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Review

Mediators in psychological and psychoeducational interventions for the prevention of depression and anxiety. A systematic review

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HIGHLIGHTS

- Little is known about the mediators of interventions to prevent depression and anxiety.
- Twenty-eight mediator studies nested within randomized control trials were included.
- Potential cognitive, behavioral, emotional, and interpersonal mediators were evaluated.
- Moderate evidence was found for cognitive mediators in depression and anxiety.
- Moderate evidence was found for negative thinking in depression for adults.

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ABSTRACT

Although efforts have been undertaken to determine how psychological interventions exert their effects, research on mediators and mechanisms of change remains limited, especially in the field of prevention. We aimed to assess available evidence on mediators of psychological and psychoeducational interventions for the prevention of depression and anxiety in varied populations. A systematic review using PubMed, PsycINFO, Web of Science, Embase, OpenGrey, and the Cochrane Central Register of Controlled Trials was performed. Two independent reviewers assessed the eligibility criteria of all articles, extracted data, determined the risk of bias in randomized controlled trials, and the requirements for mediators. The outcomes were mediators of the incidence of depression or anxiety and/or the reduction of symptoms of depression or anxiety. We identified 28 nested mediator studies within randomized controlled trials involving 7442 participants. Potential cognitive, behavioral, emotional and interpersonal mediators were evaluated in different psychological and psychoeducational interventions to prevent depression and anxiety. The effects were mediated mainly by cognitive variables, which were the most commonly assessed factors. For depression, the mediator with the strongest empirical support was negative thinking in adults. Cognitive change is an important mediator in preventive psychological and psychoeducational interventions for both anxiety and depression.

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1. Introduction

1.1. The importance of the prevention of depression and anxiety

According to the Global Burden of Disease Study, 322 and 264 million people worldwide suffered from depression and anxiety, respectively in 2015. This is an increase of 18.4% and 14.9% over the 2005 figures (Vos et al., 2016). The disease burden attributable to depression and anxiety, measured in years lived with disability (YLD), increased by 17.8% and 14.8%, respectively, between 2005 and 2015 (Kassebaum et al., 2016). Treatments for depression and anxiety are often not provided adequately (Fernández et al., 2007). Even if it were possible to provide appropriate treatments to all persons affected by a depressive or anxiety disorder, the effect on disease burden would be limited because of the steady influx of new cases; therefore, treatments alone are not sufficient to eliminate the disease burden attributable to these disorders (Andrews, Issakidis, Sanderson, Corry, & Lapsley, 2004). Accordingly, the prevention of depression and anxiety has emerged as a complementary strategy to treatment.

The onset of depression and anxiety is influenced by a wide range of biological, psychological and social factors that occur in different stages of people's lives (King et al., 2008; Moreno-Peral et al., 2014; Sajjadi et al., 2013; World Health Organization, 2004). Some of them, such as loneliness and alcohol misuse, are modifiable risk and protective factors; therefore, they can be changed (World Health Organization, 2004). The identification of these factors is necessary for the development of appropriate preventive strategies (Jacka et al., 2013).These preventive strategies have been found to strengthen protective factors (e.g. problem solving skills, self-esteem or social support), to reduce risk factors (e.g. loneliness, family conflicts or stressful life events), to reduce symptom severity at prodromal stages, to improve physical and mental health, and to generate social and economic benefits (Saxena, Janeé-Llopis, & Hosman, 2006).

The most used preventive interventions have been psychological and psychoeducational (Conejo-Cerón et al., 2017; Moreno-Peral et al., 2017; van Zoonen et al., 2014; Werner-Seidler, Perry, Calear, Newby, & Christensen, 2017). Psychological interventions are aimed at modifying behaviors, cognitions and emotions through different types of psychotherapeutic techniques, while psychoeducational interventions provide information and support to better understand and cope with these illnesses through conferences, videos, lectures or fact sheets (Merry et al., 2011). However, it is complicated to differentiate between these two types of interventions since they share common mechanisms of action. The community approaches to prevent depression and anxiety have comprised three types of interventions which are universal, selective and indicated. Universal prevention strategies target the entire population, regardless of risk factors; selective strategies are applied to individuals or subgroups of the general population with identified risk factors; and indicated prevention interventions are centered on individuals who are experiencing sub-clinical symptoms but without meeting the diagnostic criteria for a full-blown diagnosis (Mrazek & Haggerty, 1994; Muñoz, Cuijpers, Smit, Barrera, & Leykin, 2010).

1.2. Effectiveness of interventions to prevent depression and anxiety

Many randomized controlled trials (RCTs) have been conducted to investigate the effectiveness of psychological or psychoeducational interventions for the prevention of depression and anxiety in all types of populations, and there are sufficient systematic reviews and meta-analyses on this subject (e.g. Bellón et al., 2015; Conejo-Cerón et al., 2017; Cuijpers, Karyotaki, Reijnders, & Huibers, 2018; De Silva et al., 2009; Hetrick, Cox, Witt, Bir, & Merry, 2016; van Zoonen et al., 2014). These interventions are effective, but the effect sizes range from small to moderate. Most preventive programs targeted children, adolescents and high-risk populations and delivered cognitive behavioral approaches provided by mental health specialists (Bellón et al., 2015;Moreno-Peral et al., 2017; van Zoonen et al., 2014). To date, there is no conclusive evidence demonstrating the superiority of any particular intervention (Moreno-Peral et al., 2017; van Zoonen et al., 2014).

1.3. Reason for studying mediators in psychological and psychoeducational preventive interventions

The challenge today is not only to develop and test new preventive interventions with greater effect sizes, but also to understand and improve existing interventions in order to optimize their effectiveness. Research into mediators focuses on establishing the mechanisms through which an intervention leads to its effect. Identification of the factors that account for the effects of therapy enables refinement of existing therapies and the use of the most effective components of therapy with the aim of increasing the effectiveness of the interventions (Kazdin & Nock, 2003). It is important to discriminate between mediators and mechanisms of change. According to Kazdin (2007), a mediator is a construct that shows important statistical relations between an intervention and an outcome, mechanism of change reflects the steps or processes through which the intervention produces the change and explains how the intervention translates into events that lead to the outcome. A mediator is a construct that shows important statistical relations between an intervention and an outcome. The study of mediators is the way mechanisms (which are often very difficult to assess themselves) can be operationalized in research.

1.4. Requirements for a mediator

Baron and Kenny (1986) developed the most used and influential causal step methods to determine statistical mediation (MacKinnon, Fairchild, & Fritz, 2007a). According to this method, four conditions should be satisfied in order to establish a mediator: 1) the independent variable (treatment) must be significantly associated with the dependent variable; 2) the treatment and the mediator must be related; 3) the mediator and the dependent variable must be associated once the effect of the treatment is controlled; and 4) the relationship between the treatment and the outcome must be significantly reduced when the effect of the mediator is controlled.

Regardless of its influence, this method presents some limitations which have already been pointed out (MacKinnon, Fritz, Williams, & Lockwood, 2007b). There are many cases where significant mediation exists but the requirement of a significant association between treatment and outcome is not obtained, especially in the field of psychology. This absence of association could be due to the existence of non-identified suppressing or mode-rating variables that are altering that relationship or that different mediator variables are producing opposite effects (MacKinnon, Krull, & Lockwood, 2000). Kraemer, Wilson, Fairburn, Argas, and H. (2002) pointed out that this first requirement from Baron & Kenny can be overlooked as long as there is an interaction between treatment and the mediator. In addition, the requirement of the association between treatment and outcome substantially reduces the power to detect mediation. This problem of sample size also occurs with the test to demonstrate the reduction of the effect of the treatment after controlling by the mediator. Resampling methods (Preacher & Hayes, 2004) and other newer approaches (MacKinnon, Fritz, et al., 2007b) address such sampling problems. They are also likely to be more accurate than traditional mediation analysis according to Baron & Kenny (MacKinnon, Fairchild, & Fritz, 2007a). Other limitations appear when multiple mediators are hypothesized, which is common in prevention programs (Silverstein et al., 2018). The single mediator model proposed by Baron & Kenny does not address more than one mediator. MacKinnon, Lockwood, Hoffman, West, and Sheets (2002) presented several standard error formulas for comparing different mediated effects and other advances have been performed in the multiple mediators model (Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001; Kraemer et al., 2002; MacKinnon, Lockwood, & Williams, 2004; Preacher & Hayes, 2004). Many studies measure data clustered at several levels, such as at the individual level in schools or health centers. Attending to this cluster effect provides more accurate estimates than traditional mediation analysis, such as the Baron and Kenny (1986) method. To address this issue, multilevel mediation models have been developed by authors such as Bauer, Preacher, and Gil (2006) and Muthén and Muthén (1998). Furthermore, mediation according to Kazdin requires temporal precedence from treatment to mediation to outcome, whereas Baron & Kenny's model assumes the causal relationship a priori and uses theory regarding mediational processes. Models such as latent-growth modeling (LGM) (Muthén & Curran, 1997; Singer & Willett, 2003) and latent difference score (LDS) (Ferrer & McArdle, 2003; McArdle, 2001; McArdle & Nesselroade, 2003) can be used to analyze longitudinal mediation data.

In psychological research, Kazdin & Nock, 2003, Kazdin, 2007) described seven requirements for a factor to be established as a mediator. The first and the most basic requirement is the demonstration of a strong association which means an observed relation should be found between the intervention, the proposed mediator and the therapeutic change expressed by statistical significance ($p < .05$). The second is the *specificity* of the association, which means that the mediator is specific for a particular type of therapy. The third is *consistency*. A mediator is consistent when it is found and replicated across studies, samples and conditions. *Experimental manipulation*, the fourth requirement, refers to direct manipulation of the mediator through an experiment. The fifth is the *temporal relation*, which means the mediator should precede the outcome in time. *Gradient* is the sixth requirement and pertains to dose-response relationship, in which greater activation of the mediator is associated with greater change in the outcome. Finally, the seventh requirement concerns a plausible or *coherent explanation* of how a mediator exerts its effect, in such a way that it can be integrated into previous scientific knowledge. Compliance with these requirements should enhance the strength of evidence, mainly, the requirements of strong association, specificity and temporal relation according to Kazdin and Nock (2003).

1.5. Research on mediators in treatment and prevention of depression and anxiety

Different types of mediators through which psychological interventions exert their clinical effects have been identified. In treatment for depression (Gu, Strauss, Bond, & Cavanagh, 2015; Lemmens, Müller, Arntz, & Huibers, 2016; van der Velden et al., 2015) and anxiety (Powers, de Kleine, & Smits, 2017; Smits, Julian, Rosenfield, & Powers, 2012), systematic reviews have been carried out with the aim of providing a global view of the mechanisms of changes or mediators involved in the process of therapeutic change. Most of these systematic reviews have been performed in adult populations. However, it is possible that some mediators are unique to specific populations, such as children and adolescents. Some mediators identified in these systematic reviews were rumination and worries (Lemmens et al., 2016; van der Velden et al., 2015), threat reappraisal (Smits et al., 2012), fear of extinction (Powers et al., 2017) and positive and negative affect (van der Velden et al., 2015).

Lemmens et al. (2017) explored models of the direct and indirect effects of psychotherapy (cognitive and interpersonal) on depression severity through five potential mediators. Candidate mediators included both therapy-specific as well as common factors and were the following: dysfunctional beliefs, interpersonal functioning, rumination, self-esteem and therapeutic alliance. These models of change received little empirical support.

However, in the case of prevention, the therapeutic target is different. In treatment, it is necessary to address dysfunctional thoughts and behaviors, but in the case of prevention (especially in universal prevention), it is possible that the mechanisms by which the change occurs are more associated with strengthening, improving or training positive aspects in order to face determinants or predispositions of depression (Cuijpers, Shields-Zeeman, Walters, & Petrea, 2016).

In the prevention of depression and anxiety, research on mediators of psychological and psychoeducational interventions continues to be much more limited, although some mediators have been identified, such as reducing negative thinking, ruminations and worries, or increasing self-efficacy (Allart-van Dam, Hosman, Hoogduin, & Schaap, 2007; Meulenbeek, Spinhoven, Smit, Van Balkom, & Cuijpers, 2010; Topper, Emmelkamp, Watkins, & Ehring, 2017). To our knowledge, there are no systematic reviews of mediators of psychological and/or psychoeducational interventions to prevent depression and/or anxiety that have differentiated mediators by type and by population (children/adolescents and adults).

1.6. Aim of the current systematic review

The aim of the current review was to identify the mediators of psychological and/or psychoeducational interventions for the prevention of depression and anxiety in varied populations. We also sought to assess the quality of the studies and the global scientific evidence following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2. Methods and analysis

This systematic review is in accordance with PRISMA guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). The study protocol has been registered in the International Prospective Register of Systematic Reviews (registration number: CRD42018092393).

2.1. Search procedures

A literature search was conducted in five major bibliographic databases: MEDLINE (via PubMed), PsycINFO, Embase, Web of Science (WOS) and the Cochrane Central Register of Controlled Trials (CENTRAL). In order to identify grey literature, we consulted OpenGrey Repository (System for Information on Grey Literature in Europe). The electronic searches were carried out from inception up to July 10, 2019. We manually checked the reference list of retrieved articles and existing systematic reviews on this topic to find additional publications. In addition, experts in the field were consulted to suggest relevant articles.

Two of the authors (PMP and SCC) independently conducted the database searches.

The search was built by combining terms indicative of depression, anxiety, psychological/educational preventive interventions, mediators, moderators, and RCTs. We only included the word 'mediation' in the search strategy with the aim to be more inclusive, to generate a broader search and to obtain a large number of studies. Then, we manually revised the studies in order to cheek if they had used mediation analysis and not only 'talks about' mediation. A detailed description of the search strategy for each database can be found in Appendix A.

2.2. Eligibility criteria and study selection

We exclusively included RCTs because they are not only considered a reference standard for clinical trials (Piantadosi, 2005) but can also be valuable in revealing mediators of therapeutic change (Kraemer et al., 2002). Studies had to examine the psychological mediators and, in addition, they had to conduct statistical mediation analyses (Baron & Kenny, 1986 or more advanced methods). We focused on psychological and psychoeducational preventive interventions excluding trials that implemented pharmacological or physical interventions (e.g. physical activity or exercise). Psychoeducational interventions provide psychological information through videos, lectures or fact sheets, and psychological interventions (psychotherapy) attempt to modify different aspects of the person using a variety of strategies including individual, group or computerized interventions. The comparators allowed were active treatments, care-as-usual, no intervention, a waiting list for intervention, or attention control. In order to be able to distinguish preventive interventions from treatments, in selected and indicated intervention studies, participants were excluded if they had a diagnosis of depression or anxiety through standardized interviews (e.g., Structured Clinical Interview for DSM Disorders), through validated self-reports with standard cut-off points (e.g., Beck Depression Inventory-II; Beck Anxiety Inventory-II), or diagnosis by a mental health specialist in selected and indicated intervention studies. In universal prevention, participants were included without ruling out baseline depression or anxiety because the requirement for excluding individuals with full-blown disorders would undermine the inherent nature of these study designs. We excluded those trials aimed at people with a previous diagnosis of depression or anxiety (the prevention of recurrence or relapse). There were no other restrictions on the characteristics of the participants. Participants could be recruited in any setting. All languages were considered.

The full study selection process was carried out independently by two reviewers (SCC and PMP). After removing duplicate studies, all records were reviewed and those that did not meet the inclusion criteria based on the title or abstract were removed. Studies selected as potentially relevant were reviewed in full text for further assessment. Any disagreements between the reviewers were resolved by discussion.

2.3. Data extraction

Data were independently extracted by two reviewers (SCC and PMP) using a purposefully designed data extraction form. Discrepancies between the reviewers were resolved by discussion among the team members. If necessary study information was missing, the reviewers contacted the authors to attempt to obtain it. The following data were extracted: author(s), year of publication, country, target population, study setting, type of prevention (universal, selected or indicated), exclusion criteria at baseline (only in studies of selective or indicated prevention), inclusion criteria, sample size (control and intervention), experimental conditions, orientation and intervention type, provider (who implemented the intervention), outcomes and follow-up time.

2.4. Assessing methodological quality

In this systematic review, two separate methods were used to assess quality. One was designed to assess the overall quality of the RCTs through the Cochrane Collaboration's tool to assess risk of bias (Higgins & Green, 2011), and the other used the most relevant criteria of requirements to assess the quality of the mediation studies according to Kazdin and Nock (2003) and Lemmens et al. (2016).

The Cochrane Collaboration's tool to assess risk of bias (Higgins & Green, 2011), assessed the methodological quality of the RCTs through six criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. Because in psychological and psychoeducational interventions it is not generally possible to blind participants or staff, we considered this criterion "not applicable". Each of these criteria was rated as 'high', 'low', or 'unclear'. In order to account for the risk of bias, a score was assigned to each of the criteria, so that 'high' was given 2 points, 'unclear' 1 point and 'low' 0 points. Therefore, we classified the RCTs as having a low risk of bias if the total score of the criteria was less than or equal to 4; moderate risk of bias if the total score was 5 or 6; and high risk of bias if the total score was more than or equal to 7. All assessments of trial quality were performed independently by two reviewers (SCC and PMP). Any discrepancies were resolved by discussion.

To evaluate the strength of the mediation studies, we used the most relevant criteria proposed by Kazdin (Kazdin, 2007; Kazdin & Nock, 2003) and previously described: *specificity* (which refers to the crucial role of the proposed mediator in a concrete intervention) and *temporal relation* (change in the mediator should precede change in the outcome). Strong association (as expressed by statistical significance of $p < .05$) was not considered to reflect the methodological quality of the studies. Rather, we used it to ascertain whether or not there was an association between variables. In line with Lemmens et al. (2016), we also evaluated whether multiple mediators had been examined since they recommend including several mediators to examine rival hypotheses, test alternative explanatory models and map out interactions between theorized processes. Each study was evaluated as meeting (+) or not meeting (−) each of these criteria. Both the risk of bias and the

Table 1
Methodological quality.

	Requirements				
		3/3	**2/3**	**1/3**	**0/3**
Risk of bias	**Low**	Good	Satisfactory	Satisfactory	Satisfactory
	Moderate	Satisfactory	Satisfactory	Satisfactory	Satisfactory
	High	Satisfactory	Unsatisfactory	Unsatisfactory	Unsatisfactory

quality assessment for mediation was conducted by two of the authors. Any disparities were discussed with the reviewers enabling full agreement on criteria.

If the total score for the risk of bias in an RCT was low and the mediation study met three out of three requirements, the study was classified as having 'good quality'. We classified studies as of 'satisfactory quality' when the risk of bias was moderate or high and the mediation study met three out of three requirements or the risk of bias was low and the mediation study met less than three out of three requirements or the risk of bias was moderate and the mediation study met less than three out of three requirements. Finally, a study was considered to have 'unsatisfactory' quality when the risk of bias was high and the mediation study met less than three out of three requirements. The strong association requirement proposed by Kazdin was assessed through statistical significance ($p < .05$) (see Table 1).

2.5. Levels of scientific evidence

To be able to draw a narrative conclusion of findings we used an adaptation of the Best Evidence Synthesis Rating System (BESRS) which is a system used by other reviews carried out in this field (Gu et al., 2015; Singh, Mulder, Twisk, Van Mechelen, & Chinapaw, 2008; Van Stralen et al., 2011). This rating system considers the number of studies that evaluated the same mediator (in at least three studies), the statistically significant association criteria (strong association requirement) for mediation and the methodological quality of each of the studies (good/ satisfactory/ unsatisfactory). Thus, we classified the scientific evidence into three levels: (a) *strong evidence* (at least 65% of the potential mediators are significantly associated with change across at least three RCTs with the quality between good and satisfactory); (b) *moderate evidence* (at least 65% of the potential mediators are statistically significant across at least three RCTs with the quality mixed between good, satisfactory and unsatisfactory); and (c) *insufficient evidence* (< 65% of the potential mediators are statistically significant or at least three independent studies have not been identified, or at least 65% of the potential mediators are statistically significant across at least three RCTs but all of them had unsatisfactory quality). The 65% threshold was chosen to establish a slightly stronger criterion than merely 50% of the studies (see Fig. 1). Therefore, we based our system to obtain the levels of scientific evidence on counting the number of significant results, weighting the quality of the studies, that is, gives greater value to those studies of higher quality.

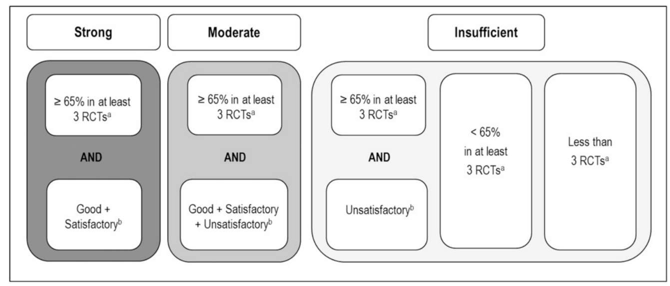

Fig. 1. Scheme about levels of scientific evidence.

3. Results

3.1. Search results

As a result of the search strategies, we obtained 8656 records. After eliminating the duplicates, a total of 6657 abstracts were reviewed. Of these, 451 articles were included for full-text review, and 28 mediation studies, reported in 26 RCTs, met our inclusion criteria (Fig. 2).

3.2. Characteristics of included studies

The characteristics of the 28 mediation studies are shown in detail in Table 1-Appendix B. Seventeen studies were published on the prevention of depression, five on the prevention of anxiety disorders and six on both. Indicated prevention was evaluated in 12 RCTs, universal prevention was evaluated in nine and selective prevention in the remaining five. A total of 7442 subjects were enrolled in all of the RCTs, the sample sizes ranged from 55 to 697 ($Me = 230.5$). Ages ranged between 6 and 90 years, 10 studies included adults, 11 included children or adolescents, three were performed in young adults, and two in older adults. Settings in these studies included 15 schools or universities, seven communities, four medical clinics, and one primary care clinic. Interventions were based on the principle of cognitive behavioral therapy (CBT) in 16 RCTs, whereas 10 RCTs were based on other types of interventions (five integrated different orientations, one for acceptance and commitment therapy (ACT), one for interpersonal therapy (IPT), one for behavioral, one for mindfulness and another for pure cognitive therapy). Interventions were delivered in group format in 15

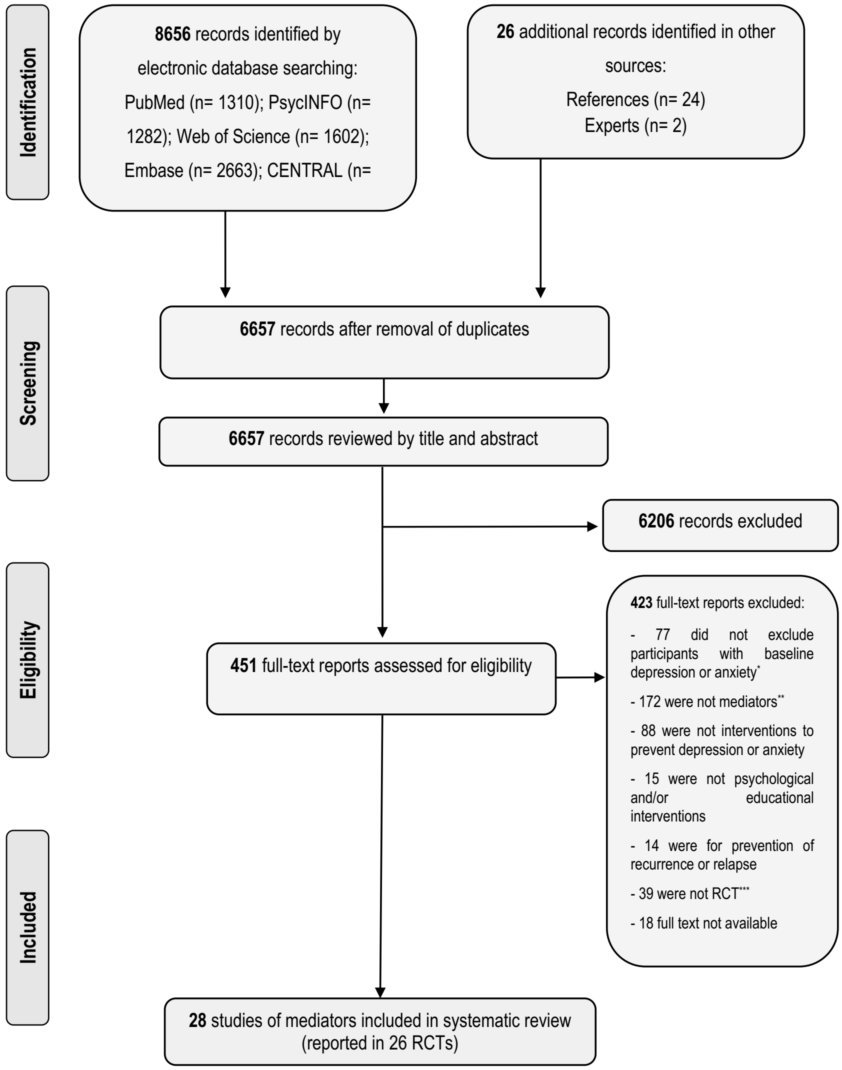

Fig. 2. PRISMA Flowchart of the studies reviewed and included.

RCTs, in individual format in five RCTs, and in combined group and individual format in five RCTs. Two RCTs included interventions with a guided computerized self-help format. Interventions were delivered by a mental health specialist in 19 RCTs, by teachers in two RCTs, by teachers and mental health specialists in one RCT and by other professionals in four RCTs. The number of sessions ranged from 4 to 12 (*Me* = 8), in two studies the number of sessions was not available. The comparator care-as-usual was used in nine RCTs, seven had no intervention, six used a waiting list and the rest used an active control. Follow-up periods ranged from one week to 10 years (*Me* = 10.5 months). The duration of follow-up exceeded 12 months in five RCTs.

3.3. Mediators identified

The identified RCTs examined 63 potential mediators (Table 2 and Fig. 3). Specifically, we found 12 potential mediators tested for both depression and anxiety, 34 were evaluated exclusively for depression (identified in 20 studies) and 18 exclusively for anxiety (identified in eight studies). Given the high number of studies that examined interventions based on CBT, the majority of the mediators evaluated mainly referred to this type of orientation. The mediators were classified by type of population (adults and children/adolescents) and into four categories: cognitive, behavioral, emotional and interpersonal mediators. In order to facilitate comprehension, Box 1 presents the definitions of some of the identified mediators in the present systematic review.

Table 2
Characteristics, results and meeting requirements of the 28 mediation studies.

Study characteristics and results					Requirements[e]			Methodological quality[f]
Authors	Interventions[a]	Statitical Method[b]	Potential Mediador(s) & Results (strong association)[c]	RCT Risk of bias[d]	Specificity	Multiple Mediators	Temporality (≥ 2 ass.)	
Depression								
Adults								
Allart-Van Dam et al. (2003)	1. Coping with depression course 2. No intervention, advice	Baron and Kenny (1986)	↓ Negative thoughts (+) ↑ Frequency of social support (−) ↑ Pleasant activities (−) ↑ Social skills (−) ↑ Self-esteem (+)	Moderate (6: uuhuul)	−	+	−	Satisfactory
Allart-van Dam et al. (2007)	1. Coping with depression course 2. No intervention, advice	Baron and Kenny (1986)	↓ Negative thoughts (+) ↑ Pleasant activities (−) ↑ Social skills (−) ↑ Self-esteem (−)	Moderate (6: uuhuul)	−	+	−	Satisfactory
Fledderus et al. (2013)	1. ACT intervention with minimal and extensive email support 2. Waiting-list	Preacher and Hayes (2004)	↑ Psychological flexibility (+)	Moderate (6: luhhlu)	−	−	+	Satisfactory
Li et al. (2014)	1. STrAtegies for RelaTives (START) intervention 2. TAU	MacKinnon et al. (2000) Muller et al., (2005)	↑ Emotion-focused coping (+)	Low (3: llhull)	−	−	−	Satisfactory
Muñoz et al. (1995)	1. CBT 2. No intervention or information by videotape	Baron and Kenny (1986)	↓ Negative thoughts (+) ↑ Positive thoughts (+) Pleasant activities (−) Social activities (−)	Moderate (6: uuhulu)	−	+	−	Satisfactory
Rovner et al. (2014)	1. Behavior activation + low vision rehabilitation 2. Supportive therapy + low vision rehabilitation	SEM	Social impairment (+)	Low (4: llhllu)	−	−	−	Satisfactory
Seligman et al. (1999)	1. Workshop 2. No intervention	Sobel (1982)	Explanatory style (+) Dysfunctional attitudes (+) Self-esteem (−) Hopelessness (+)	Low (2: llhlll)	−	+	+	Satisfactory
Seligman et al. (2007)	1. Classroom based workshop; web-based materials, coach e-mails and face-to-face-boosters 2. Control group	Sobel (1982)	Optimistic explanatory style (+)	High (7: uuhuuu)	−	−	−	Unsatisfactory
Silverstein et al. (2018)	1. Problem-solving education 2. Usual Head Start services	Muthén and Muthén (2016)	Problem-solving skills (−) Mastery (−) Self-esteem (−) ↓ Perceived stress (+) Behavioral activation (−) Avoidant coping (−) Problem focused coping (−) Social coping (−)	Low (2: llhlll)	−	+	−	Satisfactory

(continued on next page)

Table 2 (*continued*)

Study characteristics and results					Requirements[e]			Methodological quality[f]
Authors	Interventions[a]	Statitical Method[b]	Potential Mediador(s) & Results (strong association)[c]	RCT Risk of bias[d]	Specificity	Multiple Mediators	Temporality (≥ 2 ass.)	
Thompson et al. (2015)	1. UPLIFT intervention 2. Waiting list	SME DWLS	Knowledge/skills (+) Self efficacy (−) Self compassion (−) Physical and mental health qualities of life (−) Satisfaction with life (+)	High (7: uuhlhu)	−	+	−	Unsatisfactory
Westerhof et al. (2010)	1. Life review intervention 'Looking for Meaning' 2. Educational video movie	Preacher and Hayes (2004)	Personal meaning (+)	High (7: uuhhlu)	−	−	−	Unsatisfactory
Children and adolescents								
Brunwasser et al. (2018)	1. Penn Resiliency Program 2. Penn Enhancement Program placebo 3. No intervention control	Muthén & Muthén, 1998Preacher and Hayes (2004)	Explanatory style (+)	High (7: lhhuhl)	−	−	−	Unsatisfactory
David et al. (2018)	1. Therapeutic videogame (*RET*hink) 2. Rational Emotive Behavior Education (REBE) group intervention 3. Waiting list	Hayes (2013)	Irrational beliefs (+) Dysfunctional thoughts (−)	Moderate (5: llhhul)	−	+	−	Satisfactory
Duong et al. (2016)	1. Positive Thoughts and Actions 2. Active control group	MacKinnon, Fairchild, and Fritz (2007a)	↑ Parent-child communication (−) ↑ Health behavior (−) ↓ Attitudes toward school (−)	Moderate (6: llhhhl)	−	+	−	Satisfactory
Fosco et al. (2016)	1. The Family Check-Up 2. CAU	Fosco et al. (2014)	↓ Family conflict (+)	High (7: uuhuuu)	−	−	−	Unsatisfactory
Horowitz et al. (2007)	1. Cognitive-behavioral 2. Interpersonal Psychotherapy 3. No intervention	Sobel (1982) MacKinnon et al. (1993,1995,2002)	Attributional style (CB: partially; IPT-AST:-) Coping (−) Conflict (−) Knowledge checks (CB: -; IPT-AST: partially)	Moderate (5: luhluu)	+	+	−	Satisfactory
Pössel et al. (2005)	1. Training the Ease of Handling Social Aspects in Everyday Life – LISA 2. Control group	Baron and Kenny (1986)	Dysfunctional thoughts (−) Network size (−) Frequency of the use of the network (−)	High (8: lhhhhl)	−	+	−	Unsatisfactory
Stice et al. (2010)	1. CB intervention 2. Supportive-expressive group 3. Bibliotherapy 4. No intervention	Stice et al. (2010)	Negative cognitions (−) Pleasant activities (−) Emotional expression (−) Loneliness (−)	Low (3: llhllu)	+	+	+	Good

(*continued on next page*)

Table 2 (*continued*)

Study characteristics and results					Requirements[e]			Methodological quality[f]
Authors	Interventions[a]	Statitical Method[b]	Potential Mediador(s) & Results (strong association)[c]	RCT Risk of bias[d]	Specificity	Multiple Mediators	Temporality (≥ 2 ass.)	
Topper et al. (2017)	1. Rumination-focused CBT group version 2. Rumination-focused CBT internet version 3. Waiting list	Hayes (2009) MacKinnon (2008) Muthén & Muthén (2007)	↓ Worry and rumination (+)	Moderate (5: llhhlu)	−	−	−	Satisfactory
Trudeau et al. (2016)	1. LifeSkills Training and Strengthening Families Program: For Parents and Youth 2. LifeSkills Training 3. Control condition	SEM Muthén & Muthén, 1998, 2010)	Relationship problems age 21 (+) Illicit use of substances age 21 (+)	Moderate (6: luhuuu)	−	+	−	Satisfactory
Van der Gucht et al. (2018)	1. School-based mindfulness program 2. No intervention	MacKinnon & Luecken (2008) Bauer et al. (2006)	Cognitive reactivity (+) Self-compassion: Self-coldness (+) Self-kindness (−)	High (7: llhhhu)	−	+	−	Unsatisfactory
Vuijk et al. (2007)	1. Good Behavior Game intervention 2. Control condition	SEM Muthén & Muthén, 1998, (2006)	↓ Relational victimization (+) ↓ Physical victimization (−)	High (7: uuhuuu)	−	+	−	Unsatisfactory
Yang et al. (2015)	1. Attention Bias Modification training 2. Placebo 3. Control condition	Preacher and Hayes (2004) MacKinnon et al. (2007)	Change of attention bias (−) Rumination (+)	Low (4: luluuu)	−	−	−	Satisfactory
ANXIETY **Adults**								
Fledderus et al. (2013)	1. ACT intervention with minimal and extensive email support 2. Waiting-list	Preacher & Hayes (2008)	↑ Psychological flexibility (+)	Moderate (6: luhhlu)	−	−	+	Satisfactory
Li et al. (2014)	1. STrAtegies for RelaTives (START) intervention 2. TAU	MacKinnon et al. (2002) Muller et al., (2005)	Emotion-focused coping (+)	Low (3: llhull)	−	−	−	Satisfactory
Meulenbeek et al. (2010)	1. 'Don't Panic' course 2. Waiting list	Baron and Kenny (1986) Preacher & Hayes (2008) MacKinnon et al. (2007) Finkel (1995) Spinhoven et al. (2007)	Perceived likelihood of panic occurrence (+) Perceived negative consequences of panic occurrence (−) Perceived self-efficacy in coping with panic (+) Locus of control (−)	Low (3: llhull)	−	+	−	Satisfactory
Seligman et al. (1999)	1. Workshop 2. No intervention	Sobel (1982)	Explanatory style (−) Dysfunctional attitudes (+) Self-esteem (−) Hopelessness (−)	Low (2: llhlll)	−	+	+	Satisfactory

(*continued on next page*)

Table 2 (*continued*)

Study characteristics and results					Requirements[e]			Methodological quality[f]
Authors	Interventions[a]	Statitical Method[b]	Potential Mediador(s) & Results (strong association)[c]	RCT Risk of bias[d]	Specificity	Multiple Mediators	Temporality (≥ 2 ass.)	
Zoellner et al. (2011)	1. Brief Cognitive Behavior Therapy 2. Supportive Counseling 3. Assessment conditions	Kraemer et al. (2002) Hofmann (2004)	Changes in perceptions of self (B-CBT = +; SC = −) Changes in perceptions of one's safety (B-CBT = +; SC = -)	Moderate (6: uuhluu)	+	+	−	Satisfactory
Children and adolescents								
Casline et al. (2018)	1. Coping and Promoting Strength intervention 2. Information-monitoring condition	Goldstein (2011) Selig & Preacher (2009)	↓ Reinforcement of dependence (+)	Moderate (6: luhhlu)	−	−	−	Satisfactory
Essau et al. (2012)	1. FRIENDS program 2. Waiting list	PRODCLIN MacKinnon et al. (2007)	Perfectionism (+) Coping strategies: Assistance seeking (−) Problem solving (−) Cognitive avoidance (+) Behavioral avoidance (+)	High (8: uuhuhu)	−	+	−	Unsatisfactory
Ginsburg et al. (2015)	1. Coping and Promoting Strength intervention 2. Information-monitoring condition	Kraemer et al. (2002)	Parental global distress (+) Parental modeling of anxiety (+) Parental anxiety (−) Child maladaptive cognitions (−)	Moderate (6: luhhlu)	−	+	−	Satisfactory
Topper et al. (2017)	1. Rumination-focused CBT group version 2. Rumination-focused CBT internet version 3. Waiting list	Hayes (2009) MacKinnon (2008) Muthén & Muthén (2007)	↓ Worry and rumination (+)	Moderate (5: llhhlu)	−	−	−	Satisfactory
Van der Gucht et al. (2018)	1. School-based mindfulness program 2. No intervention	MacKinnon & Luecken (2008) Bauer et al. (2006)	Cognitive reactivity (+) Self-compassion: Self-coldness (+) Self-kindness (−)	High (7: llhhhu)	−	+	−	Unsatisfactory
Vuijk et al. (2007)	1. Good Behavior Game intervention 2. Control condition	SEM Muthén & Muthén, 1998, (2006)	↓ Relational victimization (+) ↓ Physical victimization (−)	High (7: uuhuuu)	−	+	−	Unsatisfactory

[a] ACT: Acceptance and Commitment Therapy; TAU: Treatment as Usual; CBT: Cognitive Behavioral Therapy; CAU: Care as Usual; CB: Cognitive Behavioral.
[b] SEM: Structural Equation Models; DWLS: Diagonally Weighted Least Squares.
[c] CB: Cognitive Behavioral; IPT-AST: Interpersonal Psychotherapy- Adolescent Skills Training; B-CBT: Brief Cognitive Behavioral Therapy; SC: Supportive Counseling; (+): statistically significant association; (−): statistically non-significant association.
[d] Risk of bias: High score means higher risk of bias: low risk (l) = 0 points, unclear risk (u) = 1 point, high risk (h) = 2 points; indicate rating of six quality criteria: random sequence; allocation concealment; blinding of participants and providers; blinding of outcome assessment; incomplete outcome data; selective reporting.
[e] (+) = Present/Yes; (−) = Absent/No.
[f] Good: if the total score for the risk of bias in an RCT is low and the study meets three out of three requirements; Satisfactory: if the total score for the risk of bias in an RCT is moderate or high and the study meets three out of three requirements or the risk of bias is low and the mediation study meets less than three out of three requirements or the risk of bias is moderate and the study meets less than three out of three requirements; Unsatisfactory: if the total score for the risk of bias in an RCT is high and the study meets less than three out of three requirements.

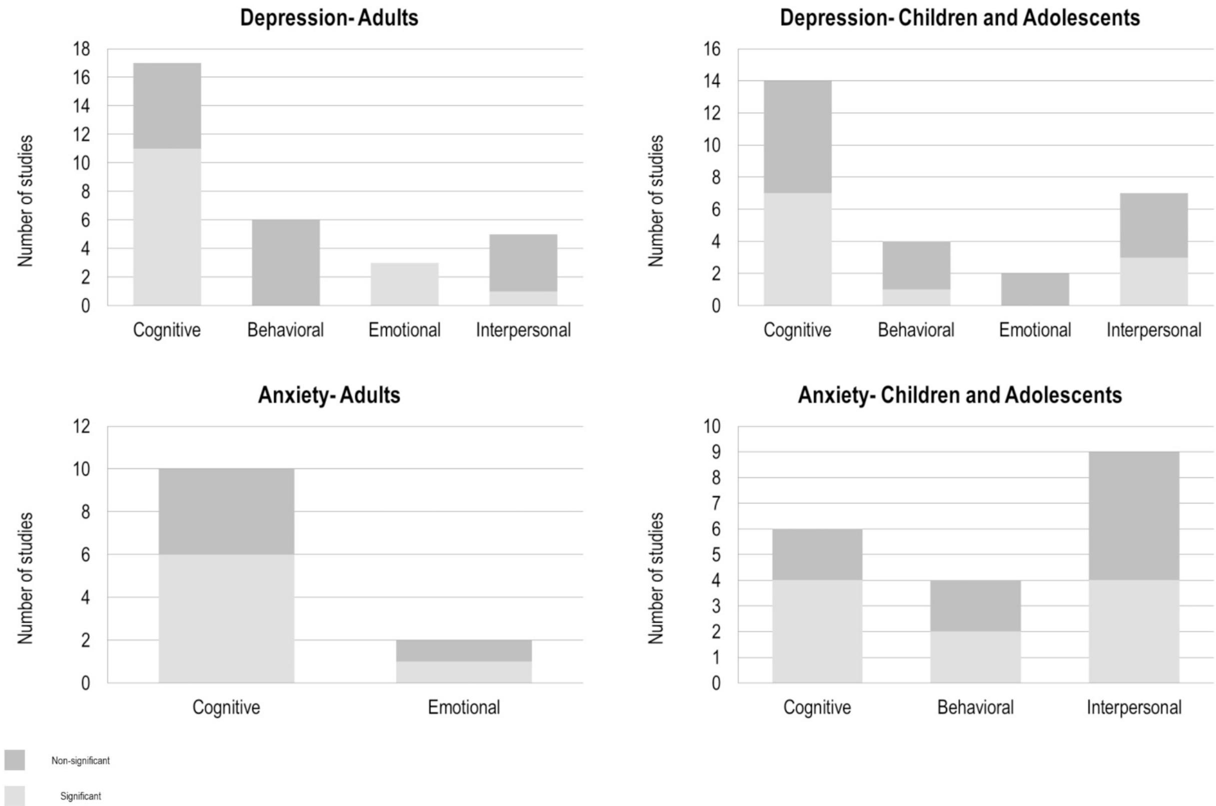

Fig. 3. Mediators identified by group of age and by pathology.

Box 1
. Definitions of some of the mediators included.

Mediator	Definition
Cognitive	
Attributional style	Attribution process that people do about particular events. Some individuals exhibit a general tendency to attribute negative events to internal, stable, global factors and to view these events as very important whereas other individuals do not.
Attention bias	Tendency for people's perception to direct the attention, selectively, toward the processing of the material that has content congruent with the state of mind.
Explanatory style (optimistic)	The way in which people routinely explain events, either positive or negative, in their lives. An optimistic explanatory style is characterized by the attribution of problems to rare, specific and external causes. This style is also associated with higher levels of motivation, achievement, and physical well-being and lower levels of depressive symptoms.
Locus of control	Perception of degree to which people believe that they have control over their lives.
Mastery	Degree to which people perceive themselves as experts of their lives.
Personal meaning	Cognitive and motivational process of making sense out of experience and discovering a purpose in life.
Psychological flexibility	Competence that includes how a person: (1) adapts to fluctuating situational demands, (2) reconfigures mental resources, (3) shifts perspective, and (4) balances competing desires, needs, and life domains.
Self-compassion	Psychological aspect that implies treating oneself with kindness, being understanding and mindful when considering negative aspects of oneself.
Behavioral	
Avoidant coping	Strategies oriented to the effort to avoid dealing with a stressor.
Behavioral activation	Strategies aimed at initiating behaviors as well as healthy behaviors.
Behavioral avoidance	Behavioral coping strategies to avoid dealing with specific problems.
Cognitive avoidance	Cognitive coping strategies to avoid dealing with specific problems.
Coping	Behavioral and/or cognitive strategies oriented at managing specific situational demands which are appraised as taxing or exceeding one's ability to adapt.
Problem focus coping	Strategies aimed at changing, alleviating or eliminating the source of the stress.
Problem solving	Proactive strategies to find solutions to problems encountered in life.
Emotional	
Emotion focused coping	Strategies oriented toward managing the emotions that accompany the perception of stressful events.
Interpersonal	
Physical victimization	Specific form of victimization consisting of being the victim of physically aggressive acts or threats.
Relational victimization	Specific form of victimization consisting of being the target of people's attempts to harm or control their relationship with others, e.g. hostile rumor or being excluded.
Social coping	Strategies oriented toward seeking social support from others.
Social impairment	Condition in which a person has difficulties in relating to other people.

3.4. Depression

3.4.1. Cognitive mediators

We identified 12 potential cognitive mediators based on adult populations in eight different studies. Six of them evaluated indicated prevention programs and the remaining two evaluated selective prevention programs. In seven studies, the intervention was based on cognitive-behavioral (CB) orientation and one study used ACT. *Explanatory style* (Seligman, Schulman, DeRubeis, & Hollon, 1999), *optimistic explanatory style* (Seligman, Schulman, & Tryon, 2007), *positive thoughts* (Muñoz et al., 1995), *perceived stress* (Silverstein et al., 2018), *personal meaning* (Westerhof, Bohlmeijer, van Beljouw, & Pot, 2010) and *knowledge and skills* (Thompson et al., 2015) were all found to be associated with change in depressive symptomatology although three were classified as having satisfactory quality and the other three as having unsatisfactory quality. *Negative thinking* (referring to dysfunctional attitudes, dysfunctional thoughts, negative cognitions, maladaptive cognitions or cognitive reactivity) was evaluated in three studies that had satisfactory quality (Allart-van Dam et al., 2007; Allart-Van Dam, Hosman, & Hoogduin, 2003; Muñoz et al., 1995; Seligman et al., 1999) and in all of them, these cognitions mediated the effect. The study by Fledderus, Bohlmeijer, Fox, Schreurs, & Spinhoven, 2013classified as having satisfactory quality, found that *psychological flexibility* was a variable through which ACT exerted its effects. *Self-esteem* was found to be associated with change at post-intervention (Allart-Van Dam et al., 2003) but not in the follow-up of the same study that was classified as having satisfactory quality (Allart-van Dam et al., 2007). Two other studies with satisfactory quality also found no significant association for mediation (Seligman et al., 1999; Silverstein et al., 2018). *Self-efficacy*, *self-compassion, physical and mental health quality of life* (Thompson et al., 2015) and *mastery* (Silverstein et al., 2018) were not found to be associated with change.

Regarding children and adolescents, we identified ten potential cognitive mediators in nine different studies. Universal prevention programs were evaluated in five studies, indicated in three and selective in one. In six studies, the intervention was based on CB, one study used an exclusively cognitive intervention (Yang, Ding, Dai, Peng, & Zhang, 2015), one study used a mindfulness program (Van der Gucht, Takano, Raes, & Kuppens, 2018) and in one study CBT and IPT were used (Horowitz, Garber, Ciesla, Young, & Mufson, 2007). *Attributional style*, measured in the study by Horowitz et al. (2007), which was of satisfactory quality, was partially associated with change in the CB intervention but did not satisfy the criteria for mediation in the IPT intervention. Conversely, in the same study, *knowledge checks* were associated with a decrease in depressive symptomatology in the IPT intervention but did not satisfy the criteria for mediation in the CB intervention. *Attitudes toward school* (Duong et al., 2016), *change of attention bias* (Yang et al., 2015) and *explanatory style* (Brunwasser, Freres, & Gillham, 2018) were found not to be associated with change in depressive symptomatology, with one potential mediator in each study. In the same way, *negative thinking* was evaluated in four studies and in none of them, except in one with unsatisfactory quality (Van der Gucht et al., 2018), the mediation effect was found (David, Cardoș, & Matu, 2018; Pössel, Baldus, Horn, Groen, & Hautzinger, 2005; Stice, Rohde, Seeley, & Gau, 2010). *Irrational beliefs* (David et al., 2018) and *worry* and *rumination* (Topper et al., 2017; Yang et al., 2015), were found to be significantly associated with change in studies that had satisfactory quality. Van der Gucht et al. (2018) assessed the construct of *self-compassion*, which was composed of *self-coldness* and *self-kindness*. Only *self-coldness* proved to be related to change.

3.4.2. Behavioral mediators

Five potential behavioral mediators were identified in three different studies that evaluated CB interventions in adult populations. Two out of three employed indicated preventive interventions and the remaining one employed a selective preventive intervention. None of the studies classified as having satisfactory quality found that *avoidant coping, behavioral activation, problem focus coping, problem solving* (Silverstein et al., 2018) and *pleasant activities* (Allart-Van Dam et al., 2003; Allart-van Dam et al., 2007; Muñoz et al., 1995) satisfied the criteria for mediation.

Four potential behavioral mediators were assessed in four different studies in child and adolescent populations. Two studies focused on universal prevention programs and the other two focused on indicative prevention programs. Neither *health behavior* (Duong et al., 2016) nor *pleasant activities* (Stice et al., 2010) were found to be associated with change in CB interventions in these studies with satisfactory and good quality, respectively. *Coping* (Horowitz et al., 2007) was not related to change in either IPT or CBT. Trudeau et al. (2016) found that the *use of illicit substances* at 21 years of age mediated the effect of CB interventions. This study was rated as having satisfactory quality.

3.4.3. Emotional mediators

In adult populations, three potential emotional mediators were evaluated in three different studies which evaluated a CB intervention. Two of the studies used selective prevention strategies and one used an indicated prevention strategy. Both *hopelessness* (Seligman et al., 1999) and *satisfaction with life* (Thompson et al., 2015) were mediators of the effect of the interventions. *Emotion focused coping* (Li et al., 2014) was associated with change in a study classified as having satisfactory quality in which the outcome was both depression and anxiety together (measured with HADS-T).

Regarding child and adolescent populations, two potential emotional mediators were assessed in a study that used an indicated prevention program and evaluated a CB intervention. Stice et al. (2010) found that neither *emotional expression* nor *loneliness* was related to change in depressive symptomatology. This study was rated as having good quality.

3.4.4. Interpersonal mediators

We identified five potential interpersonal mediators assessed in four different studies that evaluated CB interventions in adult populations. Three studies evaluated indicated prevention programs and one evaluated a selective prevention program. It was found that frequency of *social support* (Allart-van Dam et al., 2003), use of the *network* (Muñoz et al., 1995), *social skills* (Allart-van Dam et al., 2003; Allart-van Dam et al., 2007) and *social coping* (Silverstein et al., 2018) were not mediators of change. With respect to *social impairment*, Rovner et al. (2014) found a significant association with change. All these studies had satisfactory quality.

We identified six potential interpersonal mediators assessed in six different studies in children and adolescents. Universal prevention programs were used in five studies and an indicated prevention program was used in one study. Five RCTs evaluated CB interventions and one assessed both CBT and IPT interventions. Variables concerning interpersonal conflicts and problems were significantly related to change in CB interventions in two different studies. Specifically, these mediators were *family conflicts* (Fosco, Van Ryzin, Connell, & Stormshak, 2016) and *relationship problems* (Trudeau et al., 2016). However, in another study rated as having satisfactory quality, *interpersonal conflicts* (Horowitz et al., 2007) did not mediate change in either CBT or IPT. The use of the *network* and its size were evaluated in one RCT (Pössel et al., 2005), but were not associated with change in CB interventions. *Parent-child communication* was not related to change in one study (Duong et al., 2016). Another study that was classified as having unsatisfactory quality (Vuijk, van Lier, Crijnen, & Huizink, 2007) evaluated *relational* and *physical victimization*. The first study mediated the effect of the intervention; however, the second was not associated with change.

3.5. Anxiety

3.5.1. Cognitive mediators

In adult populations, we identified 10 potential cognitive mediators in four different studies. Three evaluated indicative prevention programs and the fourth a selective prevention program. The interventions assessed in these studies were CB orientation, supportive counseling, and ACT. While changes in *negative thinking* (referring to dysfunctional attitudes) were related to changes in anxious symptomatology, conversely, *self-esteem* and *explanatory style* were not related to changes in a study that had satisfactory quality (Seligman et al., 1999). Regarding perceiving processes, Meulenbeek et al. (2010) found that *perceived likelihood of panic occurrence* and *perceived self-efficacy in coping with panic* mediated the effect of a CB intervention in the prevention of panic disorder. However, in the same study, *perceived negative consequences of panic occurrence* and *locus of control* was not related to change (Meulenbeek et al., 2010). In the study by Zoellner, Feeny, Eftekhari, and Foa (2011), which was assessed as having satisfactory quality, *perceptions of self* and *perceptions of one's safety* were related to changes in CB orientation, but the changes were not related to *supportive counseling* (Zoellner et al., 2011). Another cognitive mediator was *psychological flexibility*, which was significantly associated with the effect in one study with satisfactory quality where an intervention based on ACT was used (Fledderus et al., 2013).

In children and adolescents, four studies that used two universal programs and two selective programs, evaluated four different potential mediators. *Negative thinking* (maladaptive cognitions and cognitive reactivity) was not associated with the effect of the intervention in one study with satisfactory methodological quality (Ginsburg, Drake, Tein, Teetsel, & Riddle, 2015); however, it was found to be significantly associated with change in another study that was classified as having unsatisfactory quality (Van der Gucht et al., 2018). *Worry* and *rumination* satisfied the criteria for mediation in one study with satisfactory quality (Topper et al., 2017). With respect to the construct *self-compassion*, Van der Gucht et al. (2018) found that *self-coldness* was related to changes in a mindfulness program, but the changes were not related to *self-kindness*. Finally, *perfectionism* was related to change in one study with unsatisfactory quality where a CB intervention was used (Essau, Conradt, Sasagawa, & Ollendick, 2012).

3.5.2. Emotional mediators

Two potential emotional mediators in two different RCTs performed in adult populations were evaluated in this category. Both RCTs tested selective programs. The first, *hopelessness* (Seligman et al., 1999), was not related to change in a CB intervention to prevent anxiety. The second was *emotion focused coping* (Li et al., 2014), and it satisfied the criteria for mediation in a study with satisfactory quality in which the outcome jointly evaluated depression and anxiety.

We did not find emotional mediators for children and adolescents.

3.5.3. Behavioral mediators

In adult populations, we did not identify behavioral mediators.

With respect to child and adolescent populations, one universal preventive study used a CB orientation to evaluate coping strategies. Coping strategies referred to *assistance seeking, problem solving, cognitive avoidance* and *behavioral avoidance*. Cognitive and behavioral avoidance were significantly associated with change and the other two were not in a study rated as having unsatisfactory methodological quality (Essau et al., 2012).

3.5.4. Interpersonal mediators

We did not find interpersonal mediators in adults.

In children and adolescents, nine potential interpersonal mediators were identified in four different RCTs to prevent anxiety with CB interventions. Of these prevention programs, two were universal and two were selective. *Parental global distress*, *parentalmodelinganxiety* and *parental anxiety* were evaluated in the study by Ginsburg et al. (2015), which had satisfactory quality. The first two were related to changes; however, parental anxiety did not satisfy the criteria for mediation. Parental satisfaction evaluated in another study (Essau et al., 2012) was also not associated with change. Vuijk et al. (2007) found that *relational victimization* mediated the effect of the intervention; however, *physical victimization* was not associated with change in anxious symptomatology. Reinforcement of dependence did not mediate the effect of the intervention in the study by Casline et al. (2018). Finally, *social and adaptive functioning* and *social skills* were also evaluated in the study by Essau et al. (2012). None of these variables were associated with change.

3.6. Methodological quality

The Cochrane risk of bias (Higgins & Green, 2011) for each RCT is reported in Appendix B. Seven RCTs had a low risk of bias, 10 had a moderate risk, and nine had a high risk.

Requirements for mediators are shown in Table 3. More than half (64.3%) of the mediation studies evaluated multiple potential mediators; 10.7% of the mediation studies met the specificity aspect and 10.7% also assessed temporality. The requirement regarding the statistically significant association criteria for mediation is shown in Table 2, in Appendix C and in Appendix D.

Concerning the total number of requirements met by each mediation study, nine studies did not meet any criteria, 15 studies fulfilled one out of three, three studies fulfilled two out of three and only one study met three out of three. An overview can be found in Fig. 4.

The methodological quality of a study was estimated by combining the risk of bias of the RCT and the number of requirement met in the mediation study. The majority of studies (n = 18, 64.3%) had satisfactory methodological quality, nine studies (32.1%) obtained an unsatisfactory score and one (3.6%) presented good methodological quality (Fig. 5).

3.7. Global evidence (levels of scientific evidence)

The information about levels of scientific evidence can be found in Table 4 and in more detail in Appendix C and in Appendix D. According to our adaptation of BESRS, cognitive variables constituted moderate evidence as mediators both for depression in adults and for anxiety in children and adolescents. More specifically, negative thinking was moderately related to the effect of psychological interventions in preventing depression in adults, but not anxiety.

Behavioral factors did not seem to constitute evidence as a mediator for depression. In adults, six studies evaluated five different mediators and none were related to change. In children and adolescents, behavioral mediators were evaluated in four studies, with the use of illicit substances being the only one related to effect, in one study. With respect to anxiety, potential behavioral mediators were not studied in adults. In children and adolescents, four potential mediators were evaluated, and two of them, behavioral avoidance and cognitive avoidance, showed a significant association.

The three emotional mediators, emotion focused coping, hopelessness and satisfaction with life, evaluated for preventing depression in adults were significantly associated with change. However, neither of the two emotional mediators evaluated in children and adolescents was

Table 3
Number (%) of studies meeting requirements for process research.

Requirement	n studies (%)
Specificity (yes)	3 (10.7)
Multiple mediators, (yes)	18 (64.3)
Temporality (≥ 2 assessment) (yes)	3 (10.7)

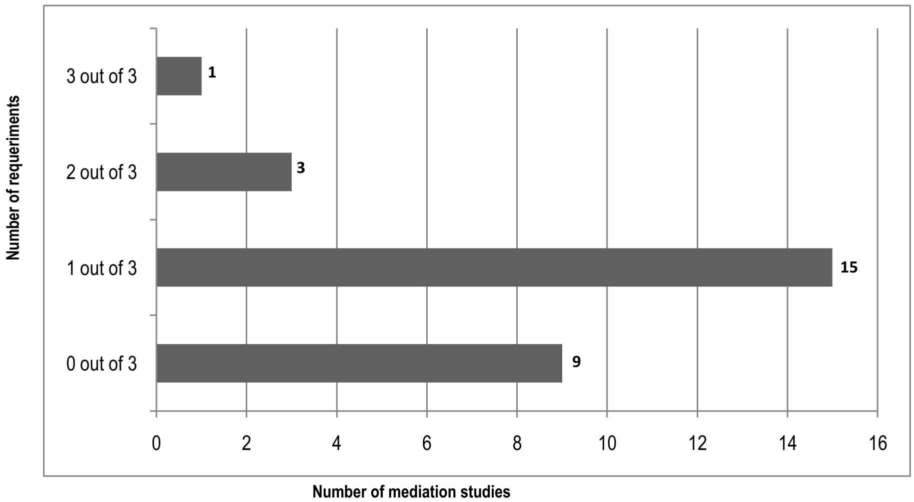

Fig. 4. Requirements: number of mediation studies per number of requirements met.

found to be a mediator for depression. Regarding anxiety, one of the two emotional mediators evaluated was related to change in adults and, therefore, failed to show evidence; in children and adolescents, no potential emotional mediators were found.

Interpersonal mediators showed insufficient evidence both for depression and for anxiety in all population types. Specifically, we found no interpersonal mediators for anxiety in the adult populations.

4. Discussion

4.1. Main findings

Through a systematic review, we selected 26 RCTs with mediator analyses for the prevention of depression and/or anxiety including 7442 people from seven different countries on three continents. The selected studies examined a total of 63 potential mediators in six different types of interventions. Potential cognitive, behavioral, emotional and interpersonal mediators were evaluated in different populations and in various interventions to prevent depression and anxiety. Cognitive mediators were the most frequently assessed potential mediators for both depression and anxiety. Within cognitive mediators, negative thinking for depression was the most commonly assessed. In general, we found insufficient evidence for all categories of potential mediators with the exception of cognitive. Cognitive mediators showed moderate evidence for both depression (in adults) and anxiety (in children and adolescents). Moreover, negative thoughts constituted a mediator demonstrating moderate evidence of psychological and psychoeducational interventions to prevent depression in adults. Emotional mediators also showed moderate evidence for depression in adults; however, this result was based on just three studies. Only one study presented good methodological quality and it did not find evidence for mediation. Most of the studies performed in adult populations

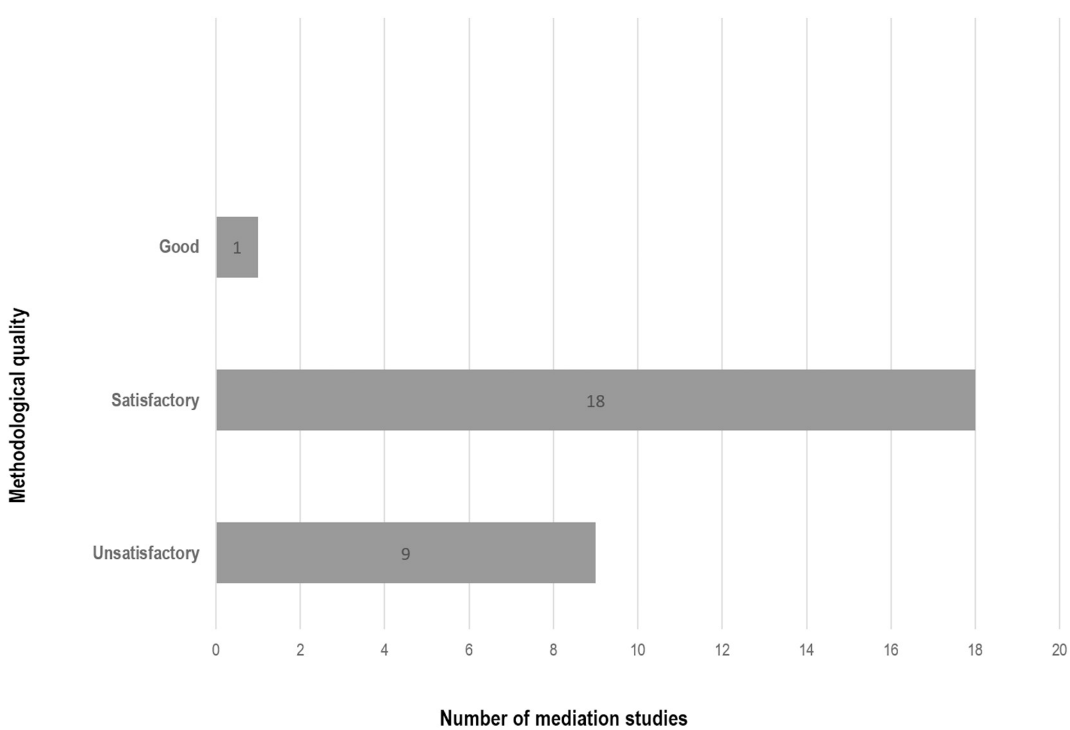

Fig. 5. Methodological quality of each of the mediation studies.

Table 4
Global evidence of the type of potential mediators identified for depression and anxiety.

Depression	Examined (studies[*])	Significant studies			Global evidence[d]
Adults		Good[a]	Satisfactory[b]	Unsatisfactory[c]	
Cognitive	12 (17)	–	8	3	Moderate
Behavioral	5 (6)	–	–	–	Insufficient
Emotional	3 (3)	–	2	1	Moderate
Interpersonal	5 (5)	–	1	–	Insufficient
Children and adolescents					
Cognitive	10 (14 studies/16 comparisons)	–	5	2	Insufficient
Behavioral	4 (4)	–	1	–	Insufficient
Emotional	2 (2)	–	–	–	Insufficient
Interpersonal	6 (8)	–	1	2	Insufficient
Anxiety					
Adults					
Cognitive	10 (10)	–	5	1	Insufficient
Emotional	2 (2)	–	1	–	Insufficient
Children and adolescents					
Cognitive	5 (6)	–	1	3	Moderate
Behavioral	4 (4)	–	–	2	Insufficient
Interpersonal	9 (9)	–	3	1	Insufficient

[*] Studies which evaluated more than one potential mediator in the same category were counted more than once.
[a] Good: if the total score for the risk of bias in an RCT was low and the study met three out of three requirements.
[b] Satisfactory: if the total score for the risk of bias in an RCT was moderate or high and the study met three out of three requirements or the risk of bias is low and the mediation study meets less than three out of three requirements or the risk of bias was moderate and the study met less than three out of three requirements.
[c] Unsatisfactory: if the total score for the risk of bias in an RCT was high and the study met less than three out of three requirements.
[d] Strong: at least 65% of the potential mediators were statistically significant across at least three RCTs with the quality between good and satisfactory; Moderate: at least 65% of the potential mediators were statistically significant across at least three RCTs with the quality mixed between good, satisfactory and unsatisfactory; Insufficient: < 65% of the potential mediators were statistically significant or at least three independent studies have not been identified or at least 65% of the potential mediators were statistically significant across at least three RCT but all of them had unsatisfactory quality.

examined indicative prevention programs while in children and adolescents the most used prevention programs were universal programs.

4.2. Strengths

To the best of our knowledge, this is the first systematic review of mediators of psychological interventions to prevent depression and/or anxiety. We included a reasonable number of RCTs in which mediator analyses were employed, representing a large population with different characteristics and from diverse settings. This systematic review involved a large number of potential mediators for depression and anxiety and different types of psychological and psychoeducational interventions. We used multiple electronic databases and complemented our search with hand searching. The search terms used were wide enough for the search to have adequate sensitivity. The selection of studies, evaluation of the risk of bias and requirement for mediators and extraction of data from trials were performed by two reviewers who resolved any discrepancies by discussion. In addition, we only selected RCTs as these designs provide the strongest evidence of causality.

4.3. Limitations

Several limitations should be considered. Results should be interpreted with caution given the relatively small number of studies per potential mediator. Only negative thinking has been evaluated in more than four independent studies and only for depression. This hampered a meta-analytical approach. Ideally, a meta-analysis of individual participant data could provide greater precision since this would increase power. Consequently, additional studies assessing the same potential mediators are needed.

This qualitative synthesis is based on the count of significant results and we are aware that this measure is highly influenced by sample size. Regarding this issue, we could not establish the factors that showed evidence of lack of mediation. RCTs are mostly underpowered for secondary outcomes, such as mediator analysis. Therefore, the lack of statistical association could just as easily be related to a problem of sample size as to a lack of association.

Although most of the RCTs ranged from having a low to moderate risk of bias, nine out of 26 RCTs had a high risk of bias. Only one RCT had a low risk of bias and met three out of three requirements for mediators, and therefore classified as having 'good methodological quality' (Stice et al., 2010). Some important methodological differences between studies were found. In the study by Stice et al. (2010), the authors reported that negative cognitions and increased pleasant activities predicted change in a CBT intervention. In addition, the intervention effect became weaker when controlling for these potential mediators. However, due to the requirement of temporality being met, an observed change in depression appeared before a change in the mediator. Therefore, Stice et al. (2010) concluded that neither variable mediated the intervention effects. This highlights the importance of fulfilling the requirements in order to strengthen the evidence.

Our selection of quality criteria might have influenced our findings since both the selection of the criteria and their combination were arbitrary. Regarding the requirements for the mediators considered, although these are based on the most relevant criteria proposed by Kazdin (Kazdin, 2007; Kazdin & Nock, 2003) and Lemmens et al., 2016, are based on both methodological quality and obtained outcomes; the latter, specifically, for the specificity requirement. Our general definition of quality criteria was potentially very demanding, negatively affecting our results.

In general, the studies used modern statistical methods. However, some earlier studies included classical analyses such as that of Baron and Kenny (1986) and the Sobel test (1982), which are less sophisticated and present the above-mentioned limitations. The type of analysis used has an impact on the outcome and should therefore be taken into account.

The established categories for classifying mediators are not mutually exclusive. It is difficult to separate cognitive, behavioral, and emotional variables. For example, some potential interpersonal mediators could also be cognitive, behavioral or emotional variables.

The degree of evidence found was weak for most categories, and we did not find strong evidence in any of the categories. These results may have been influenced by some of the aspects previously mentioned. Perhaps our required criteria for meeting strong evidence were too demanding. It could be that it is difficult to find an RCT with a low risk of bias that satisfies all the requirements to assess the quality of the mediation study and, in addition, obtains a statistically significant association between the intervention, the mediator and the therapeutic change (strong association). Moreover, obtaining a strong association, as stated above, is highly influenced by sample size.

4.4. Comparison with previous results

Other systematic reviews on mediators in psychological interventions for depression and anxiety report similar results (Gu et al., 2015; Lemmens et al., 2016; Powers et al., 2017; Smits et al., 2012; van der Velden et al., 2015). Cognitive, behavioral, emotional, and interpersonal mediators have been found in other reviews. However, these reviews have been carried out for treatment and not for prevention.

Regarding cognitive mediators, previous reviews found similar results, showing greater evidence for cognitive variables, specifically, negative thinking. A recent systematic review (Lemmens et al., 2016) on mediators in psychotherapy for depression identified that negative thoughts, dysfunctional attitudes, ruminations, worries and mindfulness skills, were associated with changes in depressive symptomatology. Other reviews of mediation studies for treatment of depression with mindfulness (Gu et al., 2015; van der Velden et al., 2015) found rumination, worry or meta-awareness to be associated with the effect of the intervention. With regard to anxiety, threat reappraisal (Smits et al., 2012) has been one of the most studied cognitive variables. In our systematic review, we were unable to identify studies that evaluated this potential mediator. The explanation for this may be that in our systematic review the focus was prevention not treatment. Powers et al., 2017 also found threat reappraisal to be responsible for anxiety symptom improvement with CBT. Furthermore, the authors identified another mediator: fear of extinction, in this case, a behavioral mediator. We obtained insufficient evidence to explain how therapies work through potential behavioral mediators for depression or anxiety in children and adolescents. In adults, these mediators have scarcely been studied, which could be due to the existing overlap between potential cognitive and behavioral mediators.

Concerning emotional mediators, a systematic review of the treatment of depression found that positive and negative affect might play a role in how mindfulness-based cognitive therapy works (van der Velden et al., 2015). The role of the emotional mediator in our review was controversial and was dependent on the population and the disorders. More specifically, this type of mediator reported moderate evidence only for depression in adults.

Potential interpersonal mediators were only studied in children and adolescents in the case of anxiety. The explanation for this could be that in anxiety disorders the relationship with other people and especially with family is a very important factor in children and adolescents. In the case of depression, however, interpersonal factors were assessed in both adults and children/adolescents, showing insufficient evidence.

The results were similar when comparing the potential mediators for depression and anxiety. Nevertheless, more cognitive factors were identified for depression, such as negative thoughts, which have shown moderate evidence in interventions to prevent depression only in adults. Cristea et al. (2015) performed a meta-analysis of the effects of CBT on dysfunctional thinking in adults with depression. The finding of this study showed a strong association between the effects on dysfunctional thinking and those on depression. According to the authors, this result can be interpreted as confirmation that cognitive change is indeed a mediator (a specific factor in symptom change) as well as supporting the idea that dysfunctional thoughts are simply another depression symptom that changes with the intervention; since the authors had no way of assessing temporal precedence (dysfunctional thoughts and depressive symptoms were assessed at the same point in time). Negative thoughts have also been studied in children and adolescents, (although to a lesser extent); however, they have not been associated with change in depressive symptomatology. Perhaps in children and adolescents, psychological and/or psychoeducational interventions do not exert their preventive effect through change in thoughts. It is possible that work with thoughts is a more complex task in this population.

4.5. Practical implications and future research

Understanding the mechanisms through which psychological interventions achieve success in preventing depression and anxiety is essential. Indeed, without knowing what leads to therapeutic change, it is difficult to identify strategies to optimize clinical outcomes (Kazdin, 2007). Better clinical outcomes are a challenge in psychological interventions, both in treatment and in prevention. However, in prevention, from the perspective of public health, small effects could have a high impact, thereby improving quality of life and reducing costs as long as preventive programs can be scalable, reaching a large population. This could be attained through different strategies such as extensive school, workplace or primary care programs or information and communication technologies.

Progress has been made in the identification of mediators and mechanisms of change in psychological interventions and in the development of methodologies for this type of research, creating a theoretical basis for design requirements to establish mediation (Kazdin, 2007). As a result, studies increasingly meet more requirements and are methodologically more correct. Although studies have progressively paid more attention to the consensus of these requirements (temporalization, sample size, the inclusion of multiple possible mediators, etc.), it is still difficult to find studies that specifically consider the requirements of temporality and manipulability. Consequently, studies with better designs are required to increase the strength of the evidence. Most notably, the evaluation of temporality and the use of longitudinal mediation models will allow us to clarify the mediational processes in the prevention of depression and anxiety. An important topic for future research is the development of causal inference models, methods to combine qualitative as well as quantitative information about meditational processes, to clarify mediation relations (MacKinnon, Fairchild, & Fritz, 2007a). In addition, compliance with standardized methodological protocols for this type of research would make it possible to standardize research and facilitate comparison between studies. With a sufficient number of studies per evaluated mediator, this would also allow individual participant data meta-analysis to be carried out. In line with this, examination of multiple mediators within the same study through the multiple-mediator model (MacKinnon, 2000) is needed in order to discover which processes are truly important. To achieve this, the multiple-mediator model has been shown to be an accurate way (MacKinnon et al., 2000).

Discovering *how* psychological interventions actually work remains a challenge and mediation analyses are merely a first step. Demonstrating causality is difficult even in studies designed to explain therapeutic change in terms of causal process, as changes are not gradual, linear, unicausal, or unifactorial. It is even more difficult to explain the entire process by which an intervention achieves its effect. Psychological interventions are complex and multidimensional, involving the interaction of various types of mechanisms (Lemmens et al., 2016). In addition, it is plausible that psychological and psychoeducational interventions work differently depending on the particular characteristics of each individual. Research on moderators of effects is necessary and complementary knowledge that should be considered in order to further understanding of how psychological and psychoeducational interventions, in general, and psychotherapy, in particular, exert their effect (Huibers & Cuijpers, 2015; Lorenzo-Luaces, German, & DeRubeis, 2015).

The potential mediators evaluated correspond mainly to the theoretical model of the most studied interventions (CBT). When designing an intervention, the specific mechanisms of the intervention that can contribute to the effect must be taken into account. However, given that to date no single intervention for the treatment or for the prevention of depression or anxiety has been proven to be superior to another, it would be reasonable to assume that a series of common factors might also be responsible for clinical changes. It would thus be appropriate to examine how the same mediators work in different interventions and to deepen the analysis of specific and non-specific factors, with the aim of identifying and establishing common factors that can contribute to and improve the effectiveness of the interventions.

In the case of prevention, it is possible that psychological and psychoeducational interventions are more non-specific. For example, in universal prevention, the strategy may focus more on strengthening or improving aspects of the person than on addressing specific symptomatology. Bearing this in mind, it is possible that the factors common to the different interventions have a greater influence on prevention than on treatment. Nonetheless, it is not currently known whether the factors that bring about change in psychotherapy are specific, non-specific, or both (Cuijpers, Reijnders, & Huibers, 2019).

5. Conclusions

Cognitive factors in particular have been considered as potential mediators, which explains why most of the evidence was found in this area. Cognitive mediators provided the strongest evidence for both depression and anxiety and, specifically, negative thoughts for depression in adults. However, there is great heterogeneity among the studies regarding the mediators evaluated, methodology and study quality. Accordingly, more homogeneous research with improved designs is needed to further assess causal relationships. Advances in this knowledge will aid in the development of more effective and cost-effective interventions.

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Contributors

PMP, JAB, MJHH and SCC designed the study and the other authors collaborated on the design. PMP, JAB, MJHH, JMM, LJGL, ST, ARM, FB, CMDS and SCC acquired, analyzed and interpreted the data. PMP and SCC drafted the manuscript and JAB, MJHH, JMM, LJGL, ST, ARM, FB and CMDS conducted a critical revision of the manuscript for important intellectual content. All authors discussed and approved the final version. PMP and SCC are the guarantors.

Ethics

As this systematic review is based on published data, approval from the local ethics committee was not required.

Declaration of Competing Interest

The authors all declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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