A Triple Threat: Alcohol Use Disorders in the Presence of Comorbid Chronic Pain Conditions and Depressive Disorders in the Collaborative Psychiatric Epidemiology Surveys, 2001-2003

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Dedication

The author wishes to dedicate this thesis to her mother, who is her greatest support, cheerleader, and friend. This is also dedicated to the rest of her friends and family who have helped her keep her sanity and sense of humor, even when it wasn't an easy job. Finally, this thesis is dedicated to all of the horses who have carried me through the good and bad times while teaching me responsibility, persistence, trust, and humility—especially Tag, Spidey, Tarr, and Britannia.

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Abstract of Thesis

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Background

Patients with chronic pain conditions frequently have comorbid depressive disorders. The relationship between the diagnoses is often bidirectional, with the effects of one condition exacerbating the effects of the other. Alcohol use disorders are also independently associated with both conditions. This study aims to determine the prevalence of alcohol use disorders among patients with comorbid chronic pain conditions and depressive disorders in a nationally representative sample of US adults and to ascertain the characteristics of patients with all three diagnoses.

Methods

This cross-sectional study utilizes the Collaborative Psychiatric Epidemiology Surveys (CPES), 2001-2003. The outcome is a dichotomous measure of past 12 month alcohol use disorder, meeting Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria. The exposure variable is a categorical variable with three levels representing a range of past 12 month comorbid chronic pain condition(s) and DSM-IV depressive disorder(s). Prevalence odds ratios were obtained using logistic regression analysis accounting for survey weights.

Results

The crude, unadjusted model showed that participants with comorbid chronic pain conditions and depressive disorders during the past 12 months had 1.941 (0.394, 9.569) times the odds of having an alcohol use disorder during the past 12 months than participants without chronic pain conditions or depressive disorders during the past 12 months. The same model determined that participants with at least one chronic pain condition but no depressive disorders during the past 12 months had 0.333 (0.068, 1.63) times the odds of having an alcohol use disorder during the past 12 months than participants without chronic pain conditions or depressive disorders during the past 12 months. Neither of these associations were statistically significant at α=0.05.

The adjusted model that included age, the only statistically relevant confounder, determined that participants with comorbid chronic pain conditions and depressive disorders during the past 12 months had 2.464 (0.529, 11.477) times the odds of having an alcohol use disorder during the past 12 months than participants without chronic pain conditions or depressive disorders during the past 12 months, after adjusting for age. Participants with at least one chronic pain condition but no depressive disorders during the past 12 months had 0.676 (0.149, 3.046) times the odds of having an alcohol use disorder during the past 12 months than participants without chronic pain conditions or depressive disorders during the past 12 months, after adjusting for age. Again, these results fail to achieve statistical significance. Age [POR=0.941, (0.918, 0.965)], however, has a significant impact on past 12 month alcohol use disorder, after adjusting for chronic pain and depressive disorder comorbidity status. One defining characteristic of the group

of participants with comorbid chronic pain conditions and depressive disorders is that males constitute only 33.7% (S.E. = 3.0) of this category.

Conclusions

Despite the failure to achieve statistically significant results, the elevated odds of past 12 month alcohol use disorders among participants with comorbid chronic pain conditions and depressive disorders during the past 12 months, in combination with the established, independent associations between alcohol use disorder, chronic pain, and depressive disorders suggest that patients presenting with both depression and chronic pain should be carefully evaluated and monitored for signs of alcohol use disorder. The results from this study should be interpreted with caution due to the potential effect of categories with few observations and the methodological limitations of the dataset.

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Glossary of Terms

Alcohol Abuse: "a maladaptive pattern of drinking, leading to clinically significant impairment or distress, as manifested by at least one of the following occurring within a 12-month period" and never meeting the criteria for alcohol dependence: use of alcohol resulting in failure to fulfill major obligations, alcohol use in situations that are physically hazardous, alcohol related legal problems, continued alcohol use despite interpersonal problems derived from alcohol use.[1]

Alcohol Dependence: "a maladaptive pattern of drinking, leading to clinically significant impairment or distress, as manifested by three or more of the following occurring at any time in the same 12-month period:" need to increase alcohol intake for desired effect, pattern of withdrawal syndrome, drinking larger amounts over a longer period than intended, persistent desire to continue drinking even after attempts to quit or cutback, important activities reduced or eliminated due to drinking, significant time spent acquiring alcohol, drinking, or recovering from drinking, and recurrent drinking despite knowledge of its ill effects.[1]

Alcohol Use Disorder: illness with symptoms meeting the DSM-IV diagnostic criteria for either alcohol abuse or alcohol dependence.[2]

Criteria for Confounding: the three conditions that must be met for a variable to confound the relationship between an exposure and an outcome, 1) the confounding variable is independently associated with the exposure variable, 2) the confounding variable is independently associated with the outcome variable among the unexposed, and 3) the confounder is not on the causal pathway between the exposure and the outcome.[3]

Chronic Pain Condition: a self-reported diagnosis of arthritis/rheumatism, frequent or severe headaches, chronic back/neck pain, chronic pain unrelated to the aforementioned conditions, or medically unexplained chronic pain lasting 6 months or more.

Comorbid Group: the subpopulation of the sample population of participants reporting at least one chronic pain condition during the past 12 months and a depressive disorder during the past 12 months.

Depressive Disorder: illness with symptoms meeting the DSM-IV diagnostic criteria for dysthymia, major depressive disorder, or major depressive episode.[2]

Dysthymia: Depressed mood for most of the day, for more days than not, for at least 2 years without a remission of symptoms for more than 2 months at a time.[4] Diagnosed when symptoms are not better described by major depressive disorder or major depressive episode.[4]

Major Depressive Disorder: a state primarily characterized by depressed mood and/or anhedonia unrelated to other physical diagnosis that lasts most of the day, nearly every day for 2 weeks or more.[5]

Major Depressive Episode: a state primarily characterized by depressed mood and/or anhedonia unrelated to other physical diagnosis or bereavement that lasts most of the day, nearly every day for 2 weeks or more in a patient who has never had an episode of mania or hypomania.[5]

Reference Group: the subpopulation of the sample population of participants reporting no chronic pain conditions or depressive disorders during the past 12 months.

Chapter I: Background and Specific Aims

There is a known link between certain physical medical conditions and psychiatric illnesses, particularly depressive disorders.[6-8] Comorbid physical illness and depressive disorders are complicated for medical professionals to diagnose and treat because the association between the conditions can be bidirectional, independent, or caused by a third factor, such as medication.[6] Fibromyalgia, rheumatoid arthritis, back pain, and migraine headaches are all chronic pain conditions that have been associated with comorbid depressive disorder diagnosis.[6,9-12] Unfortunately for patients, depressive disorders are often underdiagnosed in physically ill patients. An estimated 50-percent of depressive disorders go undiagnosed by primary care providors.[9] This is concerning because 15 to 100% of chronic pain patients will develop major depressive disorder following diagnosis with chronic pain.[8,9,13-16] This association is important enough that the Institute for Clinical Systems Improvement (ICSI) includes the need to screen chronic pain patients for mental health conditions and substance use disorders in their treatment guidelines.[17]

There is evidence of an association between chronic pain conditions and alcohol use disorders.[14,18-20] Depressive disorders are also associated with higher rates of alcohol use disorders.[19,21-24] Since depressive disorders and chronic pain conditions are often co-occurring, and both disorders are independently associated with alcohol use disorders, it is plausible that patients with comorbid chronic pain conditions and depressive disorders have an increased risk of alcohol use disorders compared to patients with either condition alone. Several studies evaluated the independent, population-level associations and biological processes underlying the association between chronic pain disorders and

depressive disorders and alcohol use disorders, respectively, but little is known about how comorbidity influences this relationship. [14,18-24] Since these conditions are known to occur in tandem, understanding the risk of alcohol use disorders among patients with comorbid depressive disorders and chronic pain disorders is of clinical importance for evaluating treatment plans and diagnostic recommendations.[17,23,25]

This study utilized data from the Collaborative Psychiatric Epidemiology Surveys (CPES) from 2001-2003, which is a nationally representative survey available for public download.[26] The CPES includes a number of variables asking about chronic pain conditions and evaluates participants for depressive disorders and alcohol use disorders.

Chronic pain can encompass many types of pain conditions. The chronic pain conditions available in the CPES dataset include arthritis/rheumatism, frequent or severe headaches, chronic back/neck pain, other chronic pain, and medically unexplained chronic pain. The CPES dataset also indicates the presence of three different depressive disorders among participants: major depressive disorder, major depressive episode, and dysthymia. The CPES dataset also gathered data indicating the presence of two types of alcohol use disorder: alcohol abuse and alcohol dependence. Since the CPES collected data on all three variables of interest, it lends itself to answering the following research questions.

Specific Aim 1: To determine the association between alcohol use disorders during the past 12 months among adults, 18 and over, in the United States and comorbid

depressive disorders and chronic pain conditions during the past 12 months, among people reporting chronic pain at any time during their life. Using a cross-sectional study design and logistic regression analysis, the association between the outcome (alcohol use disorders) and the exposure (comorbid depressive disorder and chronic pain conditions) will be modeled. It is hypothesized that alcohol use disorders will be positively associated with comorbid depressive disorder and chronic pain conditions among participants in the CPES, 2001-2003.[26]

Specific Aim 2: To ascertain the prevalence of different demographic characteristics of adults in the United States with comorbid chronic pain conditions and depressive disorders during the past 12 months, among people reporting chronic pain at any time during their life. It is hypothesized that the prevalence of alcohol use disorders and other indicators of poor health and economic disadvantage will be higher among adults with comorbid chronic pain conditions and depressive disorders than among adults with only chronic pain or neither chronic pain nor depression during the past 12 months.

Chapter II: Methods

This study utilizes a cross-sectional design and analyzes data from the Collaborative Psychiatric Epidemiology Surveys (CPES) from 2001-2003, which is a nationally representative survey available for public download.[26] The goal of the CPES was to collect data on psychiatric health outcomes and treatments from an ethnically diverse sample. The CPES combined three previous national surveys to achieve this goal-- the National Comorbidity Survey Replication (NCS-R), the National Survey of American Life (NSAL), and the National Latino and Asian American Study (NLAAS).[26] This is the most recent nationally representative survey that focuses on psychiatric conditions among people over 18 years of age in the United States. The National Institute of Mental Health sponsored the CPES, and researchers from the University of Michigan's Survey Research Center (SRC) of the Institute for Social Research collected the data from 2001 to 2003.[26]

The Collaborative Psychiatric Epidemiology Surveys (CPES) used a multistage area probability sampling method.[26] The researchers followed the University of Michigan Survey Research Center's (SRC) National Sample design when selecting the sample. Data was collected by interviewers trained to screen participants and administer the surveys. The results were weighted to account for the multistage sampling method.[26] Surveys were conducted using telephone interviews, computer-assisted personal interviews, and computer-assisted telephone interviews.[26]

The sample for this study consisted of a subpopulation from the full dataset. To be included in the sample, study participants must have reported having experienced at least one

chronic pain condition (arthritis/rheumatism, back/neck pain, head aches or migraines, other chronic pain, and/or medically unexplained pain) during their lifetime. This criteria was established due to the methodology of the survey. Only participants who indicated they had ever experienced a chronic pain condition during their lifetime were asked the questions about chronic pain conditions during the past 12 months. Also, since lifetime arthritis/rheumatism was the only timeframe evaluated for these conditions, it was decided to exclude all participants who had never experienced a chronic pain condition from the sample, to be more consistent across conditions.

The full sample from the Collaborative Psychiatric Epidemiology Surveys (CPES) from 2001-2003 contains data collected from 20,013 participants aged 18 years or older in the United States.[26] The eligible subpopulation for this study contained 3,610 participants. Any participants reporting at least one chronic pain condition during their lifetime, but not during the past 12 months, and a depressive disorder during the past 12 months were excluded from the sample. These participants were excluded to increase the validity of the final analysis due to insufficient sample size (45 participants) and no observed cases of alcohol use disorder among that subpopulation.

The CPES used several established instruments to determine if study participants experienced clinical manifestations of psychiatric conditions. The variables associated with DSM-IV criteria for diagnosis of alcohol dependence, alcohol abuse, major depressive episode, major depressive disorder, and dysthymia were used to determine presence of a depressive disorder for this study.[2] To arrive at a DSM-IV diagnoses, the survey used

diagnostic algorithms.[2] For more detailed information on the specific algorithms used to code participant's diagnosis based on the survey questions, the "Diagnostic Algorithms" booklet is available from the same source as the dataset.[26]

The exposure of interest was comorbid depressive disorder(s) and/or chronic pain condition(s) during the past 12 months. The exposure was represented as a categorical variable with three groups. The three groups were defined as follows: (1) no depressive disorder(s) or chronic pain conditions during the past 12 months, (2) at least one chronic pain condition during the past 12 months but no depressive disorders during the past 12 months, and (3) at least one depressive disorder and at least one chronic pain condition during the past 12 months.[16] The group that had not experienced comorbid chronic pain condition(s) and depressive disorder(s) during the past 12 months served as the reference group for all analyses.

The primary outcome variable was meeting DSM-IV diagnostic criteria for an alcohol use disorder during the past 12 months.[2] This was represented as a dichotomous variable: any DSM-IV diagnosis of alcohol abuse or alcohol dependence in past 12 months (yes) and no DSM-IV diagnosis of either alcohol dependence or abuse during the past 12 months (no).[2,27,28] The "no alcohol use disorder" category served as the reference for all analyses.

The following list of potential confounding variables was identified: age, sex, race/ethnicity, years of education, smoking status, male/female childhood caregiver experiencing periods of sadness for 2+ weeks, marital status, employment status, and

region of residence.[11,13,15,18,22,25,29-33] See Appendix A for the variable codes in the original dataset that correspond to the variables used in this analysis. The variables that were not represented by a single question in the dataset were created by combining answers to several questions from the survey.

All potential confounders were represented in the dataset by individual questions except for male/female childhood caregiver experiencing periods of sadness for 2+ weeks and smoking status. Male/female childhood caregiver experiencing periods of sadness for 2+ weeks served as a proxy variable for family history of depression. Family history of depression was represented as a dichotomous variable. If a participant reported having a male and/or female childhood caregiver who experienced periods of sadness for 2+ weeks (determined based on two separate questions), the participant was classified as having a family history of depression. Otherwise, the participant was classified as not having a family history of depression.

The variable representing smoking status was derived by creating a categorical variable with three groups—current smoker, former smoker, and never smoker—based on the responses to the survey questions asking participants if they had smoked more than 100 cigarettes in their lifetime and if they currently smoked cigarettes. Participants reporting they had smoked more than 100 cigarettes in their lifetime but did not currently smoke were classified as former smokers, and participants affirming both of those statements were classified as current smokers. Participants reporting never having smoked 100 or more cigarettes in their lifetime were classified as never smokers.

Before conducting any analyses, the variables required to complete all analyses was isolated from the full study dataset, and a dataset containing only the variables of interest was created. All observations from the original dataset were included in this new dataset.

After creating this new, smaller dataset, the data was recoded so it could be used for logistic regression analysis. In the original download of the CPES data, the dichotomous variables were coded as '1' for presence of the condition (yes) and '5' for absence of the condition (no). The dichotomous variables were recoded as '1' for presence of the condition and '0' for absence of the condition. Missing data remained coded as it is in the original dataset (.). The original dataset also includes codes for 'refused to answer' (-9) and 'don't know' (-8). Responses of 'refused to answer' and 'don't know' were recoded as missing values (.), which is the standard coding for missing data in SAS. In the case of categorical variables with more than two groups, the data was recoded so that the reference group was coded as '0.' Any missing data was recoded in the same way that missing data for the dichotomous variables was handled. The reference group for each variable was selected by using frequency distributions to determine the group with the lowest prevalence of alcohol use disorder, as defined below.

Several new variables were created from the original data. First, the outcome variable, alcohol use disorder during the past 12 months was created. Questions V07519 and V07521—DSM-IV diagnosis of alcohol abuse in past 12 months and DSM-IV diagnosis

of alcohol dependence in past 12 months, respectively—were used to construct the dichotomous outcome variable.[2] The outcome variable takes the following values:[26]

0. No DSM-IV diagnosis of either alcohol dependence or alcohol abuse in past 12 months (reference group).
1. Any DSM-IV diagnosis of alcohol abuse or alcohol dependence in past 12 months.

Similarly, a variable for the primary exposure variable was created: depressive disorder and chronic pain condition comorbidity status. This was done in three steps: creating a dichotomous chronic pain condition variable from the results of several survey questions, creating a dichotomous depressive disorder variable from the results of several survey questions, and creating the variable to represent the three combinations of comorbid depressive disorders and chronic pain conditions.

The chronic pain condition variable was defined as '0' if no chronic pain condition was reported in the past 12 months, and it took the value of '1' if a chronic pain condition was reported during the past 12 months. Subjects were assigned a '1' if they responded 'yes' to any for the follow questions in the original dataset:[26]

- V04079: 12 months still have chronic back/neck problems
- V04080: Frequent or severe headaches in past 12 months
- V04044: Ever had arthritis/rheumatism (note that the survey does not include a question about past 12 month prevalence of arthritis/rheumatism, because they are unremitting conditions)

- V04082: Still have other chronic pain in past 12 month
- V04236: Had medically unexplained pain for 6+ months in past year

The dichotomous depressive disorder variable was defined as '0' if no depressive disorder was reported in the past 12 months, and it took the value of '1' if a depressive disorder was reported during the past 12 months. Subjects was assigned a '1' if they endorsed any for the follow questions in the original dataset:[26]

- V07603: DSM-IV Dysthymia (12 month)
- V07655: DSM-IV Major Depressive Disorder w/ hierarchy (12Mo)
- V07659: DSM-IV Major Depressive Episode (12Mo)

The final step was to create the primary exposure variable was to code the new variable, comorbid chronic pain condition and depressive disorder during past 12 months, as a categorical variable, as follows:[2]

0. No report of DSM-IV diagnosis of any depressive disorder nor report of any chronic pain condition in past 12 months (reference group).
1. No report of DSM-IV diagnosis of depressive disorder in past 12 months, but report of at least one chronic pain condition in past 12 months.
2. Report of DSM-IV diagnosis for at least one depressive disorder and report of at least one chronic pain condition in past 12 months.

Any categorical potential confounding variables were recoded with the reference group as '0.' Any continuous potential confounding variables remained coded as they were in the original dataset.

First, descriptive analyses of the study sample, reported by the three exposure categories, were conducted. These included analyses of demographic and other characteristics. The characteristics of the of participants with comorbid chronic pain conditions, depressive disorders, and alcohol use disorders were evaluated by running a series of frequency distributions for categorical variables and univariate analyses for continuous variables. The descriptive statistics were calculated using the procedures for complex survey data in SAS 9.4. For categorical variables, number of participants and percentage were reported. For continuous variables, means and standard deviations were reported.

In addition to the number of participants in each exposure category, the distribution of the following sample characteristics were reported, by exposure category, using means and standard errors for continuous variables or percentages and standard errors for categorical variables: age, sex, race/ethnicity, education level, smoking status, male/female childhood caregiver experiencing periods of sadness for 2+ weeks, marital status, employment status, and region of residence. At this stage, continuous variables were assessed for normality. Any continuous variables with skewness greater than 2 or less than -2 and/or kurtosis greater than 3 or less than -3 were considered as candidates for transformation using the appropriate transformation. Finally, the amount of missing data in the sample was assessed and noted. If greater than or equal to 10 percent of the subpopulation had been missing data

for the outcome, a sensitivity analysis or multiple imputation would have been conducted to minimize/determine the impact of the missing data.

After determining the descriptive characteristics of the sample, the potential confounding variables were assessed using the criteria for confounding. Each potential confounding variable was assessed for these three criteria before being included in the final logistic regression model.

1. The potential confounding variable must be associated with comorbid chronic pain conditions and depressive disorders during the past 12 months.
2. The potential confounding variable must be associated with alcohol use disorders during the past 12 months, among those without a chronic pain condition or depressive disorder during the past 12 months.
3. The potential confounding variable must not be one the causal pathway between the exposure, comorbid chronic pain conditions and depressive disorders during the past 12 months, and the outcome, alcohol use disorder during the past 12 months.

To test these three criteria, a series of bivariate models were fit. In cases where cells with zero observations complicated evaluation of these criteria, i-1 (i=number of categories) dichotomous dummy variables were created and evaluated using Rao-Scott Chi-Squared tests to evaluate the nature of the association between each category of observations and a reference group. If at least one dummy variable from a potential confounding variable met the criteria under evaluation, the potential confounding variable was considered to have

met that criteria for confounding. An example of how these dummy variables were coded follows for employment status, where i=3.

- Dummy variable A: 1=participant was employed, 0=participant was unemployed or not in the labor force
- Dummy variable B: 1=participant was unemployed, 0=participant was employed or not in the labor force

The results from the analysis of the criteria for confounding informed which variables were included in the logistic regressions. Potential effect-measure modification (interaction) was not evaluated in this analysis.

It should be noted that due to the way the exposure was coded, the analysis is effectively an analysis of the interaction between chronic pain conditions and depressive disorders during the past 12 months on the outcome of alcohol use disorders during the past 12 month. What separates this analysis from a more traditional interaction analysis, where a researcher might introduce a variable derived by taking the product of two covariates, is that by coding the exposure as defined above, a more refined understanding of the interaction between chronic pain conditions and depressive disorders is possible. This is because taking the product of the dichotomous variables representing each condition would result in participants reporting only one of the two conditions during the past 12 months being included in the same group as participants not experiencing either condition during the past 12 months. This does not allow analysis of differences between all potential combinations of disease states. Coding the exposure as a categorical variable with four

groups (three groups, in this case, due to limitations related to analysis of secondary data), facilitates an analysis that captures the full spectrum of potential associations between the exposure and the outcome. This feature is unique to the analysis of comorbid conditions as an exposure, and can affect the results of the study.

Next, logistic regression was used to assess the prevalence odds ratio of alcohol use disorders, as defined by the DSM-IV, during the past 12 months among adults in the United States meeting the DSM-IV conditions for at least one depressive disorder in the past 12 months and experiencing comorbid chronic pain condition(s).[2]

The crude association between the exposure and outcome was assessed by fitting a logistic regression model containing only the exposure as an independent variable. Finally, the association between comorbid chronic pain conditions and depressive disorders during the past 12 months and past 12 month alcohol use disorder was evaluated using multivariable logistic regression models. The first multivariable logistic regression model, the standard model, was fit and had the exposure and all of the variables identified as potential confounding variables during the literature review as independent variables. Finally, a logistic regression model containing only the exposure and the confounding variables that were significant at $\alpha=0.05$ in the standard model was fit, and called the adjusted model. Prevalence odds ratios, regression coefficients, standard errors, 95% confidence intervals, and model fit statistics were reported for each model.

All analyses were conducted using the procedures for complex survey data in SAS software for Windows, version 9.4. The license for this software is provided by The George Washington University.

The study used secondary, publicly available data with no identifying information. The study was deemed exempt from oversight by The George Washington University's IBR.

Chapter III: Results

Table 1 shows the characteristics of the sample population by exposure group. The prevalence of alcohol use disorders during the past 12 months among the full sample was 1.08% (S.E. = 0.15). The subpopulation analysis showed that the prevalence of alcohol use disorders by group was as follows: no chronic pain condition and no depressive disorder during the past 12 months was 2% (S.E. = 1.36), at least one chronic pain condition but no depressive disorder during the past 12 months was 0.68% (S.E. = 0.15), and comorbid chronic pain condition and depressive disorder during past 12 months (comorbid group) was 3.82% (S.E. = 1.13).

Age was the only continuous variable used in the model, and it was determined to be approximately normally distributed (skewness = 0.551, kurtosis = -0.421), therefore it was not transformed. Average age for each exposure category and overall was 40.1-41.5 years of age, except in the group with comorbid chronic pain and depression during the past 12 months, as shown in Table 1. With a mean age of 56.4 (S.E. = 0.5), the group with only chronic pain during the past 12 months differed significantly from the other two exposure categories at α=0.05. Table 2 shows the Rao-Scott chi-square statistics (t-statistic for age) and associated p-values for the variables included in the analysis of sample characteristics and shows that the ages differ significantly from the expected value for the mean ($t = 20.97$, $p < 0.0001$).

With regards to sex, the comorbid group had an average age of 33.7 years (S.E. = 3.0). The sample population consisted of 40.5% (S.E. = 1.2) males. The group without chronic

pain or a depressive disorder during the past 12 months and the group with only chronic pain during the past 12 months had a similar percentage of males, 40.7% (S.E. = 4.4) and 41.5% (S.E. = 1.5), respectively. The group with comorbid conditions during the past 12 months had the lowest percentage of males, with only 33.7% (S.E. = 3.0) of participants in this exposure category being male, however this was not a statistically significant difference compared to the other two groups. Table 2 shows that the proportion of males to females does not differ from the expected value ($\chi^2 = 5.2379$, $p = 0.0729$).

Non-Hispanic whites made up the majority of the overall sample population, at 74.2% (S.E. = 2.0). The subpopulation analysis by exposure category, shown in Table 1, found that non-Hispanic whites accounted for a similar proportion of each group, except the group with neither chronic pain nor depression during the past 12 months for which (the reference group). In the reference group, non-Hispanic whites made up only 37.4% (S.E. = 5.0) of the subpopulation. The difference between the reference group and the other two groups was statistically significant at $\alpha=0.05$. Table 1 lists the specific percentages for each race/ethnicity by exposure category. The only racial group that was not statistically different in proportional representation across the three exposure groups was African Americans (Table 1). The proportion of each exposure category that was composed of people from other racial backgrounds was the only racial demographic that exhibited statistically significant differences across all three exposure groups, however this should be interpreted with caution due to low numbers of observations. Asians, Hispanics, and non-Hispanic Whites represented a different proportion of the sample in the reference group than in the chronic pain only group and the comorbid group.

Participants who reported being employed (50.7%, S.E. = 1.5) or not in the labor force (42.2%, S.E. = 1.6) made up the vast majority of the sample, as shown in Table 1. The comorbid group and the group with only chronic pain during the past 12 months had the highest proportion of people not being in the labor force, 41.8% (S.E. = 1.7) and 50.6% (S.E. = 3.0), respectively. The reference group was mostly employed (65.5%, S.E. = 4.8), but 29.0% (S.E. = 4.8) reported not being in the labor force, still. The chronic pain only group and the comorbid group had significantly different proportions of employed participants than the reference group. The proportion of unemployed participants did not differ significantly between exposure categories. Finally, the comorbid group had a higher proportion of participants who were not in the labor force than the other two exposure categories—this difference was statistically significant. For employment status, the Rao-Scott chi-squared statistic was 19.47 ($p = 0.0006$).

Table 1 also shows the proportions of participants in each exposure category by geographic region of residence. There was no significant difference in the proportion of participants living in the Northeast and South between all three exposure categories. The proportion of participants who did not report a chronic pain condition or a depressive disorder during the past 12 months was significantly higher than the proportion of participants in the chronic pain only group and the comorbid group for participants reporting living in the West. In the comorbid group, the proportion of participants living in the Midwest was significantly higher than in the reference group but was not significantly different from the chronic pain only group.

The proportion of participants in each exposure category was surprisingly similar with regard to years of education (Table 1). The proportion of participants in each exposure category did not differ significantly for 0-11 years of education, 12 years of education, or 13-15 years of education. Among participants reporting greater than or equal to 16 years of education, the proportion of respondents in the comorbid group did not differ significantly from either the reference group or the chronic pain only group. However, the chronic pain only group did contain a significantly smaller proportion of participants reporting greater than or equal to 16 years of education. Overall, there were significant differences between categories of education within each exposure category, as demonstrated by the Rao-Scott Chi-Square test results ($\chi^2 = 16.8$, $p = 0.0099$).

Never smokers were most prevalent in the sample, overall (44.9%, S.E. = 1.7), as seen in Table 1. Similarly, the distribution of the group with only chronic pain during the past 12 months by smoking status was 45.3 percent (S.E. = 1.7) never smokers, 32.2% (S.E. = 1.8) former smokers, and 22.5% (S.E. = 1.1) current smokers. The reference group consisted of 59.3% (S.E. = 5.4) never smokers, 24.3 (S.E. = 5.3) current smokers, 16.4% (S.E. = 3.0) former smokers. The comorbid group was mostly current smokers (40.5, S.E. = 3.3), with never smokers (35.0%, S.E. = 2.9) and former smokers (24.5%, S.E. = 3.0) following. Notably, the proportion of never smokers in the comorbid group is significantly lower than in the other two exposure categories. Also, current smokers represent a significantly higher proportion of the comorbid group than the chronic pain only group, but do not the reference group.

Table 1: Sample characteristics by depressive disorder and chronic pain condition diagnosis

Variable	-DD, -CP* (n = 305)	-DD, +CP (n = 2807)	+DD, +CP (n= 498)	Overall (N= 3610)
Alcohol Use Disorder (Yes)	2.00 (1.36) [a]	0.68 (0.15) [a]	3.82 (1.13) [a]	1.08 (0.15)
Age^	41.5 (1.28)[a]	56.4 (0.52)[b]	45.9 (0.95)[a]	54.4 (.50)
Sex (Male)	40.66 (4.42)[a]	41.48 (1.48)[a]	33.68 (2.95)[a]	40.53 (1.21)
Race				
Non-Hispanic White	37.35 (5.04) [a]	76.78 (1.89)[b]	70.70 (3.71)[b]	74.17 (2.04)
African American	2.28 (1.36) [a]	1.81 (0.28) [a]	1.27 (0.35) [a]	1.78 (0.27)
Asian	16.82 (2.37) [a]	5.48 (0.62)[b]	4.19 (0.76)[b]	5.89 (0.62)
Hispanic	42.63 (4.46) [a]	13.62 (1.29)[b]	17.76 (2.61)[b]	15.50 (1.43)
Other	0.91 (0.78) [a]	2.32 (0.45)[b]	6.08 (1.32)[c]	2.65 (0.48)
Employment Status				
Employed	65.52 (4.82) [a]	30.65 (1.71)[b]	45.00 (2.96)[b]	50.70 (1.51)
Unemployed	5.53 (2.10) [a]	7.60 (0.98) [a]	4.44 (1.01) [a]	7.13 (0.83)
Not In The Labor Force	28.96 (4.79) [a]	41.75 (1.69) [a]	50.56 (3.03)[b]	42.17 (1.62)
Region of Country				
Northeast	17.75 (3.63) [a]	19.48 (4.20) [a]	26.04 (6.50) [a]	20.09 (4.18)
Midwest	10.85 (3.04) [a]	25.46 (2.52)[a,b]	19.81 (2.84)[b]	24.12 (2.28)
South	26.47 (5.19) [a]	28.92 (3.31) [a]	30.25 (4.33) [a]	29.02 (3.14)
West	44.93 (4.58) [a]	26.14 (2.50)[b]	23.89 (2.91)[b]	26.79 (2.36)
Years of Education				
0-11	21.72 (2.52)[a]	19.9 (8.42) [a]	27.96 (2.81)[a]	25.10 (1.35)
12	23.54 (3.78)[a]	32.89 (1.18) [a]	26.66 (3.13) [a]	31.70 (1.03)
13-15	27.30 (4.44) [a]	25.76 (1.42) [a]	25.89 (2.83) [a]	25.86 (1.34)
Greater than or equal to 16	27.45 (3.76) [a]	16.39 (1.12)[b]	19.48 (2.34) [a,b]	17.33 (1.08)
Smoking Status				
Current Smoker	24.28 (5.31) [a,b]	22.52 (1.12) [a]	40.48 (3.32)[b]	24.58 (1.04)
Former Smoker	16.41 (3.03) [a]	32.19 (1.77) [b]	24.51 (3.03) [a,b]	30.52 (1.69)
Never Smoker	59.31 (5.44) [a]	45.29 (1.72) [a]	35.01 (2.93)[b]	44.91 (1.65)
Marital Status				
Never Married	20.38 (3.55) [a]	7.63 (0.83)[b]	18.83 (2.59) [a]	9.64 (0.84)
Married/Cohabitating	64.96 (4.16) [a]	62.65 (1.53) [a]	45.49 (3.02)[b]	60.62 (1.36)
Separated/Divorced/Widowed	14.66 (2.90) [a]	29.72 (1.57)[a]	35.67 (3.50)[b]	29.74 (1.29)
FHDD (Yes)	14.11 (6.17) [a]	10.57 (1.50) [a]	24.21 (2.96) [a]	12.13 (1.41)

***Reference Group=No past 12 month depressive disorder and no chronic pain condition**
Values reported are % (S.E.) unless otherwise noted [^ = mean (S.E.)]
Percentages are weighted percentages
CP=chronic pain condition, DD=depressive disorder
FHDD=Family History of Depressive Disorder
Values within each row that do not share subscripts differ significantly ($p<0.05$).

Table 2: Rao-Scott χ^2 Statistics, p-values, and number of missing observations for alcohol use disorder and potential confounding variables.

Variable	Rao-Scott χ^2 Statistic	p-value	# of Missing Observations
Alcohol Use Disorder Diagnosis	20.9739	< 0.0001	0
Age*	109.51	< 0.0001	0
Sex	5.2379	0.0729	0
Race	214.708	< 0.0001	0
Employment Status	19.4736	0.0006	3
Region of Country	25.2706	0.0003	0
Years of Education	16.839	0.0099	0
Smoking Status	48.0087	< 0.0001	0
Marital Status	63.4879	<. 0.0001	0
Family History of Depression	23.3298	< 0.0001	2262

* t-statistic
Note: Race and Alcohol Use Disorder Diagnosis each had one cell with fewer than 5 observations.
n=3610

Table 1 shows the overall proportions of participants by marital status, as well as the proportions within each exposure category. Separated/divorced/widowed participants constituted 29.7% (S.E. = 1.3) of the overall sample, 14.7% (S.E. = 2.9) of the reference group, 10.6% (S.E. = 1.5) of the group with only chronic pain during the past 12 months, and 35.7% (S.E. = 3.5) of the comorbid group. Never married participants represented 9.6% (S.E. = 0.8) of the overall sample, 20.4% (S.E. = 3.6) of the reference group, 7.6% (S.E. = 0.8) of the group with only chronic pain during the past 12 months, and 18.8% (S.E. = 2.6) of the comorbid group. The proportion of participants who were married/cohabitating or separated/divorced/widowed in the comorbid group differed significantly from the proportions in the other two exposure groups. Participants reporting never being married made up a significantly small proportion of the chronic pain only group than the reference group or the comorbid group.

The distribution of participants reporting their male and/or female childhood caretaker experienced periods of sadness lasting 2 or more weeks (representing family history of depressive disorders) was also calculated and is displayed in Table 1. In the sample, overall, 12.1% (S.E. = 1.4) of participants indicated a family history of depression. The prevalence of family history of depression in the reference and comorbid groups was 14.1% (S.E. = 6.2) and 24.2% (S.E. = 3.0), respectively. The group of participants reporting only chronic pain during the past 12 months had the lowest percentage of participants reporting a family history of depression (10.6%, S.E. = 1.5). The Rao-Scott chi-square statistic for family history of depression was 23.33 ($p = <0.0001$), however this variable was missing observations for greater than 60% of the populations, making the validity of this measurement questionable.

During the analysis of the characteristics of the sample, the amount of missing data was noted for each variable. Note that missing values indicated the number of missing observation among the 3,610 participants included in the subpopulation analysis. Age, alcohol use disorder, sex, years of education, smoking status, marital status, region, and race had no missing observations. Employment status was missing for three participants (0.1%). Family history of depression had the most missing data, with 2,262 (62.7%) missing observations (Table 2). Since the outcome variable was not missing any data, no imputation or sensitivity analyses were conducted.

Before conducting the logistic regression analysis, each potential confounding variable identified in the literature was evaluated using the criteria for potential confounding variables (see methods section for descriptions of the three criteria). The results of these analyses are presented in Table 3. Age, years of education, and smoking status met all three criteria, as written in the methods section, and were considered important confounding variables. No other confounders met all three criteria as written in the methods section.

Due to many empty or small cells, analyzing the second criteria was not straightforward for many of the potential confounding variables. For potential confounding variables with insufficient numbers of observations in each category, i-1 (i=number of categories) dichotomous dummy variables were created, and all i-l dummy variables were included in the bivariate analysis used to evaluate criteria two. The results of these analyses are displayed in Table 3.

After using two dummy variables to evaluate criteria two, employment status met all three criteria for confounding. For years of education and region of the country, the creation of dummy variables did not completely eliminate the problem of cells containing zero observations. Despite this challenge, the data was sufficient to determine that years of education met criteria two for confounding and region of the country did not.

Marital status, race/ethnicity, and family history of depression did not have a sufficient number of observations among the reference group to assess criteria two. For marital status and race/ethnicity, all of the dummy variables also had insufficient observations in the

reference to evaluate criteria two. Due to this feature of the sample, it is not possible to determine if these three potential confounding variables meet all three criteria for confounding. These results are displayed in Table 3.

After evaluating the descriptive statistics for the subpopulation and the criteria for confounding, logistic regression analysis was conducted to determine the association between comorbid chronic pain conditions and depressive disorders during the past 12 months and alcohol use disorders during the past 12 months. The results of these analyses are presented in Table 4.

The first logistic regression analysis, resulting in the crude model, included only the exposure (comorbid) as an independent predictor of past 12 month alcohol use disorder. The crude model showed that participants with comorbid chronic pain conditions and depressive disorders during the past 12 months had 1.941 (0.394, 9.569) times the odds of having an alcohol use disorder during the past 12 months than participants without chronic pain conditions or depressive disorders during the past 12 months. Participants with at least one chronic pain condition but no depressive disorders during the past 12 months had 0.333 (0.068, 1.63) times the odds of having an alcohol use disorder during the past 12 months than participants without chronic pain conditions or depressive disorders during the past 12 months. Neither associated was found to be statistically significant α=0.05. The fit statistics for the crude model were c = 0.584 and AIC (intercept with covariates) = 6,230,285.70.

Table 3: Test results from the *a priori* method for identifying confounding variables. (α=0.05)				
Potential Confounders	**Dummy Variables**	**Criteria #1**	**Criteria #2**	**Criteria #3**
Sex		not met p=0.0729	not met p=0.8299	met
Years of education	Ref= at least 16	met p=0.0099	met*^	met
	0-11	< Ref.	< Ref.	
	12	< Ref.	I.O.	
	13-15	< Ref.	< Ref.	
Smoking status	Ref= Former	met p<.0001	met p<.0001	met
	Current	< Ref.	> Ref.	
	Never	< Ref.	< Ref.	
Marital status	Ref= Previously	met p<.0001	I.O.*	met
	Never	< Ref.	I.O.	
	Married	> Ref.	I.O.	
Region	Ref= Northeast	met p=0.0003	not met‡	met
	South	< Ref.	p=0.1760	
	West	< Ref.	p=0.7959	
	Midwest	< Ref.	I.O.	
Employment status	Ref= NILF**	met p=0.0006	met*	met
	Employed	> Ref.	> Ref.	
	Unemployed	< Ref.	p=0.0782	
Race/ethnicity	Ref= Other	met p<.0001	I.O.*	met
	Asian	< Ref.	I.O.	
	Hispanic	< Ref.	p=0.9415	
	African American	< Ref.	I.O.	
	White	> Ref.	p=0.4678	
Family history of depression		met Yes > No p<.0001	I.O.	met
Age		Met (+) p<.0001	Met (-) p<.0001	met

P-values derived by Rao-Scott Chi-Squared statistic for categorical variables and t-tests for continuous variables.
I.O. = Insufficient Observations (unable to evaluate relationship due to empty cells)
***based off analysis of (i-1) dummy variables, where i=number of categories (criteria met if at least one dummy variable is significant at α=0.05).**
****Not In Labor Force, (+) = positive association, (-) = negative association**

Table 4: Results from Logistic Regression Analyses of Alcohol Use Disorders and Comorbid Chronic Pain and Depressive Disorders. Unadjusted and Adjusted models.

Parameter	Estimate	Standard Error	POR	95% Confidence Limits	
Crude Model					
Intercept	-3.8894	0.69			
Comorbid (+DD, +CP)	0.6632	0.8051	1.941	0.394	9.569
Comorbid (-DD, +CP)	-1.1005	0.8021	0.333	0.068	1.63
Standard Model					
Intercept	-0.2752	2.5147			
Comorbid (+DD, +CP)	-0.9601	0.8182	0.383	0.073	1.996
Comorbid (-DD, +CP)	-1.6463	1.0557	0.193	0.023	1.623
Sex	-1.2805	0.5169	0.278	0.098	0.789
Years of Education	0.3676	0.4795	1.444	0.549	3.801
Employment Status	0.0346	0.3464	1.035	0.515	2.083
Marital Status	0.1558	0.4032	1.169	0.518	2.637
Smoking Status	0.4127	0.4623	1.511	0.594	3.841
Region of the Country	0.0247	0.3068	1.025	0.552	1.904
Race/Ethnicity	-0.1305	0.4174	0.878	0.378	2.038
Family History of Depression	0.728	0.8673	2.071	0.36	11.921
Age	-0.0759	0.0181	0.927	0.894	0.961
Adjusted Model					
Intercept	-1.6865	0.8952			
Comorbid (+DD, +CP)	0.902	0.7763	2.464	0.529	11.477
Comorbid (-DD, +CP)	-0.3919	0.7627	0.676	0.149	3.064
Age	-0.0607	0.0127	0.941	0.918	0.965

CP=Chronic pain condition, DD=Depressive disorder
Reference for comorbid= -DD, -CP
POR=prevalence odds ratio

The second model, the standard model, included all variables identified as potential confounding variables in the existing literature, regardless of the potential confounding variable meeting the criteria for confounding. The standard model showed that participants with comorbid chronic pain conditions and depressive disorders during the past 12 months

had 0.383 (0.073, 1.996) times the odds of having an alcohol use disorder during the past 12 months than participants without chronic pain conditions or depressive disorders during the past 12 months after adjusting for sex, years of education, smoking status, marital status, employment status, region of the country, family history of depression, age, and race/ethnicity. Participants with at least one chronic pain condition but no depressive disorders during the past 12 months had 0.193 (0.023, 1.623) times the odds of having an alcohol use disorder during the past 12 months than participants without chronic pain conditions or depressive disorders during the past 12 months, after adjusting for sex, years of education, smoking status, marital status, employment status, region of the country, family history of depression, age, and race/ethnicity. In both cases, we fail to reject the hypothesis that there is no association between the exposure and outcome, because neither prevalence odds ratio achieves statistical significance at α=0.05. The only potential confounding variables to achieve statistical significance in the standard model were sex [POR=0.278 (0.098, 0.789)] and age [POR=0.927 (0.894, 0.961)]. Although age, smoking status, employment status, and years of education met all three criteria for confounding, smoking status and employment status were not significant at α=0.05 in the standard model. The fit statistics for the standard model were c = 0.841 and AIC (intercept with covariates) = 2,841,554.80.

The initial adjusted model was derived by retaining the two confounding variables that achieved statistical significance at α=0.05 in the standard model, age and sex. However, after removing all of the nonsignificant confounding variables, sex (p= 0.1693) did not achieve significance at α=0.05 when it was included with only age and the exposure

variable in a logistic model. Since sex did not meet the criteria for confounding and was not statistically significant, it was dropped from the adjusted model, as well.

The final, adjusted model, reported in Table 4, includes the exposure variable and age as covariates. In the final adjusted model, participants with comorbid chronic pain conditions and depressive disorders during the past 12 months had 2.464 (0.529, 11.477) times the odds of having an alcohol use disorder during the past 12 months than participants without chronic pain conditions or depressive disorders during the past 12 months, after adjusting for age. Participants with at least one chronic pain condition but no depressive disorders during the past 12 months had 0.676 (0.149, 3.046) times the odds of having an alcohol use disorder during the past 12 months than participants without chronic pain conditions or depressive disorders during the past 12 months, after adjusting for age. In both cases, the association did not achieve statistical significance at α=0.05. Age was the only variable to achieve statistical significance in the adjusted model, with a prevalence odds ratio of 0.941 (0.918, 0.965). This can be interpreted as, for each one year increase in age, the odds of having an alcohol use disorder during the past 12 months decrease by 5.49%, after adjusting for comorbidity status of chronic pain conditions and depressive disorders during the past 12 months. The fit statistics for the adjusted model were c = 0.761 and AIC (intercept with covariates) = 5,757,003.40.

Comparing the fit statistics for the three models, the crude model fit most poorly. This is evident because the c-statistic was lowest and the AIC was highest for the crude model, compared to the other two models. The standard model was the best fitting model, with c

= 0.841 and AIC (intercept with covariates) = 2,841,554.80. The AIC value for the next best fitting model, the adjusted model, is more than twice as high as the AIC value of the standard model, indicating the standard model is a much better fit for the data.

Chapter IV: Discussion

Despite the association between comorbidity status of chronic pain conditions and depressive disorders during the past 12 months and alcohol use disorder during the past 12 months not achieving statistical significance in any of the logistic regression models, much can still be learned from the results of this analysis. First, our results suggest a positive association between comorbid pain and depressive disorders and alcohol use disorders, although we did not achieve statistical significance. Knowing that depressive disorders and chronic pain conditions are each independently associated with alcohol use disorders, the results of this analysis suggest that further investigation into the effect of comorbid diagnosis on alcohol use disorder is warranted.[14,18,20,23,34]

Further study is also warranted because the direction of the association between comorbidity status and alcohol use disorder changed after adjusting for all potential confounding variables found in the literature. This could be a result of inadequate sample size to model all of the variables in the model. Since many of the confounding variables did not meet the criteria for confounding, and several had insufficient numbers of observations, it's probable that the estimates of the prevalence odds ratios for all model variables are unreliable. This is particularly true because SAS does not have procedures for analyzing complex survey data when some cells contain zero observations. Given the limitations of this dataset, it's reasonable to evaluate the results based off the most parsimonious model, which was the adjusted model.

The finding that after adjusting for age the participants with comorbid chronic pain and depression during the past 12 months have 2.5 times the odds of alcohol use disorder during the past 12 months, compared to participants with neither chronic pain nor depression during the past 12 months is interesting, even if it isn't statistically significant. It is also consistent with the original hypothesis. The direction of the association between participants with chronic pain but not depression during the past 12 months compared to participants with neither chronic pain nor depression during the past 12 months is unexpected. Since chronic pain is independently associated with alcohol use disorders, it follows that the association between participants with chronic pain conditions but not depressive disorders during the past 12 months and participants without chronic pain or depression during the past 12 months would result in a prevalence odds ratio greater than or equal to one.[14,18-20] However, although not statistically significant, all three models result in a prevalence odds ratio that is less than one for the comparison between these two groups.

Regarding the characteristics of participants with comorbid chronic pain conditions and depressive disorders during the past 12 months, one trait that sticks out is that family history of depression is about twice as prevalent in the group with comorbid chronic pain and depression (24.2%), compared to the overall sample (12.1%). Despite this, the differences in the proportion of participants in each exposure category reporting a family history of depression was not achieve statistical significance (Table 1). Family history of depression did have the highest proportion of missing data out of all the variables analyzed, therefore this observation should be interpreted with caution.

Another notable characteristic is that the group of participants with comorbid chronic pain conditions and depressive disorders is only 33.7% (S.E. = 3.0) male. The other two exposure categories are approximately 41 percent male. It's also interesting that the overall sample is 40.5% (S.E. = 1.2) male. Since one of the inclusion criteria for this analysis is that the participant must have reported experiencing at least one chronic pain condition during their lifetime, it's not entirely surprising that the proportion of the subpopulation who is male is less than 50 percent, because chronic pain is more prevalent among females.[35]

It is also notable that the group with chronic pain but not depression during the past 12 months has an average age (56.4 years that is 10 years or more above the average age for the other two exposure categories. This category also has the largest number of observations, so it is the least prone to the effects of extreme values artificially inflating the mean. One potential explanation for this difference between groups is that at least one of the conditions (e.g. arthritis/rheumatism) included in the chronic pain variable is associated with advanced age.[36] Additionally, since arthritis/rheumatism is assumed to be present during the past 12 months but was not confirmed by a specific survey question, it's possible that some participants in this group were misclassified and belong in the reference group. An example of how this could happen is if a participant experienced arthritis in the past but received a joint replacement to correct the arthritis greater than 12 months prior to being surveyed. Admittedly, it is unlikely that misclassification of this sort would be on a scale that would affect the outcome of the analysis.

In general, the results of the descriptive analysis don't show a clear pattern of characteristics that correlate more strongly with comorbid chronic pain and depression than the other two exposure categories. However, the comorbid group did demonstrate significant differences from the other two exposure categories for some risk factors. One explanation for the lack of clear patterns of correlation between comorbidity status and risk factors is that chronic pain and depression share many risk factors. Additionally, the bidirectional relationship between the two conditions may be masking some of the differences between groups when evaluating risk factors. There is some evidence that this may be an accurate explanation since the chronic pain only group and the comorbid group often do not differ from each other but do differ from the reference group, with respect to the characteristics shown in Table 1.

One major limitation of this study is that it is impossible to definitively conclude that the participants were experiencing their depressive disorder and their chronic pain condition at the same time. By using reports of depressive disorders and chronic pain conditions during the past 12 months, this limitation is partially addressed. Using past 30-day reports of each condition would better ensure the conditions were truly comorbid; however, the available sample size was insufficient to conduct any analyses using this criteria. Even using the inclusion criteria specified, the study encountered problems with small cell sizes and zero cells. To that end, several exposure categories have single digit cell sizes. Although the sample size is adequate, the distribution of the population is different than what was expected from studies evaluating pairwise prevalence of chronic pain conditions, depressive disorders, and alcohol use disorders. [11,12,14,30]

Another limitation is that the data utilized in this study were not specifically collected to answer this research question and the sample used may not adequately reflect the US population as a whole. Evidence of this is that the prevalence of alcohol use disorders in the overall sample is 1.1%, while the prevalence of alcohol use disorders during the past 12 months among the US population over the age of 18 from 2001-2002 was 8.5%, according to data from the National Institute of Alcohol Abuse and Alcoholism.[37] The low prevalence of alcohol use disorders in the sample would likely bias the association towards the null, since the misclassification is likely consistent across exposure categories and thus non-differential.

Due to the distribution of the outcome across the exposure categories, the analysis was not able to evaluate odds of alcohol use disorders during the past 12 months among participants reporting no chronic pain but experiencing a depressive disorder during the past 12 months. Evaluating this association would be of use because it can help determine the effect of comorbidity as opposed to experiencing only one exposure condition.

Another limitation is that the severity of the chronic pain conditions and depressive disorders are unknown. To control for this, employment status was included as a potential confounding variable, although it is an imperfect proxy variable. Additionally, although the survey utilized DSM-IV diagnostic criteria to determine if participants had symptoms meeting the definition of a depressive disorder or alcohol use disorder, the participants were not evaluated by a mental health professional, and the diagnostics are based on self-

report data.[2] Also, none of the chronic pain conditions, were medically confirmed, and participant's definitions of the various chronic conditions may not conform with medical diagnostic criteria. These features of the dataset increase the possibility for misclassification bias. Despite this, the misclassification is likely to be non-differential, biasing the results towards the null.

Since the data is cross-sectional, it is impossible to determine the temporal relationship between the exposures and outcome as well as the timeline for development of comorbid conditions. That is to say, it cannot be determined if the alcohol use disorder preceded the comorbid chronic pain and depressive disorder or vice versa. It also cannot be determined if chronic pain preceded the depressive disorder or vice versa. If significant temporal associations emerged, these relationships could be of clinical importance when treating patients with any of the three conditions evaluated in this study, as one or more condition may be a risk factor for the others.

Another limitation is that the dataset was collected more than 15 years ago. Despite the prevalence of mental illness in the United States population, the CPES is the most current, nationally representative dataset that describes the burden of disease from mental illness. Since the data was collected, the definition, level of medical acceptance, and treatment of chronic pain has changed significantly during this period. Also, the diagnostic criteria for alcohol abuse and dependence changed from the DSM-IV to DSM-V.[2,38] Another change from the DSM-IV to the current edition is that dysthymia is no longer recognized, and was replaced by persistent depressive disorder in DSM-V.[2,4,38] These changes do not invalidate

the results of this study, however interpreting the results using today's diagnostic standards may be misleading.

This study also has several strengths. First, it utilizes a nationally representative sample that accounts for the racial/ethnic diversity of the population. Second, very little research exists about the occurrence of alcohol use disorders among patients with chronic pain conditions and comorbid depressive disorder. Since some pharmaceuticals used to treat depressive disorders and chronic pain conditions often have contraindications for alcohol use, it's important to evaluate the potential risk of triple comorbidity.[25,39] Finally, this study provides some indication of factors that predict the occurrence of alcohol use disorders in patients with chronic pain conditions and major depressive disorders.

Based on these results, there are several potential directions for future research. First, evaluating the association studied under this analysis using a dataset with the same prevalence of alcohol use disorders as among the source population would provide a more reliable assessment of the relationship between chronic pain, depression, and alcohol use disorder. This line of research also lends itself to determining the impact of chronic pain severity and duration on depression and substance use patterns. Overall, analyzing the impact of comorbid chronic pain and depression on a third variable may be a case of putting the cart before the horse. Since the causal relationship between depression and chronic pain is still unclear, focusing future research efforts on teasing out the temporal nature of this relationship may have the most far reaching impact.[6]

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Appendix A: Original CPES Variable Codes

Family History
V05846 Growing up-mother/woman had periods of sadness for 2+ wks
V05879 Growing up-father/man had periods of sadness for 2+ wks

Chronic Pain
V04044 Ever had arthritis/rheumatism
V04079 12 months still have back/neck problems
V04080 Frequent or severe headaches in past 12 months
V04082 Still have other chronic pain in past 12 months
V04236 Had medically unexplained pain for 6+ mths in past year

Demographics
V09154 Work Status 3 categories
V09036 Sex
V07306 Age
V08992 Region of country
V08172 Years of education-4 categories
V08759 Marital Status-3 categories
V04594 Smoked more than 100 cigarettes in lifetime
V04597 Currently smoke
RANCEST Race/Ancestry

Complex Survey Parameters
SESTRAT SAMPLING ERROR STRATUM
SECLUSTR SAMPLING ERROR CLUSTER

Alcohol Use
V07519 DSM-IV Alcohol Abuse (12Mo)
V07521 DSM-IV Alcohol Dependence (12 month)

Depressive Disorders
V07603 DSM-IV Dysthymia (12 month)
V07655 DSM-IV Major Depressive Disorder w/ hierarchy (12Mo)
V07659 DSM-IV Major Depressive Episode (12Mo)