APPENDIX A. Search strategies

PubMed (MEDLINE, CINHAL): 1310 (07/10/2019)

((“depressive disorder” OR “major depressive disorder” OR depress* OR “depression”) OR ("anxiety disorders"[MeSH Terms] OR ("anxiety"[All Fields] AND "disorders"[All Fields]) OR "anxiety disorders"[All Fields] OR ("anxiety"[All Fields] AND "disorder"[All Fields]) OR "anxiety disorder"[All Fields] OR "anxiety"[MeSH Terms] OR "anxiety"[All Fields])) AND (prevent*[Title/Abstract] OR "Primary Prevention"[Title/Abstract]) AND (“psychological techniques”[MeSH] OR psychoeducat* OR psychol*) AND (mechanism* OR mediat* OR predict* OR process* OR “structural equation modelling” OR caus* OR correlat* OR relationship OR associat* OR moderat*) AND (randomized controlled trial[Publication Type] OR (random*[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]) OR (controlled[Title/Abstract] AND trial[Title/Abstract]))

The Cochrane Library: 1770 (07/10/2019)

(("depression":ti,ab,kw or "depressive disorder":ti,ab,kw or “major depressive disorder”:ti,ab,kw or depress*:ti,ab,kw) OR ("anxiety":ti,ab,kw or "anxiety disorder":ti,ab,kw)) AND (psychological techniques:ti,ab,kw or psychoeducat*:ti,ab,kw or psychol*:ti,ab,kw) AND (mechanism*:ti,ab,kw OR mediat*:ti,ab,kw OR predict*:ti,ab,kw OR process*:ti,ab,kw OR “structural equation modelling”:ti,ab,kw OR caus*:ti,ab,kw OR correlat*:ti,ab,kw OR relationship:ti,ab,kw OR associat*:ti,ab,kw OR moderat*:ti,ab,kw) AND (prevent*:ti,ab,kw or incidence:ti,ab,kw) AND (effectiveness:ti,ab,kw or trial:ti,ab,kw or controlled trial:ti,ab,kw or randomi*:ti,ab,kw or intervention:ti,ab,kw or efficacy:ti,ab,kw)

Embase: 2663 (07/10/2019)

('depression':ti,ab,kw OR depression:ti,ab,kw OR 'depressive disorder':ti,ab,kw OR (depressive AND disorder) OR 'major depressive disorder':ti,ab,kw OR (major AND depressive AND disorder) OR depress*:ti,ab,kw OR 'anxiety':ti,ab,kw OR 'anxiety disorder':ti,ab,kw) AND ('psychoeducation':ti,ab,kw OR psychoeducat*:ti,ab,kw OR 'health education':ti,ab,kw OR psychol*:ti,ab,kw OR educat*:ti,ab,kw OR'psychological techniques':ti,ab,kw) AND ('mechanism*':ti,ab,kw OR 'mediat*':ti,ab,kw OR 'predict*':ti,ab,kw OR 'process*':ti,ab,kw OR 'structural equation modeling'/exp OR 'caus*':ti,ab,kw OR 'correlat*':ti,ab,kw OR 'relationship'/exp OR 'associat*':ti,ab,kw OR 'moderat*':ti,ab,kw) AND ('prevent*':ti,ab,kw OR 'incidence'/exp) AND ('effectiveness':ti,ab,kw OR 'trial':ti,ab,kw OR 'controlled trial':ti,ab,kw OR 'randomi*':ti,ab,kw OR 'intervention':ti,ab,kw OR 'eficacy':ti,ab,kw)

Web of Science: 1602 (07/10/2019)

TS= ((anxiety disorders OR (anxiety AND disorders) OR anxiety) OR (depressive disorder OR (depressive AND disorder) OR depression OR major depressive disorder) OR (depressive disorder OR (depressive AND disorder) OR depression OR major depressive disorder)) AND TS= ((Health Education OR psychoeducat* OR educat* OR psychol* OR psychological techniques)) AND TS= (mechanism* OR mediat* OR predict* OR process OR structural equation modeling OR caus* OR correlat* OR relationship OR associat* OR moderat*) AND (TI= (prevent* OR incidence)) AND TS= ((effectiveness OR trial OR (controlled AND trial) OR randomi* OR intervention OR eficacy))

Psycinfo: 1282 (07/10/2019)

((anxiety OR anxiety disorders OR (anxiety AND disorder)) OR (if(depressive disorders) OR (depressive disorder) OR depress*)) AND (if(educational health) OR psychoeducat* OR intervention* OR program* OR strateg*) AND (prevent* OR incidence) AND (effectiveness OR trial OR (controlled AND trial) OR randomi* OR intervention OR efficacy) AND (mediator* OR structural equation modeling OR moderator*)

Open Grey: 29 (07/10/2019)

(anxiety OR depress*) AND (prevent*) AND (mechanism* OR mediat* OR predict* OR process* OR "structural equation modelling" OR caus* OR correlat* OR relationship OR associat*) AND AND (effectiveness OR trial OR (controlled AND trial) OR randomi* OR intervention OR efficacy)

APPENDIX B. Characteristics of included studies.

Author/ year Country	Mental Disease	Target population/ Setting/ Type of prevention	Exclusion at baseline	Inclusion criteria	Sample (control/ intervention)	Experimental conditions	Provider	Outcomes	Follow-up (months)
Allart-van Dam et al., (2003, 2007) Netherland	Depression	Adults (18-65 years) Community (newspapers and on local television) Indicated	MD (CIDI)	Depressive symptoms (BDI ≥10)	110 (42/68)	1. Coping with depression course (CBI; 12 sessions; group) 2. No intervention, advice	Psychologist	Depressive symptoms (BDI) Incidence of depression (CIDI)	12
Brunwasser et al., (2018) United States	Depression	Adolescents (mean age 12.5 years) Middle schools Universal	NA	NA	697 (234/232/231)	1. Penn Resiliency Program (CB; 12 sessions; group) 2. Penn Enhancement Program placebo (No CB skills training; 12 sessions; group) 3. No intervention control	Trained middle school teachers/counselors or graduate students in psychology or education	Depressive symptoms (CDI)	0.5-6-12-18-24-30-36
David et al., (2018) Romania	Depression	Children and adolescents (10-16 years) Schools Universal	NA	NA	165 (56/55/54)	1. Therapeutic videogame (REThink) (CB; 7 sessions; computerized; group meetings and debriefing session) 2. Rational Emotive Behavior Education (REBE) (CB; 7 sessions; group; group meetings and debriefing session) 3. Waiting list	Psychologist	Depressive symptoms (EATQ-R)	1
Duong et al., (2016) United States	Depression	Children (mean age 12.7 years, standard deviation 0.73) Schools Indicated	Depression (PHQ-9)	No depression (Mood and Feelings Questionnaire ≥14 and PHQ-9)	120 (62/58)	1. Positive Thoughts and Actions (Tailored CB prevention program;12 sessions; group) 2. Active control group (Individual Support Program)	Masters or doctoral level therapists	Depressive symptoms (PHQ-9)	12
Essau et al., (2012) Germany	Anxiety	Children (9-12 years) Schools Universal	NA	NA	638 (336/302)	1. FRIENDS program (CB techniques; 10 and 2 booster sessions one month and three months after the 10th session; group) 2. Waiting list	Graduate students in clinical child psychology with 2 years of experience in working with children with anxiety and depressive disorders	Anxious symptoms (SCAS) Depressive symptoms (RCADS)	12
Fledderus et al., (2013) Netherland	Depression and anxiety	Adults (18-73 years) Community (Dutch newspapers) Indicated	Anxiety (HADS-A <15; CES-D)	Moderate depressive symptom (>10 and <39 CES-D)	376 (126/250)	1. ACT intervention with minimal email (9 sessions; individual computerized) 2. ACT intervention with extensive email support (9 sessions; individual computerized) 3. Waiting list	Psychology masters students trained	Anxious symptoms (HADS-A) Depressive symptoms (CES-D)	2,25
Fosco et al., (2016) United States	Depression	Adolescents (6th grade) and their parents Schools Universal	NA	NA	593 Families (207/386)	1. The Family Check-Up (A family-centered, school-based preventive intervention designed to reduce coercive family interactions by increasing parents' positive reinforcement, effective limit setting, monitoring, and effective family problem-solving skills. Tailor intervention; variable number of sessions; individual) 2. CAU	Not available	Depressive symptoms (adapted from the Child Depression Inventory)	48
Ginsburg et al., (2015) Casline et al., (2018)	Anxiety	Children (6-13 years) and parents with mental problems (mean age 40.82 years) Community	Anxiety (ADIS-IV); or treatment for anxiety	Parents: at least one parent meeting DSM-IV criteria for a current primary	136 Families (66 Families/ 70 Families)	1. Coping and Promoting Strength intervention (Coping and promoting strength intervention CB and psychoeducational; 11 sessions; individual). First 2 sessions parents alone the subsequent all	Trained therapist	Incidence of child anxiety disorders (ADIS-IV)	6-12

United States		Selective	reduction	anxiety disorder (ADIS)		interested family members 2. Information-monitoring condition			
Horowitz et al., (2007) United States	Depression	Adolescents (mean age 14.43 years, standard deviation 0.7) High schools Universal	NA	NA	380 (169/112/99)	1. CB (Psychoeducational CB intervention derived from the Coping with Stress Course; 8 sessions; group) 2. Interpersonal psychotherapy adolescent skills training (Interpersonal therapy; 8 sessions; group) 3. No intervention	Group leaders: master's-level clinical psychology graduate students or recent clinical psychology PhDs. Group coleaders: clinical graduate students or undergraduate honors students	Depressive symptoms (CDI and CES-D)	6
Li et al., (2014) United Kingdom	Depression and anxiety	Adults (not available) Medical clinics Selective	Depression and anxiety (HADS ≥8)	Depression and anxiety (HADS<8)	*55 (12/43)	1. STrAtegies for RelaTives (START) intervention (Stress Appraisal and Coping Model (8 sessions; individual) 2. TAU	Therapists undergraduate degrees in psychology	Anxious and depressive symptoms (HADS-T)	4-8
Meulenbeek et al., (2010) Netherlands	Anxiety	Adults (20-75 years) (mean age 42, standard deviation 12.4) Community Indicated	MINI-Plus DSM-IV PD presence of current comorbid agoraphobia, and/or severe MD	Symptoms of PD (PDSS-SR<13)	217 (108/109)	1.'Don't Panic' course (CB principles; 8 sessions; group) 2. Waiting list	Psychologist and prevention workers	Anxious symptoms (PDSS-SR, HADS-A)	3-6
Muñoz et al., (1995) United States	Depression	Adults (18-69 years) Primary care Selective	MD in past 6 months (DIS)		150 (78 / 72)	1.CBT (CB; 8 sessions; group) 2.No intervention or information by videotape	Psychologists	Incidence of depression (DIS) Depressive symptoms (BDI, CES-D)	12
Pössel et al., (2005) Germany	Depression	Children (mean age 14, standard deviation 0.75) Schools Universal	NA	NA	342 (142/200)	1. Training the Ease of Handling Social Aspects in Everyday Life – LISA (Social information processing model of social competence and CBT; 10 sessions; group) 2. CAU	Psychologists or graduate students experienced in working with adolescents	Depressive symptoms (CES-D)	3
Rovner et al., (2014) United States	Depression	Older people (>65 years) with age-related macular degeneration Large private retina practice associated with the Wills Eye Hospital Indicated	MD (DSM-IV)	Depressive symptoms (PHQ-9>5)	188 (92/96)	1. Behavior activation + low vision rehabilitation (CBT; 6 sessions; individual) 2. Supportive therapy + low vision rehabilitation	Occupational therapists	Incidence of depression (PHQ-9)	4
Seligman et al., (1999) United States	Depression and anxiety	Adults (not available) Universities Selective	MD, anxiety disorders (BDI > 19 and SCID)	Bottom quartile of the ASQ	231 (not available)	1. Workshop (CB techniques; 8 sessions in group and 6 individual) 2. No intervention	Cognitive therapists and students enrolled in the clinical psychology program	Depressive symptoms (BDI) Anxious symptoms (BAI) Incidence of depression and anxiety (SCID)	36
Seligman et al., (2007) United States	Depression	Adults (not available) Universities Indicated	Depression (BDI ≥ 24)	No depression (9 < BDI ≤ 24)	240 (127/113)	1. Classroom based workshop; web-based materials, coach e-mails and face-to-face-boosters (Workshop: CB techniques based on Beck's and colleagues' cognitive therapy for depression; 8 sessions; group) Web-based (any time; individual)	Trained and experienced cognitive therapists	Depressive symptoms (BDI) Incidence of depression (SCID)	6

						Coach e-mails (6 e-mails that contained refreshers of the skills they learned in the workshop) Face-to-face boosters (when participants had an increase of four or more points on the BDI) 2. CAU			
Silverstein et al., (2018) United States	Depression	Low income mothers (mean age 31.4, standard deviation 7.3 years) Community (Preschool centers) Indicated	Current MDE (MINI)	At risk for depression (PHQ-2) or recent history of depression (CIDI)	230 (119/111)	1. Problem-solving education (CB intervention; 6 sessions, individual) 2. Usual Head Start services	Trained lay intervention providers (not licensed mental health clinicians)	Depressive symptoms (QIDS) Incidence of depression (SCID)	2-4-6-8-10-12
Stice et al., (2010) United States	Depression	Adolescents (14-19 years) Schools Indicated	Current MD (adapted version of the K-SADS)	Depression symptoms (CES-D ≥20)	341 (80/84/ 88/89)	1. CB intervention (CB program; 6 sessions; group) 2. Supportive-expressive group (nonspecific factors in supportive-expressive treatment; 6 sessions; group) 3. Bibliotherapy (CB skills in bibliotherapy) 4. No intervention	Clinical graduate student	Incidence of depression and depressive symptoms (adapted version of the K-SADS)	6
Thompson et al., (2015) United States	Depression	Adults (21-70 years) with epilepsy Medical clinics Indicated	Depression (CES-D>27 or PHQ-9)	Depression symptoms (CES-D >8)	118 (56/62)	1. UPLIFT intervention (Activities and discussions are designed to increase knowledge about depression; monitoring, challenging, and changing of thoughts; coping and relaxing; attention and mindfulness; focusing on pleasure; the importance of reinforcement; and preventing relapse (8 sessions; individual and group) 2. Waiting list	Graduate students with a Mental Health concentration in Public Health, and selected adults with epilepsy	Depressive symptoms (BDI) Incidence of depression (PHQ-9)	2,5
Topper et al., (2017) Netherlands	Depression and anxiety	Adolescents and adults (15-22 years) Schools and universities Selective	GAD (GADQ-IV) Self-report Diagnosis of depression (PHQ-9)	75th percentile on PSWQ (≥ 50) or RRS (≥ 40) and 66th percentile on PSWQ (≥ 47) or RRS (≥ 38). No MD and/or GAD (PHQ-9) and absence of concurrent treatment for mental health problems	251 (85/166)	1. Rumination-focused CBT group version (CBT; 6 sessions; group or internet) 2. Rumination-focused CBT internet version (CBT; 6 sessions; group or internet) 3. Waiting list control	Therapists graduated in clinical psychology	Depressive symptoms (BDI-II) Incidence of generalized anxiety disorder (GADQ-IV)	3-12
Trudeau et al., (2016) United States	Depression	Young adults (mean age 12.3 years) and their families Schools Universal	NA	NA	670 (219/451)	1. LifeSkills Training (LST) and Strengthening Families Program (SFP): For Parents and Youth (LST is based on social learning theory -Bandura 1977- and problem behavior theory -Jessor and Jessor 1977-; 15 sessions and booster sessions; group; SFP program is based upon empirically-supported family risk and protective factors; 7 sessions and booster sessions; group) 2. LifeSkills Training (LST) only 3. CAU	Trained teachers	Depressive symptoms (Young Adult Depression Symptoms the Diagnostic Interview Schedule)	120
Van der Gucht et al., (2018) Belgium	Depression and anxiety	Adolescents (14-17 years) Schools Universal	NA	NA	408 (207/201)	1. School-based mindfulness program (Mindfulness; 8 sessions; group) 2. No intervention	Experienced mindfulness trainers: psychologists and a medical doctor	Depressive symptoms (DASS-21) Anxious symptoms (DASS-21)	0.25-6
Vuijk et al., (2007)	Depression	Early adolescents; 2nd grade	NA	NA	448	1. Good Behavior Game intervention (Behavior	Trained teachers	Anxious and depressive	24

Netherlands	and anxiety	(7 years) Schools Universal			(not available)	management strategy that promotes prosocial behavior and reduces aggressive and disruptive behaviour; number of sessions not available; group) 2. CAU		symptoms (RCADS)	
Westerhof et al., (2010) Netherlands	Depression	Older adults (51-90 years) (mean age 64.3, standard deviation 7.4) Community (newspapers and magazines targeted) Indicated	Depression (CES-D≤4)	No major depressive disorder (MINI)	171 (88/83)	1. Life review intervention 'Looking for Meaning' (Life review, elements of creative therapy and problem-solving therapy; 12 sessions; group) 2. Educational video movie "The Art of Growing Older"	Mental health care professionals	Depressive symptoms (CES-D)	3-9
Yang et al., (2015) China	Depression	Young adults (18-22 years) (mean age 19.57, standard deviation 0.87) Schools Indicated	Depression BDI-II < 14 and Major depressive disorder (SCID-IV)	Symptoms of depression (BDI-II≥14)	77 (27/23/27)	1. Attention Bias Modification training (Stimuli; 8 sessions; individual and group) 2. Placebo 3. CAU	Screen computer / None provider	Depressive symptoms (BDI-II)	3-7
Zoellner et al., (2011) United States	Anxiety	Adults women (mean age 33.7, standard deviation 11.14) Emergency rooms, victim assistance agencies, police officers and advertisements. Indicated	PTSD (SCID-IV)	DSM-IV symptom, not duration, criteria for PTSD (SCID-IV)	90 (30/29/31)	1. B-CBT (CB procedures: pychoeducation, breathing retraining, imaginal exposure, in vivo exposure and cognitive restructuring; 4 sessions; group) 2. Supportive Counseling (Active listening only; 4 sessions; group) 3. CAU	Master's or Ph.D. therapists	PTSD symptoms (PSS-I)	2-3-6-9-12

Notes to **Exclusion at baseline-** MD= Major depression, CIDI= Composite International Diagnostic Interview, PHQ-9= Patient Health Questionnaire-9, HADS-A= Hospital Anxiety and Depression Scale-anxiety subscale, CES-D= Center for Epidemiological Studies Depression Scale, ADIS-IV= Anxiety Disorders Interview Schedule for DSM-IV, NA= not applicable, DSM-IV= Diagnostic and Statistical Manual of Mental Disorders-IV, MDE= Major Depressive Episode, MINI= Mini International Neuropsychiatric Interview, PD= Panic disorder, DIS= Diagnostic Interview Schedule, BDI= Beck Depression Inventory, SCID=Structured Clinical Interview for DSM-IV, K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age children, GAD= Generalized Anxiety Disorder, GADQ-IV= Generalized Anxiety Disorder Questionnaire-IV, SCID= Structured Clinical Interview for DSM-IV, PTSD= Post-traumatic Stress Disorder. **Inclusion criteria-** BDI= Beck Depression Inventory, PHQ-9= Patient Health Questionnaire-9, NA= not applicable, CES-D= Center for Epidemiological Studies Depression Scale, ADIS= Anxiety Disorders Interview Schedule, CDI= Children's Depression Inventory, HADS= Hospital Anxiety and Depression Scale, PD= Panic disorder, PDSS-SR= Panic Disorders Severity Scale-Self Report, ASQ= Attributional Style Questionnaire, PHQ-2= Patient Health Questionnaire-9, CIDI= Composite International Diagnostic Interview, PSWQ= Penn State Worry Questionnaire, RRS= Ruminative Response Scale, GAD= Generalized Anxiety Disorder, MINI= Mini International Neuropsychiatric Interview, PTSD= Post-traumatic Stress Disorder, SCID= Structured Clinical Interview for DSM-IV. **Sample-** *= only the sample categorised as non-cases (HADS 0–7). **Experimental conditions-** CBI= Cognitive Behavioral Intervention, CB= Cognitive Behavioral, ACT= Acceptance and Commitment Therapy, CAU= Care As Usual, TAU= Treatment As Usual, B-CBT= Brief Cognitive Behavioral Therapy. **Outcomes-** BDI= Beck Depression Inventory, CIDI= Composite International Diagnostic Interview, CDI= Children's Depression Inventory, EATQ-R= Early Adolescent Temperament Questionnaire Revised- depressive mood subscale, PHQ-9= Patient Health Questionnaire-9, SCAS= Spence Children's Anxiety Scale, RCADS= Revised Child Anxiety and Depression Scale, HADS-A= Hospital Anxiety and Depression Scale- anxiety subscale, CES-D= Center for Epidemiological Studies Depression Scale, ADIS-IV= Anxiety Disorders Interview Schedule for DSM-IV, HADS-T= Hospital Anxiety and Depression Scale- total score, DIS= Diagnostic Interview Schedule, BAI= Beck Anxiety Inventory, SCID= Structured Clinical Interview for DSM-IV, QIDS= Quick Inventory of Depressive Symptoms, BDI-II= Beck Depression Inventory II, GADQ-IV= Generalized Anxiety Disorder Questionnaire-IV, DASS-21=The 21-item Depression Anxiety Stress Scales, PTSD= Post-traumatic Stress Disorder, PPSS-I= PTSD Symptom Scale- Interview Version.

APPENDIX C. Evidence of the identified potential mediators for depression.

Mediators	**All studies (n= 23)**				
Depression	**Studies**	**Significant studies**			**No significant studies**
Adults		**Good** [a]	**Satisfactory** [b]	**Unsatisfactory** [c]	
Cognitive					
Explanatory style (optimistic)	Seligman et al. (1999)		✓		
	Seligman et al. (2007)			✓	
Knowledge/skills	Thompson et al. (2015)			✓	
Mastery	Silverstein et al. (2018)				✓
Negative thinking	Allart-van Dam et al. (2003-2007)		✓		
	Muñoz et al. (1995)		✓		
	Seligman et al. (1999)		✓		
Perceived stress	Silverstein et al. (2018)		✓		
Personal meaning	Westerhof et al. (2010)			✓	
Physical and mental health qualities of life	Thompson et al. (2015)				✓
Positive thoughts	Muñoz et al. (1995)		✓		
Psychological flexibility	Fledderus et al. (2013)		✓		
Self-compassion	Thompson et al. (2015)				✓
Self-efficacy	Thompson et al. (2015)				✓
Self-esteem	Allart-van Dam et al. (2003-2007)		✓		
	Seligman et al. (1999)				✓
	Silverstein et al. (2018)				✓
Behavioral					

Avoidant coping	Silverstein et al. (2018)			✓
Behavioral activation	Silverstein et al. (2018)			✓
Pleasant activities	Allart-van Dam et al. (2003-2007) Muñoz et al. (1995)			✓ ✓
Problem focus coping	Silverstein et al. (2018)			✓
Problem solving	Silverstein et al. (2018)			✓
Emotional				
Emotion focused coping	Li et al. (2014)	✓		
Hopelessness	Seligman et al. (1999)	✓		
Satisfaction with life	Thompson et al. (2015)		✓	
Interpersonal				
Frequency of social support	Allart-van Dam et al. (2003)			✓
Social coping	Silverstein et al. (2018)			✓
Social impairment	Rovner et al. (2014)	✓		
Social skills	Allart-van Dam et al. (2003-2007)			✓
Use of network	Muñoz et al. (1995)			✓
Children and adolescents				
Cognitive				
Attributional style	Horowitz et al. (2007)	✓ (CB partially)		✓ (IPT)
Attitudes toward school	Duong et al. (2016)			✓
Change of attention bias	Yang et al. (2015)			✓

Explanatory style	Brunwasser et al., (2018)			✓
Irrational beliefs	David et al. (2018)	✓		
Knowledge/skills	Horowitz et al. (2007)	✓ (IPT partially)		✓ (CB)
Negative thinking	David et al. (2018)			✓
	Pössel et al. (2005)			✓
	Stice et al. (2010)			✓
	Van der Gucht et al. (2018)		✓	
Self-compassion				
Self-coldness	Van der Gucht et al. (2018)		✓	
Self-kindness	Van der Gucht et al. (2018)			✓
Worry-rumination	Topper et al. (2017)	✓		
	Yang et al. (2015)	✓		
Behavioral				
Coping	Horowitz et al. (2007)			✓
Health behavior	Duong et al. (2016)			✓
Pleasant activities	Stice et al. (2010)			✓
Use of illicit substances at 21 years old	Trudeau et al. (2016)	✓		
Emotional				
Emotional expression	Stice et al. (2010)			✓
Loneliness	Stice et al. (2010)			✓
Interpersonal				
Interpersonal conflicts/problems	Fosco et al. (2016)		✓	
	Horowitz et al. (2007)			✓
	Trudeau et al. (2016)	✓		
Network size	Pössel et al. (2005)			✓

Parent-child communication	Duong et al. (2016)		✓
Physical victimization	Vuijk et al. (2007)		✓
Relational victimization	Vuijk et al. (2007)	✓	
Use of network	Pössel et al. (2005)		✓

Notes: CB= cognitive-behavioral, IPT= Interpersonal Psychotherapy

[a]Good: if the total score for the risk of bias in an RCT is low and the study meets three out of three requirements.

[b]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.

[c]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.

APPENDIX D. Evidence of the identified potential mediators for anxiety.

Mediators	**All studies (n= 11)**				
Anxiety	**Studies**	**Significant studies**			**No significant studies**
Adults		**Good** [a]	**Satisfactory** [b]	**Unsatisfactory** [c]	
Cognitive					
Explanatory style	Seligman et al. (1999)				✓
Locus of control	Meulenbeek et al. (2010)				✓
Negative thinking	Seligman et al. (1999)		✓		
Perceived likelihood of panic occurrence	Meulenbeek et al. (2010)		✓		
Perceived negative consequences of panic occurrence	Meulenbeek et al. (2010)				✓
Perceptions of one's safety	Zoellner et al. (2011)		✓		
Perceptions of self	Zoellner et al. (2011)		✓		
Perceived self-efficacy	Meulenbeek et al. (2010)		✓		
Psychological flexibility	Fledderus et al. (2013)		✓		
Self-esteem	Seligman et al. (1999)				✓
Emotional					
Emotion focused coping	Li et al. (2014)		✓		
Hopelessness	Seligman et al. (1999)				✓
Children and adolescents					
Cognitive					

Negative thinking	Ginsburg et al. (2015) Van der Gucht et al. (2018)		✓	✓
Perfectionism	Essau et al. (2012)		✓	
Self-compassion				
Self-coldness	Van der Gucht et al. (2018)		✓	
Self-kindness	Van der Gucht et al. (2018)			✓
Worry-rumination	Topper et al. (2017)	✓		
Behavioral				
Assistance seeking	Essau et al. (2012)			✓
Behavioral avoidance	Essau et al. (2012)		✓	
Cognitive avoidance	Essau et al. (2012)		✓	
Problem solving	Essau et al. (2012)			✓
Interpersonal				
Parental anxiety	Ginsburg et al. (2015)			✓
Parental global distress	Ginsburg et al. (2015)	✓		
Parental modelling of anxiety	Ginsburg et al. (2015)	✓		
Parental satisfaction	Essau et al. (2012)			✓
Physical victimization	Vuijk et al. (2007)			✓
Reinforcement of dependence	Casline et al. (2018)	✓		
Relational victimization	Vuijk et al. (2007)		✓	
Social and adaptative functioning	Essau et al. (2012)			✓
Social skills	Essau et al. (2012)			✓

[a]Good: if the total score for the risk of bias in an RCT is low and the study meets three out of three requirements.
[b]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.
[c]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.

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.

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 7,442 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.

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

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INTRODUCTION

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 et al., 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; WHO, 2014). Some of them, such as loneliness and alcohol misuse, are modifiable risk and protective factors; therefore, they can be changed (WHO, 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, Jané-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).

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~~, were aimed at reducing symptoms (depression or anxiety),~~ 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).

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, ~~but may not explain the precise process through which change comes about. M~~mechanism of change ~~refers to a greater level of specificity than does the term mediator and~~ reflects the steps or processes through which the intervention produces the change~~. Mechanism~~ 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. ~~often a first step toward understanding the mechanisms of change.~~

Requirements for a mediator

~~In psychological research, Kazdin (2003, 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 ($p<0.05$). The second is the *specificity* of the association, which means that the mediator is specific for a particular type of therapyother apparently possible constructs do not explain the change in the outcome with the exception~~

of the one proposed. 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 all of these requirements should enhance the strength of evidence, specially/mainly, in line with Kazdin, the requirements of .

Prior to the requirements proposed by Kazdin (2003, 2007), Baron & 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 et al., 2007a). 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, & Agras (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, Williams, & Lockwood, 2007b) address such sampling problems. They are also likely to be more accurate than traditional mediation analysis according to Baron & Kenny (Mackinnon et al., 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, & 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, & Gil (2006) and Muthén & 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 & Willet 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 (2003, 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 ($p<0.05$). 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).

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 ~~M~~mediators identified in these systematic reviews were ~~can be organized into cognitive:~~ rumination and worries (Lemmens et al., 2016; van der Velden et al., 2015), ~~or~~ threat reappraisal (Smits et al., 2012), ~~; behavioral:~~ fear of extinction (Powers et al., 2017) and ~~; and emotional:~~ 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).

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.

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).

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.

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, Wilson, Fairburn, & Argas, 2002). Studies had to examine the psychological mediators and, in addition, they had to ~~include~~ conduct statistical mediation analyses ~~in their analysis plan~~ (Baron and 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.

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.

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 ~~a set~~ 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: ~~*strong association* (as expressed by statistical significance of p<0.05),~~ *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<0.05) 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 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 ($p < 0.05$) (see Table 1).

****Insert Table 1 ****

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* (less than 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 Figure 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.

****Insert Figure 1 ****

RESULTS

Search results

As a result of the search strategies, we obtained 8,656 records. After eliminating the duplicates, a total of 6,657 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 (Figure ~~1~~2).

****Insert Figure ~~1~~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 7,442 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 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.

Mediators identified

The identified RCTs examined 63 potential mediators (Table ~~1~~2 and Figure 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.

****Insert Table ~~1~~ 2 ****

****Insert Figure 3 ****

****Insert Box 1****

Depression

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, Hosman, & Hoogduin, 2003; Allart-van Dam et al., 2007; 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 (2013) classified 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, Cardos & 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.

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; 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.

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.

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; 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.

Anxiety

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 counselling, 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, & 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).

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.

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).

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*, *parental modelling anxiety* 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, Pella, Zheng, Harel, Drake, & Ginsburg (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.

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 ~~2~~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 ~~1~~2, in Appendix C and in Appendix D.

****Insert Table ~~2~~ 3 ****

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 Figure ~~2~~4.

****Insert Figure ~~2~~ 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 (Figure ~~3~~5).

****Insert Figure ~~3~~ 5 ****

Global evidence (levels of scientific evidence)

The information about levels of scientific evidence can be found in Table ~~3~~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 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.

~~All this information can be found in Table 3 and in more detail in Appendix C and in Appendix D.~~

****Insert Table ~~3~~ 4 ****

DISCUSSION

Main findings

Through a systematic review, we selected 26 RCTs with mediator analyses for the prevention of depression and/or anxiety including 7,442 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 examined indicative prevention programs while in children and adolescents the most used prevention programs were universal programs.

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.

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 & 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.

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 ~~strong~~greater evidence for cognitive variables. ~~.~~ s~~S~~pecifically, negative thinking. ~~provided the strongest evidence.~~ 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 Valden 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.

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 et al., 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, 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).

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.

Conflict of Interest

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

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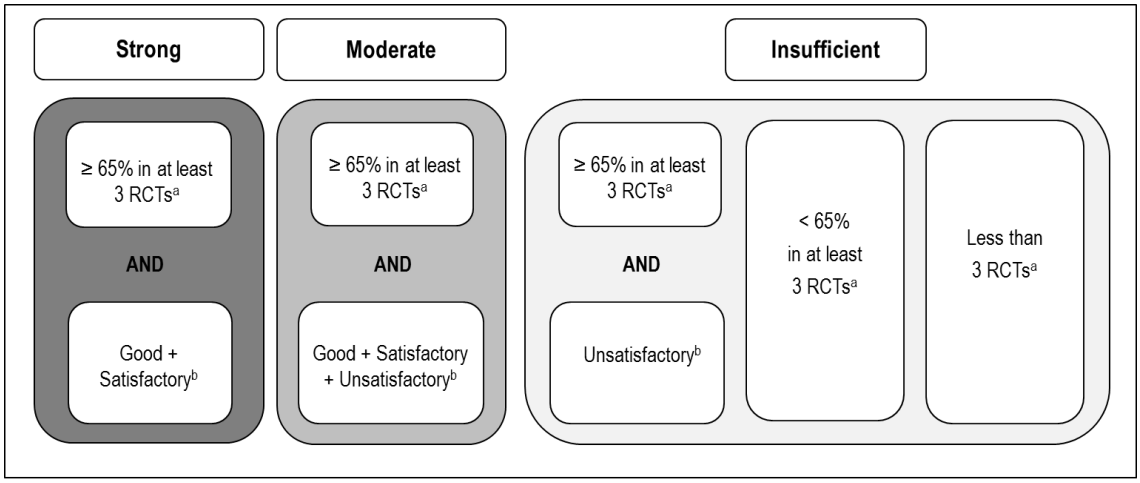
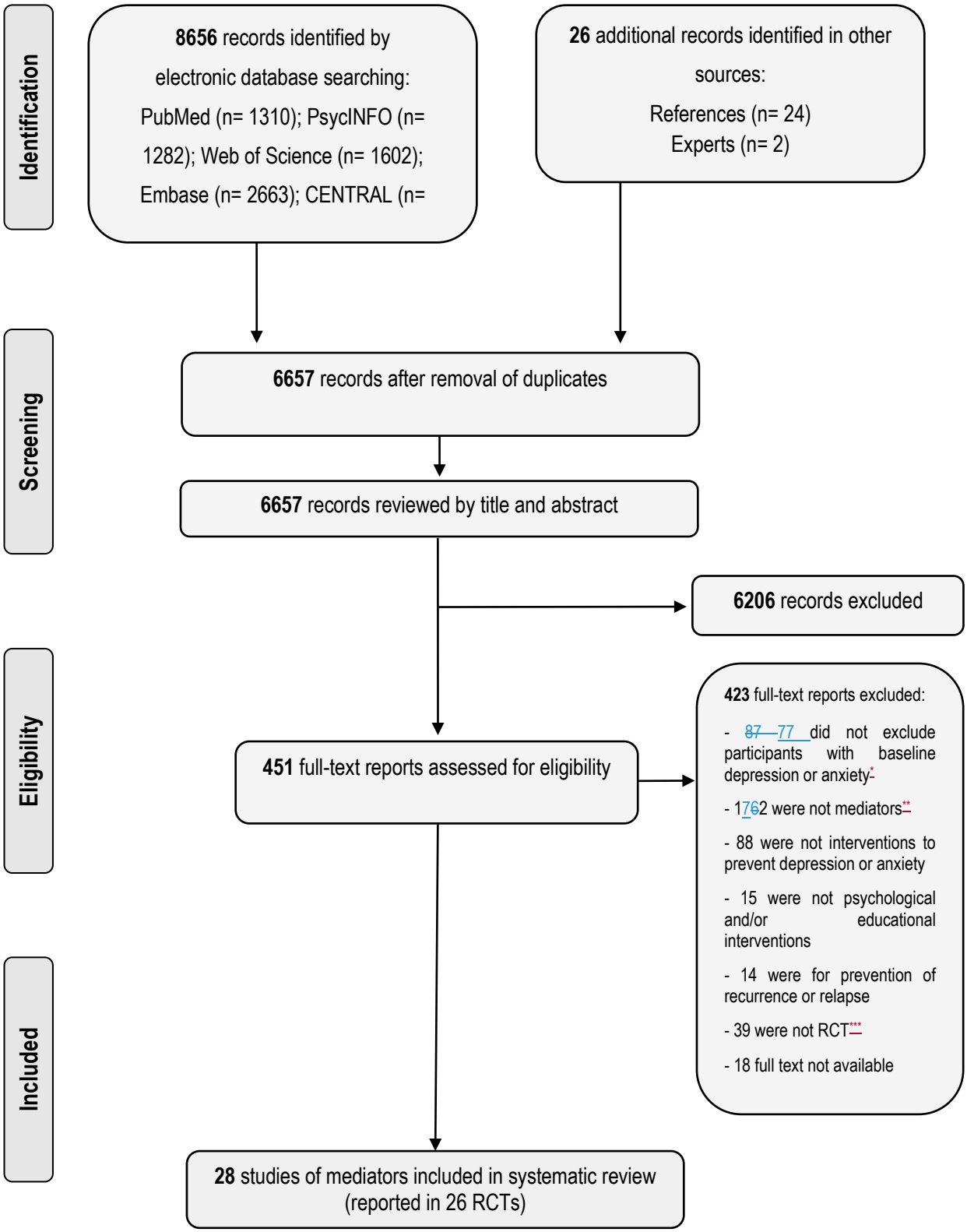
* Studies included in the review.

Figure



[a]Mediators significantly associated [b]Combination of methodological quality

Figure 1. Scheme about levels of scientific evidence.



*At the beginning of the study all the participants in the trial for the prevention of depression or anxiety were not free of depression or anxiety. **The study was not focus on mediators; they had not the aim of finding statistical mediators associated with the change. ***Many studies talk or proposed the performance of a RCT but the study was not a RCT indeed

Figure ~~1~~2. PRISMA Flowchart of the studies reviewed and included.

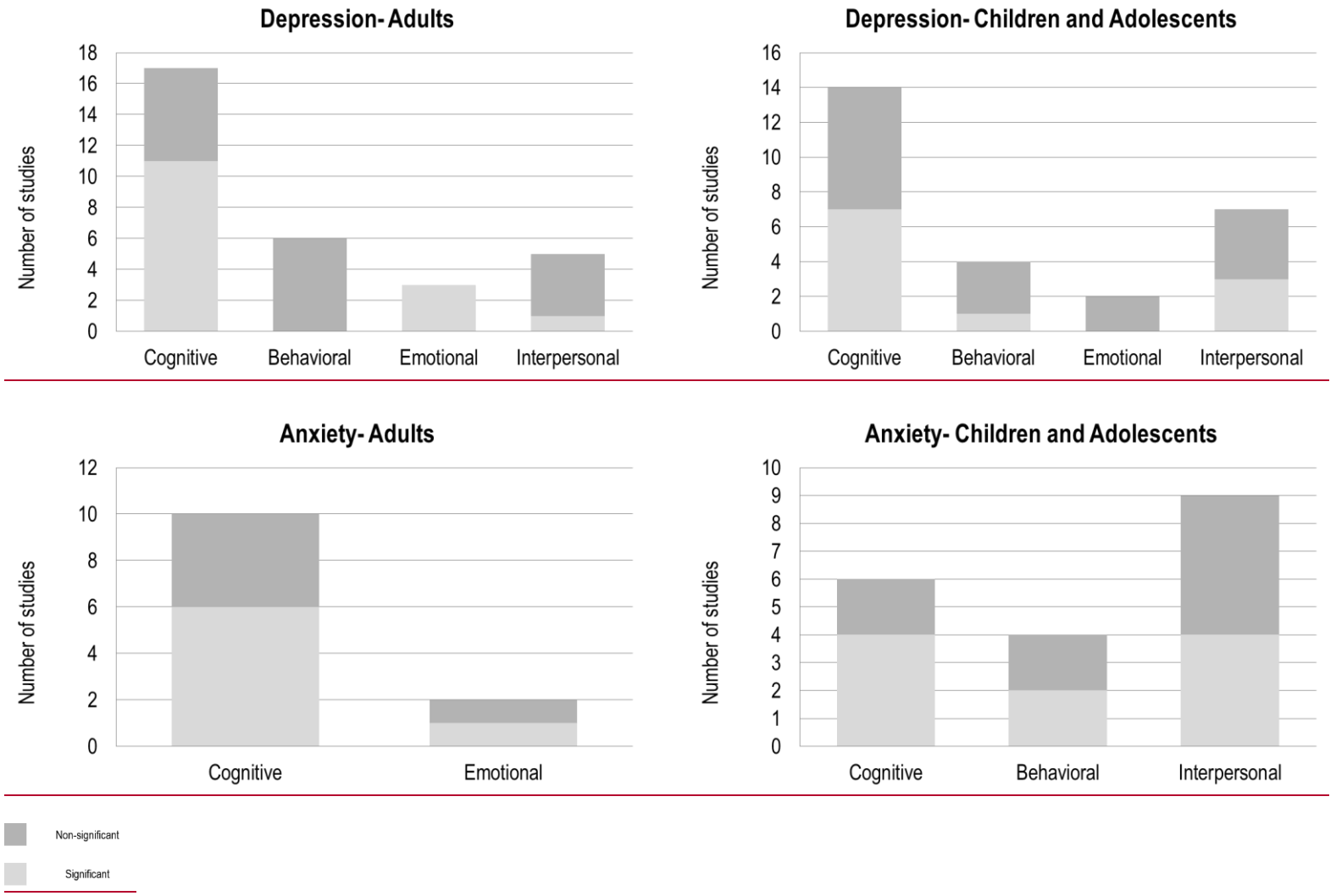


Figure 3. Mediators identified by group of age and by pathology.

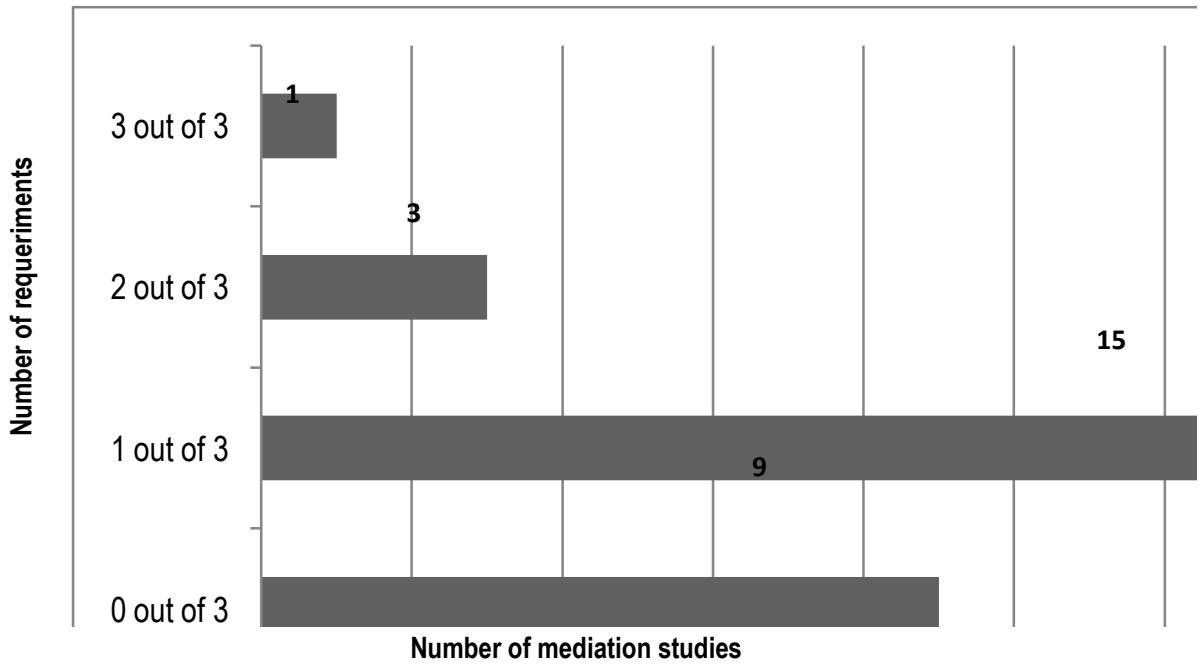


Figure ~~2~~4. Requirements: number of mediation studies per number of requirements met.

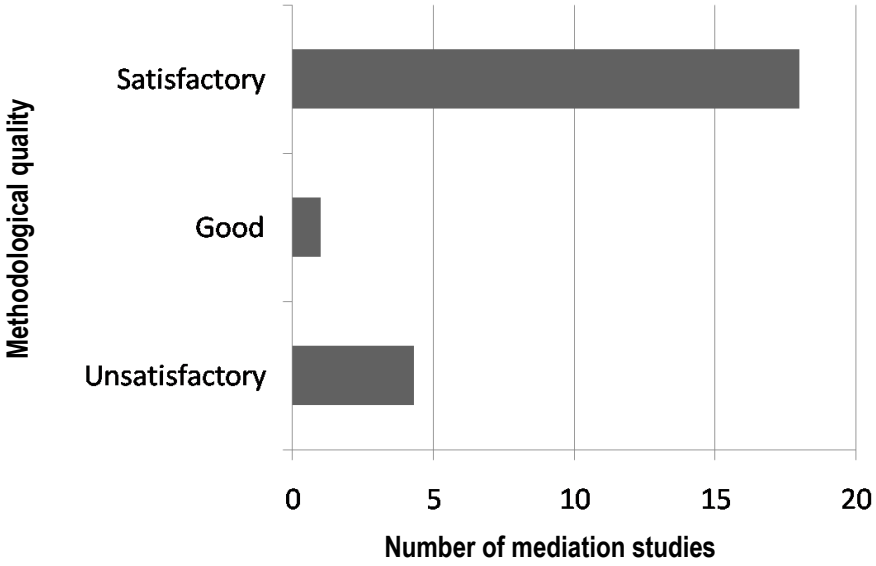


Figure ~~35~~. Methodological quality of each of the mediation studies.

Table

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Conflict of Interest

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

Appendix