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PII: S0306-4603(22)00344-6
DOI: https://doi.org/10.1016/j.addbeh.2022.107578
Reference: AB 107578

To appear in: *Addictive Behaviors Addictive Behaviors*

Received Date: 13 August 2022
Revised Date: 13 November 2022
Accepted Date: 8 December 2022

Please cite this article as: C. Kiyak, M.E. Simonetti, S. Norton, P. Deluca, The Efficacy of Cue Exposure Therapy on Alcohol Use Disorders: A Quantitative Meta-Analysis and Systematic Review, *Addictive Behaviors Addictive Behaviors* (2022), doi: https://doi.org/10.1016/j.addbeh.2022.107578

The Efficacy of Cue Exposure Therapy on Alcohol Use Disorders: A Quantitative Meta-Analysis and Systematic Review

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Abstract

Background: Cue exposure therapy (CET) techniques involves repeated and controlled exposures to alcohol stimuli which rest upon the well-established principles of Pavlovian extinction (Byrne et al., 2019). However, the efficacy of CET while treating alcohol use disorders (AUDs) is still a matter of debate. Therefore, we aimed to investigate the efficacy of CET on AUDs by using previous meta-analysis study on the same topic from Mellentin et al. (2017) as a base.

Methods: A computer-assisted search of relevant articles identified 879 studies in Medline, PsycInfo and Embase, of which 11 studies (published between 1992 and 2019) were selected. Three outcome measures were extracted: alcohol consumption defined as drinks per day (drinking intensity) and alcohol reduction defined as drinking days and relapse (drinking frequency). This study is registered with PROSPERO (Registration no: #CRD42021259077).

Results: The present meta-analytical review found small to medium effect on drinks per day (g=-.35; 95%CI -.72 to .03), drinking days (g=-.30; 95%CI -.54 to -.06) and relapse (OR=-.58; 95%CI .29 to 1.15) while investigating the efficacy of CET on AUDs. GRADE assessment was used to evaluate the overall quality, and it was assessed as low. Regarding Risk of Bias, the studies in this systematic review were evaluated with "some concerns".

Conclusion: The present meta-analysis demonstrated that CET has small to medium effect on drinks per day, drinking days and relapse. Future research should strive to conduct larger scale multi-site CET trials with additional methodological innovations and increase retention.

1. Introduction

Alcohol use disorders (AUDs) is highly prevalent and results in significant mental and/or physical health problems. Worldwide, 3 million deaths (7.6% in men, and 4.0% in women) are caused annually by alcohol misuse, representing about 5.1% of all deaths (Kranzler & Soyka, 2018). The consequences of alcohol-related diseases are enormous, and AUDs continue to be a major public health concern all over the world. Alcohol misuse is associated with severe medical conditions, such as mouth, throat, stomach, liver, and breast cancers, high blood pressure, gastrointestinal diseases like cirrhosis of the liver, and mental health problems such as depression (Iranpour & Nakhaee, 2019). Consequently, AUDs are a leading risk factor for premature mortality and disability among those

aged 15 to 49 years (WHO, 2018). Moreover, alcohol is a legal drug which affects not only the individual's life and environment but the society as well. Considerable economic costs, such as health care and law enforcement expenditures, lost productivity, and other direct and indirect costs, along with the social issues including harm to others, are all associated with alcohol-related health burden ("Global statistics on alcohol, tobacco and illicit drug use", 2021).

1.1.Theoretical background

The significant prevalence and negative consequences of AUDs have led to an improvement in screening, treatment, and interventions. Substantial evidence has demonstrated the importance of psychological approaches in treating AUDs (Monti et al., 1993; Drummond & Glautier, 1994; Rohsenow et al., 2001; Loeber, 2006). Cue Exposure Therapy (CET) is one of the most important psychological approaches which is specifically designed to treat the cravings that perpetuate AUDs (National Collaborating Centre for Mental Health UK, 2011). CET is based on Cognitive Behavioural Therapy (CBT) in which individuals are exposed to relevant addictive cues (Byrne et al., 2019; Conklin & Tiffany, 2002). CET aims to reduce cue reactivity through exposure to conditioned stimuli (e.g., alcohol) while preventing their habitual response, i.e., alcohol use (Marissen et al., 2007; Drummond, 2000; Everitt, 2014; Pavlov & Anrep, 2003). The approach relies on Pavlovian learning theory which includes classical conditioning component (Pavlov & Anrep, 2003). Pavlovian classical conditioning theory (Pavlov, 1927) suggests that some contexts or objects (e.g., bottles, glasses, and bars) are associated with addictive substances which are called unconditioned stimuli (US), and the effects of the addictive substances are called unconditioned response (UR) (Drummond, 1990). The contexts or objects can turn into conditioned stimuli (CS) and become capable of triggering craving which is called conditioned response (CR) (Lee et al., 2007). Therefore, Pavlovian learning theory propounds that alcohol addiction is learnt through reinforcement process, consequently conditioned response (craving) can be extinct (e.g., unlearned or weakened by new learning) by exposing individuals with addiction problems to relevant cues (Mellentin et al., 2017; Drummond, 1990; Marlatt, 1990). It is suggested that CR loses their reinforcing characteristics with prolonged exposure (Pavlov & Anrep, 2003; Bouton, 2002; Myers & Davis, 2002; Skinner, 1938). Moreover, CET involves exposing individuals with AUDs to the sight and smell of alcohol without allowing them to consume it to weaken the CS-US relationship through extinction and, as a result, reducing cravings. Whilst the foundation of CET is placed in classical conditioning, in practice when implemented this is done in conjunction with coping or refusal skills training. And when training is not offered, the exposure on its own would allow the participants/patients to train their own skills.

However, the literature demonstrates inconsistency on the efficacy of CET on AUDs so far. While some research reported that CET reduces cravings, increases the time to relapse and reduces the amount of alcohol use compared to control treatment (Drummond & Glautier, 1994; Niaura et al., 1999; McClernon et al., 2007), some other studies suggest that CET does not produce long-term and complete abstinence for alcohol-dependent patient (Marissen et al., 2007; Sithartan et al., 1997; Monti et al., 1993).

1.2.Previous review

A meta-analysis, of 7 randomised controlled trials, (Mellentin et al., 2017) assessing the efficacy of CET targeting AUDs reported that CET has no to small effects on drinking intensity at 3 and 6 months follow up (g = 0.07; 95%CI −0.34 to 0.49; g = −0.21; 95%CI −0.48 to 0.06) and drinking frequency (g = −0.02; 95%CI −0.38 to 0.41) compared with control groups. However, small effects on total drinking scores (g = −0.21; 95%CI −0.78 to 0.37) were observed and a single study reported a moderate additional effect SMD=0.68 (95%CI −1.40 to 0.04) on latency to relapse. The meta-analysis also reported that CET applied with urge-specific coping skills training might be a better alternative for treating AUDs compared to applying CET only. However, since relatively few CET studies targeting AUDs were available, most with high risk of bias, and studies targeting applications of technology (e.g., video-enabled interventions, use of smartphones) were not included in this meta-analytical review, the results provide low quality evidence about the efficacy of CET on AUDs. Therefore, in this review, we included missing studies in the previous systematic review (Mellentin et al., 2017) along with the new studies investigating the effectiveness of CET on AUDs published up to now.

1.3.Objectives

Therefore, the current study aims to fill this gap in the literature by systematically identifying, reviewing, and synthesizing evidence of the efficacy of CET on AUDs by adding missing studies in the previous systematic review on the same topic along with the new studies published since then up to today to see if there is a stronger effect with more results. The objective of the present study is (a) to determine the efficacy, measured by reduction in alcohol consumption and/or abstinence rates, of CET on AUDs; (b) to evaluate how implementation and the features of CET reflect on reduction of alcohol consumption. To do so, we examined the overall efficacy of CET targeting AUDs in comparison to control conditions (e.g., no treatment, standard treatment, cognitive behavioural therapy – CBT, treatment as usual – TAU, or any other active interventions) in an explorative systematic review and meta-analysis.

2. Methods

2.1.Protocol and registration

The present meta-analysis was conducted according to recommendations in the Cochrane Handbook for Systematic Reviews of Interventions (Collaboration, 2011). The protocol for the

review, developed a priori, is registered with Prospective Register of Systematic Reviews (PROSPERO; Registration no: #CRD42021259077). Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA; Moher, Liberati, Tetzlaff, & Altman, 2009) guidelines were followed for reporting of this review.

2.2.Eligibility criteria

2.2.1. Study design

The present meta-analysis followed a PICO framework for identification and selection of relevant publications for the systematic review. Full-text studies published up to August 2022 (the publication of relevant non-English literature was also cross-checked during a preliminary stage) were included in this review if they employed randomised controlled trial (RCT) or a controlled trial (CT) with a comparison group (e.g., no treatment, standard treatment, cognitive behavioural therapy – CBT, treatment as usual – TAU, or any other active interventions).

2.2.2. Participants and settings

Adult population (≥18 years old) diagnosed with an alcohol use disorder was included in this review (AUDs; DSM–5; American Psychiatric Association, 2013). Procedures for diagnosis must have included a general and structured clinical interview (based on DSM criteria applied by the study authors dependent upon the version current at the time), written history and sociodemographic questionnaires, either over the telephone, online, or in person, or validated/reliable scales for the condition.

2.2.3. Interventions

Any study including cue exposure therapy (CET) and exposure therapy (ET) for the management and treatment of alcohol use disorders (e.g., in vivo exposure, imaginal exposure, and interoceptive exposure) was included. The settings for interventions were outpatient settings, inpatient, telemedicine-based settings, smart-phone app settings, and research intervention settings. On the other hand, studies on the application of Virtual, Augmented and Mixed Reality Cue Exposure Therapy on AUDs were not included in this review because those studies were not eligible and did not comply the inclusion criteria in terms of the type of study (e.g., RCT or CT).

2.2.4. Outcome measures

The focus of the review is alcohol consumption, defined in terms of quantity and frequency of drinking. Quantity was captured as an outcome in terms of the number of drinks per day (continuous). Frequency was captured in terms of the number of drinking days reported during follow up (continuous) and whether the participant had relapsed and restarted alcohol consumption by the end of the trial (categorical). The outcomes were measured both at the longest follow-up available and immediately after the treatment/intervention.

2.2.5. Exclusion criteria

Articles were excluded if they are (a) non-peer reviewed literature (conference abstracts, posters, theses); (b) studies reporting participants with substance use disorder (e.g., cannabis, tobacco, opioids); (c) population under the age of 18-year-old; (d) studies focusing specifically on pharmacological treatment was excluded as well.

2.3.Search strategy

A comprehensive search strategy was developed in line with the recommendations set by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2020) with controlled vocabulary and free-text term searching in order to maximise the sensitivity and precision of the search strategy. The search was conducted by two authors (CK; MES) on the following electronic databases: MEDLINE (via OVID), Embase (via OVID), and PsycINFO (via APA), up to August 2022. When unavailable, full texts for relevant papers were sought by contacting the corresponding authors of the study. To complement the systematic search, an additional manual literature search was sought by consulting reference lists of relevant identified studies as well as bibliographies full-text papers to be included in the review, after the selection process.

An initial pilot testing of the search strategy was conducted for a sample of papers that have been identified as relevant during the preliminary search (e.g., included in the previous review) to ensure sensitivity of the strategy. An exhaustive literature search was then conducted by using the following terms “cue exposure therapy”, “cue exposure treatment”, “exposure therapy”, and “exposure treatment” for the intervention; “alcohol use disorder”, “alcohol addiction”, “harmful drinking” and “alcohol misuse” for the condition. The search strategy was further refined according to the outcomes of the pilot search and the following terms were entered to find the most relevant studies: “cue exposure” and “alcohol”. The search strategy was rerun regularly to check if any further studies were published during the writing process of this systematic review up to August 2022.

2.4.Study selection

Two authors (CK; MES) independently screened titles and abstracts of articles identified by using the web-based software Rayyan (https://rayyan.ai; Ouzzani, Hammady, Fedorowicz & Elmagarmid, 2010) and excluded ineligible and irrelevant studies. The same authors subsequently read the full text versions of all the remaining articles and excluded the articles which did not comply with eligibility criteria. Afterwards, the same authors independently screened the references of the retrieved articles for any further relevant citations. Eventually, articles identified as relevant were added to full analysis. Disagreements regarding the eligibility of studies were discussed between the two authors (CK; MES). If an agreement could not be reached, the reviewers consulted a third reviewer (PD) who provided input and the final decision was reached by consensus across the three reviewers.

2.5.Data extraction and data analysis

After an agreement was reached on inclusion of eligible studies, a reviewer (SN) extracted data from all included studies and tabulated it in terms of study design/population, follow-up period, study objective, sample size, results/statistics, and the conclusion. The outcome measures were alcohol consumption, defined as drinks per day (drinking quantity) and alcohol reduction, defined as drinks per day (drinking frequency) and relapse (drinking frequency).

2.6.Risk of bias in individual studies

Risk of bias was also assessed by two independent reviewers (CK; MES) using the Cochrane Risk of Bias tool 2.0 (Sterne et al., 2019) for the following domains: 1) bias arising from the randomization process; 2) bias due to deviations from the intended interventions; 3) bias due to missing outcome data; 4) bias in measurement of the outcome; and 5) bias in selection of the reported result. All studies were rated on each domain as low, high, or some concerns risk of bias. Data were extracted and input into a Microsoft Excel spreadsheet by each coder. After independent extraction, the codes were reviewed, and discrepancies were resolved by discussion and consensus. If questions about coding were not resolved, a third reviewer (SN) was consulted, and final decisions were made by consensus across the three reviewers. GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) is an emerging method for controlling and evaluating studies and systematic reviews. This tool used five different measures to create a transparent summary of the studies considered by the systematic review, they are: risk of bias, imprecision, inconsistency, indirectness, and publication bias.

2.7.Synthesis of results

Effect sizes for drinking days and drinks per day were calculated as the standardised mean difference between the control and intervention groups using Hedge's *g* with correction for small sample size (White & Thomas, 2005). For relapse, where the outcome was binary, the effect size was calculated as the odds ratio for relapse in the intervention versus control group. The meta-analytic pooled effect between studies was calculated based on a random effects analysis using the restricted maximum likelihood estimator. The I^2 statistic was calculated to quantify statistical heterogeneity in terms of the variability in effect sizes across studies. Where I^2 was greater than 40% and the significance test was significant at the 5% level the level of statistical heterogeneity was considered to impact on the robustness of inferences based on the pooled effect (Higgins et al., 2011). The impact of individual studies on the pooled effect estimate was assessed using leave-one-out meta-analysis. Specifically, the range of pooled effects was considered after recomputing the pooled effect estimate sequentially removing each study from the analysis. Indications of publication bias were assessed using funnel plots and Egger's funnel asymmetry test (Egger et al., 1997) and an estimate of the intervention effect adjusting for publication bias estimated by the precision-effect test and precision-effect estimate with standard errors (PET-PEESE) approach (Stanley & Doucouliagos, 2014).

3. Results

3.1.Study selection

The literature search resulted in 879 studies including both English and non-English studies. The search did not yield any non-English studies. After removing duplicates, 530 reports were assessed for eligibility. A total of 11 studies met the inclusion criteria with publication dates ranging from 1992 to 2019 (Figure 1). Manual search was also conducted by screening the references of 11 studies and citations in the relevant journals. However, the manual search did not yield any additional studies up to date.

3.2.Study Characteristics

Table 1 summarizes the 11 included studies. All studies were published in peer-reviewed journals. The country of origin of the studies included Australia (*N*=3), the United States (*N*=3), the United Kingdom (*N*=2), Denmark (*N*=1), Germany (*N*=1), and India (*N*=1). Most of these studies were published between 1992 and 2006 (*N*=9, 82%), while only two studies were published after 2006 (in 2017 and 2019). The studies have two different goals: abstinence (*N*=6) or moderation (*N*=5).

3.3.Participant Characteristics

A total of 1271 adults participated across the studies with sample sizes ranging from 40 to 293 (mean 115.5 participants per study). Due to drop out analysis sample included only 954 of the 1271 participants (mean dropout 25%). Of these, 944 participants were diagnosed with AUDs, and only 10 participants had problems controlling consumption when dysphoric. The mean age of participants overall was 41,76 years of age. Included studies used different diagnostic tools such as DSM-III-R (American Psychiatric Association, 1987); DSM-IV-Patient Version: Structured Clinical Interview (SCID-II; First et al., 1995); DSM-IV-R (American Psychiatric Association, 1994); Alcohol Problems Questionnaire (APQ; Williams & Drummond, 1994); The Severity of Alcohol Dependence Questionnaire (SADQ; Stockwell et al., 1979); The Severity of Alcohol Dependence Questionnaire Community (SADQ-C; Stockwell et al., 1994); Alcohol Dependence Scale (ADS; Skinner & Allen, 1982); the International Classification of Diseases, Tenth Revision Diagnostic Criteria for Research (ICD-10; WHO, 1992); and the Addiction Severity Index (McLellan et al., 1992). All studies used severe mental illness as an exclusionary criterion.

3.4.Intervention and control group characteristics

While 6 studies were conducted in outpatient settings, 5 were in inpatient settings. 5 studies conducted CET only, while 4 studies employed CET and CST (coping skills treatment), one conducted CET and ECET (emotional cue exposure therapy), and one of them applied CET and CBT (cognitive behavioural therapy). All interventions were delivered on an individual basis in all studies. Within the 11 studies there was a variability in the choice of the control group. In particular, 6 of the studies applied CBT, 3 of them applied relaxation techniques and 1 applied each daily contact and TAU.

3.5.Risk of bias and study quality across studies

Figures 2 and 3 show the Risk of Bias assessment. Regarding the overall risk of bias, most of the studies (five of eleven) were overall considered to have some concerns, while four were classified as high and two as likely low risk of bias. Beginning with the first domain, the bias of the randomization process, the majority of the studies were considered low risk of bias and four as high risk, while in two studies there were some concerns. Overall, this was one of the lower risk domains, and this is particularly important because of the nature of the study. The second domain, bias due to deviations from the intended outcome, was, instead, the most problematic domain. Only four studies were considered low

risk, while the majority (*N*=7) were judged as high. D2 can be considered the major concern of this review. The opposite pattern can be found in the third domain, bias due to missing outcome data, in this case most of the studies were considered as low risk (*N*=7) and only four studies were judged as high risk.

D4 and D5 presented both a more mixed situation. Regarding the bias in measurement of the outcome, most of the studies were considered as low risk (*N*=5), but four of them were judged with some concerns and only two as high risk. Lastly D5, bias in selection of the reported result, was a very unclear situation for most of the studies (*N*=4) and they were judged with some concerns, while three studies were considered as high and the same number as low risk.

3.6.Quantitative synthesis of results

3.6.1. Quantity: drinks per day: A small to medium effect (g=-.35; 95%CI -.72 to .03) in favour of CET versus control was observed across 7 studies (total *N*=557). There was substantial heterogeneity in effect sizes between studies (I^2=77%), mainly driven by Nattala et al. (2018), and the test for heterogeneity was significant indicating that inferences based on the pooled estimate may not be robust. It was not possible to conduct a sensitivity analysis including only low risk of bias studies due to the small number of studies meeting these criteria. Leave-one-out sensitivity analysis, where each study was sequentially omitted from the meta-analysis, indicated that the estimate of the treatment effect was generally robust, except when Nattala et al. (2018) was excluded. Specifically, Hedge's g was -.14 when Nattala et al. (2018) was excluded) and varied between -.45 and -.31 where any other study was excluded. Inspection of the funnel plot provided evidence of small-sample effects but the Egger test for funnel asymmetry was non-significant (z=-1.13, *p*=.260). The PET-PEESE estimate of the effect adjusting potential publication bias indicated the true effect may be considerably smaller (g=-.18; 95% CI -.99 to .63). Figure 4 presents the forest plot of treatment effect estimates for studies assessing the number of drinks per day at 6 to 8 months follow-up.

3.6.2. Frequency: drinking days: A small to medium effect (g=-.30; 95%CI -.54 to -.06) in favour of CET versus control was observed across 9 studies (total *N*= 779). There was moderate heterogeneity in effect sizes between studies (I^2=59%) and the test for heterogeneity was significant. Therefore, inferences based on the pooled estimate may not be robust. However, leave-one-out sensitivity analysis, indicated that the estimate of the treatment effect was relatively robust (Hedge's g varied between -.36 and -.19) and thus inference concerning the direction of the effect are likely to be sound, assuming no publication bias. Inspection of the funnel plot provided evidence of small-sample effects but the Egger test for funnel asymmetry was non-significant (z=-.043, *p*=.668). Given the indication of small sample effects, the PET-PEESE estimate of the pooled effect adjust for potential bias was estimated and indicated a slightly smaller true effect (g=-.22; 95%CI -.56 to .11). Figure 5 presents the forest plot of treatment effect estimates for studies assessing the number of drinking days at 6 to 8 months follow-up.

3.6.3. Frequency: relapse: A medium effect (OR=-.58; 95%CI .29 to 1.15) in favour of CET versus control was observed across 5 studies (total *N*= 462). There was moderate heterogeneity in effect sizes between studies (I^2=64%) and the test for heterogeneity was significant. Leave-one-out sensitivity analysis, where each study was sequentially omitted from the meta-analysis, indicated that the estimate of the treatment effect varied considerably, which is unsurprising given the small number of studies included: the odds ratio varied between .43 and .73. Inspection of the funnel plot provided evidence of small-sample effects but the Egger test for funnel asymmetry was non-significant (z=1.41, *p*=.157). Again, a PET-PEESE estimate of the true effect adjusting for publication bias indicated a smaller effect (OR=.20; 95%CI -.04 to .99). Figure 6 presents the forest plot of treatment effect estimates for studies assessing relapse at 6 follow-ups.

3.6.4. Quality of assessment

To assess the quality of evidence of the systematic review, we used "GRADE" (Grading of Recommendations, Assessment, Development and Evaluations). This assessment is composed of 5 domains: risk of bias, imprecision, inconsistency, indirectness, and publication bias. Each domain of evidence is evaluated from "very low" to "high". Risk of bias was evaluated in the paragraph above, overall, we judged most of the studies as "some concerns", and, for this reason, the risk of bias is here considered as moderate. Regarding imprecision, we found a small to medium effect considering the intensity (CI -.72 to .03), the drinking days (CI -.54 to -.06) and the relapse (CI .29 to 1.15). All were wide intervals, and in the first one the direction of the effect could not even be identified. For this reason, the imprecision was judged as low. Inconsistency was judged regarding the heterogeneity between studies calculated through I^2. It was high for intensity (I^2=77%), while it was moderate for drinking days (I^2=59%), and relapse (I^2=64%). For these reasons, the inconsistency was judged as low. The fourth measure, indirectness, regards the population of interest. We judged this as moderate because our inclusion criteria were narrow, but the control interventions and the specific nature of the CET

interventions differed between studies. Lastly, for the publication bias, our judgement is also moderate. This decision was made by looking at the Egger test which was not significant for all three variables. However, visual inspection of the funnel plots provided some indication that there were potentially small-sample effects, and thus potentially publication bias. Furthermore, power for the Egger's of these studies was low, as there were few studies included and few participants overall. Overall, the included studies were considered as "low". Another major concern derived from the ten years gap that is present between the included studies. It cannot be ignored that some studies may have been done in these years, but they may not have been published because they did not have important results.

4. Discussion

This review provided further evidence that, CET has a small to medium effect on drinks per day, drinking days and relapse while investigating the efficacy of CET on AUDs. CET for AUDs is centred on both learning theory and social learning theory models, and it propounds that environmental cue associated to drinking might induce conditioned response which may ultimately lead to a relapse (National Collaborating Centre for Mental Health UK, 2011). The efficacy of CET both on substance and alcohol use disorders has been questioned many times by researchers and is considered to be somehow controversial (Byrne et al., 2019; Martin, LaRowe & Malcolm, 2010). Therefore, CET is not widely used in the clinical settings for the treatment of addiction problems and its efficacy still remains a subject of debate (Byrne et al., 2019; Mellentin et al., 2017).

While previous meta-analytical reviews showed that there is no consistent evidence for the efficacy of CET on substance use disorders (SUDs) (Conklin & Tiffany, 2001; Martin, Larowe & Malcolm, 2010), a comprehensive meta-analysis on the effectiveness of CET on AUDs (Mellentin et al., 2017) found no to small effects on drinking quantity and drinking frequency; and small effects on total drinking score and a moderate additional effect on latency to relapse. In their narrative review Byrne et al. (2019) reported that while CET is ineffective for SUDs, CET for AUDs might have a greater potential than its current use. Conklin and Tiffany (2001) explained the inefficacy of CET by pointing out the methodological weaknesses of identified studies in the previous systematic reviews and meta-analytical studies and remarked what animal extinction research and theory reveal about extinguishing learned behaviour. They proposed that basic animal research has several factors and processes that can threaten the development and maintenance of extinction training and consequently interfere with extinction process during CET in which they define as "threats to extinction". These factors are *a) renewal effect (return of extinguished behaviour within a novel context), b) spontaneous recovery, c) reinstatement (return of extinguished behaviour in the presence of the UCS), and d) failure to distinguish the conditioned cues (e.g., saliency). Moreover, they suggested that based on animal extinction research, psychotherapy approaches preparing individuals with addiction problems to cope effectively with lapses and maintain further abstinence may be the most useful supplement to CET.* In fact, Mellentin et al (2017) found that based on stratification and analysis of a priori defined trial covariates CET combined with urge specific coping skills

training (USCS) might be a better alternative while treating AUDs compared to conventional CET. Moreover, in this current meta-analysis, we also found that CET combined with coping skills training is more effective compared to CET alone (Monti et al., 1993; Monti et al., 2001; Loeber et al., 2006). It is also important to highlight that 6 of the 11 studies included in this review had CBT as a comparison group which is an active and evidence-based treatment.

The inconsistency results of CET on AUDs are surprising considering its successful application on other disorders such as anxiety disorders (e.g., phobia and obsessive-compulsive disorder) and other addictive disorders (e.g., cannabis, gambling tobacco). Buckfield et al. (2021) proposed an explanation for this contrast by stating the fact that USs (e.g., alcoholic beverages, substances) are typically appetitive for addiction but USs (e.g., spiders, height) are aversive for anxiety disorders. They furthered this argument by indicating although this explanation clarifies some aspects of the inconsistent results, it is not clear enough considering the effectiveness of CET on over-eating and binge-eating in which the USs are also appetitive (Toro et al., 2003; Koskina et al., 2013). To examine possible explanations for alcohol cue exposure treatment paradox (ACETP) they conducted computer based associative learning task and concluded that abstinent alcohol-dependent individuals may have slower extinction learning for alcohol-related cues compared to non-dependent light drinkers. Similar to this, in their narrative review Byrne et el. (2019) proposed several reasons why CET for addiction is less effective than exposure therapy (ET) for anxiety disorders even though both techniques involve repeated and controlled exposures to certain stimuli; "*a) they might simply have different level of efficacy; b) there might be trait differences between individuals with anxiety disorders and alcohol use disorders in terms of engagement to treatment; c) individuals with AUDs have usually a variety of psychosocial and interpersonal factors which might affect their abstinence such as availability of alcoholic beverages and environment that can trigger cravings".*

Moreover, studies on CET have shown to be effective on craving reduction in cannabis use and gambling disorders. For instance, Norberg et al. (2018) suggested that providing CET in a relevant drug use environment was found more effective at building tolerance of cravings. Bouchard et al. (2017) reported that Virtual Reality Exposure Therapy (VRET) similar to a real-life exposure was found effective on reducing desire to gamble. Overall, VRCET has been suggested that is has the potential to exceed the limits that traditional CET has by ensuring a virtual immersion in virtual environments close to everyday life and typical use scenarios in order to trigger craving better in a personalised and progressive level (Segawa et al. 2020).

Nevertheless, research on CET for AUDs has not been a focus in the literature for a long time. To our knowledge, no RCT or CT studies were published between 2006 and 2016 and only two studies published with control group and follow-up sessions since 2016 (Nattala et al. 2018; Mellentin et al., 2019). Mellentin et al. (2017) explains this ten-year gap due to lack of empirical evidence supporting the use of CET for treating addictive disorders. Even though there have been innovations in terms of delivering CET (e.g. Virtual, Augmented and Mixed Reality, smartphone applications) to enhance the impact of CET, those studies employed these innovations

assessed only the level of cue-induced cravings in one single session instead of measuring reduction in alcohol consumption and abstinence in the follow-up sessions and most of them were lack of control groups (Hernández-Serrano et al., 2021; Ghiţă et al., 2021; Ghiţă et al., 2019; Kim & Lee, 2015; Choi & Lee, 2015; Spagnoli et al., 2014; Lee et al., 2009; Moon & Lee, 2009; Lee et al., 2007; Kwon et al., 2006; Lee et al., 2005).

Lastly, another limitation of this meta-analysis is the interpretation of the treatment effect due the methodological heterogeneity. Specifically, due to variability in the specification of CET in the intervention groups, the nature of the control condition used, and differences in treatment goal (i.e., abstinence vs harm reduction). If there were a larger number of studies, a network meta-analysis could have been undertaken to estimate treatment effects relative to each of the different controls, which could also have considered effects of individual components of the intervention and control groups. This was not feasible in the present review due to the number of studies. A future larger review focusing broadly on interventions for AUD should consider this approach.

5. Conclusion

Our meta-analysis demonstrated that CET has small to medium effect on drinks per day, drinking days and relapse. However, the results provide low quality of evidence. Future research should strive to conduct multi-site CET trials with additional methodological innovations (e.g., Virtual, Augmented and Mixed Reality, wearable devices, and smartphone applications) and increase retention. Until sounder methodological trials are conducted, CET for AUDs might remain controversial and its use in clinical setting might not be commonly recognised.

References

American Psychiatric Association. (1987). *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed., revised).

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.).

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.).

American Psychiatric Association (Ed.). (2013). Diagnostic and statistical manual of mental disorders: DSM-5 (5. ed). Washington, DC: American Psychiatric Publ.

Bouchard, S., Robillard, G., Giroux, I., Jacques, C., Loranger, C., St.-Pierre, M., et al. (2017). Using virtual reality in the treatment of gambling disorder: the development of a new tool for cognitive behavior therapy. *Front. Psychiatr.* 8:27. doi: 10.3389/fpsyt.2017.00027

Bouton, M. E. (2002). Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. *Biological psychiatry*, *52*(10), 976-986. DOI: 10.1016/s0006-3223(02)01546-9

Buckfield, C., Sinclair, J. M., & Glautier, S. (2021). Slow associative learning in alcohol dependence and the alcohol cue exposure treatment paradox. *Addiction*, *116*(4), 759-768. DOI: 10.1111/add.15210

Byrne, S. P., Haber, P., Baillie, A., Giannopolous, V., & Morley, K. (2019). Cue Exposure Therapy for Alcohol Use Disorders: What Can Be Learned from Exposure Therapy for Anxiety Disorders?. *Substance use & misuse*, *54*(12), 2053-2063. DOI: 10.1080/10826084.2019.1618328

Choi, Y. J., and Lee, J. H. (2015). The effect of virtual covert sensitization on reducing alcohol craving in heavy social drinkers. *Virtual Real.* 19, 111–117. doi: 10.1007/s10055-015-0264-6

Clay, J.M.; Parker, M.O. Alcohol use and misuse during the COVID-19 pandemic: A potential public health crisis? *Lancet Public Health* 2020, *5*, e259. DOI:https://doi.org/10.1016/S2468-2667(20)30088-8

Collaboration, C. (2011). In J. P. Higgins, & S. Green (Eds.), Cochrane handbook for sys- tematic reviews of interventions version 5.1.0.

Conklin, C. A., & Tiffany, S. T. (2002). Applying extinction research and theory to cue- exposure addiction treatments. Addiction, 97(2), 155–167. DOI: 10.1046/j.1360-0443.2002.00014.x

Dawe, S., Rees, V. W., Mattick, R., Sitharthan, T., & Heather, N. (2002). Efficacy of moderation-oriented cue exposure for problem drinkers: a randomized controlled trial. *Journal of Consulting and Clinical Psychology*, *70*(4), 1045. https://doi.org/10.1037/0022-006X.70.4.1045

Drummond, D. C., Cooper, T., & Glautier, S. P. (1990). Conditioned learning in alcohol dependence: Implications for cue exposure treatment. British Journal of Addiction, 85(6), 725–743. DOI: 10.1111/j.1360-0443.1990.tb01685.x

Drummond, D. C., & Glautier, S. (1994). A controlled trial of cue exposure treatment in alcohol dependence. *Journal of consulting and clinical psychology*, *62*(4), 809. DOI: 10.1037//0022-006x.62.4.809

Drummond, D. C. (2000). What does cue-reactivity have to offer clinical research?. *Addiction*, *95*(8s2), 129-144. DOI: 10.1080/09652140050111708

Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *Bmj*, *315*(7109), 629-634. doi: https://doi.org/10.1136/bmj.315.7109.629

Everitt, B. J. (2014). Neural and psychological mechanisms underlying compulsive drug seeking habits and drug memories–indications for novel treatments of addiction. European Journal of Neuroscience, 40(1), 2163–2182. doi: 10.1111/ejn.12644

First, M. B., Spitzer, R. L., Gibbon, M., Williams, J. B., Davies, M., Borus, J., ... & Rounsaville, B. (1995). The structured clinical interview for DSM-III-R personality disorders (SCID-II). Part II: Multi-site test-retest reliability study. *Journal of personality disorders*, *9*(2), 92. DOI:10.1521/pedi.1995.9.2.92

Ghiţă A, Hernández-Serrano O, Fernández-Ruiz J, Moreno M, Monras M, Ortega L, Mondon S, Teixidor L, Gual A, Gacto-Sanchez M, Porras-García B, Ferrer-García M, Gutiérrez-Maldonado J. Attentional Bias, Alcohol Craving, and Anxiety Implications of the Virtual Reality Cue-Exposure Therapy in Severe Alcohol Use Disorder: A Case Report. Front Psychol. 2021 Feb 22;12:543586. doi: 10.3389/fpsyg.2021.543586. PMID: 33692713; PMCID: PMC7937649.

Ghiţă A, Hernández-Serrano O, Fernández-Ruiz Y, Monras M, Ortega L, Mondon S, Teixidor L, Gual A, Porras-García B, Ferrer-García M, Gutiérrez-Maldonado J. Cue-Elicited Anxiety and Alcohol Craving as Indicators of the Validity of ALCO-VR Software: A Virtual Reality Study. J Clin Med. 2019 Aug 2;8(8):1153. Doi: 10.3390/jcm8081153. PMID: 31382353; PMCID: PMC6723764.

Global statistics on alcohol, tobacco, and illicit drug use: 2017 status report. (2021). Retrieved 31 January 2021, from https://onlinelibrary.wiley.com/doi/epdf/10.1111/add.14234

Heather, N., Brodie, J., Wale, S., Wilkinson, G., Luce, A., Webb, E., & McCarthy, S. (2000). A randomized controlled trial of Moderation-Oriented Cue Exposure. Journal of Studies on Alcohol, 61(4), 561–570. DOI: 10.15288/jsa.2000.61.561

Hernández-Serrano O, Ghiţă A, Fernández-Ruiz J, Monràs M, Gual A, Gacto M, Porras-García B, Ferrer-García M, Gutiérrez-Maldonado J. Determinants of Cue-Elicited Alcohol Craving and Perceived Realism in Virtual Reality Environments among Patients with Alcohol Use Disorder. J Clin Med. 2021 May 21;10(11):2241. Doi: 10.3390/jcm10112241. PMID: 34064120; PMCID: PMC8196721.

Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., ... & Sterne, J. A. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj*, *343*. doi: https://doi.org/10.1136/bmj.d5928

Higgins, J., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M., & Welch, V. (2020). *Cochrane Handbook for Systematic Reviews of Interventions*. DOI:10.1002/9781119536604

Iranpour, A., & Nakhaee, N. (2019). A review of alcohol-related harms: A recent update. *Addiction & health*, *11*(2), 129. doi: 10.22122/ahj.v11i2.225

Kavanagh, D. J., Sitharthan, G., Young, R. M., Sitharthan, T., Saunders, J. B., Shockley, N., & Giannopoulos, V. (2006). Addition of cue exposure to cognitive-behaviour therapy for alcohol misuse: a randomized trial with dysphoric drinkers. *Addiction*, *101*(8), 1106-1116. doi:10.1111/j.1360-0443.2006.01488.x

Kim, D.-Y., & Lee, J.-H. (2015). Development of a virtual approach- avoidance task to assess alcohol cravings. Cyberpsychology, Behavior, and Social Networking, 18, 763–766. DOI: 10.1089/cyber.2014.0490

Koskina A., Campbell I. C., Schmidt U. Exposure therapy in eating disorders revisited. Neurosci Biobehav Rev 2013; 37: 193–208. DOI: 10.1016/j.neubiorev.2012.11.010

Kranzler HR, Soyka M. Diagnosis and pharmacotherapy of alcohol use disorder: a review. *JAMA* 2018; 320: 815–24. DOI: 10.1001/jama.2018.11406

Kwon, B. A., Choi, J., Roh, S., Yang, B.-H., & Lee, J.-E. (2006). Application of virtual reality cue exposure therapy for reducing alcohol craving. Annual Review of Cybertherapy and Telemedicine, 4, 161–166. DOI:10.1037/e695432011-082

Lee, J.-H., Lim, Y., Wiederhold, B. K., & Graham, S. J. (2005). A functional magnetic resonance imaging (fMRI) study of cue-induced smoking craving in virtual environments. Applied Psychophysiology and Biofeedback, 30, 195–204. doi:10.1007/ s10484-005-6377-z

Lee, J. H., Kwon, H., Choi, J., & Yang, B. H. (2007). Cue-exposure therapy to decrease alcohol craving in virtual environment. *CyberPsychology & Behavior*, *10*(5), 617-623. DOI: 10.1089/cpb.2007.9978

Lee, S.-H., Han, D. H., Oh, S., Lyoo, I. K., Lee, Y. S., Renshaw, P. F., & Lukas, S. E. (2009). Quantitative electroencephalographic (qEEG) correlates of craving during virtual reality therapy in alcohol-dependent patients. Pharmacology, Biochemistry, and Behavior, 91, 393–397. doi:10.1016/j.pbb.2008.08.014

Loeber, S., Croissant, B., Heinz, A., Mann, K., & Flor, H. (2006). Cue exposure in the treatment of alcohol dependence: Effects on drinking outcome, craving and self-efficacy. British Journal of Clinical Psychology, 45(4), 515–529. DOI: 10.1348/014466505X82586

Marissen, M. A., Franken, I. H., Blanken, P., van den Brink, W., & Hendriks, V. M. (2007). Cue exposure therapy for the treatment of opiate addiction: results of a randomized controlled clinical trial. *Psychotherapy and psychosomatics*, *76*(2), 97-105. DOI: 10.1159/000097968

Marlatt, G. A. (1990). Cue exposure and relapse prevention in the treatment of addictive behaviors. Addictive Behaviors, 15(4), 395–399. DOI: 10.1016/0306-4603(90)90048-3

Martin, T., LaRowe, S. D., & Malcolm, R. (2010). Progress in cue exposure therapy for the treatment of addictive disorders: A review update. The Open Addiction Journal, 3(1). **DOI:** 10.2174/1874941001003010092

McClernon, F. J., Hiott, F. B., Liu, J., Salley, A. N., Behm, F. M., & Rose, J. E. (2007). IMAGING STUDY: Selectively reduced responses to smoking cues in amygdala following extinction-based smoking cessation: results of a preliminary functional magnetic resonance imaging study. *Addiction biology*, *12*(3-4), 503-512. DOI: 10.1111/j.1369-1600.2007.00075.x

McLellan, A. T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., ... & Argeriou, M. (1992). The fifth edition of the Addiction Severity Index. *Journal of substance abuse treatment*, *9*(3), 199-213. DOI: 10.1016/0740-5472(92)90062-s

Mellentin, A. I., Skøt, L., Nielsen, B., Schippers, G. M., Nielsen, A. S., Stenager, E., & Juhl, C. (2017). Cue exposure therapy for the treatment of alcohol use disorders: a meta-analytic review. *Clinical psychology review*, *57*, 195-207. DOI: 10.1016/j.cpr.2017.07.006

Mellentin, A. I., Nielsen, B., Nielsen, A. S., Yu, F., Mejldal, A., Nielsen, D. G., & Stenager, E. (2019). A mobile phone app featuring cue exposure therapy as aftercare for alcohol use disorders: an investigator-blinded randomized controlled trial. *JMIR mHealth and uHealth*, *7*(8), e13793. DOI: 10.2196/13793

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. (2009). Preferred Reporting Items for Systematic Reviews andMeta-Analyses: The PRISMA Statement. *PloS Medicine, 6*(7). https://doi.org/10.1371/journal.pmed.1000097

Monti, P. M., Rohsenow, D. J., Rubonis, A. V., Niaura, R. S., Sirota, A. D., Colby, S. M., ... & Abrams, D. B. (1993). Cue exposure with coping skills treatment for male alcoholics: A preliminary investigation. *Journal of Consulting and Clinical Psychology*, *61*(6), 1011. https://doi.org/10.1037/0022-006X.61.6.1011

Monti, P. M., Rohsenow, D. J., Swift, R. M., Gulliver, S. B., Colby, S. M., Mueller, T. I., ... & Asher, M. K. (2001). Naltrexone and cue exposure with coping and communication skills training for alcoholics: treatment process and 1-year outcomes. *Alcoholism: Clinical and Experimental Research*, *25*(11), 1634-1647. https://doi.org/10.1111/j.1530-0277.2001.tb02170.x

Moon, J. B. A., & Lee, J.-H. (2009). Cue exposure therapy in a virtual environment to reduce nicotine craving: A functional MRI study. Cyberpsychology and Behavior, 12, 43–45. doi:10.1089/ cpb.2008.0032

Mourad Ouzzani, Hossam Hammady, Zbys Fedorowicz, and Ahmed Elmagarmid. Rayyan — a web and mobile app for systematic reviews. Systematic Reviews (2016) 5:210, DOI: 10.1186/s13643-016-0384-4.

Myers, K. M., & Davis, M. (2002). Behavioral and neural analysis of extinction. Neuron, 36(4), 567–584. DOI: 10.1016/s0896-6273(02)01064-4

National Collaborating Centre for Mental Health (UK) (2011). *Alcohol-Use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence*. British Psychological Society. (NICE Clinical Guidelines, No. 115.) 2, Alcohol dependence and harmful alcohol use. Available from: https://www.ncbi.nlm.nih.gov/books/NBK65500/

Nattala, P., Murthy, P., Leung, K. S., Rentala, S., & Ramakrishna, J. (2018). Video-enabled cue-exposure-based intervention improves postdischarge drinking outcomes among alcohol-dependent men: A prospective study at a government addiction treatment setting in India. *Journal of Ethnicity in Substance Abuse*, *17*(4), 532-547. DOI: 10.1080/15332640.2017.1310641

Niaura, R., Abrams, D. B., Shadel, W. G., Rohsenow, D. J., Monti, P. M., & Sirota, A. D. (1999). Cue exposure treatment for smoking relapse prevention: a controlled clinical trial. *Addiction*, *94*(5), 685-695. https://doi.org/10.1046/j.1360-0443.1999.9456856.x

Norberg, M. M., Barnier, E., Weidemann, G., Chakerian, K., Cornish, J. L., & Rapee, R. M. (2018). Randomised pilot study of cannabis cue exposure: Reducing cue reactivity while building tolerance. *Clinical Psychologist*, *22*(2), 126-136. doi:10.1111/cp.12157

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. Rayyan — a web and mobile app for systematic reviews. Systematic Reviews (2016) 5:210, DOI: 10.1186/s13643-016-0384-4.

Pavlov, P. I. (1927). Conditioned reflexes: An investigation of the physiological activity of the cerebral cortex. doi: 10.5214/ans.0972-7531.1017309

Pavlov, I. P., & Anrep, G. V. (2003). Conditioned reflexes. Courier Corporation. doi: 10.5214/ans.0972-7531.1017309

Rohsenow, D. J., Monti, P. M., Rubonis, A. V., Gulliver, S. B., Colby, S. M., Binkoff, J. A., & Abrams, D. B. (2001). Cue exposure with coping skills training and communication skills training for alcohol dependence: 6-and 12-month outcomes. Addiction, 96(8), 1161–1174. DOI: 10.1046/j.1360-0443.2001.96811619.x

Sitharthan, T., Sitharthan, G., Hough, M. J., & Kavanagh, D. J. (1997). Cue exposure in moderation drinking: A comparison with cognitive–behavior therapy. *Journal of Consulting and Clinical Psychology*, *65*(5), 878. https://doi.org/10.1037/0022-006X.65.5.878

Skinner, B. (1938). The behavior of organisms. An experimental analysis. New York: D. Appleton-Century Company. Inc, 61–74.

Skinner, H. A., & Allen, B. A. (1982). Alcohol dependence syndrome: Measurement and validation. Journal of Abnormal Psychology, 91(3), 199. https://doi.org/10.1037/0021-843X.91.3.199

Spagnoli, G., Gatti, E., Massari, R., Sacchelli, C., and Riva, G. (2014). Can virtual reality be useful to assess subjects with alcohol dependency? Development of a new assessment protocol for patients with alcoholism. *Eur. Int. J. Sci. Technol.* 3, 82–94.

Stanley, T. D., Doucouliagos, C. H. (2014). Meta-regression approximations to reduce publication selection bias. Research Synthesis Methods, 5, 60–78. DOI: 10.1002/jrsm.1095

Sterne, J. A., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., ... & Higgins, J. P. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. bmj, 366. DOI: 10.1136/bmj.l4898

Stockwell, T., Hodgson, R., Edwards, G., Taylor, C., & Rankin, H. (1979). The development of a questionnaire to measure severity of alcohol dependence. *British journal of addiction*. DOI: 10.1111/j.1360-0443.1979.tb02415.x

Stockwell, T. I. M., Sitharthan, T., McGRATH, D. A. V. I. D., & Lang, E. (1994). The measurement of alcohol dependence and impaired control in community samples. *Addiction*, *89*(2), 167-184. DOI: 10.1111/j.1360-0443.1994.tb00875.x

Toro J., Cervera M., Feliu M. H., Garriga N., Jou M., Martinez E., et al. Cue exposure in the treatment of resistant bulimia nervosa. Int J Eat Disord 2003; 34: 227–34. DOI: 10.1002/eat.10186

White, I. R., & Thomas, J. (2005). Standardized mean differences in individually-randomized and cluster-randomized trials, with applications to meta-analysis. *Clinical Trials*, *2*(2), 141-151. DOI: 10.1191/1740774505cn081oa

Williams, B. T., & Drummond, D. C. (1994). The alcohol problems questionnaire: reliability and validity. *Drug and alcohol dependence*, *35*(3), 239-243. DOI: 10.1016/0376-8716(94)90080-9

World Health Organization. (1992). The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. World Health Organization. https://apps.who.int/iris/handle/10665/37958

World Health Organization (WHO). Mortality Database Health statistics and information systems, Geneva, Switzerland 2018: WHO http:// www.who.int/healthinfo/statistics/mortality_

HIGHLIGHTS

- The efficacy of CET while treating AUDs is still a matter of debate.
- We reviewed and analysed the efficacy of CET targeting AUDs.
- CET has only a small to medium effect on drinks per day, drinking days and relapse.
- The overall quality of evidence of included studies was graded as low due to high risk of bias, inconsistency, imprecision, and suspected publication bias.
- More studies with multi-site CET trials with additional methodological innovations and increased retention is needed.

Author Agreement Statement

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We understand that the Corresponding Author is the sole contact for the Editorial process. She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

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Contributors: CK and PD conceived and developed the protocol. CK and MES conducted the literature research, study selection, and Risk of Bias. SN did data extraction, performed statistical analysis and contributed to the results section. MES conducted the quality assessment. CK wrote the paper. All authors had access to the data, critically reviewed the manuscript for important intellectual content, and approved the final version of the manuscript.

Declaration of interests: None

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. PD was supported by the NIHR Specialist Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London. He was also supported by the NIHR Collaboration for Leadership in Applied Health Research and Care at King's College Hospital NHS Foundation Trust and the National Institute for Health Research (NIHR) Applied Research Collaboration South London (NIHR ARC South London) at King's College Hospital NHS Foundation Trust.

Contributors: CK and PD conceived and developed the protocol. CK and MES conducted the literature research, study selection, and Risk of Bias. SN did data extraction, performed statistical analysis and contributed to the results section. MES conducted the quality assessment. CK wrote the paper. All authors had access to the data, critically reviewed the manuscript for important intellectual content, and approved the final version of the manuscript.

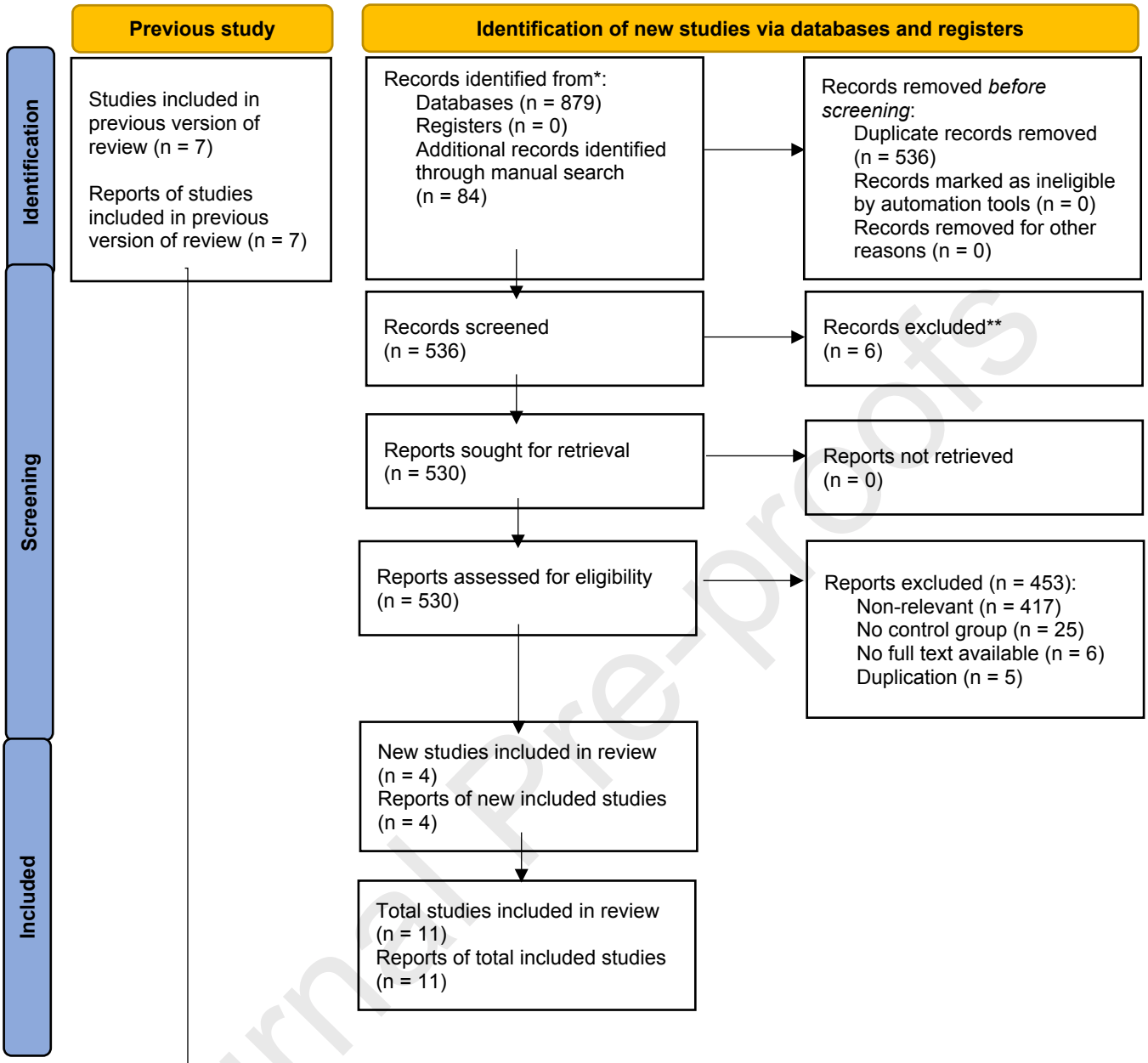

Figure 1. Prisma Flow Chart showing the number of potentially relevant references identified during the searches and the number included in the review

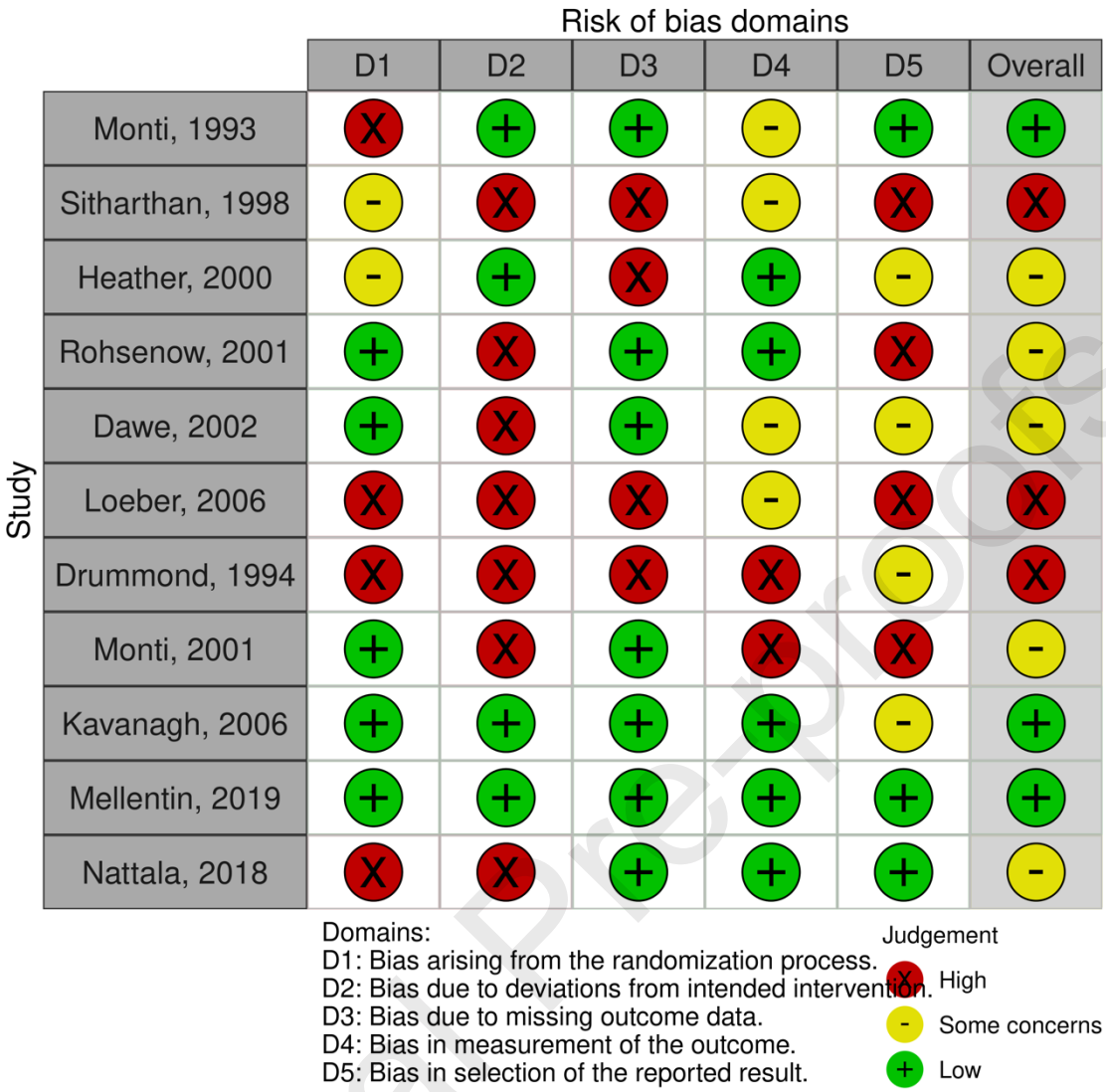

Figure 2. Risk of bias in the individual studies

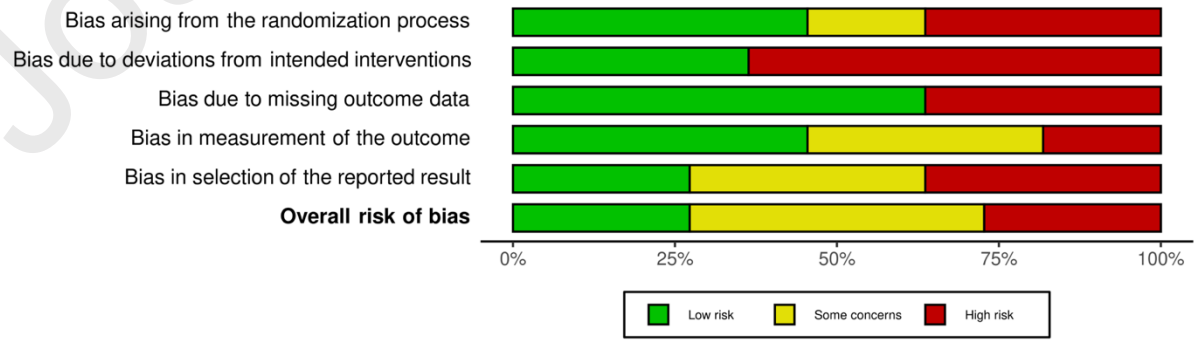

Figure 3. Percentage of risk of bias in the individual studies

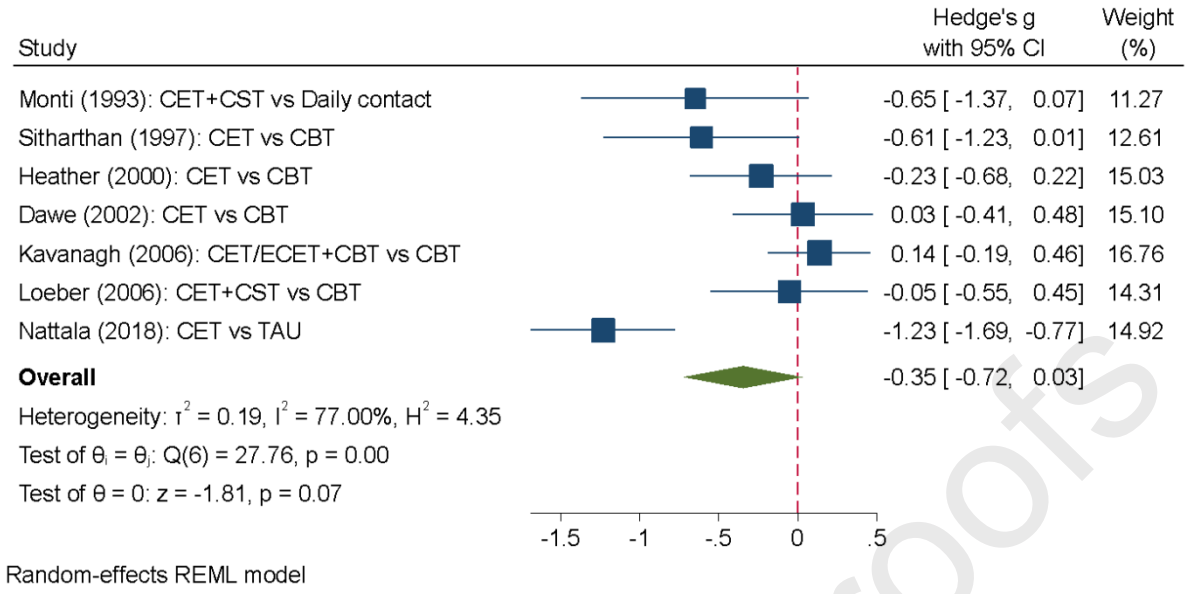

Figure 4. Forest plot of treatment effect estimates for studies assessing the number of drinks per day at 6 to 8 months follow-up

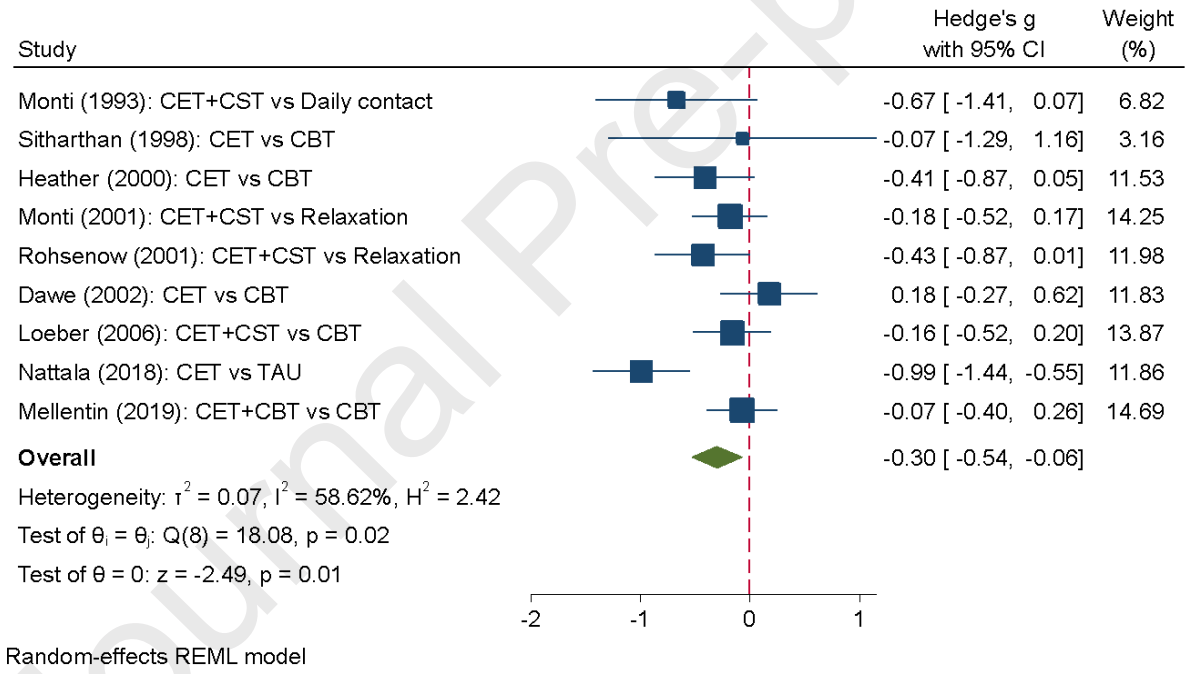

Figure 5. Forest plot of treatment effect estimates for studies assessing the number of drinking days at 6 to 8 months follow-up

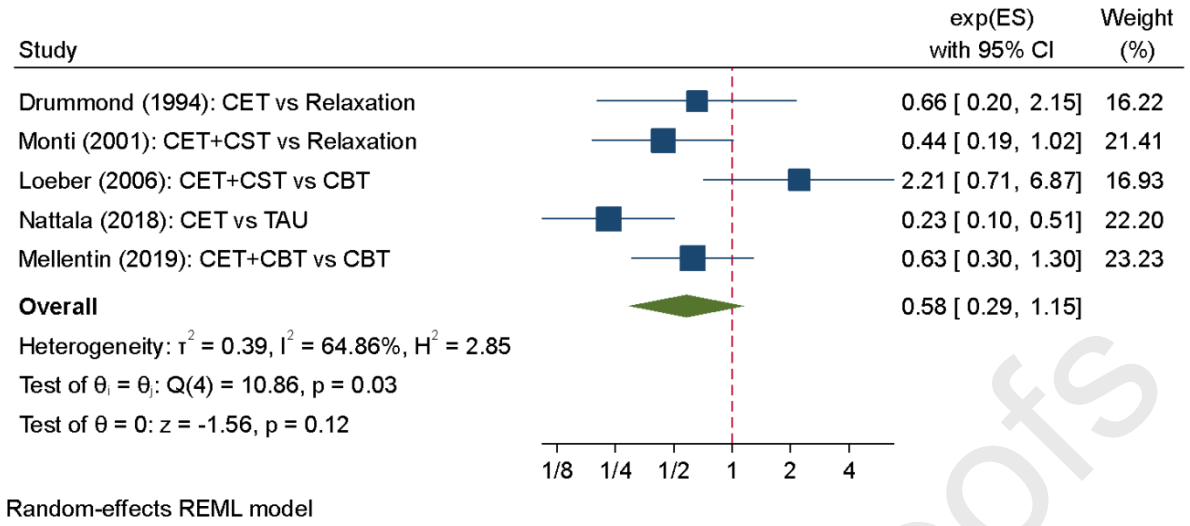

Figure 6. Forest plot of treatment effect estimates for studies assessing relapse at 6 follow-ups

Table 1. Study characteristics

Study	Year	Country	Pps	Female	Mean age	Intervention	Control	Goal	Outcome		
									Frequency of drinking days	Intensity of drinks per day	Frequency of relapse
Monti	1993	US	40	0	42.9 ± 12.7	CET+CST	Daily contact	Abstinence	Yes	No	No
Drummond	1994	UK	35	0	43 ± 1.5	CET	Relaxation	Abstinence	No	No	Yes
Sitharthan	1997	US	42	9	n.a.	CET	CBT	Moderation	Yes	Yes	No
Heather	2000	US	91	23	41.43 ± 9.92	CET	CBT	Moderation	Yes	Yes	No
Rohsenow	2001	US	100	22	n.a.	CET+CST	Relaxation	Abstinence	Yes	No	No
Monti	2001	US	128	31	39.2 ± 9.3	CET+CST	Relaxation	Abstinence	Yes	No	Yes
Dawe	2002	US	76	15	41.8 ± 10	CET	CBT	Moderation	Yes	Yes	No
Loeber	2006	Germany	63	27	46.25 ± 9.27	CET+CST	CBT	Abstinence	Yes	Yes	Yes
Kavanagh	2006	Australia	163	92	43.2 ± 9.21	CET/ECET+CBT	CBT	Moderation	No	Yes	No
Nattala	2018	India	85	0	37.87 ± 7.98	CET	TAU	Moderation	Yes	Yes	No
Mellentin	2019	Denmark	154	27	46 ± 13	CET+CBT	CBT	Moderation	Yes	No	Yes