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Title: **Effectiveness of online interventions in preventing depression: A protocol for systematic review and meta-analysis of randomized controlled trials.**

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ABSTRACT

Introduction: Although evidence exists for the efficacy of psychosocial interventions in preventing depression, little is known about its prevention through online interventions. The objective of this study will be to conduct a systematic review and meta-analysis of randomized controlled trials assessing the effectiveness of online interventions in preventing depression in heterogeneous populations.

Methods and analysis: We will conduct a systematic review and meta-analysis of randomized controlled trials that will be identified through searches of PubMed, PsycINFO, WOS, Scopus, OpenGrey, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and Australia New Zealand Clinical Trials Register (ANZCTR). We will also search the reference lists provided in relevant studies and reviews. Experts in the field will be contacted to obtain more references. Two independent reviewers will assess the eligibility criteria of all articles, extract data and determine their risk of bias (Cochrane Collaboration Tool). Baseline depression will be required to have been discarded through standardized interviews or validated self-reports with standard cut-off points. The outcomes will be the incidence of new cases of depression or/and the reduction of depressive symptoms as measured by validated instruments. Pooled standardized mean differences will be calculated using random-effect models. Heterogeneity and publication bias will be estimated. Predefined sensitivity and subgroup analyses will be performed. If heterogeneity is relevant, random-effect meta-regression will be performed.

Ethics and dissemination: The results will be disseminated through peer-reviewed publication and will be presented at a professional conference. Ethical assessment is not required as we will search and assess existing sources of literature.

PROSPERO Registration number: CRD42014014804.

Strengths and limitations of this study

- This is the first systematic review and meta-analysis of randomized controlled trials assessing the effectiveness of online interventions in preventing depression in a heterogeneous population.
- The study will be conducted according to PRISMA-P guidelines for protocols, addressing those aspects that the PRISMA-P consensus suggests for a SR-MA to have the highest scientific quality.
- The effect size, robustness and quality of evidence found in this meta-analysis will help determine whether depression can be prevented through online interventions.
- This study will have the limitations inherent to any systematic review and meta-analysis, such as the loss of information on outcome variables, or the assumption that the evaluation techniques are consistent across studies.
- The number and quality of the RCTs included, heterogeneity, and occurrence of publication bias might limit the interpretation of results. Yet, the magnitude and direction of these potential limitations will be assessed.

INTRODUCTION

Depression is a common, resource-consuming and disabling mental disorder that reduces life expectancy [1]. There are currently 322 million people with depression in the world [2]. The average lifetime and 12-month prevalence estimates of DSM-IV Major Depression Episode in high-income countries are 14.6% and 5.5%, respectively [3]. In the last ten years, the burden of major depression measured as years lived with disability (YLD) increased by 17.8%, ranking third in the world in disease burden [3] and will rank first in high-income countries by 2030 [4]. In addition, depression is the primary cause of disability in the world attributable to mental and substance use disorders [5].

Current treatments for depression show several constraints such as accessibility issues, limited efficacy, or lack of adherence [6–8]. Even if it was possible to provide appropriate treatments to all persons affected by a depressive disorder, the effect on averting YLD would be limited because of the steady influx of new cases of depression [9]. For all these reasons the burden of depression can only be reduced by 20-30% [10]. Prevention may offer new possibilities to reduce the disease burden of depressive disorders [11,12].

Hundreds of randomized controlled trials (RCTs) and dozens of systematic reviews / meta-analysis (SR/MA) have been published on interventions to prevent depression [13–17]. A systematic review of SR/MA of psychological and/or educational interventions to prevent depression included 12 SR/MA (156 non-repeated trials and 56,158 participants) and found a small-moderate preventive effect [18]. If preventive interventions reach a significant part of the population, even if this effect size is small, the impact on health, quality of life and healthcare costs could be relevant. From this point of view, scalability is crucial to prevention interventions. Solutions may leverage technological advances, such as mHealth-based counselling, computer and web-based resources [19].

Interest in online prevention programs for depression has increased substantially in recent years [20–22]. Online interventions offer some advantages over face-to-face interventions for both, patients and the health system. Its advantages include greater intimacy, lower economical costs, the opportunity of joining the intervention at any time and place, easy access to a wider range of people (disabled population, rural areas, etc.) and a reduction in the time of waiting, among others [23–27].

So far, three SR/MA on the effectiveness of online interventions in preventing mental disorders have been published [28, 29, 30]. To our knowledge, these previous reviews have some limitations. One [28] was focused on several mental disorders altogether (Eating, Anxiety, Insomnia, Post-Traumatic Stress, Depression and Common Mental Health Disorders) and included only four trials on the prevention of depression. A limitation was the inclusion of some studies that only reported mean scores and did not clearly state that participants did not exceed clinical cut-offs at baseline, thus making it difficult to separate treatment from prevention. The other [29] was focused on the online cognitive behavioural therapy for subthreshold depression, which restricts its inference for that kind of psychotherapy and only for a type of prevention, indicated prevention; not addressed, thus, universal and selective prevention strategies. In addition new RCTs on online interventions for the prevention of depression have been published [31–35]. The last SR/MA [30] found a small preventive effect of the eHealth interventions to prevent anxiety and

depression; however, there were some exclusion criteria which limited their inferences: age (18-64 years), language (English), date (from 2000) and non-specific population (e.g. post-natal or comorbid). Therefore, the objective of this study will be to conduct a systematic review and meta-analysis of randomized controlled trials assessing the effectiveness of online interventions in preventing depression in heterogeneous populations.

METHODS AND ANALYSIS

We followed PRISMA-P guidelines for reporting systematic reviews and meta-analysis protocols [36]. The protocol of this study has already been registered with the International Prospective Register of Systematic Reviews, (PROSPERO) on 20 November 2014 and was last updated on 23 November 2017 (registration number: CRD42014014804).

Eligibility criteria

The rationale for the inclusion and exclusion criteria outlined below is to obtain a comprehensive overview of the RCTs performed so far assessing the effectiveness of online interventions in preventing depression in different populations and settings.

Study design

We will focus on randomized controlled trials (RCT) since this design provides more evidence on causality and is considered a gold-standard for clinical trials [34]. Cluster randomized trials will only be included if there are at least two intervention and control sites and outcomes are reported adjusted for clustering effect. Controlled non-randomized clinical trials or before-after trials will be excluded.

Participants and exclusion of depression at baseline

Participants may have any sociodemographic (age, sex, etc.) or clinical (healthy, chronic physical illness, etc.) characteristic and all settings (community, schools, primary care, etc.) will be considered. To make a clear distinction between the effectiveness of prevention interventions from that of treatments, baseline depression will be required to have been discarded through standardized interviews (eg. CIDI) or validated self-reports with standard cut-off points (eg, BDI-II). In a preventive context, the most useful parameter of validity of a diagnostic instrument to discard depression at baseline is the “negative predictive value” (NPV): probability of having a depressive disorder when the result of a diagnostic tool is negative. The NPV is influenced by three main parameters: cut-off selected, sensitivity associated with that cut-off and prevalence of anxiety disorders in the reference population of the study. Higher sensitivity, lower cut-off and prevalence will increase the NPV and minimize false negatives. Structured standardized interviews generally have greater validity than symptom scales and, therefore, the former are preferable. However, structured standardized interviews tend to have greater specificity than sensitivity; therefore, false positives will be minimized at the expense of increasing false negatives. From this point of view, a

symptoms scale with a diagnostic threshold associated with high sensitivity could guarantee as valid as a structured standardized interview, especially if the study is carried out on a reference population with a low prevalence of depressive disorders, as it is usual in prevention studies.

Type of interventions

We will only include RCTs assessing the effectiveness of psychological and/or educational and/or social interventions, since they share the same mechanism of action that facilitates changes in attitudes and behaviours and because most interventions to prevent depression are of this type. Interventions must be accessible online and the study should include at least an internet-delivered intervention program. If no on-line intervention is implemented in any of the experimental arms, the RCT will be excluded. Intervention arms where active pharmacological therapies are administered will also be excluded.

Comparators

Comparator groups could be “only assessments”, “no treatment”, “usual care”, “waiting list”, or any type of active control which has no effect on depression. All types of placebo (psychological or pill) will also be accepted as comparators. Comparator arms which intervention (psychological, physical or pharmacological) has been proven to be effective in preventing depression will also be excluded.

Outcomes

RCTs which primary or secondary outcomes were the incidence of new cases of depression and/or the reduction of depression symptoms will be included. Outcomes will be required to have been measured by standardized interviews or validated symptom scales. When more than a symptom scale has been used to measure outcomes in a RCT, the data from the highest validity scale will be employed, while at equal validity; the largest effect size will be used. If depression outcomes are measured together with other outcomes (e.g. anxiety) and data are not provided separately, RCTs will be excluded.

Information sources and search strategy

A literature search of the following electronic databases will be carried out: PubMed, PsycINFO, WOS and Scopus. Search will be supplemented by searching for trial protocols on Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and Australia New Zealand Clinical Trials Register (ANZCTR). We will also examine OpenGrey (System for Information on Grey Literature in Europe), where grey literature is indexed. PROSPERO will be searched for ongoing or recently completed systematic reviews. To ensure literature saturation we will also review reference lists from relevant systematic reviews and meta-analysis and those from the RCTs included in our SR/MA. In addition, expert authors will be contacted in order to identify missing articles in our search. Literature search strategies will be developed using medical subject headings (MeSH) and text words related to prevention, depression and internet

intervention. No limits will be imposed on study publication language or publication date. The search will be updated toward the end of the review. A draft MEDLINE search strategy is included in supplementary file 1. We will adapt the MEDLINE strategy to the syntax and subject headings of the other databases.

Study selection

The entire selection process will be conducted independently by two reviewers. After elimination of duplicate studies, all records will be reviewed. Based on their titles and abstracts, the studies that do not meet inclusion criteria will be ruled out. The full text of the studies selected as potentially relevant will be reviewed for further assessment. Any disagreements will be discussed and resolved by consensus or by a third independent reviewer, if necessary. We will seek additional information from corresponding authors when necessary to resolve questions about eligibility. We will record the reasons for excluding trials. The reviewers will not be blind to the journal titles or the study authors or institutions. Inter-agreement of the total selection will be assessed using Kappa [37], which can be interpreted as follows: < 0.20 as poor, 0.21 - 0.40 as fair, 0.41 - 0.60 as moderate, as 0.61 - 0.80 as good and 0.81 - 1.00 as excellent.

Data extraction

Data extraction from each eligible study will be conducted independently by two reviewers. Any disagreement will be discussed and resolved by consensus or by a third independent reviewer. We will also contact authors to get incomplete or unclear information, where appropriate. Abstracted data will include author/year and country; setting, target population characteristics (age, sex, etc.) and type of prevention (universal, selective or indicate); sample size (control/intervention); exclusion of depression criteria at baseline and validated instruments used; orientation and intervention type and intervention details in both experimental and control groups (type, modes of application, frequency, intensity and level of adherence); prevention depression outcomes and validated instruments used; and follow-up. Whenever possible, we will use results from intention-to-treat analysis.

Risk of bias

The quality of the articles will be assessed using the six criteria of risk bias proposed by the Cochrane Collaboration tool: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data (e.g. dropouts and withdrawals) and selective reporting. To manage the risk of bias as a quantitative variable in meta-regression, it will be assessed by assigning the zero points to low-risk criteria, one to unclear and two to high-risk criteria. Therefore, the highest risk of bias score will be 12 and the lowest zero. The risk of bias will be assessed independently by two reviewers. In case of disagreement, a third reviewer will be consulted. The inter-agreement will be rated using Intraclass Correlation Coefficient [37]. The original study investigators will be contacted for more information, when necessary.

Assessment of publication bias

Publication bias will be evaluated by inspecting the funnel plot on the primary outcome measure and by Duval and Tweedie's trim-and-fill procedure [38], which yields an estimate of the effect size after adjusting for publication bias. The funnel plot is expected to be symmetric, equally dispersed on the general effect. If there are missing studies the trim and fill procedure imputes these studies and adds them to the analysis. We will also perform Begg and Mazumdar rank correlation [39] and Egger's test [40]. If asymmetry is potentially caused by publication bias, we expect to see high standard errors (small studies) associated with larger effect sizes.

Statistical analysis

All statistical analyses will be performed using the Comprehensive Meta-Analysis (CMA) software package, version 2.2.021 and STATA-Release-14.2. Standardized mean difference (SMD) will be used as effect size as most RCTs included in our meta-analysis are expected to report differences in symptoms of depression. For each study, we will first calculate the SMD by merging the SMD at different follow-up times into a single average estimate. We then will calculate the pooled SMD of all RCTs as well as its 95% confidence interval (CI). If some RCT only reports new cases of depression" (incidence of depression) CMA will be used to obtain the equivalent SMD. Negative SMDs (standardized mean differences between intervention and control group) will indicate a better outcome (reduction of depressive symptoms) in the intervention group. Following the interpretation proposed by Cohen for this effect size: -0.2 is small; -0.5 medium and -0.8 large [40]. We will inflate the standard errors of the nested comparisons in the same RCT following the suggestions of Cates [42]. *A priori*, we selected a random-effects model for our meta-analysis under the assumption that the RCTs to be included in our study will be performed in heterogeneous 'populations' that may differ from each other [43].

To test the heterogeneity of effect sizes, I^2 and its 95% confidence interval will be calculated and expressed as percentages, where a value of 0-40% might be unimportant heterogeneity, 30-60% moderate, 50-90% substantial and 75-100% considerable [43]. We will also calculate the Cochran's Q statistic and its P value.

We will perform the following sensitivity analyses: at first and last follow-up, using fixed effects and Hedges'g and excluding some RCTs from analysis (e.g. those which cause the greatest increase in heterogeneity).

We will use a mixed-effects model for sub-group analyses based on a set of variables selected a priori, as follows: type of prevention (universal, selective, or indicated), prevention of depression as primary or secondary outcome, type of outcome measure (symptoms scale versus standardized diagnostic interview), country, population age, setting (school, primary care,…), comparator (waiting list, usual care,

active control), intervention orientation (CBT, other), intervention format, intervention guidance (guided or unguided), number of sessions or impacts, follow-up, level of usability or adherence (if it was measured), sample size and risk of bias.

Random-effect meta-regressions will be performed to investigate whether there are differences in effect sizes over time or according to the risk of bias. Normality of quantitative variables will be verified by the Skewnes and Kurtosis normality test prior to inclusion in meta-regression analysis [44]; transformations will be conducted, when appropriate, to get approximation to normality when necessary. If significant heterogeneity is observed, the covariables with a $p<0.15$ which were not removed from the model due to collinearity will be also included in meta-regression models. Risk of bias and sample size will be forced into meta-regression models to adjust for them, the latter only in case of detection of publication bias. Standard error and confidence intervals will be calculated using the Knapp & Hartung method [45]. P-values will be calculated using Higgins & Thompson [46] permutation test approach, taking into account multiplicity adjustment, when necessary. A normal probability plot of standardized shrunken residuals will be used to estimate the goodness of fit of meta-regression models.

The quality of evidence

The quality of evidence in the domains of risk of bias, consistency, directness, precision and publication bias will be assessed using the Grading of Recommendations Assessment, Development and Evaluation working group methodology [47]. Additional domains may be considered, where appropriate.

Ethics and dissemination

The results will be disseminated through peer-reviewed publication and will be presented at a professional conference. Ethical assessment is not required as we will search and assess existing sources of literature.

Authors' contributions

AR is the guarantor. EM, PMP and JAB designed the study and the other authors collaborated on the design. AR drafted the protocol and EM and JAB revised the manuscript. AR, DMR, SCC and DSC will independently screen the potential studies, extract data, assess the risk of bias and finish data synthesis. JAB and PMP will perform data analysis. All authors read, provided feedback, discussed and approved the final manuscript.

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Competing interests

The authors all declare they have no competing interests. The funders had no direct role in the design of the study and they will have no input on the interpretation or publication of the study results.

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Supplementary file 1. Search Strategy.

The keywords and index terms we used in PubMed database were the following: ("depressive disorder"[MeSH Terms] OR "depressive disorder" OR depress* OR "depression"[MeSH Terms] OR "anxiety"[MeSH Terms] OR "anxiety"[All Fields]) AND prevent* AND ("internet"[MeSH Terms] OR "internet"[All Fields] OR web-based OR technology intervention OR "telemedicine"[MeSH Terms] OR "telemedicine"[All Fields] OR "ehealth"[All Fields] OR online OR "social networking"[MeSH Terms] OR ("social"[All Fields] AND "networking"[All Fields]) OR "social networking"[All Fields] OR computer* OR interactive OR "software"[MeSH Terms] OR "software"[All Fields]) AND (randomized controlled trial[Publication Type] OR trial[Title/Abstract]). Searches were piloted in PubMed then adapted to run across PsycINFO, WOS and Scopus. The search strategy was performed by two independent researchers (AR and DMR).

PRISMA-P checklist

Section and topic	Item No	Checklist item	Page
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2,5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	10
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	10
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	4,5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6,7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6,7
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7,8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7,8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	8,9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's, τ)	8,9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8,9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

BMJ Open

Effectiveness of online interventions in preventing depression: A protocol for systematic review and meta-analysis of randomized controlled trials.

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Keywords:	Depression & mood disorders < PSYCHIATRY, Prevention, Online, randomized controlled trial, Systematic review, Meta-analysis

Title: **Effectiveness of online interventions in preventing depression: A protocol for systematic review and meta-analysis of randomized controlled trials.**

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ABSTRACT

Introduction: Although evidence exists for the efficacy of psychosocial interventions in preventing depression, little is known about its prevention through online interventions. The objective of this study will be to conduct a systematic review and meta-analysis of randomized controlled trials assessing the effectiveness of online interventions in preventing depression in heterogeneous populations.

Methods and analysis: We will conduct a systematic review and meta-analysis of randomized controlled trials that will be identified through searches of PubMed, PsycINFO, WOS, Scopus, OpenGrey, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and Australia New Zealand Clinical Trials Register (ANZCTR). We will also search the reference lists provided in relevant studies and reviews. Experts in the field will be contacted to obtain more references. Two independent reviewers will assess the eligibility criteria of all articles, extract data and determine their risk of bias (Cochrane Collaboration Tool). Baseline depression will be required to have been discarded through standardized interviews or validated self-reports with standard cut-off points. The outcomes will be the incidence of new cases of depression or/and the reduction of depressive symptoms as measured by validated instruments. Pooled standardized mean differences will be calculated using random-effect models. Heterogeneity and publication bias will be estimated. Predefined sensitivity and subgroup analyses will be performed. If heterogeneity is relevant, random-effect meta-regression will be performed.

Ethics and dissemination: The results will be disseminated through peer-reviewed publication and will be presented at a professional conference. Ethical assessment is not required as we will search and assess existing sources of literature.

PROSPERO Registration number: CRD42014014804.

Strengths and limitations of this study

- This is the first systematic review and meta-analysis of randomized controlled trials assessing the effectiveness of online interventions in preventing depression in a heterogeneous population.
- The study will be conducted according to PRISMA-guidelines for reporting systematic reviews and meta-analysis to meet the highest scientific quality.
- The effect size, robustness and quality of evidence found in this meta-analysis will help determine whether depression can be prevented through online interventions.
- This study will have the limitations inherent to any systematic review and meta-analysis, such as the loss of information on outcome variables, or the assumption that the evaluation techniques are consistent across studies.
- The number and quality of the RCTs included, heterogeneity, and occurrence of publication bias might limit the interpretation of results.

INTRODUCTION

Depression is a common, resource-consuming and disabling mental disorder that reduces life expectancy [1]. There are currently 322 million people with depression in the world [2]. The average lifetime and 12-month prevalence estimates of DSM-IV Major Depression Episode in high-income countries are 14.6% and 5.5%, respectively [3]. In the last ten years, the burden of major depression measured as years lived with disability (YLD) increased by 17.8%, ranking third in the world in disease burden [3] and will rank first in high-income countries by 2030 [4]. In addition, depression is the primary cause of disability in the world attributable to mental and substance use disorders [5].

Current treatments for depression show several constraints such as accessibility issues, limited efficacy, or lack of adherence [6–8]. Even if it was possible to provide appropriate treatments to all persons affected by a depressive disorder, the effect on averting YLD would be limited because of the steady influx of new cases of depression [9]. For all these reasons the burden of depression can only be reduced by 20-30% [10]. Prevention may offer new possibilities to reduce the disease burden of depressive disorders [11,12].

Hundreds of randomized controlled trials (RCTs) and dozens of systematic reviews / meta-analysis (SR/MA) have been published on interventions to prevent depression [13–17]. A systematic review of SR/MA of psychological and/or educational interventions to prevent depression included 12 SR/MA (156 non-repeated trials and 56,158 participants) and found a small-moderate preventive effect [18]. If preventive interventions reach a significant part of the population, even if this effect size is small, the impact on health, quality of life and healthcare costs could be relevant. From this point of view, scalability is crucial to prevention interventions. Solutions may leverage technological advances, such as mHealth-based counselling, computer and web-based resources [19].

Interest in online prevention programs for depression has increased substantially in recent years [20–22]. Online interventions offer some advantages over face-to-face interventions for both, patients and the health system. Its advantages include greater intimacy, lower economical costs, the opportunity of joining the intervention at any time and place, easy access to a wider range of people (disabled population, rural areas, etc.) and a reduction in the time of waiting, among others [23–27].

So far, three SR/MA on the effectiveness of online interventions in preventing mental disorders have been published [28–30]. To our knowledge, these previous reviews have some limitations. One [28] was focused on several mental disorders altogether (Eating, Anxiety, Insomnia, Post-Traumatic Stress, Depression and Common Mental Health Disorders) and included only four trials on the prevention of depression. A limitation was the inclusion of some studies that only reported mean scores and did not clearly state that participants did not exceed clinical cut-offs at baseline, thus making it difficult to separate treatment from prevention. The other [29] was focused on the online cognitive behavioural therapy for subthreshold depression, which restricts its inference for that kind of psychotherapy and only for a type of prevention, indicated prevention; not addressed, thus, universal and selective prevention strategies. In addition new RCTs on online interventions for the prevention of depression have been published [31–35]. The last SR/MA [30] found a small preventive effect of the eHealth interventions to prevent anxiety and

depression; however, there were some exclusion criteria which limited their inferences: age (18-64 years), language (English), date (from 2000) and non-specific population (e.g. post-natal or comorbid). Therefore, the objective of this study will be to conduct a systematic review and meta-analysis of randomized controlled trials assessing the effectiveness of online interventions in preventing depression in heterogeneous populations.

METHODS AND ANALYSIS

We followed PRISMA-P guidelines for reporting systematic reviews and meta-analysis protocols [36]. The protocol of this study has already been registered with the International Prospective Register of Systematic Reviews, (PROSPERO) on 20 November 2014 and was last updated on 23 November 2017 (registration number: CRD42014014804).

Eligibility criteria

The rationale for the inclusion and exclusion criteria outlined below is to obtain a comprehensive overview of the RCTs performed so far assessing the effectiveness of online interventions in preventing depression in different populations and settings.

Study design

We will focus on randomized controlled trials (RCT) since this design provides more evidence on causality and is considered a gold-standard for clinical trials [37]. Cluster randomized trials will only be included if there are at least two intervention and control sites and outcomes are reported adjusted for clustering effect. Controlled non-randomized clinical trials or before-after trials will be excluded.

Participants and exclusion of depression at baseline

Participants may have any sociodemographic (age, sex, etc.) or clinical (healthy, chronic physical illness, etc.) characteristic and all settings (community, schools, primary care, etc.) will be considered. To make a clear distinction between the effectiveness of prevention interventions from that of treatments, baseline depression will be required to have been discarded through standardized interviews (eg. CIDI) or validated self-reports with standard cut-off points (eg, BDI-II). In a preventive context, the most useful parameter of validity of a diagnostic instrument to discard depression at baseline is the “negative predictive value” (NPV): probability of having a depressive disorder when the result of a diagnostic tool is negative. The NPV is influenced by three main parameters: cut-off selected, sensitivity associated with that cut-off and prevalence of anxiety disorders in the reference population of the study. Higher sensitivity, lower cut-off and prevalence will increase the NPV and minimize false negatives. Structured standardized interviews generally have greater validity than symptom scales and, therefore, the former are preferable. However, structured standardized interviews tend to have greater specificity than sensitivity; therefore, false positives will be minimized at the expense of increasing false negatives. From this point of view, a

symptoms scale with a diagnostic threshold associated with high sensitivity could guarantee as valid as a structured standardized interview, especially if the study is carried out on a reference population with a low prevalence of depressive disorders, as it is usual in prevention studies.

Type of interventions

We will only include RCTs assessing the effectiveness of psychosocial and/or educational, since they share the same mechanism of action that facilitates changes in attitudes and behaviours and because most interventions to prevent depression are of this type. Educational interventions provide information sessions or fact sheets, whereas psychosocial interventions attempt to change how people think and behave by using a variety of strategies (e.g. cognitive-behavioral or interpersonal). However, in real practice psychosocial and educational interventions can overlap, being difficult to distinguish them. Interventions must be accessible online and the study should include at least an internet-delivered intervention program. If no on-line intervention is implemented in any of the experimental arms, the RCT will be excluded. Intervention arms where active pharmacological therapies are administered will also be excluded.

Comparators

Comparator groups could be “only assessments”, “no treatment”, “usual care”, “waiting list”, or any type of active control which has no effect on depression. All types of placebo (psychological or pill) will also be accepted as comparators. Comparator arms which intervention (psychological, physical or pharmacological) has been proven to be effective in preventing depression will also be excluded.

Outcomes

RCTs which primary or secondary outcomes were the incidence of new cases of depression and/or the reduction of depression symptoms will be included. Outcomes will be required to have been measured by standardized interviews or validated symptom scales. When more than a symptom scale has been used to measure outcomes in a RCT, the data from the highest validity scale will be employed. If the validation data of the scales, in the country and setting where the study was conducted, are not reported in the article, they will be searched in the literature and other sources. The parameters that will be used to select the scale of symptoms are: higher Youden's J statistic (J=Sensitivity+Specificity-1), Cronbach alpha, and Intraclass Correlation Coefficient (test-retest), and sensitivity to change over time (Yes/no/not available). For each trial, the scale of symptoms that provide more validation data and of higher quality will be chosen. If depression outcomes are measured together with other outcomes (e.g. anxiety) and data are not provided separately, RCTs will be excluded.

Information sources and search strategy

A literature search of the following electronic databases will be carried out: PubMed, PsycINFO, WOS, Scopus and Cochrane Central Register of Controlled Trials (CENTRAL). Search will be supplemented by searching for trial protocols on ClinicalTrials.gov and Australia New Zealand Clinical Trials Register (ANZCTR). We will also examine OpenGrey (System for Information on Grey Literature in Europe), where grey literature is indexed. PROSPERO will be searched for ongoing or recently completed systematic reviews. To ensure literature saturation we will also review reference lists from relevant systematic reviews and meta-analysis and those from the RCTs included in our SR/MA. In addition, expert authors will be contacted in order to identify missing articles in our search. Literature search strategies will be developed using medical subject headings (MeSH) and text words related to prevention, depression and internet intervention. No limits will be imposed on study publication language or publication date. The search will be updated toward the end of the review. A draft MEDLINE search strategy in PICOS format is included in supplementary file. We will adapt the MEDLINE strategy to the syntax and subject headings of the other databases.

Study selection

The entire selection process will be conducted independently by two reviewers. After elimination of duplicate studies, all records will be reviewed. Based on their titles and abstracts, the studies that do not meet inclusion criteria will be ruled out. The full text of the studies selected as potentially relevant will be reviewed for further assessment. Any disagreements will be discussed and resolved by consensus or by a third independent reviewer, if necessary. We will seek additional information from corresponding authors when necessary to resolve questions about eligibility. We will record the reasons for excluding trials. The reviewers will not be blind to the journal titles or the study authors or institutions. Inter-agreement of the total selection will be assessed using Kappa [38], which can be interpreted as follows: < 0.20 as poor, 0.21 - 0.40 as fair, 0.41 - 0.60 as moderate, as 0.61 - 0.80 as good and 0.81 - 1.00 as excellent.

Data extraction

Data extraction from each eligible study will be conducted independently by two reviewers. Any disagreement will be discussed and resolved by consensus or by a third independent reviewer. We will also contact authors to get incomplete or unclear information, where appropriate. Abstracted data will include author/year and country; setting, target population characteristics (age, sex, etc.) and type of prevention (universal, selective or indicate); sample size (control/intervention); exclusion of depression criteria at baseline and validated instruments used; orientation and intervention type and intervention details in both experimental and control groups (type, modes of application, frequency, intensity and level of adherence); prevention depression outcomes and validated instruments used; and all follow-up provided from the RCTs. Whenever possible, we will use results from intention-to-treat analysis.

Risk of bias

The quality of the articles will be assessed using the six criteria of risk bias proposed by the Cochrane Collaboration tool: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data (e.g. dropouts and withdrawals) and selective reporting. To manage the risk of bias as a quantitative variable in meta-regression, it will be assessed by assigning the zero points to low-risk criteria, one to unclear and two to high-risk criteria. Therefore, the highest risk of bias score will be 12 and the lowest zero. The risk of bias will be assessed independently by two reviewers. In case of disagreement, a third reviewer will be consulted. The inter-agreement will be rated using Intraclass Correlation Coefficient [38]. The original study investigators will be contacted for more information, when necessary.

Assessment of publication bias

Publication bias will be evaluated by inspecting the funnel plot on the primary outcome measure and by Duval and Tweedie's trim-and-fill procedure [39], which yields an estimate of the effect size after adjusting for publication bias. The funnel plot is expected to be symmetric, equally dispersed on the general effect. If there are missing studies the trim and fill procedure imputes these studies and adds them to the analysis. We will also perform Begg and Mazumdar rank correlation [40] and Egger's test [41]. If asymmetry is potentially caused by publication bias, we expect to see high standard errors (small studies) associated with larger effect sizes.

Patient and public involvement

No patients or public were involved in the study.

Statistical analysis

All statistical analyses will be performed using the Comprehensive Meta-Analysis (CMA) software package, version 2.2.021 and STATA-Release-14.2. Standardized mean difference (SMD) will be used as effect size as most RCTs included in our meta-analysis are expected to report differences in symptoms of depression. For each study, we will first calculate the SMD by merging the SMD at different follow-up times into a single average estimate. We then will calculate the pooled SMD of all RCTs as well as its 95% confidence interval (CI). If some RCT only reports new cases of depression" (incidence of depression) CMA will be used to obtain the equivalent SMD. Negative SMDs (standardized mean differences between intervention and control group) will indicate a better outcome (reduction of depressive symptoms) in the intervention group. Following the interpretation proposed by Cohen for this effect size: -0.2 is small; -0.5 medium and -0.8 large [42]. We will inflate the standard errors of the nested comparisons in the same RCT following the suggestions of Cates [43]. *A priori*, we selected a random-effects model for our meta-analysis under the assumption that the RCTs to be included in our study will be performed in heterogeneous 'populations' that may differ from each other [44].

To test the heterogeneity of effect sizes, I^2 and its 95% confidence interval will be calculated and expressed as percentages, where a value of 0-40% might be unimportant heterogeneity, 30-60% moderate, 50-90% substantial and 75-100% considerable [44]. We will also calculate the Cochran's Q statistic and its P value.

We will perform the following sensitivity analyses: at first and last follow-up, using fixed effects and Hedges'g and excluding some RCTs from analysis (e.g. those which cause the greatest increase in heterogeneity).

We will use a mixed-effects model for sub-group analyses based on a set of variables selected a priori, as follows: type of prevention (universal, selective, or indicated), prevention of depression as primary or secondary outcome, type of outcome measure (symptoms scale versus standardized diagnostic interview), country, population age, setting (school, primary care,…), comparator (waiting list, usual care, active control), intervention orientation (CBT, other), intervention format, intervention guidance (guided or unguided), number of sessions or impacts, follow-up, level of usability or adherence (if it was measured), sample size and risk of bias.

Random-effect meta-regressions will be performed to investigate whether there are differences in effect sizes over time or according to the risk of bias. Normality of quantitative variables will be verified by the Skewness and Kurtosis normality test prior to inclusion in meta-regression analysis [45]; transformations will be conducted, when appropriate, to get approximation to normality. If significant heterogeneity is observed, the covariables with a $p<0.15$ which were not removed from the model due to collinearity will be also included in meta-regression models. Risk of bias and sample size will be forced into meta-regression models to adjust for them, the latter only in case of detection of publication bias. Standard error and confidence intervals will be calculated using the Knapp & Hartung method [46]. P-values will be calculated using Higgins & Thompson [47] permutation test approach, taking into account multiplicity adjustment, when necessary. A normal probability plot of standardized shrunken residuals will be used to estimate the goodness of fit of meta-regression models.

The quality of evidence

The quality of evidence in the domains of risk of bias, consistency, directness, precision and publication bias will be assessed using the Grading of Recommendations Assessment, Development and Evaluation working group methodology [48]. Additional domains may be considered, where appropriate.

Ethics and dissemination

The results will be disseminated through peer-reviewed publication and will be presented at a professional conference. Ethical assessment is not required as we will search and assess existing sources of literature.

Authors' contributions

AR is the guarantor. EM, PMP and JAB designed the study and the other authors collaborated on the design. AR drafted the protocol and EM and JAB revised the manuscript. AR, DMR, SCC and DSC will independently screen the potential studies, extract data, assess the risk of bias and finish data synthesis. JAB and PMP will perform data analysis. All authors read, provided feedback, discussed and approved the final manuscript.

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Competing interests

The authors all declare they have no competing interests. The funders had no direct role in the design of the study and they will have no input on the interpretation or publication of the study results.

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Supplementary file : PICOS Search Strategy

PICOS	Population	No restriction
	Intervention	("internet"[MeSH Terms] OR "internet"[All Fields] OR web-based OR technology intervention OR "telemedicine"[MeSH Terms] OR "telemedicine"[All Fields] OR "ehealth"[All Fields] OR online OR "social networking"[MeSH Terms] OR ("social"[All Fields] AND "networking"[All Fields]) OR "social networking"[All Fields] OR computer* OR interactive OR "software"[MeSH Terms] OR "software"[All Fields])
	Comparator	No restriction
	Outcome	("depressive disorder"[MeSH Terms] OR "depressive disorder" OR depress* OR "depression"[MeSH Terms] OR "anxiety"[MeSH Terms] OR "anxiety"[All Fields]) AND prevent*
	Study design	(randomized controlled trial[Publication Type] OR trial[Title/Abstract])

No population and comparator restrictions included in the search strategy. The selection was performed using the inclusion and exclusion criteria.

PRISMA-P checklist

Section and topic	Item No	Checklist item	Page
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2,5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	10
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	10
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	4,5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6,7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6,7
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7,8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7,8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	8,9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's, τ)	8,9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8,9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9