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ALCOHOL USE AS A PRECIPITANT AND COMORBIDITY IN PRIMARY HEADACHE

A Dissertation
presented in partial fulfillment of requirements
for the degree of Doctor of Philosophy
in the Department of Psychology
The University of Mississippi

by

RACHEL ELIZABETH DAVIS

August 2016

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ABSTRACT

Migraine and tension-type headache (TTH) are two of the most prevalent pain conditions diagnosed throughout the world and can be extremely disabling with many economic, social, physical and psychological health costs. A plethora of research indicates a strong, positive association between co-occurring psychiatric disorders (e.g., major depressive disorder, anxiety, panic) and migraine and TTH, however co-occurring alcohol-use disorders are relatively unexplored. The limited studies that have explored alcohol-use disorders have produced mixed findings, potentially as a result of differing methodology, sample source, and the debated precipitating nature of alcohol use on headache. An abundance of research suggests that many environmental and physiological factors precipitate or “trigger” headache, including stress, hormonal fluctuations (in women), weather events, and changes in sleep and eating habits, although prevalence rates for many triggers vary greatly across studies, including alcohol (6.1-51.5%). The inconsistencies in trigger endorsement may be influenced by the retrospective nature of most prior studies, medical advice to avoid known triggers, and various assessment approaches. Given the conflicting data regarding alcohol use and headache, the purpose of the current study was to examine existing literature related to alcohol and headache using a meta-analysis and in-depth qualitative review.

The meta-analysis explored the precipitating effects of alcohol on migraine and TTH. The meta-analysis and subsequent meta-regressions were run in R statistical software utilizing DerSimonian-Laird random-effects methods. Forty-five articles met inclusion criteria for the

study. Results of the meta-analysis found significant heterogeneity across and within these 45 studies $\tau^2 = 0.95$; $I^2 = 97.5\%$ (95% CI: 97.1% to 97.8%), which limited interpretation. Overall, 22% (95% CI: .17 to .28) of headache sufferers ever queried about alcohol as a trigger endorsed its precipitating effect. This precipitating effect did not significantly differ between migraine and TTH ($p = .15$) nor between migraine with and without aura ($p = .90$). Twenty-eight percent of individuals endorsed red wine as a trigger, 14% endorsed spirits, 12% endorsed white wine, and 10% endorsed beer or sparkling wine; however difference in endorsement rates was not significantly different ($p = .06$). The precipitating effect in relation to frequency and quantity of consumption was not analyzed statistically due to too few studies meeting inclusion criteria. Endorsement rates were not impacted by method of assessment. These findings aggregate the literature on alcohol as a trigger for headache and indicate future directions in research on this topic.

The in-depth qualitative review highlighted three main areas of current research in nine studies that explored alcohol-use disorders (AUDs) and headache: 1) alcohol-use disorders among headache sufferers, 2) headache disorders among individuals diagnosed with alcohol-use disorders, and 3) problematic alcohol use (PAU) assessed with validated measures among headache sufferers. In studies that explored rates of AUDs in headache samples, migraineurs without aura and TTH sufferers did not endorse high rates of AUDs, however migraineurs with aura and migraineurs among a chronic pain sample did endorse higher rates of AUD compared to individuals without migraine. Additionally, in studies that examined rates of headache disorders among substance use disorders inpatients, risk of migraine was significant among individuals with an alcohol dependence (but not alcohol abuse) diagnosis. Furthermore, in studies that investigated PAU in headache samples, TTH sufferers reported moderate rates (16.1%) of PAU

whereas migraineurs reported comparatively low rates (4.6%-5.2%). However, differences in validated measures used limit comparisons of these endorsement rates. Differences in this area of research suggest the need for a more uniform approach to future research on this topic.

LIST OF ABBREVIATIONS

AUD Alcohol Use Disorder

HA Headache

MA Migraine With Aura

MWA Migraine Without Aura

PAU Problematic Alcohol Use

SUD Substance Use Disorder

TTH Tension-Type Headache

TABLE OF CONTENTS

ABSTRACT.....	ii
LIST OF ABBREVIATIONS.....	v
LIST OF TABLES.....	viii
LIST OF FIGURES.....	ix
INTRODUCTION.....	1
Diagnosis of Migraine and Tension-Type Headache.....	1
Role of Alcohol and Substance Use in Migraine.....	3
Alcohol Use Among Headache Sufferers.....	11
Goals of the Present Study.....	13
Hypotheses.....	14
METHODS.....	16
Procedures.....	16
Statistical Analyses.....	17
RESULTS.....	19
Study Goal 1 Search and Selection.....	19
Alcohol as a Trigger for All Headache Diagnoses.....	19
Alcohol as a Trigger for Specific Headache Diagnoses.....	20
Migraine vs. Tension-Type Headache.....	20
Migraine With Aura vs. Without Aura.....	21
Alcohol as a Trigger by Type.....	21

Alcohol as a Trigger by Quantity and Frequency of Consumption.....	22
Method of Assessment.....	23
Study Goal 2 Search and Selection.....	24
Alcohol Use Disorder Among Headache Sufferers.....	24
Headache Conditions Among Substance Abusers.....	27
Problematic Alcohol Use Among Headache Sufferers.....	28
DISCUSSION.....	31
Study Goal 1.....	31
Study Goal 2.....	36
General Conclusions.....	40
BIBLIOGRAPHY.....	44
Bibliographies for Meta-Analysis.....	58
Bibliographies for Qualitative Review.....	63
APPENDIX.....	65
VITA.....	96

LIST OF TABLES

1. Characteristics of Study Samples.....	70
2. Meta-Analysis of Trigger by Headache Diagnosis.....	73
3. Meta-Analysis of Trigger by Alcohol Type.....	74
4. Meta-Regression of Trigger by Alcohol Type.....	75

LIST OF FIGURES

1. Flowchart of Meta-Analysis.....	66
2. Flowchart of Qualitative Review.....	67
3. Forest Plot of Alcohol as a Trigger for any Headache Diagnosis.....	76
4. Meta-Regression of Headache Diagnosis.....	77
5. Meta-Regression of Type of Alcohol.....	78
6. Meta-Regression of Year in All Headache Diagnoses.....	79
7. Meta-Regression of Proportion of the Sample Female in All Headache Diagnoses.....	80
8. Forest Plot of Alcohol as a Trigger for Migraine.....	81
9. Forest Plot of Alcohol as a Trigger TTH.....	82
10a. Meta-Regression of Year in Migraine v. TTH.....	83
10b. Meta-Regression of Year by each Diagnosis.....	83
11a. Meta-Regression of Proportion of the Sample Female in Migraine v. TTH.....	84
11b. Meta-Regression of Proportion of the Sample Female by each Diagnosis.....	84
12. Forest Plot of Alcohol as a Trigger for Migraine With Aura.....	85
13. Forest Plot of Alcohol as a Trigger for Migraine Without Aura.....	86
14a. Meta-Regression of Year in MA v. MWA.....	87
14b. Meta-Regression of Year by each Diagnosis.....	87
15a. Meta-Regression of Proportion of the Sample Female in MA v. MWA.....	88
15b. Meta-Regression of Proportion of the Sample Female by each Diagnosis.....	88

16. Forest Plot of Trigger Effect of Beer.....	89
17. Forest Plot of Trigger Effect of Red Wine.....	90
18. Forest Plot of Trigger Effect of Sparkling Wine.....	91
19. Forest Plot of Trigger Effect of Spirits.....	92
20. Forest Plot of Trigger Effect of White Wine.....	93
21a. Meta-Regression of Year by Alcohol Type.....	94
21b. Meta-Regression of Year by each Alcohol Type.....	94
22a. Meta-Regression of Proportion of the Sample Female by Alcohol Type.....	95
22b. Meta-Regression of Proportion of the Sample Female by each Alcohol Type.....	95

CHAPTER 1

INTRODUCTION

Diagnosis of Migraine and Tension-Type Headache

Migraine and tension-type headache (TTH) are two of the most prevalent neurological disorders and pain conditions diagnosed throughout the world. In a systematic analysis of global burden of disease, Vos and colleagues (2012) found TTH and migraine to be the second and third most prevalent sequelae in the world, with only dental cavities having greater prevalence. Epidemiological data indicate that in the United States (US), 18% of women and 6% of men currently have migraine (Fukui et al., 2008; Hu, Markson, Lipton, Stewart, & Berger, 1999; Jette, Patten, Williams, Becker, & Wiebe, 2008) and 45% of women and 38% of men currently have TTH (Stovner et al., 2007). The prevalence of migraine in the US is comparable to prevalence rates throughout the world, although Europe has higher rates for both men (12%) and women (24%; Leonardi, Musicco, & Nappi, 1998). Similarly, prevalence of TTH in the US falls in the median range of global TTH prevalence, again with Europe having the highest rates for both men (72%) and women (65%; Stovner et al., 2007). Headache is often regarded as a women's health issue because migraine and TTH have significantly higher prevalence among women (3:1 Mig; 1.5:1 TTH) (Jelinski et al., 2006; Lyngberg, Rasmussen, Jorgensen, & Jensen, 2005; Stewart,

Lipton, Celentano, & Reed, 1992; Stovner et al., 2007). Migraine and TTH affect individuals throughout life, with both headache conditions reaching peak prevalence among individuals aged 25 to 44 (Jette et al., 2008; Lipton et al., 2002; Pryse-Phillips et al., 1992; Stovner et al., 2007). Migraine and TTH are associated with numerous negative consequences including significant reduction in quality of life, decreased work performance, increased health care costs, and other practical liabilities (Baskin & Smitherman, 2009; Hu et al., 1999; Lipton, Hamelsky, Kolodner, Steiner, & Stewart, 2000; Pryse-Phillips et al., 1992; Von Korff, Stewart, Simon, & Lipton, 1998). The frequency of headache and severity of associated negative consequences resulted in the World Health Organization ranking headache as one of the top 20 causes of disability worldwide (Leonardi et al., 1998).

The *International Classification of Headache Disorders* (ICHD-3 beta) classifies the most common headache types that are not attributable to secondary causes as primary headaches. Primary headaches include migraine and TTH, as well as other less common subforms. Migraine is characterized by recurrent attacks of severe headache and associated symptoms of autonomic nervous system dysfunction that may occur with or without aura symptoms (e.g., visual, sensory, or speech symptoms that precede the onset of head pain by no more than 60 minutes). Migraine pain is typically unilateral, pulsating/throbbing in quality, moderate to severe in intensity, and aggravated by routine physical activity. The onset of migraine is usually gradual and typically lasts between 4 and 72 hours (Lipton, Scher, Silberstein, & Bigal, 2008); however some data indicate that younger adult migraineurs often have otherwise prototypical attacks lasting fewer than four hours (Rains, Penzien, Lipchik, & Ramadan, 2001). Other common symptoms are nausea, vomiting, and sensitivity to light (i.e., photophobia) and sound (i.e., phonophobia) (Lipton et al., 2008). Migraine attacks that occur more than 15 days per month meet the criteria

for chronic migraine; a rare complication of migraine often associated with overuse of acute migraine pharmacological agents. (Lipton, Silberstein, & Dodick, 2008). While TTH is associated with recurrent attacks of headache, it differs from migraine in that TTH pain is typically bilateral, pressing/tightening in quality, mild to moderate in intensity, is not made worse by routine activity, is generally not accompanied by nausea, vomiting, photophobia, or phonophobia, and episodes can last between 30 minutes and 7 days. Tension-type headache is classified as infrequent (i.e., occurring ≤ 1 day per month), frequent (i.e., occurring > 1 day but < 15 days per month), or chronic (i.e., occurring ≥ 15 days per month), with chronic headaches sometimes unremitting (Lenaerts & Newman, 2008). Even though migraine and TTH are phenotypically different, both disorders have a wealth of literature supporting strong, positive associations between headache and co-occurring (comorbid) psychiatric disorders such as major depressive disorder (MDD), generalized anxiety disorder (GAD), panic disorder, social phobia, and bipolar disorder (Baskin, Lipchik, & Smitherman, 2006; Baskin & Smitherman, 2009; Beghi et al., 2010; Breslau & Davis, 1992; Breslau & Davis, 1993; Jette, et al., 2008; Marchesi et al., 1989; McIntyre et al., 2006; Oedegaard et al., 2006; Saunders, Merikangas, Low, Von Korff, & Kessler, 2008; Stewart, Breslau, & Keck, 1994; Swartz, Pratt, Armenian, Lee, & Eaton, 2000).

Role of Alcohol and Substance Use in Headache

Compared to the abundance of literature examining the prevalence and impact of mood and anxiety disorders among migraineurs and TTH sufferers, very few studies have examined relations between substance use disorders and headache, with these limited studies producing mixed findings. An early study of young adults by Breslau, Davis, and Andreski (1991) indicated that migraineurs were at greater risk to develop all substance use disorders than were individuals without headache. Comparably, a recent study by McDermott, Tull, Gratz, Houle, and

Smitherman (2014) among substance use inpatients found that migraine patients had higher rates of alcohol dependence than non-migraine patients. Additionally, patients with an alcohol dependence diagnosis were 3 times more likely to experience migraine than any other substance use diagnoses. Contrastingly, a population-based study by Saunders, Merikangas, Low, Von Korff, and Kessler (2008) found only drug dependence to be associated with migraine and TTH, while the other substance use disorders were not uniquely related to headache. Similarly, Breslau and Davis (1993) found among young adults illicit drug abuse and dependence to be significantly more common in migraineurs, however alcohol abuse and dependence were not. Moreover, in Domingues and Domingues' (2011) study of disordered alcohol use among medical students, results indicated that individuals without headache reported significantly higher rates of alcohol abuse and problematic drinking behaviors than migraineurs and TTH sufferers. Additionally, Beckmann, Seçkin, Manavgat, and Zorlu (2012) found a significantly higher incidence of migraine among methylamphetamine, cocaine, and heroin abusers than alcohol or cannabis abusers; however incidence of TTH was not significantly associated with any specific type of drug abuse. Furthermore, rates of alcohol abuse were not significantly different between migraineurs and TTH sufferers. Contrarily, in a study among neurology clinic patients, Domingues and colleagues (2013) found significantly higher rates of disordered alcohol use among TTH sufferers than migraineurs.

Additionally, some population-based studies have not observed higher prevalence rates of substance use disorders among migraineurs versus nonmigraineurs (Jette et al., 2008; Merikangas, Angst, & Isler, 1990; Swartz et al., 2000). In the most recent large-scale study on this topic, Jette et al. examined 36,984 individuals who were administered a structured diagnostic interview for psychiatric disorders and self-reported whether they had been diagnosed with

migraine by a physician. Results indicated no difference in 12-month prevalence of drug, alcohol, or substance dependence between migraineurs and nonmigraineurs. Differences in findings between the aforementioned studies may be a result of varying adherence to different DSM substance use disorders criteria as well as ICHD-II criteria for headache. Earlier studies conducted by Breslau et al. and Merikangas et al. utilized DSM-III criteria for diagnosing substance use disorders, whereas later studies utilized DSM-IV criteria, the latter of which more strictly defines dependence (Hasin et al., 2003). Moreover, Jette et al. and Merikangas et al. did not use ICHD-II criteria for migraine to diagnose migraine, which may have contributed to both studies' null findings regarding differences in prevalence rates between migraineurs and nonmigraineurs.

Furthermore, the mixed findings regarding comorbid headache and substance use disorders may be due to the debated precipitating nature of substance use, specifically alcohol use, on headache. A variety of both external and internal factors can precipitate, or “trigger,” headache (Fukui et al., 2008; Hauge, Kirchmann, & Olesen, 2010; Kelman, 2007; Van den Bergh, Amery, & Waelkens, 1987). Research on headache triggers has spanned decades, with the limitation that most studies have utilized retrospective recall, in which individuals are asked to identify environmental and physiological factors they believe may have caused previous headaches (Aamodt, Stovner, Hagen, Brathen, & Zwart, 2006; Fukui et al., 2008; Boardman, Thomas, Millson, & Croft, 2005; Hauge et al., 2010; Ierusalimschy & Filho, 2002; Karli, Zarifoglu, Calisir, & Akgoz, 2005; Kelman, 2007; Peatfield, 1995; Peatfield, Glover, Littlewood, Sandler, & Rose, 1984; Spierings, Ranke, & Honkoop, 2001; Van den Bergh et al., 1987; Wang et al., 2013). Using these methods, most studies indicate stress, environment (e.g., weather, wind, pollution), hormones in women, and diet (e.g., specific foods, alcohol, fasting) are the most

common triggers for headache, with many people endorsing more than one headache trigger (Aamodt et al., 2006; Fukui et al., 2008; Kelman 2007; Wang et al., 2013). Wang et al. provided headache patients with a list of 12 common triggers and asked them to identify how many items precipitated their headaches. Among migraineurs, 27.8% reported one trigger, 17.4% reported two triggers, 21.1% reported three triggers, 15.2% reported four triggers, and 18.5% reported at least five triggers. Among TTH patients, 35.8% reported one trigger, 29.3% reported two triggers, 15.9% reported three triggers, 9.1% reported four triggers, and 9.9% reported at least five triggers. Chi-square analyses indicated that reporting two triggers significantly differentiated TTH from migraine, whereas reporting four triggers significantly differentiated migraine from TTH. Kelman asked migraineurs to rate the frequency of triggers precipitating their migraine attacks and found that 40.4% reported triggers precipitated migraine occasionally, 26.7% reported triggers precipitated migraine frequently, and 8.8% reported triggers precipitated migraine very frequently. Boardman, Thomas, Millson, and Croft (2005) had headache sufferers indicate whether a specific trigger precipitated some headaches, most headaches, or all headaches and found that stress was the number one trigger endorsed by 71% of the sample (46% some headaches, 21% most headaches, 4% all headaches). Alcohol was reported as a trigger by 33% of the sample (28% some headaches, 4% most headaches, 1% all headaches). Even though the number of triggers and frequency of precipitation are important factors to consider in headache research and management, the majority of studies have focused solely on the types of triggers that precipitate headache.

In a comparison study of specific triggers for migraine and TTH among headache patients, Spierings and colleagues (2001) listed 18 triggers and asked participants to identify which items triggered their headaches. Stress/tension (84% M; 82% TTH), not eating on time

(82% M; 76% TTH), fatigue (79% M; 65% TTH), and lack of sleep (74% M; 71% TTH) were equally common triggers reported for both migraine and TTH, indicating that these items may be general headache triggers, possibly due to their involvement with the sympathetic nervous system. Weather (71% M; 35% TTH), smell (61% M; 24% TTH), smoke (61% M; 29% TTH), and light (50% M; 18% TTH) differentiated migraine from TTH, indicating that the olfactory system/sinuses may be more influential in migraine than TTH. No triggers differentiated TTH from migraine, suggesting some shared pathophysiology between the disorders. Alcohol was endorsed as a trigger by 42% of migraineurs and 29% of TTH patients. Additionally, Wang et al. (2013) compared 12 headache triggers in migraine and TTH patients and found sleep disturbance (40.1% M; 28.8% TTH), negative affect (34.2% M; 32.3% TTH), and sunlight (32.7% M; 20.9% TTH) to be the three most frequently endorsed triggers in both groups. Despite commonality in the type of headache triggers most frequently endorsed, migraineurs endorsed sleep disturbance and sunlight significantly more than TTH patients. Furthermore, change of weather (23.1% M; 9.6% TTH), wind (23.9% M; 14.5% TTH), odor (9.9% M; 4.4% TTH), noise (10.2% M; 4.4% TTH), and menstrual cycle (8.8% M; 2.3% TTH) were endorsed significantly more by migraineurs. Alcohol was reported as a trigger in 11.4% of migraineurs and 7.6% of TTH patients.

Similarly, Karli et al. (2005) examined trigger differences in headache patients with TTH, migraine with aura (MA), and migraine without aura (MwA), and found that out of the 18 triggers listed, 11 were common to all headache groups and two (i.e., pregnancy, oral contraceptives) were not endorsed by any headache group. Head and neck movements (48.4% TTH; 8.7% MA; 9.1% MwA) triggered TTH significantly more than MA and MwA; hunger (38.7% TTH; 73.9% MA; 72.7% MwA) and odors (0% TTH; 30.4% MA; 27.3% MwA)

triggered MA and MwA significantly more than TTH; and foods (6.5% TTH; 43.5% MA; 27.3% MwA) and sleeplessness (25.8% TTH; 65.2% MA; 45.5% MwA) triggered MA significantly more than MwA and TTH. Alcohol reportedly triggered TTH in 6.5% of patients and MwA in 6.1% of patients, however no patients with MA reported alcohol as a trigger. Dora, Yilmaz, Apaydin-Dogan, Özdemir-Karahasan, and Turkay, (2010) also examined trigger differences between headache patients with TTH, MA, and MwA by providing a list of 37 triggers and asking patients to identify which ones triggered at least one headache attack. The mean number of triggers reported did not differ between headache groups (11.87±5.14 TTH; 14.43±5.17 MA; 13.78±5.71 MwA), although women with MwA reported significantly more triggers than men with MwA (14.40±5.53 F; 8.71±4.66 M). The 10 most common triggers for each group were the same and endorsed with similar frequency. Bright light (43.6% TTH; 86.8% MA; 75.9% MwA), skipping meals (64.1% TTH; 88.7% MA; 89.1% MwA), and fermented foods (7.7% TTH; 20.8% MA; 21.7% MwA) triggered MA and MwA significantly more than TTH, whereas milk (25.6% TTH; 11.3% MA; 10.1% MwA) triggered TTH significantly more than MA and MwA. Overall, alcohol precipitated headache in 15.4% of TTH patients, 18.9% of MA patients, and 24.0% of MwA patients; however, within the TTH group a disproportionate number of men reported alcohol as a trigger (35.7% M; 4.0% F). Despite frequent endorsement of headache triggers, most existing studies in this area inquire only about broad categories of stimuli (e.g., diet/food, environment/weather, sleep) without attempting to parse out specific individual triggers (e.g., types of food/beverage, particular weather conditions, aspects of sleep).

In an attempt to isolate potential differential precipitation of headache attacks, some studies have made a distinction between alcohol (all forms), clear spirits, red wine, and white wine (Fukui et al., 2008; Littlewood et al., 1988; Mannix, Frame, & Solomon, 1997; Peatfield,

1995). Fukui et al. presented 200 migraineurs with a list of common triggers and asked them to select any items they believed triggered their migraine. They found that all migraineurs reported at least one trigger, with the most common being related to diet (e.g., cheese, chocolate, coffee, aspartame, alcohol) (84.5%), sleep (75.5%), environmental factors (e.g., allergy, pollution, wind, rain, changes in weather, odors) (68.5%), and stress (65%). Thirty-four percent of patients endorsed alcohol as a trigger, 19.5% endorsed red wine as a trigger, and 10.5% endorsed white wine as a trigger. Red wine precipitated migraine significantly more for women (22.2%) than men (7.9%). Other research relying on retrospective recall indicates that individuals are sensitive to alcohol (all forms) as a trigger and more sensitive to red wine than white wine or clear spirits, regardless of headache diagnosis (Mannix et al., 1997; Peatfield, 1995). Contrastingly, an experimental study by Littlewood et al., (1988) in which migraineurs with dietary triggers were randomly assigned to receive either red wine or a disguised vodka mixture, found that 80% of migraineurs who ingested red wine experienced migraine shortly thereafter, compared with none who received the vodka mixture. Similarly, Kaufman and Starr (1991) instructed 12 headache patients to ingest 90ml of red wine and found that all 12 patients developed a headache within two hours of consumption.

Various components of red wine (e.g., sulfites, tannins, histamines, phenols) are hypothesized to be responsible for higher incidence of headache following wine consumption compared to other alcohols (Krymchantowski & Jevoux, 2014). In an attempt to better understand the effects of specific wine components, Krymchantowski and Jevoux (2012/2013) conducted two studies with headache patients, one examining type of wine (i.e., cabernet sauvignon, tannat, malbec, merlot) and the other examining region of wine production (i.e., France, South America). In the first study (2012), 87.8% reported at least one headache within

12 hours of consuming any type of wine (33.4% of these patients reported a headache following consumption of each type of wine) and 12.2% reported no headache from any type of wine. Tannat triggered headache in 51.7% of patients, malbec triggered headache in 48.2% of patients, and cabernet sauvignon and merlot both triggered headache in <30% of patients. In the second study (2013), French wine triggered headache significantly more than South American wine (60.9% Fr; 39.1% SA) with only 17.4% of the sample reporting both wines triggering headache. Results of these studies indicate that tannins and phenolic flavonoid may be the wine components most responsible for headache following red wine consumption; however more research is needed to confirm this finding. The differences in endorsement of various types of alcohol as a trigger for headache may be attributable to differences in research methodology, lack of specificity regarding types of wine, and underlying behavioral differences in consumption. For instance, the results of Littlewood et al. (1988) suggest that red wine has a greater precipitating effect than alcohol when consumed at the same frequency and quantity. Whether real-world drinking behaviors reflect these patterns remains unexplored empirically.

Even though the majority of studies indicate similar findings regarding the general presence and nature of alcohol-related triggers, reported prevalence rates of alcohol as a trigger range from 6.1% to 51.5%. These wide differences in trigger endorsement may be influenced by medical advice to avoid known triggers (among clinic patients vs. non-treatment seeking samples), differences in regional attitudes towards alcohol, and the retrospective nature of most prior studies (Hauge et al., 2010; Karli et al., 2005; Kelman, 2007; Mannix et al., 1997; Nicoletti et al., 2008; Panconesi, 2008; Peatfield, 1995; Spierings et al., 2001; Van den Bergh et al., 1987). In view of limited knowledge concerning the physiological mechanisms involved in precipitation of headache, research has begun to focus on genetic vulnerability and neural activation in the

presence of triggers. One potential link between alcohol and headache is the presence (or lack thereof) of the alcohol dehydrogenase-2 genotype (ADH2), an enzyme integral to the metabolism of ethanol (García-Martín et al., 2010). Ethanol itself can potentiate neurogenic inflammatory responses (e.g., arterial vasodilation) that release sensory neuropeptides from trigeminal neurons, and the trigeminovascular system is widely acknowledged to be the central source of headache pain (Nicoletti et al., 2008). García-Martín and colleagues found a significantly lower prevalence of the ADH2 genotype among patients with migraine than healthy controls, suggesting the absence of this genotype may be associated with increased risk of headache attacks after alcohol consumption. Continuing research on alcohol as a trigger factor may shed light on the underlying mechanisms involved in headache attacks, as well as have implications for how to better manage the disorder (Fukui et al., 2008; Panconesi et al., 2011; Yokoyama et al. 2012).

Alcohol Use Among Headache Sufferers

Despite the numerous aforementioned studies indicating a precipitating relationship between alcohol consumption and headache, little research has been conducted examining relations between specific factors associated with alcohol consumption (e.g., frequency, quantity, type) and clinically-relevant headache variables beyond a diagnosis (e.g., frequency, intensity, headache-related disability). Most prior studies exploring the nature of alcohol use among migraineurs and TTH sufferers have utilized retrospective recall, included large population-based samples not at specific risk of alcohol abuse, and assessed quantity and frequency of consumption only (Aamodt et al., 2006; Boardman et al., 2005; Milde-Busch et al., 2010; Molarius, Tegelberg, & Öhrvik, 2008; Yokoyama et al., 2012; Yokoyama et al., 2009; Zlotnik et al., 2014). For instance, Milde-Busch et al. examined frequency of beer, wine, and cocktail

consumption among high school students with migraine, TTH, both migraine and TTH, and no headache. Beer and wine were not associated with increased prevalence of any headache; however consumption of cocktails were associated with a higher prevalence of headache for individuals with both migraine and TTH (OR = 3.4 for ≥ 1 cocktail per week, OR = 2.6 for < 1 cocktail per month, OR = 2.0 for < 1 cocktail per week). Overall, students with migraine, TTH, both headache conditions, and no headache reported similar frequencies and quantities of beer, wine, and cocktail consumption. Additionally, Molarius and colleagues studied headaches in relation to heavy drinking (half a bottle of strong liquor or corresponding amount of wine or beer at the same occasion) and found that 27.8% of female heavy drinkers reported having headaches, compared with 20.6% of women who never drank, although no association between heavy alcohol use and headache was found for men. Overall, there was an inverse association between heavy alcohol use and headache, with the prevalence of headache decreasing as frequency of heavy alcohol use increased (Odds Ratio [OR] = 1 for non-heavy drinkers, OR = .90 for seldom heavy drinkers, OR = .70 for at least monthly heavy drinkers).

Similarly, Aamodt et al. (2006) found the prevalence of migraine to be inversely related to units of alcohol consumed over the past 2 weeks (OR = 1 for abstainers, OR = .80 for 1-4 units, OR = .60 for 4-14 units, OR = .50 for > 14 units); however prevalence of TTH remained stable across units of alcohol consumed over the past 2 weeks (OR = 1 for abstainers, OR = .90 for 1-4 units, OR = .90 for 4-14 units, OR = .80 for > 14 units). Overall, 63% of the sample reported alcohol consumption in the past 2 weeks, with an equal distribution between headache sufferers and non-headache controls. Yokoyama et al. (2009) examined specific units of alcohol consumed per day and also found an inverse dose-response relationship for both men (OR of headache = 1 for non-drinkers, OR = .76 for < 1 unit, OR = .56 for < 2 units, OR

= .55 for < 3 units, OR = .51 for \geq 3 units) and women (OR = 1 for non-drinkers, OR = .77 for < 1 unit, OR = .72 for < 2 units, OR = .39 for < 3 units, OR = .59 for \geq 3 units).

Researchers generally attribute this inverse relationship to avoidance of alcohol, especially in large quantities, because of its potential to trigger an attack as described previously (Aamodt et al., 2006; Molarius et al., 2008; Panconesi, 2008; Panconesi et al., 2011; Yokoyama et al., 2012; Yokoyama et al., 2009).

To better understand alcohol consumption among headache sufferers within a clinical setting, Mannix and colleagues (1997) reviewed 8 years of medical charts at a specialty headache center and found that 12% of treatment-seeking patients reported drinking more than 1 alcoholic beverage per week. The percentage of headache patients who consumed alcohol was comparable to the percentage of general medicine patients. Although Mannix and colleagues did not assess quantity of consumption, their results indicate a lower prevalence of alcohol consumption among treatment-seeking headache sufferers than among headache sufferers in the general population (31%; Aamodt et al., 2006), perhaps because clinic patients have more severe headache and receive instructions to avoid common triggers (Fukui et al., 2008; Panconesi et al., 2011). Further research is needed to better understand relations between alcohol consumption and headache among different populations, using prospective designs, and assessing the impact of alcohol on other headache-related variables.

Goals of Present Study

The overall aim of this dissertation was to meta-analytically and systematically explore extant literature related to alcohol and headache. To achieve this overall goal, the project comprised of one meta-analysis and one qualitative analysis. The aim of the meta-analysis was to integrate the findings of all the literature pertaining to alcohol as a trigger for migraine and

tension-type headache. Research on this topic has been conducted utilizing various methods and has produced inconsistent findings. A meta-analysis of these findings provided a more precise understanding of the potential precipitating effects of alcohol on headache. While a meta-analysis of the relationship between headache and alcohol-use disorders was planned, due to the limited amount and heterogeneous nature of the current research, a qualitative analysis was more appropriate. The aim of the qualitative analysis was to explore relationships between headache and alcohol-use disorders. Given that comorbid relationships between primary headache disorders and many other psychological disorders are well established, a systematic review of the literature regarding alcohol-use disorders would expand the field's understanding of another comorbid disorder with headache.

Hypotheses

The following goals and hypotheses were proposed:

Study Goal 1: To examine the precipitating effects of alcohol on migraine and tension-type headache.

Hypothesis 1a: Alcohol consumption would be significantly associated with an increased probability of both migraine and tension-type headache.

Hypothesis 1b: Alcohol consumption would have a stronger precipitating relationship with migraine than tension-type headache.

Hypothesis 1c: The increased probability of migraine and tension-type headache would not be affected by the type of alcohol consumed.

Hypothesis 1d: Alcohol consumption would equally precipitate migraine with aura and migraine without aura.

Hypothesis 1e: Higher quantity of alcohol consumed per sitting would be associated with increased probability of headache.

Hypothesis 1f: Higher frequency of alcohol consumption would be associated with higher probability of headache.

Hypothesis 1g: The method of assessment would moderate the inconsistent findings of previous studies.

Study Goal 2: To examine the relationship between alcohol-use disorders and primary headache disorders.

Hypothesis 2a: Compared to the general population, individuals with migraine and tension-type headache would be at greater risk for diagnosed alcohol-use disorders.

Hypothesis 2b: Compared to the general population, individuals with migraine and tension-type headache would be at a greater risk for problematic alcohol use as assessed by validated measures.

Hypothesis 2c: Among headache sufferers, migraineurs would be at a greater risk for diagnosed alcohol-use disorders than tension-type headache sufferers.

Hypothesis 2d: Among headache sufferers, migraineurs would be at a greater risk for problematic alcohol use as assessed by validated measures than tension-type headache sufferers.

CHAPTER 2

METHODS

Procedure

To address the first study goal, a multi-database (i.e., Academic Search Premiere, PsycARTICLES, Psychology and Behavioral Sciences Collection, PsycINFO, MEDLINE) search was conducted on May 6, 2015 using the terms “migraine OR headache” AND “trigger OR precipitant” AND “alcohol.” Abstracts of the resulting articles were reviewed for study eligibility. Articles that were written in English, utilized human participants, adhered to ICHD criteria for headache diagnosis, and used either retrospective recall or experimental manipulation to observe the effects of alcohol on headache were kept for statistical analyses. The bibliographies of these retained articles were reviewed for other possible relevant articles fitting study criteria. Articles excluded from the study were editorials, review articles, case studies, treatment studies, or ones that focused on pathophysiology, employed static variables, or utilized animals. Date of publication was not a factor contributing to study eligibility. From the retained articles, demographic information (e.g., age, race, gender), method of assessment (e.g., experimental manipulation, retrospective recall), potency estimates of alcohol as a trigger, alcohol consumption data (e.g., frequency of consumption, quantity of consumption, type of alcohol consumed), and headache data (e.g., frequency, intensity) were extracted.

To address the second study goal, a different multi-database (i.e., Academic Search Premiere, PsycARTICLES, Psychology and Behavioral Sciences Collection, PsycINFO, MEDLINE) search was conducted on March 17, 2015 using the terms “alcohol OR alcohol abuse OR alcohol dependence OR substance use” AND “migraine OR headache.” Abstracts of the resulting articles were reviewed for study eligibility. Articles that were written in English, utilized human participants, used retrospective recall, adhered to DSM or ICD criteria for substance use disorders or utilized validated measures of problematic substance use, and adhered to ICHD criteria for headache diagnosis were kept for analysis. The bibliographies of these retained articles were reviewed for other possible pertinent articles fitting study criteria. Articles excluded from the study were editorials; review or experimental articles; case studies; or studies that focused on pathophysiology of alcohol-use disorders or primary headache, employed static variables, or used animals. Date of publication was not a factor contributing to study eligibility. From the retained articles, demographic information (e.g., age, race, gender), headache data (e.g., diagnosis, frequency, intensity), alcohol diagnosis (e.g., abuse, dependence, problematic use assessed by validated measures), and alcohol consumption data (e.g., frequency, quantity) were extracted. To address possible publication bias in both study goals, an email asking for unpublished manuscripts and data was sent on November 20, 2015 to researchers and clinicians who study headache triggers and alcohol-use disorders among headache sufferers (i.e., both the Behavioral Issues and Methodology, Design, and Statistical Issues Special Interest Sections of the American Headache Society). No unpublished data was received.

Statistical Analyses

All of the extracted data for the first study goal was statistically analyzed using the DerSimonian-Laird random-effects method with odds ratios approach (DerSimonian, 1986). The

DerSimonian-Laird random-effects method is a conservative approach to analyzing data that takes into account heterogeneity between and within studies. I^2 and τ^2 indices were used within the model to assess heterogeneity. The I^2 index describes the percentage of variation across studies that is due to heterogeneity rather than chance and is calculated from the chi-squared statistic and degrees of freedom (Higgins & Thompson, 2002; Higgins, Thompson, Deeks, & Altman, 2003). An I^2 index greater than 75% indicates considerable heterogeneity and limits interpretation of findings (Higgins & Thompson, 2002). The τ^2 index represents an estimate of the between-study variance and is calculated from the chi-squared statistic and effect size (Higgins, 2008). The random-effects model reported proportions of participants across all studies who endorsed alcohol as a trigger with estimated 95% confidence intervals (95% CIs). One random-effects model was used to estimate the proportion of individuals with any type of headache who endorsed any form of alcohol as a trigger. From this model, meta-regressions were then used to assess potential moderator variables (i.e., headache diagnosis, alcohol type, year of publication, proportion of females in sample). Separate random-effects models were used to estimate the proportion of individuals with each headache diagnosis who endorsed any form of alcohol as a trigger. Additional random-effects models were used to estimate the proportion of individuals with any type of headache who endorsed specific types of alcohol as trigger. R meta-analysis software was used to run the aforementioned statistical analyses.

CHAPTER 3

RESULTS

Study Goal 1

Study Search and Selection

Figure 1 depicts the flow diagram from the initial literature search to the retained articles. The initial multi-database search yielded 1,929 candidate articles. After the titles and abstracts of these candidate articles were reviewed, 43 articles met inclusion criteria. The bibliography review of the aforementioned included articles yielded 2 additional articles appropriate for the study. This search process resulted in 45 articles retained for the current meta-analysis.

Alcohol as a Trigger for All Headache Diagnoses

Forty-four of the 45 articles retained provided sufficient data for calculating the proportion of participants endorsing alcohol as a perceived headache trigger. These studies were published between 1984 and 2014. The proportions of participants with each headache diagnosis endorsing alcohol as a trigger are presented in Table 2, and results of the random effects model are presented in Figure 3. Out of 12,763 participants across 44 studies queried about alcohol as a trigger for their headaches, 22% (95% CI: .17 to .28) endorsed any form of alcohol as a trigger. While prevalence rates of alcohol as a trigger generally range from 6.1% to 51.5% across studies this study indicates that 22% may be a more accurate representation of the precipitating effect. Substantial heterogeneity was observed across studies, $\tau^2 = 0.95$; $I^2 = 97.5\%$ (95% CI: 97.1%

to 97.8%), which prompted several post-hoc meta-regressions. The proportion of females in the sample mildly impacted the proportion of trigger endorsement such that for every 1% increase in proportion of women in the sample the odds of endorsing alcohol increased by 2% (OR = 1.02; 95% CI: 1.01 to 1.05; $p = .04$). Headache diagnosis (i.e., migraine, migraine with aura [MA], migraine without aura [MwA], TTH) impacted trigger endorsement for some diagnoses, with migraine with aura and migraine without aura endorsing significantly lower proportions compared to migraine (unspecified; MA OR = .32; 95% CI: .14 to .76; $p = .01$; MwA OR = .15; 95% CI: .12 to .73; $p = .01$). However, TTH diagnosis did not significantly impact trigger endorsement ($p = .06$). Year of publication ($p = .09$) and type of alcohol (i.e., beer, red wine, sparkling wine, spirits, white wine; $p = .06$) also did not significantly impact proportion of trigger endorsement. The results of the meta-regressions are presented in Figures 3-7.

Alcohol as a Trigger for Specific Headache Diagnoses

Migraine vs. TTH

Forty-two articles provided sufficient data on participants endorsing alcohol as a trigger specifically for either migraine or TTH. Of those 42, all reported data for migraine, but only 12 reported the triggering effects for TTH. These studies were published between 1984 and 2014. The proportions of participants with each headache diagnosis endorsing alcohol as a trigger are presented in Table 2, and results of the separate random effects models are presented in Figures 4-5. Migraineurs (23%) endorsed alcohol as a trigger slightly more than TTH sufferers (14%), but this difference was not statistically significant (OR = .59; 95% CI: .29 to 1.21; $p = 0.15$). Substantial heterogeneity was observed across studies, $\tau^2 = 0.96$; $I^2 = 96.8\%$ (95% CI: 96.4% to 97.3%), which resulted in several meta-regressions. Year of publication mildly impacted proportion of trigger endorsement such that for each additional (more recent) year of publication,

the odds of endorsement decreased by 4% (OR = .96; 95% CI: .93 to .99; $p = .05$). The proportion of females in the sample did not significantly impact trigger endorsement ($p = .09$).

The results of these meta-regressions are presented in Figures 8-11.

Migraine With Aura vs. Without Aura

Eleven articles provided sufficient data on participants endorsing alcohol as trigger for migraine with or without aura. Of these 11 articles, five articles provided data on both headache diagnoses, four provided data on MA exclusively, and two provided data on MWA exclusively. These studies were published between 1988 and 2013. The proportions of participants with each headache diagnosis endorsing alcohol as a trigger are presented in Table 2, and the results of the separate random effects models are presented in Figures 7-8. Individuals with MA (11%) and with MWA (10%) equally endorsed alcohol as a headache trigger (OR = .93; 95% CI: .32 to 2.76; $p = .90$). Substantial heterogeneity was observed across studies, $\tau^2 = 0.87$; $I^2 = 91.1\%$ (95% CI: 87.1% to 93.8%), which resulted in several meta-regressions. Neither year of publication ($p = .11$) nor proportion of females in the sample ($p = .13$) significantly impacted trigger endorsement. The results of the meta-regressions are presented in Figures 12-15.

Alcohol as a Trigger by Type

Twelve articles provided sufficient data on the triggering effects of specific types of alcohol for either migraine or TTH. Of these 12 studies, 10 provided data on red wine consumption; seven provided data on beer; white wine, or spirits consumption; and three provided data on sparkling wine. These studies were published between 1988 and 2013. The proportions of participants endorsing each alcohol type as a trigger are presented in Table 3, and the results of the separate random effects models are presented in Figures 16-20. Red wine (28%) was endorsed most frequently, followed by spirits (14%), white wine (12%), and beer or

sparkling wine (10%). Overall differences in endorsement rates were not significant for each type, though endorsement rates for red wine compared to beer approached statistical significance (OR = 3.67; 95% CI: .92 to 14.67; $p = .06$). The odds of endorsement for each type of alcohol are presented in Table 4. Again, substantial heterogeneity was observed across studies, $\tau^2 = 1.58$; $I^2 = 98.3\%$ (95% CI: 98% to 98.5%). Meta-regression indicated that year of publication was modestly associated with a decrease in endorsement of alcohol as a trigger over time such that for each additional year of publication, the odds of endorsement decreased by 9% (OR = .91; 95% CI: .85 to .98; $p = .01$). Additionally, gender affected endorsement rates such that for every 1% increase in proportions of females in the sample the odds of endorsement increased by 9% (OR = 1.09; 95% CI: 1.04 to 1.16; $p < .001$). The results of the meta-regressions are presented in Figures 21-22.

Alcohol as a Trigger by Quantity and Frequency of Consumption

The hypotheses that higher quantity of alcohol consumed per sitting and higher frequency of alcohol consumption would be associated with increased probability of headache could not be analyzed due to the limited number of studies exploring these variables. While literature exists that explores the typical quantity or frequency of alcohol consumed by headache sufferers (Aamodt et al., 2006; Boardman et al., 2005; Milde-Busch et al., 2010; Molarius, Tegelberg, & Öhrvik, 2008; Yokoyama et al., 2012; Yokoyama et al., 2009; Zlotnik et al., 2014) as well as how frequency of alcohol consumption affects headache (Kelman, 2007; Rains & Penzien, 1996; Scharff et al., 1995), relatively few studies examine the triggering effects of quantity or frequency of consumption on specific headache attacks. Of the 45 retained articles, only three studies reported triggering effect as a function of quantity of consumption. Milde-Busch et al. (2012) asked high school students if “too much alcohol” triggered a headache, although “too

much alcohol” was not operationalized. Of the 1,028 students in the sample, 7% endorsed “too much alcohol” as a trigger for their headache. Andress-Rothrock et al. (2010) reported that of the 200 participants with migraine given a list of common headache triggers, one participant wrote in that “too much of any alcohol” triggered their headache. Littlewood et al. (1988) provided migraineurs with either 300ml of Spanish red wine or 300ml of a vodka-lemonade mixture. Of the 11 participants drinking red wine, nine developed a headache within 3 hours of consumption; whereas none of the eight participants who drank the vodka mixture developed a headache within the same time frame ($p < .001$).

Of the 45 retained articles, only one examined triggering effect as a function of frequency of consumption. Wober et al. (2007) had participants keep daily headache diaries for 90 days and track 52 potential items related to migraine attacks. Of the 327 participants, 60-80% consumed alcohol on 7-10% of the diary days. Drinking alcoholic drinks (i.e., red wine, white wine, sparkling wine, spirits) did not unfavorably impact next day headache or persistence of headache. Surprisingly, risk of headache and persistence of headache were decreased on days following consumption of beer ($p = .02$).

Method of Assessment

The hypothesis that method of assessment would moderate inconsistent findings also could not be analyzed due to the limited number of articles using differing methods. Of the 45 retained articles, only 2 articles utilized experimental methods to assess the triggering effect of alcohol (Littlewood, 1988; Wober, 2007). The other 43 articles used retrospective recall survey methods. Running the primary random-effects model with all of the articles resulted in a 22.22% endorsement rate and an I^2 index of 97.5%, whereas running the same model without the 2 experimental articles resulted in a 21.03% endorsement rate and an I^2 index of 97%, indicating

that method of assessment did not contribute to higher rates of trigger endorsement nor heterogeneity between studies.

Study Goal 2

Study Search and Selection

Figure 2 depicts the flow diagram from the initial literature search to the retained articles. The initial multi-database search yielded 1,325 candidate articles. After the titles and abstracts of these candidate articles were reviewed, nine articles met inclusion criteria. The bibliography review of the aforementioned included articles did not yield any additional articles appropriate for the study. The initial plan had been to quantitatively review these nine articles, but after observation of substantial between-study heterogeneity of sample composition, diagnostic criteria, and methodology, the extracted data was deemed not appropriate for statistical analyses. Thus, the following results are an in-depth qualitative (i.e., narrative) review of the aforementioned nine articles.

Alcohol Use Disorders Among Headache Sufferers

Four of the nine retained articles investigated rates of AUDs among individuals with headache. Comparison groups and diagnostic criteria for AUDs were not consistent across studies, with one study exploring rates of current alcohol dependence among a mixed headache group (i.e., comprised of migraine, TTH, and MOH); one study comparing odds of combined lifetime abuse or dependence between young adults with MA, MWA, and without migraine; one study examining 12-month prevalence of alcohol dependence in migraineurs compared to individuals without migraine; and one study investigating risk of AUDs between individuals with various pain conditions and those without pain conditions. The publication dates for these four

studies range from 1991 to 2013, which contributed to authors adhering to different versions of the DSM for diagnosing substance use disorders.

Hansen, Bendtsen, and Jensen (2007) explored psychological factors that influence treatment outcomes among headache patients at a headache center in Denmark. Headache diagnosis was based on 1988 ICHD criteria and psychological variables (including alcohol dependence) were based on DSM-IV criteria as assessed by the Millon Clinical Multiaxial Inventory III (MCMI-III: Millon & Davis, 1997). A total of 58 patients participated in the study, with 71% of the sample being female. Thirteen of the patients had migraine, 19 had TTH, 17 had MOH, and nine had other headache disorders; all were collapsed into one group for analyses. Out of the total sample, only one patient's scores on the MCMI-III indicated some features of alcohol dependence. Anxiety was the most commonly endorsed psychiatric disorder among this sample, with 19 patients endorsing at least some features and 4 meeting criteria for a definitive diagnosis.

Unlike Hansen and colleagues (2007), Breslau et al. (1991) utilized a comparison group of individuals without migraine and examined rates of migraine, psychiatric disorders, and suicidality in young adults in the United States. Headache diagnosis was based on 1988 ICHD criteria, and psychiatric disorder diagnoses were based on DSM-III-R criteria. The study consisted of 1,007 participants between the ages of 21 and 30 who were members of a large Health Maintenance Organization (median age = 36 years; 61.7% female). Within the total sample, 12.8% endorsed a lifetime diagnosis of migraine (7% in males, 16.3% in females). Of the 879 participants without migraine, 20.6% met criteria for lifetime alcohol abuse or dependence, compared to 24.6% of the 69 participants with MWA, and 30.5% of the 59 participants with MA. After adjusting for gender differences, compared to those without

migraine the odds of alcohol abuse/dependence were significantly greater for MA (OR = 2.1), but not for MwA (OR = 1.6). Compared to those without migraine, MA was associated with higher rates of all psychiatric disorders explored, whereas MwA was only associated with higher rates of mood disorders and some anxiety disorders (e.g., GAD, OCD).

Similar to Breslau et al. (1991), Jette and colleagues (2008) investigated rates of migraine and psychiatric disorders in a large Canadian population sample and used migraine-free individuals as the comparison group. Contrastingly though, Jette et al. only examined 12-month prevalence of alcohol dependence using DSM-IV criteria. Psychiatric diagnoses were assessed with the World Mental Health Composite International Diagnostic Interview (CIDI: Kessler & Üstün, 2004), and headache diagnosis was based off a modified checklist of medical disorders listed on the CIDI. (During the interview, participants were read the list of medical disorders and indicated whether a physician had previously diagnosed them with each disorder.) A total of 36,984 individuals participated in the study. Overall, the prevalence of migraine in the total sample was 15.2% for women and 6.1% for men. The 12-month prevalence of alcohol dependence did not differ between migraineurs (2.3%) and non-migraineurs (2.6%). While Jette et al. assessed lifetime prevalence of some psychiatric disorders, SUDs were only assessed according to 12-month prevalence. However, migraineurs did have higher rates of other psychiatric disorders (e.g., MDD, bipolar, panic) for both 12-month and lifetime prevalence.

Unlike any of the aforementioned studies, Subramaniam, Vaingankar, Abdin, and Chong (2013) assessed lifetime AUDs among a variety of chronic pain conditions (i.e., arthritis, back, migraine) in the general population of Singapore. Similar to Jette et al. (2008), this study utilized the CIDI to assess psychiatric conditions and a modified checklist of medical disorders on the CIDI to identify pain conditions. A total of 6,616 participants completed the study. Six percent of

the sample had arthritis, 7% had back pain, and 5.6% had migraine; the prevalence of at least one pain condition was 15.3%. Of those with arthritis, 4.7% had a lifetime AUD; 5.3% of participants with back pain had an AUD, and 7.8% of migraineurs had an AUD. Compared to individuals without migraine, migraineurs had higher prevalence of an AUD (OR = 2.1); however, compared to individuals without any pain condition, migraineurs who suffered exclusively from headache did not have higher prevalence of AUDs.

Headache Conditions Among Substance Abusers

Two studies of the retained nine studies examined risk of headache among patients diagnosed with SUDs. Both studies examined multiple SUDs. Although these studies both adhered to similar diagnostic criteria for AUDs, they differed on the alcohol and headache diagnoses explored, the comparison groups utilized, and geographic location of sample. The studies are recent publications and were published in 2012 and 2013.

Beckman and colleagues (2012) examined risk of headache among psychoactive substance abuse inpatients in Turkey. The study consisted of 1015 participants (97.2% male) who were currently diagnosed with substance abuse and had never received a diagnosis of substance dependence based on DSM-IV-TR criteria. Cannabis (80.5%) was the mostly commonly used substance, followed by alcohol (74.6%), methamphetamine (18.7%), and benzodiazepines (10.4%). Headache diagnosis was based on 2004 ICHD criteria. Two hundred and sixty men (26.3%) endorsed headache, whereas 13 (46.4%) women endorsed headache ($p = .018$). Those with alcohol abuse did not endorse more headache compared to other substance abusers, with only 27.9% of alcohol abusers endorsing any headache ($p = .25$). Opioid abusers reported the highest rates of headache with 60% endorsing any headache ($p = .04$). Among alcohol abusers, 25.1% had migraine and 6.2% had TTH.

Similar to the aforementioned study, McDermott and colleagues (2013) explored headache among substance use inpatients; however, their sample consisted of individuals diagnosed with substance dependence based on DSM-IV criteria and solely examined risk of migraine. Migraine was identified using a combination of the ID Migraine (Lipton et al., 2003) and Brief Headache Screener (BHS; Maizels & Burchette, 2003), which prioritize migraine symptomatology and headache frequency, respectively. The dual use of the measures corresponds to ICHD criteria for migraine. Participants were 181 inpatients at a treatment facility in the United States (64% male). Rates of current dependence were highest for cocaine (35.9%), alcohol (29.3%), and cannabis (35.9%). Forty-four of the 181 inpatients met criteria for migraine. Migraineurs endorsed higher rates of current and lifetime alcohol dependence compared to non-migraineurs (OR = 2.63 current; OR = 2.64 lifetime). Multivariate analyses found patients diagnosed with current alcohol dependence were more than three times as likely to experience migraine (OR = 3.79) as those without alcohol dependence.

Problematic Alcohol Use Among Headache Sufferers

Three of the nine retained articles explored PAU among individuals with headache. Participants' headache diagnoses and comparison groups varied across studies, with two studies exploring migraine compared to no headache and one study investigating migraine compared to TTH. Across these three studies, two different validated measures of PAU were used. Two studies used the same validated measure (i.e., Alcohol Use Disorders Identification Tests (AUDIT): Bohn, Babor, & Kranzler, 1995), but each used different cutoff scores to denote PAU. The publication dates of these three studies range from 2006 to 2013.

Domingues and colleagues (2013) explored PAU with the AUDIT among a sample of outpatients at a headache clinic in Brazil. All participants had a headache diagnosis consistent

with ICHD-II criteria. Eighty-one participants had migraine and 62 had TTH. Gender did not differ significantly between the headache groups, as 91.4% of migraineurs were female and 82.3% of TTH sufferers were female ($p = .10$). A validated Portuguese version of the AUDIT was used and a cutoff score of eight was chosen to indicate a diagnosable alcohol use disorder. Migraineurs reported significantly less PAU compared to TTH sufferers (5.2% vs. 16.1%, $p = .044$).

Unlike the aforementioned study utilizing the AUDIT, Domingues and Domingues (2011) compared PAU among headache sufferers and headache-free individuals. This study sample consisted of Brazilian medical students and used the ID-migraine to screen for migraine. Three hundred and ninety-eight people participated in the study (56.3% female). Seventy-five participants did not suffer from any headache disorder, 125 participants had migraine, and 198 had non-migrainous headaches. The authors divided the AUDIT scores into groups of <8 (non-concerning alcohol use), 8-11 (concerning alcohol consumption), 12-15 (serious indication of drinking problem), and >15 (definite drinking problem); however they combined groups 12-15 and >15 for statistical comparisons. Similar percentages of headache-free individuals (21.2%) and headache sufferers (27.3%) reported no alcohol consumption. The majority of migraineurs (86.4%) and non-migrainous headache sufferers (80.3%) reported non-concerning alcohol use (including abstinence). Headache-free participants (20%) endorsed higher rates of PAU compared to migraineurs (4%; $p < .001$) and non-migrainous headache sufferers (6.8%; $p < .001$).

Similar to the Domingues and Domingues (2011) study, Aamodt and colleagues' (2006) population of interest was migraineurs, non-migrainous headache sufferers, and headache-free individuals. Additionally, they examined alcohol and tobacco overuse and adhered to 1988 ICHD criteria for headache diagnoses. A total of 51,383 individuals from the general population

of Norway participated in the study, with 12% having migraine, 27% having non-migrainous headaches, and 61% denying having headaches. Unlike the aforementioned studies, Aamodt et al. used the Cutting down, Annoyance by criticism, Guilty feeling, and Eye-openers measure (CAGE: Ewing, 1984) to assess PAU among 38,508 participants. A positive answer of one or more on this measure was indicative of alcohol overuse. Individuals with migraine and non-migrainous headaches did not differ significantly from headache-free individuals on alcohol overuse (OR = 0.9 migraine; OR = 1.1 non-migrainous). However, the odds of alcohol overuse, were significantly higher in chronic migraine sufferers compared to non-headache individuals (OR = 1.5).

Overall, nine studies examined the relationship between headache and unhealthy alcohol consumption. The findings across these studies are inconsistent. In studies that explored rates of AUDs in headache samples, migraineurs without aura and TTH sufferers did not endorse high rates of AUDs, however migraineurs with aura and migraineurs among a chronic pain sample did endorse higher rates of AUD compared to individuals without migraine. Additionally, in studies that examined rates of headache disorders among SUD inpatients, risk of migraine was significant among individuals with an alcohol dependence (but not alcohol abuse) diagnosis. Furthermore, in studies that investigated PAU in headache samples, TTH sufferers reported moderate rates (16.1%) of PAU whereas migraineurs reported comparatively low rates (4.6%-5.2%). With these general findings in mind, differences in validated measures used limit comparisons of these endorsement rates.

CHAPTER 4

DISCUSSION

Study Goal 1

The first aim of the current paper was to meta-analytically explore the triggering effect of alcohol on primary headaches disorders. The major finding of this meta-analysis and the accompanying meta-regressions is that there is extreme heterogeneity both between and within studies exploring alcohol as a trigger for migraine and TTH. The amount of heterogeneity found in each meta-analysis indicates interpreting the results with extreme caution and limits generalizability of findings. Additionally, the heterogeneity suggests that the ability for alcohol to trigger headache may be a complex interaction effect in that alcohol consumption may trigger most in conjunction with other variables (e.g., behavioral, biological, environmental). With these caveats regarding the aforementioned heterogeneity, the following conclusions can be judiciously drawn from this study: 1) alcohol is modestly perceived as a trigger for migraine and TTH; 2) the precipitating effects do not differ by headache diagnoses; 3) red wine appears to be a somewhat more potent trigger than other forms of alcohol.

The meta-analyses revealed that 22% of participants ever queried about alcohol as a trigger for headache endorse some precipitating effect. This percentage is somewhat higher than was expected given that several large-scale studies reported <10% of headache sufferers endorsed alcohol as a trigger (Fukui et al., 2008; Karli et al., 2006; Tellez-Zeneto et al., 2005;

Wang et al., 2013), although two large-scale studies reported >35% of migraineurs endorsed alcohol in some form as a trigger (Kelman, 2007; Schurks, Buring, & Kurth, 2011). However, this percentage is comparable to another meta-analysis that examined all triggers of headache and found that 21% of headache sufferers endorsed alcohol as a trigger (Walters, Davis, Houle, Turner, & Smitherman, in preparation). Notably, this endorsement rate is modest compared to the most commonly reported triggers for headache (i.e., stress, hormones in women, sleep, environmental factors), triggers that are typically endorsed by at least 40% of headache samples (Aamodt et al., 2006; Fukui et al., 2008; Kelman, 2007; Wang et al., 2013). This endorsement rate is similar to the endorsement rate of other dietary triggers (27%) yet considerably higher than endorsement rates of other triggers (i.e., traveling [11%], allergens [6%], and medications [2%]) identified in the aforementioned meta-analysis (Walters et al., in preparation).

A 22% endorsement rate may be an underestimate given the amount of heterogeneity found between studies. Meta-regressions run to assess moderator variables and sources of heterogeneity indicated that a TTH headache diagnosis, alcohol type, and year of publication did not impact the proportion endorsing alcohol as a trigger nor account for significant heterogeneity. One factor that did influence endorsement of alcohol as a trigger was the proportion of women in the sample. Studies that examined the precipitating effects of alcohol with higher proportions of women were more likely to obtain higher endorsement rates. While many studies have not found significant differences between gender and types of triggers endorsed (Andress-Rothrock et al., 2010; Iliopoulos et al., 2015; Russell, Rasmussen, Fenger, & Olesen, 1996; Turner, Molgaard, Gardner, Rothrock, & Stang, 1995), the higher endorsement rate of alcohol as a trigger among women may be confounded by other environmental factors that precipitate headache. For example, Andress-Rothrock and colleagues (2010) found that many women in their sample

reported that consumption of red wine triggered their headache only if it was consumed during menses, an already well-established trigger for migraine in women (Aamodt et al., 2006; Boardman et al., 2005; Fukui et al., 2008; Karli et al., 2005; Kelman 2007; Spierings et al., 2001; Wang et al., 2013). An additional factor that impacted endorsement rate was a headache diagnosis of MA or MwA when compared to migraine. Studies that specifically asked about MA or MwA had significantly lower proportions endorsed than studies that did not differentiate the two diagnoses. This difference in endorsement rate did not account for significant heterogeneity in the analysis, which suggests that differences in endorsement rates may be related to some other variable other than specific headache diagnosis (e.g., headache severity, clinical sample, age).

In the meta-regression exploring the precipitating effect of alcohol on migraine compared to TTH, there was a small but non-significant difference found in endorsement rates between the two headache disorders. The similarity in proportion endorsing alcohol as a trigger could indicate that despite their phenotypic differences, these headache disorders are triggered through similar mechanisms (Karli et al., 2005; Ulrich, Russell, Jensen, & Olesen, 1996). In a recent study by Turner et al. (2015), taxometric analyses examined headache nosology and found migraine and TTH were similar entities (i.e., on a continuum of severity) among frequent headache (>15 days per month) sufferers and younger individuals (<24 years old). However, too few studies utilized in this meta-analysis provided data on headache frequency or mean age of the sample to be able to statistically explore these variables. Despite year of publication not being a significant moderator variable in the primary meta-analysis that grouped all headache disorders into one category, year of publication was a factor that impacted endorsement rates between these two specific diagnoses, with more recent studies reporting somewhat lower endorsement rates. One

possible explanation for the decline is that over the years the clinical advice to avoid known triggers of headache has become increasingly disseminated to migraineurs (Panconesi, 2008). Although year of publication did moderate endorsement rates, it did not account for much heterogeneity. Furthermore, gender did not affect endorsement rates between the two diagnoses nor account for significant heterogeneity, perhaps because both migraine and TTH are more prevalent among women than men (Jelinski et al., 2006; Lyngberg et al., 2005; Stewart et al., 1992; Stovner et al., 2007).

Additionally, in the meta-regression investigating the precipitating effects of alcohol on migraine with aura compared to migraine without aura, rates of trigger endorsement were almost identical between both headache conditions. While researchers often intensely debate whether these two headache disorders should be considered distinct subtypes or part of the same disease spectrum (Kallela et al., 1999; Manzoni & Torelli, 2008; Ranson, Igarashi, MacGregor, & Wilkinson, 1991; Rasmussen, 1995; Russell et al., 1996; Zhang et al., 2015), these findings indicate that the two headaches are similar entities with regards to this specific trigger. This finding is consistent with other studies that have found similar endorsement of triggers between the two headache disorders (Dora et al., 2010; Karli et al., 2005). Additionally, meta-regressions found neither gender nor time were significant moderators of endorsement rates nor accounted for much heterogeneity. The significant heterogeneity remaining after meta-regressions highlights the presence of considerable differences between studies, which may contribute to findings that they are distinct entities (Manzoni & Torelli, 2008; Russell et al., 1996).

The meta-regression exploring the ability of different types of alcohol to precipitate headache strengthens the argument that red wine may be a more potent precipitant than other forms of alcohol. While the odds of red wine precipitating a headache were not statistically

greater than beer, spirits, or other forms of wine, more than twice as many individuals endorsed red wine as trigger than any other type of alcohol, indicative of a large effect size. To better understand why red wine has a potentially stronger precipitating effect, future research needs to isolate the various components unique to red wine (e.g., sulfites, tannins, histamines, phenols) potentially responsible for this somewhat higher incidence of headache (Krymchantowski & Jevoux, 2014). Studies that experimentally manipulate exposure to each component would be valuable in this regard. Additionally, the gender effect on endorsement rates may be related to the aforementioned hormonal connection and suggests that alcohol's ability to precipitate headache is often an interactive effect (Andress-Rothrock et al., 2010).

While this study aim has a strong data-analytic framework and retained high quality studies strictly adhering to ICHD headache criteria, the major limitation of this study is the large amount of heterogeneity present in existing literature. This heterogeneity limits interpretation of results and generalizability of the findings. Multiple meta-regressions were used to help analyze possible sources of heterogeneity; however significant heterogeneity still remained even after these analyses. The amount of heterogeneity found in this study highlights a need for uniformity or standardization in assessing alcohol as a trigger for headache. An additional limitation of this study is that the overwhelming majority of data analyzed came from studies that used self-report cross-sectional designs. While this review was not limited to articles utilizing self-report measures, the small percentage of included experimental studies precludes determination of cause-effect relationships and of adequate comparisons between endorsement rates as a function of study design. Clearly there is a substantial need for more studies experimentally manipulating alcohol as a trigger, as prior studies of this type with other triggers (e.g. chocolate) have not always verified patient perceptions of their potency (Marcus, Scharff, Turk, & Gourley, 1997).

Study Goal 2

The second of aim of the current paper was to examine the relationship between alcohol use disorders and primary headache disorders given established comorbidity of other mental health problems among headache sufferers (Baskin, Lipchik, & Smitherman, 2006; Baskin & Smitherman, 2009; Beghi et al., 2010; Breslau & Davis, 1992; Breslau & Davis, 1993; Jette, et al., 2008; Marchesi et al., 1989; McIntyre et al., 2006; Oedegaard et al., 2006; Saunders, Merikangas, Low, Von Korff, & Kessler, 2008; Stewart, Breslau, & Keck, 1994; Swartz, Pratt, Armenian, Lee, & Eaton, 2000). The inability to statistically quantify the findings in this research area highlights the need for more systematic observation of the relationship between headache and unhealthy alcohol consumption. The articles reviewed narratively took three major forms: 1) risk of alcohol use disorders in headache sufferers; 2) risk of headache among individuals diagnosed with alcohol use disorders; and 3) rates of problematic alcohol use among headache sufferers.

Within the scarce amount of research examining risk of substance use disorders among headache sufferers, the findings evidence some inconsistencies. One noticeable inconsistency in this area was the significant risk of AUD in migraineurs found by Breslau et al. (1991) compared to the lack of risk found by Hansen et al. (2007), Jette et al. (2008), and Subramaniam et al. (2013). The use of DSM-III criteria in the Breslau study may contribute to this discrepancy as DSM-III defines alcohol dependence more strictly than the more recent version of the DSM-IV-TR (Hasin et al., 2003). Some differences were evident in prevalence rates among those assessed with DSM-IV criteria. Jette et al. found migraineurs had a prevalence rate of 2.3% for alcohol dependence; Subramaniam et al. found migraineurs had a prevalence rate of 7.8% for alcohol use disorders; and Hansen et al. found no migraineurs met criteria for alcohol dependence. The

higher percentage reported by Subramaniam et al. may be a result of their inclusion of alcohol abuse, which is less severe than alcohol dependence (Hasin et al., 2003). Despite the variability in percentages reported, these estimates in general are no higher than those typically found among the general population (Merikangas, Angst, & Isler, 1990; Swartz et al., 2000).

Additionally, the lack of alcohol dependence found by Hansen et al. may be related to the fact that this sample consisted of only treatment-seeking headache sufferers, a population known to experience more severe headaches and generally have lower alcohol consumption (Fukui et al., 2008; Mannix et al., 1997). The variability in specific DSM criteria explored may be minimized in future research by the changes within the most recent diagnostic manual (DSM-V), which no longer dichotomizes alcohol abuse and dependence but instead conceptualizes “alcohol use disorder” as occurring on a continuum of severity (American Psychiatric Association, 2013).

Regarding headache among those with AUDs, very little research has been conducted and thus comparisons between these studies are limited. Two studies that met inclusion criteria for this study goal explored rates of headache disorders among substance use populations. Neither study examined the same alcohol use disorder, with Beckman and colleagues (2012) exploring alcohol abuse and McDermott and colleagues (2013) exploring alcohol dependence; however both studies utilized substance use inpatient samples and adhered to both DSM-IV and ICHD criteria. Additionally, McDermott et al. examined risk of migraine, whereas Beckman et al. examined prevalence rates of multiple headache diagnoses, although both studies reported similar rates of migraine. The similarities in prevalence rates despite differing alcohol diagnoses may be a function of the samples, in that substance use inpatients have high rates of psychiatric disorders (Compton, Cottler, Jacobs, Ben-Abdallah, & Spitznagel, 2003) commonly comorbid with headache (Baskin, Lipchik, & Smitherman, 2006; Baskin & Smitherman, 2009; Beghi et al.,

2010; Breslau & Davis, 1992; Breslau & Davis, 1993; Jette, et al., 2008). Although Beckman did not investigate psychiatric disorders in the sample, McDermott's multivariate analyses suggest that high rates of comorbid psychiatric disorders contributed to their high rates of migraine. Furthermore, both samples included polysubstance users, which could inflate prevalence of migraine given that cocaine and opioid use were strongly linked to headache in these studies. More clarity regarding the relationship between alcohol abuse or dependence and headache could be established using studies enrolling individuals with alcohol use disorders without polysubstance use.

Within the limited amount of research exploring problematic alcohol use in headache sufferers, findings have been inconsistent. One possible contributing factor to these inconsistencies may be the use of different validated measures across studies. For example, a study utilizing the CAGE found no differences between headache-free individuals and migraineurs on PAU, whereas a study using the AUDIT found headache-free individuals endorsed more PAU than migraineurs. These differences in findings are consistent with the Philpot et al. (2003) study comparing the psychometric properties of these two measures that found the AUDIT was superior to the CAGE in specificity of and sensitivity to problematic drinking. These differences highlight the need for a more consistent approach to assessing problematic alcohol use using the best-validated measures.

An additional factor contributing to these inconsistent findings is that those studies using the same measure have utilized differing cutoff scores. In the two studies using the AUDIT, cutoffs ≥ 8 , and ≥ 12 were used for group comparisons, and these different cutoff score are indicative of differing drinking habits. Based on of a large validation study that assessed sensitivity and specificity of AUDIT cutoff scores to the gold standard Composite International

Diagnostic Interview 2.1 (CIDI: World Health Organization, 1997), a score of ≤ 7 on the AUDIT indicates a lack of a “diagnosable alcohol problem,” 8-11 indicates “concerning alcohol consumption,” 12-15 suggests “serious indication of a drinking problem,” and >15 indicates a “definite drinking problem” (Alvarado et al. 2009). Domingues et al. (2013) used a cutoff of ≥ 8 and found more than twice as many TTH sufferers met criteria than Domingues and Domingues (2011), who used a cutoff of ≥ 12 . If Domingues and Domingues had combined all individuals who scored ≥ 8 , the percentage of non-migrainous headache sufferers meeting this criterion would have more closely resembled the percentages reported by Domingues et al. These differences suggest that using established cutoff scores in comparable study samples could help unify interpreting results across studies.

While this review provides an in-depth look at the state of research exploring the relationship between primary headache disorders and alcohol use, several limitations that exist. The primary limitation is that data provided by these studies could not be statistically analyzed due to the varied nature of the research. A data-analytic approach would have allowed for stronger comparisons between the studies and given a more precise understanding of the relationship between the two disorders. However the inability to statistically compare this relationship highlights the need for unified research in this area. Furthermore, the varied nature of the research limited direct comparisons between studies, although this review thoroughly explored where differences existed and made recommendations for remedies of these differences in future research. An additional limitation is the sparse number of studies examined in this study despite a large multi-database search and soliciting unpublished manuscripts on the topic. Fortunately, the past decade has seen an increase in studies on this topic indicative of growing interest in this comorbid relationship. While this review has several limitations, a major strength

is the strict adherence to ICHD criteria for headache and DSM criteria for AUDs/validated measures of PAU. These stringent inclusion criteria were chosen in order to preemptively limit between-study heterogeneity and resulted in identifying high quality studies.

General Conclusions

This dissertation aggregated the literature on alcohol and headache through the use of a meta-analysis and an in-depth qualitative review. Both study goals highlighted the heterogeneous nature of research in this area. The heterogeneity observed in the meta-analysis indicated interpreting the results with caution, whereas the heterogeneity observed in the in-depth review prevented statistical analysis of the data and limited comparisons between studies. With this heterogeneity in mind, the primary conclusions of the meta-analysis are: 1) alcohol is perceived to trigger headache in one out of 5 individuals with migraine or TTH; 2) the precipitating effect of alcohol does not significantly differ between migraine and TTH nor migraine with aura and migraine without aura; 3) there appears to be a stronger precipitating effect for women than men; and 4) red wine is a somewhat more common precipitant than other forms of alcohol. The primary conclusions of the in-depth review are: 1) migraineurs without aura and TTH sufferers do not endorse elevated rates of AUDs, however migraineurs with aura and migraineurs among a chronic pain sample do endorse higher rates of AUD compared to individuals without migraine; 2) headache sufferers generally report prevalence rates of AUDs comparable to general population rates; 3) risk of migraine is increased among individuals with alcohol dependence but not alcohol abuse; 4) TTH sufferers report moderate rates of PAU, whereas migraineurs report comparatively low rates.

Future research examining alcohol as a precipitant should utilize experimental methods and should assess the role of frequency and quantity of consumption in this precipitating effect.

Assessing frequency of consumption could answer the question as to whether alcohol's ability to precipitate a headache attack is an acute agent requiring only a single administration of alcohol or a compound effect requiring multiple exposures to alcohol in a brief period of time.

Additionally, exploring quantity of consumption could specify the threshold needed in order for alcohol to precipitate an attack. Headache diaries via mobile phone applications may be an effective approach to assessing frequency and quantity of consumption related to headache onset. Experimental manipulation of headache triggers would alleviate recall bias frequently found in retrospective, self-report methods. Furthermore, future research via experimental methods should experimentally manipulate different alcohol types in order to better understand the precipitating effects of wine versus beer versus spirits. Moreover, research should experimentally explore the various components of red wine (e.g., tannins, sulfites, histamines) to elucidate why red wine appears to be a more potent trigger than other forms of alcohol. Future research should attempt to replicate real-world drinking behaviors (e.g., in a social setting, feeling stressed, during sporting event) in order to understand possible moderator contextual variables affecting the precipitating relationship.

In order to more fully understand the comorbid relationship between headache and unhealthy alcohol, substantially more research on this topic is needed. Future research in this area needs to be unified in substance use diagnoses explored and best-validated measures used to assess PAU so that accurate comparisons can be made between studies. The recent change in DSM criteria may alleviate some issues with differing diagnoses given that abuse and dependence are no longer treated as separate entities. Using these new changes, future research should explore how severity of AUD affects different headache variables (e.g., diagnosis, frequency, severity, disability), as well as examine this comorbid relationship among a sample of

individuals exclusively with AUD in order to limit confounding effects of other substances. Future research investigating PAU in headache sufferers should utilize the same validated measure and culturally established cutoffs to compare problematic drinking behaviors between disorders. In order to identify the best-validated measure of PAU, a large-scale validation study needs to be conducted among a clinical and general population sample that identifies appropriate cutoffs of the AUDIT that coincide with new DSM-V criteria for alcohol use disorders. Furthermore, future research needs to adhere to ICHD criteria for headache so that symptomatology does not differ significantly between studies reporting the same diagnoses. Unified headache criteria could help reduce variability in reported rates of AUD/PAU and provide clearer distinctions between rates of unhealthy alcohol use and different headache diagnoses.

Research done in primary care or hospital settings where doctors diagnose both physical and mental health disorders may be the most appropriate setting for future research assessing rates of AUD/PAU and headache. In addition to having the benefit of a single doctor give multiple diagnoses, these settings are typically the first place people go when seeking health care (Dixon-Woods et al., 2006). Administering a battery of the Brief Headache Screener, ID Migraine, and AUDIT during all primary care appointments or emergency department visits could be an effective method of monitoring rates of headache and disordered alcohol use among a large proportion of people in a time-efficient manner. Additionally, using these screeners could help physicians identify individuals who would be appropriate referrals for specialty services (i.e., headache clinic, substance use treatment program) and potentially improve their treatment outcomes. Furthermore, within substance use treatment programs, service providers should assess for headache disorders given that alcohol dependence is associated with greater risk for

migraine. Within neurology and headache clinics, physicians should assess alcohol use, particularly red wine consumption, due to its precipitating effect and make recommendations regarding consumption.

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APPENDIX

APPENDIX A: STUDY SEARCH AND SELECTION

Figure 1. Flowchart of Meta-Analysis

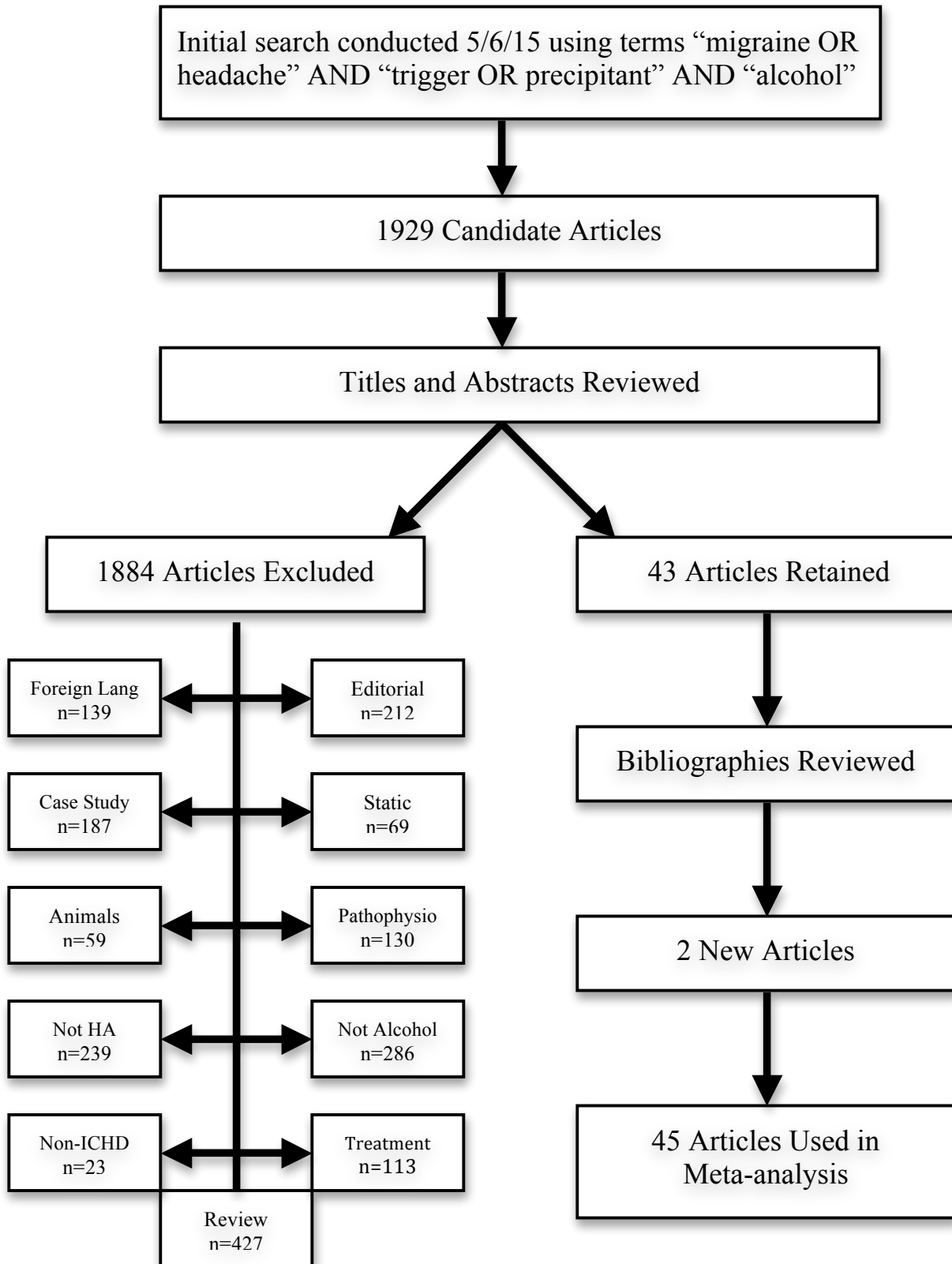
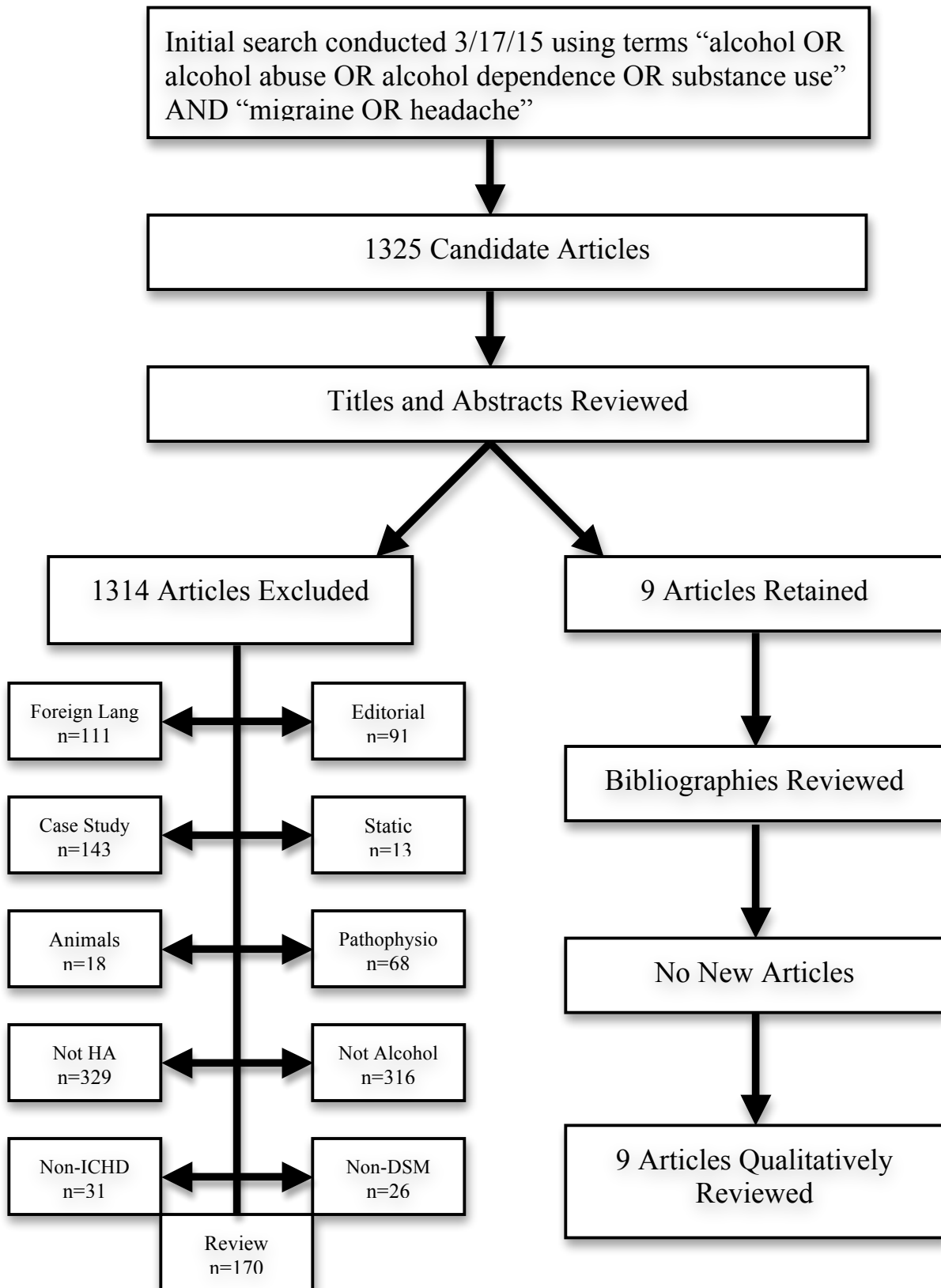


Figure 2. Flowchart of Qualitative Review



APPENDIX B: STUDY SAMPLE CHARACTERISTICS

Table 1. Characteristics of Study Samples

Study, Year	Sample Size (N)	Headache Diagnoses	Females in Sample %	Mean Age (SD)
Ying, 2014	23	Migraine	82.6	32.9 (13.3)
Tonini, 2012	60	Migraine, TTH	79	-
Fraga, 2013	100	Migraine	72	-
Savi, 2002	58	MA, MWA, TTH	69.3	38.19 (15.41)
Hung, 2008	63	Migraine	76.2	30.3 (8.3)
Lipton, 1989	63	Migraine	77.1	37.95 (-)
Sjostrand, 2010	60	Migraine	100	30.4 (-)
Kelman, 2007	1207	Migraine, TTH	84.3	37.67 (12)
Wober, 2006	120	Migraine, TTH	-	36.8 (11.4)
Kelman, 2006	1009	Migraine	86.3	37.7 (11.7)
Karli, 2006	1001	MA, MWA, TTH	57.3	14.67 (1.74)
Karli, 2005	87	MA, MWA, TTH	86.5	-
Blau, 2005	45	Migraine	-	-
Fragoso, 2003	163	Migraine, TTH	87.1	25 (-)
Spierings, 2001	55	Migraine, TTH	78.2	48 (12.8)
Fishbain, 2001	85	MA, MWA, TTH	-	42.2 (12.7)
Bank, 2000	78	Migraine	71.8	38 (6.1)
Russell, 1996	333	MA, MWA	44	-
Haimonot, 1995	454	Migraine	73.4	40.2 (-)
Mountstephen, 1995	62	Migraine	41.9	-
Matuja, 1991	139	Migraine, HA	66.8	28.8 (-)
Rasmussen, 1993	286	Migraine, TTH	46	-
Phanthumchinda, 1989	157	Migraine	91.1	-
Van den Bergh, 1987	217	Migraine	81.1	-
Ulrich, 2000	169	MA	59.2	-
Rains 1996	81	Migraine	93	-
Ieruslimschy, 2000	100	MWA	84	33.6 (-)
Peatfield, 1995	387	Migraine, TTH	-	-
Scharff, 1995	121	MWA, TTH	85.6	36.9 (12.27)

Table 1. Characteristics of Study Samples Cont'd

Study, Year	Sample Size (N)	Headache Diagnoses	Females in Sample %	Mean Age (SD)
Hauge, 2010a	126	MA, MWA	77.8	-
Andress-Rothrock, 2010	200	Migraine	89	41.1 (-)
Galinovic, 2009	220	Migraine, TTH	77.3	-
Fukui, 2008	200	Migraine	81	37.7 (-)
Panconesi, 2013	371	MA, MWA, TTH	75.2	40 (14)
Tellez-Zeneto, 2005	1147	Migraine	80	37.1 (13.6)
Baldacci, 2013	120	Migraine	86.7	38.7 (11.7)
Schurks, 2011	1675	Migraine	100	-
Mollaoglu, 2012	126	Migraine	68.2	36.2 (10.1))
Hauge, 2010b	347	MA, MWA	-	-
Wang, 2013	738	Migraine, TTH	-	-
Peatfield, 1984	493	Migraine	67.1	-
Amery, 1987	217	Migraine	81.1	-
Wober, 2007	327	Migraine	86.5	41.9 (12.1)
Littlewood, 1988	19	Migraine	-	-

APPENDIX C: TABLES AND FIGURES FOR TRIGGER META-ANALYSIS

Table 2. Trigger Meta-Analysis by Headache Diagnosis (Proportion of sample reporting alcohol [any form] as a headache trigger)

Headache Diagnosis	Proportion	95% CI	I²	Studies	Total N
All HA diagnoses	0.22	0.17, 0.28	97.5	44	12763
Migraine	0.23	0.18, 0.29	97.2	42	11304
TTH	0.14	0.07, 0.27	93.3	12	1506
Migraine w/ Aura	0.11	0.06, 0.21	89.3	9	984
Migraine w/o Aura	0.10	0.05, 0.20	92.5	7	1077

Table 3. Trigger Meta-Analysis by Alcohol Type (Proportion of sample reporting each type of alcohol as a trigger)

Alcohol Type	Proportion	95% CI	I²	Studies	Total N
Beer	0.10	0.03, 0.24	98.0	7	1882
Red Wine	0.28	0.16, 0.45	97.7	10	3166
Sparkling Wine	0.10	0.00, 0.82	98.8	3	901
Spirits	0.14	0.03, 0.41	98.5	7	1543
White Wine	0.12	0.05, 0.28	98.3	7	2996

Table 4. Meta-Regression by Alcohol Type (Odds Ratio of endorsing each type of alcohol compared to red wine.)

Alcohol Type	OR	95% CI	P value
Beer	0.27	0.07, 1.10	.06
Red Wine	3.67	0.92, 14.67	.06
Sparkling Wine	0.39	0.06, 2.69	.34
Spirits	0.42	0.10, 1.75	.23
White Wine	0.36	0.09, 1.45	.15

Note: OR of red wine is compared to beer

Figure 3. Forest Plot of Alcohol as Trigger for any Headache Diagnosis

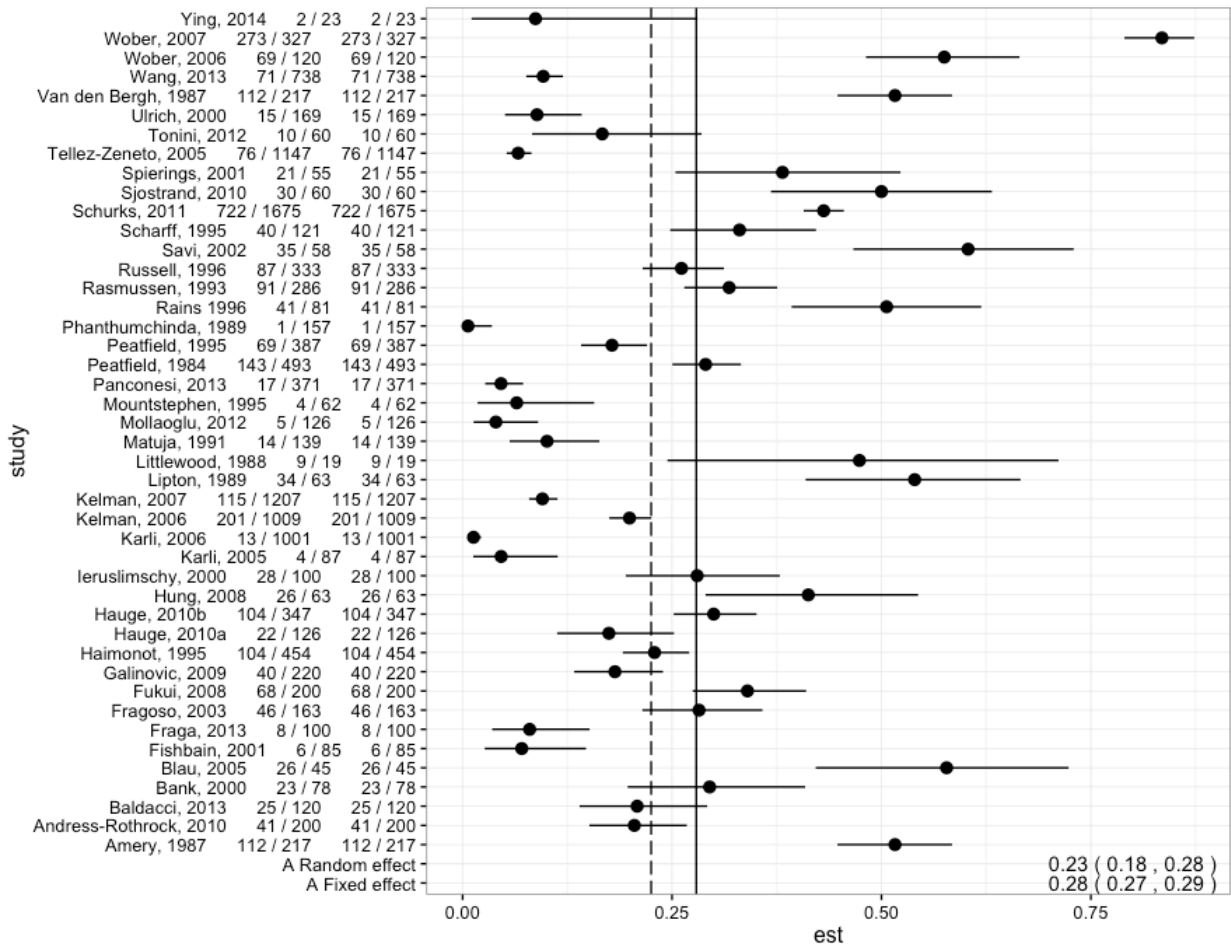
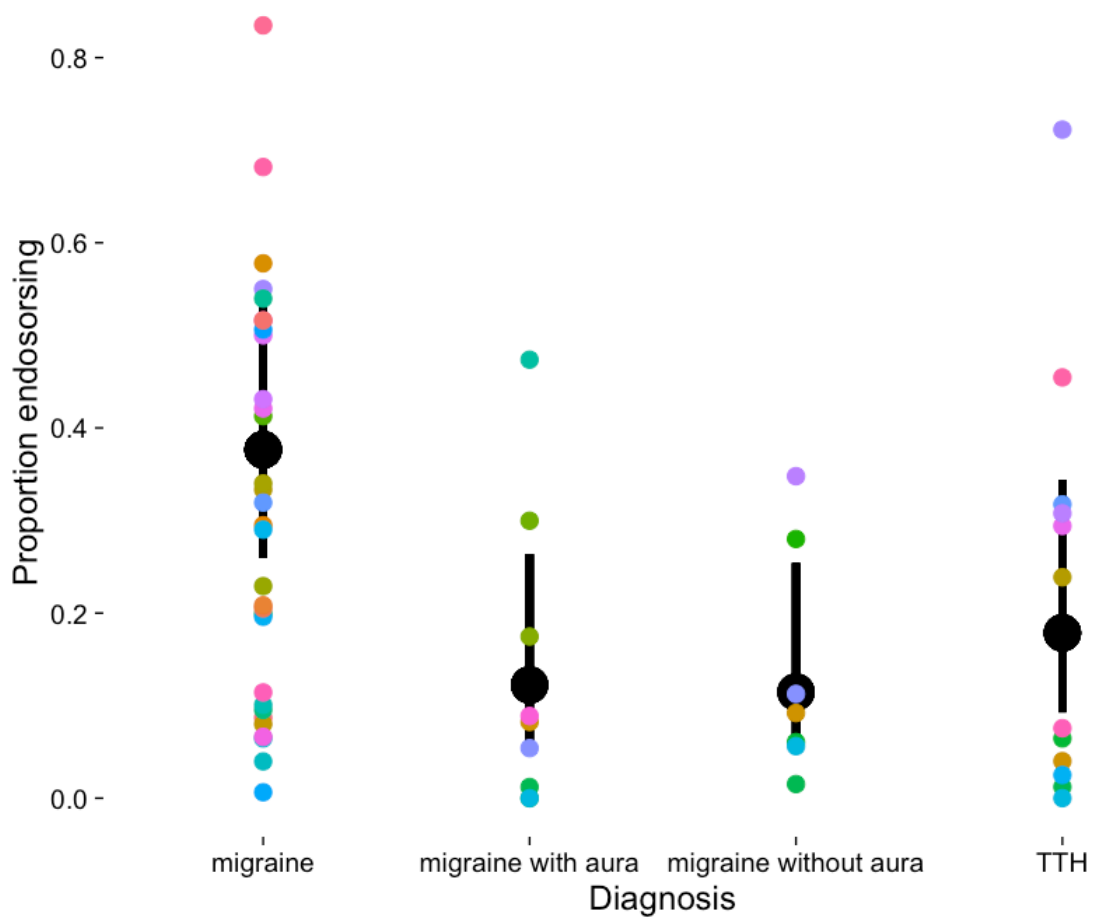
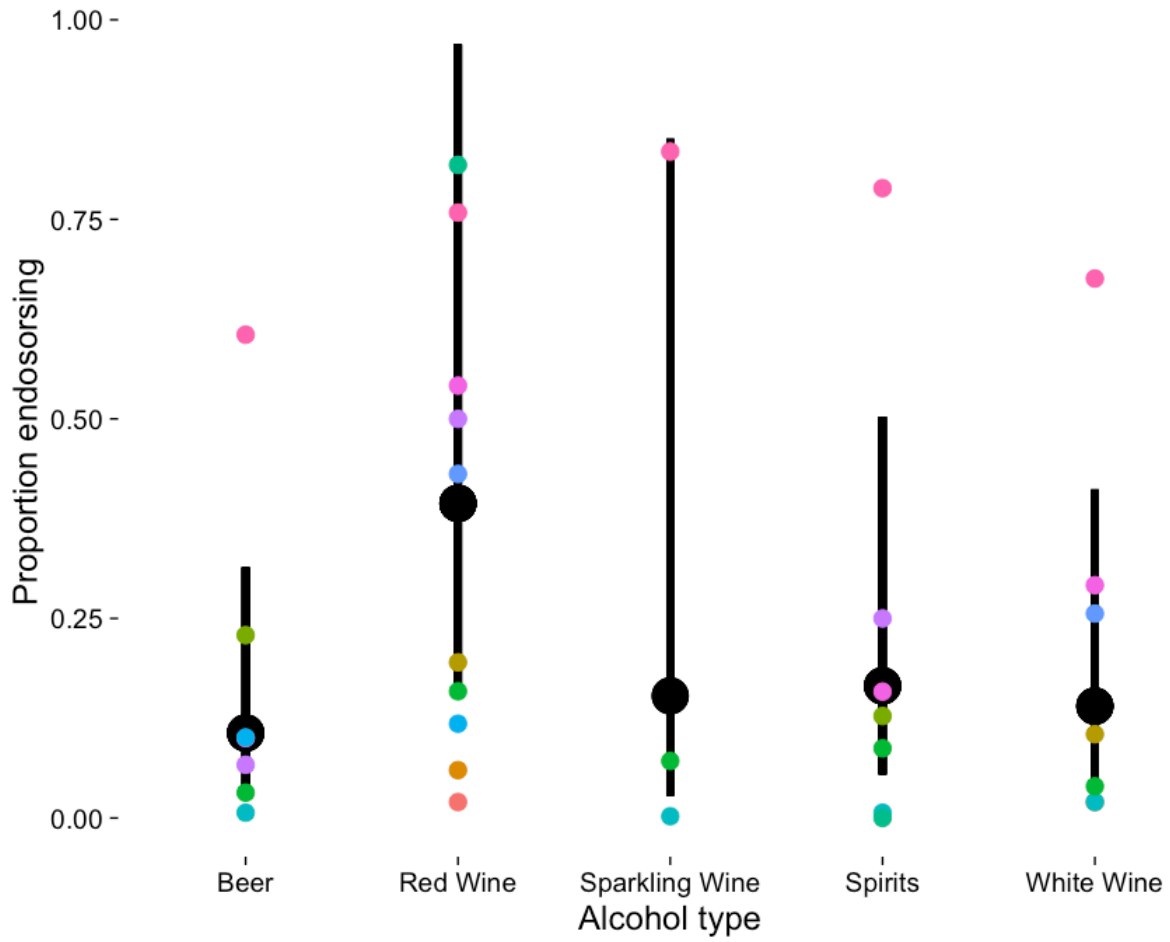


Figure 4. Meta-Regression of Headache Diagnosis



Note: each colored dot denotes a single study

Figure 5. Meta-Regression of Type of Alcohol



Note: each colored dot denotes a single study

Figure 6. Meta-Regression of Year in All HA Diagnoses

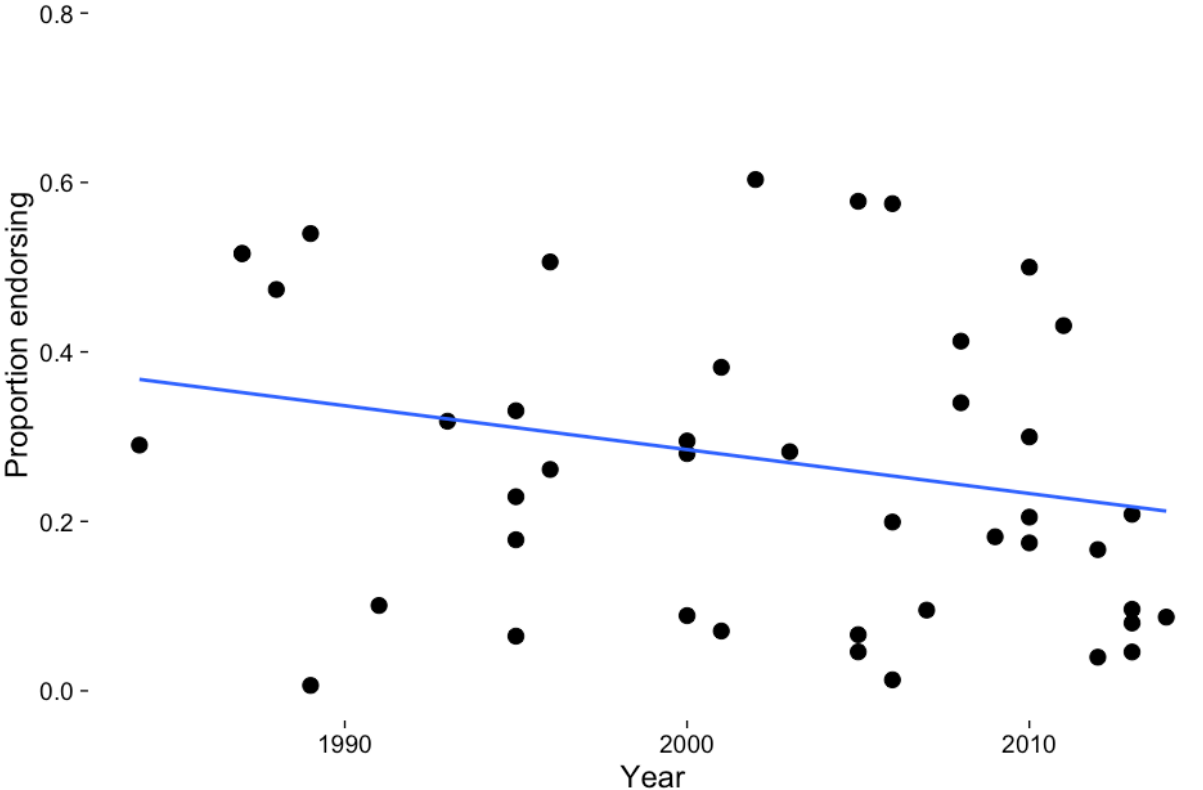


Figure 7. Meta-Regression of Proportion Female Sample in All HA Diagnoses

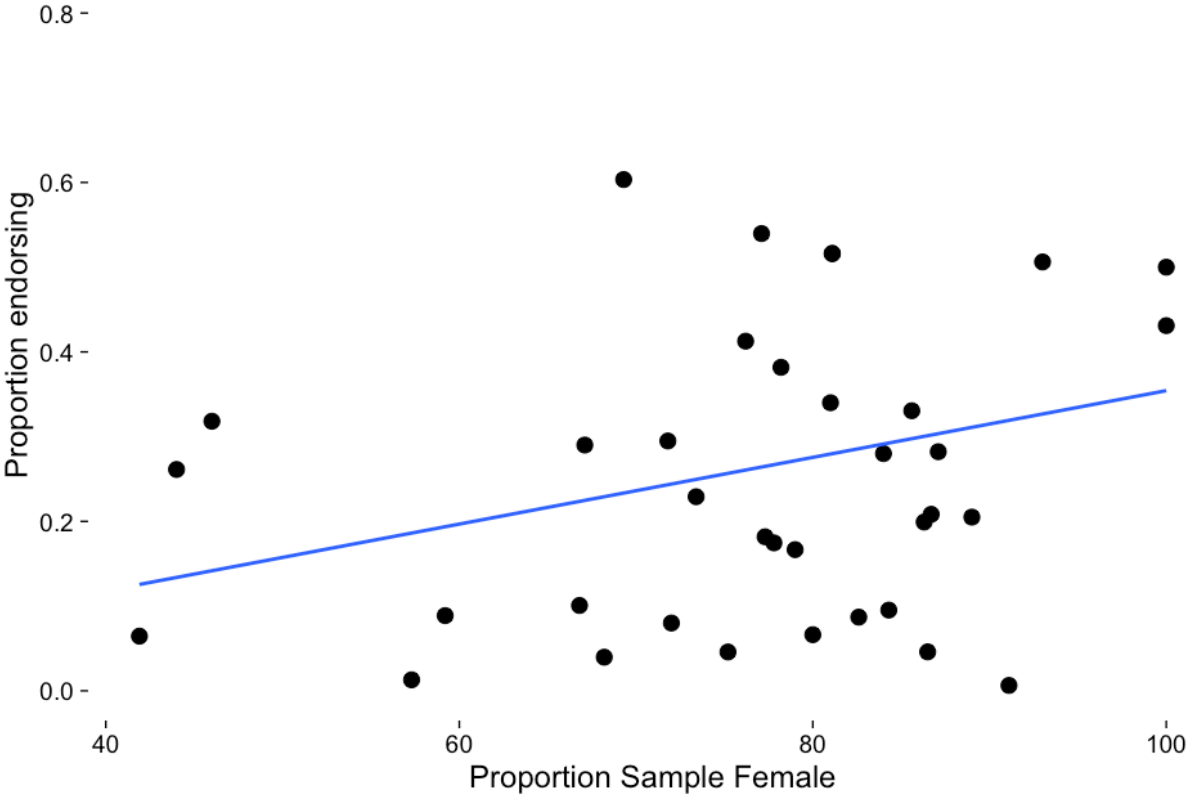


Figure 8. Forest Plot of Alcohol as Trigger for Migraine

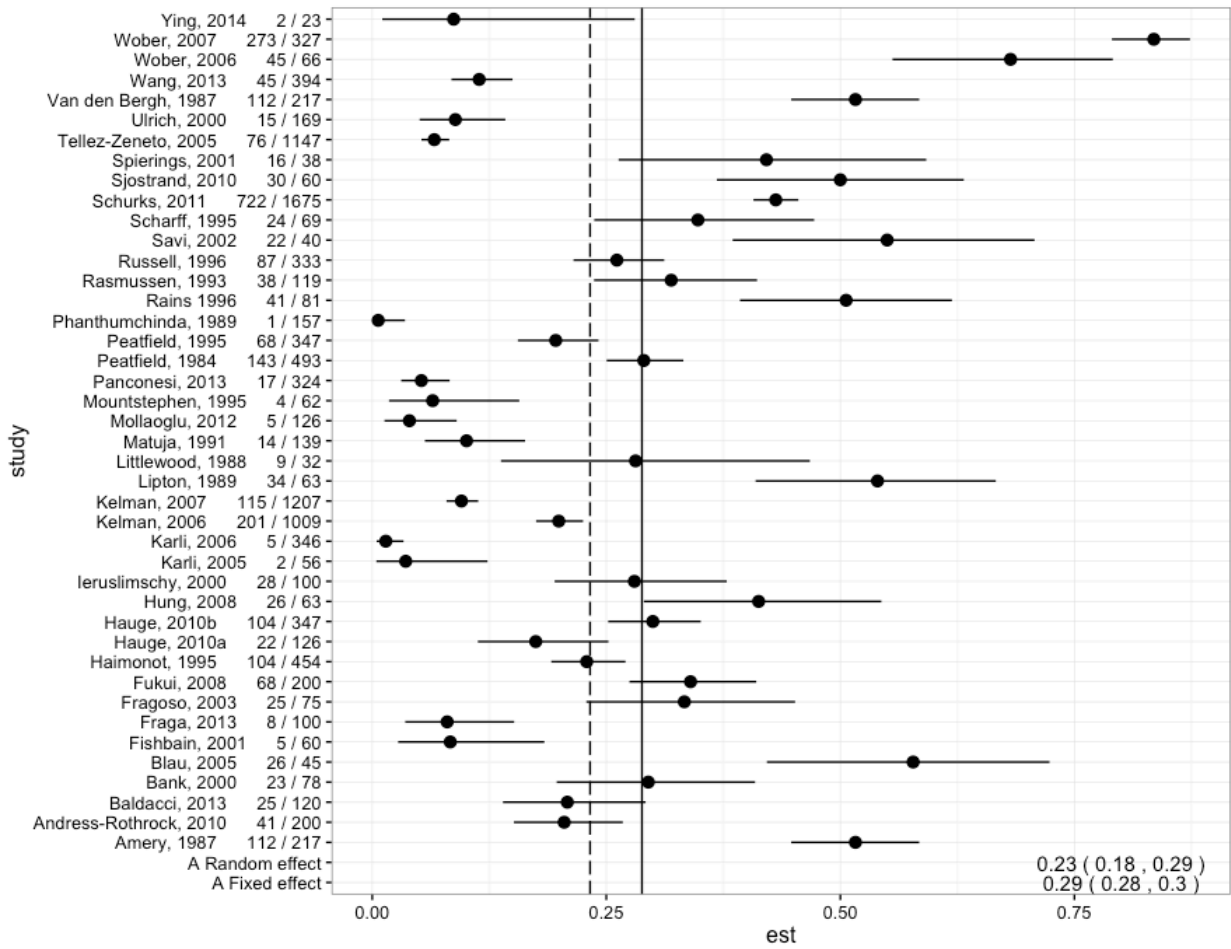


Figure 9. Forest Plot of Alcohol as Trigger for TTH

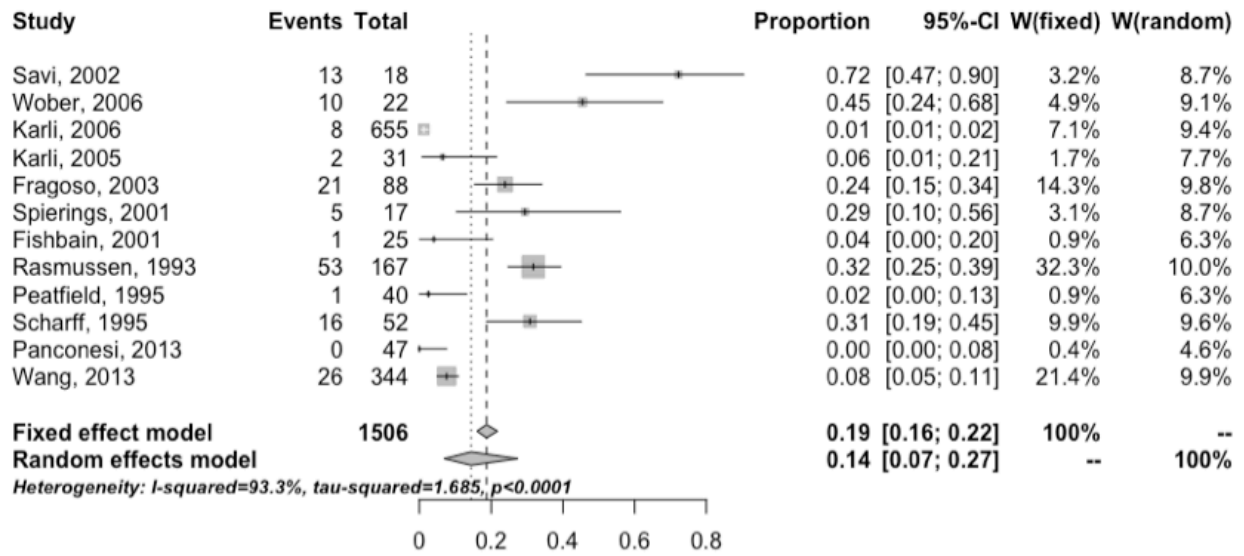


Figure 10a. Meta-Regression of Year in Migraine v. TTH

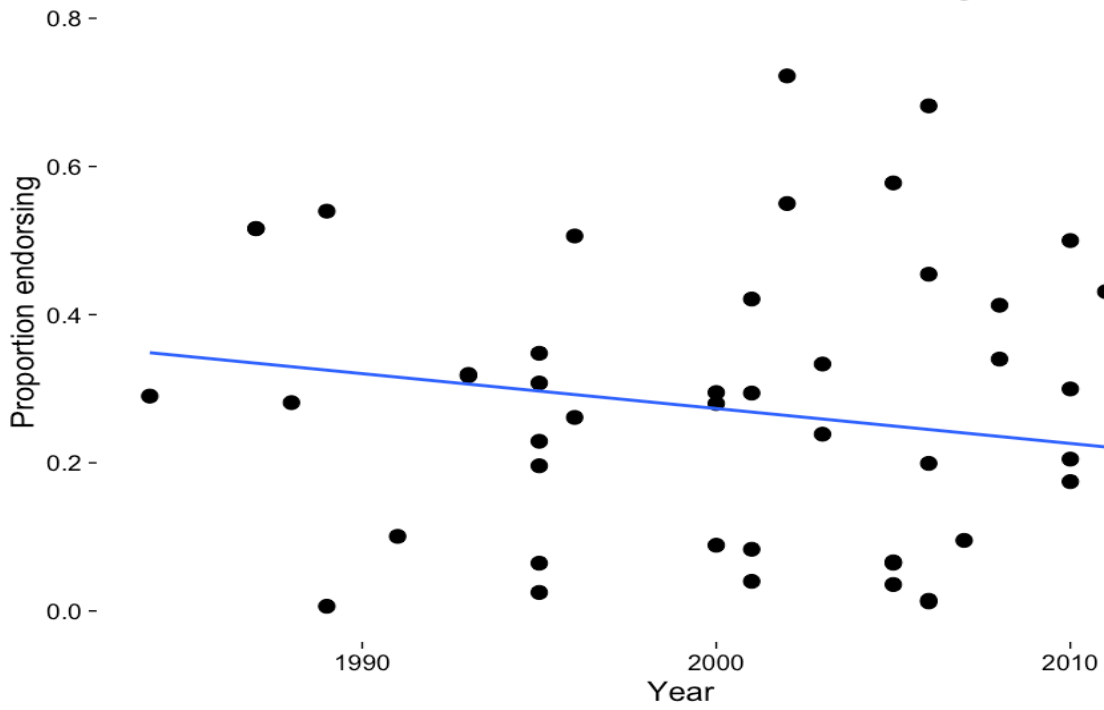


Figure 10b. Meta-Regression of Year by each Diagnosis

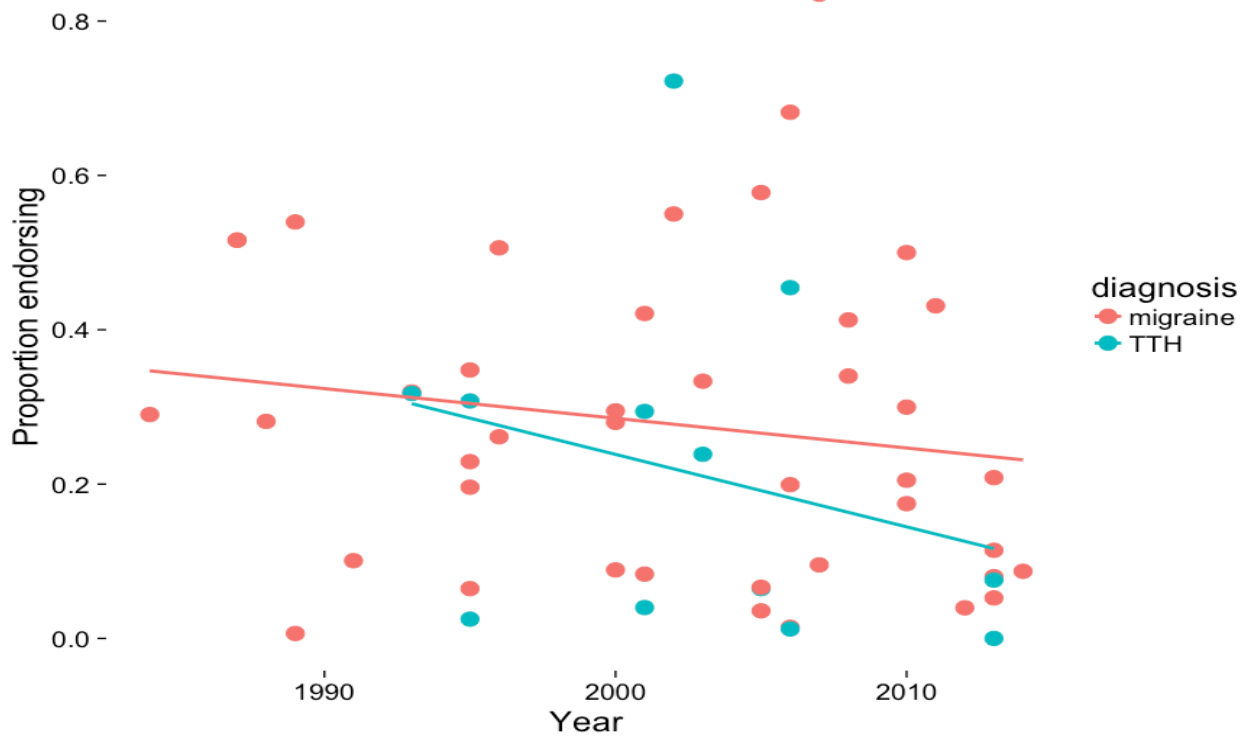


Figure 11a. Meta-Regression of Proportion Sample Female in Migraine v. TTH

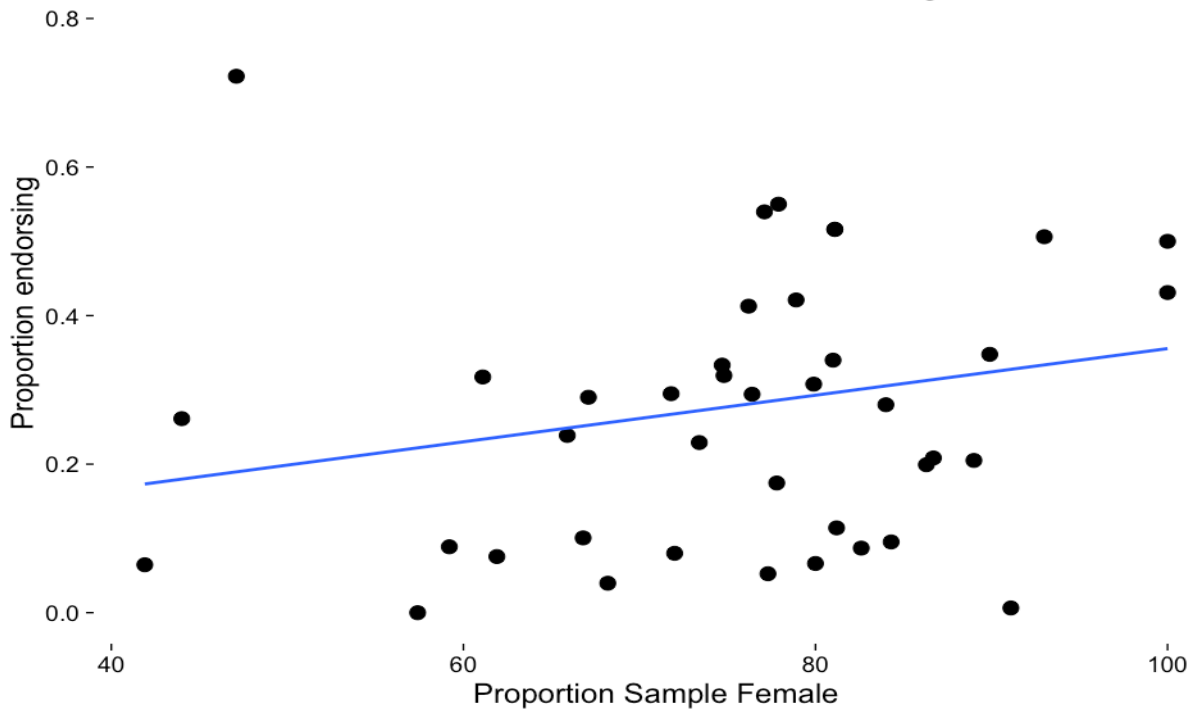


Figure 11b. Meta-Regression of Proportion Sample Female by each Diagnosis

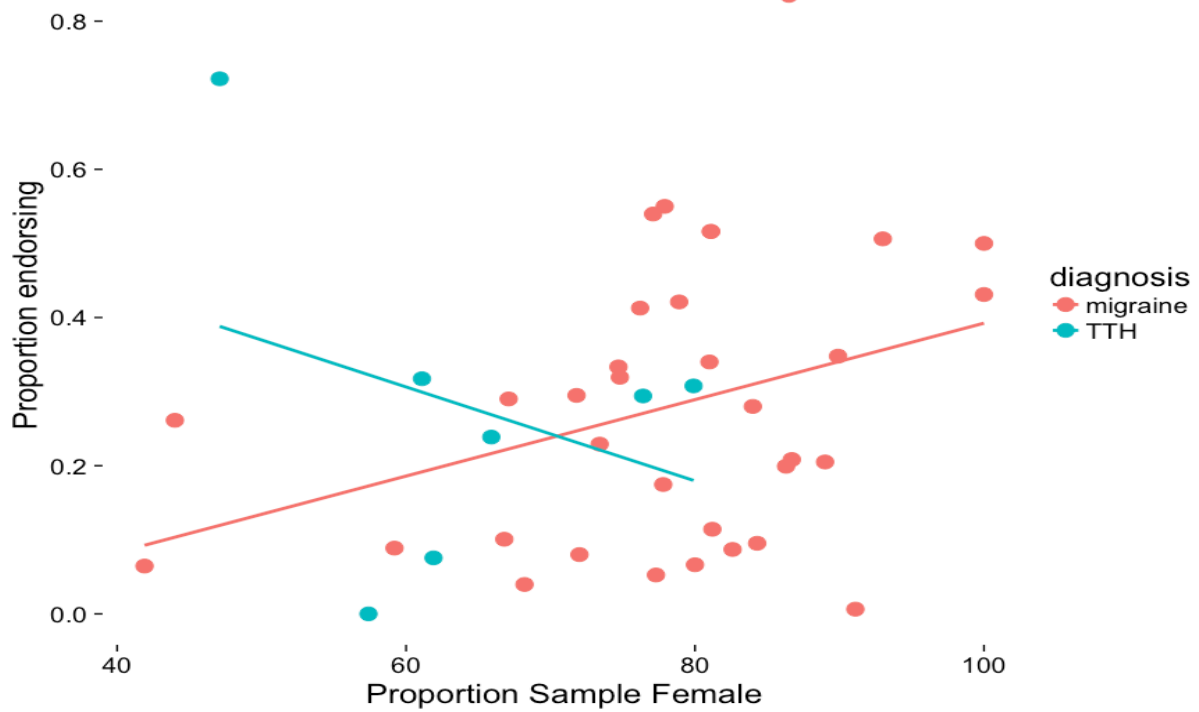


Figure 12. Forest Plot of Alcohol as Trigger for Migraine With Aura

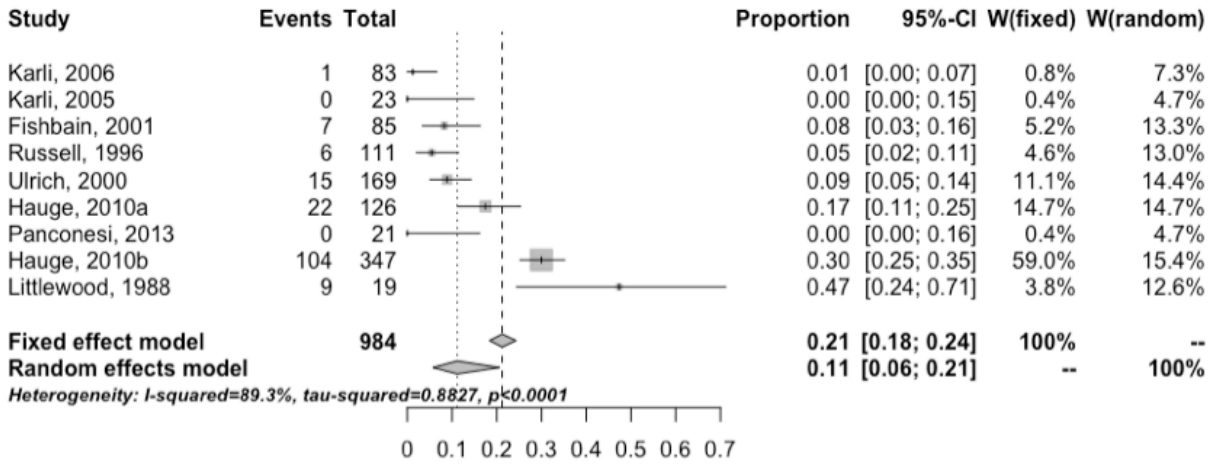


Figure 13. Forest Plot of Alcohol as Trigger for Migraine Without Aura

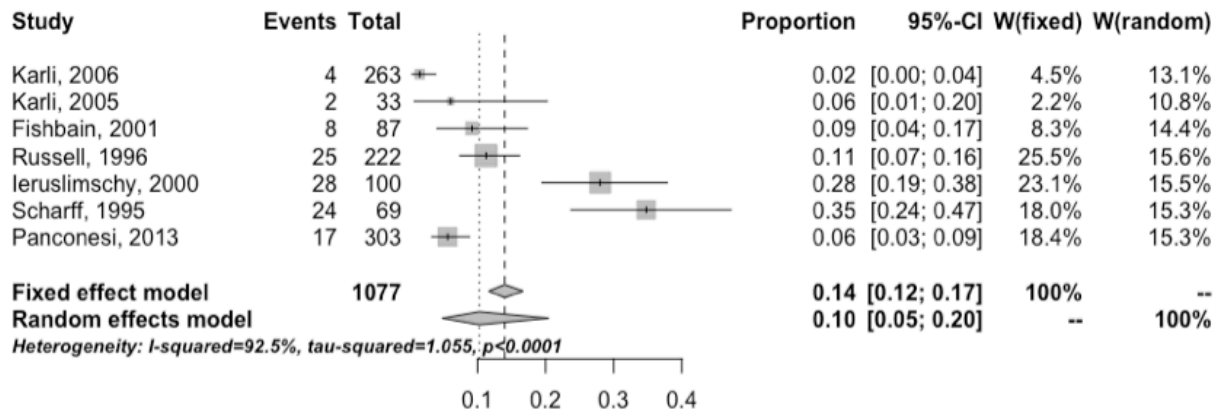


Figure 14a. Meta-Regression of Year in MA v. MWA

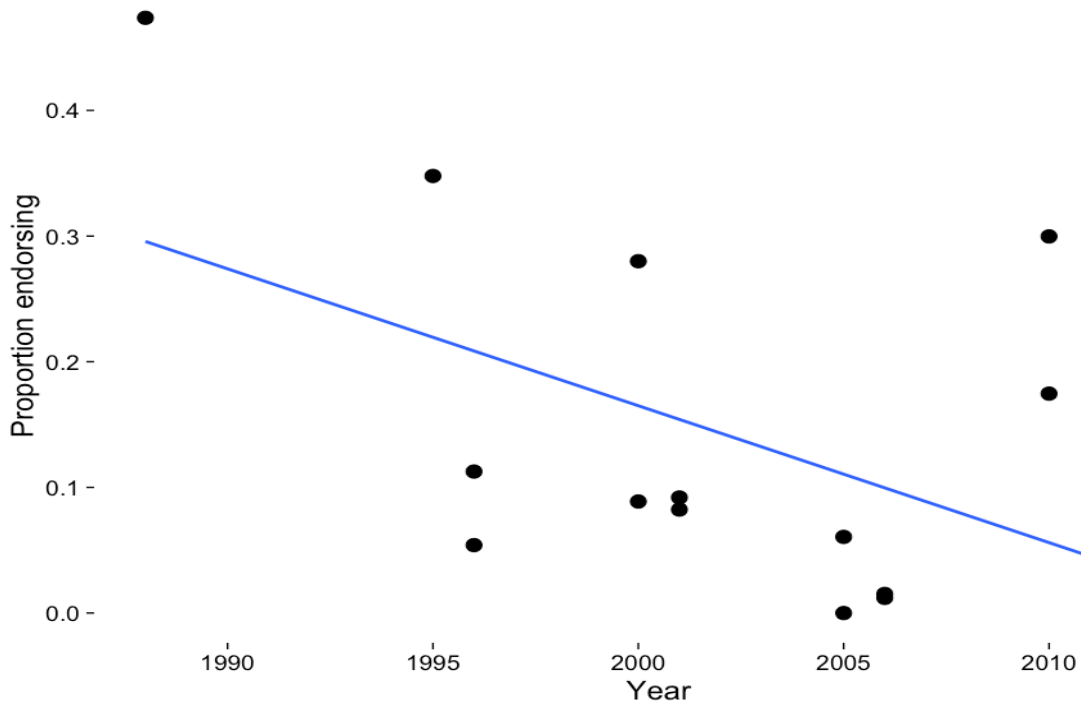


Figure 14b. Meta-Regression of Year by each Diagnosis

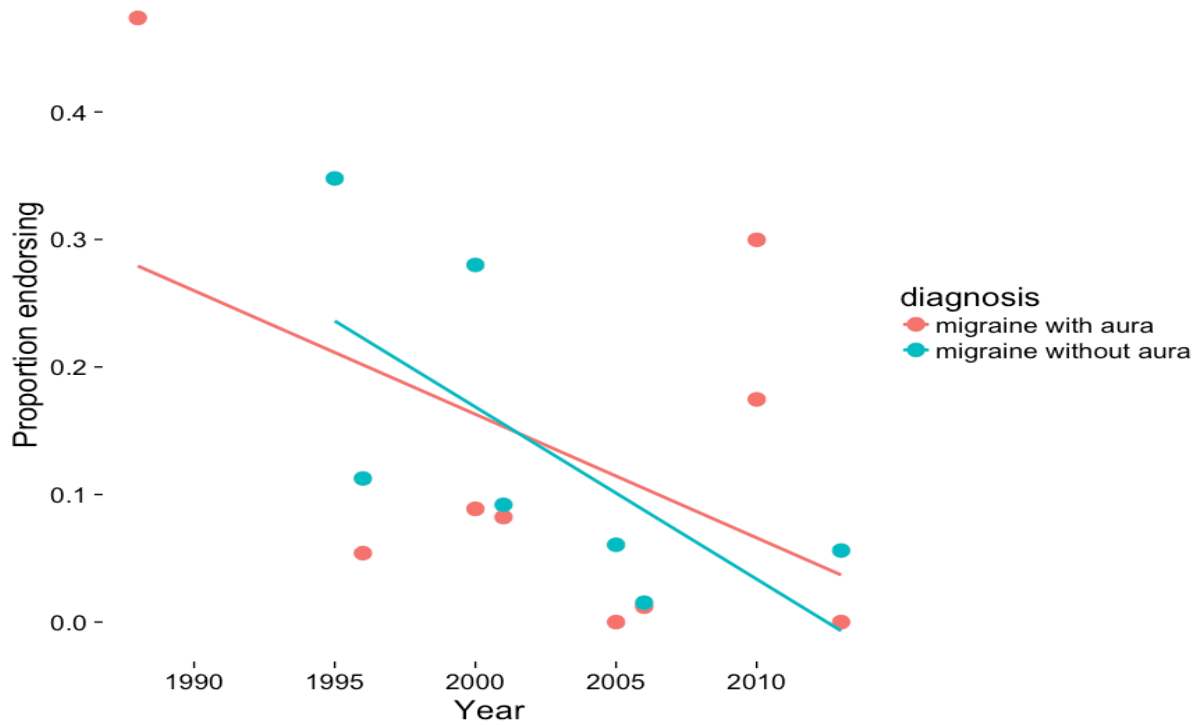


Figure 15a. Meta-Regression of Proportion Sample Female in MA v. MwA

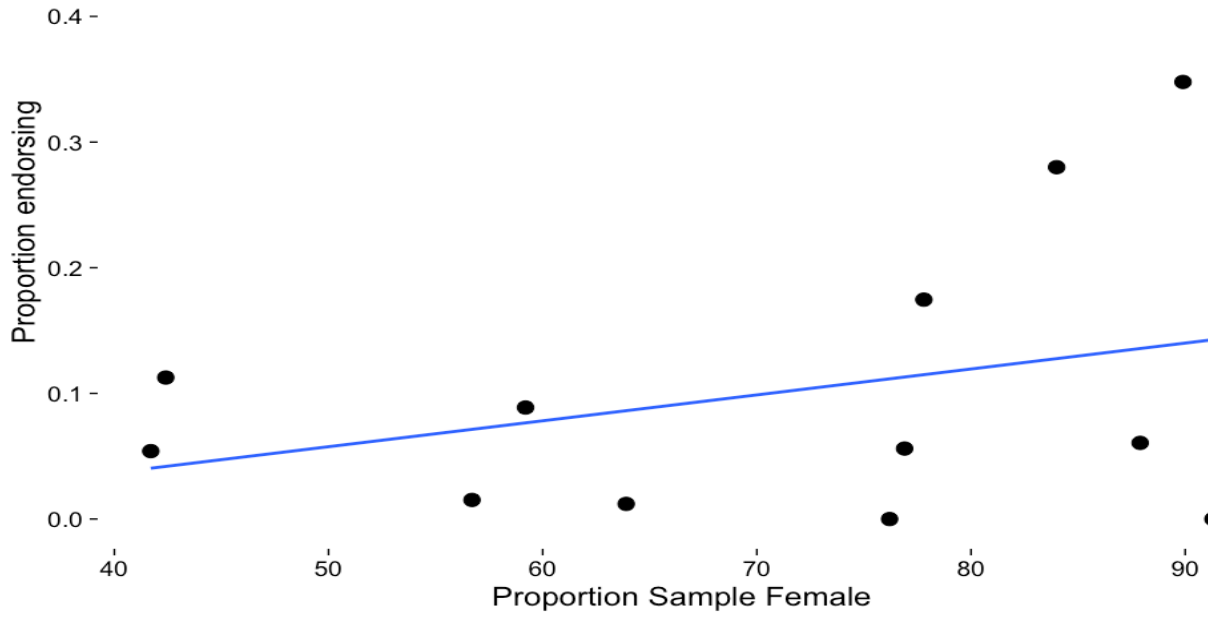


Figure 15b. Meta-Regression of Proportion Sample Female by each Diagnosis

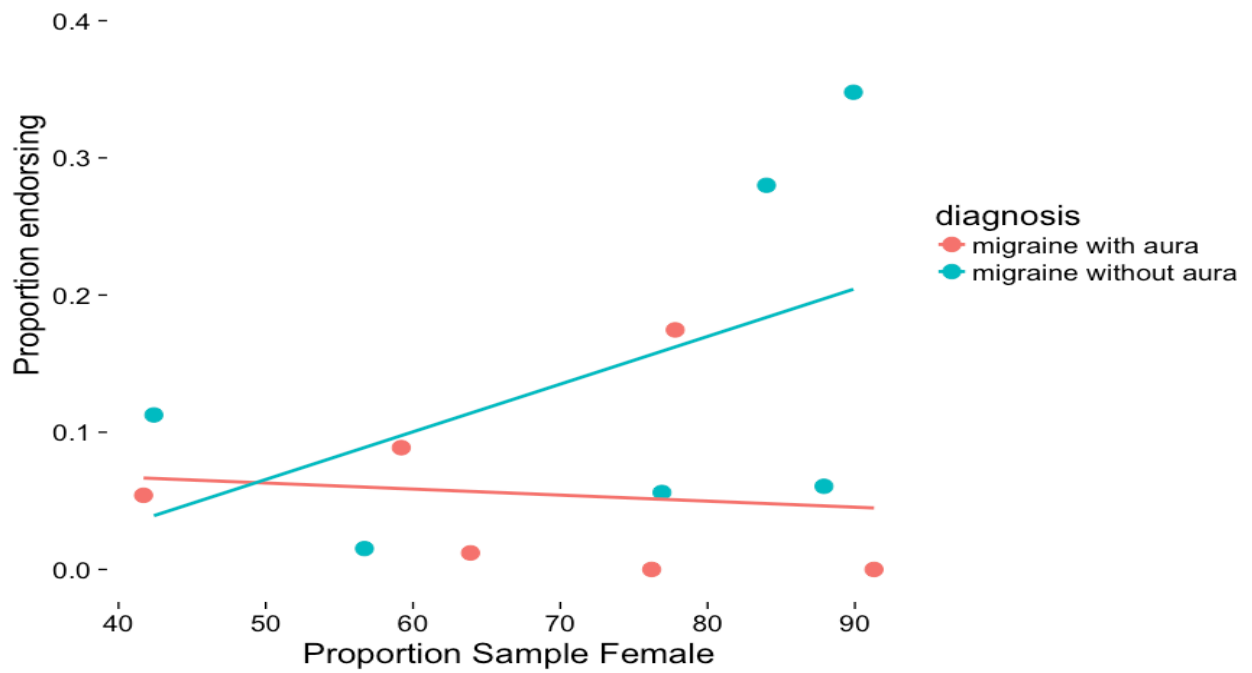


Figure 16. Forest Plot of Trigger Effect of Beer

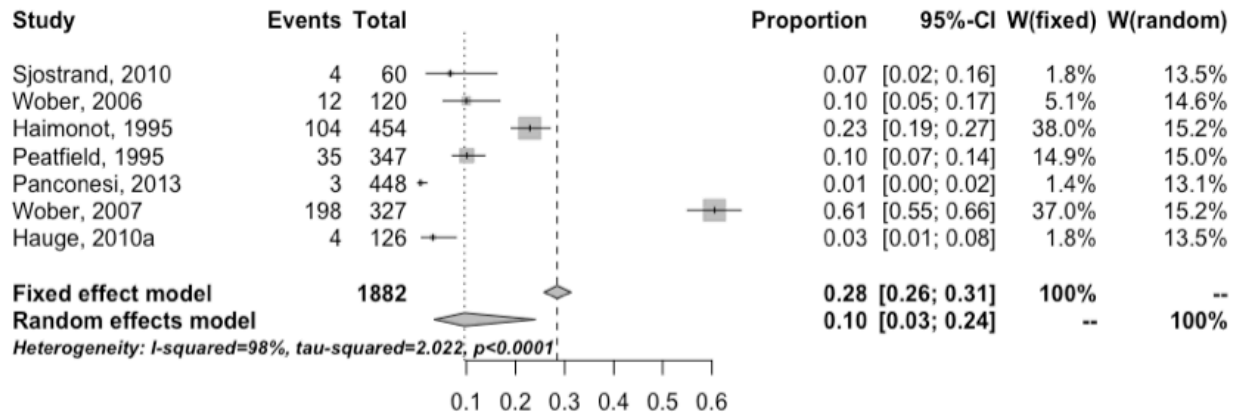


Figure 17. Forest Plot of Trigger Effect of Red Wine

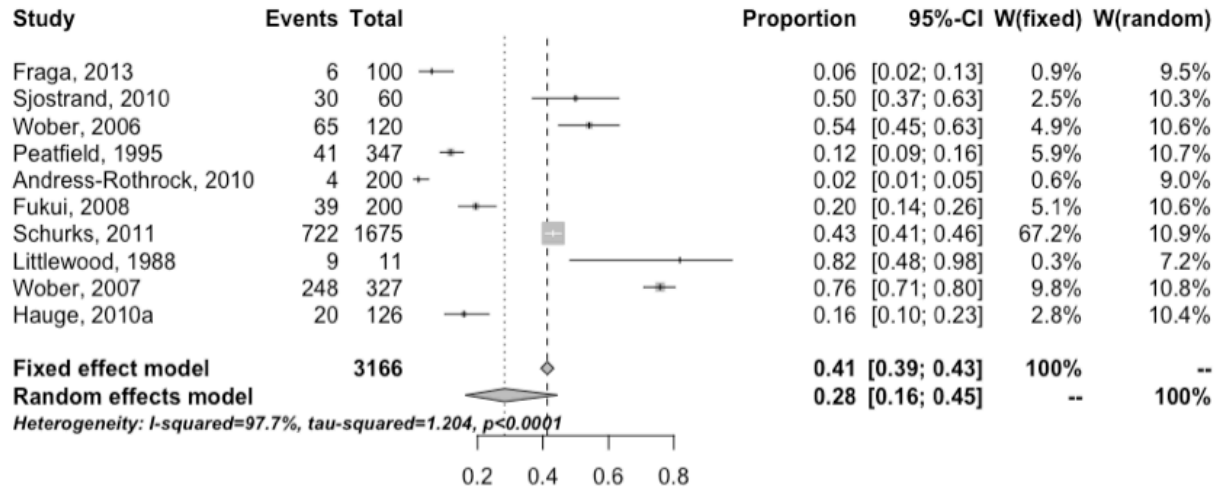


Figure 18. Forest Plot of Trigger Effect of Sparkling Wine

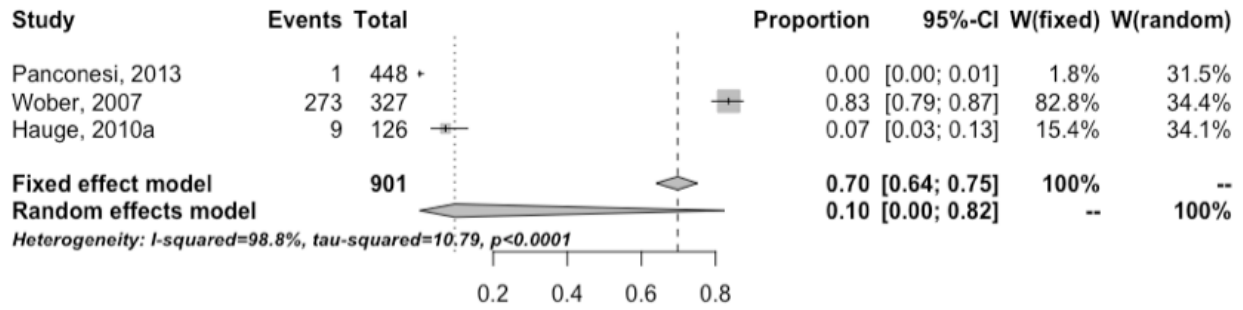


Figure 19. Forest Plot of Trigger Effect of Spirits

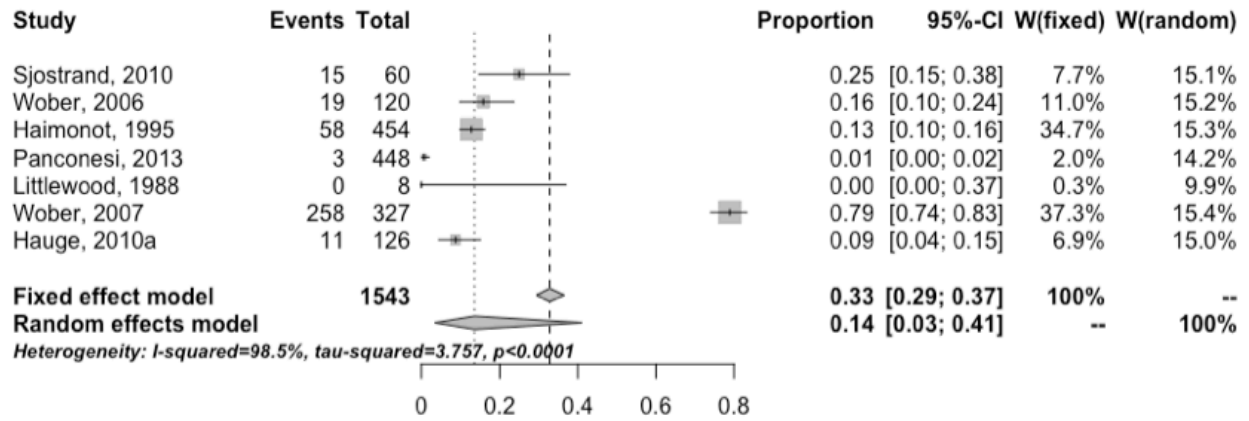


Figure 20. Forest Plot of Trigger Effects of White Wine

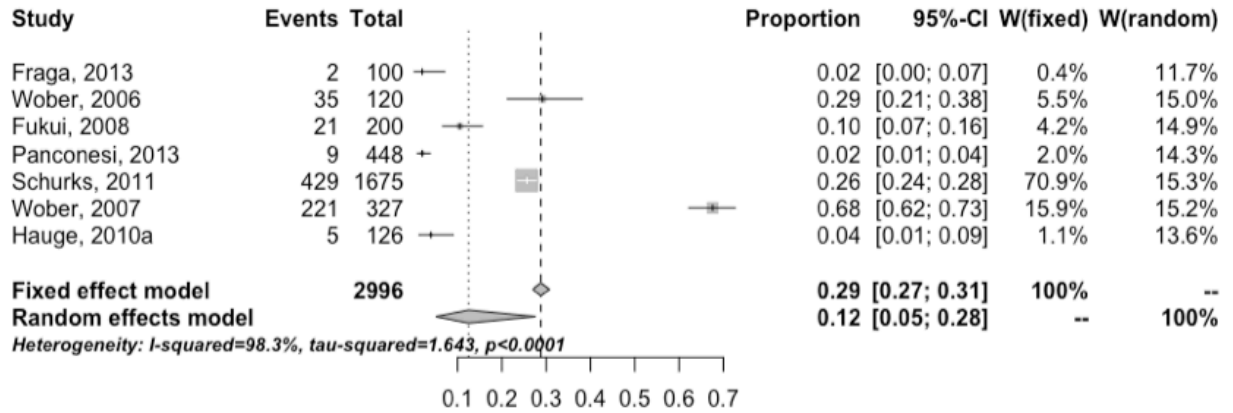


Figure 21a. Meta-Regression of Year by Alcohol Type

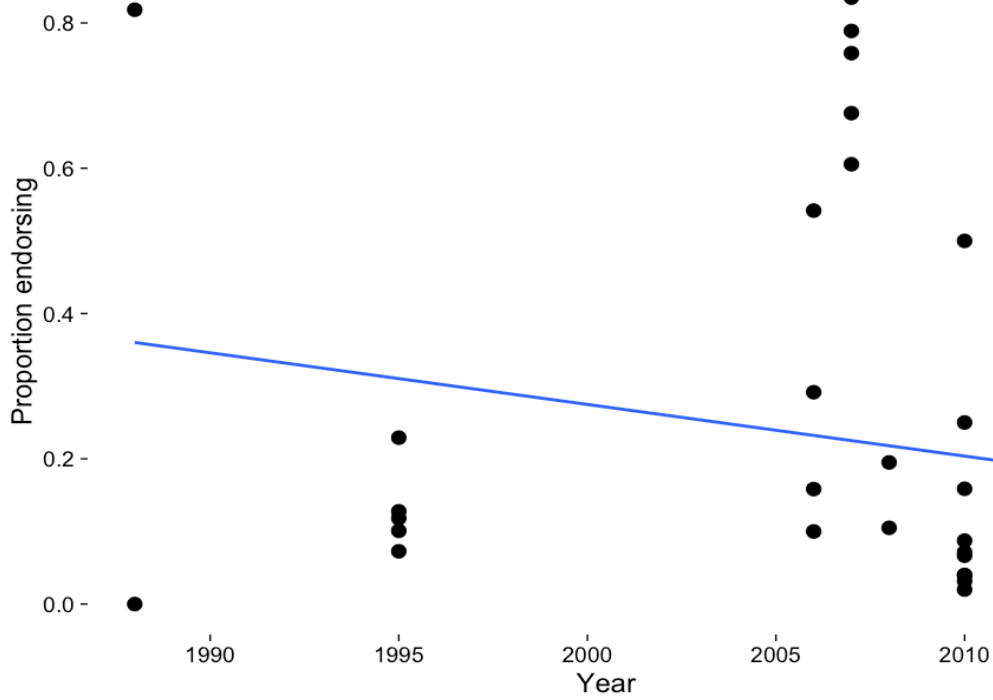


Figure 21b. Meta-Regression of Year by each Alcohol Type

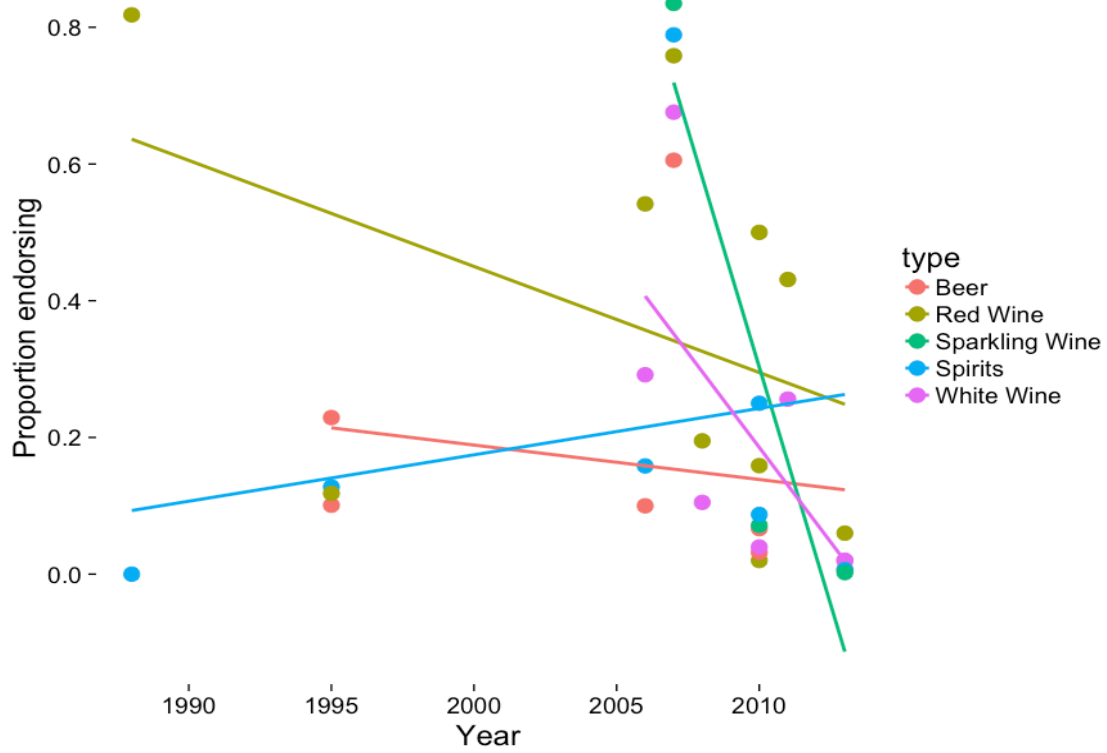


Figure 22a. Meta-Regression of Proportion Sample Female by Alcohol Type

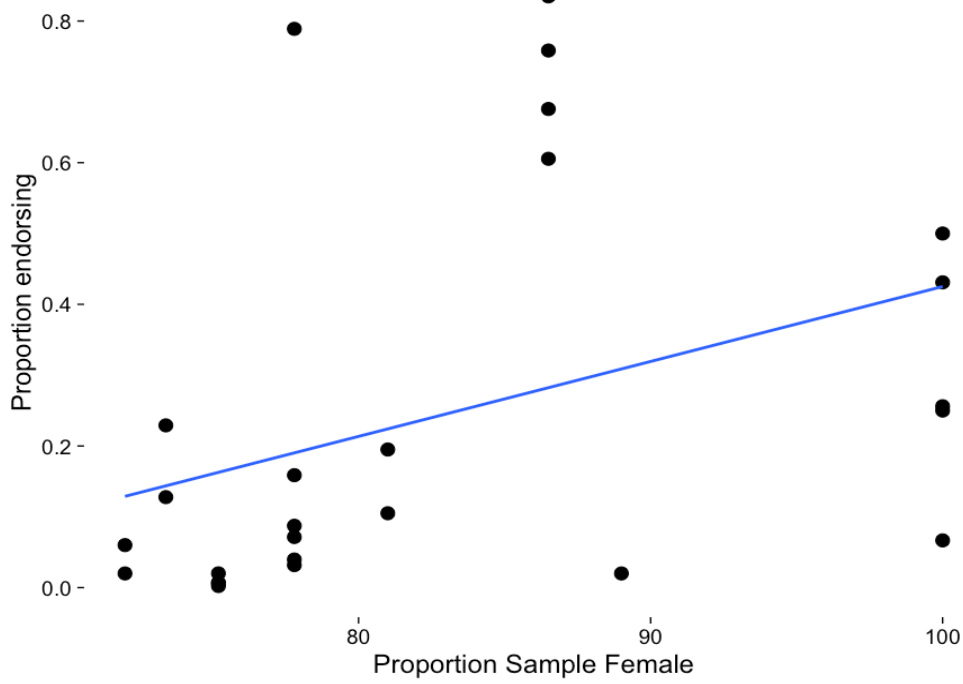
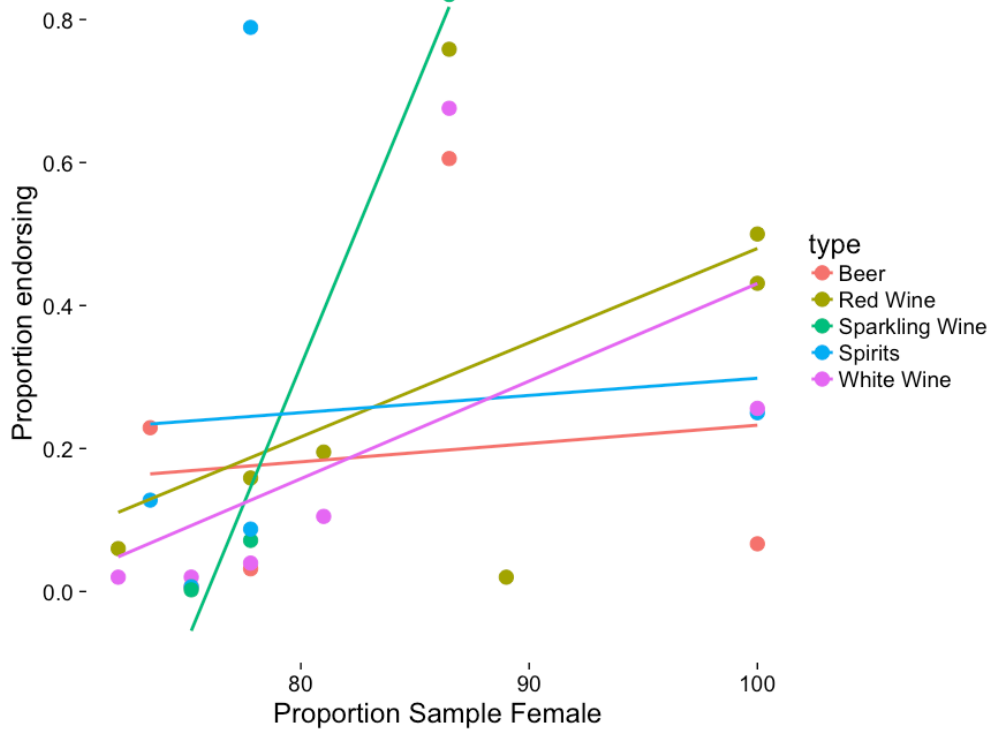


Figure 22b. Meta-Regression of Proportion Sample Female by each Alcohol Type



VITA

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EDUCATION

Pre-Doctoral Internship in Clinical Psychology, University of Texas Health Science Center San Antonio 7/2015–6/2016
Doctoral Student in Clinical Psychology, University of Mississippi 2010 – Present
Dissertation: *Alcohol Use as Precipitant and Comorbidity in Primary Headache* Anticipated Graduation 08/2016
M.A. Clinical Psychology, University of Mississippi 2013
Thesis: *Relations between alcohol use and migraine among a college sample*
B.A. Psychology, *summa cum laude*: University of Alabama 2010
B.A. English, *summa cum laude*: University of Alabama 2010

PROFESSIONAL MEMBERSHIPS

Association for Behavioral and Cognitive Therapies (ABCT) Student Member 2011 – Present
American Psychological Association (APA) Student Member 2009 – Present
American Headache Society (AHS) Student Member 2010 – 2011

HONORS AND AWARDS

John and Lillian Wolfe Award for Graduate Student Excellence 2014

University of Alabama Undergraduate Student Research Excellence	2010
Psi Chi National Honor Society in Psychology	2009
Sigma Tau Delta National Honor Society in English	2009
Emerson R. Loomis English Scholarship	2009
Lambda Sigma National Honor Society	2007 – 2008
Alpha Lambda Delta National Honor Society	2007
Phi Eta Sigma National Honor Society	2007
Knights of Columbus Women’s Auxiliary Scholarship	2006
Lucy Blankenship Piper Memorial Scholarship	2006 – 2010
University of Alabama Alumni Association Scholarship	2006 – 2010

LICENSES/CERTIFICATIONS

Provisionally Certified Mental Health Therapist (Jurisdiction: MS)
 Examination for Professional Practice in Psychology (EPPP)
Passed at Doctoral Level 05/2014

PUBLICATIONS AND PRESENTATIONS

Publications in Peer-Reviewed Journals

Walters, A. B., **Davis, R. E.**, Houle, T. T., & Smitherman, T. A. (in preparation). Perceived headache triggers: A meta-analysis of over 50 years of literature.

Sufka, K. J., Staszko, S. M., Johnson, A. P., Davis, M. E., **Davis, R. E.**, & Smitherman, T. A. (2016). Clinically Relevant Behavioral Endpoints in a Recurrent Nitroglycerin Migraine Model in Rats. *Journal of Headache and Pain*.

Smitherman, T. A., Walters, A. B., **Davis, R. E.**, Ambrose, C. E., Roland, M., Houle, T. T., & Rains, J. (2016). Randomized controlled trial of behavioral insomnia treatment for chronic migraine with comorbid insomnia. *Headache*.

Smitherman, T. A., **Davis, R. E.**, Walters, A. B., Young, J., & Houle, T. T. (2015). Anxiety sensitivity and headache: Diagnostic differences, impact, and relations with perceived headache triggers. *Cephalalgia*.

Rains, J. C., **Davis, R. E.**, & Smitherman, T. A. (2015). Tension-type headache and sleep. *Current Neurology and Neuroscience Reports*.

Davis, R. E., Smitherman, T. A., & Baskin, S. M. (2013). Personality traits, personality disorders, and migraine: A review. *Neurological Sciences*, 34(Suppl. 1), 7-10.

Published Abstracts (presented as posters at national and international conferences)

Smitherman, T. A., Walters, A. B., Ambrose, C. E., **Davis, R. E.**, Roland, M., Houle, T. T., & Rains, J. (2014, June). Randomized controlled trial of behavioral insomnia treatment for chronic migraine with comorbid insomnia: Preliminary results of a sham-controlled pilot study. *Headache*, *54*, 33. Poster presented at the annual scientific meeting of the American Headache Society, Los Angeles, CA.

Davis, R. E., Peck, K. R., Hamer, J. D., & Smitherman, T. A. (2013). Relations between alcohol use and migraine among young adults. *Cephalalgia*, *33*(Suppl.1), 266. Poster presented at the convention of the International Headache Society, Boston Massachusetts.

Davis, R. E., & Smitherman, T.A. (2012). Anxiety sensitivity as a predictor of headache frequency and disability among individuals with episodic migraine and tension type headache. *Headache*, *52*, 911. Poster presented at the annual convention of the American Headache Society, Los Angeles, California.

Poster Presentations

Walters, A. B., **Davis, R. E.**, Turner, D. P., Houle, T. T., & Smitherman, T. A. (2015, June). *A Meta-Analytic Review of Perceived Triggers of Migraine and Tension-Type Headache*. Poster presented at the annual convention of the American Headache Society, Washington, DC.

Sufka, K. J., Stasko, S. M., Johnson, A. P., Davis, M. E., **Davis, R. E.**, & Smitherman, T. A. (2014, November). *Clinically relevant endpoints in a recurrent nitroglycerin migraine model in rats*. Poster accepted for presentation at the annual convention of the Society for Neuroscience, Washington, D.C.

Wencel, L. W., Person, J. M., Rattliffe, G. M., Black, A. K., **Davis, R. E.**, & Smitherman, T. A. (2014, April). *Exploring the influence of headache triggers on disability and self-efficacy*. Poster presented at the 2014 UM Conference on Psychological Science, Oxford, MS.

Davis, R. E., McDermott, M. J., Smitherman, T. A., Gratz, Kim. L., & Tull, M. T. (2011, November). *Migraine among substance dependent individuals in residential substance abuse treatment*. Poster presented at the annual convention of the Association for Behavioral and Cognitive Therapies, Toronto, Canada.

Walters, A. B., **Davis, R. E.**, Hamer, J. D., Townsend, E. A., Blann, K. R., Schulenberg, S. E., & Smitherman, T. A. (2011, November). *Relations between migraine, psychological variables, and meaning in life in a college population*. Poster presented at the annual convention of the Association for Behavioral and Cognitive Therapies, Toronto, Canada.

Walters, A. B., Smitherman, T. A., **Davis, R. E.**, Townsend, E. A., Hamer, J. D., & Blann, K. R.

(2011, June). *Sleep hygiene and psychiatric comorbidity in episodic migraineurs*. Poster presented at the annual convention of the American Headache Society, Washington, DC.

Paper Presentations and Panel Discussions

Peck, K.R., **Davis, R.E.**, Foote, H., & Smitherman, T.A. (2015, April). *Differential Effects of Mental Health Disorders: Are Female and Treatment-Seeking Migraineurs More Disabled by Migraine?* Paper presented at the 2015 UM Conference on Psychological Science, Oxford, MS.

Walters, A. B., **Davis, R. E.**, Houle, T. T., & Smitherman, T. A. (2014, April). *Perceived headache triggers: A meta-analysis of over 50 years of literature*. Paper presented at the 2014 UM Conference on Psychological Science, Oxford, MS.

Titcomn, C., Brodsky, S. L., Nagle, J., Guadagno, R., & **Davis, R. E.** (2012, March). *From First Impressions to Verdict: Predictive pathways in mock-juror decision-making*. Paper presented at the annual convention of the American Psychology Law-Society, San Juan, Puerto Rico.

Schulenberg, S. E., **Davis, R. E.**, & Magee, L. J. (2011, June). *Logotherapy and psychological assessment: Integrating theory with research and practice*. Paper presented at the Eighteenth World Congress on Viktor Frankl's Logotherapy, Dallas, TX.

Barnes, R. C., Rogina, J. M., Hutzell R. R., Schulenberg, S. E., Wimberly, C., Winters, M., **Davis, R. E.**, Magee, L. J., & Schnetzer, L. W. (2011, June). Clinical Colloquium at the Eighteenth World Congress on Viktor Frankl's Logotherapy, Committee Member, Dallas, TX.

Grant-Funded Research Experience

Project Coordinator. *Efficacy of behavioral insomnia treatment for chronic migraine: A randomized controlled pilot study*. Migraine Research Foundation. (August 2012-May 2013). \$49,858. (PI: Todd A. Smitherman, Ph.D.)

Project Coordinator. *Efficacy of mental health interventions in response to the effects of the Deepwater Horizon Oil Spill*. Mississippi Department of Mental Health. (November 2010-July 2011). \$281,556. (PI: Stefan E. Schulenberg, Ph.D.)

Other Research Experience

Graduate Lab Member: Migraine and Behavioral Health Laboratory, Oxford, MS (2010 – Present)

Examined primary headache disorders in relation to patterns of alcohol use, sleep, and psychological factors (eg, stress, anxiety, depression) among college students.

University of Mississippi Clinical-Disaster Research Collaborative, Oxford, MS, (2010 – 2011)

Worked with the Mississippi Department of Mental Health to collect information regarding the services funded through the Gulf Oil Spill Behavioral Health Grant Program. Examined psychological factors (eg, stress, anxiety, self-efficacy, purpose in life, and environmental concern), in addition to directly assessing how individuals were affected by the Gulf Oil Spill.

EDITING AND REVIEWING

Ad Hoc Reviewing

Cochrane Collaboration (Pain, Palliative and Supportive Care Review Group)

Cephalalgia

Headache

Professional Psychology: Research and Practice

International Journal of Clinical Practice

Behaviour Research and Therapy

Sattler, J. M. (2014). Intellectual Disability. In J. M. Sattler (Eds.), *Foundations of Behavioral, Social, and Clinical Assessment of Children*. La Mesa, CA: Jerome M. Sattler, Publisher, Inc. Reviewed chapters 3 and 8.

CLINICAL EXPERIENCE

Advance Clinic, San Antonio, TX (2015 – Present)

Individual cognitive-behavioral therapy and acceptance and commitment therapy for adult community outpatients with Axis I and II disorders.

Robert Brady Green Hospital, San Antonio, TX (2015 – Present)

Primary integrated care providing individual cognitive-behavioral therapy and acceptance and commitment therapy for individuals with diabetes, hypertension, obesity, and chronic pain conditions.

PROXIMA, San Antonio, TX (2015 – Present)

Individual cognitive-behavioral therapy and family systems therapy for children and adolescents with ADHD, ODD, conduct disorder, and mood disorders.

South Texas Research Organizational Network Guiding Studies on Trauma And Resilience, San Antonio, TX (2015 – Present)

Individual cognitive processing therapy for individuals with posttraumatic stress disorder.
Individual comprehensive behavioral intervention for tics for individuals with Tourette syndrome and other tic disorders.

Head Start, *Oxford, MS; Batesville, MS; Ashland, MS* (2014 – 2015)

Mental health consultant conducting classroom observations, assessing disruptive behaviors, and providing behavioral support for preschoolers, parents, and teachers.

Communicare, *Pittsboro, MS* (2013 – 2014)

Individual and group cognitive-behavioral therapy and acceptance and commitment therapy for adult and children community mental health outpatients with Axis I and II disorders.

The Baddour Center, *Senatiobia, MS* (2011 – 2013)

Individual and group cognitive-behavioral therapy for adults living in a residential facility for individuals with intellectual and developmental disabilities.

University of Mississippi Psychological Services Center, *Oxford, MS*, (2011 – 2015)

Individual cognitive-behavioral therapy and acceptance and commitment therapy for adult community outpatients with Axis I and II disorders.

TEACHING EXPERIENCE

Instructor of Record, University of Mississippi (Fall 2012, Spring 2013)

PSY 201: Introductory Psychology

Guest Lecturer, University of North Alabama (Fall 2014)

SRM 200: Leisure in Contemporary Life

Topics: Empirically supported techniques for stress reduction in daily life and the long-term effects of stress and anxiety

Guest Lecturer, University of Mississippi (Spring 2013)

PSY 309: Learning

Topics: Classical conditioning and application of classical conditioning in advertising and psychotherapy. Operant conditioning and successful application of positive/negative reinforcement/punishment.

REFERENCES

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Department of Psychology
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Professor and Director Clinical Training
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