



## Alcohol use disorder relapse factors: A systematic review

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### ARTICLE INFO

#### Keywords:

Remittance  
Recurrence  
Relapse determinants  
Dual diagnosis  
Biopsychosocial model  
Spiritual

### ABSTRACT

A relapsing-remitting course is very common in patients with an Alcohol Use Disorder (AUD). Understanding the determinants associated with alcohol resumption remains a formidable task. This paper examines relapse determinants based on a systematic review of recent alcohol literature (2000–2019). Relevant databases were consulted for articles that contained information about specific relapse determinants and reported statistical significance of each relapse determinant in predicting relapse. Relapse was broadly defined based on the characterization in the included articles. From the initial identified 4613 papers, a total of 321 articles were included. Results encompass multiple relapse determinants, which were ordered according to biopsychosocial and spiritual categories, and presented, using a descriptive methodology. Psychiatric co-morbidity, AUD severity, craving, use of other substances, health and social factors were consistently significantly associated with AUD relapse. Conversely, supportive social network factors, self efficacy, and factors related to purpose and meaning in life, were protective against AUD relapse. Despite heterogeneity in different methods, measures, and sample characteristics, these findings may contribute to a better therapeutic understanding in which specific factors are associated with relapse and those that prevent relapse. Such factors may have a role in a personalized medicine framework to improve patient outcomes.

### 1. Introduction

Alcohol Use Disorder (AUD) is a highly prevalent psychiatric disorder. According to recent epidemiologic data, an estimated 23 million people have an AUD in the European Union (Rehm et al., 2015) and an estimated 32.6 million people have an AUD in the United States (Grant et al., 2017, 2015).

Importantly, most people with AUD recover without any formal treatment (Cohen et al., 2007; Grant et al., 2015). Yet, for numerous individuals, having an AUD encompasses a chronic, recurring condition involving multiple cycles of treatment, abstinence, and relapse (McKay and Hiller-Sturmhofel, 2011). This is particularly common among individuals with AUD and psychiatric co-morbidity, where the course of AUD is typically chronic and disabling (Durazzo and Meyerhoff, 2017; Tuithof et al., 2014). For instance, AUD alone and in combination with psychiatric disorders is often associated with heightened suicide risk (Flensborg-Madsen et al., 2009; Kölves et al., 2017).

#### 1.1. Defining relapse

In AUD treatment and research, a semantic controversy exists, regarding the definition of “relapse”. For instance, terms like ‘slip’ and ‘lapse’, indicating single instances of drinking, are commonly used in the literature. Despite a vast amount of research, the definition of relapse remains a semantic ambiguity (McKay et al., 2006; Miller, 1996), whereby “the heuristic value of AUD relapse as currently studied is low” (Maisto et al., 2016a).

Half a century ago Hunt, Barnett, and Branch (1971) found relapse rates (with relapse defined as any substance use) among multiple substances (alcohol, tobacco, and heroin) in addiction treatment were strikingly similar with most individuals returning to substance use within the first three months following treatment and less than 30% continuously abstinent at one year following treatment. A recent meta-analysis shows that at most 50% of people with an AUD, after a longer follow up period of several years, achieve remission (Fleury et al., 2016). To counteract the high relapse rates, Marlatt and Gordon (1985)

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<https://doi.org/10.1016/j.psychres.2019.05.038>

Received 2 March 2019; Received in revised form 23 May 2019; Accepted 24 May 2019

Available online 25 May 2019

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proposed ‘Relapse Prevention’ skills to reduce relapse risk (Larimer et al., 1999; Roozen and van de Wetering, 2007), which is still a hallmark in addiction treatment (Hendershot et al., 2011). More recently, several psychological and psychobiological models have been postulated and tested for their validity in characterizing relapse (Connors et al., 1996; Hendershot et al., 2011; Witkiewitz, 2011; Witkiewitz and Marlatt, 2007, 2004).

### 1.2. Theories of relapse

Examining determinants that are frequently associated with relapse, as well as those factors that are protective in preventing relapse, is an important avenue for further research. Several studies have examined relapse determinants from a specific framework, such as social learning or cognitive behavioral framework (Witkiewitz and Marlatt, 2004), social factors (Hunter-Reel et al., 2009), neurobiological (Cui et al., 2015), and the ‘disease concept’ (McKay and Hiller-Sturmhofel, 2011).

In the last two decades, light has been shed on the neurobiology of addictive behaviors, including AUD (Koob and Volkow, 2016; Noël et al., 2013; Uhl et al., 2019), and heuristic neurobiological relapse models have been hypothesized. Dysfunctions in three major neuro-circuits have been proposed: the basal ganglia (including the striatum), the extended amygdala, and the prefrontal cortex (Koob and Volkow, 2016), while other research has put an emphasis on the role of the insula (Noël et al., 2013). These theoretical frameworks have fostered the development of several behavioural and medical interventions (Volkow et al., 2016), but the ‘translation’ into clinical practice remains a challenge (Noël and Bechara, 2016). In addition, it must be noted that few studies have attempted to integrate social, psychological and neurobiological findings.

### 1.3. Current study

Engel’s biopsychosocial (BPS) model (Engel, 1977) has proven validity (Wade and Halligan, 2017), and may be appropriate for examining determinants of AUD relapse that might foster translation into a clinical setting (Álvarez et al., 2012). Determinants leading to relapse, in the perspective of an integrative view like the BPS model, could be used as a practical clinical guide (Borrell-Carrio et al., 2004). Recently, this model has been expanded to the ‘biopsychosocial-spiritual’ (BPSS) model (Sulmasy, 2002), which may be particularly useful for characterizing relapse given the importance of spirituality in many AUD treatment and mutual help approaches. The objective of this exploratory narrative review is to provide an update on the latest research examining established relapse determinants, as well as to review the literature to identify novel relapse determinants. The BPSS model was used to catalog our results. As such, a general overview of identified relapse determinants will be provided. These relapse determinants could be integrated in the practice of current treatments and our findings could give rise to more extensive and systematic research on particular categories of the BPSS model.

## 2. Methods

### 2.1. Search strategy

Based on the Cochrane methodology, three databases (PubMed, PsycINFO and the Cochrane database) were consulted (January 2000–April 2019) for ‘English’ articles highlighting alcohol relapse in adult humans (18–65 years). The search was commenced on April 24th 2019. The search term ‘Alcohol Use Disorder’ (AUD) and relevant synonyms were coupled with the terms ‘Relapse’ or ‘Remission’ using the Boolean search operators ‘AND’ and ‘OR’. The term ‘recurrence’ did not yield any relevant extra articles, so was discarded in the final search. In ‘PICO’ terms, the Population (‘adults with an AUD’), the Intervention/determinant (‘relapse determinants’), the Comparison (‘remission

**Table 1**

Search details.

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(Alcoholism [MeSH Terms] OR Alcoholism [all] OR Alcohol Use Disorder [all] OR Alcohol Abuse [all] OR Alcohol Dependence [all]) AND (relapse [all] OR remission [all])  
 #1 Alcoholism (MeSH and All Fields)  
 #2 Alcohol Use Disorder  
 #3 Alcohol Abuse  
 #4 Alcohol Dependence  
 #5 #1 OR #2 OR #3 OR #4  
 #6 Relapse  
 #7 Remission  
 #8 #6 OR #7  
 Combining: #5 AND #8  
 Filters added: Human / English / Adult / Year 2000- (April) 2019

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determinants’) and the Outcome (‘AUD remission or relapse’) could be formulated. The final search strategy used in PubMed is displayed in Table 1. For the two other databases, similar search terms were used. The search in the Cochrane database yielded no articles describing AUD relapse factors. Books and dissertations were excluded.

### 2.2. Study selection

The first author screened all abstracts on AUD, relapse or remittance terms. The retained abstracts were independently read by two individual reviewers (WS & RdW) to make a selection for considering full length articles.

#### 2.2.1. Inclusion

We included studies describing relapse determinants, accounting for relapse or remission in AUD. All studies that described any specific determinant associated with relapse were included; for example, qualitative and quantitative reviews, randomized controlled trials, controlled clinical trials, uncontrolled studies, correlational, and descriptive studies. Based on abstract / full text reading, articles were identified that explicitly mentioned factors associated with remission or relapse of AUD.

#### 2.2.2. Exclusion

Articles were excluded that described various unhealthy or problematic drinking patterns that did not meet DSM IV or DSM 5 AUD criteria. Also, case reports describing a theoretical effect on relapse were excluded.

Of all 393 full-length articles assessed for eligibility, eventually 72 articles were excluded. Of these excluded articles, two studies were omitted, because they were duplicates. With respect to the final number of 393 articles, two studies were questioned whether they were eligible to include in this review (Bauer et al., 2007; Karriker-Jaffe et al., 2018) which was resolved by both reviewers, by eventually excluding one (Bauer et al., 2007). In case of non-consensus, a third reviewer (HR) could be consulted to make a final decision.

Papers with a mixed drugs/alcohol use population, whereby data regarding alcohol samples could not be uniquely distinguished (White et al., 2013), were omitted. Furthermore, we excluded studies whereby the effect of the reported relapse factor was not further explained in regard to AUD relapse (Sullivan and Covey, 2002), or despite our search terms only dealt with animal studies (Schank et al., 2012). We also excluded articles describing a possible relapse hypothesis (Simioni et al., 2012), intervention studies (Sugaya et al., 2012), or in which no new determinants were described, but an adjusted model was tested on already known determinants (Witkiewitz and Marlatt, 2007). Several studies describing treatment methods were excluded, if besides the treatment effect, no other independent risk factors for relapse were mentioned. In case the data of an original study was used more than once, for example as result of inclusion into a systematic review (Bottlender and Soyka, 2005a; Foulds et al., 2017; Gong and Minuk,

2018; Kelly et al., 2006), data on specific relapse determinants were used only a single time (Adamson et al., 2009; Henkel, 2011). For longitudinal studies that reported on multiple moments in time the sample size at baseline-only was reported (Moos et al., 2006; Moos and Moos, 2007, 2006). Eventually, 321 unique articles were included.

During the writing process, we checked the quality of our own review work by using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) method (Moher et al., 2009). A PRISMA checklist is provided in supplement 1.

### 2.3. Relapse definition

No uniform definition of relapse could be retrieved from the included articles, which is consistent with the findings of a recent systematic review of relapse definitions (Maisto et al., 2016a). The definitions varied largely across studies, varying from returning to any drinking, to the percentage of heavy drinking days, or the persistence of AUD over time. Associations that were examined focused on the relationship between each of the relapse factors and outcome, which was variably defined across the included studies. Thus, our “relapse” outcome was defined as it was defined in the original study. Roughly defined, relapse in our review can be seen as ‘an absence of abstinence’.

### 2.4. Data extraction

From the included articles, the following data were extracted and tabulated in terms of study design/population, follow-up period, study objective, sample size, results/statistics and the final conclusion (supplement 2). Finally, the mentioned determinants of relapse/remission were tabulated according to Engel's biopsychosocial model expanded to the ‘biopsychosocial-spiritual’ (BPSS) model. Based on this model, 37 subgroups were composed, which are displayed in Table 2. These subgroups are partly known relapse categories from already existing and tested models (like ‘self efficacy’ or ‘emotion(al) states’) (Witkiewitz and Marlatt, 2004), ‘psychiatric comorbidity’ or ‘stress’ (Blaine and Sinha, 2017). Determinants such as ‘genetics’ or ‘gender’ were considered biological. ‘Stress’, psychiatric and addiction related determinants were categorized psychological and ‘a supportive relationship’ was categorized as social. The determinant ‘Living for a higher purpose in life’ was categorized as spiritual.

Overall, we regarded a  $p$ -value  $< 0.05$  as statistically significant. Several papers only mentioned  $p$ -values and the clinical relevance was not made clear and very few studies reported effect sizes (Sullivan and Feinn, 2012). A few papers did not mention patient numbers or statistical analysis (McKay et al., 2006; Snelleman et al., 2018). Findings from these papers were categorized as ‘statistically not significant’, when these figures could not be retrieved after contacting the corresponding author. Quality assessment of included studies, identified 53 studies with a small sample size, eight studies where description of figures/ statistics was unclear or omitted. Of the 15 included reviews, only a few could be identified as ‘systematic’ and 5 were qualitative reviews not mentioning numerical data.

The most frequently reported determinants, or determinants found among a relatively large population are reported in Section 3. In cases where determinants were interrelated, we chose to report only the main findings and omitted the correlating determinant (Wiers et al., 2015).

To visualize the selection and data extraction process see the flow chart in Fig. 1.

## 3. Results

### 3.1. Study selection

In PubMed, we obtained a total of 2689 references, 1915 in PsycINFO, and in the Cochrane database 9 (from which none described AUD relapse), thus making up a total of 4613 articles.

The two individual reviewers went through the abstracts and eventually 393 unique articles were marked as probably relevant to include in the actual review. From these, after comprehensive reading, another 72 were excluded. We included 321 articles in the actual review.

Because of the enormous diversity in described determinants, sample sizes and methodological quality and heterogeneity of the several studies, statistical analyses were not conducted and a narrative review was the focus of identifying those relapse determinants that consistently yielded statistically significant effects across studies.

### 3.2. Findings

Identified relapse determinants are reported in Tables 2 and 3. A complete overview of included articles can be found in Table 3. The results (number of studies and total sample size) are arranged using the BPSS model. The nature of each factor (in terms of relapse or remission) is described, as well as some relevant exemplary articles.

#### 3.2.1. Biological factors

The factor ‘age’ was identified in 31 studies as having a statistically significant effect on relapse (aggregated sample size of 49,258 persons), whereas 15 studies found no statistically significant effect of age on relapse (aggregated sample size of 2184 individuals). Generally, older age of onset of AUD was associated with a higher probability of remission (Abdin et al., 2014). A younger onset of AUD was associated with relapse (Vito Agosti, 2013).

The factor ‘gender’ was not a consistent predictor of relapse across studies. Some studies found that female gender was significantly associated with better prognosis (Boschloo et al., 2012; Dawson et al., 2005), whereas a greater number of studies found no statistically significant association between gender and relapse rates (Jakubczyk et al., 2013; Nalpas and Boulze-Launay, 2018; Spruyt et al., 2013).

‘Brain’ based determinants of relapse, measured via neuroimaging, were examined in 25 studies, however sample sizes tend to be smaller in neuroimaging studies. Generally results are consistent with neurobiological models of addiction (Koob and Volkow, 2016; Noël et al., 2013) and studies have found dysfunction in the brain reward system, executive control network, and insula, among other regions were associated with significantly greater relapse rates. Only one study (Gross et al., 2013) failed to find an association between hippocampal volume and relapse risk among abstinent individuals with AUD.

The association between ‘family history’, reflecting genetic and shared environment variance, and ‘genetic’ factors (i.e., specific single nucleotide polymorphisms) and relapse has yielded mixed results. Generally, slightly more studies have identified family history and genetics to be associated with greater relapse risk, however a large number of studies have failed to find associations between family history or genetic factors and relapse risk.

The impact of ‘health’ as a relapse determinant was identified as statistically significant predictor of relapse or remission in nine studies with a total sample of 11,541 people. Across studies worse physical health was significantly associated with higher relapse risk (Satre et al., 2012) and only one study failed to find a significant association between health and relapse (Rus-Makovec and Cebasek-Travnik, 2008).

Eight studies with more than 400 patients found disturbed ‘sleep’ was associated with significantly greater relapse rates, and only one study found no effect of poor sleep on relapse (Jakubczyk et al., 2013).

‘Hormonal’ factors and specific ‘biomarkers’ of alcohol use (e.g., liver enzymes) have generally been less frequently studied and with smaller sample sizes, however most studies have found impaired hormone and elevated biomarkers are associated with relapse. For example, greater stress-induced craving was associated with a blunted cortisol response which predicted shorter time to relapse among outpatients with AUD (Higley et al., 2011).

**Table 2**  
Search results per category (BPSS model).

Determinant category	Statistically significant factor Number of studies (total n across studies)	Statistically non- significant factor Number of studies (total n across studies)	Number and percentage of significant studies (within relapse factor category)
<b>Biological</b>			
Age	31 (n = 49,258)	15 (n = 2184)	31/46 = 67%
Gender	14 (n = 14,212)	20 (n = 13,850)	14/34 = 41%
Brain ( <i>Thalamus, Vermis<sup>a</sup>, Frontal white Matter, Mesolimbic, Brain Reward System, Amygdala, Basal ganglia, Rostral ACC<sup>a</sup>, Medial frontal gyrus, brain-injury, Gray Matter Volumes, Gray matter volume Cuneus &amp; connectivity, Gray matter volume in medial orbito frontal cortex, impaired medial prefrontal cortex function, cingulate cortex functional connectivity, volumes of: the right caudal anterior cingulate cortex (ACC), right rostral ACC, and total right frontal gray matter, bilateral frontal Gray Matter, Gray Matter volume caudate/ amygdala, ventral medial prefrontal cortex (VmPFC) dysfunction, White matter microstructure deficits: corpus callosum/ stria terminalis/fornix/left anterior corona radiata, Nucleus accumbens (NAcc) activation</i> )	25 (n = 1388)	2 (n = 49) ( <i>hippocampus, Thalamic N-acetylaspartate (NAA) deficits</i> )	25/27 = 93%
Family history	8 (n = 1921)	6 (n = 552)	8/14 = 57%
Genetics ( <i>PDYN rs2281285, HTR2A, GABRA2, KIBRA, DRD2, BDNF, 5-HTTLPR, rs1789891</i> )	7 (n = 1136)	4 (n = 517) ( <i>OPRM1, TPH2, SLC6A4, HTR1A, HTR2A, CHRM2, ANKK1, BDNF, COMT, DAD2, DAD3</i> )	7/11 = 64%
Health	7 (n = 6530) 2 (n = 5011) <sup>a</sup>	1 (n = 222)	7/10 = 70% 2/10 = 20% <sup>a</sup>
Sleep	8 (n = 404)	1 (n = 254)	8/9 = 89%
Receptor/hormones ( <i>GATA4&gt;ANP, BDNF, Cortisol in CSF, Cortisol response, D2 Dopamine receptor responsivity on Prolactin, basal cortisol:ACTH,Leptin levels</i> )	8 (n = 351)	1 (n = 38)	8/11 = 73%
Biological markers ( <i>liver enzymes, MCV, baseline urine ethyl glucuronide (EtG), Body Mass Index (men)</i> )	2 (n = 148) <sup>a</sup> 5 (n = 866)	( <i>DAT methylation</i> ) 2 (n = 121)	2/11 = 18% <sup>a</sup> 5/7 = 71%
		( <i>Body Mass Index, blood glucose/ lipids</i> )	
<b>Psychological</b>			
Psychiatric ( <i>Anxiety, Depression, Suicidality, ADHD, Social phobia, Dysthymia, Panic disorder, Bipolar disorder, mood disorder</i> )	44 (n = 24,889) 2 (n = 384) <sup>a</sup>	19 (n = 6819)	44/65 = 68% 2/65 = 3% <sup>a</sup>
Severity AUD	45 (n = 34,160)	10 (n = 920)	45/55 = 82%
Craving	29 (n = 12,343)	6 (n = 384)	29/35 = 83%
Abstinence duration	12 (n = 6891)	3 (n = 249)	12/15 = 80%
Emotion	25 (n = 10,139)	8 (n = 724)	25/33 = 76%
Self-efficacy	25 (n = 10,172)	3 (n = 163)	25/28 = 89%
Comorbid SUD	20 (n = 45,382)	3 (n = 310)	20/23 = 87%
Smoking	15 (n = 20,092) 1 (n = 557) <sup>a</sup>	5 (n = 456)	15/21 = 71% 1/21 = 5% <sup>a</sup>
Treatment history	20 (n = 8660)	2 (n = 213)	20/22 = 91%
Coping	17 (n = 6241)	2 (n = 130)	17/19 = 89%
Neurocognitive	18 (n = 2521)	4 (n = 120)	18/21 = 82%
Personality disorder	7 (n = 14,508)	5 (n = 5083)	7/12 = 58%
Life events ( <i>trauma, 'rock bottom'</i> )	9 (n = 8155) 1 (n = 659) <sup>a</sup>	2 (n = 148)	9/12 = 75% 1/12 = 8% <sup>a</sup>
Stress	12 (n = 4470)	2 (n = 34)	12/14 = 86%
Impulsivity	9 (n = 554) 1 (n = 20) <sup>a</sup>	5 (n = 827)	9/15 = 60% 1/15 = 7% <sup>a</sup>
Number of prior detoxifications	5 (n = 930)	5 (n = 1976)	5/10 = 50%
Insight	6 (n = 2272)	–	6/6 = 100%
Personality traits	4 (n = 5768)	1 (n = 61)	4/5 = 80%
Seeking help	1 (n = 168) 4 (n = 7332) <sup>a</sup>	–	1/5 = 20% 4/5 = 80% <sup>a</sup>
Drinking goal	4 (n = 2308)	–	4/4 = 100 %
Outcome expectancies	3 (n = 334)	–	3/3 = 100%
Motivation	2 (n = 689)	–	2/2 = 100 %
Drinking consequences	1 (n = 952) <sup>a</sup>	–	1/1 = 100 %
<b>Social</b>			
Social <sup>b</sup> ( <i>cultural, education, employment, -economic, -pressure, non drinking</i> )	43 (n = 47,866)	18 (n = 85,013)	43/61 = 70 % <sup>b</sup>
Support <sup>b</sup>	44 (n = 33,845)	6 (n = 1155)	44/50 = 88% <sup>b</sup>
Child	1 (n = 300) 2 (n = 6869) <sup>a</sup>	–	1/3 = 33% 2/3 = 66% <sup>a</sup>
<b>Spiritual</b>			
Social spiritual	1 (n = 102) 7 (n = 14,970) <sup>a</sup>	3 (n = 530)	1/11 = 9 % 7/11 = 64% <sup>a</sup>
Life purpose	6/5415 <sup>a</sup>	1 (n = 48)	6/7 = 86% <sup>a</sup>

<sup>a</sup> Protective.

<sup>b</sup> Direction of social factors on relapse/ remission is context dependent (see paragraph 3.2.3).

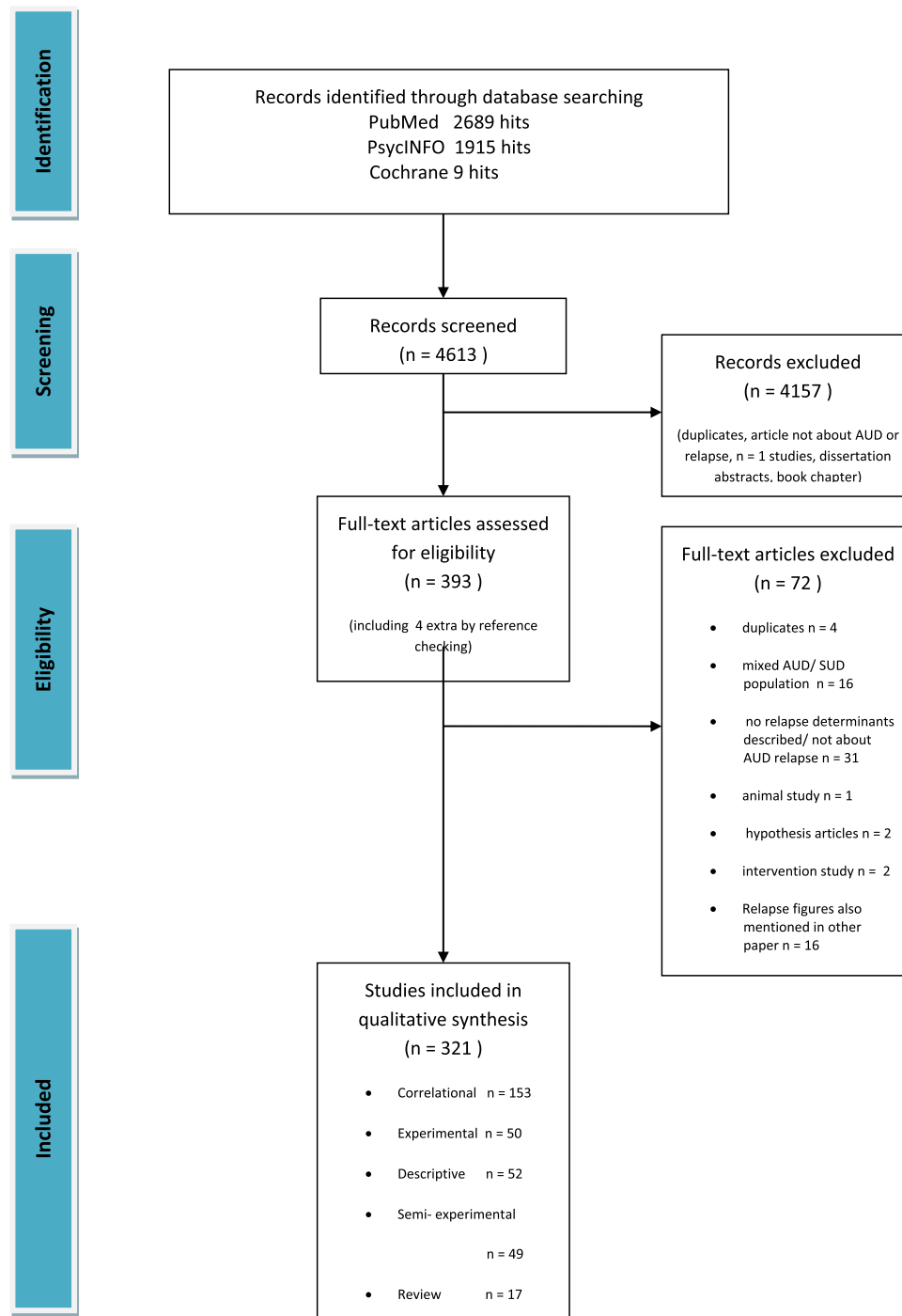


Fig. 1. Flowchart (Prisma based).

### 3.2.2. Psychological determinants

In 44 studies (aggregated  $n = 24,889$ ) '**psychiatric comorbidity**', often diagnosed as affective disorder or attention deficit hyperactivity disorder (ADHD), was significantly related to an increased relapse risk (Schellekens et al., 2015; Trocchio et al., 2013). Conversely, in two studies, the presence of affective disorder was associated with remission (Terra et al., 2008; Tómasson and Vaglum, 2000). In 19 studies ( $n = 6819$ ) no statistically significant association between psychiatric disorders and relapse risk was found (Haller et al., 2014; Possemato et al., 2017; Sher et al., 2004).

'**Severity of AUD**' as a relapse factor was mentioned in 45 publications, with a total sample size of 34,160 persons. Generally, it was

found that having more AUD symptoms was associated with relapse. A higher AUD severity is characterized by a chronic relapsing course (Chiappetta et al., 2014; Tuithof et al., 2014). However, ten studies (total  $n = 920$ ) did not find that severity was associated with relapse.

In 29 studies (total  $n = 12,343$ ) '**craving**' was found to be a statistically significant predictor of relapse (McHugh et al., 2016; Roos et al., 2015; Weinland et al., 2019). In only six studies (total  $n = 384$ ) craving was not found to be significantly associated with relapse (Charlet et al., 2014; McKay et al., 2006; Mo and Deane, 2016).

The factor '**abstinence duration**' was significantly inversely related to relapse in 12 studies (6891 participants). For example, the influence of abstinence duration on relapse was shown in a US national



**Table 3**  
Cross references per category (BPSS model).

Determinant category	Studies where factor is statistically significant predictor of relapse/remission	Studies where factor is not a statistically significant predictor of relapse/remission
<b>Biological</b>		
Age	(Gong and Minuk, 2018), (Abdin et al., 2014), (Sau et al., 2013), (Tuithof et al., 2013), (Agosti, 2013), (Trim et al., 2013), (Farren et al., 2013), (Mertens et al., 2012), (Satre et al., 2012), (Demirbas et al., 2012), (Heffner et al., 2011), (Silveira et al., 2011), (Lopez-Quintero et al., 2011), (Suliman et al., 2010), (Mattoo et al., 2009), (Kalaydjian et al., 2009), (Lee et al., 2009), (Gilder et al., 2008), (Dawson et al., 2007), (Gelernter et al., 2007), (Hingson et al., 2006), (Demmel et al., 2006), (Perney et al., 2005), (Bowden-Jones et al., 2005), (Junghanns et al., Aug 2005), (Dawson et al., 2005), (Moos and Moos, 2003), (Pelc et al., 2002), (Russell et al., 2001), (Schutte et al., 2001), (Ojesjö et al., 2000)	(Cranford et al., 2014), (Jakubczyk et al., 2013), (Spruyt et al., 2013), (Evren et al., 2012), (Milne et al., 2009), (Müller et al., 2008), (Landheim et al., 2006), (Krampe et al., 2006), (Sander and Jux, 2006), (Jorge et al., 2005), (Björnsson et al., 2005), (Miguet et al., 2004), (Oslin et al., 2002), (Tómasson and Vaglum, 2000), (Platz et al., 2000)
Gender	(Gong and Minuk, 2018), (Farren et al., 2013), (Satre et al., 2012), (Boschloo et al., 2012), (Heffner et al., 2011), (Lopez-Quintero et al., 2011), (Gilder et al., 2008), (Edens et al., 2008), (Moos et al., Sep 2006), (Bottlender and Soyka, Oct 2005b), (Dawson et al., 2005), (Garbutt et al., 2005), (Moos and Moos, 2003), (Schutte et al., 2001)	(Nalpas and Boulze-Launay, 2018), (Khan et al., 2013), (Gross et al., 2013), (Jakubczyk et al., 2013), (Spruyt et al., 2013), (Berking et al., 2011), (Suliman et al., 2010), (Müller et al., 2010), (Müller et al., 2008), (Diehl et al., 2007), (Krampe et al., 2006), (Sander and Jux, 2006), (Walitzer and Dearing, 2006), (Jorge et al., 2005), (Björnsson et al., 2005), (Miguet et al., 2004), (Callaghan and Cunningham, 2002), (Willinger et al., 2002), (Tómasson and Vaglum, 2000), (Greenfield et al., 2000)
Brain	(Zou et al., 2018), (Wu et al., 2018), (Wang et al., 2018), (Zois et al., 2017), (Sebold et al., 2017), (Zakiniacis et al., 2017), (Durazzo et al., 2017a), (Durazzo et al., 2017b), (Blaine et al., 2017), (Zois et al., 2016), (Garbusow et al., 2016), (Segobin et al., 2014), (Charlet et al., 2014), (Charlet et al., 2013), (Janu et al., 2012), (Sorg et al., 2012), (Cardenas et al., 2011), (Durazzo et al., 2011), (Rando et al., 2011), (Durazzo et al., Mar 2010), (Durazzo et al., May 2010), (Wojnar et al., 2009), (Wrase, 2008), (Jorge et al., 2005), (Noël et al., 2002)	(Zahr et al., 2016), (Gross et al., 2013)
Family history	(Gong and Minuk, 2018), (McCutcheon et al., 2017), (Deruytter et al., 2013), (Farren and McElroy, 2010), (Mattoo et al., 2009), (Milne et al., 2009), (Perney et al., 2005), (Hufford et al., 2003)	(Trim et al., 2013), (Knop et al., 2007), (Junghanns et al., Aug 2005), (Miguet et al., 2004), (Junghanns et al., 2003), (Russell et al., 2001)
Genetics	(Bach et al., 2019b), (Preuss et al., 2013), (Jakubczyk et al., 2013), (Bauer et al., 2012), (Dahlgren et al., 2011), (Wojnar et al., 2009), (Pinto et al., 2008)	(Bach et al., 2015), (Bauer et al., 2012), (Wojnar et al., 2009), (Wiesbeck et al., 2003)
Health	(Damian and Mendelson, 2017), (Gong and Minuk, 2018), (Jakubczyk et al., 2016), (Dakwar et al., 2012), (Satre et al., 2012), (Penick et al., 2010), (Pedersen and Hesse, 2009), (Moos and Moos, 2007), (Pelc et al., 2002)	(Rus-Makovec and Cebasek-Travnik, 2008)
Sleep	(Garcia and Salloum, 2015), (Smith et al., 2014), (Arnedt et al., 2007), (Feige et al., 2007), (Conroy et al., 2006), (Gann et al., 2002), (Gann et al., 2001), (Brower et al., 2001)	(Jakubczyk et al., 2013)
Receptor/hormones	(Bach et al., 2019a), (Adinoff et al., 2017), (Zois et al., 2016), (Jorde et al., 2014), (Higley et al., 2011), (Costa et al., 2011), (Walter et al., Jul 2006b), (Junghanns et al., Jan 2005), (Junghanns et al., 2003), (Markianos et al., 2001)	(Wiers et al., 2015)
Biological markers	(Weinland et al., 2019), (Barrio et al., 2017), (Flórez et al., 2015), (Aguilar et al., 2012), (Pfefferbaum et al., 2004)	(Bach et al., 2019a), (Budzyński et al., 2016)
<b>Psychological</b>		
Psychiatric	(Gong and Minuk, 2018), (Durazzo et al., 2017a), (Schellekens et al., 2015), (Chiappetta et al., 2014), (Tuithof et al., 2013), (Trocchio et al., 2013), (Jakubczyk et al., 2013), (Samet et al., 2013), (Boschloo et al., 2012), (Bauer et al., 2012), (Prisciandaro et al., 2012), (Copeland et al., 2012), (Wilens et al., 2011), (Suter et al., 2011), (Witkiewitz, 2011), (McKee et al., 2011), (Lejoyeux and Lehert, 2011), (Farren and McElroy, 2010), (Gamble et al., 2010), (Dom et al., 2010), (Xie et al., 2010), (Pedersen and Hesse, 2009), (Wojnar et al., 2008), (Gilder et al., 2008), (Terra et al., 2008), (Landheim et al., 2006), (Moos et al., Sep 2006), (Gordon et al., 2006), (Waldrop et al., 2007), (Sander and Jux, 2006), (Pirkola et al., 2006), (Kushner et al., 2005), (Bottlender and Soyka, Jun 2005c), (Ilgen and Moos, 2005), (Strakowski et al., 2005), (Greenfield et al., 2003), (Moos and Moos, 2003), (Ercan et al., 2003), (Hufford et al., 2003), (Schadé et al., 2003), (Lucht et al., 2002), (Pelc et al., 2002), (Greenfield et al., 2002), (Driessen et al., 2001), (Tómasson and Vaglum, 2000), (Curran et al., 2000)	(Possemato et al., 2017), (Haller et al., 2014), (Huntley and Young, 2014), (Berking et al., 2011), (Lopez-Quintero et al., 2011), (Müller et al., 2010), (Rus-Makovec and Cebasek-Travnik, 2008), (Pinto et al., 2008), (Di Sclafani et al., 2008), (Terra et al., 2006), (Krampe et al., 2006), (Bradizza et al., 2006), (Marquenie et al., 2006), (Kelly et al., 2006), (Bischof et al., 2005), (Sher et al., 2004), (Mann et al., 2004), (Junghanns et al., 2003), (Russell et al., 2001)

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Table 3 (continued)

Determinant category	Studies where factor is statistically significant predictor of relapse/remission	Studies where factor is not a statistically significant predictor of relapse/remission
Severity AUD	(Gong and Minuk, 2018), (Weinland et al., 2017), (Conde et al., 2016), (Zandberg et al., 2016), (Chiappetta et al., 2014), (Tuithof et al., 2014), (Sau et al., 2013), (Tuithof et al., 2013), (Jakubczyk et al., 2013), (McCutcheon et al., 2012), (Boschloo et al., 2012), (Bauer et al., 2012), (Copeland et al., 2012), (Witkiewitz, 2011), (Rando et al., 2011), (Mattoo et al., 2009), (Pedersen and Hesse, 2009), (Udo et al., 2009), (Witkiewitz and Masyn, 2008), (Dawson et al., 2007), (Knop et al., 2007), (Diehl et al., 2007), (Gelernter et al., 2007), (Walter et al., Feb 2006a), (Jackson et al., 2006), (Krampe et al., 2006), (De Bruijn et al., 2006), (Garbutt et al., 2005), (Turkcapar et al., 2005), (Moos and Moos, Feb 2006), (Perney et al., 2005), (Bottlender and Soyka, June 2005c), (McAweeney et al., 2005), (Moos and Moos, 2005), (Dawson et al., 2005), (Ilgen and Moos, 2005), (Greenfield et al., 2003), (Moos and Moos, 2003), (Vaillant, 2003), (Schutte et al., 2003), (Hufford et al., 2003), (Haver et al., 2001), (Russell et al., 2001), (Bischof et al., 2001), (Schutte et al., 2001)	(Charlet et al., 2013), (Spruyt et al., 2013), (Pinto et al., 2008), (Sander and Jux, 2006), (Kelly et al., 2006), (Miguet et al., 2004), (Junghanns et al., 2003), (Tómasson and Vaglum, 2000), (Platz et al., 2000), (Allsop et al., 2000)
Craving	(Weinland et al., 2019), (Ledda et al., 2019), (McHugh et al., 2016), (Roos et al., 2015), (Flórez et al., 2015), (Papachristou et al., 2014), (Preuss et al., 2013), (Abulseoud et al., 2013), (Schneekloth et al., 2012), (Witkiewitz et al., 2013), (Connolly et al., 2013), (Prisciandaro et al., 2012), (Copeland et al., 2012), (Higley et al., 2011), (Witkiewitz, 2011), (Farren and McElroy, 2010), (Oslin et al., 2009), (Wrase, 2008), (Krampe et al., 2008), (Zywiak et al., Dec 2006a), (Gordon et al., 2006), (Brady et al., 2006), (Turkcapar et al., 2005), (Junghanns et al., Aug 2005), (Bottlender and Soyka, June 2005c), (Verheul et al., 2005), (Bottlender and Soyka, 2004), (Zywiak et al., Dec 2003b), (Tatsuzawa et al., 2002)	(Mo and Deane, 2016), (Charlet et al., 2013), (Spruyt et al., 2013), (Cooney et al., 2007), (McKay et al., 2006), (Krahn et al., 2005)
Abstinence duration	(Maisto et al., 2018), (Gong and Minuk, 2018), (Farren et al., 2013), (Ludwig et al., 2013), (Farren and McElroy, 2010), (Dom et al., 2010), (Witkiewitz and Masyn, 2008), (Dawson et al., 2007), (Cooney et al., 2007), (Perney et al., 2005), (Vielva and Iraurgi, 2001), (Platz et al., 2000)	(Kelly et al., 2006), (Junghanns et al., 2003), (Bellamy et al., 2001)
Emotion	(Karpayak et al., 2016), (Engel et al., 2016), (Witkiewitz et al., 2015), (Abulseoud et al., 2013), (Oberleitner et al., 2013), (Trocchio et al., 2013), (Baars et al., 2013), (Berkling et al., 2011), (Gillihan et al., 2011), (Witkiewitz, 2011), (Witkiewitz and Villarroel, 2009), (Zywiak et al., Dec 2006a), (Moos et al., Sep 2006), (Zywiak et al., June 2006b), (Walitzer and Dearing, 2006), (Hammerbacher and Lyvers, 2006), (Sher et al., 2004), (Verheul et al., 2005), (Zywiak et al., Dec 2003b), (Hufford et al., 2003), (Lucht et al., 2002), (Strowig, 2000), (Platz et al., 2000), (Miller and Wilbourne, 2000), (Long et al., 2000)	(Snelleman et al., 2018), (Mo and Deane, 2016), (Garfield et al., 2014), (Gross et al., 2013), (Connolly et al., 2013), (Oslin et al., 2009), (Cooney et al., 2007), (McKay et al., 2006)
Self-efficacy	(Shaw and DiClemente, 2016), (Kelly et al., 2012), (Witkiewitz, 2011), (Mattoo et al., 2009), (Romo et al., 2009), (Krampe et al., 2008), (Tate et al., 2008), (Cooney et al., 2007), (Levin et al., 2007), (Moos and Moos, 2007), (Moos et al., Sep 2006), (Gordon et al., 2006), (Demmel et al., 2006), (Moos and Moos, Feb 2006), (McKay et al., 2005), (Humke and Radnitz, 2005), (Moos and Moos, 2003), (Hufford et al., 2003), (Walton et al., 2003), (Russell et al., 2001), (Vielva and Iraurgi, 2001), (Miller and Harris, 2000), (Long et al., 2000), (Greenfield et al., 2000), (Allsop et al., 2000)	(Trucco et al., 2007), (McKay et al., 2006), (Sher et al., 2004)
Comorbid SUD	(Gong and Minuk, 2018), (Weinberger et al., 2016), (Mojarrad et al., 2014), (Chiappetta et al., 2014), (Vito Agosti, 2013), (Schepis and Hakes, 2013), (Aguiar et al., 2012), (Bauer et al., 2012), (Copeland et al., 2012), (Schepis and Hakes, 2011), (Lopez-Quintero et al., 2011), (Farren and McElroy, 2010), (Xie et al., 2010), (Borders et al., 2010), (Karno et al., 2008), (Aharonovich et al., 2005), (Hufford et al., 2003), (Pelc et al., 2002), (Haver et al., 2001), (Russell et al., 2001)	(Björnsson et al., 2005), (Sher et al., 2004), (Brunette et al., 2003)
Smoking	(Gong and Minuk, 2018), (Hufnagel et al., 2017), (Durazzo et al., 2017a), (Weinberger et al., 2015), (Cosgrove et al., 2014), (Chiappetta et al., 2014), (Holt et al., 2012), (Tsoh et al., 2011), (Kalman et al., 2010), (Dawson et al., 2007), (Cooney et al., 2007), (Schmidt and Smolka, 2007), (Pirkola et al., 2006), (Friend et al., Oct 2005), (Junghanns et al., Aug 2005), (Friend et al., Apr 2005)	(Nieva et al., 2010), (Müller et al., 2010), (Sher et al., 2004), (Schmidt and Smolka, 2001), (Gulliver et al., 2000)
Treatment history	(Nalpas and Boulze-Launay, 2018), (Gong and Minuk, 2018), (Possemato et al., 2017), (Wigg et al., 2017), (Cranford et al., 2014), (Mertens et al., 2012), (Witkiewitz, 2011), (Henkel, 2011), (Pedersen and Hesse, 2009), (Schutte et al., 2009), (Terra et al., 2008), (Schmidt and Smolka, 2007), (Dawson et al., 2007), (Bottlender and Soyka, Jun 2005c), (McAweeney et al., 2005), (Bottlender and Soyka, Oct 2005b), (Wagner et al., 2004), (Moos and Moos, 2003), (Haver et al., 2001), (Tómasson and Vaglum, 2000)	(Trucco et al., 2007), (Krampe et al., 2006)

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Table 3 (continued)

Determinant category	Studies where factor is statistically significant predictor of relapse/remission	Studies where factor is not a statistically significant predictor of relapse/remission
Coping	(Lehavot et al., 2014), (Dolan et al., 2013), (Demirbas et al., 2012), (Mattoo et al., 2009), (Witkiewitz and Masyn, 2008), (Krampe et al., 2008), (Levin et al., 2007), (Moos and Moos, 2007), (Moos et al., Sep 2006), (Rask et al., 2006), (Moos and Moos, Feb 2006), (Walitzer and Dearing, 2006), (Tapert et al., 2004), (Moos and Moos, 2003), (Russell et al., 2001), (Miller and Harris, 2000), (Walton et al., 2000)	(McKay et al., 2006), (Walter et al., 2006a)
Neurocognitive	(Rupp et al., 2017), (Field et al., 2017), (Charlet et al., 2014), (Seo et al., 2013), (De Wilde et al., 2013), (Camchong et al., 2013), (Spruyt et al., 2013), (Garland et al., 2012), (Sorg et al., 2012), (Penick et al., 2010), (Loeber et al., 2010), (Bowden-Jones et al., 2005), (Junghanns et al., Jan 2005), (Verheul et al., 2005), (Zywiak et al., Dec 2003b), (Noël et al., 2002), (Bauer, 2001), (Allsop et al., 2000)	(Manning et al., 2016), (Pitel et al., 2009), (Becker, 2008), (Bartels et al., 2007)
Personality disorder	(Elliott et al., 2016), (Chiappetta et al., 2014), (Lopez-Quintero et al., 2011), (Penick et al., 2010), (Dawson et al., 2005), (Wagner et al., 2004), (Gish et al., 2001)	(Fein and Nip, 2012), (Bradizza et al., 2006), (Sher et al., 2004), (Russell et al., 2001)
Life events	(Zandberg et al., 2016), (McCutcheon et al., 2012), (Heffner et al., 2011), (North et al., 2010), (Mattoo et al., 2009), (Waldrop et al., 2007), (Walitzer and Dearing, 2006), (Matzger et al., 2005), (Bottlender and Soyka, Oct 2005c), (Zywiak et al., June 2003a)	(Jessup et al., 2014), (Greenfield et al., 2002)
Stress	(Gong and Minuk, 2018), (Maisto et al., 2017), (Possemato et al., 2017), (Law et al., 2016), (Grella and Stein, 2013), (O'Daly et al., 2012), (Sinha, 2011), (Witkiewitz, 2011), (Tate et al., 2008), (Moos et al., Sep 2006), (Walter et al., Jul 2006b), (Tate et al., 2005)	(Gross et al., 2013), (Becker, 2008)
Impulsivity	(Quoilin et al., 2018), (Wang et al., 2018), (Bernhardt et al., 2017), (Rupp et al., 2016), (Czapla et al., 2016), (Papachristou et al., 2014), (Sorg et al., 2012), (Evren et al., 2012), (Zikos et al., 2010), (Bowden-Jones et al., 2005)	(Matheus-roth et al., 2016), (Charlet et al., 2013), (Jakubczyk et al., 2013), (Fein et al., 2004), (Moos and Moos, 2003)
Number detoxifications	(Weinland et al., 2017), (Czapla et al., 2016), (Müller et al., 2010), (Perney et al., 2005), (Pelc et al., 2002)	(Loeber et al., 2010), (Pinto et al., 2008), (Krampe et al., 2006), (Sander and Jux, 2006), (Callaghan and Cunningham, 2002)
Insight	(Gong and Minuk, 2018), (Gilder et al., 2008), (Krampe et al., 2008), (Moos and Moos, 2005), (McKay et al., 2005), (Moos and Moos, 2003)	–
Personality traits	(Foulds et al., 2017), (Schuckit and Smith, 2011), (Schmidt and Smolka, 2007), (Willinger et al., 2002)	(Paulino et al., 2017)
Seeking help	(Grella and Stein, 2013), (Dawson et al., 2012), (Farren and McElroy, 2010), (Dawson et al., 2006), (Moos and Moos, Feb 2006)	–
Drinking goal	(Haller et al., 2014), (Bujarski et al., 2013), (Ludwig et al., 2013), (Mertens et al., 2012)	(Pitel et al., 2009), (Becker, 2008), (Bartels et al., 2007)
Outcome expectancies	(Humke and Radnitz, 2005), (Sher et al., 2004), (Miller and Harris, 2000)	(Jessup et al., 2014), (Greenfield et al., 2002)
Motivation	(Gong and Minuk, 2018), (Pedersen and Hesse, 2009)	–
Drinking consequences	(Davis and Clifford, 2016)	–
<b>Social</b>		
Social	(Degenhardt et al., 2018), (Mericle et al., 2018), (Gong and Minuk, 2018), (Durazzo et al., 2017a), (Zandberg et al., 2016), (Castaldelli-Maia and Bhugra, 2014), (Sau et al., 2013), (Abdin et al., 2014), (Troccchio et al., 2013), (Dawson et al., 2012), (Trim et al., 2013), (Aguar et al., 2012), (Mertens et al., 2012), (Boschloo et al., 2012), (Demirbas et al., 2012), (Henkel, 2011), (Silveira et al., 2011), (Kelly et al., 2011), (Penick et al., 2010), (Xie et al., 2010), (Pedersen and Hesse, 2009), (Kalaydjian et al., 2009), (Lee et al., 2009), (Tucker et al., 2008), (Moos and Moos, 2007), (Walter et al., Feb 2006), (Zywiak et al., June 2006b), (Pirkola et al., 2006), (Jorge et al., 2005), (McAweeney et al., 2005), (Moos and Moos, 2005), (McKay et al., 2005), (Zywiak et al., Dec 2003b), (Greenfield et al., 2003), (Schutte et al., 2003), (Hufford et al., 2003), (Walton et al., 2003), (Pelc et al., 2002), (Greenfield et al., 2002), (Bischof et al., 2001), (Schutte et al., 2001), (Platz et al., 2000), (Walton et al., 2000)	(Karriker-Jaffe et al., 2018), (Connolly et al., 2013), (Evren et al., 2012), (Arndt et al., 2010), (Suliman et al., 2010), (Hunter-Reel et al., 2009), (Müller et al., 2008), (Krampe et al., 2006), (Sander and Jux, 2006), (Kelly et al., 2006), (McKay et al., 2006), (Jorge et al., 2005), (Björnsson et al., 2005), (Moos and Moos, 2003), (Brower and Carey, 2003), (Russell et al., 2001), (Tómasson and Vaglum, 2000), (Platz et al., 2000)
Support	(Gong and Minuk, 2018), (Wigg et al., 2017), (Schellekens et al., 2015), (McCutcheon et al., 2014), (Sau et al., 2013), (Troccchio et al., 2013), (Grella and Stein, 2013), (Dolan et al., 2013), (Satre et al., 2012), (McCutcheon et al., 2012), (Demirbas et al., 2012), (Kelly et al., 2012), (Witkiewitz, 2011), (McKee et al., 2011), (Dom et al., 2010), (Haraguchi et al., 2009), (Kalaydjian et al., 2009), (Rus-Makovec and Cebasek-Travnik, 2008), (Terra et al., 2008), (Krampe et al., 2008), (Müller et al., 2008), (Bischof et al., 2007), (Trucco et al., 2007), (Moos and Moos, 2007), (Walter et al., Feb 2006), (Zywiak et al., Dec 2006a), (Moos et al., Sep 2006), (Demmel et al., 2006), (Pirkola et al., 2006), (Walitzer and Dearing, 2006), (McAweeney et al., 2005), (Moos and Moos, 2005), (Dawson et al., 2005), (Sher et al., 2004), (Greenfield et al., 2003), (Hufford et al., 2003), (Walton et al., 2003), (Pelc et al., 2002), (Greenfield et al., 2002), (Rumpf et al., 2002), (Noda et al., 2001), (Russell et al., 2001), (Bischof et al., 2001), (Schutte et al., 2001)	(Evren et al., 2012), (Krampe et al., 2006), (Sander and Jux, 2006), (Björnsson et al., 2005), (Miguet et al., 2004), (Moos and Moos, 2003)

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Table 3 (continued)

Determinant category	Studies where factor is statistically significant predictor of relapse/ remission	Studies where factor is not a statistically significant predictor of relapse/ remission
Child	(Gong and Minuk, 2018), (McCutcheon et al., 2014), (McCutcheon et al., 2012)	–
<b>Spiritual</b>		
Social spiritual	(Tonigan et al., 2017), (Castaldelli-Maia and Bhugra, 2014), (Tusa and Burgholzer, 2013), (Sau et al., 2013), (Dawson et al., 2012), (Kelly et al., 2012), (Sterling et al., 2007), (Matzger et al., 2005)	(Borders et al., 2010), (Gordon et al., 2006), (Sher et al., 2004)
Life purpose	(Roos et al., 2015), (Cranford et al., 2014), (McCutcheon et al., 2014), (Dawson et al., 2012), (Pagano et al., 2004), (Walton et al., 2000)	(Jessup et al., 2014)

epidemiologic three-year follow-up study (Dawson et al., 2007). Three studies did not find an association between abstinence duration and relapse (Bellamy et al., 2001; Junghanns et al., 2003; Kelly et al., 2006).

The factor ‘*emotion*’ (or ‘negative affect’) has shown a robust statistically significant effect on relapse in most studies (25 studies,  $n = 10,139$ ), with more negative emotion associated with greater relapse risk (Moos et al., 2006). In eight studies ( $n = 724$ ) the impact of emotion in predicting relapse was not statistically significant (Cooney et al., 2007).

The factor ‘*self-efficacy*’ is considered a protective factor (Witkiewitz and Marlatt, 2007), and data from 25 studies ( $n = 10,172$ ) indicated a higher level of self-efficacy was significantly associated with lower relapse risk (Shaw and DiClemente, 2016). In three small studies, this association was not statistically significant (McKay et al., 2006; Sher et al., 2004; Trucco et al., 2007).

Comorbid ‘*Substance Use Disorder*’ (e.g. harmful use of cocaine, opiates or benzodiazepines) was significantly associated with relapse in 20 studies (total  $n = 45,382$ ). In three studies ( $n = 310$ ) the effect of comorbid substance use disorder on relapse was not statistically significant.

Similarly, fifteen studies ( $n = 20,092$ ) reported on the influence of co-occurring ‘*smoking*’, accounting for a larger relapse risk.

Only in one study ( $n = 557$ ) the opposite was found, such that smoking predicted lower relapse risk (Schmidt and Smolka, 2007). Five other studies (total  $n = 456$ ) did not find an association between smoking and relapse.

Although represented in fewer studies, ‘*treatment history*’, ‘*coping*’, and ‘*neurocognitive*’ factors were significantly associated with relapse risk in almost all studies, such that prior treatment, worse coping skills, and neurocognitive deficits predicted greater risk of relapse.

Seven studies ( $n = 14,508$ ) found that having a ‘*personality disorder*’, increases the relapse risk. In five studies ( $n = 5083$ ), this relationship was absent. A recent systematic review (with meta-analysis on a limited number of included studies) found that having personality disorders do not worsen AUD outcomes (Newton-Howes et al., 2017). In one paper, precise patient numbers could not be obtained and therefore the paper was included in the ‘not significant’ column (Bradizza et al., 2006). Similarly, maladaptive ‘*personality traits*’ were significantly associated with greater risk of relapse in four ( $n = 5768$ ) out of five studies.

‘*Life events*’, particularly trauma, and ‘*stress*’ were both associated with significantly higher relapse rates. For example, in a secondary analysis of COMBINE data ( $n = 1383$ ), last weeks’ perceived stress level was significantly associated with relapse (Witkiewitz, 2011). Only two studies of life events and two studies of stress did not provide support for a significant association between these determinants and relapse.

The findings about the determinant ‘*impulsivity*’ appear to be inconclusive, with nine studies ( $n = 554$ ) showing a statistically significant association for several different measurement instruments used (Bernhardt et al., 2017; Rupp et al., 2016), and no statistically significant association in five other studies ( $n = 827$ ). Most sample sizes of the included studies were small. Notably, one study ( $n = 20$ ) showed a

protective effect of higher impulsivity on relapse (Papachristou et al., 2014).

The ‘*number of prior detoxifications*’ was not strongly associated with relapse risk, with five out of ten studies finding that prior detoxification was significantly associated with relapse.

The remaining psychological factors, including ‘*insight*’, ‘*seeking help*’, ‘*drinking goals*’, ‘*outcome expectancies*’, ‘*motivation*’ and (negative) ‘*drinking consequences*’ were less widely studied and with fewer subjects per study. Yet, all of these factors were significantly associated with relapse, such that lower insight, less help seeking, non-abstinent goals, positive outcome expectancies, less alcohol-related negative consequences (Davis and Clifford, 2016), and lower motivation were associated with significantly greater relapse risk.

### 3.2.3. Social factors

Several studies showed that ‘*social*’ factors and the quality of social ‘*support*’ might be associated with diminished relapse risk. Consistently, it was found that having a positive social context and functioning (e.g., employment, greater socioeconomic status, education) was associated with reduced relapse risk in 43 publications ( $n = 47,866$ ). On the other hand, in a systematic review ( $n = 5140$ ) (Castaldelli-Maia and Bhugra, 2014), it was found, that living in a ‘heavy drinking culture’, is a strong risk factor for relapse. From a longitudinal cohort study, data showed that ‘Alcohol availability’ (neighborhood alcohol outlets) was a risk factor associated with an AUD, but not relapse (Karriker-Jaffe et al., 2018).

Living in a supportive relationship (e.g. marriage) was mentioned in 44 papers ( $n = 33,845$ ). For example, in a follow-up study ( $n = 686$ ), by McCutcheon et al. (2014), social support by friends, was associated with reduced relapse risk. However, in 17 articles ( $n = 11,136$ ) no evidence for an effect of social factors on relapse were found. Furthermore, six articles (total  $N = 1155$ ) did not find a statistically significant link between ‘support’ and relapse.

We also found in two studies, that having a (first-born) ‘*child*’, for women was related to reduce relapse risk (total sample size  $n = 6869$ ).

### 3.2.4. Spiritual factors

Several articles examined the association between ‘*spiritual*’ concepts and relapse. Seven studies ( $n = 14,970$ ) demonstrated a protective effect of spirituality on relapse rates and only three studies failed to confirm this association ( $n = 530$ ). It should be noted that in one small study Muslim religion was significantly associated with greater risk of relapse (Sau et al., 2013).

A closely related concept is considered ‘*life purpose*’. Six studies ( $n = 5415$ ) reported on the positive effect of having a higher life purpose on reducing risk of relapse (Roos et al., 2015).

## 4. Discussion

Our systematic review delves into a broad array of relapse factors as described in recent literature. To our knowledge, no broad systematic review on AUD relapse factors has been conducted recently. The results give a timely update of significant relapse and protective factors

covering almost twenty years of research.

Relapse and protective determinants were grouped by using the BPPS framework. Notably, **biological** factors such as having younger ‘age’ and poor ‘health’ seem to be important relapse predictors. So, more attention should be paid to prevention of alcohol use at younger ages (Kraus et al., 2018) and medical attention regarding co-existing health and somatic conditions.

In the last two decades the neurobiology of addiction (Koob and Volkow, 2016) has received increased attention, and neurobiological factors, mostly focused on the brain reward system, were identified in our search. Likewise, genetic factors, stress induced cortisol responses, and biomarkers were each unique predictors of relapse. Typically, research on neurobiological factors included smaller sample sizes limiting the generalizability. Future research with larger sample sizes is warranted to further identify biological predictors of relapse.

The effect of sleep disturbances on relapse has been previously substantiated in the literature (Miller et al., 2017), but seems not to be an area of extensive current research. Sleep management might be an important topic in addiction treatment (Miller et al., 2017).

The role of gender in relapse remains inconclusive, but warrants further research to specify segregated outcomes for males and females. Nonetheless, there is important pre-clinical work suggesting sex differences in relapse (Becker et al., 2017), and it is important to consider social and cultural factors when examining the association between gender and relapse (Becker et al., 2016). Some research suggest a ‘telescoping effect’ that suggests AUD in women may be followed by a more severe and progressive addiction course (Greenfield et al., 2010).

Results of the examination of **psychological** factors confirm prior findings that psychiatric comorbidity, addiction severity, craving and use of other substances are important relapse factors, as well as emotion, coping, and major life events. These factors were found in many studies with large sample sizes. Clinical treatment should take these factors into account, regarding relapse management, and treatment of co-occurring disorders (Bender et al., 2018; Tiet and Mausbach, 2007). Our findings also confirm the necessity for offering help in smoking cessation (Castaldelli-Maia et al., 2018; Skelton et al., 2018).

Stress could be an interesting subject of further research, as it seems to be an important relapse factor (Blaine and Sinha, 2017; Kwako and Koob, 2017). Despite heterogeneity in stress-measures used, recent promising research focuses on neurobiological and hormonal factors and also points out the interrelationship with ‘negative affect’.

Remarkably, we did not identify studies measuring ‘positive affect’ as a relapse or protective determinant; although this has been frequently studied in the past century (Larimer et al., 1999). This factor deserves renewed attention in future research.

Identifying different phenotypes of drinkers could be of clinical relevance (Helton and Lohoff, 2015), as recent work has suggested that individuals who drink alcohol to relieve negative emotions have a better treatment response to acamprosate (Roos et al., 2017), whereas those who drink for reward seeking have a better treatment response to naltrexone (Mann et al., 2018). Others have postulated different AUD ‘typologies’, each with a different probability regarding AUD course and treatment outcome (Weinland et al., 2017). Future pharmacogenetic treatment allocation might lead to improved personalized medicine for AUD (Sluiter et al., 2018).

Interestingly, many top-ranked treatments encompass ‘motivational’ interviewing / enhancement strategies (Miller and Moyers, 2017). However, only two studies delved into motivation as a relapse factor, so apparently a huge gap exists between this clinical practice and scientific findings that should be abridged in future research.

We could not confirm a clear link between impulsivity and relapse (Reyes-Huerta et al., 2018), since we found only a few studies. Difficulties in measurement of impulsivity, which is often considered a multidimensional construct (Dom et al., 2007; Herman et al., 2018; Stevens et al., 2014), could explain discrepancies across studies. For example, impulsivity measures were tested by using self-reports (Evren

et al., 2012; Papachristou et al., 2014; Zikos et al., 2010), brain imaging correlates (Sorg et al., 2012) and neuropsychological tests (Fein et al., 2004; Quoilin et al., 2018). Recent research shows different aspects of impulsivity, including ‘delay discounting’, ‘disinhibition’ and ‘decision making’ (Reyes-Huerta et al., 2018; Stevens et al., 2014).

Previous studies have demonstrated that the cumulative amount of previous alcohol detoxifications may account for relapse (Duka and Stephens, 2014), but this was not confirmed in our review. Given the different definitions regarding supervised and unsupervised detoxification attempts, more research is needed on how the role of the number of detoxifications impacts relapse and the course of AUD.

**Social factors** seem to have a robust impact on relapse, whereby a positive social context and non-drinking social support appear to be protective. On the other hand, our results suggest that heavy drinking social network support is associated with greater relapse risk. So, clinically it is important to assess the characteristics of patients’ social network to promote positive treatment outcomes (McKay, 2017). Having children could be a protective factor for women.

Finally, factors concerning the **spiritual** aspects and giving meaning to life were protective against relapse in a small number of studies.

Overall, the impact of impaired health, sleeping problems, psychiatric comorbidity, use of other substances (including nicotine), lack of coping skills, and addiction related factors like craving, diminished self-efficacy, AUD severity and the duration of abstinence, seem to have a more pronounced negative effect on the course of AUD. Important protective factors seem to be ‘spiritual’ involvement, and a positive, supportive social environment.

Importantly, a number of the reviewed papers did not include standardized measures of effect sizes and only the most recent literature examined the impact of different relapse factors using effect size measures, such as odds- or hazard ratios. For example, in a national survey study (N = 4828) it was found, that being physically active is associated with higher odds (OR:1.67, 95% CI: 1.28, 2.17) of 12 month AUD remission (Damian and Mendelson, 2017). In another recent study, the effect of smoking on alcohol relapse was quantified with a hazard ratio of 3.96 (Hufnagel et al., 2017).

Clinicians should assess those factors that are most strongly associated with relapse risk and offer treatment for psychiatric problems, use of other substances, and health and sleep- problems. Recommending mutual support group involvement, particularly for patients who are lacking a positive social environment that is supportive of recovery, may also be helpful.

As found in the ‘Mesa Grande’ study (Miller and Wilbourne, 2002), specific interventions (for example ‘social skills training’, ‘marital therapy’, case management, medication and the ‘Community Reinforcement Approach/ Contingency Management’ (Roozen & Smith, submitted)) could aim at several of the relapse factors we found. At the behavioral level reinforcement based interventions could help people link to other attractive reinforcers to compete with alcohol/drug use as a substitute for direct gratification tendencies (McKay, 2017). Also, social skills training could help patients build up a positive social network. It must be noted, that given the role of stress sensitivity in addiction (Blaine and Sinha, 2017; Volkow et al., 2016), a stress-enhancing, confronting way of approaching those with an AUD should be avoided.

## 5. Strengths and limitations

We used a search strategy to include a broad array of relevant relapse factors. Data were obtained from multiple studies, often reporting on similar determinants. Conversely, sometimes just a few studies were identified mentioning relapse factors that have been understudied.

We limited our search to studies from the year 2000 and onwards to be able to make a synoptic overview of relapse determinants, but we realize a lot of important research was already done before (Becker, 1998; Marlatt, 1996; McKay, 1999), which has been summarized in

prior reviews (Hendershot et al., 2011; Witkiewitz and Marlatt, 2004).

Unique in our review is the use of the BPSS model to arrange our findings. In comparison to earlier reviews some ‘new’ relapse determinants emerged, such as ‘sleeping problems’, ‘impulsivity’, ‘health’, ‘smoking’ and ‘alcohol related negative consequences’. The amount of research for some other factors, like ‘stress’ and specific ‘brain’ areas, has increased in recent years.

As an integrative framework we chose the BPSS model to arrange our findings. In several cases, the allocation of factors to BPSS categories is open to multiple interpretations, as it can be argued that determinants could also be assigned to another category as well. In several cases categories are interrelated, as for example ‘genetics’ and ‘receptor/ hormones’ or ‘psychiatric comorbidity’ and ‘personality disorder’. It should be noted that in several cases we could not ensure construct validity within one specific category, as in many cases the relapse factor was not consistently defined. This could lead to an observer bias. The number of publications in which a certain relapse factor was found, might also reveal a research or publication bias. On our part, we wanted to lower the risk of publication bias, by also mentioning statistically not significant outcomes. A large range of definitions for ‘relapse’ (Maisto et al., 2016a,b) also complicates a sound comparison among research results, preventing us from drawing firm conclusions. From this perspective, ‘relapse’ was considered an ‘absence of abstinence’. Furthermore, in general, a wide range of follow up periods (weeks to years) in which a relapse could occur was used across studies.

Given the enormous heterogeneity in different methods, measures, and sample characteristics of the identified studies, we were unable to conduct a rigorous quality assessment of each study with respect to the identified relapse factor, and employed a descriptive methodology to summarize the findings. Statistical analyses (e.g., meta-analysis) were not possible given the extensive heterogeneity in our comprehensive assessment of relapse determinants. A narrower review within each category of determinants may be more amenable to meta-analytic investigation. However, where others conducted reviews and/or meta-analyses on -for example- the impact of ‘personality disorder’ on AUD relapse, only a few studies could be included for additional quantification (Newton-Howes et al., 2017).

We confirm the danger of a ‘language bias’ by limiting our search to the English language, mainly covering research from the western World. From this perspective, our findings may not be generalized to other parts of the World; although we also included several Asian studies.

Finally, it must be noted that most included research studies focused on abstinence-based approaches. In clinical practice, we encounter patient groups that are not able to achieve stable abstinence. As such, other treatment goals including moderation, harm-reduction and palliative care are considered complementary. Consequently, the label ‘relapse’ may be considered conflicting and may discount valuable clinical benefits that can be obtained in non-abstinent patient groups who achieve drinking reductions and improved quality of life (Hasin et al., 2017; Maisto et al., 2018; Mann et al., 2017; Palpacuer et al., 2018; Witkiewitz et al., 2019, 2017).

The definition of relapse has been the subject of debate for decades, and in the current paper we did not require a specific definition of relapse, remission, or recurrence to be included in the review. Yet, many empirical papers included in this review did consider a return to any drinking or percent days abstinent as the definition of relapse. For many patients an abstinence based drinking goal might be optimal, and abstinence is typically associated with better treatment outcome (Maisto et al., 2018; Witkiewitz and Masyn, 2008). At the same time, such a goal might not be attainable for everyone, and consequently, aiming at drinking reduction goals might be preferable and drinking reductions are also associated with improvements in functioning for some patient groups (Falk et al., 2019; Witkiewitz et al., 2019).

## 6. Conclusions

In this study, identified relapse factors encompassed psychiatric comorbidity, addiction severity, craving, negative emotion, use of other substances, health and social factors. Several supportive social factors, self-efficacy, and factors related to life purpose and spiritual involvement were recognized as protective. Many factors, including sleep, sex differences, neurobiological factors, genetics, impulsivity, positive affect, and motivation warrant further research.

Despite decades of research, the factors that lead to an AUD relapse are still highly variable and likely contextual. An integrative BPSS approach may help in gaining a better understanding of individual risk and protective factors in future studies. Future directions for applying our findings could be to consider specific interventions that may be most helpful for specific individual relapse risks (personalized medicine). Expansion of integrated treatment options for co-occurring psychiatric disorders seems to be a research area of particular interest. In addition, focusing on quality of life, in addition to reductions in alcohol consumption, should be taken into consideration.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Conflict of interests

The fourth author (HR) receives honoraria for providing CRA workshops at universities, mental health institutes, conferences, and local city governments. In addition, the author receives royalties from publishers for scientific books and chapters. The other authors report no conflicts of interest.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2019.05.038](https://doi.org/10.1016/j.psychres.2019.05.038).

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