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Association of Drug Cues and Craving With Drug Use and Relapse
A Systematic Review and Meta-analysis

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IMPORTANCE Craving, which is a strong desire for drugs, is a new *DSM-5* diagnostic criterion for substance use disorders (SUDs), which are the most prevalent, costly, and deadly forms of psychopathology. Despite decades of research, the roles of drug cues and craving in drug use and relapse remain controversial.

OBJECTIVE To assess whether 4 types of drug cue and craving indicators, including cue exposure, physiological cue reactivity, cue-induced craving, and self-reported craving (without cue exposure), are prospectively associated with drug use and relapse.

DATA SOURCES Google Scholar was searched for published studies from inception through December 31, 2018. In addition, backward and forward searches were performed on included articles to identify additional articles.

STUDY SELECTION Included studies reported a prospective statistic that linked cue and craving indicators at time 1 to drug use or relapse at time 2, in humans.

DATA EXTRACTION AND SYNTHESIS The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed. Study characteristics and statistics were extracted and/or coded by 1 of the 2 authors and then checked by the other. Statistical analyses were performed from May to July 2021.

MAIN OUTCOMES AND MEASURES Random-effects models were used to calculate prospective odds ratios (ORs) representing the association between cue and craving indicators and subsequent drug use/relapse.

RESULTS A total of 18 205 records were identified, and 237 studies were included. Across 656 statistics, representing 51 788 human participants (21 216 with confirmed SUDs), a significant prospective association of all cue and craving indicators with drug use/relapse was found (OR, 2.05; 95% CI, 1.94-2.15), such that a 1-unit increase in cue and craving indicators was associated with more than double the odds of future drug use or relapse. A Rosenthal fail-safe analysis revealed that 180 092 null studies would need to be published to nullify this finding. Trim-and-fill analysis brought the adjusted effect size to an OR of 1.31 (95% CI, 1.25-1.38). Moderator analyses showed that some of the strongest associations were found for cue-induced craving, real cues or images, drug use outcome, same-day time lag, studies using ecological momentary assessment, and male participants.

CONCLUSIONS AND RELEVANCE Findings from this systematic review and meta-analysis suggest that drug cue and craving indicators play significant roles in drug use and relapse outcomes and are an important mechanism underlying SUDs. Clinically, these results support incorporating craving assessment across stages of treatment, as early as primary care.

Supplemental content

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Substance use disorders (SUDs) are the most prevalent and deadly forms of psychopathology.[1-3] Specifically, lifetime prevalence is estimated at approximately 35% and results in 11.8 million deaths annually, or about 1 in 5 deaths.[3,4] Consistently, SUDs incur staggering social costs and economic costs exceeding $740 billion annually in the US.[5] Further, treatments for SUDs have limited efficacy[6] with relapse rates of approximately 40% to 60%, comparable with other chronic illnesses.[7] These sobering statistics underscore the urgent need to identify reliable predictors of drug use and relapse in order to improve diagnosis, tracking, and treatment.[8]

Drug cue reactivity and craving have been suggested as important underlying mechanisms as well as predictors of drug use and relapse.[6,9-11] Cue reactivity includes physiological and neural markers that arise in response to conditioned cues previously paired with drug use. In learning-based models of behavior, drug responses are unconditioned.[12] Cues that are repeatedly present during drug use become linked with drugs (and drug-related actions) and elicit conditioned responses.[13] Consistently, decades of preclinical work documented that animals respond to drug-associated cues with strong conditioned responses (ie, cue reactivity), including sympathetic activation and dopamine release.[14,15] This work has also suggested that drug-cue exposure increases drug-seeking behavior and use.[16]

For humans, conditioned drug cues are typically environmental and can include the sight of drugs, paraphernalia, and interoceptive cues (eg, stress[17,18]). Clinical studies have consistently shown that humans respond to such drug-associated cues with craving[19] along with conditioned sympathetic activation, dopamine release, and associated neural activity in regions like the ventral striatum.[9,20-23] Some evidence suggests that cue exposure may lead to drug-seeking in humans, whereas the magnitude of cue reactivity may predict drug use.[6,23]

Craving, a complex psychological phenomenon,[24,25] has long been conceptually linked to drug use.[26-28] Recently, drug craving was added as an SUD diagnostic criterion in *DSM-5*, where it is defined as a "strong desire for drugs."[29(p491)] Importantly, craving is (1) cited by drug users as the cause of relapse in retrospective studies[26,30,31]; (2) associated with subsequent drug use in prospective studies[32,33]; and (3) linked to drug use in Ecological Momentary Assessment (EMA) studies.[34,35] Craving that arises in response to drug-associated cues (ie, cue-induced craving) has also been shown to predict drug use[36-39] and relapse,[39-42] including in EMA studies.[37,42] Further, craving has been a target of treatment, with studies suggesting that reduction in craving is a mechanism of action in effective treatment.[43,44]

Despite this suggestive evidence, the effect of cues and craving on drug use remains controversial[45-47]; featured as core components in some models,[48] their significance is questioned in others.[49] Some have doubted whether exposure to cues increases use and relapse in humans; others have doubted whether the magnitude of cue reactivity and craving can predict use and relapse.[46,47,50-52] Some have specifically doubted the predictive role of cue-induced craving compared with other forms of craving.[47]

Key Points

Question Are drug cues and craving associated with drug use outcomes?

Findings This systematic review and meta-analysis, including 656 statistics from 237 studies and representing 51 788 participants, yielded a significant association between drug cues and craving and subsequent drug use and relapse.

Meaning Results suggest that drug cues and craving are core mechanisms underlying drug use that are reliably and prospectively associated with drug use.

Previously, we conducted a meta-analysis that suggested that food cue reactivity and craving predict eating and weight outcome.[53] Given the controversial role of craving and cue reactivity in the context of SUDs, here we evaluated the strength and consistency of evidence across the published literature, asking whether drug cues and craving can predict drug use and relapse. To that end, we conducted a systematic review and meta-analysis to assess and estimate the prospective association (ie, time 1 association with time 2) of 4 cue and craving indicators, including (1) cue exposure, (2) cue reactivity, (3) cue-induced craving, and (4) self-reported craving (without cue exposure), with drug use and relapse. We hypothesized a significant prospective association across cue and craving indicators, different drugs, craving measurements, and cue types, among others.

Methods

Search and Selection

This systematic review and meta-analysis was conducted from May to July 2021. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[54] reporting guidelines (**Figure 1**). We conducted separate literature searches for each drug using Google Scholar (chosen for its full-text search capabilities) up to the end of 2018 (eMethods and eTable 1 in the Supplement). We then reviewed titles and abstracts and selected a subset for full-text review. Next, we read full-text articles and applied final inclusion and exclusion criteria. In addition, we performed forward and backward searches on each included article to identify additional articles. In total, we reviewed 12 105 abstracts and 913 full-text articles.

Included studies met the following criteria: (1) at time 1, participants were exposed to drug cues and/or completed a self-report craving measure; (2) at time 2, at least 1 drug use outcome was reported; (3) time 1 occurred before time 2; (4) at least 1 reported analysis assessed the prospective association between time 1 measures and time 2 outcomes (excluding retrospective/cross-sectional statistics); and (5) statistics could be included in a meta-analysis (eMethods and eTable 1 in the Supplement; **Table 1**).[55] Final study inclusion and exclusion were determined independently by the 2 authors, yielding 656 statistics from 237 studies that were included in the omnibus

Figure 1. Study Selection and Exclusion Preferred Reporting Items for Systematic Reviews and Meta-Analyses Diagram

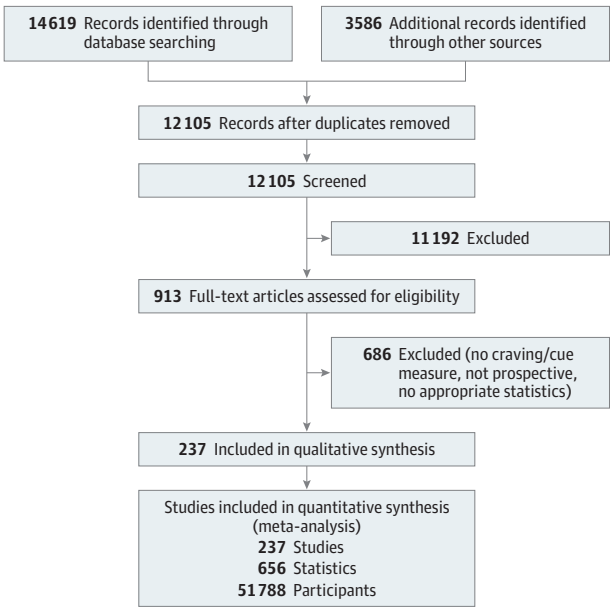


Table 1. Included Statistical Types and Relevant Study Designs[a]

Reported statistic	Represented study design
Pearson correlation coefficient (*r*)	Cue condition, cue reactivity, cue-induced craving, and self-reported craving
Standardized weights (β)	Cue condition, cue reactivity, cue-induced craving, and self-reported craving
Odds ratios	Cue condition, cue-induced craving, and self-reported craving
Independent group means and SD	Between-group comparison between participants randomized to a cue condition vs those randomized into a no cue condition
	Between-group comparison between those who abstained and those who relapsed
χ^2	Cue condition, cue reactivity, cue-induced craving and self-reported craving
F statistic, *t* statistic, *P* value	Within-group cue condition
Paired group means and *P* value	Within-group comparison cue condition
F statistic, *t* statistic, *P* value	Between-group cue condition

[a] Eight statistical categories were included in the meta-analysis. For β weights, we followed Peterson and Brown[55] guidelines for imputations (eMethods in the Supplement).

analysis, representing 51 788 participants. Disagreements were discussed until an agreement was reached.

Extraction and Coding

For each included statistic, we extracted N (number of participants represented by that statistic), as well as information about cue type, drug type, outcome, lag from time 1 to time 2, assessment setting, questionnaire type, and participant gender, in order to identify potential moderators of associations (eMethods and eTable 1 in the Supplement; **Table 2**). Based on the study design, we coded each statistic into cue and craving indicators: (1) cue exposure statistics differentiated between drug use outcomes after exposing participants to drug-

Table 2. Details of Moderator Categories

Moderator	Moderator category	Additional details
Study type (cue/craving indicators)	Cue condition	Exposure to drug cues vs neutral cues in time 1
	Cue reactivity	Biological measures in response to drug cues in time 1
	Cue-induced craving	Craving measures in presence of drug cues in time 1
	Self-reported craving	Self-reported craving measures (without drug cue presentation) in time 1
Cue type	Imagery	eg, Descriptions of high-risk situations
	Images	Photographic stimuli
	Media	eg, Movies depicting drug use
	Mixed	Combination of multiple cue types, such as real cues paired with imagery
	Real	eg, Paraphernalia, drug of choice
	Stress	Stress-induced craving, eg, cold pressor task
Drug type	Alcohol	NA
	Cannabis	
	Cocaine	
	Nicotine	
	Opioids	
	Other	Including polydrug use and other drugs (eg, methamphetamine)
Outcome	Drug use	Direct measures of drug use
	Drug use latency	Latency from measurement in time 1 to drug use in time 2
	Drug use proxy	Proxy measures of drug use (eg, Alcohol Purchase Task)
	Relapse	Drug use in individuals who were previously abstinent
	Relapse latency	Latency from measurement in time 1 to relapse in time 2
Lag from time 1 to time 2	Same day	NA
	Short term	1 d-1 mo
	Medium term	1 mo-6 mo
	Long term	>6 mo
Assessment setting	Clinical	Time 1 and time 2 measured in everyday life
	EMA	Either or both time 1/time 2 measured using EMA
	Laboratory	Time 1 and time 2 measured in laboratory settings
	Lab/clinical	Time 1 in laboratory, time 2 measured in everyday life
Questionnaire type (cue-induced craving)	Multiple item	Multiple-item measures (eg, PACS, QSU)
	Single item	Single-item Likert or VAS measure
Questionnaire type (self-reported craving)	Multiple item	NA
	Single item	
Gender	Both	NA
	Female	
	Male	

Abbreviations: EMA, Ecological Momentary Assessment; NA, not applicable; PACS, Penn Alcohol Craving Scale; QSU, Questionnaire of Smoking Urges; VAS, visual analog scale.

related cues vs neutral cues; (2) cue reactivity linked biological measures in response to drug cues (eg, heart rate, neural activity) with subsequent outcomes; (3) cue-induced craving linked self-reported craving in response to drug cues with outcomes; and (4) self-reported craving linked a craving measurement (without cue exposure) with outcome. Within cue-reactivity studies, we only selected functional magnetic resonance imaging statistics for the ventral striatum, which has been consistently implicated in Pavlovian conditioning and cue reactivity.[9,56-59] Within craving and cue-induced craving studies, we specifically coded the measure type as single item or multiple item because it has been argued by some that multiple-item measures would be more predictive, and we wanted to test that hypothesis.[60,61] Outcomes were coded into (1) drug use for direct measures of drug consumption; (2) drug use latency for latency from time 1 to drug use in time 2; (3) drug use proxy for proxy measures of drug consumption (eg, the Alcohol Purchase Task[62]); (4) relapse for drug use in previously abstinent individuals; and (5) relapse latency for latency from time 1 to relapse in time 2. Hereinafter, we refer to drug use and relapse outcomes as the combination of all 5 outcome types. Each piece of information was extracted and/or coded by 1 of the 2 authors and then checked by the other. Disagreements were discussed until agreement was reached.

Statistical Analyses

All analyses were conducted using Comprehensive Meta-Analysis software, version 3.0 (Biostat),[63] following our own and others' published meta-analyses.[50,53,64] We treated statistics as dependent if they came from the same population (both within and across studies). Within Comprehensive Meta-Analysis software, each statistic was weighted by its sample size; we then used random-effects models to calculate a mean prospective odds ratio (OR) and effect size *r* with 95% CIs for all analyses. We chose random-effects models to account for the heterogeneity among included studies, and calculated *Q* statistics that assessed for homogeneity among moderators. The omnibus analysis collapsed across all included statistics (including all cue and craving indicators and all outcomes), whereas other analyses addressed specific moderators. Lastly, we carried out publication bias analyses, including Rosenthal fail-safe N, trim and fill, Egger regression intercept, and a prediction interval for the omnibus results. Rosenthal fail-safe N gives a measure of how many studies with nonsignificant results would need to be published in order to make the meta-analytic results null.[65] Trim-and-fill analysis identifies and corrects for publication bias by estimating missing studies.[66] Egger regression intercept inspects asymmetry in a funnel plot of outcome by SE.[67] Prediction interval is an index of dispersion that indicates how much the true effect size varies.[68] Statistical analyses were performed from May to July 2021.

Results

As summarized in Figure 1, from a total of 18 205 identified records, 237 studies were included in the omnibus meta-analysis, including 656 statistics, representing 51 788 participants (21 216 with confirmed SUD diagnoses) (eMethods and eTable 1 in the Supplement). This primary analysis yielded an OR of 2.05 (95% CI, 1.94-2.15), indicating that each unit increase of cue and craving indicators was associated with more than double the odds of drug use and relapse (**Table 3**).

We tested several specific hypotheses regarding the association of each cue and craving indicator with drug use and relapse. Unless specified for a particular analysis (eg, study type, outcome type), we ran moderator analyses across all cue and craving indicators and/or across all outcome types to preserve power (eMethods, eTable 1, and eFigure in the Supplement). As hypothesized, cue exposure was associated with increased drug use and relapse across studies (OR, 2.28; 95% CI, 1.88-2.76). Further, the magnitude of cue-induced craving (OR, 3.01; 95% CI, 2.5-3.63), craving (OR, 2.16; 95% CI, 1.98-2.37), and cue reactivity (OR, 2.15; 95% CI, 1.62-2.86) was prospectively associated with increased odds of drug use and/or relapse. Cue-induced craving produced the strongest effect size (Q_3 = 10.08; P = .02).

All cue types were significantly associated with drug use and relapse (images OR, 3.42; 95% CI, 2.51-4.66; real OR, 2.59; 95% CI, 2.25-2.98; stress OR, 2.11; 95% CI, 1.55-2.88; mixed OR, 1.76; 95% CI, 1.31-2.37; imagery OR, 1.67; 95% CI, 1.04-2.67; media OR, 1.35; 95% CI, 1.02-1.8). Images and real cues showed the greatest effect (Q_5 = 27.46; images-real z test = 1.6; P = .12) (eFigure, eResults, and eTable 2 in the Supplement).

All cue and craving indicators were prospectively associated with outcomes across all categories of drug use and relapse (use OR, 2.56; 95% CI, 2.36-2.78; use latency OR, 2.2; 95% CI, 1.8-2.68; use proxy OR, 3.17; 95% CI, 2.25-4.46; relapse OR, 1.72; 95% CI, 1.59-1.86; relapse latency OR, 1.66; 95% CI, 1.32-2.09). Drug use outcomes were associated with stronger effect sizes compared with relapse (Q_4 = 58.18; P < .001). Importantly, we found the strongest associations for studies in which participants had confirmed SUD diagnoses (eTable 2 and eTable 3 Supplement).

Cue and craving indicators were prospectively associated with drug use and relapse across drug types. The 3 types representing the majority of included statistics were alcohol (OR, 2.47; 95% CI, 2.21-2.75), cocaine (OR, 1.98; 95% CI, 1.61-2.44), and nicotine (OR, 1.87; 95% CI, 1.73-2.02). The following 3 drug types represent a smaller subsample of statistics: cannabis (OR, 3.54; 95% CI, 2.1-5.98), opioids (OR, 1.91; 95% CI, 1.43-2.56), and other (OR, 3; 95% CI, 2.27-3.98), which includes polydrug use and other drugs (eg, methamphetamine).

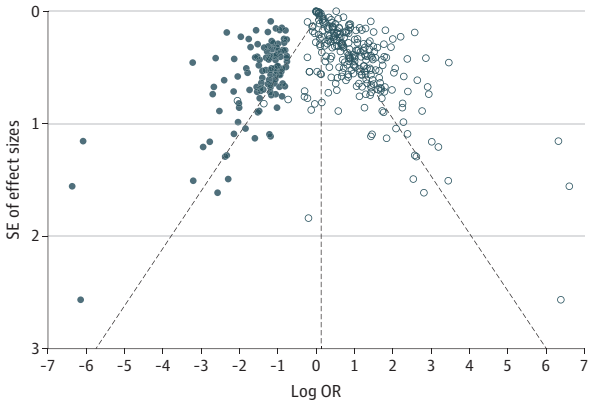
To assess whether cue and craving indicators were prospectively associated with drug use and relapse across time lags, we coded statistics as reflecting drug use with the following time lags: same day, short term (1 day to 1 month), medium term (1-6 months), and long term (longer than 6 months). Cue and craving indicators were significantly associated with drug use and relapse across all time lags (same-day OR, 2.37; 95% CI, 2.18-2.57; short-term OR, 1.63; 95% CI, 1.54-1.73; medium-term OR, 1.64; 95% CI, 1.54-1.74; long-term OR, 1.73; 95% CI, 1.59-1.88). Although there was a significant association with time lags over 1 year, same day results showed the strongest

Table 3. Detailed Summary of the Results

Variable	No. of statistics	No. of studies	No. of participants	Pearson *r*	OR (95% CI)	Cochran *Q* (*df*)	*P* value
Study type (cue/craving indicators)							
Cue condition	95	34	9430	0.2	2.28 (1.9-2.76)	9.87 (3)	.02
Cue reactivity	61	25	1422	0.2	2.15 (1.6-2.86)		
Cue-induced craving	120	58	6408	0.3	3.01 (2.5-3.63)		
Self-reported craving	380	166	41 440	0.2	2.16 (2-2.37)		
Cue type							
Imagery	22	4	693	0.1	1.67 (1-2.67)	27.46 (5)	<.001
Images	41	18	1022	0.3	3.42 (2.5-4.66)		
Media	19	10	4959	0.1	1.35 (1-1.8)		
Mixed	27	11	2519	0.2	1.76 (1.3-2.37)		
Real	137	53	9167	0.3	2.59 (2.3-2.98)		
Stress	29	12	746	0.2	2.11 (1.6-2.88)		
Drug type							
Alcohol	200	79	16 352	0.3	2.47 (2.2-2.75)	28.37 (5)	<.001
Cannabis	9	6	321	0.3	3.54 (2.1-5.98)		
Cocaine	35	21	2311	0.2	1.98 (1.6-2.44)		
Nicotine	371	120	30 925	0.2	1.87 (1.7-2.02)		
Opioids	23	9	975	0.2	1.91 (1.4-2.56)		
Other	18	13	1716	0.3	3 (2.3-3.98)		
Outcome							
Drug use	309	113	19 507	0.3	2.56 (2.4-2.78)	58.18 (4)	<.001
Drug use latency	69	25	4791	0.2	2.2 (1.8-2.68)		
Drug use proxy	21	11	516	0.3	3.17 (2.3-4.46)		
Relapse	240	99	29 219	0.2	1.72 (1.6-1.86)		
Relapse latency	17	10	1353	0.2	1.66 (1.3-2.09)		
Lag from time 1 to time 2							
Same day	196	75	6533	0.3	2.37 (2.2-2.57)	62.887 (3)	<.001
Short term	198	75	14 259	0.1	1.63 (1.5-1.73)		
Medium term	171	80	16 054	0.1	1.64 (1.5-1.74)		
Long term	90	31	18 273	0.2	1.73 (1.6-1.88)		
Assessment setting							
Clinical	200	89	31 633	0.1	1.47 (1.4-1.54)	94.79 (3)	<.001
EMA	106	43	7698	0.2	2.05 (1.9-2.23)		
Laboratory	182	65	5519	0.2	2.18 (2-2.37)		
Laboratory/clinical	168	49	9105	0.2	1.82 (1.7-1.97)		
Questionnaire type (cue-induced craving)							
Multiple item	42	20	2631	0.3	3.42 (2.4-4.9)	0.31 (1)	.58
Single item	78	38	3777	0.3	3.02 (2.3-3.91)		
Questionnaire type (self-reported craving)							
Multiple item	202	95	24 971	0.2	1.97 (1.8-2.19)	1.64 (1)	.20
Single item	179	81	18 611	0.2	2.17 (2-2.42)		
Gender							
Both	538	205	47 775	0.2	2.05 (1.9-2.18)	6.01 (2)	.05
Female	42	14	2671	0.2	1.82 (1.5-2.22)		
Male	70	21	1318	0.3	2.61 (2.1-3.25)		
Omnibus							
Random effects	656	237	51 788	0.2	2.05 (1.9-2.15)	17 070.93 (252)	<.001

Abbreviations: EMA, Ecological Momentary Assessment; OR, odds ratio.

Figure 2. Funnel Plot Depicting Standard Error (SE) of Effect Sizes



Funnel plot showing minimal publication bias in the overall model using the calculated log odds ratio (OR) value for each study in a trim-and-fill analysis. Black circles represent studies included in the analysis, and white circles represent filled-in studies.

association (Q_6 = 47.32; P < .001) (eResults and eTable 2 in the Supplement).

In a moderation analysis, we further evaluated the assessment setting, comparing studies in which (1) both measurements pertained to everyday life outside of laboratory settings (clinical OR, 1.47; 95% CI, 1.40-1.54); (2) studies that used EMA (OR, 2.05; 95% CI, 1.90-2.23); (3) both time 1 and time 2 were in the laboratory (OR, 2.18; 95% CI, 2.00-2.37); and (4) studies wherein time 1 pertained to measurements in the laboratory and time 2 to drug use and relapse in everyday life (OR, 1.82; 95% CI, 1.68-1.97). Across all methods, cue and craving indicators were prospectively associated with drug use and relapse, with the strongest association shown in laboratory and EMA studies (Q_3 = 94.79; P < .001).

We then assessed whether single-item measures of both craving and cue-induced craving were as effective as multiple-item measures. We found that for both self-reported and cue-induced craving, single-item measures were as prospectively associated with drug use and relapse as multiple-item measures. Specifically, for cue-induced craving (multiple-item OR, 3.42; 95% CI, 2.39-4.9; single-item OR, 3.02; 95% CI, 2.33-3.91; Q_1 = 0.31; P = .58) and for self-reported craving (multiple-item OR, 1.97; 95% CI, 1.78-2.19; single-item OR, 2.17; 95% CI, 1.96-2.42; Q_1 = 1.64; P = .20).

Lastly, another moderation analysis also evaluated sex and gender within the small subset of studies that included separate statistics for male and female participants (both sexes/genders OR, 2.05; 95% CI, 1.94-2.18; male OR, 2.61; 95% CI, 2.1-3.25; female OR, 1.82; 95% CI, 1.5-2.22). Statistics representing male participants showed the stronger association (Q_3 = 6.01; P = .05; male vs female z test = 2.39; P = .02 (eResults; eTable 2 in the Supplement).

To determine publication bias, Rosenthal fail-safe N revealed that 180 092 null studies would need to be published to nullify the meta-analytic results. Kendal τ did not indicate a risk of publication bias (τ = 0.03; $z\tau$ = 0.596; P = .55); Egger regression intercept detected some publication bias (intercept = 2.12; SE = 0.52; t_{251} = 4.25; P < .001). Trim-and-fill analysis added 114 studies left of the mean and zero studies right of the mean (**Figure 2**), which brought the adjusted effect size to an OR of 1.31 (95% CI, 1.25-1.38). The prediction interval for the omnibus analysis was 1.21 to 3.44.

Discussion

To our knowledge, this was the first and most comprehensive systematic review and meta-analysis on the association of multiple types of cue and craving indicators with drug use and relapse for all drug types. These cue and craving indicators were included: cue exposure, physiological cue reactivity, cue-induced craving, and self-reported craving (without cue exposure). The primary analysis revealed, across all studies and all 4 cue and craving indicators, a significant prospective association with drug use and relapse outcomes (OR, 2.05; 95% CI, 1.94-2.15), such that a 1-unit increase in cue and craving indicators was associated with more than double the odds of future drug use and relapse. Moreover, each of the 4 cue and craving indicators was prospectively associated with more than double the odds of drug use/relapse. This association held across cue types, drug types, outcome, time lags, assessment settings, questionnaire types, and gender. To our knowledge, these consistent and significant prospective associations provide the strongest evidence to date that cues and craving may reliably predict drug use and relapse outcomes and may be core mechanisms underlying drug use.[48,69,70]

Notably and contrary to doubts raised about the degree to which cue-induced craving can influence drug use outcomes,[47] the results demonstrate that cue-induced craving has the strongest meta-analytic effect size. Specifically, a 1-point increase in cue-induced craving more than tripled the odds of drug use and/or relapse. Interestingly, although learning-based models suggest that craving responses to real-life cues (eg, cigarettes, pipes) would be the best estimators of drug use and relapse outcomes, results indicate that responses to drug images are as strongly associated with drug use outcomes as real-life cues. This suggests that laboratory models that use such images may be particularly useful in estimating drug use and relapse outcomes.

Among assessment settings, we found that EMA and laboratory settings produced the strongest associations between cues and craving indicators and drug use and relapse outcomes.[71] Given that EMA methods capture real-life behaviors in vivo, results from such studies may better represent the true effect size for the association of cue and craving indicators with drug use and relapse compared with studies that rely on retrospective reports.[72] Thus, it is possible that this meta-analysis, which includes 84% non-EMA statistics, may, in fact, be underestimating the size of the true effect size for the association between cue and craving indicators with drug taking and relapse in everyday life.

Importantly, although we have so far not used predictive language to describe the results, the meta-analysis is composed of prospective studies with statistical analyses of associations between variables/risk factors at time 1 and a subsequent, prospective, and clinical outcome at time 2. Additionally,

60% of the included studies, representing 77% of the included participants, came from analyses of the type that some describe as prediction models, such as logistic and linear regressions. Indeed, an analysis isolating these statistics (representing 144 studies, 384 statistics, and 40 109 participants) suggests that the aggregate effect size was significant (eFigure in the Supplement). This is consistent with the idea that cue and craving indicators may predict drug use and relapse and are not only prospectively associated with them.

These results may support a potential causal inference for the role of cues and/or craving with drug use and relapse. Specifically, they satisfy multiple dimensions of potential causal inference.[73,74] Indeed, we report a significant association between cues and craving and drug use, as well as consistency of results across types of cue and craving indicators and numerous study- and participant-related factors. Additionally, the prospective nature of all included statistics provides support for the temporal sequence of these associations. Further, biological rationale and coherence have been previously demonstrated for cue and craving indicators as a core mechanism in SUDs. Notably, the effect sizes for the cue exposure indicator type specifically support the experimental evidence dimension of the criteria; however, craving is a subjective experience that can be provoked—not directly manipulated experimentally—and therefore does not fulfill this criterion. Nevertheless, together, these factors suggest a potential causative role for drug cues as well as craving in drug use and relapse, with the evidence being particularly strong for cue exposure owing to the subjective and nonexperimental nature of craving.

Although significant overall, the results also suggest some variability between studies, as the effect sizes ranged from 1.21 to 3.44. Accordingly, the results indicate that a unit increase in cues and craving was associated with 3 times higher likelihoods of drug use or relapse for some populations and a lesser likelihood for other subpopulations. The observed heterogeneity also affects the interpretation of publication bias analyses.[75] For example, the trim-and-fill method produced an adjusted effect size of 1.03. Although trim and fill is an informative method for assessing the presence of bias in a meta-analysis, its interpretive utility is limited in the presence of high variability.[76]

The variability observed in this meta-analysis was likely attributable to individual differences, whereby certain SUD phenotypes could differentially show these associations. Indeed, it has been argued the heterogeneity of response to SUD treatments could stem from a lack of granular understanding of individual differences.[77] Consistently, in personalized-medicine approaches, the identification of different mechanisms of action is considered crucial for addressing the onset and maintenance of SUDs and for identifying treatment targets that are based on individual needs.[78] We expect future work can elucidate these mechanisms further, which in turn may aid in risk assessment and selection of targeted treatments.

The results have important potential implications for public health interventions and clinical treatment of SUDs. First, identification of empirically supported, variables and risk factors associated with drug use and relapse are essential tools in managing disease. In line with recommendations to use science-based action to limit the rise of SUDs,[79] the current results support the use of craving as a clinical estimator of drug use and SUDs, including strong recommendations to incorporate assessment of craving into clinical practice across settings. Furthermore, the lack of difference in predictive power between single- and multiple-item measures of craving is especially important in this context, as it suggests that a relatively simple and easy-to-collect single-item measure of craving could be used as early as primary care and emergency medicine, to estimate drug use and relapse. Importantly, cue and craving indicators remained significantly associated with drug use outcomes not only in the short term, as would be expected, but also in the long term—6 months and even years afterward. This suggests that repeated measures of cue and craving indicators (in particular cue-induced craving) during care and treatment could be used to educate patients and to assess treatment adherence and efficacy.

Second, the results support the removal or avoidance of drug cues as a treatment target. Indeed, many effective SUD treatments already include management of cues (eg, avoidance of high-risk situations[80]) especially in early recovery. One classic example is the adage "people, places, and things" that may trigger drug use. Similarly, the results support craving—and the regulation of craving—as treatment targets.[51] Again, many effective treatments already include training in strategies to regulate or cope with craving (eg, cognitive-behavioral[81,82] and mindfulness-based[83,84] treatments), and brief trainings that focus on regulation of craving reduce substance use.[85,86] Indeed, behavioral and pharmacological studies have both suggested that reduction of craving is one key mechanism of action of SUD treatment.[43,44] The results of this meta-analysis further support developing interventions that target craving directly.[86]

Third, the results support the use of craving as an outcomes measure in SUD treatment studies—alongside drug use—as it satisfies multiple proposed criteria,[87] including clinical significance, ease of assessment using a variety of psychometrically validated measures, being altered by treatment, and predicting drug use across substances. Consistently, craving can be used during and after treatment to monitor treatment adherence, serve as an early warning sign during recovery, and estimate the risk of relapse in individuals who are already abstinent.

Limitations

There was heterogeneity among studies, and we carried out moderator analyses to parse out potential causes of this variability. Study type, assessment setting, lag from time 1 to time 2, drug type, and gender, among others, were factors that moderated the meta-analytic results. However, some moderator analyses were underpowered. For example, within drug type, cannabis and opioids were represented by only 6 and 9 statistics, respectively. Consequently, the ORs estimated for these drug types must be cautiously interpreted. Indeed, the main limitation of this meta-analysis results from the nature of the literature itself. Specifically, we found great variability in sta-

tistical reporting (eg, which statistics were reported), and most studies did not parse out statistics by crucial moderators, such as gender.[88] Indeed, the higher prevalence of SUDs in male participants,[89] coupled with the finding of stronger meta-analytic outcome in male participants compared with their female counterparts, makes differentiating across such moderators imperative, with important consequences for treatment and outcome (eResults in the Supplement). Overall, this curtailed our ability to assess the roots of this variability. Relatedly, we found a substantial number of studies with poor statistical reporting practices. Examples include studies reporting betas without specifying if they were standardized, reporting means without SDs, or reporting results without test statistics. With this, we call on researchers to adhere to best practice reporting guidelines[90,91] to allow for more studies to be included in future meta-analyses in this and other fields.

Conclusions

Taken together, the results of this systematic review and meta-analysis may be used as a methodological blueprint for future studies aiming to better elucidate the role and mechanism of action of cues and craving in SUDs. Results of this systematic review and meta-analysis suggest the use of craving as a measurable variable to estimate risk of drug use or relapse across assessment and clinical settings to aid in assessment and treatment.

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