses comparing smokers with tobacco quitters also revealed a significant group by time interaction, showing a decrease in hangover across time for quitters, and an increase for smokers. These interactions remained significant after controlling for sex, family history status, and changes in drinking over time. Results from logistic regression analyses showed that hangover was associated with risk for AUD, and that this effect remained even after controlling for smoking status, suggesting the relation between early hangover and later AUD is not simply an artifact of failing to account for smoking behavior. Taken together, these findings raise the intriguing possibility that smoking contributes to individual variation in hangover, and that smoking might be a permissive factor in the escalation of drinking.

INTRODUCTION

Alcohol "hangover" is a set of aversive symptoms experienced the morning after excess alcohol consumption. Though the hangover state is familiar to most drinkers, researchers have paid relatively little attention to this phenomenon. The lack of attention to hangover is surprising in light of the estimated prevalence of hangover. Self-report data suggest hangover is the most commonly experienced negative consequence of alcohol use (Wiese, Shlipak, & Browner, 2000), with close to three quarters of those who drink to intoxication reporting experiencing a hangover at least some of the time (Harburg, Gunn, Gleiberman, Difran-Ceisco, & Andschork 1993). Despite its ubiquity, the research community has not yet reached a consensus regarding the significance of hangover.

It is difficult to know precisely why hangover has not been well studied in alcohol research. It seems likely that investigators have tended to view hangover as an *inevitable consequence* of alcohol intoxication that is expressed similarly across all persons and has little theoretical significance and limited practical importance. In other words, hangover may be viewed as an epiphenomenon or meaningless side effect of drinking, and therefore be presumed to be a "blind alley" for alcohol research. If this is, in fact, the prevailing view of hangover, some emerging lines of evidence suggest it is in error.

Most research on hangover has been focused on performance decrements in the time period following intoxication, such as cognitive deficits (Alterman & Hall, 1989; Collins & Chiles, 1980; Finnigan, Hammersley, & Cooper, 1998; Lemon, Chesher, Fox, Greeley, & Nabke, 1993; Schroeder & Collins, 1979; Verster, van Duin, Volkerts, Schreuder, & Verbaten, 2003) and motor impairment (Collins, 1980; Seppala, Leino,

Linnoila, Huttunen, & Ylikahri, 1976; Yesavage, Dolhert, & Taylor, 1994; Yesavage & Leirer, 1986). These investigations have been inspired by the obvious potential for hangover to have a deleterious impact on the safety of drinkers and those around them. Fewer investigations have considered the possibility that hangover or hangover susceptibility might serve as a marker of individual differences in risk for alcohol use disorder (AUD) or problem drinking.

Recent research suggests that drinkers differ meaningfully in their susceptibility to hangover (e.g., Newlin & Pretorious, 1990; Slutske, Piasecki, & Hunt-Carter, 2003) and that individual differences in hangover may be related to risk for alcohol use disorders (Piasecki, Sher, Slutske, & Jackson, 2005). Such findings (discussed at greater length below) set the stage for more systematic inquiry into hangover's *determinants* and *long-term consequences*. The goal of the current project is to advance this important, broad research agenda by exploring whether a robust concomitant of drinking—cigarette use—moderates the expression of hangover.

Smoking and drinking behaviors are strongly associated, and are especially tightly coupled in persons with alcohol use disorders (Madden, Bucholz, Martin, & Heath, 2000). Some recent research (Madden, Heath, Starmer, Whitfield, & Martin, 1995; Rose et al., 2004) has demonstrated that smoking may alter physiologic and subjective responses to alcohol consumption, and that the relation between smoking and subjective reactions to alcohol (e.g. feeling intoxicated) is under partial genetic control.
Given such findings, it is surprising that smoking behavior has often been overlooked in alcohol research. In fact, smoking may be construed as a meaningful cofactor or an uncontrolled confounder in much alcohol research. The project proposed here will

examine whether smoking behaviors can help explain individual differences in hangover frequency. If this hypothesis is corroborated, it may have significant implications for understanding hangover. By extension, it might also help us to better understand the ontogenesis of alcoholism and the robust associations between smoking and problem drinking outcomes.

An association between hangover propensity and smoking may be hypothesized to result from diverse causal processes. It may be the case that cigarette smoking, hangover, and alcohol use disorders are clustered in individuals because these behaviors are external indicators of the presence of a broader underlying trait-like susceptibility or risk process. That is, there may be a single, higher-order construct (for example, drug sensitivity) that explains the tendency for these to co-occur. Alternatively, smoking may moderate hangover because of a pharmacological interaction between tobacco/nicotine and alcohol.[1]

Symptoms of Hangover

Hangover encompasses physical, cognitive and autonomic nervous system disturbances (Swift & Davidson, 1998). Physical symptoms include headache, nausea, fatigue, thirst sweating, tremor, and increases in heart rate and blood pressure. Cognitive and mood symptoms such as decreased ability to concentrate, irritability, depression and anxiety are also often endorsed as symptoms of hangover.

[1] When attempting to interpret a correlation, one must consider causality occurring in either direction. Therefore, another possible interpretation of a correlation between hangover and smoking identifies hangover as a cause of smoking; however, this interpretation seems rather unlikely. While a hangover may acutely instigate smoking in a smoker, it seems improbable that a hangover would inspire a non-smoking individual to initiate smoking, or would account for any sizable proportion of smoking events.

Studies attempting to identify which of these symptoms are most commonly experienced have yielded mixed results. In an early study of hangover symptomatology, current drinkers were asked to rate the their experience of a variety of hangover symptoms, and headache was found to be the most commonly endorsed symptom, followed by diarrhea, and loss of appetite (Harburg, Davis, Cummings, & Gunn, 1981). Another study of hangover symptom frequency also identified headache as the most commonly endorsed symptom of hangover (79% of those who report ever having a hangover), followed by nausea (57%), and vomiting (34%) (Smith & Barnes, 1983). In a large sample of college students, the most commonly experienced hangover symptoms included thirst or dehydration (75% of drinkers experienced this in the past year), fatigue (72%), headache (51%), nausea (49%), and feeling very weak (49%) (Slutske, et al., 2003). These mixed results have perhaps arisen because investigators have employed diverse assessment tools and assessed samples with differing demographic compositions. For instance, items assessing thirst/dehydration, fatigue, and feeling weak (the most prevalent symptoms in one sample) were not included in other studies (Harburg, et al., 1981; Smith & Barnes, 1983). Because assessments are not directly comparable across studies, prevalences of individual symptoms and their importance or centrality to the overall hangover syndrome remain open questions.

Mechanisms of Hangover

Questions remain about the causal mechanisms underlying the hangover state. While the mechanisms of hangover have not been definitively identified, a number of possible causes have been suggested.

Some hypotheses focus on the direct effects of alcohol on the body. For instance, nausea and vomiting associated with hangover may be explained by the irritating effect alcohol has on the stomach lining (Swift & Davidson, 1998). Alcohol reduces the amount of time spent in REM sleep, so perhaps sleep quality disturbances resulting from alcohol intoxication cause fatigue associated with hangover. Or, perhaps because drinking usually occurs in the evening and nighttime hours, sleep is usurped by drinking activities, and hangover fatigue is simply the consequence of lack of sleep (Swift & Davidson, 1998).

Dehydration has long been thought to be a contributor to the development of hangover. Alcohol has been shown to affect the endocrine system, causing changes in levels of vasopressin (an antidiuretic hormone), as well as several other hormones (Anylian, Dorn, & Swerdlow, 1978). Decreased levels of vasopressin result in the kidneys' failure to retain water, which leads to increased urinary output and subsequent dehydration. Thirst, fatigue, and dizziness are common symptoms of dehydration, and their presence in the hangover symptom cluster may be explained by alcohol's dehydrating effects. Additional symptoms of hangover that result in fluid loss (such as sweating, vomiting, and diarrhea) may exacerbate the dehydration (Swift & Davidson, 1998).

Alcohol consumption leads to decreased levels of blood glucose, which has also been implicated in the development of hangover. Specifically, alcohol metabolism causes the accumulation of both triglycerides in the liver and lactic acid in the body's fluids, which each result in a decrease in production of glucose. The effects of low blood sugar include fatigue and mood disturbances, and thus these "hangover" symptoms may

actually be a manifestation of alcohol-induced hypoglycemia (Swift & Davidson, 1998; Vartia, Forsander, & Krusius, 1960).

Biologically active compounds called congeners are present as a byproduct of alcohol fermentation, and are sometimes added to alcoholic beverages to improve the taste, smell, and appearance of the beverage. These compounds are usually present in dark or colored drinks, such as whisky, red wine, brandy and tequila, and are not as common in clear beverages, such as vodka or gin. Hangover is more often reported after consumption of alcoholic beverages containing high quantities of congeners, indicating that congeners may play a role in the development of hangover. However, hangover does still occur after drinking those beverages low in congener content, suggesting that while congeners may contribute to hangover, they are likely not the sole cause (Smith & Barnes, 1983; Swift & Davidson, 1998; Wiese, et al., 2000)

In a theoretically interesting causal explanation, hangover is hypothesized to be an acute alcohol withdrawal syndrome. Many of the symptoms of hangover are similar to those of alcohol withdrawal. Further, those who are at heightened risk for alcohol use disorders experience more frequent hangovers, possibly suggesting that those who experience this "acute withdrawal" are also more likely to be subject to "acute alcohol dependence" (Newlin & Pretorius, 1990). Withdrawal has been shown to be a strong indicator of AUD severity, and is the dependence criterion most predictive of alcohol involvement (Langenbucher et al., 2000; Schuckit, et al., 1998; Schuckit et al., 2003). Evidence for withdrawal's centrality in the AUD syndrome indicates that "acute withdrawal" may be a meaningful and important construct worthy of future investigation.

While these proposed etiological pathways have each received some degree of support, no single explanation adequately addresses the cause of hangover. The best causal model may include a number of parallel physiological processes which each contribute to the larger syndrome known as hangover (Swift & Davidson, 1998).

Hangover, Drinking Motivation, and Alcohol Use Disorders

Hangover has the potential to affect drinking motivation. Because hangover is an aversive state caused by drinking, it may have a meaningful effect on subsequent drinking behavior. Logically, one might speculate that because hangover is an aversive state, it functions as a punisher, decreasing the likelihood of subsequent drinking. Alternatively, it has been hypothesized that hangover actually leads to *increased* drinking by setting the stage for negative reinforcement by alcohol. In other words, the drinker may self-administer alcohol during the hangover state in an effort to relieve hangover symptoms (Newlin & Pretorius, 1990; Span & Earleywine, 1998). Though many contemporary models of drug motivation have deemphasized negative reinforcement (e.g. Lyvers, 1998; Robinson & Berridge, 1993; van Ree, Gerrits, & Vanderschuren, 1999), most allow that it plays some role in drug use, and other models (e.g. Baker, Piper, McCarthy, Majeskie, & Fiore, 2004) assert that it is *the* cardinal feature of drug motivation. Negative reinforcement models of addiction propose that drug use is motivated by the desire to reduce or avoid negative affect. The user detects interoceptive cues of impending negative affect, and self-administers a drug to evade or eliminate that affective state (Baker, et al., 2004). From this perspective, one might predict that the hangover-prone drinker associates alcohol consumption with the relief of negative affect. Therefore, s/he may be more likely to drink again in the future in an effort to ameliorate

similar moods or physical discomfort. It is important to recognize that this perspective does not require that the hungover individual drink to alleviate their hangover during every hangover episode. Rather, this view posits that every time the hungover individual does drink to alleviate their hangover (or when drinking coincidentally alleviates hangover symptoms), that event represents a formative learning experience. The individual's experience alleviating physical discomfort by drinking may be generalized to other situations, making them more likely to self-administer alcohol in an effort to reduce physical or emotional distress again in the future.

Alternatively, hangover may play no direct role in the development of alcohol use disorders. Hangover may be a marker of an underlying sensitivity to alcohol and thus be associated with risk for alcohol use disorders even though the two are not causally connected. Hangover may be a "complication" that affects some individuals more than others and promotes role interference and functional impairment, making some more likely to meet diagnostic criteria for AUD. These conceptualizations suggest that a direct causal link between hangover and motivation for future drinking is not necessary for hangover to forecast future alcohol use disorders.

Recent research on hangover's association with alcohol use disorders has indicated that hangover proneness is, in fact, related to *increased* risk for alcohol use disorders. The most consistent suggestive evidence has been derived from familial risk group studies of alcoholism.

Researchers have identified the presence of familial alcoholism as a marker of risk for psychopathology in general, and alcohol use disorders, specifically. That is, evidence from research using individuals with a family history of alcoholism suggest that

offspring of alcoholics are at higher risk for developing alcohol use disorders themselves (Sher, Walitzer, Wood & Brent, 1991). Therefore, variables that differentiate offspring of alcoholics from those of non-alcoholics are potential markers for an underlying alcoholism risk process (Newlin & Thompson, 1991).

Newlin and Pretorius (1990) assessed individual differences in propensity to experience hangover among those at high and low risk for alcoholism based on familial presence of alcoholism. In a retrospective survey, they assessed hangover frequency among thirteen sons of alcoholics (SOAs) and twenty-five sons of non-alcoholics (SONAs). Hangover experiences were assessed using a 13 item questionnaire which was constructed by the authors (Hangover Questionnaire, or HQ). The HQ was administered in 2 forms: one assessing recent hangover experiences, and one assessing hangover symptoms at the outset of the drinking career.

Newlin and Pretorius hypothesized that if hangover acts as a punisher, those at low risk for alcoholism would report experiencing more frequent hangovers after drinking, while those at high risk would report experiencing relatively few hangovers. Alternatively, they hypothesized that hangover may reflect an acute withdrawal syndrome that reflects an underlying "dependence proneness." If this were the case, those at high risk for alcoholism would report greater hangover frequency than those at low risk. Results supported the latter hypothesis; hangover scores for early experiences were not significantly different for SOAs and SONAs, but recent experiences were significantly different for the two groups (SOA mean = 34.4, SD = 9.0, SONA mean = 25.8, SD = 5.8). This effect remained even when controlling for quantity/frequency of drinking, which did differ across groups (such that SOAs currently drink more).

Complementary findings were obtained using an alcohol challenge design (McCaul, Turkkan, Svikis, & Bigelow, 1991). Thirty-two college-aged men (16 SOAs, 16 SONAs) consumed 1.0 g/kg of alcohol or placebo, and physiological, subjective and psychomotor assessments were made throughout the 8 hours post-ingestion, and again at 18 hours post-ingestion. Questions assessing current hangover symptomatology included 10 items from a "withdrawal/hangover" scale that tapped the following domains: sweating, loss of appetite, shaking, trouble concentrating, racing heart, anxiety, alcohol craving, fatigue, restlessness, and irritability (headache was not included in this assessment). There was a significant between-groups main effect on this measure such that SOAs scored higher on the withdrawal/hangover scale than SONAs. There was also a significant group by time interaction such that SOAs took longer to return to placebo levels than SONAs (McCaul, et al., 1991).

In a retrospective survey of 1,230 currently drinking college students, hangover frequency was assessed using the Hangover Symptoms Scale (HSS)[2] (Slutske, et al., 2003). Ninety percent of the sample stated they had experienced at least one hangover symptom during their first few drinking episodes, and 87% reported at least one symptom in the past year. Twenty-three percent of participants were identified as having a positive

[2] This study also provided preliminary validation data on a new assessment of hangover, the HHS, which assesses the frequency of 13 hangover symptoms both during the first few drinking episodes, and during the past year. These authors developed the HSS in an effort to address some of the limitations of the HQ. For instance, the HQ includes items that assess experiences which occur during the drinking episode, rather than during the time period following that episode (for instance, one HQ item reads "I got a headache while drinking"). Also, some of the items assess the individual's subjective evaluation of the consequences of the drinking experience (e.g. "I regretted my behavior while drinking"). Newlin & Pretorius report that there was adequate internal consistency among the HQ items (Cronbach's alpha = .85 for early hangover items, .77 for recent hangover items). However, it is notable that in an item by item analysis, the most discriminating items (such as "I got a headache while drinking" and "I vomited after drinking") do not necessarily assess hangover as it is commonly understood.

history of alcohol problems in one or both parents. Results showed that these potentially high-risk individuals reported being more prone to experience hangover than their low risk counterparts (family history positive [FHP] mean=5.9, *SD*=3.6, family history negative [FHN] mean=4.9, *SD*=3.4).

Other data indirectly support a link between alcoholism and increased hangover propensity. Earleywine (1993) examined the relationship between personality risk for alcoholism (as measured by scores on the MacAndrew Alcoholism Scale, or MAC) and hangover, and found those who show elevated personality risk for alcoholism also report experiencing more hangovers over the previous year. Span and Earleywine (1999) attempted to replicate these results, but did not find an association between personality risk for alcoholism (as assessed by the MAC) and hangover. However, in an alcohol challenge paradigm, they did observe significant differences in hangover among those with a positive family history and those without. In this study, the sample of 20 sons of alcoholics and 20 sons of non-alcoholics received placebo during the first of three challenge sessions, and were administered 0.5 g ethanol/kg of body weight during two subsequent sessions. They completed a modified version of McCaul's withdrawal scale, and Newlin and Pretorius' Hangover Questionnaire on the morning following each session. Results showed that the two groups did not differ in their typical quantity and frequency of drinking, peak BAC during challenge sessions, or expectancies about hangover. However, they did differ in their experience of hangover, such that sons of alcoholics reported more hangover symptoms the morning after drinking, compared to sons of non-alcoholics. Sons of alcoholics also reported experiencing hangover

symptoms after receiving the placebo, suggesting that factors beyond alcohol consumption per se may influence hangover reports.

Piasecki and colleagues (2005) conducted the first direct test of the relationship between early hangover propensity and subsequent alcohol use disorder diagnosis. Using data collected in an ongoing 11- year longitudinal study of college students at high and low risk for alcoholism (as defined by family history status), the authors assessed the relationship between hangover frequency early in the drinking career, and alcohol use disorder at later assessments. Their results indicated that hangover frequency, as measured at the first wave of data collection (during the freshman year of college), predicted diagnosis of alcohol use disorders at the 7 and 11 year follow-up assessments. Those who reported more frequent hangovers at baseline were at heightened risk for developing alcohol use disorders later in life. When the question was reversed, those with a diagnosis of AUD at a later time point in the study had higher ratings of hangover early in the study, and distinctive patterns of elevated hangover across time.

Taken together, the available findings suggest that those who are at high risk for alcoholism tend to experience more frequent hangovers than those at low risk. Furthermore, hangover is prospectively related to alcohol use disorders, even controlling for family history status. Thus, hangover may actually be a marker for a latent risk for alcohol use disorders, or may play a direct, motivational role in the development of alcohol use disorders. Clearly more work is needed, but the extant findings suggest hangover is a promising research area, and one that has the potential to shed new light on the nature of alcohol use disorder risk.

Smoking, Drinking, and Alcohol Use Disorders

Epidemiological data suggest that smoking and alcohol use commonly co-occur. Among current drinkers over the age of 18, approximately 37% report current tobacco use, and 82% report either current or past tobacco use. This stands in sharp contrast to lifetime non-drinkers, of whom only 13% report current smoking, and 32% report current or past tobacco use (Bobo & Husten, 2000). Smoking is especially prevalent among heavy drinkers, particularly those diagnosed with alcohol use disorders. In an analysis of the relationship between the severity of an individual's alcohol use disorder and their current smoking status, Madden and colleagues (2000) found that as dependence symptom count (as defined by DSM-III) increases, so does the likelihood of current smoking. For instance, among women who met criteria for 1 dependence symptom, 54% were current smokers, and among those who met criteria for 4 symptoms, 87.5% were smokers. In a more extreme example, among those who met criteria for 7-9 symptoms, 94.1% report current smoking. Smoking rates for men followed a similar pattern (Madden, et al., 2000).

Smoking and drinking seem to be interrelated such that consumption of one drug influences motivation to consume the other. In laboratory studies, smokers report more desire to smoke and more enjoyment of their cigarette while drinking than while not drinking (Glautier, Clements, White, Taylor & Stolerman, 1996; Keenan, Hatsukami, Pickens, Gust, & Stretlow, 1990; King & Epstein, 2005; Sayette, Martin, Wertz, Perrott, & Peters, 2005). While under the influence of alcohol, smokers take more puffs than they do while sober (Griffiths, Bigelow, & Liebson, 1976). Field research using palm-top computers shows that smokers are about twice as likely to smoke while drinking than

when not drinking, even when controlling for contextual factors such as location, day of the week, time of day, others' smoking, environmental regulations on smoking, and activity type (e.g. work vs. leisure) (Shiffman, et al., 1994). Recent evidence has also suggested that nicotine administration may inspire increased alcohol consumption (Barrett, Tichauer, Leyton, & Pihl, 2006; Perkins, Fonte, & Grobe, 2000), though this effect has only been demonstrated in men.

Rationale for Considering Smoking as a Moderator between Drinking and Hangover

The findings summarized above indicate that hangover differentiates high and low risk drinkers such that individuals at high risk for alcohol use disorders are more likely to experience frequent hangovers. There is also strong evidence suggesting that those individuals at high risk for alcohol use disorders are likely to be smokers (Madden, et al., 2000). However, these studies do not reveal whether hangover is truly a marker of risk, or if this effect is the result of some confound or cofactor, such as smoking. Because smoking status has never been taken into account in studies of hangover among high-risk individuals, we are left with the open question: What association, if any, does smoking have with hangover?

Several conceptualizations of this possible relationship can be imagined. It may be that smoking and hangover are related to each other because they are both associated with the same higher-order variable. For instance, it may be true that smoking and hangover are associated because drinking often occurs in locations where smoking is permitted. Research suggests drinking and smoking often occur together, and so perhaps when the drinker spends more time in a smoke-friendly setting, s/he tends to both smoke more and acquire a hangover as a result of drinking. Alternatively, it may be true that

those who are at high risk for alcohol use disorders experience more frequent hangovers, and are also pharmacologically susceptible to nicotine/tobacco. In this conceptualization of the relationship between AUD risk, smoking status, and hangover frequency, smoking and hangover can be thought of as behavioral markers for an underlying risk propensity. These are essentially "third variable" explanations, in which smoking has no pharmacological effect on hangover, but both are associated with an external or higher-order variable.

However, it also seems plausible that tobacco smoke may interact pharmacologically with alcohol and contribute to the development of hangover. Tobacco smoke is pharmacologically potent in its own right, and may contribute to hangover symptomatology. As noted above, field research indicates that drinking and smoking often occur together, suggesting there is ample opportunity for these two substances to interact pharmacologically (Shiffman, et al., 1994). Research describing the acute systemic effects of nicotine and/or tobacco smoke suggests a direct pharmacological effect of smoking is plausible. Tobacco can elicit central nervous system effects such as headache, dizziness, and insomnia, gastrointestinal effects such as nausea, vomiting, diarrhea, and dry mouth, musculoskeletal effects such as myalgia (diffuse muscle pain) and arthralgias (joint pain or stiffness), and sleep disturbance (Palmer, Buckley, & Faulds, 1992; Phillips & Danner, 1995), all of which are commonly reported as symptoms of hangover.

The current study prospectively examined the relationship between drinking and hangover among individuals who vary according to smoking status. The goal of this project was to determine whether smoking status can help explain individual differences

in hangover frequency. Data from an 11 year longitudinal study of young adults were used to address this question. We predicted that those who smoke would also report increased hangover. Due to the nature of the data used in this study (i.e. retrospective surveys widely spaced in time), the level of detail necessary to assess particular mechanistic processes is not available. Therefore, this project does not aim to draw definitive conclusions about which of the competing conceptualizations posited above are true. However, these data are well suited to determine whether an association between these variables exists. This study is an important first step being conducted in the "context of discovery," and will potentially set the stage for future research in this area. If results do demonstrate a relationship between these variables, future investigations into the nature of that relation will be warranted. Alternatively, if this study produces null findings, future research may not be necessary.

METHOD

Recruitment, Participants, and Procedure

Data used in this project were drawn from the Alcohol Health and Behavior Study (AHB; Sher, et al., 1991). This sample was used in a prior study of hangover (Piasecki et al., 2005; described above). AHB is an ongoing longitudinal study that assessed alcohol and drug use, psychopathology, and personality among college students at a large Midwestern university beginning in the freshman year, with follow up assessments at years 2, 3, 4, 7 and 11. Thus, data available in this study span approximate ages 18 through 30 with more frequent assessments in the college years, and two post-college assessments. The available data cover an important developmental period in terms of drinking, and include subjects in a particularly informative age group and drinking-

permissive context. Ages 18 through 30 contain not only the peak in drinking behavior, but also considerable variation in drinking. College students report more drinking than their non college attending peers (Slutske, 2005).

First-time college freshman who were 18 years or older were recruited through mailings, classes and phone calls to participate in a screening session. Approximately 80% (n = 3156) of first-time freshman were screened, and were paid $5 for their participation. These screening sessions were conducted in residence halls, fraternity and sorority houses, and classrooms, and included the following assessments: undercontrolled personality traits; alcohol use quantity and frequency measures; heavy drinking frequency measures; drug use frequency and consequences measures; the Michigan Alcoholism Screening Test (MAST; Selzer, 1971); and the Short Michigan Alcoholism Screening Test (SMAST; Selzer, Vinokur, & van Rooijen, 1975) modified to assess the biological mother's and father's drinking. Those who scored a 4 or more on either the father or mother versions of the SMAST were tentatively classified as high risk, and those who scored a 0 or 1 on both parents were tentatively classified as low risk. A subset of these tentatively classified subjects (n = 808) were contacted to complete a second round of screening assessments, and all other screening participants were excluded from the study. Further assessments were conducted either over the phone or in person, and included the following: the Diagnostic Interview Schedule (Version III-A; DIS; Robins, Helzer, Croughan, & Ratcliff, 1981); portions of the Family History- Research Diagnostic Criteria interview (Endicott, Andreasen, & Spitzer, 1978); and assessments of alcohol and drug abuse, antisocial personality disorder, and depression in all living first-degree relatives aged 18 or older, and alcohol and drug abuse in all second-degree relatives.

High-risk subjects were included in the final sample if their father met criteria for alcoholism as assessed by the FH-RDC. Low risk subjects were included if none of their first-degree relatives met criteria for alcoholism, drug abuse, or antisocial personality disorder, and if none of their second-degree relatives met criteria for alcoholism or drug abuse. Of those who completed this second round of assessments (n = 601), 490 subjects were enrolled in the study, with approximately equal numbers of high-risk and low-risk subjects (FHP = 253, FHN = 237). The mean age of participants was 18.2 years (SD = .7) and the sample was 87.5% Caucasian.

Once enrolled, subjects were contacted by phone to schedule three appointments. During the first appointment, subjects were administered the DIS by a trained, blind interviewer. During the second appointment, they completed a battery of cognitive assessments. During the third appointment, subjects completed an assessment battery which included measures of alcohol and drug use patterns, alcohol expectancies, negative consequences of alcohol and drug use, personality, and general psychiatric distress. Completion of these three appointments earned subjects $25.00 (alternatively, they were offered the equivalent amount in research participation credits needed for Introductory Psychology courses).

Follow-up assessments were conducted at years 2, 3, 4, 7, and 11 post-baseline (roughly corresponding with the sophomore, junior and senior years in college, and 3 and 7 years post-college). At year 11 of the study, 84% of the enrolled participants were retained. Whenever possible, follow-up assessments were conducted in person; however, those who had relocated away from the study area were assessed using a telephone

interview and were mailed questionnaires. A more detailed description of the study procedures is provided elsewhere (e.g. Sher, et al., 1991).

Measures

Family History of AUD. As described above, family history of alcoholism was assessed using the MAST and an adaptation of the SMAST modified to assess the biological mother's and father's drinking. Those who scored a 4 or more on the SMAST for either their father or mother also completed portions of the Family History- Research Diagnostic Criteria interview and assessments of alcohol and drug abuse, antisocial personality disorder, and depression in all living first-degree relatives aged 18 or older, and alcohol and drug abuse in all second-degree relatives. Subjects were classified as high risk subjects if their father met criteria for alcoholism as assessed by the FH-RDC. Approximately half (51.1%, n=250) of those enrolled in the study were family history positive (two participants later learned they had been adopted, and were coded as missing on this variable). Family history status was coded 1 for family history positive and 0 for family history negative participants. Among those who were family history positive, 52.8% (n=132) were female.

Sex. Just over half of those enrolled (52.6%, n=257) were female. At the final wave 54.4% (n=223) were female. Sex was coded 0 for female and 1 for male in all analyses.

Drinking Variables. Drinking was assessed at each wave using a battery of questions. The primary drinking measure used in the present study was a measure of *weekly alcohol quantity/frequency over the past year*. The combination of measures of quantity and frequency of drinking has been recognized as a useful approach to

measuring current levels of alcohol consumption (Dawson, 2003), and represents a measure of the total volume of alcohol consumed. This measure is calculated as the product of two items, one tapping the responder's estimate of the number of times in a given time period he or she has consumed alcohol, and another assessing his or her estimated modal number of drinks consumed on any given drinking occasion during that time period. In this study, the quantity and frequency items assessed drinking during the past year using the following two items. The quantity item asked, "In the past year, when you were drinking alcohol, how many cans of beer, glasses of wine, bottles of wine cooler, or drinks of liquor did you usually have on any one occasion?" There were 10 response options, ranging from "I did not drink at all during the past 12 months," which was scored as 0, to "Nine or more total" drinks, scored as 10. The frequency item asked, "Think of all the times in the past year when you had something to drink—how often have you had some kind of beverage containing alcohol?" Responses were scored to represent the average number of drinking occasions per week, over the past year. There were 10 response options, ranging from "I didn't drink this past year," scored as 0, to "Twice a day or more," scored as 15. The product of each individual's scores on these two questions was calculated, resulting in a measure of alcohol quantity/frequency score. Scores ranged from 0 to 150 (indicating the individual reported drinking twice per day with 9 or more total drinks per occasion). See the appendix for more information about the alcohol quantity/frequency variable.

Because alternative measures of alcohol consumption were assessed and are available, supplemental analyses were conducted using two additional drinking measures. The Harvard School of Public Health College Alcohol Study (Wechsler, Davenport,

Dowdall, Moeykens, & Castillo, 1994) introduced a measure of binge drinking that has been widely adopted as a measure of problematic drinking. Binge drinking has been defined as "the consumption of a sufficiently large amount of alcohol to place the drinker at increased risk of experiencing alcohol-related problems and to place others at increased risk of experiencing secondhand effects" (Wechsler & Nelson, 2001). Binge drinking is typically operationalized as four or more drinks in a row for women, and five or more drinks for men. In this study, the men's definition of binge drinking (i.e. five or more drinks) was used to assess heavy drinking among men and women. *Weekly binge drinking frequency over the past 30 days* was measured at each wave of the study with an item asking, "In the past 30 days, how many times have you had five or more drinks at a single setting, either of beer, wine, or liquor, or some combination of these?" Scoring was recoded to reflect number of binge drinking episodes per week. Response options ranged from "I didn't drink 5 or more drinks during this past 30 days," scored as 0, to "Every day," scored as 7. For more information on the weekly binge drinking frequency variable, see the appendix.

A second heavy drinking measure, referred to as the *Past-month heavy drinking composite*, was also included in analyses. This measure is a composite of the following three items: number of times drunk in the past month, number of times "high on alcohol" in the past month, and number of binge drinking episodes (as defined by consumption of 5 or more standard drinks on one occasion) in the past month. Each item was recoded from a monthly frequency rating into a weekly frequency rating, and the average of the three items was calculated. The result is an estimate of weekly heavy drinking, which has been shown elsewhere to have good internal consistency and validity (e.g. O'Neill &

Sher, 2000; Piasecki, et al., 2005; Wood, Sher, & McGowen, 2000). Additionally, it should be noted that Piasecki and colleagues (2005) showed the heavy drinking composite to be robustly correlated with hangover.

Smoking Variables. Smoking was also assessed at each wave with numerous items. *Smoking status* was used as the primary index of smoking behavior in an effort to plainly characterize the individual's current level of smoking behavior. *Smoking frequency* was assessed with the question, "How often do you smoke cigarettes currently?" Seven response options were scored to reflect number of smoking days per month, and ranged from "I don't smoke now," scored as 0, to "Every day," scored a 30. Subjects were categorized into three discrete smoking status groups (daily smokers, non-daily smokers, and non-smokers) based on their response to this question (see the appendix for more information). Partitioning individuals who smoke into two groups (i.e. daily and non-daily smokers) is conceptually useful. Daily smokers are very likely to be tobacco dependent. Non-daily smokers may be casual tobacco experimenters who with no dependence risk, persons at risk for future dependence, or tobacco chippers (Shiffman, 1989; Shiffman, Paty, Kassel, Gnys, & Zettler-Segal, 1994; Wetter et al., 2004). Although non-daily smokers could be heterogeneous, they are all likely to be nondependent and, by definition, to smoke at lower rates than daily smokers.

Alternative measures of smoking behavior were included in the assessments and are available for analysis. Therefore, in supplemental analyses, this project also used a measure of W*eekly smoking quantity/frequency* as an alternative to the smoking status measure. This measure is calculated as the product of two items, one tapping the responder's estimate of the number of days per month he or she smoked, and another

assessing his or her estimated modal number of cigarettes smoked on any given smoking day. In this study, smoking frequency was assessed with the item summarized above. The smoking quantity item asked, "On an average day when you do smoke, how many cigarettes do you smoke?" There were 7 response options, ranging from "None at all (I don't smoke)," which was scored as 0, to "About 2 packs or more a day," scored as 40. The product of each individual's scores on these two questions was calculated, resulting in a measure of monthly cigarette quantity/frequency. Scores ranged from 0 (indicating the individual reported no smoking days and no cigarettes per day) to 1200 (indicating the individual reported smoking 40 or more cigarettes per day every day of the month). Some analyses used a recoded version of these variables for more tailored purposes. See the appendix for more information about the smoking quantity/frequency variable.

Hangover. This study was launched prior to the development of new multi-item assessments of hangover such as the HQ and the HSS. Assessment of specific hangover symptoms was sparse; however, negative consequences of drinking were assessed using the Young Adult Alcohol Problems Screening Test (YAAPST; Hurlbut & Sher, 1992). Included in the 27 items assessed in the YAAPST are four items which may be conceptualized as assessments of hangover-related symptomatology. The item perhaps most obviously relevant to hangover assesses *past-year hangover/headache frequency*. This question asks, "Have you had a headache (hangover) the morning after you had been drinking?" Other items ask, "Have you shown up late for work or school because of drinking, a hangover, or an illness caused by drinking?", "Have you not gone to work or missed classes at school because of drinking, a hangover, or an illness caused by drinking?", and "Have you felt sick to your stomach or thrown up after drinking?"

Response formats were the same for all four items, with ten response options ranging from "No, never," scored as 0, to "Yes, 40 or more times in the past year," scored as 8. While it can be argued that these additional three items assess possible symptoms or consequences of hangover, they do not *necessarily* assess hangover. For instance, the last item may tap into vomiting that occurs during acute intoxication, rather than vomiting on the morning after drinking. Because of this ambiguity, inclusion of these items might contribute error to a measure of hangover. Prior work using this sample suggested that a composite of these four items performs very similarly to the single headache item. Moreover, the other putative hangover items were endorsed at low rates—meaning that scores on the 4-item composite are dominated by the headache item (Piasecki, et al., 2005). Also, as stated above, previous research has tended to identify headache as the prototypical symptom of hangover, since it has emerged as a top complaint across studies, and accords with popular depictions of hangover. Additionally, Slutske and colleagues found that various hangover symptoms cluster together on one latent factor, and that headache loads strongly on that factor (Slutske, et a.l, 2003). Piasecki and colleagues also demonstrated this study's single-item hangover measure has good construct validity, showing it's relation to drinking, AUD, and family history status (Piasecki, et al., 2005). For these reasons, the headache item was used as the primary index of hangover in this study. See the appendix for more information about this item.

Statistical Analyses

Preliminary Exploratory Analyses. This study aims to explore the relationship between risk for alcoholism, smoking, and hangover. As a preliminary step to determine whether more detailed analyses were warranted, a series of cross-sectional regression

analyses were conducted, predicting hangover from drinking, smoking, and their interaction at each study wave, while controlling for sex and family history of alcoholism (which, as described above, have been shown to be associated with hangover in prior research). Such models allow for estimation of the extent to which smoking predicts hangover, as well as the extent to which smoking moderates the relationship between drinking and hangover. Various definitions of smoking (i.e. smoking status, smoking quantity/frequency) and alcohol use (i.e. drinking quantity frequency and binge drinking) were utilized in these analyses.

Multilevel Growth Models. Multilevel modeling provides an elegant statistical framework for exploring repeated-measures data (e.g. Luke, 2004; Raudenbush & Bryk, 2002). Multilevel modeling allows for estimation of relations between variables that occur at differing levels within a nested data structure. Often the concept of nested data is exemplified by the problem of students within classrooms. Students who share a classroom teacher are more like one-another than a sample of randomly selected students. Therefore, data drawn from students within classrooms violates the assumption of independence of observations that is made in ordinary least squares regression. Multilevel models allow us to make predictions about higher level variables (e.g. classrooms), and incorporate this information into predictions about lower level variables (e.g. individual students). A less obvious example of nested data is repeated measures data collected on individuals over time. Because observations taken from an individual over time are likely to be more like one another than are the same number of observations taken from a random sample of individuals, we must account for the hierarchical nature of this data structure by employing an analytical methodology that does not assume

independence of observations. Multilevel modeling addresses repeated measures data by portioning prediction into two (or more) levels. In this case, higher order variables (level 2 variables) are stable characteristics of the individual being observed, such as sex or family history status. Lower order variables (level 1 variables) characteristics of the individual that change across the repeated observations, such as drinking level.

Piasecki and colleagues (2005) used multilevel modeling to examine the relationship between family history of alcoholism and hangover propensity in this sample. The current project expands these models by including smoking related variables in the analyses. Two multilevel models will be performed to address the role of smoking in hangover. First, in a direct extension of Piasecki and colleague's (2005) analyses, an omnibus model was conducted, predicting hangover across time with drinking level and smoking quantity/frequency entered as level one variables (i.e. time varying covariates). The level 1 equation was:

$$[1] \quad HANGOVER_t = \beta_0 + \beta_1 (YEAR\text{-}1) + \beta_2 (ALCOHOL\ Q/F_t) + \beta_3 (SMOKE\ Q/F_t) + e$$

In this equation, $HANGOVER_t$ is the score on the hangover measure at time t. β_0 is the intercept term, which represents the predicted mean score at Year 0 (freshman year) on the hangover measure after controlling for drinking level (i.e. scores on ALCOHOL Q/F) and smoking level (i.e. scores on SMOKE Q/F), which are both allow to vary across time in this model. β_1 is the regression coefficient representing the slope of hangover across time (defined as study year minus 1, so that Year 1 = 0, Year 2 = 1, etc.) and hangover score, and β_2 is the regression coefficient representing the relation between drinking level and hangover at a given point in time. β_3 represents the relation between

smoking level and hangover, and will be the critical test of this model, representing the unique impact of smoking status on hangover, over and above developmental (time) trends and alcohol use. This coefficient, if found to be significant, will be interpreted as evidence for a relation between hangover and degree of smoking. Finally, e is the residual, or random error.

Level 2 equations were built by adding theoretically important between-subjects variables, such as family history of AUD status and sex, as predictors of variability in individual growth parameters (that is, as predictors of βs modeled at level 1). These models allow for prediction of individual differences in hangover scores (while controlling for drinking and smoking level) from family history status and sex:

$$[2] \quad \beta_0 = \gamma_{00} + \gamma_{01}\,(FH) + \gamma_{02}\,(SEX) + u_0$$

$$[3] \quad \beta_1 = \gamma_{10} + \gamma_{11}\,(FH) + \gamma_{12}\,(SEX) + u_1$$

$$[4] \quad \beta_2 = \gamma_{20} + \gamma_{21}\,(FH) + \gamma_{22}\,(SEX) + u_2$$

$$[5] \quad \beta_3 = \gamma_{30} + \gamma_{31}\,(FH) + \gamma_{32}\,(SEX) + u_3$$

In these equations, β. is the regression weight representing the relation between hangover and the associated level 1 variable (i.e. intercept, time, alcohol quantity/frequency, and smoking quantity/frequency). $\gamma_{.0}$ is the intercept of the level 2 equation, and $\gamma_{.1}$ and $\gamma_{.2}$ are the regression coefficients representing the relation between β. and the predictor variables family history status and sex. In these level 2 equations, u. represents random error.

The first multilevel model treated smoking as a time-varying covariate (see equation [1]). A disadvantage of this approach is that participants who display no variability in smoking behavior over time (e.g. consistent non-smokers) cannot contribute

to the estimation of the model. Including smoking status as a between-subjects variable allows all subjects to contribute to the analyses. Therefore, a second set of multilevel regression models which include smoking status as a level two variable was conducted. In these analyses, smoking was not allowed to vary across time; rather, anyone who reported smoking (daily or non-daily) at any wave of the study was categorized as an "ever-smoker" and was included as such in the model. This approach treats smoking as a discrete characteristic of the person, and considers whether smoking behavior was *ever present* as more important than information about *when* smoking was present. Inclusion of smoking status as a level two (or between-subjects) variable more closely approximates an analysis of the "third variable" or "person factor" hypothesis described above; that is, by categorizing those who smoked at at least one time-point during the study as "smokers," we might identify individuals who possess a broad risk for smoking, and examine their experience of hangover as compared to those who never smoked. This approach implicitly assumes that smoking is a marker of some stable person-factor or trait, not just an acute pharmacological driver of hangover. To the extent that this assumption is unwarranted, this model may be in error. Equations for this model were constructed similarly to those described above:

$$[6] \quad HANGOVER_t = \beta_0 + \beta_1 (YEAR\text{-}1) + \beta_2 (ALCOHOL\ Q/F_t) + e$$

$$[7] \quad \beta_0 = \gamma_{00} + \gamma_{01} (EVERSMOKER) + \gamma_{02} (FH) + \gamma_{03} (SEX) + u_0$$

$$[8] \quad \beta_1 = \gamma_{10} + \gamma_{11} (EVERSMOKER) + \gamma_{12} (FH) + \gamma_{13} (SEX) + u_1$$

$$[9] \quad \beta_2 = \gamma_{20} + \gamma_{21} (EVERSMOKER) + \gamma_{22} (FH) + \gamma_{23} (SEX) + u_2$$

Hangover and Smoking in Tobacco Quitters and Initiators. The relationship between drinking, smoking and hangover was also explored by assessing hangover

among participants who either began smoking or quit smoking during their participation in the study. This approach can be thought of as utilizing a "natural experiment" to assess the impact of changes in smoking status on hangover.

Four classes of participants were identified. Participants who reported smoking at each of the 6 waves of data collection were classified as *Stable Smokers* (n = 31). Those who reported being non-smokers at each of the 6 waves were classified as *Stable Abstainers* (n = 204). Two groups of participants who changed smoking status during the study were also identified. *Initiators* were those who reported being non-smokers at Year 1, but initiated smoking at some point during the study (Years 2-11) and reported smoking at each subsequent wave of data collection (i.e. from their initiation through Year 11; n = 21). *Quitters* were those who reported smoking at Year 1, but quit smoking at some point during their participation in the study (Years 2-11) and reported no smoking at each subsequent wave of data collection (n = 50). Participants with unstable transitions in smoking status (e.g. cycled between quitting and using, n = 153) and those who had incomplete smoking data (n = 20) were excluded from these analyses.

To explore hangover trends among these natural groups, mixed between-within ANOVA models were conducted. In both models, a group who retained their smoking status across study years was compared to a group who changed smoking status at some point between Year 1 and Year 11. Because the transition groups were small, and because there were very few transitions in any given year, transitioning participants were collapsed across waves in an effort to maximize power. Model 1 compared hangover at Year 1 and Year 11 between Stable Abstainers and Initiators, and tested the interaction of time and group status. Model 2 was identical to model 1, but contrasted Quitters to

Stable Smokers. Parallel analyses were conducted comparing these groups on alcohol consumption. Additionally, ANCOVA models compared Abstainers with Initiators and Quitters with Smokers while controlling for sex, family history status, and drinking change score calculated at Year 11 alcohol quantity/frequency minus Year 1 alcohol quantity/frequency.

Logistic Models Predicting Later AUDs. Previous research has identified hangover as a predictor of later development of AUD; using this data set, Piasecki and colleagues (2005) found that hangover predicts alcohol use disorders at Years 7 and 11. This effect remained even when controlling for family history, sex, any AUD diagnosis at Year 1, and heavy drinking at Year 1. However, smoking was not taken into account in these models. In this project, these prospective models were expanded to include a smoking variable. Logistic regression models were used to determine if smoking helps account for the association between early hangover propensity and later development of alcohol use disorders. This was assessed first by predicting the presence or absence of AUD diagnosis at Years 4, 7 and 11 from hangover at Year 1, while controlling for sex, family history status, Year 1 alcohol quantity/frequency, and Year 1 AUD diagnostic status. A second set of logistic regression models was conducted predicting AUD diagnosis at Years 4, 7 and 11 from Year 1 hangover and Year 1 smoking, while adjusting for the same covariates.

RESULTS

Preliminary Descriptive Analyses

The appendix provides the means and standard deviations of past-year hangover frequency, past-month alcohol consumption, and past-month cigarette consumption for

the sample at each wave of the study. The correlations among several variables of interest are provided in Table 1. As expected, alcohol consumption was significantly related to hangover at all time points, and was also significantly correlated with smoking variables. The smoking status variable (treated as a three-level ordinal measure in these correlational analyses) and smoking quantity/frequency were both significantly related to hangover at each time point.

Frequencies of participants in each smoking status group are presented in Figure 1. As can be seen from the figure, nonsmokers greatly outnumber smokers at every study wave. Figure 2 depicts the mean frequency of hangover across all study waves for nonsmokers, non-daily smokers, and daily smokers. In this illustration, individuals' smoking status was considered at each year when creating groupings. There was a tendency for both daily and non-daily smokers to report more hangover than nonsmokers at each time-point (however, it is notable that group differences in alcohol consumption were not taken into account in these analyses). Mean hangover frequency by sex is reported in Figure 3. These raw means suggest that men have more hangover, in general, than women. Figure 4 shows mean hangover frequency among family history positive participants to be higher than that reported by family history negative participants. Each figure also illustrates a tendency towards decreased hangover across time. These preliminary analyses suggest sex, smoking status, and family history status may be important covariates in hangover analyses.

Cross-sectional Regression Analyses

Table 2 displays the standardized beta coefficients from cross-sectional hierarchical linear regression models predicting hangover frequency from the set of

predictor variables. In each of the models, sex and family history were entered at step one, main effects of drinking and smoking status were entered at step two (smoking status was represented with dummy coding such that non-smokers were the comparison group for daily smokers and non-daily smokers), and the interaction terms for drinking X dummy coded smoking status was entered at step three. Tabled betas represent the simultaneous results from the final model step. All continuous predictors were centered (i.e. alcohol quantity/frequency, binge drinking, and heavy drinking composite). As stated above, several representations of drinking and smoking behavior were available in this dataset, and analyses were conducted using a variety of these variables. In the top portion of Table 2, hangover is predicted from sex, family history status, alcohol quantity/frequency, current smoking status, and the interaction of alcohol quantity/frequency and smoking status. The middle portion of Table 2 shows standardized betas for these models using the binge drinking variable (rather than alcohol quantity/frequency), and the lower portion of Table 2 reports betas for these models using the heavy drinking composite.

In general, the pattern of results was consistent across models predicting hangover from sex, family history, drinking, smoking status, and the drinking by smoking interaction. As can be seen in Table 2, sex was a significant predictor only in the post-college years. Family history was not a significant predictor of hangover at any time point. As expected, alcohol consumption, (defined as either quantity/frequency, binge drinking, or the heavy drinking composite) was a significant predictor of hangover at all time points. In general, there tended to be a main effect of smoking about half of the time, such that smoking status was positively related to hangover; that is, those who

smoked (be it daily or non-daily) showed more hangover than non-smokers. The smoking status X drinking interaction was also negative and significant about half the time. The form of these interactions suggests that smokers who drank at low levels were more likely to report having a hangover than nonsmokers who drank the same amount of alcohol. However, when smokers consumed greater amounts of alcohol, their reports of hangover frequency were comparable to nonsmokers (i.e. smoker's hangover increased less than did nonsmoker's hangover at higher levels of drinking).

Table 3 reports betas for a set of parallel models in which the continuous predictor smoking quantity/frequency was substituted for the smoking status variable. Regression models were conducted using three definitions of drinking: alcohol quantity/frequency, binge drinking, and the heavy drinking composite. In these models, smoking quantity/frequency and each of the drinking variables were centered.

While patterns of results were somewhat similar to those described for the smoking status models, in general, the smoking quantity/frequency variable did not predict hangover as successfully as smoking status. As before, these results showed that sex was only a significant predictor of hangover during the post-college years, family history did not predict hangover, and drinking (defined in various ways) was a strong positive predictor of hangover. In these models, the smoking quantity/frequency was inconsistent, as was the interaction between smoking quantity/frequency and drinking.

Multi-level Growth Models

As described above, two multilevel regression models were conducted. Model 1 predicted hangover from time, alcohol consumption (alcohol quantity/frequency), and cigarette consumption (cigarette quantity/frequency) at level 1, with sex and family

history status entered at level 2. This structure allows alcohol and cigarette consumption to vary across time. Because participants who did not smoke during the study reported no variability on the cigarette consumption variable, they were dropped from this model; therefore, only participants who reported smoking (daily or non-daily) at any time-point were included in Model 1 (n = 178). Results from this model are reported in Table 4. A significant main effect of time was found, indicating that hangover frequency declines across time (γ = -.088, p < .001). Additionally, time interacted with sex, suggesting that men and women have significantly different patterns of hangover across time, with men remaining more stable over time while women reported decreasing hangover across study years. (γ = .089, p < .001). Alcohol consumption also showed a significant main effect (γ = .177, p < .0005); time points at which drinking was elevated were associated with higher hangover. Sex interacted with alcohol consumption (γ = -.068, p < .0005) suggesting that the relation between drinking and hangover was weaker among men, or that women experience greater increases in hangover as they increase drinking, relative to men. Family history also interacted with alcohol consumption (γ = -.059, p < .001), suggesting that those who were family history positive showed a weaker relation between drinking and hangover compared to those who were family history negative. The relationship between cigarette consumption and hangover was non-significant. However, the interaction between smoking and family history did significantly predict hangover (γ = .001, p < .044), suggesting that among those who were family history positive, variation in smoking quantity/frequency had a small but significant relation with hangover such that increased smoking was related to increased hangover. While this gamma coefficient is small, it should be noted that the range of the smoking

quantity/frequency variable was relatively large (i.e. 0-1200). Interpretation of the effect size associated with this coefficient should be made with this variable's range in mind.

Model 2 predicted hangover from study year and alcohol consumption at level 1 (i.e. as time-varying covariates), with sex, family history status, and ever-smoking status at level 2 (i.e. as "person-level" variables). Results from this model are presented in Table 5. As can be seen in the table, a significant main effect of sex was found ($\gamma = .434$, $p < .014$), indicating that, in general, men had more hangover than women. Ever-smoking status was related to hangover ($\gamma = .864$, $p < .0005$) suggesting that those who had smoked at some point during the study reported more hangover than those who never smoked. Time was also found to be a significant predictor ($\gamma = -.068$, $p < .0005$), with hangover scores decreasing across time. A main effect of alcohol consumption was also found ($\gamma = .216$, $p < .0005$), suggesting that hangover increased with increased alcohol consumption. The sex X alcohol consumption interaction ($\gamma = -.073$, $p < .0005$) suggested that the relation between alcohol consumption and hangover was weaker among men than among women. Finally, a significant interaction between alcohol consumption and ever-smoking status was found ($\gamma = -.042$, $p < .002$), suggesting that the relation between alcohol consumption and hangover was weaker among those who smoked at some point during the study, compared to non-smokers.

Hangover and Smoking in Tobacco Quitters and Initiators

Mean levels of hangover for Stable Abstainers and Initiators are shown in Panel A of Figure 5. At Year 1, all participants in this figure are non-smokers, and show similar levels of hangover. At Year 11, those who have initiated smoking report slightly increased hangover, and those who maintain their non-smoking status show decreased

hangover. Similarly, Panel B compares hangover at Year 1 and Year 11 among Stable Smokers and Quitters. As can be seen in the figure, at Year 1, when all participants represented in this figure report actively smoking, those who will quit and those who will continue to smoke report nearly the same amount of hangover. However, at Year 11, those who have quit smoking report decreased levels of hangover compared to the continuing smokers.

Mixed between-within ANOVA results for both contrasts (Stable Abstainers vs. Initiators and Stable Smokers vs. Quitters) are presented in Table 6. The ANOVA results comparing Stable Abstainers and Initiators showed that these two groups reported significantly different hangover scores, but there was not a significant effect of time on hangover. There was a significant time by group interaction, suggesting that the change in hangover over time was different for Abstainers vs. Initiators (Initiators showed a slight increase in hangover over time, while Abstainers showed a more marked decrease). However, the interaction's effect size was small; that is, the interaction between time and group accounted for just under 3% of the total variance in hangover. Results comparing Stable Smokers and Quitters showed significant main effects of time (suggesting that hangover did significantly decrease between Year 1 and Year 11) and group (suggesting Smokers reported elevated hangover compared to Quitters). As in the previous model, the interaction between time and group was significant: Smokers showed more stable hangover across time compared to Quitters. This interaction accounted for nearly 11% of the total variance in hangover. It should be noted that these exploratory models do not take important covariates (sex, family history status, and alcohol consumption) into account.

Complementary ANOVA models were conducted using alcohol consumption as the outcome variable in an effort to explore concurrent changes in alcohol consumption between these groups. Results from these models are presented in the lower half of Table 6. Results comparing Abstainers and Initiators show that these smoking groups do display significantly different patterns of drinking when compared with one another, and that there was a significant group X time interaction, suggesting they have differing patterns of alcohol consumption over time such that Initiators showed increased alcohol consumption over time while Abstainers showed decrease alcohol consumption. Results from the Smokers vs. Quitters model showed a main effect of time, suggesting both groups reported decreased alcohol consumption at Year 11 compared to Year 1, as well as a main effect of group, such that those who continued to smoke at Year 11 reported more alcohol consumption, in general, than those who had quit by that time-point. As can be seen in the plot of mean alcohol consumption in Panel D of Figure 5, both Smokers and Quitters reduce their alcohol consumption between Years 1 and 11; however, smokers did not show the concomitant reduction in hangover that would be expected (and is shown by Abstainers and Quitters) when alcohol consumption is reduced.

ANCOVA models were also conducted comparing Year 1 and Year 11 hangover among these naturally occurring groups while controlling for changes in drinking across time, as well as sex and family history status. Change in drinking was calculated as Year 11 alcohol quantity/frequency minus Year 1 alcohol quantity/frequency, and provided a convenient proxy for the simple slope of drinking from Year 1 to Year 11 in these models. Results from these ANCOVA models are presented in Table 7. As can be seen

in the table, a significant time x group interaction was found for both models (Abstainers vs. Initiators and Smokers vs. Quitters) despite inclusion of the drinking change variable. This suggests that changes in alcohol consumption alone do not account for the differential changes in hangover seen in these naturally occurring groups across time.

Predicting Later AUD

Results from logistic regressions are presented in Table 8. The top panel in Table 8 reports results of logistic models predicting presence or absence of AUD at years 4, 7 and 11 from Year 1 hangover, as well as sex, family history status, Year 1 alcohol quantity/frequency and Year 1 AUD diagnosis. In this model, hangover and alcohol quantity/frequency were centered. Hangover at Year 1 predicted AUD diagnosis at years 7 and 11, but not at Year 4. These results are consistent with very similar analyses reported by Piasecki and colleagues (2005).

The middle panel in Table 8 reports results from a second set of logistic regression models. These models extend the first set of analyses to include Year 1 smoking status as a predictor. The three-level smoking status variable was dummy coded, with non-smokers serving as the reference group. Results from these models suggest that Year 1 smoking did not significantly predict AUD diagnosis at any of the tested time points. The bottom panel in Table 8 presents results from logistic models which included the dichotomous ever-smoker status. When ever-smoking status was included in the model at Year 7, hangover was no longer a significant predictor of AUD diagnosis. This suggests that smoking may be accounting for some of the variance in hangover. However, it should be noted that changes in these coefficients are very small, making it difficult to draw conclusions as to the importance of these findings.

DISCUSSION

Drinkers differ meaningfully in their susceptibility to hangover, and previous research suggests that individual differences in hangover may be related to risk for alcohol use disorders. Cigarette smoking and alcohol use are highly related, particularly among persons with alcohol use disorders. This project examined whether smoking can help explain individual differences in hangover frequency.

The descriptive analyses reported in this study support several previous findings reported in the literature, and provide new insight into the relation between these constructs. Correlational analyses indicated that in these data, cigarette smoking and alcohol consumption were related, a common finding reported in prior research (Bobo & Husten, 2000; Madden, et al., 2000). Alcohol consumption was also correlated with the single-item measure of hangover used in these analyses, lending support for the construct validity of this hangover measure. Additionally, correlational analyses revealed a relation between smoking and hangover, suggesting that further research into this association between smoking and hangover is warranted.

Cross-sectional regression models predicting hangover from drinking level and smoking status (while controlling for gender and family history status) consistently revealed main effects of smoking such that that those who smoke reported experiencing more hangover than those who did not. This effect was seen for both daily and non-daily smokers.

It is possible that this finding reflects the effect of tobacco on the central nervous system, either directly or in the presence of alcohol. As described earlier, many of the

systemic effects of tobacco smoke are similar to the symptoms common identified as components of the hangover syndrome (e.g. headache, nausea, myalgia). Tobacco smoke ingested during the drinking episode may directly contribute to symptoms of hangover, interact with alcohol to amplify hangover symptomatology in smokers, or inspire hangover-like symptoms independent of drinking.

In several cross-sectional analyses, a significant drinking X smoking status interaction was found. Each significant interaction took the same form, indicating that at low levels of drinking, daily smokers experience more hangover than non-daily smokers. However, at high levels of drinking, daily smokers and non-daily smokers experience similar or reduced levels of hangover. In these models, the relation between alcohol consumption and hangover was weaker among those who smoked, compared to those who did not smoke. This suggests that smokers may be able to accelerate their drinking without experiencing increased hangover. In other words, smokers do not seem to experience the same degree of *escalating* negative consequences associated with escalating levels of drinking that non-smokers experience. Hence, smokers may not be punished by hangover in the same manner as non-smokers. If smoking renders the punishing effects of hangover less dose-dependent, smoking may allow individuals to escalate their drinking. This pattern of accelerating use with more slowly escalating punishment may contribute to the development of alcohol use disorders.

Multilevel regression models integrating data from all time points using the cigarette quantity/frequency variable at level 1 did not reveal a significant effect of smoking on hangover. This model only incorporated data from participants who reported changing their smoking status at some point during the course of the study. Because stable

abstainers and stable smokers (n = 235) did not display any variability on the smoking variable, they did not contribute any information to the model and were dropped from the analysis. Therefore, this model assesses the effect of variation in the amount smoked on hangover among smokers who showed some change in cigarette consumption (ranging from small variation in cigarette quantity/frequency to more substantial changes reflecting movement between smoking status groups).

In spite of this model's limitations, two interesting effects were found. First, those who had a positive family history of AUD showed a weaker relation between alcohol consumption and hangover. Given the elevated risk for AUD associated with positive family history, these results suggest that a diminished relation between drinking and hangover may be an important marker or mechanism for escalation of problematic drinking. This finding echoes the effect seen for smoking. Second, results suggested that individuals who had a positive family history of alcoholism showed a stronger relation between the amount they smoked and the amount of hangover they experienced when cigarette quantity/frequency was treated as a time-varying covariate. This finding could reflect an underlying drug sensitivity that is more prevalent among these high-risk individuals compared to those who smoke but are family history negative. In this scenario, drug sensitivity could function as a "third" variable influencing smoking status, hangover experience, and AUD development. At this point, the mechanism driving these effects are unknown. While future research in this area is warranted, results from the current study suggest that smoking alters hangover reports, and that this effect may be stronger in family history positive individuals, a group which may be especially susceptible to experiencing hangover.

In the second multilevel model, ever-smoking was included as a level 2 variable. Results showed that those who ever smoked reported experiencing more hangover overall, and that for smokers, the relationship between amount of alcohol consumed and hangover was weaker than for non-smokers. These effects are similar to the main effect and interactions detected in several of the cross-sectional models. Additionally, as shown in the previous model, evidence for a weaker relation between drinking and hangover among those with a positive family history was found.

In contrast to the previous multilevel model, inclusion of the ever-smoker variable allowed all participants (i.e. stable abstainers and smokers, as well as those who changed status) to contribute to this model. While the ever-smoker variable was advantageous in this regard, results from this model must be interpreted with care. The ever-smoker variable identifies those who reported non-smoking status at all available years as non-smokers, with up to two years of missing data. Fourteen per cent of those classified as never-smokers were missing 1 wave of data, and 2% were missing 2 waves. Therefore, it is possible that a portion of those who were classified as never-smokers (i.e. earned a 0 on ever-smoker) did in fact smoke during the 1 or 2 years they were not assessed. In spite of this limitation, the ever-smoker variable provides an interesting means of exploring of the potential effect of smoking. In this conceptualization, smoking's potential effect is considered not in terms of any direct or pharmacological impact. Rather, the ever-smoker variable serves to identify those who smoked at some point (48% of the sample), and thus may identify those who have an atypical sensitivity to drug effects, or who are at heightened risk for substance use disorders.

Across both cross-sectional regression models and multilevel models, smoking status variables (daily vs. non-daily vs. non-smoker, ever-smoker vs. never-smoker) were more successful predictors of hangover than the smoking quantity/frequency variable. This finding implies that the relationship between smoking and hangover may not be dose-dependent—that is, varying cigarette consumption may not be as important in hangover experience as simply the presence or absence of exposure to tobacco smoke. Alternatively, it may be the case that smoking status is a cleaner or more accurate measure compared to cigarette quantity/frequency. While cigarette quantity/frequency does contribute more fine-grained variability than the three-level smoking status variable, it is not clear that the variability contributed is meaningful. It seems plausible that a cigarette quantity/frequency variable would be more error-laden than a smoking status variable, requiring participants to retrospectively report a behavior that potentially varies widely across time and circumstances. Smoking status, on the other hand, may isolate the critical information (e.g. degree of tobacco involvement) more cleanly. The smoking status variable more efficiently represents large dose differences in tobacco self-administration, relative to the cigarette quantity/frequency variable, and it seems plausible that large differences in dose may be more informative in these exploratory analyses than small variation within and among participants.

Why might smoking be associated with a diminished relationship between alcohol consumption and hangover? Smoking may moderate hangover because of a pharmacological interaction between tobacco/nicotine and alcohol. Cigarette smoke may have a pharmacological effect, either directly diminishing hangover (after high doses of alcohol), or changing the way alcohol results in hangover. Alternatively, cigarette

smoking, hangover, and alcohol use disorders may be clustered in individuals because these behaviors are external indicators of the presence of a broader underlying pathology. That is, there may be a single "third variable" or hierarchical factor that explains the tendency for these to co-occur. Perhaps those who are at high risk for alcohol use disorders also are more likely to smoke, experience more hangover overall, and do not experience escalating hangover as a result of escalating drinking, compared to those at low risk.

Participants who changed smoking status during the study period provided opportunity to explore the relative merits of these two conceptualizations. Four naturally occurring subgroups of participants were identified: stable smokers, stable abstainers, initiators, and quitters. Unfortunately, analyses on these subgroups were limited due to the low prevalence of some of the smoking patterns. In spite of these limitations, exploration of hangover among these subgroups revealed some intriguing effects. Those who abstained from smoking throughout the study showed a decrease in drinking across time, and the expected associated decrease in hangover. Those who smoked at year 1 but had quit by year 11 also showed a decrease in drinking across time, and a decrease in hangover. Those who smoked throughout the study showed a decrease in drinking across time, and showed relatively stable hangover (as foreshadowed by cross-sectional and multilevel models). And those who began smoking during the course of the study showed increased drinking and increased hangover. Additionally, the differential patterns of hangover among naturally occurring smoking groups remained significant after controlling for changes in alcohol consumption across time. These findings are

consistent with the notion that tobacco smoking may play a contributory causal role in hangover expression.

Logistic regression analyses predicting any AUD diagnosis at Years 4, 7 and 11 of the study from hangover at Year 1 showed that year 1 hangover did predict AUD diagnosis at Years 7 and 11. The three-level smoking status variable did not significantly predict later AUD, although hangover did predict AUD at Year 4 when smoking status was included in the model. When ever-smoking status was included the model the relationship between early hangover and later AUD diagnosis was non-significant at years 4 and 7 but remained at Year 11. Results suggest that while smoking was not a significant predictor of later AUD diagnosis at any follow-up, the relation between hangover and later AUD was diminished at Years 7 and 11 when smoking was added to the model, suggesting that smoking may account for some of hangover's predictive ability. However, it should be noted that the changes in odds ratios resulting from smoking's inclusion in the model were very modest. While smoking may be an important contributor to individual differences in hangover, results from these logistic regression models suggest that the association between hangover and AUD is not a simple artifact of failing to take smoking behavior into account.

Results from the current study suggest that smoking is related to hangover expression, and that smoking should be included in future research exploring hangover. Additionally, smoking moderates the relation between alcohol consumption and hangover. Smokers show a diminished relationship between drinking and hangover which may allow them to escalate drinking without the concomitant escalating punishment associated with increased drinking experienced by non-smokers. This effect

mirrors the findings in this and previous research regarding risk for AUD and hangover expression. Based on preliminary findings in these data, further exploration of smoking's contributory role in AUD risk appear to be warranted. Findings from the current study potentially explain a piece of the puzzle that exists in the hangover literature. Hangover, a presumed punisher, has been found to be positively associated with risk for alcohol use disorders (Newlin & Pretorius, 1990; Span & Earleywine, 1999). Results from this study suggest that smoking may act as a cofactor in the relationship between alcohol consumption and hangover. Epidemiological data suggest those at risk for developing an alcohol disorder are frequently smokers (Bobo and Husten, 2000; Madden, et al., 2000). Therefore, these findings may help to explain results from previous studies, which suggest a positive association between hangover and risk for alcohol use disorders. Perhaps the relation between hangover and risk for AUD is driven in part by the positive relation between hangover and smoking.

Limitations

Several limitations to the interpretation of the results must be mentioned. Generalizability of the results must be considered when interpreting findings. Subjects were college attenders, predominantly white, and drawn from a single institution in the Midwest. It is unclear how results from this sample will generalize to other populations. Alcohol consumption, smoking behavior, and hangover were assessed at yearly intervals throughout the college years with two post-college follow-up assessments widely spaced in time, and participants were asked to retrospect over time and recall these critical experiences. Retrospection and integration of retrospective data are difficult tasks, and it is assumed that there exists the potential for significant variation in these behaviors over

the course of a year. Yearly assessments such as those we have employed restrict the interpretability of results because it is unknown if all relevant events were captured. Additionally, such widely spaced assessments do not inform us of the temporal sequencing of drinking, smoking, and hangover events. A more fine-grained data structure would be preferred to assessments widely-spaced in time. Data collection techniques such as daily diary methodologies would allow for exploration of the impact of smoking on next-day hangover, and would better address the research question. These issues could be resolved by employing event-level data in future research.

Limitations related to the measures employed must also be acknowledged. A single-item measure of hangover was used in these analyses. This single item was the only clear measure of hangover available in the data-set and previous research has demonstrated that this single hangover item shows adequate construct validity (Piasecki et al., 2005) and performs sufficiently as a measure of hangover (Slutske et al., 2003). However, a more sophisticated measure of hangover would have been preferred. While the quantity/frequency measures used to characterize smoking and drinking in this project are similar to quantity/frequency measures used throughout the literature, it should be noted that they are not diagnostic, and do not assess the presence or severity of dependence.

Future Directions

Despite the promising results reported in this study, several questions regarding smoking's role in hangover remain unanswered. Results presented in the present study suggest that smokers show a diminished relation between alcohol dose and hangover. Replication of this finding using an alcohol challenge paradigm would be a valuable next

step in hangover research. A within-subjects alcohol challenge design would allow for administration of varying doses of alcohol across multiple sessions, and would allow the investigator to compare the alcohol dose-hangover relation in smokers and non-smokers. In addition to varying dose of alcohol, future researchers may wish to vary tobacco doses within subjects. Such a study would benefit from a laboratory setting equipped to house participants overnight, so that post-intoxication events (such as continued drinking or smoking) could be controlled, and next-day hangover assessment could be completed in a controlled environment.

An alcohol challenge design such as that proposed above would also allow for investigation of the impact of nicotine vs. tobacco smoke on hangover. Tobacco smoke is pharmacologically potent and components of tobacco smoke other than nicotine may contribute to hangover. This question might also be explored by administering nicotinized and denicotinized cigarettes to current cigarette smokers during an alcohol challenge, and comparing hangover scores between groups. Inclusion of a no smoking condition as a non-equivalent control group in this kind of design would be advantageous, allowing an assessment of whether the act of smoking per se contributes to hangover. Alternative nicotine delivery mechanisms may also be administered in an alcohol challenge design. Nicotine replacement products such as the nicotine patch, gum, or nasal spray, allow for controlled administration of nicotine in the absence of tobacco smoke, and would provide an interesting contrast when compared to a tobacco smoking group and control groups (e.g. denicotinized cigarettes and placebo patches) in an alcohol challenge design. These NRT products differ in their pharmacokinetic profiles. Patches produces steady-state plasma nicotine levels, while nasal spray produces acute peaks in

blood nicotine, a pattern that more closely mimics they effects of smoking., so studies comparing different forms of NRT might produce differing results. In addition to probing the role of nicotine in hangover, findings from such studies might produce results that are informative for matching heavy drinkers to smoking cessation treatments; if some NRT products are less likely than others to result in hangover, they might be better tolerated by drinkers. Alcohol challenge designs might also test the impact of non-nicotine pharmacotherapies for smoking cessation (e.g., bupropion) and nicotine antagonists (e.g. mecamylamine) on hangover expression. A suite of such studies might provide clues as to the specific neural pathways involved in the smoking-hangover link.

Analyses exploring hangover among those who initiated and quit smoking during the course of data collection suggest that those who smoked showed increased hangover when they reported concurrent smoking relative to their own non-smoking time-points. These findings suggest acute tobacco administration (rather than "person-level" variables) may be a mechanism driving the apparent relation between smoking and hangover. Laboratory studies might also be devised to explore these important transitions in smoking status with greater experimental control and inferential rigor. However, these designs would likely be costly to conduct and limited in crucial respects by ethical constraints. Nicotine replacement therapy (NRT) products would enable investigators to administer nicotine to a random sample of tobacco-naive individuals during an alcohol challenge, and compare their next-day hangover with that of never-smokers who did not receive nicotine. NRT could also be administered to smoking individuals in this design. The importance of acute tobacco administration (and/or the moderation of hangover by tobacco withdrawal) might be investigated in a within-

subjects alcohol challenge design assessing hangover before and after tobacco cessation. A "paid abstinence" component may be useful in this design in an effort to increase the rate of successful smoking cessation attempts between alcohol challenge sessions 1 and 2. Previous research has shown that when smoking participants receive substantial monetary compensation to abstain, up to 90% are able to maintain abstinence for 31 days (Gilbert, Crauthers, Mooney, McClernon, & Jensen, 1999).

As noted above, the retrospective self-report semi-annual assessments employed in this study obscure the temporal sequencing of drinking, smoking, and hangover events among participants. Future research in this area could benefit from ecological momentary assessment (EMA) data. EMA designs combine self-monitoring assessment strategies with the experience sampling method, and yield detailed and ecologically valid data (Piasecki, Hufford, Solhan, & Trull, in press). EMA techniques would allow participants to report their alcohol and cigarette consumption, and next-day hangover experiences in real time, and would allow researchers to explore the correlates, antecedents and sequelae of hangover.

This study relied on a single-item self-report measure of hangover. As described above, more comprehensive self-report measures are now available for use in the assessment of hangover, and should be employed in future research in this area. Additionally, research exploring individual differences in hangover may benefit from the use of other objective assessment strategies. For instance, cognitive assessments (e.g Stroop Test, Wisconsin Card Sorting Test) given pre-intoxication, during the drinking episode, and over the course of the hangover would elucidate deficits in executive functioning, memory and attention associated with the hangover syndrome.

Psychophysicological measures (e.g. skin conductance, blood pressure, startle response) administered across time would reveal hangover's effect on arousal and stress response. While similar strategies have been employed in previous research exploring performance decrements associated with hangover (e.g. Collins, 1980; Finnigan, et al., 1998; Yesavage & Leirer, 1986), objective measures such as these have not been used in investigations of individual differences in hangover.

Conclusion

Recent research suggests that drinkers differ in their experience of hangover, and that hangover is related to risk for AUD. This study explored the extent to which individual variation in hangover can be accounted for by cigarette smoking. Findings across a series of analyses suggest that smoking is related to individual differences in hangover. Smoking, however, does not appear to drive the relation between hangover and risk for AUD. Results from this exploratory study suggest that future research in this area is warranted.

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APPENDIX

Weekly alcohol frequency (over the past year) item and response option coding:

Think of all the times in the PAST YEAR when you had something to drink—how often have you had some kind of beverage containing alcohol?

15	Twice a day or more
7	Once a day
5	Nearly every day
3.5	3 to 4 times a week
1.5	Once or twice a week
0.6	2 to 3 times a month
0.2	About once a month
0.16	6-11 times a year
0.06	1-5 times a year
0	I didn't drink this past year

Weekly alcohol quantity (over the past year) item and response option coding:

In the PAST YEAR, when you were drinking alcohol, how many cans of beer, glasses of wine, bottles of wine cooler, or drinks of liquor did you usually have on any one occasion?

10	Nine or more total cans of beer, glasses of wine, bottles of wine cooler, and/or drinks of liquor
7.5	Seven or eight total cans of beer, glasses of wine, bottles of wine cooler, and/or drinks of liquor
6	Six total cans of beer, glasses of wine, bottles of wine cooler, and/or drinks of liquor
5	Five total cans of beer, glasses of wine, bottles of wine cooler, and/or drinks of liquor
4	Four total cans of beer, glasses of wine, bottles of wine cooler, and/or drinks of liquor
3	Three total cans of beer, glasses of wine, bottles of wine cooler, and/or drinks of liquor
2	Two total cans of beer, glasses of wine, bottles of wine cooler, and/or drinks of liquor
1	One total can of beer, glass of wine, bottle of wine cooler, or drink of liquor
.5	Less than one can of beer, glass of wine, bottle of wine cooler, or drink of liquor
0	I did not drink at all during the past 12 months

Weekly alcohol quantity/frequency (over the past year) descriptive information for each study year:

	Year 1	Year 2	Year 3	Year 4	Year 7	Year 11
Range	0-150	0-150	0-150	0-70	0-112.5	0-112.5
Mean (SD)	8.03(13.30)	7.73(14.14)	7.10(11.91)	6.53(8.95)	5.86(9.60)	3.79(8.25)

Weekly binge drinking frequency (across the past month) item and response option coding:

In the past 30 days, how many times have you had five or more drinks at a single sitting, either of beer, wine, or liquor, or some combination of these?

7	Every day
6	Nearly every day
5.5	5-6 times a week
3.5	3-4 times a week
1.5	Once or twice a week
.6	2-3 times during the past 30 days
.2	Once during the past 30 days
0	Didn't drink 5 or more drinks during the past 30 days

Weekly binge drinking frequency (across the past month) descriptive information for each study year:

	Year 1	Year 2	Year 3	Year 4	Year 7	Year 11
Range	0-7	0-7	0-7	0-5.5	0-7	0-7
Mean (SD)	.72(1.03)	.75(1.19)	.74(1.20)	.64(.98)	.46(.92)	.30(.74)

Weekly heavy drinking composite (across the past month) descriptive information for each study year:

	Year 1	Year 2	Year 3	Year 4	Year 7	Year 11
Range	0-6	0-6.5	0-7	0-6	0-7	0-7
Mean (SD)	.76(.94)	.75(.97)	.71(.99)	.70(.95)	.49(.78)	.33(.68)

Smoking frequency item and response option coding representing monthly rate, and conversion from smoking frequency to smoking status:

How often do you smoke cigarettes currently?		Smoking status categories:
30	Every day	Daily smokers
22	5-6 days a week	
14	3-4 days a week	
6	1-2 days a week	Non-daily smokers
1.5	1-2 days a month	
.5	Less than once a month	
0	I don't smoke now	Non-smokers

Smoking quantity item and response option coding:

On an average day when you do smoke, how many cigarettes do you smoke?

40	About 2 packs or more a day
30	About 1 ½ packs a day
20	About a pack a day
10	About half-a-pack a day
3	1-5 cigarettes a day
.5	Less than one cigarette a day on the average
0	None at all (I don't smoke)

Monthly smoking quantity/frequency descriptive information for each study year:

	Year 1	Year 2	Year 3	Year 4	Year 7	Year 11
Range	0-900	0-1200	0-1200	0-1200	0-1200	0-1200
Mean (SD)	51(157)	63(174)	72(183)	88(217)	88(218)	62(190)

Past-year headache/hangover frequency item and response option coding:

Have you had a headache (hangover) the morning after you had been drinking?

0	No, never
0	Yes, but not in the past year
1	Yes, 1 time in the past year
2	Yes, 2 times in the past year
3	Yes, 3 times in the past year
4	Yes, 4-6 times in the past year
5	Yes, 7-11 times in the past year
6	Yes, 12-20 times in the past year
7	Yes, 21-39 times in the past year
8	Yes, 40 or more times in the past year

Past-year headache/hangover frequency descriptive information for each study year.

	Year 1	Year 2	Year 3	Year 4	Year 7	Year 11
Range	0-8	0-8	0-8	0-8	0-8	0-8
Mean (SD)	2.60(2.37)	2.44(2.30)	2.49(2.38)	2.48(2.30)	2.00(2.09)	1.54(1.96)

Table 1. Bivariate associations between predictors and outcomes at each time-point.

		Sex	Family History	Alcohol Q/F	Binge Drinking	Heavy Drinking Comp	Cigarette Q/F	Smoking Status
Year 1	Family History	-.005						
	Alcohol Q/F	.153**	.128**					
	Binge Drink	.188**	.084	.557**				
	Heavy Drink Comp	.158**	.102*	.566**	.922**			
	Cigarette Q/F	.008	.145**	.198**	.239**	.243**		
	Smoking Status	-.025	.155**	.202**	.289**	.311**	.733**	
	Hangover	.068	.098*	.341**	.456**	.512**	.142**	.243**
Year 2	Family History	-.005						
	Alcohol Q/F	.154**	.100*					
	Binge Drink	.254**	.055	.607**				
	Heavy Drink Comp	.223**	.074	.613**	.909**			
	Cigarette Q/F	.011	.101*	.278**	.122**	.148**		
	Smoking Status	-.002	.098*	.294**	.187**	.232**	.751**	
	Hangover	.068	.096*	.415**	.421**	.477**	.190**	.281**
Year 3	Family History	-.005						
	Alcohol Q/F	.171**	.112*					
	Binge Drink	.262**	-.017	.559**				
	Heavy Drink Comp	.258**	-.002	.638**	.919**			
	Cigarette Q/F	.001	.117*	.192**	.126**	.135**		
	Smoking Status	-.003	.147**	.216**	.150**	.173**	.784**	
	Hangover	.136**	.044	.435**	.441**	.512**	.139**	.190**
Year 4	Family History	-.005						
	Alcohol Q/F	.301**	.088					
	Binge Drink	.286**	.093*	.723**				
	Heavy Drink Comp	.287**	.072	.741**	.893**			
	Cigarette Q/F	.040	.139**	.170**	.138**	.181**		
	Smoking Status	.031	.140**	.200**	.218**	.234**	.820**	
	Hangover	.204**	.074	.586**	.500**	.546**	.108*	.188**
Year 7	Family History	-.005						
	Alcohol Q/F	.268**	.104*					
	Binge Drink	.315**	.071	.793**				
	Heavy Drink Comp	.274**	.114*	.734**	.861**			
	Cigarette Q/F	.083	.137**	.197**	.133**	.138**		
	Smoking Status	.050	.143**	.242**	.164**	.198**	.822**	
	Hangover	.229**	.017	.416**	.442**	.483**	.141**	.220**
Year 11	Family History	-.005						
	Alcohol Q/F	.222**	.121*					
	Binge Drink	.265**	.069	.487**				
	Heavy Drink Comp	.258**	.083	.478**	.904**			
	Cigarette Q/F	.083	.135**	.310**	.333**	.290**		
	Smoking Status	.068	.179**	.318**	.363**	.336**	.815**	
	Hangover	.226**	.056	.438**	.404**	.445**	.222**	.305**

* $p < .05$, ** $p < .01$, *** $p < .001$

Table 2. Standardized regression coefficients predicting hangover from sex, family history status, **one of three drinking variables** (alcohol quantity/frequency, binge drinking occasions, and the heavy drinking composite), **current smoking status**, and the drinking by smoking interaction for each time-point.

		Year 1	Year 2	Year 3	Year 4	Year 7	Year 11
Alcohol Q/F	Sex	.027	-.036	.046	.032	.127**	.114**
	Family History	.033	.040	-.023	.029	-.036	-.028
	Alcohol Q/F	.342***	1.156***	.802***	.573***	.336***	.635***
	Non-daily Smoking	.187***	.149***	.094*	.129**	.102*	.166***
	Daily Smoking	.121**	.110***	.088*	.041	.119*	.177***
	Non-daily Smk x Alc Q/F	-.071	-.544***	-.335***	-.053	-.097*	.087
	Daily Smk x Alc Q/F	-.046	-.686***	-.347**	-.016	-.004	-.373***
Binge Drinking	Sex	-.019	-.036	.032	.053	.106*	.087
	Family History	.048	.056	.039	.039	-.052	-.008
	Binge Drinking	.525***	.458***	.484***	.612***	.378***	.727***
	Non-daily Smoking	.159***	.198***	.094*	.150**	.052	.164***
	Daily Smoking	.094*	.177***	.118**	.038	.125**	.201***
	Non-daily Smk x Binge	-.123*	-.074	-.039	-.246***	.048	-.103*
	Daily Smk x Binge Drinking	-.128*	-.108*	-.119**	-.098*	.024	-.521***
Heavy Drinking Composite	Sex	-.005	-.031	.018	.052	.110*	.091*
	Family History	.038	.044	.030	.044	-.036	-.012
	Heavy Drinking Composite	.471***	.526***	.571***	.658***	.415***	.723***
	Non-daily Smoking	.105*	.183***	.091*	.141**	.066	.146**
	Daily Smoking	.062	.157***	.093*	.034	.136**	.209***
	Non-daily Smk x Heavy	.060	-.095*	-.115*	-.233***	.004	-.085
	Daily Smk x Heavy Drink	-.040	-.126**	-.073	-.103*	-.083	-.496***

Table 3. Standardized regression coefficients predicting hangover from sex, family history status, **one of three drinking variables** (alcohol quantity/frequency, binge drinking occasions, and the heavy drinking composite), **cigarette quantity/frequency**, and the drinking by smoking interaction for each time-point.

		Year 1	Year 2	Year 3	Year 4	Year 7	Year 11
Alcohol Q/F	Sex	.014	.010	.064	.033	.126**	.112*
	Family History	.044	.042	-.009	.023	-.028	-.013
	Alcohol Q/F	.359***	.479***	.483***	.572***	.375***	.646***
	Cigarette Q/F	.087	.125**	.098*	.011	.063	.153**
	Cig Q/F x Alc Q/F	-.117*	-.200***	-.153**	-.022	-.011	-.379***
Binge Drinking	Sex	-.018	-.032	.029	.062	.103*	.092*
	Family History	.054	.060	.044	.032	-.044	.020
	Binge Drinking	.455***	.415***	.445***	.472***	.416***	.583***
	Cigarette Q/F	.074	.156***	.104*	.021	.074	.176***
	Cig Q/F x Binge Drinking	-.089	-.069	-.100*	-.013	.049	-.403***
Heavy Drinking Composite	Sex	-.012	-.028	.014	.057	.106*	.091*
	Family History	.046	.049	.040	.035	-.031	-.009
	Heavy Drinking Comp	.505***	.466***	.502***	.531***	.416***	.601***
	Cigarette Q/F	.026	.142**	.075	.014	.087	.189***
	Cig Q/F x Heavy Drink	-.021	-.067	-.029	-.032	-.090	-.397***

Table 4. Results from HLM predicting hangover from study year, alcohol consumption, and cigarette consumption at level 1, and sex and family history status at level 2.

Predictor	Coefficient
Intercept	1.913***
Sex	.186
Family History	.269
Time	-.088**
Sex	.089**
Family History	-.025
Alcohol Q/F	.177***
Sex	-.068***
Family History	-.059**
Cigarette Q/F	.000
Sex	-.000
Family History	.001*

Table 5. Results from HLM predicting hangover from study year and alcohol consumption at level 1, and sex, family history status, and ever-smoker status at level 2.

Predictor	Coefficient
Intercept	1.006***
Sex	.434*
Family History	.197
Smoking Status	.864***
Time	-.068***
Sex	.037
Family History	-.004
Smoking Status	-.011
Alcohol Q/F	.215***
Sex	-.073***
Family History	-.024
Smoking Status	-.042**

Table 6. Results from mixed between-within ANOVA models comparing hangover and alcohol consumption at Years 1 and 11 among naturally occurring smoking groups.

			F	Sig.	Partial Eta Squared
Hangover	Abstainer vs. Initiator	Time	.905	.342	.004
		Group	9.966	.002	.341
		Time x Group	6.722	.010	.029
	Smoker vs. Quitter	Time	20.042	.000	.207
		Group	4.829	.031	.059
		Time x Group	9.293	.003	.108
Alcohol Q/F	Abst ainer vs. Initiator	Time	1.068	.303	.005
		Group	11.185	.001	.048
		Time x Group	7.922	.005	.034
	Smoker vs. Quitter	Time	17.32	.000	.180
		Group	9.289	.003	.105
		Time x Group	.259	.612	.003

Table 7. Results from ANCOVA models comparing hangover at Years 1 and 11 among naturally occurring smoking groups, controlling for change in drinking across time, sex and family history..

		F	Sig.	Partial Eta Squared
Abstainers vs. Initiators	Time	1.511	.220	.007
	Group	7.011	.009	.031
	Drinking Change	.024	.878	.000
	Sex	12.346	.001	.054
	Family History	.204	.652	.001
	Time x Group	4.105	.044	.018
	Time x Drinking Change	4.614	.032	.021
	Time x Sex	3.114	.079	.014
	Time x Family History	.914	.340	.004
Smoker vs. Quitter	Time	5.977	.017	.075
	Group	3.675	.059	.047
	Drinking Change	.575	.451	.008
	Sex	.059	.809	.001
	Family History	2.680	.106	.035
	Time x Group	10.139	.002	.121
	Time x Drinking Change	7.475	.008	.092
	Time x Sex	6.298	.014	.078
	Time x Family History	.996	.322	.013

Table 8. Results from logistic regression models. Top panel predicts AUD diagnosis at years 4, 7, and 11 from hangover at year 1, controlling for sex, family history status, year 1 drinking, and year 1 AUD diagnosis. Middle panel predicts AUD diagnosis at years 4, 7, and 11 from previously entered variables and year 1 smoking status. Bottom panel predicts AUD diagnosis at years 4, 7, and 11 from previously entered variables and ever-smoker status.

			Year 4 OR	CI, 95%	Year 7 OR	CI, 95%	Year 11 OR	CI, 95%
Smoking Omitted		Sex	4.56**	2.44, 8.53	3.35**	1.78, 6.32	3.27**	1.53, 7.04
		Family History	1.82*	1.01, 3.26	1.95*	1.07, 3.57	2.79**	1.29, 6.01
		Drinking, Year 1	1.02	.99, 1.04	1.01	.99, 1.03	1.01	.99, 1.03
		AUD, Year 1	2.35**	1.72, 3.21	2.03**	1.47, 2.81	.91	.59, 1.39
		Hangover, Year 1	1.06	1.00, 1.31	1.17*	1.03, 1.34	1.14**	1.14, 1.58
Smoking Included	Dummy Coded Smoking Status	Sex	4.78**	2.53, 9.02	3.50**	1.84, 6.65	3.30**	1.53, 7.09
		Family History	1.70*	.94, 3.08	1.86*	1.01, 3.42	2.78*	1.28, 6.05
		Drinking Year 1	1.02	.99, 1.04	1.05	.99, 1.03	1.01	.99, 1.03
		AUD, Year 1	2.37**	1.73, 3.24	2.05**	1.48, 2.85	.91	.59, 1.40
		Hangover, Year 1	1.15*	1.01, 1.31	1.15*	1.01, 1.32	1.34**	1.13, 1.59
		Smoking (Non-Daily), Year 1	1.19	.59, 2.38	1.54	.77, 3.07	1.09	.46, 2.56
		Smoking (Daily), Year 1	1.75	.73, 4.17	1.37	.55, 3.36	.98	.32, 2.96
	Ever-smoker	Sex	4.22**	2.07, 8.62	4.44**	2.03, 9.73	2.79*	1.26, 6.10
		Family History	1.67	.84, 3.35	1.89	.91, 3.93	2.46*	1.10, 5.48
		Drinking, Year 1	1.02	.99, 1.04	1.01	.99, 1.03	1.01	.99, 1.03
		AUD, Year 1	3.07**	2.11, 4.46	2.13**	1.44, 3.16	.85	.53, 1.34
		Hangover, Year 1	1.09	.94, 1.27	1.16	.99, 1.36	1.29**	1.09, 1.54
		Ever-smoker	1.03	.51, 2.07	1.27	.61, 2.63	2.01	.91, 4.43

Figure 1. Percentage of participants in each smoking group.

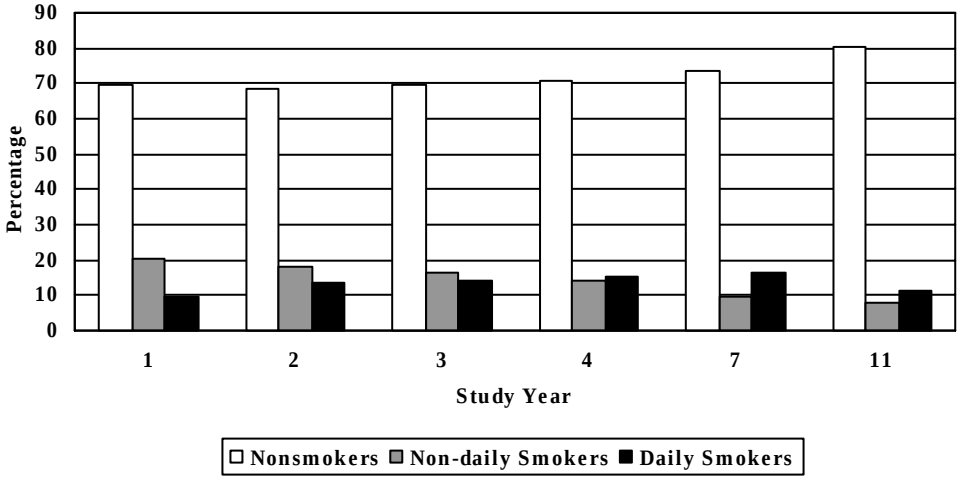

Figure 2. Mean hangover frequency for participants in each smoking group.

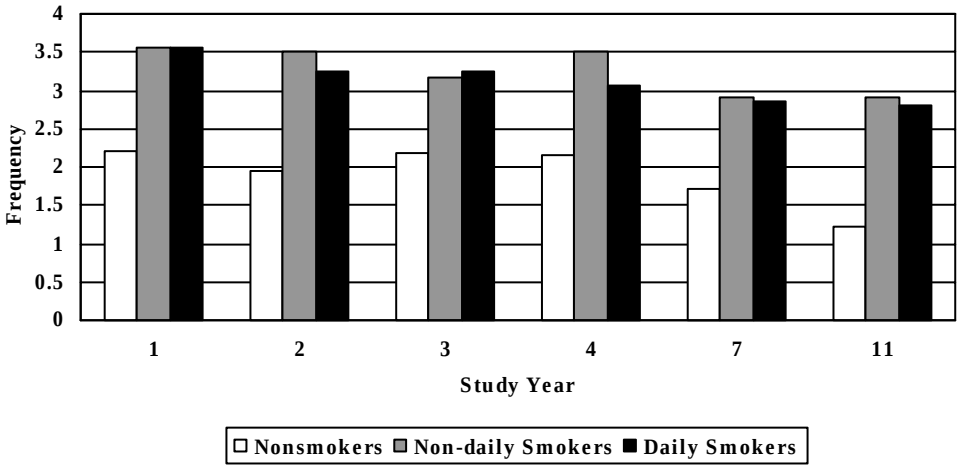

Figure 3. Mean hangover frequency for men and women.

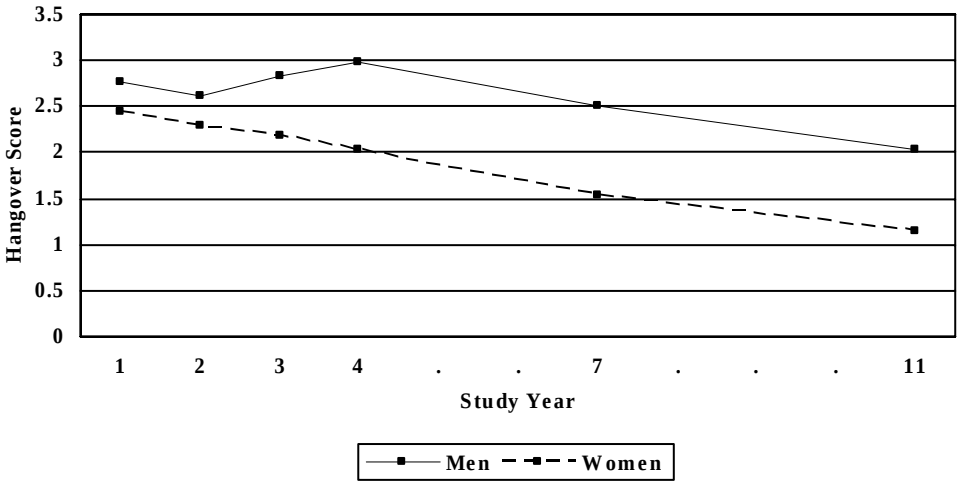

Figure 4. Mean hangover frequency for family history positive and family history negative participants.

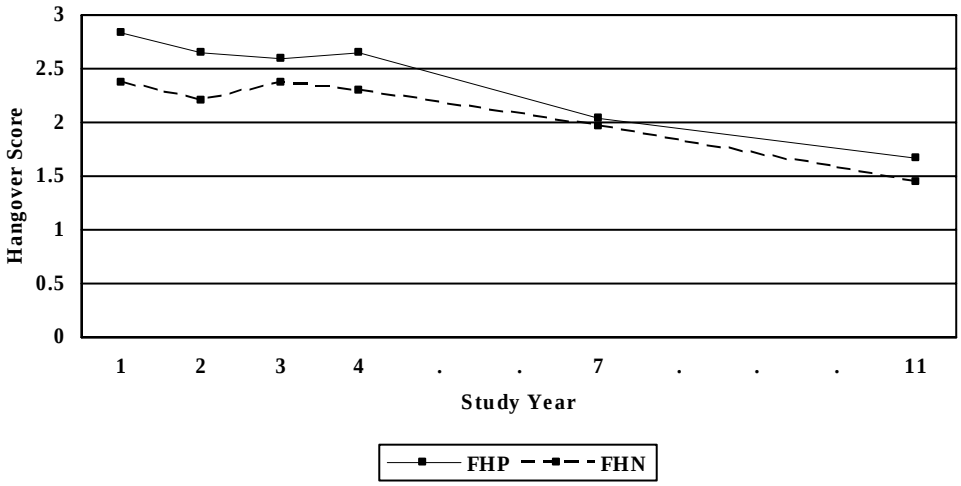

Figure 5. Mean levels of hangover and alcohol consumption among naturally occurring smoking groups.