



Review

Psychological theories of depressive relapse and recurrence: A systematic review and meta-analysis of prospective studies



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HIGHLIGHTS

- Theory-derived psychological vulnerabilities are presumed to predict depressive relapse.
- There were few prospective studies examining psychological theories of relapse.
- There is some support for cognitive, behavioural, and personality theories.
- There was no support for psychodynamic and no studies for diatheses-stress theories.
- There is an overall lack of research on psychological theories of depressive relapse.

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ABSTRACT

Psychological factors hypothesized to account for relapse of major depressive disorder (MDD) roughly originate from five main theories: Cognitive, diathesis-stress, behavioural, psychodynamic, and personality-based. In a meta-analysis we investigated prospective, longitudinal evidence for these leading psychological theories and their factors in relation to depressive relapse. Included studies needed to establish history of MDD and prospective depressive relapse through a clinical interview, have a longitudinal and prospective design, and measure at least one theory-derived factor before relapse. We identified 66 eligible articles out of 43,586 records published up to November 2018. Pooled odds ratios (OR) indicated a significant relationship between the cognitive, behavioural, and personality-based theories and depressive relapse (cognitive: $k = 17$, $OR = 1.24$, 95% CI = 1.10–1.40; behavioural, $k = 8$, $OR = 1.15$, 95% CI = 1.05–1.25; personality: $k = 12$, $OR = 1.26$, 95% CI = 1.02–1.54), but not for the psychodynamic theories ($k = 4$, $OR = 1.29$, 95% CI = 0.83–1.99). Pooled hazard ratios of the theories were not significant. There were no articles identified for the diathesis-stress theories. To conclude, there is a restricted number of prospective studies, and some evidence that the cognitive, behavioural, and personality-based theories indeed partially account for depressive relapse.

1. Introduction

Major depressive disorder (MDD) has a highly recurrent nature, as approximately 40 to 60% of people with a first-time MDD episode (MDE) develop a subsequent episode (Eaton et al., 2008; Moffitt et al.,

2010) and the risk increases with each new MDE (Moffitt et al., 2010). Due to the highly disabling and recurrent nature of MDD, there is a clear need for treatments that address the acute needs of individuals and mitigate the risks for relapse. Depressive relapse is the re-emergence of an MDE before a patient attains the status of remission, and

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recurrence is the development of a new MDE after a person has attained the status of recovery. Remission is generally defined as the period in which the patients' symptoms are normalised for approximately two months or more, and recovery is often described as the end of an MDE after a period of remission, approximately four to six months and longer (e.g. Bockting et al., 2018; Buckman et al., 2018; Frank et al., 1991). Despite the consensus on the differences between relapse and recurrence, these terms are often used interchangeably to describe the re-occurrence of depressive symptoms regardless of the timing of the MDE. Given this variation, the words relapse and recurrence will be used interchangeably throughout this review.

A previous review on psychological relapse prevention interventions showed that the risk of relapse after Cognitive Behavioural Therapy (CBT), Interpersonal Therapy (IPT), and Mindfulness-based Cognitive Therapy (MBCT), was reduced by 22% as compared to care as usual (Clarke, Mayo-Wilson, Kenny, & Pilling, 2015). Another meta-analysis similarly showed that psychological relapse prevention interventions, including Preventive Cognitive Therapy (PCT), MBCT, CBT, and IPT, reduced relative risk of depressive relapse when compared to care as usual (RR = 0.64; Biesheuvel-Leliefeld et al., 2015). The exact relapse and recurrence rates vary in the literature. High relapse rates of 39 to 54% after acute, maintenance, and preventive treatment suggest that current treatments are suboptimal and not effective for all individuals (Bockting et al., 2018; Cuijpers, 2017; Klein et al., 2018; Kuyken et al., 2016; Steinert, Hofmann, Kruse, & Leichsenring, 2014; Vittengl, Clark, Dunn, & Jarrett, 2007). Identifying factors that increase the risk of depressive relapse is therefore necessary in order to improve existing treatment options to prevent the re-occurrence of MDD, and to inform on therapeutic targets. Proposed psychological factors of depressive relapse generally originate from psychological theories that account for depression aetiology, and can roughly be allocated to the cognitive, diathesis-stress, behavioural, psychodynamic, and personality-based theories (e.g. Burcusa & Iacono, 2007; Fernald, 2008). However, the evidence for these psychological theories in relation to depressive relapse has, to our knowledge, not been reviewed thus far. The aim of the present systematic review is therefore to examine current evidence for the psychological theories and their factors that are proposed to predict depressive relapse.

Research has identified several potential factors of depressive relapse, including age of MDD onset and comorbidity of affective disorders (e.g. Burcusa & Iacono, 2007; Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2010). Recently, Buckman et al. (2018) proposed a framework of factors and mechanisms of change involved in depressive relapse, such as residual depressive symptoms, rumination, negative cognitions, neuroticism, and childhood maltreatment (Buckman et al., 2018). Other reviews and meta-analyses have generally focused on treatment effects instead of theory-derived predictors of relapse, or on the first onset of MDD (e.g. Fu et al., 2019; Mathews & MacLeod, 2005) which is believed to differ from relapse or recurrence of MDD (e.g. Lewinsohn, Allen, Seeley, & Gotlib, 1999).

Previous reviews (Buckman et al., 2018; Burcusa & Iacono, 2007; Hardeveld et al., 2010) hence provide valuable overviews of the studied predictors of recurrence. In contrast to previous reviews, the current meta-analysis focuses on stratifying the evidence for leading psychological theories that underpin current treatment options, in order to contribute to falsification of these theories. Therefore, here we provide a summary of evidence specific to the leading psychological theories and their factors. In addition, despite existing overviews of the clinical accounts for depressive relapse, there are some limits to the conclusions that can be drawn given the nature of the reviewed studies. Previous reviews comprised cross-sectional and low-quality studies, focused on a limited scope of potential factors, and/or the factors were not derived from common psychological theories or specific treatment theories. Lastly, the reviews included information on factors from individuals without necessarily meeting established criteria for the presence or absence of a MDD diagnosis. In order to investigate causal relationships

between factors derived from psychological theories and depressive relapse, longitudinal prospective studies investigating psychological theories before depressive relapse are needed among populations with established diagnoses, similar to the strategy applied by Hardeveld et al. (2010). In the current review we aim to address these issues, and provide an overview of current prospective evidence for the leading theories of depressive relapse.

Leading psychological theories are roughly based upon five major (overarching) theories, which guided our systematic search: Cognitive, diathesis-stress, behavioural, psychodynamic, and personality-based (e.g. Burcusa & Iacono, 2007; Fernald, 2008). Within these overarching theories, there are various specific theories to account for the development of MDEs. For instance, cognitive therapy is in accordance with Beck's cognitive model of depression (Beck, Rush, Shaw, & Emery, 1979) and is based on the assumption that dysfunctional beliefs and thoughts are related to the onset of a new MDE in people with a history of MDD (e.g. Brouwer, Williams, Forand, DeRubeis, & Bockting, 2019; Forand & DeRubeis, 2014; Lorenzo-Luaces, German, & DeRubeis, 2015). Therefore, dysfunctional beliefs represent a theory-derived psychological factor and therapeutic target in cognitive therapy (Beck & Bredemeier, 2016). In the initial cognitive model of Beck it was proposed that certain schemas or cognitive distortions are latent but can be activated by life events that matched these schemas, resulting in automatic negative thoughts and depressive symptomatology (Beck et al., 1979). Later, the cognitive model of Beck specified that these schemas could be activated by any event (e.g. Beck & Bredemeier, 2016), or even can be re-activated by sad mood (e.g. Segal et al., 2006; van Rijsbergen et al., 2013). Other cognitive theoretical accounts include the response style theory, including rumination (Nolen-Hoeksema, 1991), and learned helplessness as explanations for the development of MDD (Abramson, Seligman, & Teasdale, 1978).

Cognitive theories therefore often overlap with the diathesis-stress theory, explicitly including other factors ('diatheses') such as stress and biological factors (Hankin & Abela, 2005; Monroe & Simons, 1991). Generally stated, the diathesis-stress theory posits that a person may exhibit a vulnerability (such as high levels of dysfunctional beliefs or certain personality traits) that is activated by- or that in combination with- stress leads to the development of a first onset, chronic, or recurrent MDD (Conway, Slavich, & Hammen, 2015; Ingram, Miranda, & Segal, 1998; Monroe & Simons, 1991).

In terms of the historical evolution of psychological theories, the psychodynamic or psychoanalytic theories were among the earliest (Compton, 1986; Freud, 1917). Although the psychodynamic theory primarily explains the (first) onset of MDD, there are relapse prevention interventions based on this theory, including interpersonal therapy (IPT) and short-term psychodynamic psychotherapy (STPP; Driessen et al., 2015; Luyten & Blatt, 2012). Relevant psychological factors originating from the psychodynamic theory, which are often targeted in psychodynamic-oriented treatments, include parent-child attachment and interpersonal relationships (Luyten & Blatt, 2012).

Based upon animal models, and partly originating from the psychodynamic theories, behavioural theories, which includes (social) learning theory (e.g. Bandura, 2004) emerged. Within the behavioural theory there is a central role for (the levels of) positive and negative reinforcement of a person's behaviour, the person's environment, and the development of depressive symptoms, such as the lack of pleasurable events and social support, life events, daily hassles, or behaviours that lack potential reward-value such as withdrawal and inactivity (e.g. Lewinsohn, 1974). Behavioural activation is a therapy based upon this theory, where a person is stimulated to engage in activities that have potential reward-value (e.g., going for a walk with a friend) while reducing behaviours that offer limited scope for positive experiences (e.g., staying in bed all day and avoiding completing household tasks) (Dimidjian, Barrera, Martell, Muñoz, & Lewinsohn, 2011). Similar to the cognitive theories, behavioural theories may be perceived as diathesis-stress theories, as life events and stress play a major role in the

explanation of MDD.

Lastly, researchers have identified personality-based characteristics as predictors of depressive relapse, such as 'Big Five' traits, temperament, behavioural inhibition and activation, and personality disorders (Berlanga, Heinze, Torres, Apiquian, & Caballero, 1999; Buckman et al., 2018; Burcusa & Iacono, 2007; Klein, Kotov, & Bufferd, 2011). The Big Five model includes personality traits that may contribute to MDD onset and/or relapse and hence may positively correlate to relapse (i.e. negative personality traits such as neuroticism), and personality traits that may protect a person from developing new episodes (positive or protective personality traits, such as extraversion), and therefore may negatively correlate to relapse (Berlanga et al., 1999; Buckman et al., 2018; Klein et al., 2011).

Although previous research identified several vulnerability factors (Buckman et al., 2018; Burcusa & Iacono, 2007; Hardeveld et al., 2010), an overview of current evidence for leading psychological theories of depressive relapse is needed. These psychological theories are of importance since they provide a rationale who and why individuals may relapse, inform clinicians on target points, and because current treatment options are often based upon these theories. The current systematic review and meta-analysis is, to our knowledge, the first study to investigate and summarize the (prospective) evidence for the five main theories of relapse of MDD: Cognitive, diathesis-stress, behavioural, psychodynamic, and personality-based. Results of this review may in turn provide a basis for (new) therapeutic targets.

2. Method

2.1. Selection of studies

This meta-analysis followed the guidelines Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009), and was registered in Prospero (CRD42017073977). Separate searches in Pubmed, PsycInfo, Embase, and Cochrane were performed for each of the main theories. Articles needed to be published from their origin through March 2017 (see Fig. 1). The search was updated for articles published online up to November 16th, 2018. The databases were searched for relevant articles using search strings, composed using standardized vocabulary (e.g. MeSH terms), key words, terms for searching title and abstract, and Boolean operators. The four search strings included search terms relating to (1) MDD; (2) a longitudinal design or randomized controlled trials; (3) relapse/recurrence; and (4) factors derived from the five leading psychological theories. The search terms were adapted for each database in combination with database-specific filters for human, English language, original article (not review). A full overview of the search strategies is provided in Appendix A. To maximize finding eligible articles, the citations and references of included articles and related reviews were investigated (snowballing). Furthermore, several experts in the field of MDD were contacted to ask for relevant published trials, and to provide feedback on the search strategy (see acknowledgements). The search strategy and the selection of the main theories were based upon previous reviews (e.g. Biesheuvel-Leliefeld et al., 2015; Clarke et al., 2015; Guidi, Fava, Fava, & Papakostas, 2011), books that reviewed the leading psychological theories (e.g. Fernald, 2008; Hankin & Abela, 2005), and by inquiring several experts in the field of depression research (see acknowledgements).

There were several search strategies for each main theory, since the current study was part of a larger project investigating psychological and biological risk factors of MDD onset and relapse (see Fu et al., in preparation; Kennis et al., 2019). To investigate the evidence for each main psychological theory of depressive relapse, each factor derived from the theories needed to be identified in the databases. The factors derived from the psychodynamic and personality-based theories were searched simultaneously for both depressive onset and relapse (Fu et al., in preparation). A separate search strategy was performed for

factors from the cognitive and behavioural theories of relapse. A second search was performed for the cognitive theories, as some of the factors were omitted from the first search. In this second search, factors for both depressive onset and relapse were combined. For the diathesis-stress theories, an initial search was performed for psychological and biological vulnerabilities in combination with stress, daily hassles, and life events. Articles related to relapse were later identified and separately assessed for eligibility. As a result of the search strategy, factors for different theories could be identified in different searches. The flow chart of the selection process, as shown in Fig. 1, is therefore a combined overview of all searches.

2.2. Selection criteria and selection process

Criteria for studies to be included in the review were: (1) Presence of a diagnostic status of MDD (MDD absence and/or presence) for all participants, as determined through a clinical interview (e.g., SCID, K-SADS from DSM, CIDI from ICD) or by a clinician at the start of the study; (2) At some point during the study, participants needed to be in (partial) remission or recovery as determined by a clinical interview or clinician assessment; and (3) relapse or recurrence was diagnosed through a clinical interview or by a clinician. (4) The study design was longitudinal and prospective; (5) The theory-derived predictor (i.e., the proposed factors) was assessed before the relapse or recurrence of MDD; (6) The predictor was derived from one of the leading psychological theories; (7) Sufficient information was reported to calculate effect sizes (or was made available upon request). Exclusion criteria were the presence of bipolar disorder, dysthymia, seasonal affective disorder, postpartum depression, late-life MDD, or MDD due to medical disorders. Studies that solely included people with a first onset MDD when they were older than 65 years, were excluded due to potential etiological differences between late-life onset MDD and MDD at younger ages (Devanand et al., 2004; Herrmann, Goodwin, & Ebmeier, 2007; Korten, Comijs, Lamers, & Penninx, 2012). Language was restricted to English. When multiple publications from the same study cohort were available, with exactly the same factors, we included the publication with the longest follow-up time, or the largest number of participants in case of equal follow-up time.

In each step of the meta-analysis, two project members screened and selected the articles, and assessed the risk of bias using nine criteria of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for both randomized controlled trials (RCT) and observational studies. A positive score (+), indicating low risk of bias, was counted as 0, unclear (?) was scored as 1, and high risk of bias (negative score, -) was scored as 2. Hence, total scores could range from 0 to 18, with a high score indicating high risk of bias. Disagreement was solved by consultation of the research group and reaching consensus. The GRADE framework was moreover applied to assess quality of evidence for each main theory, using the criteria to potentially downgrade the evidence as recommended by GRADE. Data was extracted independently by two researchers, and fully checked by another. Extracted information included participant demographics and baseline characteristics, diagnostic instrument utilized, outcomes and time of measurement, factor assessment, and information for assessment of the risk of bias.

2.3. Theoretical factors and outcome measures

To investigate the leading psychological theories, all factors derived from that main theory were pooled and analysed: Cognitive, diathesis-stress, behavioural, psychodynamic, and personality-based. Factors derived from these theories were included in the meta-analysis, for example the dysfunctional attitudes scale alone (cognitive theories) or with the interaction of stressful events (diathesis-stress), behavioural activity (behavioural theories), attachment questionnaires (psychodynamic theories), and neuroticism (personality-based theories). In order

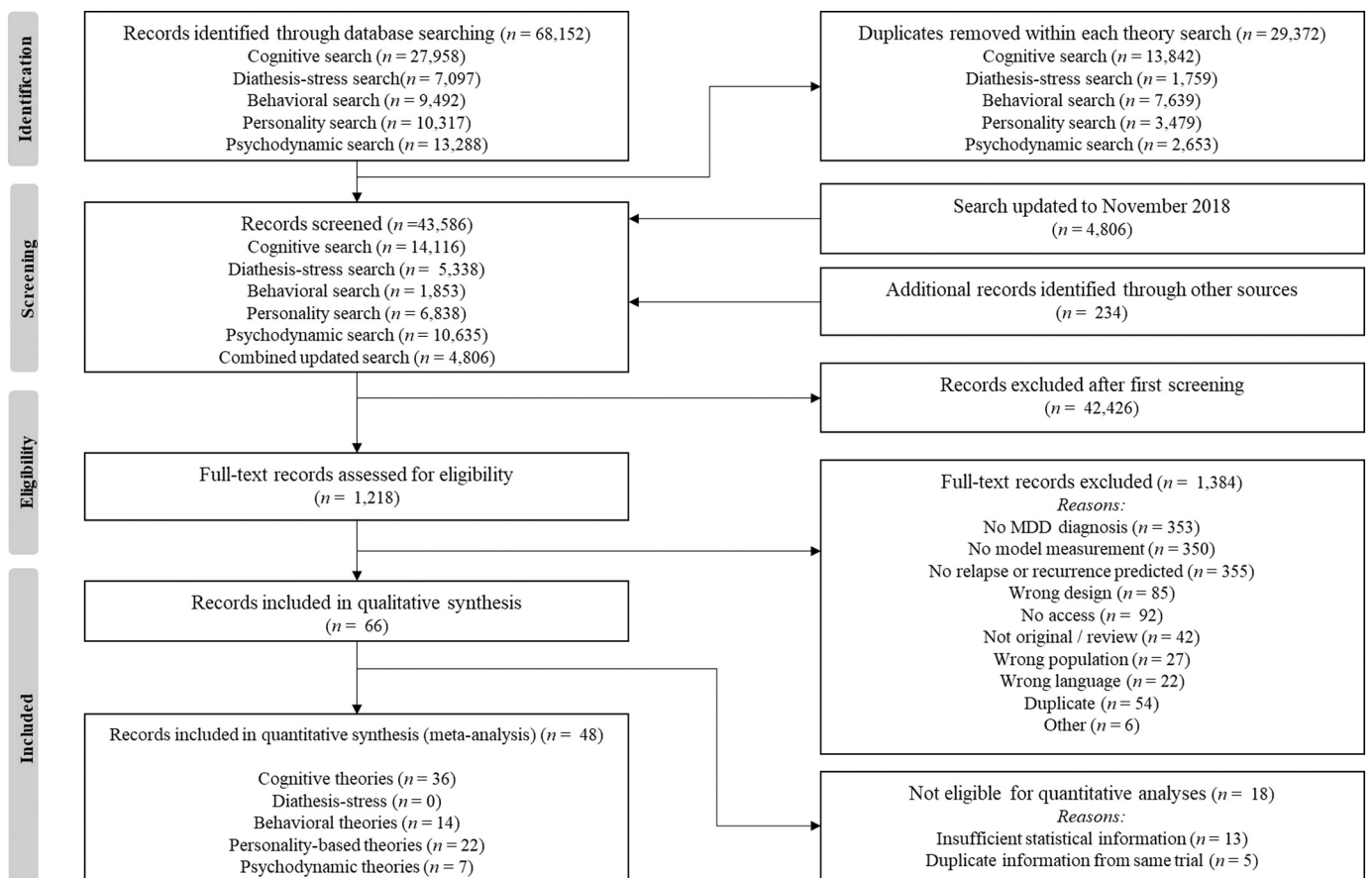


Fig. 1. Flow chart of screening process.

to be included in the quantitative analyses, each measure, or highly similar measure, needed to be reported in at least three studies. There were no restrictions on the form of reporting the factor, as long as an effect size could be calculated. There were no restrictions on the scale the factor was reported on, since the input was used to calculate standardized effect sizes. To investigate whether the psychological theory predicts depressive relapse, all factors related to that theory were combined (pooled), regardless of the scales and measures that were used. To analyse each factor separately, all scales and measures that were used to measure the same factor were pooled as well.

The factors were allocated to certain theories based upon the previous reviews and books, and upon the input of the expert team that was consulted prior to the searches. The expert team (see acknowledgements) was requested to allocate 100 randomly selected factors to the five major theories or none. Based on the consultation, 45 of the 100 factors were allocated to two theories or more by the experts. These factors were then allocated to the theories with the most votes. An overview of this process including the list of factors is available upon request.

The main outcome measure was relapse or recurrence of MDD determined through a clinical interview or expert opinion (e.g., trained psychiatrist or psychologist), consistent with current clinical practice and clinical guidelines that generally follow the DSM-5 and ICD. Self-reported depressive symptomatology was not used as an outcome measure, since this outcome depends on the cut-off scores that were used (and vary per article and questionnaire), and may not only reflect relapse of MDD. Furthermore, such indices provide insufficient information to accurately indicate remission or recovery of MDD (Levis et al., 2019; Stuart et al., 2014), while our aim was to investigate the psychological theories in people with established diagnoses according to the current classification systems. This outcome measure could be

reported as time to relapse, or as an occurrence (relapse yes/no). Alternatively, studies could report a comparison between relapse/recurrence group and a non-relapse/recurrence group. However, the studies were only included if a direct comparison was provided (relapse versus non-relapse) within the original participant group from the start of the study.

2.4. Statistical approach

The software program Comprehensive Meta-Analysis (Borenstein, Hedges, Higgins, & Rothstein, 2005) was used to calculate the pooled effect sizes, forest plots, heterogeneity, and funnel plots. Due to the nature of this review, considerable heterogeneity between studies was expected and therefore we employed a random effects model to estimate pooled effect sizes. The effect sizes Risk Ratios (RR), Hazard Ratios (HR), and Odds Ratios (OR) for all outcomes measures with 95% confidence intervals (CIs) were calculated using reported statistics from each study (including means, standard deviations, number of participants, and/or reported effect sizes). Each effect size indicates a comparison between the group of interest (the theory or factor) and outcome (depressive relapse). The OR and RR for each theory represents the increased or decreased odds or risk of depressive relapse, when a person scores one point higher on the factors related to this theory. With regard to HR, this effect size shows whether the theory predicts accelerated or decelerated time to depressive relapse, when a person scores one point higher on the factors of that theory.

As an indicator of homogeneity among the effect sizes, we used the I^2 statistics (0% = no heterogeneity to 75% = high heterogeneity) and calculated the 95% CIs (Ioannidis, Patsopoulos, & Evangelou, 2007) of each I^2 using the non-central χ^2 -based approach within the heterogeneity module for Stata (Orsini, Bortai, Higgins, & Buchan, 2006). If any study

reported multiple groups (comparison group or group of interest), the effects were combined according to the Cochrane handbook (Higgins & Green, 2011). Publication bias was investigated by inspecting funnel plots, and using Egger's test of the intercept, and Duval and Tweedie's trim and fill procedure (Duval & Tweedie, 2000).

To answer the main question (What is the current evidence for the leading theories of depressive relapse), we first analysed the evidence for each main theory, including all factors assigned to that main theory. Second, separate subgroup analyses were conducted on the factors alone. Since some theories include factors that may be protective against relapse, these factors were separately analysed in the subgroup analyses described below, if applicable. Therefore, all pooled ORs, HRs, and RRs for each main theory do not include the protective factors, but the results from subgroup analyses may (as indicated). Such factors for example include self-esteem, self-efficacy, and social support.

2.5. Meta regression and subgroup analyses

As previously stated, a random effects model (Borenstein, Hedges, Higgins, & Rothstein, 2009) was used to calculate pooled effect sizes for each main theory. To perform subgroup analyses on categorical comparisons, we used a mixed effects model (Borenstein et al., 2009). In these subgroup analyses, the pooled effect sizes within subgroups were calculated with the random effects model, and the fixed effects model was used to test the difference between subgroups. The a-priori defined subgroup comparisons included the different factors within the theories, theory-derived protective factors, and status of the depression at the moment the theory-derived factor was assessed. Where and if applicable, we aimed to run several meta-regression analyses for continuous comparisons, including baseline depressive symptoms, age, follow-up duration, gender, and risk of bias. Sensitivity analyses were conducted for each main theory, where the pooled effect size of each main theory was re-calculated with solely the studies with low risk of bias.

3. Results

3.1. Characteristics of included studies

From the original 38,780 records that were identified in the database search and through reviews, the systematic search resulted in 58 eligible articles (0.15%; see Fig. 1 for full details). The updated search up to November 2018 yielded 4806 original records, and resulted in 8 additional eligible articles (0.17%). Most studies were excluded during the full-text screening on the basis that they did not establish a MDD diagnosis (25%), did not report a theory-derived factor (25%), or did not investigate relapse or recurrence (26%). Table 1 reports the study characteristics of the articles that were included for the qualitative and quantitative analyses. The articles reported 43 unique studies, of which 15 were RCTs, and 28 had a prospective, non-randomized design. There were no articles identified reporting the diathesis-stress theories for depressive relapse. Five articles did not report (unadjusted) relapse rates. Altogether, 6874 unique participants were included, and mean reported relapse rate was 42% during follow-up assessments. Follow-up time ranged from 6 months up to 12 years (Median = 24 months). The risk of bias of the included studies was in general low to moderate, as reported in Table 1. Tables 2, 3, and 4 display the outcomes of the meta-analyses that were completed.

In total, 328 different types of theory-derived factors and analyses were reported across and within studies. These statistical analyses were generally convertible to HR or OR. One study presented a RR (Spinoven et al., 2011), and two studies reported mediation results only (Vittengl, Clark, Thase, & Jarrett, 2015b; Vittengl et al., 2015a). There were an insufficient number of factors from different articles to calculate pooled RRs, and insufficient information to recalculate the RR into OR. Since HR and OR are non-comparable, the two analyses are

presented separately. Visual inspection of the funnel plot, the Egger's test ($p < 0.01$) and Duval and Tweedie's trim and fill (studies trimmed within HR meta-analysis = 4; within OR = 6), indicated potential publication bias, with missing articles on the left side of the funnel plot (lack of published non-significant results).

Since not all included articles reported sufficient information to calculate HRs or ORs, data from 48 articles originating from 35 unique studies was analysed. First, pooled effect sizes per main theory were calculated. Figs. 1 and 2 show the forest plots for HR (18 studies) and OR (25 studies) for each main theory. Second, several meta-analyses were performed based on the factors within the theories, for HR and OR separately. There were not enough studies and participants to conduct meta-regression analyses for continuous comparisons within each theory. The outcomes of the analyses are presented below and in Tables 2 and 3 for each leading theory. Figs. 2 and 3 show the results of the theory-derived factors for all theories.

3.2. Theory-derived factors

Cognitive theory. Overall, the cognitive theories significantly increased the odds of relapse ($OR = 1.24$, 95% CI = 1.10–1.40), but did not decrease time to relapse ($HR = 1.00$, 95% CI = 0.98–1.03). Sensitivity analyses showed similar results for studies with low risk of bias only ($OR = 1.22$, 95% CI = 1.09–1.38, $k = 16$; $HR = 1.02$, 95% CI = 0.97–1.07, $k = 10$). The ORs differed significantly ($p < 0.001$) between the factors within the theory. The pooled OR and HR did not differ between diagnostic status (i.e. if the participants were depressed or not during the time of assessment of the factor; $HR p = 0.98$; $OR p = 0.19$).

The theory-derived factors that were assigned to the cognitive theory and could be analysed separately were coping, attributional style and dysfunctional attitudes. One point higher on the negative attributions questionnaire increased the odds of relapse 1.3 times ($OR = 1.26$, 95% CI = 1.07–1.48). With regard to the HR subgroup analyses, it was found that higher levels of dysfunctional attitudes were related to decreased time to depressive relapse ($HR = 1.01$, 95% CI = 1.00–1.01), i.e. one-point higher on the dysfunctional attitudes scale decreases the time to relapse by 1.01. Coping was not significantly related to time to relapse ($HR = 1.10$, 95% CI = 0.77–1.57). The strength of evidence for the cognitive theory was assessed as low, according to the GRADE framework.

Behavioural theories. The behavioural theory significantly increased the odds of relapse ($OR = 1.15$, 95% CI = 1.05–1.25), but not time to relapse ($HR = 1.06$, 95% CI = 0.94–1.19). Sensitivity analyses showed the exact same results for OR, and there were insufficient studies within HR to conduct a sensitivity analysis. Diagnostic status did not influence the relationship between the behavioural theory and the odds of depressive relapse ($p = .39$). Subgroup analyses with the factors, functioning and social support, were not significant. The overall strength of evidence for this theory was low, as assessed by means of the GRADE framework.

Psychodynamic theories. The psychodynamic theory did not significantly increase the odds of relapse ($OR = 1.29$, 95% CI = 0.83–1.99). There were not enough studies to assess time to relapse. Within the sensitivity analysis, the same results were found for studies as all studies had a low risk of bias. The separate factors within the theory could not be investigated due to high heterogeneity and an insufficient number of eligible studies. Strength of evidence for the psychodynamic theory was very low, as assessed with the GRADE framework.

Personality-based theories. The pooled OR indicated a significant relationship between the personality-based theory and odds of depressive relapse ($OR = 1.26$, 95% CI = 1.02–1.54), but not between the personality-based theory and time to relapse ($HR = 1.02$, 95% CI = 0.97–1.08). The sensitivity analyses showed similar results ($OR = 1.26$, 95% CI = 1.01–1.57, $k = 11$; $HR = 1.05$, 95%

Table 1
Characteristics of included studies.

First author, year	Design, Main study & Interventions	Country	Theory & factors	No. of participants (n female)	No. of relapse/No. non-relapse	Follow-up time in months	Diagnostic tool	Diagnostic status at assessment	Depression score at assessment, tool: <i>M</i> (<i>SD</i>)	Risk of bias score
Asano 2015	Cohort	Japan	Personality: TCI	69 (44)	39/30	48	DSM-IV criteria	2	HDRS: 3.9 (3.1)	1
Backs-Dermott 2010	Cohort	Canada	Cognitive: SAS-R, GISS Behavioural: MSPSS, social support	49 (49)	29/20	12	SCID-I DSM-IV-TR	2	BDI-II: 11.7 (8.8)	2
Berlanga 1999	RCT: Nefazodone vs. Fluoxetine	Mexico	Personality: EPQ	42 (32)	18/24	12	DSM-IV criteria & HDRS	1	HDRS: 26.9 (5.3)	1
Birmaher 2004	Cohort	USA	Behavioural: CBCL Psychodynamic: Marshall & Tanner development	68 (29)	27/68	58	K-SADS-E & K-SADS-PO	1	HDRS: 14.3 (5.5)	8
Bockting 2006; Bockting 2006b; Figueroa 2015; ten Doesschate 2010; van Rijsbergen 2013	RCT: "Delta study"; Group PCT vs. TAU	NL	Cognitive: CERQ, DAS, LEIDS Behavioural: UCL	187 (126)	135/37	66	SCID-I DSM-IV-TR	2	HDRS: 3.8 (2.8)	0; 0; 0; 0
Bouhuys 2006	Cohort	NL	Cognitive: Perception of facial expressions	77 (51)	21/56	24	CIDI interview	2	BDI: 3.6 (2.4)	1
Brouwer 2019	RCT: M-CT + TAU vs. TAU	NL	Cognitive: DAS, extreme responding	264 (197)	98/113	24	SCID-I interview	2	HDRS: 3.55 (3)	1
Chopra 2008; Fresco 2007; Segal 2006	RCT: CT vs. AD	Canada	Cognitive: DAS	127 (48)	40/38	18	LIFE interview & HDRS	1	HDRS: 5.6 (2.7)	5; 7; 1
Conradi 2008; Conradi 2018	RCT: "INSTEEL study"; TAU vs. PEP vs. Psychiatrist-enhanced PEP vs. CBT-enhanced PEP	NL	Behavioural: RSES, MOS-SF-36, Groninger list protracted difficulties and hostility scale Psychodynamic: ECR	123 (84); 103 (75)	n/a; 56/47	36; 84	CIDI interview	1	BDI: n/a	6; 6
Craighead 2011; Hart 2001; Sheets 2014**	Cohort	USA	Cognitive: DAS Personality: IPDE	130 (104); 93 (50); 119 (94)	n/a	18	SCID-I DSM & LIFE interview	2	BDI-II: 12.3 (7.1)	2; 2; 2
Farb 2018; Segal 2018	RCT: MBCT vs. CT	Canada	Psychodynamic: IP-32	166 (112)	36/130	24	SCID-I DSM-IV	2	HDRS: n/a	2; 2
Forand 2014; Strunk 2007	RCT: CT subgroup only	USA	Cognitive: DAS, EQ Cognitive: DAS, extreme responding, WOR	104 (60); 35 (18)	59/25; 13/18	24	SCID-I DSM-IV & HDRS	3	HDRS: n/a	6; 6
Gollan 2006	RCT: CBT vs. BA vs. BA + AT	USA	Cognitive: DAS, ATQ, EASQ Behavioural: PES	93 (74)	40/53	24	SCID-I DSM-III-R	3	HDRS: 4.3 (3.6)	5
Gonzales 1985; Lewinsohn 1984	Pre-post design; several CBT based interventions	USA	Personality: MCMI Behavioural: Physical functioning	167 (80); 113 (n/a)	24/21	12	SADS & Life interview	1	BDI: 22 (8.8)	2; 3
Gopinath 2007	RCT: Depression relapse prevention intervention vs. usual primary care	USA	Cognitive: Self-efficacy Personality: NEO-FFI	386 (285)	120/266	12	SCID-I DSM-III-R & LIFE interview	2	n/a	3
Grilo 2010	Cohort: "Collaborative Longitudinal Personality Disorders Study"	USA	Behavioural: MOS-SF-36 Personality: DIPD-IV	303 (196)	183/77	72	SCID-I DSM-IV & LIFE interview	2	n/a	3
Hardeveld 2013; Ormel 2004	Cohort: "NEMESIS"	NL	Personality: ABI Neuroticism, Locus of control Behavioural: SSSQ	687 (467); 680 (n/a)	135/552	36	CIDI DSM-III-R	2	n/a	0; 3
Holma 2008; Melartin 2004	Cohort: "The Vantaa Depression Study"	Finland	Cognitive: Hopelessness Behavioural: SOfAS, size of social network, PSSS-R Personality: EPQ	269 (143)	99/41	60	SCAN for DSM disorders	1	HDRS: 19.1 (6.1)	5; 4

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Table 1 (continued)

First author, year	Design, Main study & Interventions	Country	Theory & factors	No. of participants (n female)	No. of relapse/No. non-relapse	Follow-up time in months	Diagnostic tool	Diagnostic status at assessment	Depression score at assessment, tool: M (SD)	Risk of bias score
Ilardi, 1997	Cohort	USA	Cognitive: DAS, ASQ Personality: IPDE	50 (37)	34/16	84	DIS for DSM-III-R & LIFE interview	1	MADRS: 14.2 (7.7)	8
Jarrett 2012; Vittengl 2015a; Vittengl 2015b; Vittengl 2017	RCT: C-CT vs. fluoxetine 40 mg/day vs. pill placebo	USA	Cognitive: DAS Personality: SNAP	213 (137); 172 (120)	113/128; 74/98	32	SCID-I DSM-IV & LIFE interview	3	BDI, IDS-SR, and HRSD: 17.6 (7.4)	5; 2; 3; 3
Kuehner 2013	Cohort	Germany	Cognitive: ACS-24 Behavioural: MISS Cognitive: DAS	68 (37)	33/27	66	SCID-I DSM-IV	1	MADRS: 7.2 (7.8)	5
Lam 1996	Cohort	England	Cognitive: DAS	37 (21)	12/17	12	Psychiatrist diagnosis DSM-III	2	n/a	2
Lara 2000	Cohort	USA	Cognitive: RSQ Behavioural: ISEL, social support Psychodynamic: EHEI	88 (72)	12/45	6	SCID-I DSM-IV & LIFE interview	1	HDRS: 21.4 (8.7)	6
LeMoult 2017	Cohort	USA	Cognitive: SRET	100 (100)	29/30	36	SCID-I DSM-IV-R	2	BDI: 13.4 (9.5)	6
Lethbridge 2008	Cohort	Australia	Cognitive: DAS	52 (30)	24/21	12	SCID-I DSM-IV-R	2	BDI: 8.1 (6.1)	4
Lin 1998	RCT's combined	USA	Personality: Neuroticism Behavioural: MOS-SF-36	251 (190)	93/158	12	Psychiatrist diagnosis DSM-III	2	IDS: 14.2 (10.0)	2
Michalak 2011	Pre-post design: MBCT	Germany	Cognitive: RRS	24 (18)	9/15	12	SCID-I DSM-IV	2	HDRS: 1.9 (2.6)	6
Mongrain 2005; Mongrain 2006	Cohort: Toronto University packages	Canada	Cognitive: RSQ, PSI, EASQ, DAS Psychodynamic: DEQ	97 (77); 158 (119)	37/65	20	SCID-I DSM-IV	2	CES-D: 34.6 (11.2)	4; 5
Mulder 2009	RCT: "Christchurch Outcome of Depression study"; Fluoxetine vs. Nortriptyline	New Zealand	Personality: BFI Neuroticism Personality: TCI, personality disorder traits	195 (111)	57/66	18	SCID-I DSM-III-R	1	MADRS: 19.9 (4.4)	6
Mundt 1998	Cohort: Heidelberg Depression Study	Germany	Cognitive: ASQ Personality: MMPI	50 (33)	18/24	12	SCID-I DSM-III-R	3	HDRS: 8.1 (7.1)	1
Noteboom 2016; Spinhoven 2011; Spinhoven 2016; Spinhoven 2018	Cohort: "NESDA study"	NL	Personality: NEO-FFI Cognitive: AAQ-I, PSWQ, LEIDS-R, PTQ	437 (308); 722 (466); 977 (790); 790 (536)	n/a; 274/448; 360/617; 166/790	24; 24; 72; 36	CIDI for DSM-IV	2; 1; 2; 2	n/a; IDS-SR: 34.7 (11.2); 14.7 (9.5); 13.8 (9.1)	1; 1; 5; 4
O'Leary 2001	Cohort	Ireland	Personality: MPI neuroticism, MPI extraversion	84 (45)	15/68	18	SCAN and ICD-10 criteria	1	HDRS: 23.8 (0.7)	2
Otto 2007	Cohort: "The Harvard Study of Moods and Cycles"	USA	Cognitive: DAS	80 (80)	25/55	36	SCID-I DSM-IV	2	HDRS: 5.7 (4.6)	5
Petersen 2007	RCT: Fluoxetine + CBT vs. Fluoxetine	USA	Cognitive: DAS, ASQ	132 (72)	n/a	9	SCID-I DSM-III-R	1	HDRS: 18.7 (2.8)	3
Pettit 2013	Cohort: "OADP study"	USA	Behavioural: Social support, health problems Cognitive: Coping skills, DAS Psychodynamic: interpersonal dependency	59 (40)	43/16	144	K-SADS & LIFE interview	1	n/a	2
Segal 1992	Cohort: "recovery from depression"	Canada	Cognitive: DAS	59 (43)	30/29	12	SADS-L	2	BDI: 4.4 (3.3)	2
Segal 1999; Thase 1992	Pre-post design: CBT or AD	Canada	Cognitive: DAS	44 (18); 50 (35)	14/16	30; 12	SADS-L	2	HDRS: 4.1 (3.7)	6; 4
Solomon 2004	Cohort: "Collaborative Depression Study"	USA	Behavioural: LIFE-RIFT	290 (175)	143/147	135	SADS-L & LIFE interview	1	HDRS: 20 (7)	3

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Table 1 (continued)

First author, year	Design, Main study & Interventions	Country	Theory & factors	No. of participants (n female)	No. of relapse/No. non-relapse	Follow-up time in months	Diagnostic tool	Diagnostic status at assessment	Depression score at assessment, tool: <i>M</i> (<i>SD</i>)	Risk of bias score
<i>Teasdale 2001; Teasdale 2002</i>	RCT: CT + Clinical management & drug continuation vs. Clinical management & drug continuation	England	Cognitive: ASQ, DAS, BLAME, MAQ, MACAM, UNCONTROL	158 (78)	60/98	17	DSM-III-R	1	HDRS: 12.1 (2.8)	4; 7
Timm 2017	Cohort	Germany	Cognitive: PTQ, Rumination	57 (40)	28/29	36	SCID DSM-IV-R	2	BDI-II: 10.6 (8.8)	2
<i>Van Loo 2015</i>	Cohort: "VATSPSUD study"	USA	Personality: EPQ	194 (194)	101/83	66	SCID DSM-III-R	2	n/a	1
Vittengl 2010	RCT: Assessment + C-CT vs. Assessment only	USA	Personality: SNAP	84 (62)	n/a	24	SCID-I DSM-IV & LIFE interview	3	HDRS: 11.7 (6.9)	2
Woody 2016	Cohort	USA	Cognitive: Modified dot-probe task	53 (53)	15/38	24	SCID-I DSM-IV		BDI-II: 10.3 (8.8)	3

Note: ** although not explicitly reported, the study identification numbers, names, and participant groups indicate that the participants are highly overlapping or exactly the same. 1 = depressed, 2 = non-depressed / remitted, 3 = treatment responder. n/a = not applicable or not available. RCT = Randomized controlled trial; CBT = Cognitive behavioural therapy; TAU = Treatment as usual; CT = Cognitive therapy; PEP = Psycho-Educational Prevention Program; BA = Behavioural activation; AT = Automatic thought modification; C-CT = Continuation CT; M-CT = mobile preventive cognitive therapy; MBCT = Mindfulness-based cognitive therapy; PCT = Preventive cognitive therapy; AD = Antidepressant medication; CIDI = Composite International Diagnostic Interview; DIS = Diagnostic Interview Schedule; LIFE = Longitudinal Interval Follow-up Evaluation; K-SADS = Schedule for Affective Disorders and Schizophrenia-Lifetime - Age children (E = Epidemiologic version; P = present version); SADS-L = Schedule for Affective Disorders and Schizophrenia-Lifetime; SCAN = Schedules for Clinical Assessment in Neuropsychiatry; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th edition; SCID-I = Structured Clinical Interview for DSM axis-I diagnoses; BDI = Beck Depression Inventory; CES-D = Centre for Epidemiologic Studies Depression scale; HDRS = Hamilton Depression Rating Scale; IDS = Inventory of Depressive Symptomatology; MADRS = Montgomery Asberg Depression Rating Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; AAQ-I = Acceptance and Action Questionnaire-I; ABI = Amsterdam Biographic Inventory; ACS-24 = Action Control Scale; ASQ = Attributional style questionnaire; ATQ = Automatic Thoughts Questionnaire; BFI = Big Five Inventory; BLAME = Characterological Self-Blame for Depression; CBCL = Child Behaviour Checklist; CERQ = Cognitive Emotion Regulation Questionnaire; CISS = Coping inventory for stressful situations; DAS = Dysfunctional Attitudes Scale; DEQ = Depressive Experiences Questionnaire; DIPD-IV = Diagnostic interview for DSM-IV personality disorders; EASQ = Extended attributional style questionnaire; EHEI = Early home environment interview; ECR = Experiences in Close Relationships; EPQ = Eysenck Personality Questionnaire; EQ = Experiences Questionnaire; IIP-32 = Inventory of Interpersonal Problems; IPDE = International Personality Disorder Examination; ISEL = Interpersonal Support Evaluation List; LEIDS = Leiden Index of Depression Sensitivity (R = revised); LIFE-RIFT = Longitudinal Interval Follow-up Evaluation-Range of Impaired functioning Tool; MACAM = Measure of Awareness and Coping in Autobiographical Memory; MAQ = Metacognitive Awareness Questionnaire; MCMI = Millon Clinical Multiaxial Inventory; MISS = Mannheim Interview on Social Support; MMPI = Minnesota Multiphasic Personality Inventory; MOS-SF-36 = Physical functioning; MPI = Maudsley Personality Inventory; MSPSS = Multidimensional Scale of perceived social support; NEO-FFI = NEO Five-Factor Inventory; PES = Pleasant Events Scale; PSI = Personal Style Inventory; PSSS-R = Perceived Social Support Scale - Revised; PSWQ = Penn State Worry Questionnaire; PTQ = Perseverative Thinking Questionnaire; RRS = Ruminative Response Scale; RSES = Rosenberg Self-esteem scale; RSQ = Response Style Questionnaire; SAS-R = Revised Sociotropy-Autonomy Scale; SNAP = Schedule for Nonadaptive and Adaptive Personality; SOFAS = Social and Occupational Functioning Assessment Scale; SRET = Self-Referential Encoding Task; SSQS = Social Support Questionnaire for Satisfaction with the supportive transactions; TCI = Temperament and Character Inventory; UCL = Utrecht Coping List; UNCONTROL = Perceived Uncontrollability of Depression; WOR = Ways of Responding. Articles presented in *italic* were excluded from quantitative analyses.

Table 2
Results of meta-analyses on main psychological theories and subgroup analyses on diagnostic status - Hazard Ratio.

Main theory	No. of studies	No. of participants	HR (95% CI)	I ² (95% CI)	p-value*
Behavioural	3	420	1.06 (0.94–1.19)	72% (7–92)	
Theoretical factors					0.20
Cognitive	12	1490	1.00 (0.98–1.03)	51% (5–75)	
Diagnostic status					0.98
Non-depressed	7	895	1.01 (0.97–1.06)	13% (0–75)	
Depressed	5	595	1.01 (0.94–1.09)	74% (35–89)	
Personality-based	7	1509	1.02 (0.97–1.08)	68% (30–86)	
Diagnostic status					0.03
Non-depressed	5	1197	1.05 (0.98–1.12)	70% (23–88)	
Theoretical factors					0.60

Note: * = p-value for the difference between subgroups; HR = Hazard Ratio.

CI = 0.96–1.15, $k = 6$). Diagnostic status did not influence the relationships for OR ($p = 0.96$), yet did influence the relationships for HR ($p = 0.03$), although HRs remained non-significant in the non-depressed subgroup ($HR = 1.05$, 95% CI = 0.98–1.12, $k = 5$).

Subgroup analyses indicated that a one-point higher score on a negative personality trait questionnaire was related to 1.3 times increased odds of relapse ($OR = 1.28$, 95% CI = 1.04–1.58) and not to time to depressive relapse ($HR = 1.02$, 95% CI = 0.95–1.09). Specifically, one-point higher score on neuroticism was related to 1.7 times increased odds of relapse ($OR = 1.66$, 95% CI = 1.13–2.45). Again, according to the GRADE framework, the strength of evidence for the personality-based theories was low.

4. Discussion

Previous reviews have contributed greatly to clinical knowledge of depression (Buckman et al., 2018; Burcusa & Iacono, 2007; Hardeveld et al., 2010), yet a full overview of current prospective evidence and level of support for the psychological theories that explain depressive relapse was lacking. We conducted a systematic review and meta-analysis on the evidence for five leading psychological theories of depressive relapse and their factors: Cognitive, diathesis-stress, behavioural, psychodynamic, and personality-based. Overall, the literature that could be identified indicated that there was some evidence that the cognitive, behaviour, and personality-based theories partially account for the odds of prospectively assessed relapse in MDD. There were no articles for the diathesis-stress theories, and there was no significant support for a relationship between the psychodynamic theories and depressive relapse. Factors derived from the cognitive and personality theories, specifically higher levels of negative attributional style and

neuroticism were found to be related to increased odds of relapse. The cognitive variable ‘dysfunctional attitudes’ was the only identified theory-derived factor associated to an accelerated time to prospectively assessed depressive relapse. Nonetheless, this effect was very small ($HR = 1.01$). Overall, the limited number of eligible articles prevented us from drawing strong inferences on the relationship between the theories and depressive relapse, and to further investigate potential moderators of significant results, despite the large number of identified records within the field of MDD.

The overall finding regarding the theory-derived factors is consistent with previous reviews, showing that people scoring highly on questionnaires measuring neuroticism and dysfunctional beliefs were at increased risk of depressive relapse (e.g. Buckman et al., 2018; Klein et al., 2011). These results provide support for the notion that both negative personality traits and cognitive styles are related to the risk of depressive relapse, or that they both represent an underlying style that puts a person at increased risk (e.g. Brouwer et al., 2019; Forand & DeRubeis, 2014). The theory-derived factors from different theories as well as the theories themselves may at the same time overlap. For example, neuroticism and cognitive factors including dysfunctional attitudes and attributional style reflect negative emotionality and the individual's view on themselves, others, and the future (Beck & Bredemeier, 2016; Klein et al., 2011). Cognitive theory-derived factors may therefore be seen as part of the concept of neuroticism, although evidence for this overlap is mixed (e.g. Hankin, Lakdawalla, Carter, Abela, & Adams, 2007).

As previously stated, the cognitive and behavioural theories can be perceived as a diathesis-stress theories. Personality traits, attributional style, and dysfunctional attitudes all represent a style or another factor that a person exhibits, which may represent the factor for depressive

Table 3
Results of meta-analyses on main psychological theories and subgroup analyses on diagnostic status - Odds Ratio.

Main theory	No. of studies	No. of participants	OR (95% CI)	I ² (95% CI)	p-value*
Behavioural	8	1344	1.15 (1.05–1.25)	73% (46–87)	
Diagnostic status					0.39
Non-depressed	3	607	1.19 (1.08–1.32)	0% (0–90)	
Depressed	5	737	1.12 (1.01–1.24)	78% (48–91)	
Theoretical factors					0.003
Cognitive	17	2929	1.24 (1.10–1.40)	78% (65–86)	
Diagnostic status					0.19
Non-depressed	12	2503	1.33 (1.06–1.66)	86% (78–91)	
Depressed	5	426	1.11 (0.96–1.28)	73% (34–89)	
Theoretical factors					< 0.001
Personality-based	12	2755	1.26 (1.02–1.54)	61% (27–79)	
Diagnostic status					0.99
Non-depressed	7	2273	1.25 (0.94–1.67)	70% (34–86)	
Depressed	5	482	1.26 (0.90–1.74)	36% (0–76)	
Theoretical factors					0.40
Psychodynamic	4	341	1.29 (0.83–1.99)	49% (0–83)	

Note: * = p-value for the difference between subgroups; OR = Odds Ratio. Bold indicates the significant results.

Table 4
Results of subgroup analyses on theory-derived factors.

Theoretical factor	Hazard ratio					Odds ratio				
	No. of studies	No. of participants	HR (95% CI)	I ² (95% CI)	p*	No. of studies	No. of participants	HR (95% CI)	I ² (95% CI)	p*
Functioning						5	1010	1.10 (0.99–1.22)	74% (36–90)	
Social support	4	944	0.99 (0.97–1.01)	34% (0–77)		3	306	0.98 (0.91–1.05)	0% (0–90)	
Attributional style						4	274	1.26 (1.07–1.48)	0% (0–85)	
Coping						3	788	1.10 (0.77–1.57)	69% (0–91)	
Dysfunctional attitudes	6	870	1.01 (1.00–1.01)	35% (0–74)		9	681	1.03 (0.95–1.12)	33% (0–69)	0.23
Non-depressed						6	495	1.01 (1.01–1.01)		
Depressed						3	186	1.60 (0.75–3.42)		
Personality disorder traits						3	363	1.20 (0.85–1.67)	27% (0–92)	
Negative personality trait	5	1146	1.02 (0.95–1.09)	83% (61–93)		11	2713	1.28 (1.04–1.58)	74% (52–86)	
Neuroticism						7	2636	1.66 (1.13–2.45)	92% (87–96)	
Diagnostic status Non-depressed						5	2396	1.46 (0.94–2.25)	86% (70–94)	0.43

Note: * = p-value for the difference between subgroups; HR = Hazard Ratio; OR = Odds Ratio. Bold indicates the significant results.

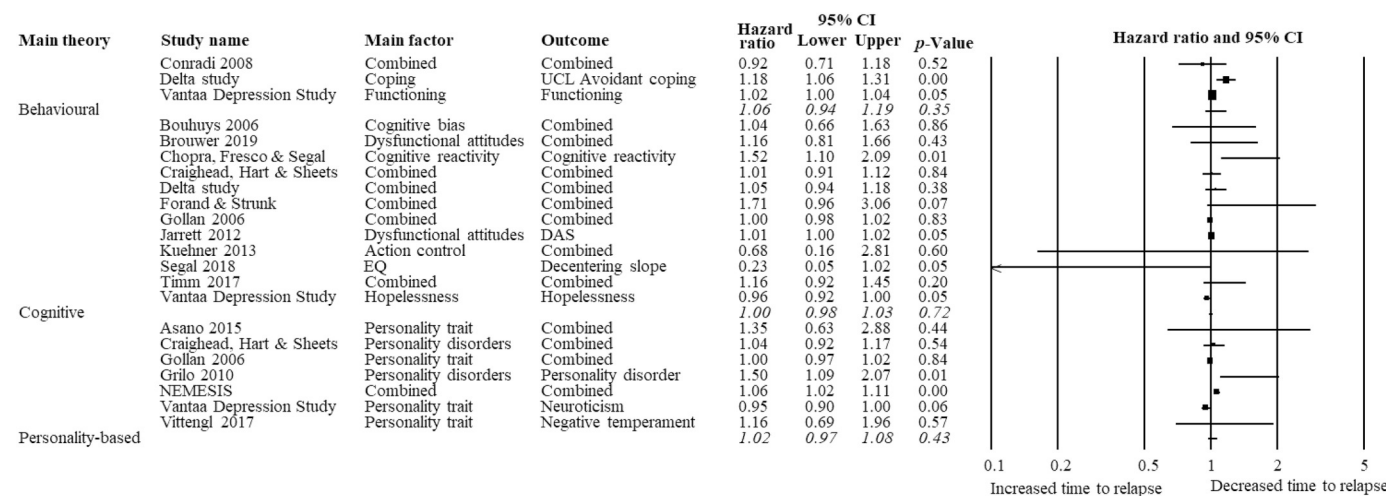


Fig. 2. Forest plot for Hazard Ratio meta-analysis.

Note: Combined = combination of variables, CI = confidence interval, EQ = Experiences Questionnaire, UCL = Utrechtse Coping List.

relapse, either alone or in interaction with or activated by stress (e.g. Conway et al., 2015; Ingram et al., 1998; Monroe & Simons, 1991; Sutton et al., 2011). However, there were no studies identified that investigated the factors in combination with stress in prospective, longitudinal trials among individuals with established diagnoses. In addition, the significant factors may as well overlap with or reflect symptomatology of depression, and therefore predict relapse better than other factors. For example, for dysfunctional attitudes, there is a debate whether this factor reflects a warning sign, or is secondary to having depressive symptoms (i.e. covaries with depression) (Lorenzo-Luaces et al., 2015). Likewise, the concept of neuroticism overlaps with the negative emotions and distress an individual experiences during a MDE. Although most of the included studies corrected for depressive symptoms, in this meta-analyses we could not investigate the direct impact of the levels of depression in a meta-regression due to a lack of

studies for each main theory. Future studies are needed to disentangle whether the factors overlap with depressive symptoms, or are in fact indeed risk factors of depressive relapse.

The discrepancy between the results of the hazard ratio (time to relapse) and odds ratio (odds of relapse) should be noted. This discrepancy may be due to the low number of studies that prospectively investigated (time to) depressive relapse. One would expect that if a person is at higher risk of relapse, that person may also deteriorate more quickly in the face of adversity and relapse sooner than a person who does not possess these vulnerabilities. Clinically, the findings could imply that an individual who is highly neurotic, or who adopts a negative attributional style, is likely to relapse, but within an unknown period of time. On the other hand, an individual who holds entrenched dysfunctional attitudes might be at a small increased risk to relapse sooner, relative to individuals who endorse more functional attitudes.

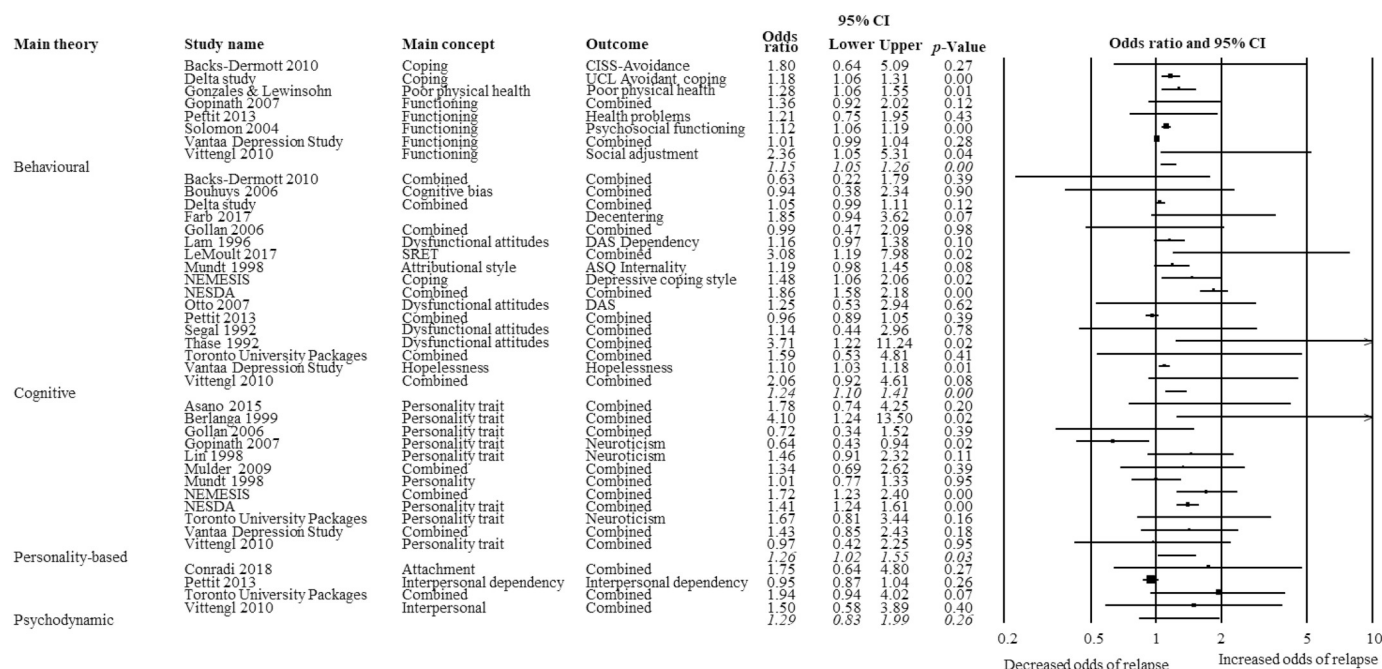


Fig. 3. Forest plot for Odds Ratio meta-analysis.

Note: Combined = combination of variables, CI = confidence interval, CISS = Coping inventory for stressful situations, UCL = Utrechtse Coping List, DAS = Dysfunctional attitudes scale, ASQ = Attributional style questionnaire, SRET = Self-Referential Encoding Task.

For clinical practice, these findings imply that the relapse prevention strategies based upon the cognitive, behavioural, and personality-based theories are most promising in the prevention of depressive relapse. In particular, the results show that the factors dysfunctional attitudes, attributional style, and neuroticism may be promising therapeutic target points. Collectively, the discrepant finding indicates that the leading psychological theories do not adequately account for the timing of depressive relapse. Given that none of the studies examined the diathesis component of the psychological theories in a prospective longitudinal study, no firm conclusion can be drawn on the evidence for these psychological theories.

The need for more research on psychological theories of depressive relapse is likewise underscored by the relatively low number of eligible studies that were identified. At the same time, the included 43 studies from 66 articles reported > 300 different measurements, likely biasing the reported effects due to multiple testing. To improve research in this domain, researchers are advised to 1) select an adequate population and prospectively assess the diagnosis; 2) use a prospective, longitudinal design (when resources permit); and 3) assess potential predictors or factors of depressive relapse before the event itself, in order to provide a better framework of potential predictors of depressive relapse. The diathesis-stress theory in particular needs to be studied in relation to depressive relapse, given that most psychological theories are in fact diathesis-stress theories. Conducting studies with prospective, longitudinal designs, established MDD status, and multiple factors from one or more psychological theories are resource intensive, as they require a significant amount of time and financial investment. A first, less expensive, step to investigate leading psychological theories would be to collect data of similar measures across studies. Sharing data and creating (or strengthening) research networks across the globe is needed to circumvent the challenges associated with this type of research. Large, collaborative efforts seem necessary to establish the robustness of current psychological theories that account for depressive relapse. When predictors of relapse are identified through clinical evidence, preventive interventions may be improved by this knowledge.

Despite the strengths of the meta-analysis, which are the inclusion of prospective, longitudinal studies that assessed the theories by means

of theory-derived factors before depressive relapse, and where MDD was established through clinical interviews, the results must be interpreted in light of a number of limitations. Firstly, the operationalisation of the psychological theories differed highly between different studies, thereby diminishing the amount of factors that could be investigated, and simultaneously increasing the heterogeneity within each theory. The search terms used to identify the factors might not have covered all concepts of the theories. Several experts were involved to discuss the search terms; however, there was a lack of consensus. This lack of consensus is not restricted to the experts: The large amount of theory-derived factors across studies implied that there are too many operationalisations of the theories. Specifically, some of the theory-derived predictors could be assigned to multiple theories, dependent on the expert and focus of the included articles. Secondly, the reported effect sizes were small with wide confidence intervals and were therefore less reliable. Third, the potential for publication bias indicates caution is warranted when drawing conclusions as non-significant results were most likely unpublished. Additionally, the included studies reported outcomes that varied on a number of dimensions. For example, data of the original studies were collected at different time points, studies included varying lengths of follow-up, and samples were comprised of individuals with a varying number of prior depressive episodes and residual depressive symptoms. Due to the limited inclusions, subgroup analyses and meta-regression analyses to account for the differences were not possible. In addition, by focusing on prospective studies that assessed theory-derived factors before depressive relapse, a causal relationship between the theories and relapse is suggested. However, prospective studies are the minimal requirement to investigate causal relationships. To explore this further, experimental studies with active manipulation of the theory-derived factor are needed to test if there is a subsequent change in outcome (i.e. depressive relapse yes/no; Kraemer et al., 1997).

Lastly, we employed a categorical approach to determine relapse and recurrence of MDD, i.e. by only including articles that established the relapse and recurrence by means of clinical interviews, in line with current clinical practice and guidelines. Our goal was to examine diagnostic status of depressive relapse according to the current

classification system. Evidence for the theories may have been missed with this approach. A number of studies debate whether or not self-reported relapse and using a dimensional/continuous approach may be more appropriate than the categorical approach (Caspi & Moffitt, 2018; Kendler et al., 2018). Although a dimensional approach is now suggested in the appendix of the latest version of the DSM-5 (American Psychiatric Association, 2013), current clinical practice still primarily focusses on the categorical system. We did not use a dimensional measure in the current study (i.e. level of depressive symptoms) because this might indicate a different population. Future research should focus on this difference in evidence for the theories between categorical and dimensional theories as well.

Overall, despite the limitations, the current meta-analysis found some evidence that the cognitive, behavioural, and personality-based theories partially explain depressive relapse, but evidence is lacking for both the psychodynamic and diathesis-stress theories. The lack of evidence for the psychodynamic theories in the current meta-analysis is based upon the fact that the results were non-significant. It might also reflect the limited number of studies, and thereby a potential lack of power, for this theory. Thus, evidence is scarce, yet, the current meta-analysis on this scarce evidence shows no support for the psychodynamic theories. This suggests that clinicians and researchers should be cautious with using the psychodynamic theories as an explanation and basis for relapse of MDD, since this is at this moment not a prospective-evidence-based aetiological theory.

A limited number of prospective studies were identified that established robust evidence for the relationship between each psychological theory and depressive relapse. The overall strength of evidence was low, according to the grade assessment, and also according to the small and inconsistent pooled effect sizes for the theories. For clinicians, the results show the value of neuroticism, attributional style, and dysfunctional attitudes as potentially therapeutically-modifiable indicators of increased odds or decreased time to the return of MDD. It is however striking that there was no convincing evidence for the theories that are believed to support or guide the widely applied treatments.

5. Conclusion

The systematic search identified a limited number of studies that prospectively assessed factors derived from leading psychological theories of depressive relapse. Very small, and potentially clinically less relevant, effects were established in this meta-analysis for the cognitive, behavioural, and personality-based theories. It therefore remains unclear if current treatments in MDD target the potential causal factors of relapse as proposed by the theories. The lack of robust evidence for the relationship between each psychological theory and depressive relapse highlights the gap between putative factors and treatment targets to prevent depressive relapse. There is a high need for more prospective, high-quality studies that investigate multiple psychological theory-derived factors as potential predictors of depressive relapse to improve current leading psychological theories.

Role of funding sources

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Contributors

CLHB initiated the project. CLHB, MEB and MK designed the study

and wrote the protocol. CLHB, MEB, ZF and MK drafted and conducted the literature searches and provided summaries of previous research studies. MEB, ZF, MK, ADW, and research assistants conducted the screening of articles, data extractions, and quality assessments. MEB conducted the statistical analyses and was advised by PC, CLHB, and ADW. MEB wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

There are none.

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Appendix A. List of included studies and references

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Appendix B. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cpr.2019.101773>.

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- Claudi L.H. Bockting**, The research program of Professor Bockting focuses on depressive disorder and related common mental health disorders. These disorders are characterized by disruptions in emotions. Professor Bockting studies potentially modifiable etiological affective-, and information processing mechanisms on an intra-, as well as, interindividual level. One of her main focuses is understanding etiological and maintenance factors in depression and related common mental health disorders.