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Alcohol Use as a Comorbidity and Precipitant of Primary Headache: Review and Meta-analysis

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Abstract
Purpose of Review In contrast to well-established relationships between headache and affective disorders, the role of alcohol use in primary headache disorders is less clear. This paper provides a narrative overview of research on alcohol use disorders (AUDs) in primary headache and presents a meta-analysis of the role of alcohol as a trigger (precipitant) of headache.
Recent Findings The majority of studies on AUDs in headache have failed to find evidence that migraine or tension-type headache (TTH) is associated with increased risk for AUDs or problematic alcohol use. The meta-analysis indicated that 22% (95% CI: 17–29%) of individuals with primary headache endorsed alcohol as a trigger. No differences were found between individuals with migraine (with or without aura) or TTH. Odds of endorsing red wine as a trigger were over 3 times greater than odds of endorsing beer.
Summary An absence of increased risk for AUDs among those with primary headache may be attributable to alcohol's role in precipitating headache attacks for some susceptible individuals. Roughly one fifth of headache sufferers believe alcohol precipitates at least some of their attacks. Considerable study heterogeneity limits fine-grained comparisons across studies and suggests needs for more standardized methods for studying alcohol-headache relationships and rigorous experimental designs.

Keywords Alcohol · Trigger · Migraine · Red wine · Headache · Comorbidity

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Introduction

The primary headache disorders of migraine and tension-type headache (TTH) are two of the most prevalent medical conditions globally [1], and migraine remains the sixth leading cause of years lived with disability worldwide [2]. The impact of these conditions is often compounded by co-occurring (comorbid) psychiatric disorders such as major depressive disorder, various anxiety disorders, and bipolar disorder [3–7]. Compared to the abundant literature on the prevalence and impact of mood and anxiety disorders among individuals with migraine or TTH, fewer studies have examined relations between alcohol use disorders (AUDs) and headache. Alcohol use disorders are classified as problematic patterns of alcohol use that result in clinically significant impairment [8]. Alcohol use is of interest also because alcohol may serve as a precipitant (i.e., trigger) of headache attacks for some individuals. The purpose of this paper is to review extant literature on the role of alcohol use in the primary headache disorders of migraine and TTH. The paper first provides a narrative overview of research on AUDs among headache suffers then presents results of a meta-analytic review on the role of alcohol as a potential headache trigger.

Alcohol Use Disorders in Primary Headache

Compared to other substance use disorders, AUDs are relatively common among adults (8.5% annual prevalence), and

prevalence peaks between ages 18–29 (16.2% annual prevalence; [8]). Unlike migraine, AUDs affect men more than women. Previously differentiated into separate diagnoses, alcohol abuse and alcohol dependence, the current fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classification of AUDs recognizes that, like other substance use disorders, maladaptive alcohol use occurs on a continuum of severity (i.e., mild, moderate, severe) and no longer distinguishes two distinct entities [8]. However, most of the studies on AUDs among individuals with headache were conducted prior to this change in diagnostic nomenclature.

The largest epidemiologic studies adhering to diagnostic criteria for AUDs used samples from the USA [6, 7, 9, 10], Canada [5], and Singapore [11]. In the earliest study, Breslau and colleagues [9] examined 1007 members of a health maintenance organization between the ages of 21 and 30. Compared to those without migraine, individuals with migraine with aura (MA) were at greater risk for lifetime alcohol abuse or dependence (20.6 vs 30.5%, odds ratio [OR] = 2.1). Those who had migraine without aura were not at statistically increased risk (24.6%; OR = 1.6). The second U.S. study of 1343 adults found no association between alcohol or drug use disorders at baseline and incident migraine over a decade later (OR = 1.05; [10]). A third large-scale U.S. study of 5692 adults also found no significant relationship between 12-month alcohol abuse or dependence and migraine (4.2% prevalence among migraineurs vs 3.0% for those without headache; OR = 1.4) or TTH (3.4% prevalence among TTH; OR = 1.1; [6]). The most recent U.S. study of 5064 adults similarly found no significant relationship between alcohol abuse (either lifetime or 12-month prevalence) and episodic migraine or chronic daily headache [7].

The Canadian study of 36,984 individuals aged 15+ found no differences in 12-month prevalence of alcohol dependence between individuals with and without migraine (2.3 vs 2.6%; [5]). Finally, Subramaniam et al. [11] assessed lifetime AUDs (i.e., abuse or dependence) among adults with various chronic pain conditions (i.e., migraine, arthritis, back pain) in Singapore. Compared to those without migraine, migraineurs had greater risk for a lifetime AUD (7.8%; OR = 2.1).

Though the findings are not entirely consistent, the majority of high-quality epidemiological studies have failed to find evidence suggesting migraine confers statistically increased risk for AUDs among the general population. Differences in findings between the aforementioned studies may be a result of varying adherence to AUD and migraine diagnostic criteria. Two of the earlier studies [9, 10] used AUD diagnostic criteria prior to publication of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [12], which more strictly defined alcohol dependence than prior editions. Of the three more recent studies, only the Saunders et al. [6] study assessed migraine via adherence to most of the migraine criteria set forth by the *International Classification of Headache Disorders* (ICHD-3 beta) [13]. To the extent that utilization of structured interviews comporting with established diagnostic criteria is indicative of study quality, existing evidence suggests lack of a clear relationship between AUDs and migraine. Though it is possible that migraine portends increased risk to develop AUDs many years later, epidemiological studies using multiple time points have not found evidence of a delayed risk effect [10, 14], and peak prevalence of AUDs is generally earlier than that of migraine [8, 15].

Other studies have evaluated relations between alcohol use and headache without attempting to formally establish AUD diagnoses, in which scores on validated measures of alcohol use were compared between different headache groups. Among a sample of outpatients at a headache clinic in Brazil, migraineurs were less likely than those with TTH to obtain a score on the Alcohol Use Disorders Identification Test (AUDIT; [16]) indicative of problematic alcohol use (PAU; 5.2 vs 16.1%; [17]). Two other studies compared rates of PAU among individuals with migraine, with non-migrainous headache, and without headache. In the first, 38,508 Norwegians were administered the CAGE questionnaire [18] to assess alcohol overuse [19]. Rates of alcohol overuse (1 or more positive CAGE endorsement) did not differ significantly between any of the three groups; increased frequency of alcohol consumption was associated with reduced odds of both types of headache. In the second study, Brazilian medical students without headache endorsed higher rates of PAU on the AUDIT than students with migraine or non-migrainous headache (20.0 vs 4.0% and 8.6, respectively; [20]). Though differences in study samples and validated measures limit comparisons, these studies do not suggest that individuals with migraine are at greater risk for PAU than individuals without headache or individuals with TTH. In this regard, their findings are similar to those from the aforementioned AUD studies.

Alcohol as a Headache Trigger

The preponderance of cross-sectional evidence suggesting that migraine does not confer increased risk for AUDs may be attributable to its role as a trigger of individual headache attacks, such that headache sufferers may abstain from alcohol to avoid precipitating headache (or be counseled to do so by their treating clinician). Although alcohol is not endorsed as a headache trigger as commonly as stress, hormones (in women), or missing meals or sleep [21], the role of diet in headache has been a source of considerable attention [22••]. Experimental research on precipitants of individual headache attacks is beset with difficulties in confirming causal relationships [23•, 24], and additional challenges present when studying alcohol specifically [25]. These include differentiating

headache that is induced rather quickly after ingesting alcohol from a more delayed headache that often occurs 5–12 h later (the latter of which is more common) and teasing out the underlying biochemical mechanisms in various alcoholic drinks. Though few studies have specifically addressed these unique challenges, the overwhelming majority of research on alcohol as a headache trigger is cross-sectional in nature. Multiple narrative reviews of this literature have been published within the last decade [22••, 25, 26•, 27], but a quantitative synthesis of existing studies is lacking. Accordingly, we conducted a meta-analytic review of such studies to quantify the effects of alcohol as a headache trigger given differences in methodologies, samples, and endorsement rates across prior studies. In this meta-analytic review, we hypothesized that alcohol consumption would be perceived as a trigger for both migraine and TTH, and we endeavored to assess variables that might moderate its role as a trigger (e.g., headache diagnosis, type of alcohol).

Methods

The meta-analysis adhered to PRISMA reporting guidelines [28]. Institutional review board approval was not necessary as this was a quantitative review of previously published data.

Search Strategy

The primary author conducted all search and eligibility review processes. On May 6, 2015, a multi-database (i.e., Academic Search Premiere, PsycARTICLES, Psychology and Behavioral Sciences Collection, PsycINFO, MEDLINE) search was conducted using the keyword terms "migraine OR headache" AND "trigger OR precipitant" AND "alcohol." All abstracts were reviewed for eligibility, bibliographies of retained articles were searched to identify additional articles fulfilling eligibility criteria, and full-texts of candidate articles were reviewed.

Eligibility Criteria

Inclusion criteria were chosen to maximize sensitivity and ensure capture of all relevant data. (1) Articles written in English (2) that utilized human participants (3) with a diagnosis of migraine or TTH that (4) used retrospective recall, prospective diary data, or experimental manipulation were included in the analyses. Exclusion criteria were editorials, review articles, case studies, treatment studies, and articles that focused on pathophysiology, employed static variables, or utilized animals.

Data Collection

Data extracted from retained articles were entered into an Excel database, including: (1) publication metadata (authors, year of publication, journal); (2) sample demographics (sample size, population drawn from, mean age, age range, % female); (3) headache characteristics (diagnostic criteria used, diagnoses, intensity, frequency [days/month or attacks/month]); (4) method of trigger assessment (open-ended query vs provided list of triggers; experimental manipulation; diary); and (5) type of alcohol endorsed as trigger (using verbatim trigger terminology).

Statistical Analyses

We used random effects models to address heterogeneity within and between studies, measured with I^2 indices and τ^2 indices. Statistical significance was set at $p < .05$. The primary random effects model quantified the weighted proportion of participants across all studies who endorsed alcohol as a trigger with estimated 95% confidence intervals (95% CIs). 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 and to estimate the proportion of individuals with any type of headache who endorsed specific types of alcohol as triggers. Post-hoc meta-regressions were also used to assess other potential moderator variables and sources of heterogeneity (e.g., proportion of females in sample, year of publication). We used R software to run all statistical analyses.

Results

Study Search and Selection

Figure 1 depicts the PRISMA flow diagram from the initial literature search to the retained articles. The initial multi-database search yielded 1929 candidate articles. After the titles and abstracts of these candidate articles were reviewed, 42 articles met inclusion criteria. The bibliography review of the included articles yielded two additional articles appropriate for the study. This process resulted in 44 articles retained for analyses. Table 1 presents summary data for each of these analyzed studies.

Alcohol as a Trigger for All Headache Diagnoses

All 44 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. Results of the random effects model are presented in Fig. 2. Out of 12,763 participants across 44 studies, 22%

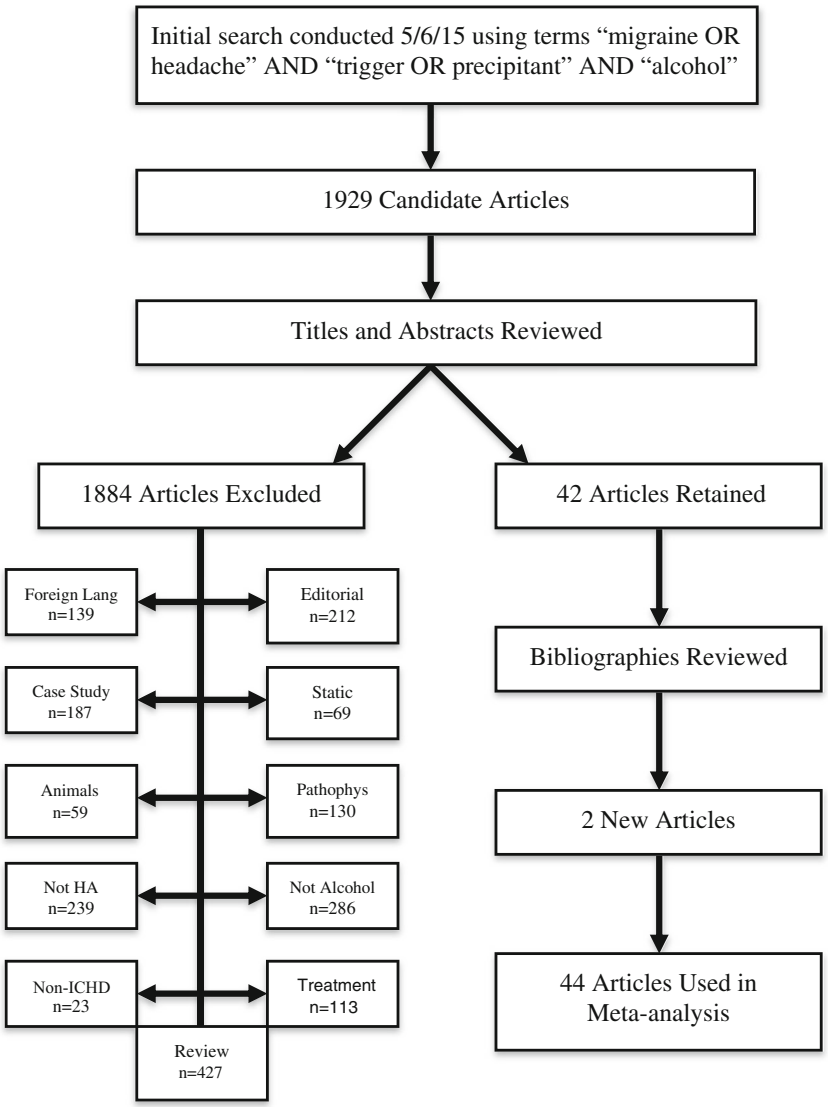

Fig. 1 PRISMA flowchart of eligibility process

(95% CI .17–.29) endorsed any form of alcohol as a trigger. Substantial heterogeneity was observed across studies, $\tau^2 = 0.95$; $I^2 = 97.5\%$ (95% CI 97.1–97.8%), which prompted meta-regressions to identify possible sources of heterogeneity. Gender 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 as a trigger increased by 2% (OR = 1.02; 95% CI 1.01–1.05; $p = .04$. Year of publication ($p = .09$) did not significantly impact proportion of trigger endorsement.

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 (11,304 participants), but only 12 reported triggering effects for TTH (1506 participants). Tension-type headache sufferers endorsed alcohol as a trigger slightly less often than migraineurs (14 vs 23%, respectively), but this difference was not statistically significant (OR = 0.59; 95% CI 0.29–1.21; $p = .15$). Substantial heterogeneity was observed across studies, $\tau^2 = 0.96$; $I^2 = 96.8\%$ (95% CI 96.4–97.3%). The proportion of females in the sample did not significantly impact trigger endorsement as a function of diagnosis ($p = .09$). Year of publication mildly impacted endorsement such that for each additional (more recent) year of publication, the odds of endorsement decreased by 4% (OR = 0.96; 95% CI .93 to .99; $p = .05$).

Migraine with Aura Vs Without Aura

Eleven articles provided sufficient data on participants endorsing alcohol as trigger for migraine with aura (MA; 984

Table 1 Characteristics of study samples

Study, year	Sample size (N)	Headache diagnoses	Females in sample %	Mean age (SD)
Amery and Vandenbergh [29]	217	Migraine	81.1	–
Andress-Rothrock et al. [30]	200	Migraine	89	41.1 (–)
Baldacci et al. [31]	120	Migraine	86.7	38.7 (11.7)
Bank and Marton [32]	78	Migraine	71.8	38 (6.1)
Blau [33]	45	Migraine	–	–
Fishbain et al. [34]	85	MA, MWA, TTH	–	42.2 (12.7)
Fraga et al. [35]	100	Migraine	72	–
Fragoso et al. [36]	163	Migraine, TTH	87.1	25 (–)
Fukui et al. [37]	200	Migraine	81	37.7 (–)
Galinović et al. [38]	220	Migraine, TTH	77.3	–
Haimanot et al. [39]	454	Migraine	73.4	40.2 (–)
Hauge et al. [40]	126	MA, MWA	77.8	–
Hauge et al. [41]	347	MA, MWA	–	–
Hung et al. [42]	63	Migraine	76.2	30.3 (8.3)
Ierusalimschy and Filho [43]	100	MWA	84	33.6 (–)
Karli et al. [44]	87	MA, MWA, TTH	86.5	–
Karli et al. [45]	1001	MA, MWA, TTH	57.3	14.67 (1.74)
Kelman [46]	1009	Migraine	86.3	37.7 (11.7)
Kelman [21]	1207	Migraine, TTH	84.3	37.67 (12)
Lipton et al. [47]	63	Migraine	77.1	37.95 (–)
Littlewood et al. [48]	19	Migraine	–	–
Matuja [49]	139	Migraine, HA	66.8	28.8 (–)
Mollaoğlu [50]	126	Migraine	68.2	36.2 (10.1))
Mounstephen and Harrison [51]	62	Migraine	41.9	–
Panconesi et al. [52]	371	MA, MWA, TTH	75.2	40 (14)
Peatfield et al. [53]	493	Migraine	67.1	–
Peatfield [54]	387	Migraine, TTH	–	–
Phanthumchinda and Sithi-Amorn [55]	157	Migraine	91.1	–
Rains and Penzien [56]	81	Migraine	93	–
Rasmussen [57]	286	Migraine, TTH	46	–
Russell et al. [58]	333	MA, MWA	44	–
Savi et al. [59]	58	MA, MWA, TTH	69.3	38.19 (15.41)
Scharff et al. [60]	121	MWA, TTH	85.6	36.9 (12.27)
Schürks et al. [61]	1675	Migraine	100	–
Sjöstrand et al. [62]	60	Migraine	100	30.4 (–)
Spierings et al. [63]	55	Migraine, TTH	78.2	48 (12.8)
Téllez-Zenteno et al. [64]	1147	Migraine	80	37.1 (13.6)
Tonini and Frediani [65]	60	Migraine, TTH	79	–
Ulrich et al. [66]	169	MA	59.2	–
Van den Bergh et al. [67]	217	Migraine	81.1	–
Wang [68]	738	Migraine, TTH	–	–
Wöber et al. [69]	120	Migraine, TTH	–	36.8 (11.4)
Wöber et al. [70]	327	Migraine	86.5	41.9 (12.1)
Ying et al. [71]	23	Migraine	82.6	32.9 (13.3)

MA migraine with aura; *MWA* migraine without aura; *Migraine* migraine (with/without aura unspecified)

participants) or migraine without aura (MwA; 1077 participants). 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. Individuals with

MA (11%) and with MwA (10%) equally endorsed alcohol as a headache trigger (OR = 0.93; 95% CI .32–2.76; p = .90). Substantial heterogeneity was observed across studies, τ^2 = 0.87; I^2 = 91.1% (95% CI 87.1–93.8%). The proportion of females in the sample did not significantly impact trigger endorsement (p = .13), nor did year of publication (p = .11). The results of the separate random effects models for each headache diagnosis are compiled in Fig. 3.

Alcohol as a Trigger by Type

Twelve articles provided sufficient data on the triggering effects of consuming specific types of alcohol. Of these 12 studies, ten provided data on red wine (3166 participants); seven provided data on beer (1882 participants), white wine (2996 participants), or spirits (1543 participants); and three provided data on sparkling wine (901 participants). The results of the separate random effects models for each alcohol type are compiled in Fig. 4. 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: .92–14.67; p = .06). Again, substantial heterogeneity was observed across studies, τ^2 = 1.58; I^2 = 98.3% (95% CI 98–98.5%). Gender affected endorsement rates, such that for every 1% increase in proportion of females in the samples, the odds of endorsement increased by 9% for any type of alcohol (OR = 1.09; 95% CI 1.04–1.16; p < .001). Year of publication was associated with a decrease in endorsement such that for each additional (more recent) year of publication, the odds of endorsement decreased by 9% (OR = .91; 95% CI .85–.98; p = .01).

Consumption Amount/Frequency and Method of Assessment

There was not a sufficient number of studies to quantify either the effects of consumption amount/frequency or method of assessment (retrospective vs non-retrospective study) on trigger endorsement. Studies have not provided comparative estimates of alcohol's trigger potency as a function of the amount of alcohol consumed, and only

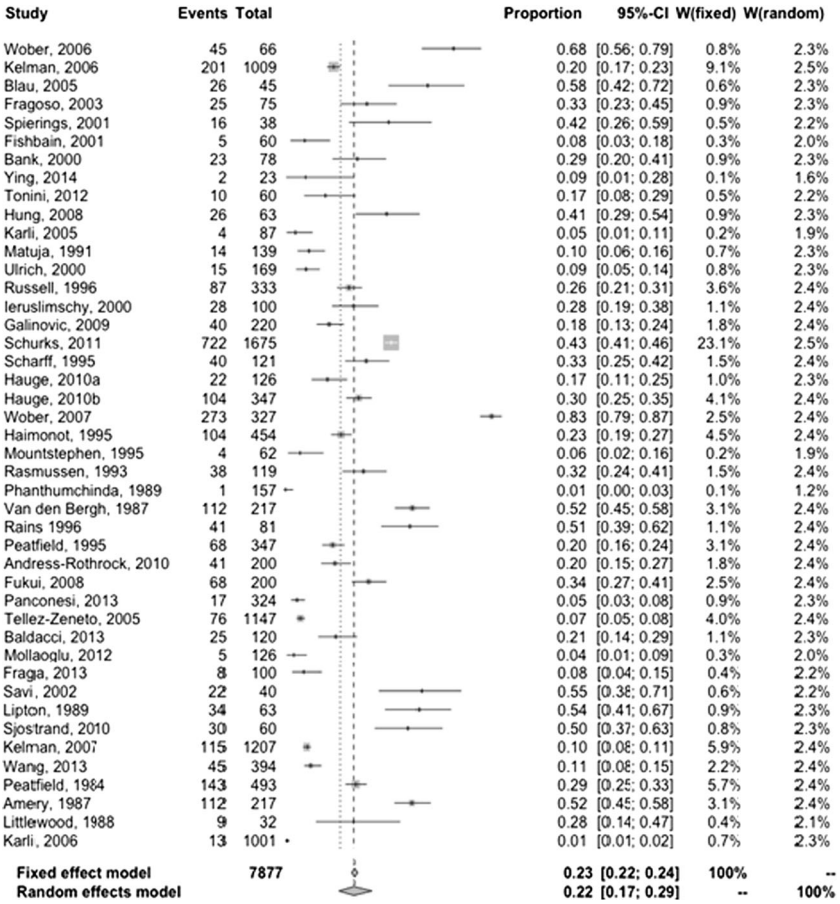

Fig. 2 Forest plot of alcohol as trigger for any headache diagnosis

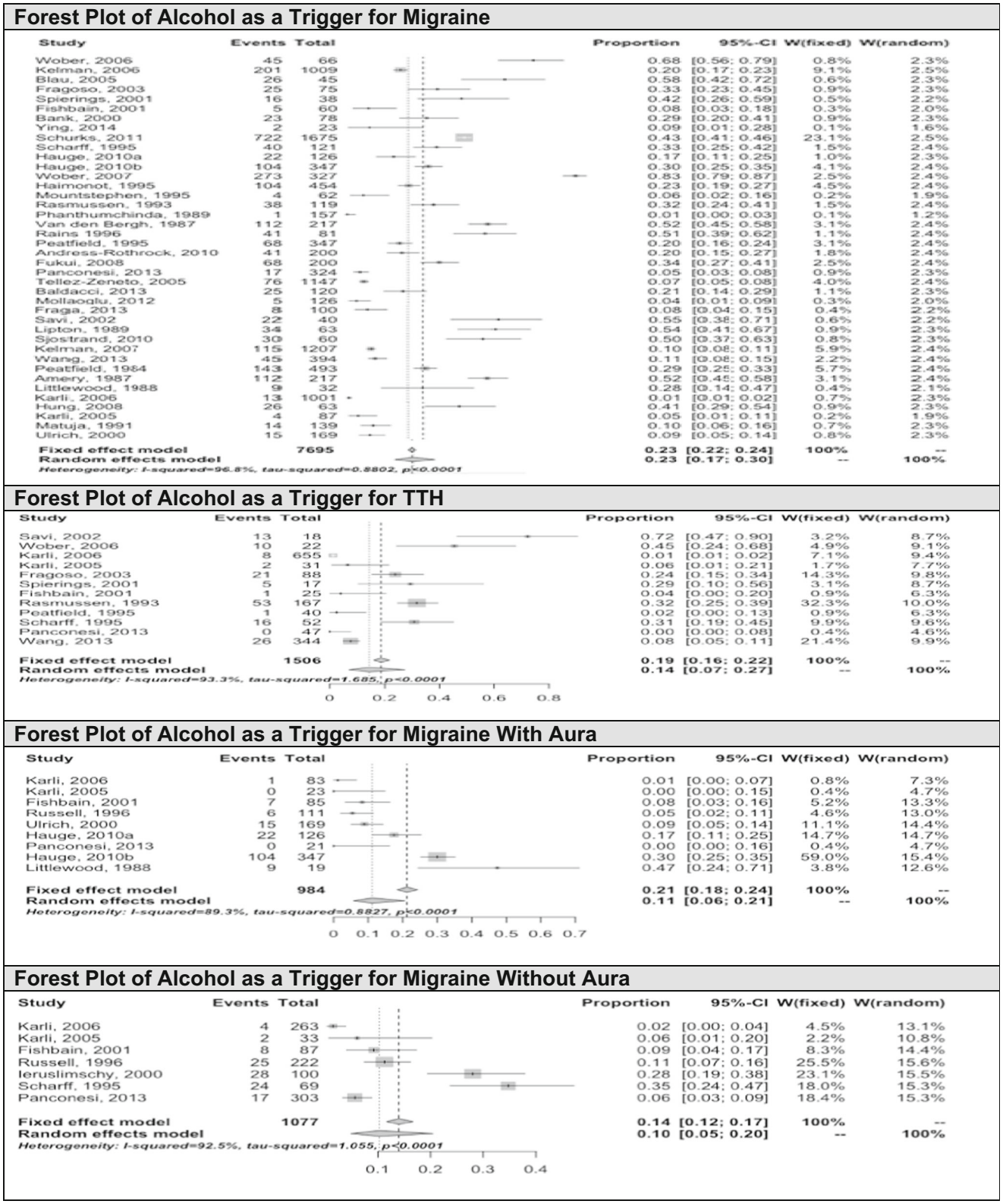

Fig. 3 Random effects models by headache diagnosis

two of the 44 retained articles quantified alcohol's role as a trigger using a non-retrospective design (one experimental manipulation and one prospective diary study). Re-running the primary random effects model without these two non-retrospective articles changed the overall endorsement rate from 22.2 to 21.0%.

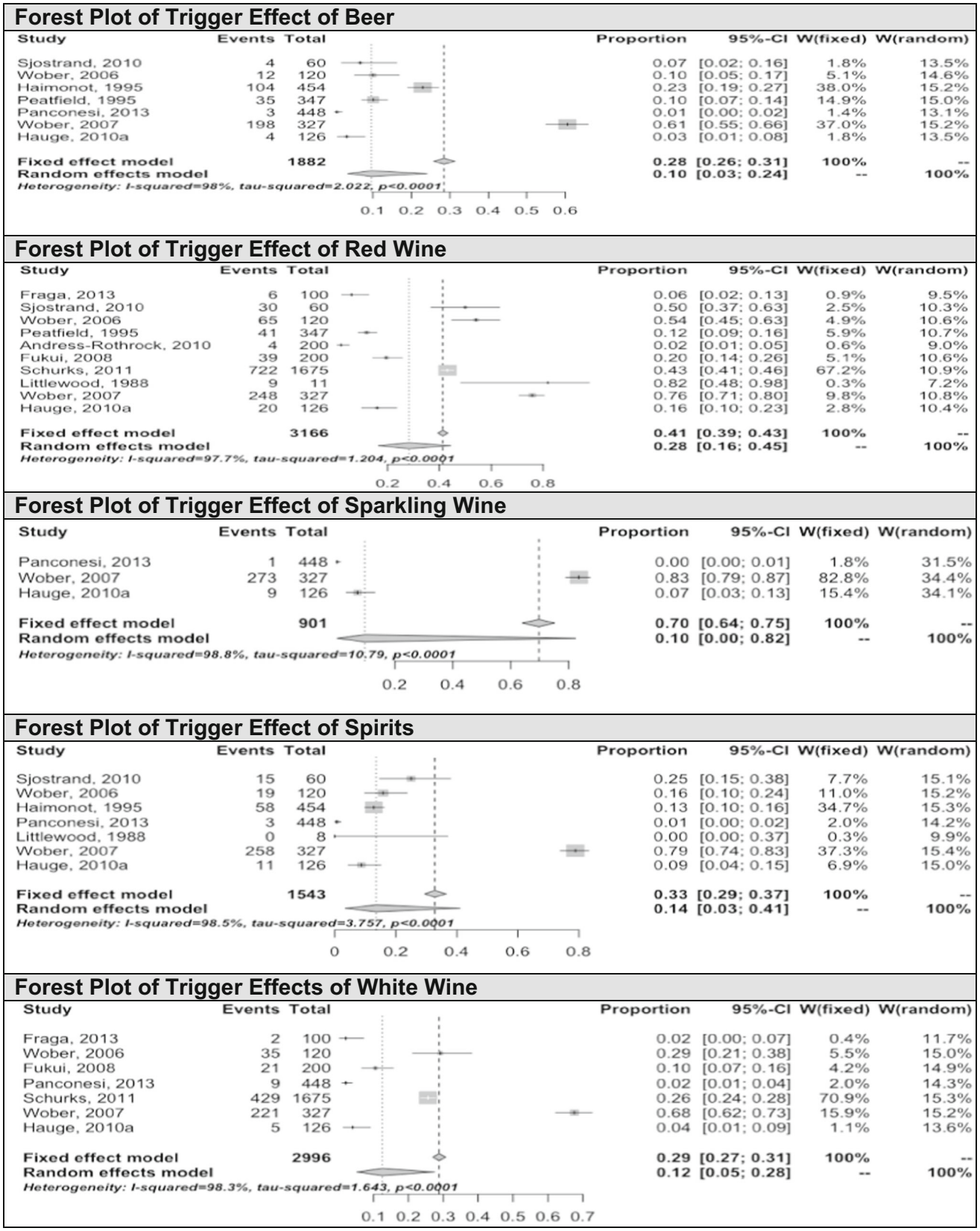

Fig. 4 Random effects models by alcohol type

Conclusions

The meta-analysis revealed substantial heterogeneity among studies exploring alcohol as a trigger of migraine and TTH, highlighting considerable methodological differences between studies and suggesting caution when interpreting results. With this caveat in mind, the general pattern of results indicates that: (1) a non-trivial proportion of individuals perceive alcohol as a trigger for migraine and TTH; (2) the precipitating effects do not differ by headache diagnoses; (3) red wine appears to be a more potent trigger than other alcohol types. Roughly one out of five headache sufferers endorse some precipitating effect of alcohol. This overall proportion is consistent with results from a larger, separate meta-analysis of all perceived headache triggers, the latter of which did not use a search strategy specific to alcohol, include non-retrospective studies, or compare types of alcohol [72]. Though this rate of endorsement is considerably less than those for more well-established headache triggers typically reported by 40–80% of headache samples (i.e., stress, hormones in women, sleep, environmental factors [19, 21, 37, 68]), among the dietary triggers alcohol is one of the most commonly endorsed [22••]. The observed endorsement rate may be an underestimate given the amount of heterogeneity found between studies.

The analyses run to assess moderator variables indicated that female gender and year of publication exerted some influence on some of the results, but these variables accounted for little of the observed heterogeneity. The small gender effect may be attributable to an interaction between alcohol and hormonal variables among women [30], and declining endorsement rates with more recent publications may indicate that the clinical advice to avoid headache triggers has become increasingly disseminated to migraineurs [25]. The separate random effects models by diagnosis found small but non-significant differences in rates of endorsement as a function of having migraine vs TTH, clarifying prior mixed findings and providing some indirect support for the notion that these headache disorders may exist on a continuum of severity rather than as discrete pathophysiological entities [73], despite their phenotypic differences. These results imply a common mechanistic effect for ethanol among these primary headache disorders. Though the primary mechanism has not been definitively confirmed, ethanol prompts release of endothelial nitric oxide and calcitonin gene-related peptide at sensory nerves, resulting in trigeminal inflammation and meningeal vasodilation [25, 27].

By comparison to the results for headache diagnoses, a large effect was observed for red wine as compared to other forms of alcohol. Though this effect fell just short of statistical significance, more than twice as many individuals endorsed red wine as a trigger than any other alcohol type. These results are concordant with Littlewood et al.'s [48] classic experimental study, in which migraineurs who believed red wine triggered their attacks consumed either a Spanish red wine or a vodka-lemonade cocktail of equivalent alcohol content. Participants were blinded to alcohol type through consumption from a dark bottle and straw. The large majority (81%) of those who consumed red wine developed a migraine within 3 h, compared to none of those given vodka. Collectively, these findings imply that, at least among some susceptible individuals, components of red wine other beyond ethanol per se (e.g., sulfites, tannins, histamines, phenols) may be responsible for higher incidence of headache following consumption [74••]. Unlike beer or white wine, red wine exerts potent releasing effects on serotonin [75].

To better understand triggering effects of certain wine components, Krymchantowski and Jevoux [76, 77] conducted two studies with migraine patients who perceived their attacks to be triggered by wine, one examining red wine type and the other examining region of production. Tannat and malbec were more potent headache triggers than cabernet sauvignon and merlot, triggering headache in 51.7 and 48.2% of patients, respectively [76]. In the second study, French cabernets triggered headache more than those from South America (60.9 vs 39.1% of patients, respectively [77]). Notably, in both of these open studies participants did not usually experience a headache after consumption. The authors concluded that tannins and phenolic flavonoids, which were most abundant in the wines most likely to induce headache, may be the underlying mechanisms of wine's triggering effects. Given that neither of these studies were double-blinded or used a non-wine control group, further experimental studies are needed both to clarify the mechanisms underlying alcohol's effects on headache and individual variables that may moderate these effects.

Collectively, our review indicates that primary headache does not appear to confer increased risk for AUDs and provides support for the commonly held notion that alcohol (and red wine in particular) is perceived as a headache trigger for a sizeable subset of individuals with migraine or TTH. Despite these general findings, numerous unanswered questions and directions for future research remain. As is evident from the large amount of heterogeneity present in existing literature, an effort toward enhancing uniformity and standardization in alcohol trigger studies is warranted. Given that the vast majority of reviewed studies used retrospective self-report designs, our review also highlights a need for rigorous experimental studies that can appropriately satisfy assumptions of causality and identify underlying mechanisms, particularly given that prior double-blind studies of other triggers (e.g., chocolate) have not always verified patient perceptions of their potency [78]. An ideal within- and between-subjects experimental design to establish causality would assign individuals to drink alcohol or a non-alcoholic drink (in double-blinded fashion) on numerous randomly

selected days over multiple weeks, allowing sufficient time between exposures to minimize carryover effects and interactions with other triggers [23•].

Future research in this area should also assess the importance of consumption frequency and quantity in attempt to determine the threshold necessary for alcohol to precipitate an attack, as well as moderator variables that make some individuals susceptible only when present simultaneously with alcohol consumption (e.g., high stress, poor sleep, menstruation). Incorporating electronic diaries may be useful in assessing frequency and consumption of alcohol in temporal relation to headache onset. Clinically, we concur with Panconesi and colleagues [27] in their assertion that there is little reason to routinely advise headache patients against modest consumption of alcohol. Such advice might be appropriate among patients for whom a relationship between consumption and headache has been definitively established, but there is little evidence that "elimination diets" are effective or practical [79] and growing evidence suggests that therapeutic exposure to headache triggers holds promise as an adaptive alternative coping strategy to complete avoidance [80, 81•].

Compliance with Ethical Standards

Conflict of Interest Ashley N. Polk and Rachel E. Davis-Martin declare that they have no conflict of interest.

Todd A. Smitherman has received personal fees from Alder Biopharmaceuticals outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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