

HIGHLIGHTS

- A systematic review of studies on moderators of preventive intervention effects on depression had not been performed to date.
- Twenty-seven studies assessing thirty-four potential moderators were included.
- Strong evidence was found that effectiveness increased in children of parents without depression.
- Moderate evidence was obtained of an indirect relationship between effectiveness and substance use.
- Moderate evidence was found that effectiveness increased as participant's age decreased.

ABSTRACT

Psychological and psychoeducational interventions have proven to be effective in preventing depression. However, the identification of the patients that benefit the most from each type of intervention has not yet been established. A systematic review was performed of the literature on moderators of preventive psychological and psychoeducational interventions for depression in all types of population. A search was performed on PubMed, PsycINFO, Web of Science, Embase, Cochrane Central Register of Controlled Trials and OpenGrey up to July 2019. Fulfillment of eligibility criteria, data collection, and study quality assessment were assessed by two independent researchers. Outcomes were moderators of the reduction of depressive symptoms or the incidence of depression. Twenty-seven moderator effect studies performed in 19 randomized controlled trials were included. Thirty-four potential sociodemographic, clinical, interpersonal, personality and life-event moderators were evaluated. Baseline depressive symptoms, gender, age, baseline parental depression and social support were the most frequently studied potential moderators. In interventions for children and adolescents, the moderator for which evidence was strongest was having parents free of depression at baseline. Psychological and psychoeducational interventions seem to be more effective in children and adolescents who exhibit a lower use of substances and whose parents do not have symptoms of depression at baseline. In adults, a lower age was associated with greater effects of preventive interventions.

Keywords: Moderator, Depression, Prevention, Systematic Review

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INTRODUCTION

Depression is a common mental disorder that affects over 300 million people in the world (WHO, 2017). It is estimated that more than 50 percent of people with depression also suffer from other mental and physical problems (Gabilondo et al., 2010; Winkler, Horáček, Weissová, Šustr, & Brunovský, 2015). Depressive disorders are strongly associated with a poorer quality of life (Guan, Cohen, Deng, & Chen, 2011), higher mortality (Cuijpers et al., 2014), which can be translated into a reduction in life expectancy of 14 years in men and 10 years in women (Laursen, Musliner, Benros, Vestergaard, & Munk-Olsen, 2016), and substantial economic costs (Gustavsson et al., 2011). The burden of disease in terms of years lived with disability attributable to major depression increased by 18 percent in the 2005-2015 period, ranking third in the world and in high-income countries (Kassebaum et al., 2016). Depression is expected to be the leading cause of disease burden in high-income countries by 2030 (Mathers, & Loncar, 2006).

The onset of depression is associated with different variables identified in the literature. These variables can be categorized into sociodemographic factors (such as gender, age, education level); clinical variables (such as worse physical and mental quality of life, depressive symptoms); personal and family history (such as lifetime depression, family history of psychological difficulties, childhood adversities) and psychosocial factors (such as experiences of discrimination, emotion regulation difficulties, dissatisfaction with living together at home) (Bellón et al., 2011; Ebert et al., 2019; King et al., 2008; Van Voorhees et al., 2008; Wang et al., 2014).

Several intervention modalities have been developed to cope with depression, including psychological and psychoeducational interventions. Psychological interventions are aimed to assist people to modify behaviors, cognitions, emotional states or feelings that cause them discomfort/distress (Campbell et al., 2013; Norcross 1990), while psychoeducational interventions provide informative materials about depression such as lectures, leaflets, emails or information websites. It is assumed that these two modalities share similar working mechanisms of action. There is considerable evidence supporting that psychological and psychoeducational interventions are effective in the treatment of depression (Cuijpers, Ebert, Acarturk, Andersson, & Cristea, 2016; Donker, Griffiths, Cuijpers, & Christensen, 2009). However, even when access to services, treatment coverage, and adherence to evidence-based treatments are satisfactory, it is estimated that the burden of depression can only be reduced by approximately one-third (Andrews, Issakidis, Sanderson, Corry, & Lapsley, 2004; Chisholm, Sanderson, Ayuso-Mateos & Saena, 2004). Hence, interest in prevention has grown in the last decades, as it emerges as a complementary strategy to reduce the disease burden of depression (Muñoz, Cuijpers, Smit, Barrera & Leykin 2010; Cuijpers, Beekman, & Reynolds 3rd, 2012). According to their target population, interventions can be classified as addressed to the entire population (universal prevention);

high-risk groups (selective prevention); and people with prodromal symptoms (indicated prevention) (Mrazek & Haggerty, 1994).

A large number of randomized controlled trials (RCTs) and meta-analyses have been performed to examine the effectiveness of a variety of psychological and psychoeducational interventions in preventing depression in different types of population (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). Although promising results have been obtained in these studies, the effectiveness of preventive interventions varied across individuals, and their effect sizes ranged from small to moderate. Preventive interventions reduce the incidence of depression by only 25 percent, as compared to control conditions (van Zoonen et al., 2014; Conejo-Cerón et al., 2017), and around 75 percent of patients do not experience significant improvements. Therefore, there is significant room for improvement in the field of psychological and psychoeducational interventions. [Efforts have been undertaken to elucidate the mechanisms through which preventive interventions obtain their effects. A systematic review of mediators in psychological and psychoeducational interventions for the prevention of depression revealed that the effectiveness of these interventions is mediated by cognitive variables, mainly negative thinking \(Moreno-Peral et al., 2020\).](#)

Outcomes in mental health [also](#) can be improved through personalized medicine (Simon & Perlis, 2010). The goal of personalized medicine is to identify the groups of patients who benefit the most from each type of intervention. The application of personalized medicine involves the identification of moderators that help choose the most appropriate prevention intervention for each patient, thereby leading to improved outcomes. Moderators indicate who will benefit from each intervention, who will not, and under what circumstances these interventions work or not (Kraemer, Wilson, Fairburn, & Agras, 2002; Frazier, Barron, & Tix, 2004). Moderators are qualitative (e.g. gender, ethnic group) or quantitative (e.g. level of symptomatology) variables that alter the direction and/or strength of the relation between independent and outcome variables (Baron & Kenny, 1986; Frazier et al., 2004). In psychological research, the use of moderating effect analyses is well-established, and moderating effects are related to interaction effects. Interaction between independent variables and moderators in analyses may reduce or increase effects on the dependent variable (Baron & Kenny, 1986). If the role of moderators of mental health interventions was clearly understood, individuals could be spared from receiving interventions that are inappropriate or even harmful to them (Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001).

In the last decade, interest in moderators has increased, and these variables are among the objectives of the National Institute of Mental Health (NIMH) strategic plan (Insel, 2009). As a result, many RCTs based on subgroup analyses have been conducted to assess a wide range of potential moderators in therapeutical interventions for depression (Gunlicks-Stoessel, Mufson, Jekal, & Turner, 2010; Huibers et al., 2015; Duong et al., 2016; Gau, Stice, Rohde, & Seeley, 2012).

Regarding the treatment of depression, there is evidence that some socio-demographic factors such as age (Donker et al., 2013) or ethnicity (Markowitz, Spielman, Sullivan, & Fishman, 2000), and clinical factors such as comorbidity (Young, Mufson, & Davies, 2006) moderate the effects of psychological treatments on patients with depression. These findings have been evaluated in systematic reviews (Bernecker, Coyne, Constantino, & Ravitz, 2017; Nilsen, Eisemann, & Kvernmo, 2013; Protogerou et al., 2015), a meta-analysis (Cuijpers et al., 2018) and in 'individual participant data' (IPD) meta-analysis (Cuijpers et al., 2014, Karyotaki et al., 2018).

However, the literature on the role of moderators in depression prevention is still limited. A variety of potential moderators has been investigated in several RCTs (Duong et al., 2016; Gau et al., 2012). Although the interest in exploring the moderator effects of psychological interventions is emerging through an IPD meta-analysis approach (Ebert, Buntrock, Reins, Zimmermann & Cuijpers, 2018), no systematic reviews have been performed to date to identify potential moderators of psychological and psychoeducational intervention effects in the prevention of depression. A review of the literature on moderators of psychological and psychoeducational interventions for the prevention of depression would help clinicians and researchers identify the subgroups of patients who benefit the most from each intervention in given circumstances. [In addition, it may provide a new body of research that will guide the development of new meta-analyses focused on more specific interventions and populations.](#)

The goal of the present study was to perform a systematic review of potential moderators of psychological and psychoeducational interventions for the prevention of depression in all types of populations.

METHODS

This systematic review was designed and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009). The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42018118248) and can be accessed at: www.crd.york.ac.uk/prospero/display_record.php?RecordID=118248.

Search strategies

A systematic literature search was conducted using the electronic databases PubMed, PsycINFO, EMBASE, CENTRAL (Cochrane Central Register of Controlled Trials), Web of Science (WOS) and Open Grey (System for Information on Grey Literature in Europe) from inception to July 29, 2019. Combinations of four search themes were used to search electronic databases. Themes covered the terms "depressive disorder", "prevention", "psychological-psychoeducative intervention", and "randomized controlled trial". The term "moderator" was not included in the search strategy, since this term is generally

not indexed or included in keywords or abstracts. The search strategy was initially developed for PubMed before being adapted for use in other electronic databases. There were no language or date restrictions. Databases were searched independently by two authors (SCC and PMP). Additional hand-searches were carried out of the references of the studies included, as well as, the reference lists of reviews on this topic. Experts in the field were also contacted to identify relevant publications. The full list of sources and search strategy are provided in Appendix A.

Eligibility criteria

Studies were eligible for inclusion if they fulfilled the following six criteria:

- Participants: All types of participants were eligible, excluding those who met diagnostic criteria for depression at baseline as determined by standardized interviews (e.g. Structured Clinical Interview for DSM Disorders), validated self-reports with standard cutoff points (e.g. Beck Depression Inventory), or diagnosed by a mental health professional. Studies that included focused exclusively on participants with a previous diagnosis of depression (prevention of recurrence or relapse) were also excluded. Studies that included participants with any other psychiatric disorder different from depression were included.
- Interventions: We focused on psychological and psychoeducational interventions since they share most of the mechanisms of action that induce changes in attitudes and behaviors. Face-to-face (individual and group) and internet-based (guided, unguided, psychoeducational websites) interventions were included. Studies focusing on physical or pharmacological interventions were excluded.
- Comparisons: Studies were included if the effects of psychological or psychoeducational interventions were compared to care as usual, no intervention, waiting list, or attention control (active control or placebo). Other types of comparators were excluded.
- Outcomes: We selected studies that examined the relationship between a moderator variable and primary prevention of depression. Preventive effects were determined through the reduction of symptoms or incidence of depression, as assessed by validated scales or standardized structured interviews. Studies were required to involve a moderating effect analysis through an interaction test (Kraemer et al., 2002). Any pretreatment moderator variable was accepted for inclusion.
- Design: Only studies based on randomized controlled trials (RCTs) were included.

Selection of studies

The selection process was performed by two independent authors (SCC and PMP). First, duplicate studies were eliminated, then titles and abstracts of the retrieved studies were screened; finally, the full texts of the remaining studies were evaluated for final inclusion. Disagreement was resolved by discussion. In cases of insufficient information, authors were contacted to clarify eligibility of studies.

Data extraction

Relevant data was extracted independently by two authors (SCC and PMP) who used a data extraction sheet designed for this systematic review. Authors were contacted for clarification, where appropriate. The following information was collected for each study: authors, year of publication, country, target population, study setting, type of prevention (universal, selected or indicated), baseline exclusion criteria, inclusion criteria, sample size (control and intervention), experimental conditions, orientation and intervention type, provider (who implemented the intervention), outcomes, follow-up time, potential moderators assessed and results of moderation effect analyses. Missing or unclear data was acquired by contacting the authors.

Due to our inclusion criteria were quite wide and we expected to obtain high heterogeneity across studies, a meta-analytical approach was not feasible and we performed a narrative review of the characteristics of the studies instead. ~~narrative review of the characteristics of the included studies was done.~~

Assessment of methodological quality

The methodological quality of the studies included was evaluated on the basis of the quality of the RCTs in general and the quality of moderation analyses. Methodological quality was assessed by two independent authors (SCC and PMP) and differences were resolved by consensus.

- Risk of bias

The quality of randomized controlled trials was examined using the Cochrane 'Risk of bias' assessment tool (Higgins & Green, 2011). The following domains were considered: sequence generation, allocation concealment, blinding of participants and personnel, blinding of evaluators of outcomes, incomplete outcome data and, finally, another source of bias, which refers to the availability of the trial protocol or registration. The risk of bias in each domain was categorized into low risk of bias, unclear risk of bias, and high risk of bias. In order to account for the risk of bias, a score was assigned to each criterion. Thus, a domain with 'high' risk of bias was given 2 points, 'unclear' was given 1 point, and 'low' was given 0 points. Therefore, a study was considered to have a low risk of bias if the total score was ≤ 4 ; a moderate risk of bias if the total score was 5 or 6; and a high risk of bias if the total score was ≥ 7 .

- **Quality of moderator analysis**

The quality of the moderating effect analysis performed in each study was evaluated using Pincus et al. (2011) criteria. This checklist is composed of five criteria that classify the level of evidence into three groups: confirmatory evidence, exploratory evidence, and insufficient evidence. The following factors were considered 1) use of an *a priori* hypothesis (when a moderating effect analysis was reported to have been planned *a priori*); 2) a theoretical or evidence-based selection of moderators (when a description of the theoretical background or evidence leading to the hypothesis was provided); 3) assessment of the moderator prior to randomization (when baseline measurements were reported to have been performed prior to randomization); and 4) adequate quality of baseline measurements (when there is published evidence to support good measurement properties of the assessment or instrument used for target population). We did not evaluate the quality of tests for assessing interaction between a moderator and the intervention because it was one of our inclusion criteria; therefore, all the RCTs included in this systematic review had to meet this criterion.

This four-item checklist had a Yes/No format. RCTs complying with the four criteria were considered to provide confirmatory evidence; those complying with criteria number three and four were considered to provide exploratory evidence. All other RCTs were classified as providing insufficient evidence. All the RCTs were included regardless their quality classification.

- **Combined quality**

The risk of bias of the RCTs and the quality of moderating effect analyses were assessed jointly to obtain an overall measure of study quality (Moreno-Peral et al., 2020). A study was classified as of 'good quality' when the total score for risk of bias was low and evidence of the moderating effect analysis was confirmatory. On the other hand, a study was considered to have a 'satisfactory' combined quality when they had either a low/moderate risk of bias and provided exploratory evidence, or a high /moderate risk of bias and provided confirmatory evidence. Studies not complying with these criteria were classified as having 'unsatisfactory' quality (Table 1).

****Insert Table 1****

- **Level of global scientific evidence**

In order to obtain global evidence of the moderators studied, we pooled the combined quality and number of studies reporting statistically significant results (Moreno-Peral et al., 2020). Global evidence was considered to be 'strong' when at least 75% of potential moderators (in at least three independent studies) were statistically significant in good combined quality studies. ~~A study provided~~ Moderate global evidence was provided when at least 65% of the potential moderators (in at least two independent

studies) were statistically significant in satisfactory combined-quality studies. Finally, evidence was considered 'insufficient' when less than 65% of potential moderators were statistically significant or more than 65% of potential moderators were statistically significant, but the combined quality of the study was unsatisfactory or the effects of the potential moderator had only been assessed in a study ([Figure 1](#)).

****Insert Figure 1****

RESULTS

Study selection

A total of 13,559 citations were identified by electronic database and hand searching. After 4,238 duplicates were removed, a total of 9,321 titles and abstracts were screened. The full texts of 468 articles were retrieved for further evaluation; 441 of these did not meet our inclusion criteria. Finally, 27 moderating analyses studies performed in 19 RCTs met our inclusion criteria. The PRISMA flowchart is shown in [Figure 42](#).

****Insert Figure 42****

Study characteristics

Most moderating effect analyses were published after 2010 (n=18), and only one analysis was published before 2005. The RCTs included were predominantly conducted in the United States (n=10). A total of 4,128 subjects were enrolled in all RCTs. Sample sizes ranged from 55 to 378 (Me= 231). Ages ranged between 11 and 65 years; ten studies involved adults, seven included adolescents and two were performed in children. Regarding settings, eight RCTs were conducted in schools or universities; three in communities; two in medical clinics; two were based on an official registry of informal caregivers; three had a mixed setting (two were performed in schools /universities and medical clinics, and one in a school and a community); and a study was performed in a primary care center. The majority of the interventions were based on a cognitive behavioral therapy (CBT) (n=13), whereas 6 RCTs were based on other types of theories (e.g. mixed approach (social competence and CBT) (n=1); interpersonal therapy (IPT) (n=1); social cognitive theory (n=1); a general psychoeducational approach (n=1); Stress Appraisal and Coping Model (n=1); and a purely cognitive approach (n=1)). Most interventions were delivered in group format (n=15); individual format (n=1); a combined group/individual format (n=1); or a guided computerized self-help format (n=3). The number of sessions ranged from 4 to 12 (Me= 8). Care as usual was used as comparator in ten RCTs; three RCTs did not involve any intervention, and six used an active control condition. In most RCTs, interventions were delivered by a mental health specialist (n=16); teachers (n=1); a social worker and a mental health specialist (n=1); and by trainers from occupational health services and human resources (n=1). Follow-up periods ranged from 1.5 to 75 months (Me= 12 months). The duration

of follow-up exceeded 12 months in six RCTs. Indicated, selective, and universal prevention were evaluated in 13, 4, and 2 RCTs, respectively. Regarding the prevention of depression, eight RCTs measured improvement of depression symptoms and five assessed reduction in the incidence of depression; both, the reduction of symptoms and incidence of depression were measured in five RCTs; and finally, both depression and anxiety symptoms together were assessed in one RCT. A detailed description of the characteristics of the RCTs included is presented in Appendix B.

Moderator variables identified

Thirty-four potential moderators were identified in the studies included. The most frequently evaluated moderator variable was baseline depressive symptoms (18~~7~~ of the 27 studies), followed by gender (n=7), age (n=5), baseline parental depression (n=4), social support (n=4), history of depressive disorders (n=4), substance use (n=3), negative life events (n=3), baseline anxiety symptoms (n=3), ethnicity (n=2), attributional style (n=2), motivation to reduce depression (n=2), ~~baseline anxiety symptoms (n=2)~~, level of education (n=2), main occupation (n=2), emotional distress (n=2) and caregiver burden (n=2). Each of the remaining potential moderators was examined in one study only. A detailed description can be found in Table 42 and Figure 3.

****Insert Table 42****

****Insert Figure 3****

Moderators were classified into five categories: sociodemographic, clinical characteristics, interpersonal functioning, personality, and life events.

1. Sociodemographic variables

1.1. Gender/ sex

Seven studies investigated gender as a potential moderator. All but one showed null interactions. In the adult population, gender was not found to be a significant moderator in two studies that employed different types of cognitive behavioral approaches (Allart-van Dam, Hosman, Hoogduin, & Schaap, 2007; Seligman, Schulman, DeRubeis, & Hollon, 1999). Consistently, gender was not observed either to have a moderating effect in children and adolescents in three studies (Brière, Rohde, Shaw, & Stice, 2014; Müller, Rohde, Gaub, & Stice, 2015; Stice, Rohde, Seeley, & Gau, 2010) belonging to the RCT by Stice et al. (2008) and in the study led by Duong et al. (2016). Stice et al. (2008) compared a cognitive behavioral prevention program against a supportive expressive intervention, a cognitive behavioral bibliotherapy and no intervention. In the ~~latter~~ study by Duong et al. (2016), an intervention based on positive thoughts and actions was compared to an active control group. In contrast, the only study that demonstrated a significant interaction effect (gender by intervention effect) compared a cognitive behavioral intervention

versus care as usual in a sample of early adolescents with depressive symptoms (Gillham, Hamilton, Freres, Patton, & Gallop, 2006). The authors concluded that Penn Resilience Program was superior to care as usual, especially in girls.

1.2. Age

Age was tested in five studies belonging to three RCTs. Two studies were carried out in female caregivers. The first showed that caregivers younger than 53 years were more likely to benefit from an intervention based on problem-solving versus care as usual (Otero, Vázquez, Ferraces, Blanco, & Torres, 2015~~ba~~). In the same line, the second study revealed that younger caregivers were more likely to benefit from ~~the~~ a brief cognitive behavioral intervention (Vázquez et al., 2016). Regarding children and adolescents, age was not found to have a moderating effect in none of the three studies in which a cognitive behavioral approach was used and where the role of age was assessed (Brière et al., 2014; Müller et al., 2015; Stice et al., 2010).

1.3. Race/ Ethnicity

In two studies in children and adolescents, race or ethnicity was evaluated as potential moderators. Duong et al. 2016 found that an intervention based on positive thoughts and actions was more beneficial for white subjects (from post to follow up) than for other ethnic groups. However, in another study, ~~psychological~~ a cognitive behavioral interventions failed to moderate outcomes in European American and Latino subjects (Marchand, Ng, Rohde, & Stice, 2010).

1.4. Other sociodemographic variables

Level of education and main occupation were evaluated as potential moderators in two studies where a problem-solving intervention was compared to care as usual in informal caregivers. None of them demonstrated significant interaction effects (Otero et al., ~~2015a~~2015b; Vázquez et al., 2016). Otero et al., (~~2015a~~2015b) also evaluated the number of children, but statistical significance was not reached. Finally, social class was not observed to have a moderating effect in the study by Vázquez et al., (2016).

2. Clinical characteristics

2.1. Depressive symptoms at baseline

In adults, the moderation effect of depressive symptoms was tested in ~~eight~~seven studies. In ~~four~~three, depressive symptoms were consistently associated with preventive effects. In the study by Allart-van Dam et al., (2007), participants who had low baseline depressive symptoms responded better to the Coping with Depression intervention, as compared to an advice. Another study reported better outcomes for a cognitive-behavioral workshop intervention in university students with higher levels of baseline depression (Seligman et al., 1999). Two studies on the prevention of post-partum depression (Barrera, Wickham, & Muñoz, 2015; Lara, Navarro, & Navarrete, 2010), where a cognitive behavioral

intervention and a psycho-educational intervention were evaluated, yielded opposite results to those reported by Allart-van Dam et al. (2007). Thus, interventions were more effective in women with higher levels of baseline prenatal depression than in control groups. Baseline depressive symptoms were not found to have a moderating effect in four studies involving cognitive behavioral interventions (Otero et al., 2015b; Vázquez et al., 2016); a social cognitive intervention (Ahola, Vuori, Toppinen-Tanner, Mutanen, & Honkonen, 2012); and a cognitive intervention (Yang, Ding, Dai, Peng, & Zhang, 2015), as compared to control groups.

The moderation effect of depressive symptoms in children and adolescents was evaluated in 10 studies. The study by Brière et al. (2014) compared two cognitive behavioral interventions –one of them group and the other one bibliotherapy– versus educational brochure control. When comparing cognitive behavioral bibliotherapy and educational brochure, participants-adolescents with high baseline depressive symptoms exhibited better outcomes at the end of the intervention. However, at 6-month follow-up, interaction tests did not reach significance. Low baseline depressive symptoms were not found to have moderation effects when a cognitive-behavioral group intervention and an educational brochure intervention were compared, or when a cognitive-behavioral group intervention was compared to cognitive-behavioral bibliotherapy upon test completion and at 6-month follow-up. In the same trial, follow-up analysis (Rohde, Stice, Shaw, & Briere, 2015) revealed that the cognitive behavioral intervention was more effective at two years than cognitive behavioral bibliotherapy in participants-adolescents with high baseline depressive symptoms. In the same line, a study revealed that participants-overweight adolescents with higher levels of baseline depression benefited more from a cognitive-behavioral intervention than those with lower depression severity, when compared to an active control (Shomaker et al., 2016). Another study documented better outcomes for a cognitive-behavioral group intervention and cognitive-behavioral bibliotherapy than for educational brochure in adolescents with higher levels of baseline depression (Müller et al., 2015). In a study assessing a cognitive behavioral program versus care as usual, the program was less effective than usual care for patients-adolescents with higher depressive symptoms (Weersing et al., 2016). Baseline depressive symptomatology were not documented to have a moderating effect in five studies involving cognitive behavioral interventions compared to control groups (Brent et al., 2015; Duong et al., 2016; Garber et al., 2009; Gau et al., 2012; Gillham et al., 2006).

2.2. History of depressive disorder

No evidence was found that history of depressive disorder had a moderating effect in two studies where cognitive behavioral interventions were used in adults (Allart-van Dam et al., 2007; Cook, Mostazir & Watkins, 2019) and in two studies involving cognitive behavioral interventions in children and adolescents (Brent et al., 2015; Garber et al., 2009).

2.3. Anxiety symptoms at baseline

The moderating effect of anxiety symptoms at baseline was investigated in [three](#) studies. A study on the prevention of post-partum depression [through a psycho-educational intervention](#), (Lara et al., 2010) reported better outcomes for women with higher baseline levels of anxiety. [In the same line, a study performed with university students found that those who had higher baseline levels of anxiety responded better to a cognitive-behavioral workshop intervention, as compared to a control group \(Seligman et al., 1999\).](#) In contrast, another study conducted in adolescents [that evaluated a cognitive behavioral intervention](#) reported that higher baseline levels of anxiety were associated with worse outcomes (Weersing et al., 2016).

2.4. Mixed depressive and anxious symptoms at baseline

Both baseline depressive and anxious symptoms were examined as a moderator in a study comparing the effectiveness of a cognitive behavioral intervention and treatment as usual in the prevention of depression and anxiety in adults (Li et al., 2014). Interaction between the intervention and baseline depressive and anxious symptoms did not reach significance.

2.5. Substance use

The role of substance use as a moderator was assessed in three studies in children and adolescents. In a study comparing a brief cognitive behavioral intervention versus educational brochure control, it was observed that low and moderate levels of substance use were associated with better prevention outcomes (Gau et al., 2012). In another study, it was indicated that a high use of substances reduced the effectiveness of a cognitive-behavioral intervention versus cognitive-behavioral bibliotherapy and educational brochure control (Müller et al., 2015). Conversely, another study comparing a cognitive-behavioral intervention versus cognitive-behavioral bibliotherapy versus educational brochure control failed to prove that substance use had a moderator effect (Brière et al., 2014).

2.6. Other clinical characteristics

Six other clinical factors were evaluated as potential moderators. In adults, people who suffered from baseline job strain obtained greater improvement of a social cognitive program compared to information only (Ahola et al., 2012). Higher levels of baseline stress were associated with preventive effects in a study involving a cognitive behavioral web-based therapy [in university students](#) (Cook, Mostazir & Watkins, 2019). On the other hand, two studies assessing a problem-solving intervention versus care as usual did not find emotional distress to have a moderating role [in women caregivers](#) (Otero et al., 2015b; Vázquez et al., 2016). Regarding children and adolescents, participants in the low-risk cluster (defined as high levels of functioning, low level of anxiety, and no current parental depression) responded better to cognitive behavioral intervention (Garber, Weersing, Hollon, Porta, & Clarke, 2016). In the study by Weersing et al., (2016), the preventive program was less effective in adolescents with lower levels of functioning and higher levels of hopelessness.

3. Interpersonal functioning

3.1. Parental clinical characteristics

In children and adolescents, four studies investigated parental clinical characteristics as moderators of cognitive behavioral program prevention effects. All clinical variables reached statistical significance. Having parents without baseline depression was proven to be a significant moderator in three studies (Beardslee et al., 2013; Brent et al., 2015; Garber et al., 2009). In the same way, Weersing et al., (2016) reported that participants whose parents had current major depressive disorder or dysthymia or parents with a history of hypomania benefited less from preventive interventions.

3.2. Social support

The effectiveness of social support in children and adolescents was assessed in three studies that evaluated cognitive behavioral programs. One of them tested both parental support and peer support, but they failed to find any moderation effects (Brière et al., 2014). No moderation effects were found either for social support deficit (Gau et al., 2012) or social support from friends and family (Müller et al., 2015).

3.3. Other interpersonal functioning

In the adult population, relationship to the person receiving care was examined as a moderator of the effects of a problem-solving intervention in a sample of informal caregivers (Otero et al., 2015b). No evidence was found that this variable had a moderating effect. In children and adolescents, a study assessing psychotherapy-adolescent skills training versus school counseling in middle- and high-school students showed that higher levels of baseline mother-child conflict resulted in greater improvement effects of the preventive intervention (Young, Gallop, & Mufson, 2009).

4. Personality

4.1. Attributional style

Two studies tested attributional style as a potential moderator in children and adolescents. Neither attributional style (Müller et al., 2015) nor negative attributional style (Brière et al., 2014) was moderated the effects of associated with cognitive behavioral interventions effect.

4.2. Motivation

Motivation to reduce depression was assessed as a potential moderator in two studies conducted in children and adolescents. One of them found that a cognitive behavioral intervention was more effective than cognitive behavioral bibliotherapy or educational brochure control in adolescents highly motivated to overcome depression (Müller et al., 2015). Opposite results were documented in the other study that evaluated a brief cognitive behavioral, where no statistically significant evidence was obtained supporting that high motivation to overcome depression was a moderator (Gau et al., 2012).

4.3. Perceptions of self

Two studies investigated the perception of the self by two different constructs. Self-esteem was not found to have a moderating effect in a study performed in female caregivers [that evaluated a problem-solving intervention](#) (Otero et al., 2015b). In contrast, the study by Pössel, Baldus, Horn, Groen, & Hautzinger (2005) in children revealed that levels of depression decreased to a greater extent in participants with low general self-efficacy who received training in the handling of social aspects of everyday life, as compared to those with high self-efficacy.

4.4. Other personality variables

Other personality variables were assessed as potential moderators in two studies in the adult population. Changes in global problem-solving and functional problem-solving skills (defined as positive orientation and rational style) were associated with intervention effects (Otero et al., 2015a). However, in the same study, no moderating effect was detected for dysfunctional problem-solving skills (defined as negative orientation, impulsive style and avoidant style) (Otero et al., 2015a). Finally, no evidence was obtained supporting that baseline attention bias score was related to changes in depressive symptoms after participation in an attention bias modification intervention, as compared to placebo or care as usual (Yang et al., 2015).

5. Life events

Five variables related to life events have been examined in the literature as potential moderators. In two studies in female caregivers, no evidence was obtained that duration of care, diagnosis of person cared (dementia or other), caregiver burden or other care factors (including relation to, diagnosis - dementia or other-, age and sex of the person cared for, and the time and duration of care) moderated the effect of a problem-solving intervention versus standard care (Otero et al., 2015b, Vázquez et al., 2016). In children and adolescents, Gau et al., (2012) documented that lower levels of negative life events moderated the effects of a brief cognitive behavioral prevention program. However, the same construct was not found to be associated with prevention outcome in two studies [involving cognitive behavioral interventions](#) in children and adolescents (Brière et al., 2014; Müller et al., 2015).

Methodological quality

Risk of bias in RCTs

Risk of bias was assessed based on the RCTs of the studies included (Table [4-2](#) and Appendix B). Eleven RCTs were considered to have a low risk of bias, four showed a moderate risk, and four were found to have a high risk of bias.

Quality of moderator analysis

Nineteen of the 27 studies (70,4%) provided confirmatory evidence, six (22,2%) provided exploratory evidence and two (7,4%) provided insufficient evidence (Table [1-2](#) and Figure [24](#)). Concerning the total number of criteria met by each study, 19 studies met the four criteria evaluated, seven studies met three criteria, and a study met two criteria.

****Insert Figure [24](#)****

Combined quality

The combined quality, estimated from the risk of bias and the quality of the moderator analysis was good in most studies (n=14, 52%) , was satisfactory in nine studies (33%), and unsatisfactory in four studies (15%) (Table [24](#) and Figure [35](#)).

****Insert Figure [35](#)****

Global evidence

In adults, the only variable for which moderate evidence has been provided of its moderating effects was young age, that was associated with effectiveness in a preventive intervention. This finding was supported by two independent studies; however, both studies involved female caregivers with elevated depressive symptoms. The potential moderating effects of the remainder of variables analyzed were not confirmed (Table [23](#)).

****Insert Table [23](#)****

In children and adolescents, two of the three studies that evaluated substance use revealed that a low baseline use of substances increased the effectiveness of preventive interventions. Therefore, moderate evidence was obtained of the moderating effects of low baseline use of substances. Having parents free of depression at baseline was demonstrated to be associated with greater preventive effects in four of the four studies where it was evaluated. Therefore, strong evidence was obtained of this variable being a moderator. We found no sufficient evidence on the role of the rest of potential moderators examined. All this information can be found in Table [34](#).

****Insert Table [34](#)****

Evidence on the role of baseline depression symptoms as a moderator was insufficient. Yet, five independent studies in children and adolescents and three in adults found significant association but in conflicting directions with the reduction of depressive symptoms (Table [2-3](#) and Table [34](#)).

DISCUSSION

Overall findings

In this systematic review, we synthesized the literature on moderators of outcomes of psychological and psychoeducational interventions for the prevention of depression. Twenty-seven moderator effect analyses from 19 RCTs were evaluated. We identified 34 potential sociodemographic, clinical, interpersonal, personality and life-event moderators in all types of population. Overall, baseline depressive symptoms were the most frequently examined variable, followed by gender, age, baseline parental depression, and social support. Moderate evidence was found of the moderating effects of lower age in adults and low use of substances in children and adolescents. Yet, evidence on the moderating role of lower age was only provided in two studies. Strong evidence was gathered of the moderating effects of having parents without depression. This variable was associated with better outcomes for psychological and psychoeducational interventions in children and adolescents. Although baseline depressive symptoms were the most frequently studied variable, the moderating role of this variable is still unclear and results regarding the direction of the effect were contradicting. No other variables have been proven to exert moderating effects.

Study strengths and limitation

These findings should be interpreted considering the strengths and limitations of this study. To the best of our knowledge, this is the first systematic review to examine moderators of psychological and psychoeducational intervention effects on the prevention of depression. We used multiple complementary electronic databases with supplementary hand searching and consultation with experts. The range of search terms was broad enough to achieve adequate sensitivity. We clearly defined the inclusion and exclusion criteria employed and the methods used to assess the methodological quality of the studies included. Selection of studies, data collection, and the assessment of risk of bias and quality of moderating effect analyses were performed by trained independent authors. Only RCTs were included in this systematic review, since this design is the least biased to provide evidence of causality. Furthermore, RCTs were required to involve at least an interaction test to ensure that the RCTs included met minimum quality standards. [We only included studies where a moderator by condition interaction test was performed since ~~assessing/testing predictors of outcome moderation effects only in an intervention condition is not sufficient to conclusively determine a moderator effect.~~](#) The review covered a variety of interventions (psychological and psychoeducational) and potential moderators that ranged from sociodemographic to clinical, interpersonal, personality and life-event variables.

This systematic review has several limitations. The most concerning limitation was that only very few moderators have been consistently measured across studies. Baseline depressive symptoms were the most frequently studied variable, as it was investigated in 13 independent studies. This makes it difficult to draw any conclusions about who is more likely to benefit from preventive interventions and who is not. Moreover, many relevant predictors and moderators associated with depression onset in the literature, such as experiences of discrimination, childhood adversities and emotion regulation difficulties

(Bellón et al., 2011; Ebert et al., 2019; King et al., 2008) were not assessed in the studies included. Thus, although there seems to be more attention to investigate differential preventive effects, as indicated by most of the identified studies being published in the last years, further research is needed to develop personalized preventive approaches. The heterogeneity of studies included in this systematic review in terms of type of population, type of intervention or format among others, also makes it difficult to draw clear conclusions about specific moderators in particular prevention interventions and populations. The reduction of depression symptoms (measured by scales) was the outcome of thirteen RCTs, although reliability and validity are widely accepted, standardized diagnostic interviews generally are considered to have greater validity. Another limitation was that some of the significant findings in moderating effect analyses were based on the same RCT sample. However, 19 studies (RCTs) with independent samples were considered in our systematic review. This number reflects that effectiveness is frequently not assessed for specific subgroups. The risk of bias of the RCTs was considered moderate/high in eight RCTs; although, in general, the combined quality –assessed based on their risk of bias plus quality of the moderating effect analysis– of the RCTs included was satisfactory. Finally, an important problem when identifying moderators in a reliable way is that RCTs are usually powered to demonstrate effects on the primary outcome, i.e. effects on depression incidence. In order to identify moderators with similar effect sizes, a sample should be inflated at least three to four times, compared to the treatment*outcome interaction (Brookes et al., 2004). This is especially a problem in the field of prevention, as preventive effects are generally smaller, compared to the treatment field, and therefore the necessary sample size. This might explain the limited number of studies published to date on moderators for the prevention of depression. ~~We therefore argue that prevention research nevertheless include a broad set of putative moderators in RCTs, even if the primary trial is underpowered to investigate such research questions. This would allow investigating moderators of preventive effects by pooling data from RCTs using individual patient data meta-analytic techniques.~~

Comparison with literature and explanation of results

This systematic review did not gather evidence supporting gender as a moderator of preventive outcomes in psychological and psychoeducational interventions. However, lower age emerged as a moderator in the adult population. Reviews and even an IPD meta-analysis of studies on moderators in the treatment of depression provided similar results. Gender was not a significant moderator of outcomes in psychotherapies for the treatment of depression (Cuijpers et al., 2014, Cuijpers et al., 2018, Bernecker et al., 2017, Van, Schoevers, & Dekker, 2008). Considering age as a moderator, the evidence provided in the literature is inconsistent, and age ranges are not clear (Bernecker et al., 2017). A meta-analysis performed by Cuijpers et al. (2018) revealed that younger people (students) benefited more from psychotherapies for depression than adults and older adults. Conversely, an IPD of online interventions for depression showed that older participants were more likely to respond to treatment compared to younger

participants (Karyotaki et al., 2018). Thus, findings for the present systematic review should be interpreted with caution since the two RCTs supporting that younger people were more likely to benefit from the intervention were based on a sample of female caregivers (Otero et al., 2015b, Vázquez et al., 2016); therefore, these results cannot be generalized to other populations, and more research is needed.

There is also controversial evidence about the role of baseline levels of depressive symptoms in the treatment of depression since it has been found that patients with more severe depression at baseline showed larger treatment effects than those who were less severely depressed (Bower et al., 2013), in others studies, the moderating role of depressive symptoms at baseline has not been found (Cuijpers et al., 2018; Weitz et al., 2015) or has only been found for the effect of the interventions on remission and not on treatment response (Karyotaki et al., 2018). In the case of prevention of depression, no previous meta-analyses have been conducted about the role of baseline levels of depressive symptoms. In this systematic review, we found that elevated baseline depressive symptoms were documented to amplify the effects of psychological and psychoeducational preventive interventions in seven independent studies. This finding could be explained by the fact that people with a higher degree of clinical distress are also more motivated to change. In the same way but in a different direction, two independent studies showed that the preventive effects of interventions were superior in patients-participants with lower initial depressive symptoms. This could reflect that this subgroup of patients-participants has more resources to cope with mood problems. This pattern was observed both, in children and adolescents and in adults.

The evidence gathered in this systematic review on the role of baseline anxiety symptoms as a moderator is insufficient. Only two Three independent studies, one in children and adolescents and another two in adults, evaluated this variable, with opposite results. In adults, a higher level of baseline anxiety was associated with effectiveness. Conversely, depression was more likely to be prevented in children and adolescents with lower baseline anxiety symptoms. Anxiety symptoms may affect subjects differently depending on their age. Adults with anxiety symptoms could be more willing to engage in a mental health intervention than children and adolescents with symptoms of anxiety. In fact, interventions may have the opposite effect, a decrease in motivation to cope with mental health problems. In addition, anxiety is a core risk factor for the onset of depression (Wittchen, Beesdo, Bittner & Goodwin, 2003), therefore more research is needed in order to clarify the role of this variable.

Concerning the moderator role of substance use, our research suggested that a lower use of substance increased the effectiveness of interventions for the prevention of depression in children and adolescents. This result indicates that substance abuse in young people may be associated with lower motivation to acquire and apply the knowledge and skills offered in psychological interventions. Another possible hypothesis is that symptoms of depression may be a consequence of substance abuse in children and adolescents. Yet, it should be taken into account that two of the studies supporting this

hypothesis used the same sample, since the study by Müller et al., (2015) used combined data from two RCTs (RCT 1: Stice, Rohde, Seeley, & Gau, 2008; RCT 2: Rohde et al., 2014), and the study by Gau et al., (2012) was performed within the framework of one of these RCTs (RCT 1: Stice et al., 2008). Further studies are required to evaluate the role of substance use in the effects of psychological and psychoeducational interventions not only in childhood but in all types of population.

Although consistent evidence has been obtained on the role of some moderators in treatment and prevention interventions in depression, evidence on the role of history of depressive disorder is controversial. This variable was not demonstrated to be a moderator in psychological and psychoeducational interventions for the prevention of depression. However, the treatment of depression, previous episodes of depression have been associated with poorer response to cognitive therapy (Hamilton & Dobson, 2002).

Two studies conducted in practically the same sample of children and adolescents (Gau et al., 2012; Müller et al., 2015, already explained above) investigated the moderating effects of motivation in reducing depression. Statistical significance was reached in only one of the two studies that evaluated this variable. Failure to reach significance could be explained by the small sample used of the latter, which was underpowered to detect significant differences. It ~~makemakes~~ senses that people who are more motivated to overcome depression will benefit more from interventions than those who have a lower predisposition.

Inconsistent findings in relation to moderators might be explained by the fact that some included studies tested intervention variants that were considered under the same umbrella. Moreover, RCTs are usually underpowered and not a priori planned to test for differential treatment effects. Subjects with a specific profile who respond favorably to an intervention may not respond well to a similar intervention. Another source of heterogeneity was the heterogeneity of samples across studies. Putative moderators may work differently across populations, which may have hindered the detection of consistent findings across studies. As the field moves towards precision interventions, future large-scale studies that are designed and powered to test not only interactions between treatment and putative single moderators, but that also allow to test complex interactions between different patient characteristics and treatment outcome.

The strongest evidence was found for the moderating effect of having parents without current depression in children and adolescents. Parental depression could negatively affect parents-children relationships by reducing the warmth of their relation, thereby attenuating the potential positive results of preventive interventions. A limitation to this finding is that two of the four studies assessing this variable were performed within the framework of the same RCT (Garber et al., 2009). Although this systematic

review found strong evidence for the moderator role of parental depression, futures studies could help to clarify the role of this moderator.

Practical implications

The identification of moderators in preventive interventions is crucial to the identification of the subgroups that benefit the most from each type of intervention and can be useful to modify or refine the preventive interventions to render them more effective (Kraemer et al., 2002; Frazier et al., 2004). According to the objectives of personalized medicine, if we seek to design a personalized intervention to prevent depression, it is important to identify the most effective interventions for each specific subgroup of patients (Cuijpers, 2009) in order to select the best treatment possible for an individual patient. Based on the finding that psychological and psychoeducational interventions are more effective in children and adolescents of parents without depression, treating parental depression would be a realistic approach to the prevention of depression in children and adolescents. Also, it may be helpful for clinicians to screen and treat substance use in their adolescent patients accordingly, prior to inclusion in a depression prevention program. Finally, another practical implication of our results is that it provides evidence supporting the implementation of more intensive interventions aimed at older female caregivers. This new approach will optimize the resources available, increase effect sizes and, hence, reduce the burden of depression.

Conclusions Future directions and conclusions

Besides increasing the numbers of studies, more methodologically robust studies are needed to establish the moderators that show evidence of the lack of moderation effect. First, studies should be properly designed with test of moderation as the primary objective with special attention on assuring appropriate statistical power. This is essential for progress in this field. However, we argue that prevention research nevertheless includes a broad set of putative moderators in RCTs, even if the primary trial is underpowered to investigate such research questions. This would allow investigating moderators of preventive effects by pooling data from RCTs using individual patient data meta-analytic techniques. Second, studies should use standard tools for assessing moderation effects and outcomes to ensure comparability across studies. Third, studies should test non-linear and linear relationship with the outcome since the majority of studies do not indicate whether they tested quadratic moderation by condition interactions. Fourth, after interaction testing, it is advisable to perform between-group testing of the entire sample to avoid significant underpower at different points along the moderator to explore the nature of interaction. Fifth, interaction between moderators should be considered in future studies, e.g. by applying appropriate machine learning techniques that could result provide hypotheses to be tested in subsequent confirmative studies. Finally, studies should first consider the moderators that have been tested in previous studies to provide a consistent corpus of evidence in moderation effect studies. Much more

[research in these terms is clearly needed in order to develop personalized prevention interventions for depression.](#)

This systematic review provides consistent evidence on the moderating role of lower substance use, having parents free of depression in children and adolescents, and lower age in the adult population. These moderator variables improved the effects of preventive interventions. In contrast, controversial results have been obtained on some potential moderators, and the role of other variables was found to have been investigated in a relatively small number of studies. In our study, we gathered empirical evidence that psychological and psychoeducational interventions for the prevention of depression are more effective in some population groups. However, more methodologically robust studies are needed to identify these subgroups of patients and the conditions required for these interventions to be effective in preventing depression.

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Contributors

SCC, JAB, and PMP designed the study and the other authors collaborated on the design. SCC, JAB, EM, HCP, CMG, DDE, CB, MG, and PMP acquired, analyzed and interpreted the data.

SCC and PMP drafted the manuscript and JAB, EM, HCP, CMG, DDE, CB and MG conducted a critical revision of the manuscript for important intellectual content. All authors discussed and approved the final version. SCC and PMP are the guarantors.

Conflict of Interest

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

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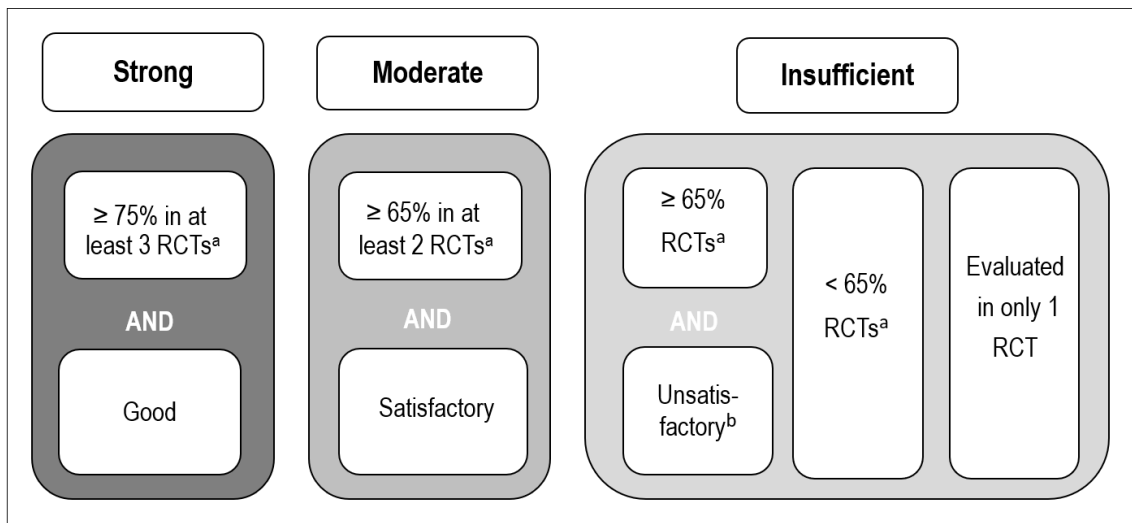
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* Studies included in the systematic review.

Figure 1. Scheme about levels of scientific evidence.



^a:Statistical significance. ^b:Combination of methodological quality.

Figure 24. PRISMA Flowchart of the studies reviewed and included

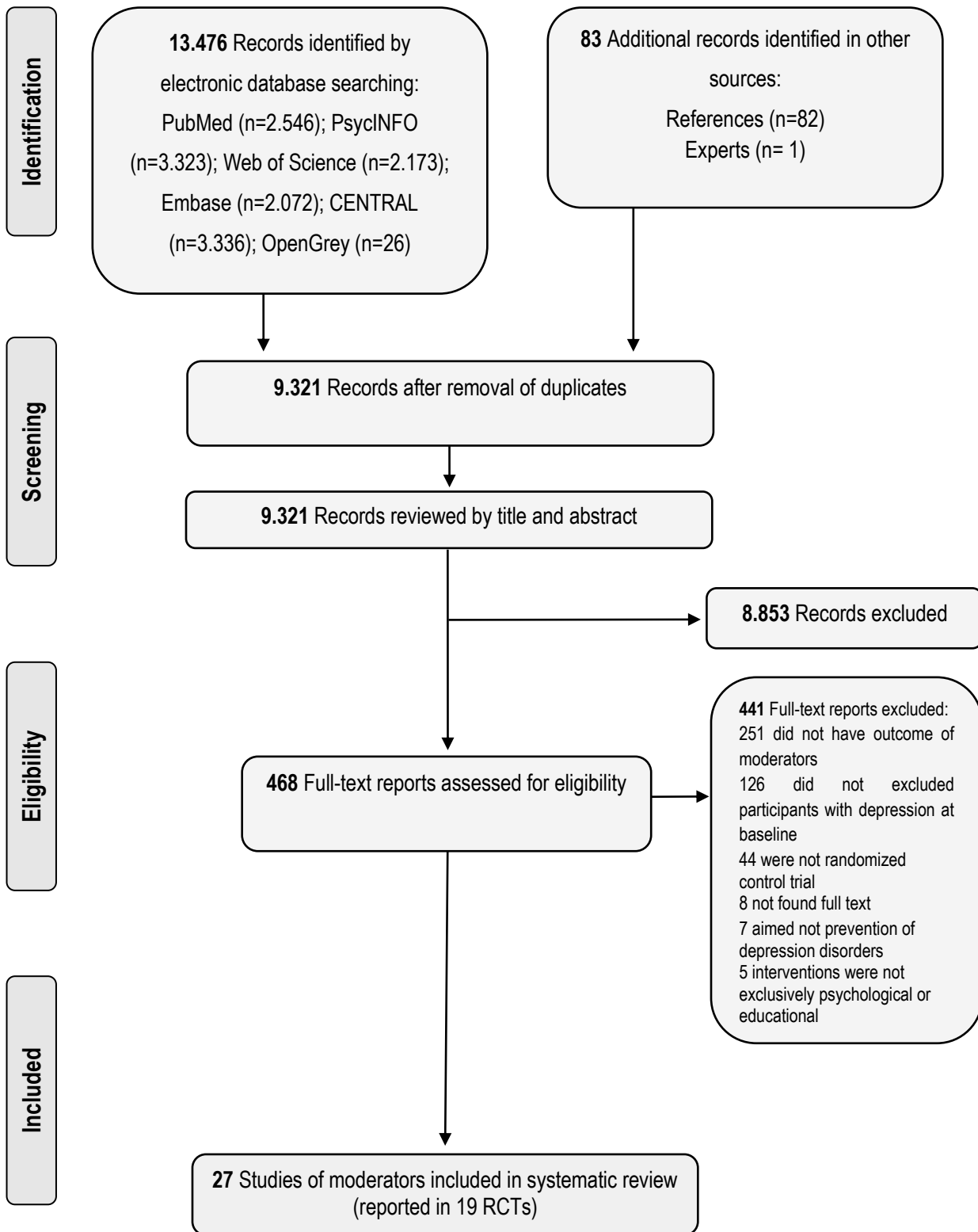


Figure 3. Moderators identified by group of age

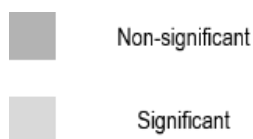
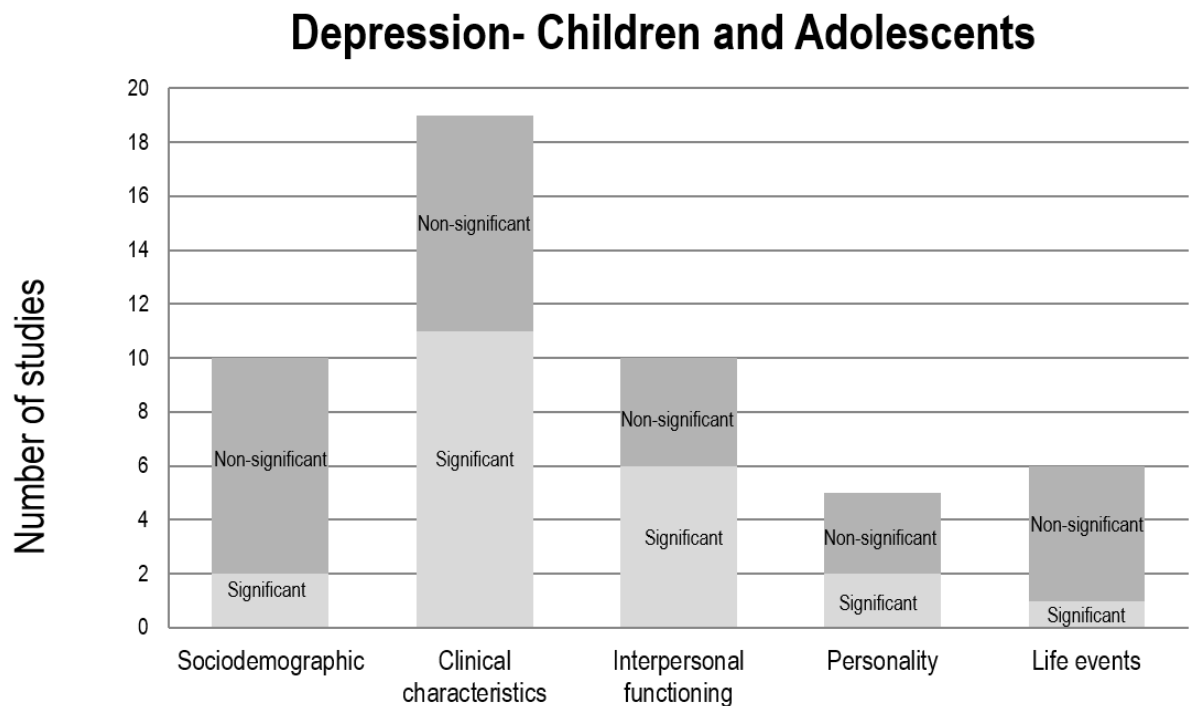
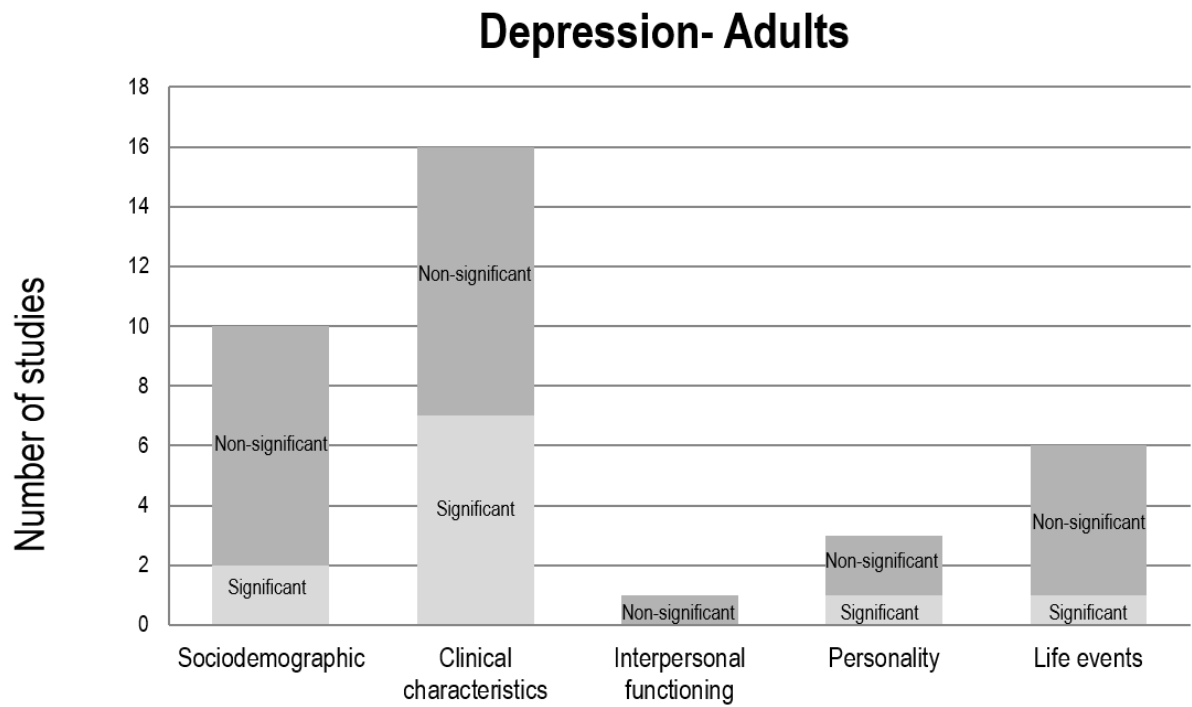


Figure 24. Quality of moderator analysis.

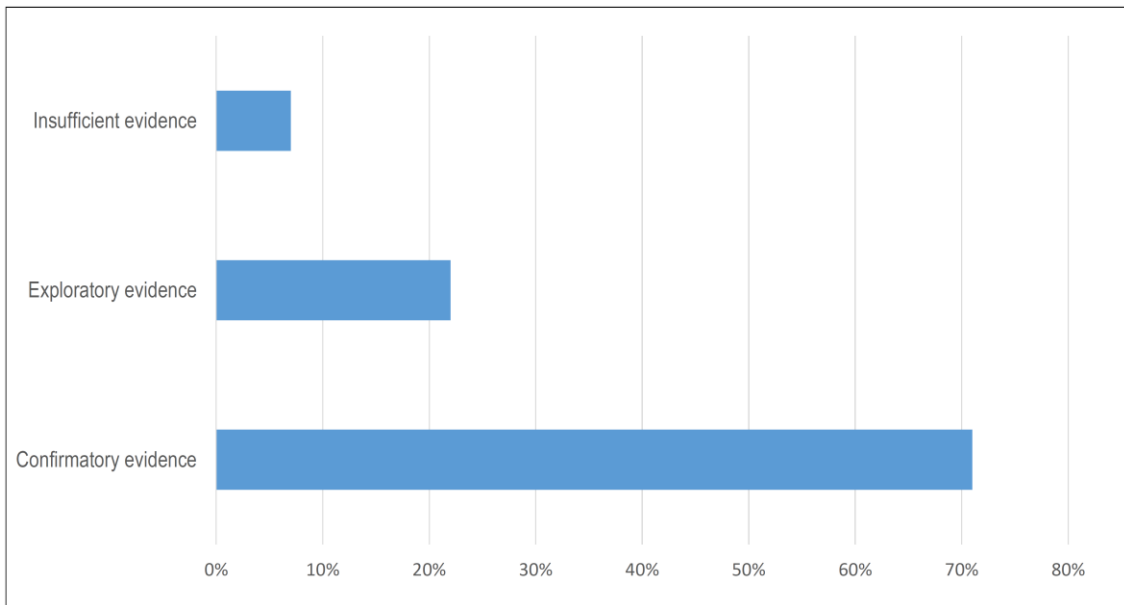
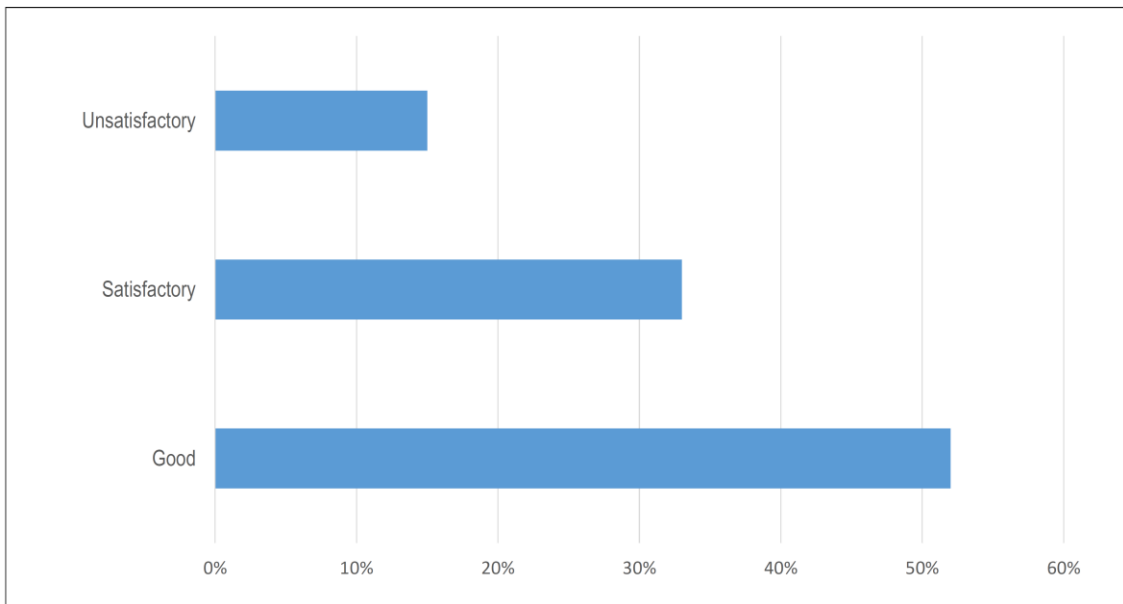


Figure 35. Combined quality.





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Table

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Sonia Conejo-Cerón

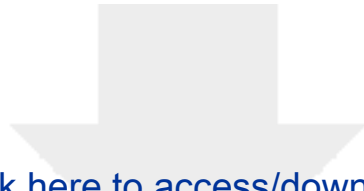
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Conflict of Interest

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



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