Effectiveness of Psychological and/or Educational Interventions in the Prevention of Anxiety

A Systematic Review, Meta-analysis and Meta-regression

Patricia Moreno-Peral, PhD[1,2,3]

Sonia Conejo-Cerón[1,2,3]

Maria Rubio-Valera, PhD[4,5,6]

Anna Fernández, PhD[5,7]

Desirée Navas-Campaña, PhD[1,2,3]

Alberto Rodríguez-Morejón, PhD[2,3,8]

Emma Motrico, PhD[2,9]

«DT1: Alina Rigabert[9]»

Juan de Dios Luna, PhD[2,10]

Carlos Martín-Pérez, MD, PhD[2,11]

Antonina Rodríguez-Bayón, MD, PhD[2,12]

María Isabel Ballesta-Rodríguez, MD, PhD[2,13]

Juan Vicente Luciano, PhD[2,4,14]

Juan Ángel Bellón, MD, PhD[1,2,3,15,16]

[1]Research Unit, Primary Care District of Málaga-Guadalhorce, Málaga, Spain

[2]Prevention and Health Promotion Research Network ~~(redIAPP)~~, Málaga, Spain

[3]Institute of Biomedical Research in Malaga ~~(IBIMA)~~, Málaga, Spain

[4]Sant Joan de Déu Research Foundation, Barcelona, Spain

[5]Network for Biomedical Research on Epidemiology and Public Health, **«DT2:** CIBERESP

[6]School of Pharmacy, University of Barcelona, Barcelona, Spain

[7]Service of Community Health, Public Health Agency of Barcelona ~~(ASPB)~~, Barcelona, Spain

[8]Department of Personality, Evaluation, and Psychological Treatment, Universidad de Málaga, Málaga, Spain

[9]Department of Psychology, University Loyola Andalucía, Seville, Spain

[10]Department of Biostatistics, University of Granada, Granada, Spain

[11]Primary Care Center of Marquesado, Área Nordeste de Granada, Granada, Spain

[12]Primary Care Center of San José, Linares, Jaén, Spain

[13]Primary Care Center of Federico del Castillo, Jaén, Spain

[14]Teaching, Research & Innovation Unit, Parc Sanitari Sant Joan de Déu, St Boi de Llobregat, Spain

[15]Primary Care Center of El Palo, Málaga, Spain

[16]Department of Preventive Medicine, Public Health and Psychiatry, University of Malaga, Málaga, Spain

Question: Are psychological and/or educational preventive interventions for anxiety effective in ~~all type of~~ varied populations?

Findings: This systematic review and meta-analysis of 29 randomized ~~controlled~~ clinical trials (36 comparisons) including 10 430 patients from 11 countries on 4 continents showed a small, but statistically significant, effect size of psychological and/or educational preventive interventions for anxiety. Sensitivity analyses and adjustment for publication bias confirmed that the results were robust.

Meaning: Although the ~~effectiveness~~ benefit of psychological and/or educational interventions in the prevention of anxiety is modest, the results obtained suggest that psychological and/or educational preventive interventions for anxiety should be further developed and implemented.

Importance No systematic reviews or meta-analyses have been conducted to assess the effectiveness of preventive psychological and/or educational interventions for anxiety in ~~all types of~~varied population~~s~~.

Objective To evaluate the effectiveness of preventive psychological and/or educational interventions for anxiety in ~~all~~ varied population types.

Data Sources A systematic review and meta-analysis was conducted based on literature search~~es~~ ~~on~~ of MEDLINE, PsycINFO, ~~WOS~~Web of Science, EMBASE, OpenGrey, Cochrane Central Register of Controlled Trials, and other sources from inception ~~up~~ to March 7, 2017.

Study Selection A search was performed of l zed ~~controlled~~ clinical trials assessing the effectiveness of preventive psychological and/or educational interventions for anxiety in ~~all types of~~ varying population~~s~~ free of anxiety at baseline ~~(~~as measured using validated instruments~~)~~. There was no setting or language restriction. Eligibility criteria assessment was conducted by ~~two~~ 2 independent investigators.

Data Extraction and Synthesis Data extraction and assessment of risk of bias (Cochrane Collaboration's tool) were performed by ~~two~~ 2 independent investigators. Pooled standardized mean differences (SMD~~s~~) were

calculated, using random-effect models. Heterogeneity was explored by random-effects meta-regression.

Main Outcomes and Measures Incidence of new cases of anxiety disorders or reduction of anxiety symptoms as measured by validated instruments.

Results Of the 3273 abstracts reviewed, 131 were selected for full-text review, and 29 met the inclusion criteria, representing 10 430 patients from 11 countries on 4 continents. Meta-analysis calculations were based on 36 comparisons. The pooled SMD was −0.31 (95% CI, −0.40 to −0.21; $P <$ .001) and heterogeneity was substantial (I^2 = 61.1%; 95% CI, **«DT3:** 44% to 73% There was evidence of publication bias, but the effect size barely varied after adjustment (**«DT4:** SMD, −0.27; 95% CI, −0.37 to −0.17; $P <$ .001) Sensitivity analisyses confirmed the robustness of effect size results. A meta-regression including ~~five~~ 5 variables explained 99.6% of between-study variability, revealing an association between higher SMD, waiting list (comparator), and a lower sample size. No association was observed with risk of bias, family physician providing intervention, ~~(provider)~~ and use of standardized interviews as outcomes.

Conclusions and Relevance Psychological and/or educational interventions had a small, but statistically significant, benefit for anxiety prevention in all ~~types of~~ populations evaluated. Although more studies with larger samples and active comparators are needed, these findings suggest that anxiety prevention programs should be further developed and implemented.

Introduction

The annual prevalence of anxiety disorders is 6.7% in the general population.[1] The burden of disease in terms of years lived with disability attributable to anxiety disorders increased by 14.8% (relative increase) between 2005 and 2015, ranking ninth in the world and eighth in high-income countries.[2] Among mental and substance use disorders, anxiety ranked second in the world.[3] Although there are effective treatments for anxiety disorders,[4-6] not all persons with anxiety receive the appropriate treatment,[7] and cost-effectiveness studies suggest that treatment alone is not sufficient to eliminate the disease burden attributable to anxiety disorders.[8] ~~Besides, a~~An additional way to reduce the burden of anxiety disorders is to ~~reduce~~ lower the incidence of new cases, which can be achieved through prevention rather than treatment.

Previous systematic reviews or meta-analyses ~~on~~ of the prevention of anxiety have been mainly undertaken in children and/or adolescents.[9-13] In adults, studies have ~~been~~ traditionally focused on specific anxiety disorders, such as posttraumatic stress disorder ~~(PTSD)~~.[14,15] ~~Only a~~One meta-analysis[16] assessed the prevention of anxiety in the general population, although it was centered on specific cognitive-behavioral interventions. To the best of our knowledge, no systematic review or meta-analysis has been performed ~~so far~~ on the effectiveness of psychological and/or educational interventions in preventing anxiety ~~in all~~ several types of populations. The aim of the present systematic review and meta-analysis was to evaluate the effectiveness of psychological and/or educational interventions in preventing anxiety in varied populations.

Methods

We followed PRISMA ~~(Preferred Reporting Items for Systematic Reviews and Meta-analyses)~~ guidelines for reporting systematic reviews and meta-analyses.[17] The protocol of this systematic review was previously registered at the International Prospective Register o~~O~~f Systematic Reviews ~~(PROSPERO registration number: CRD42016049404)~~. **«DT5: X»**

Search Strategies

We systematically searched ~~five~~ 5 electronic databases, including PubMed, PsycINFO, Embase, ~~WOS~~Web of Science, OpenGrey (System for Information on Grey Literature in Europe), and CENTRAL (Cochrane Central Register of Controlled Trials) from inception to March 7, 2017. No date or language restrictions were imposed. This search strategy was complemented with hand searching of reference lists ~~on~~ in articles and other reviews on this topic. In addition, experts in the field were contacted and asked to complete the list of selected publications. Databases were searched separately by ~~two~~ 2 reviewers (P.M.-P. and S.C.-C.). The specific search strategies used are described in the eAppendix in the Supplement.

Eligibility Criteria

We selected randomized clinical trials (RCTs) because they are the ~~gold~~ standard for clinical trials.[18] We focused on educational and/or psychological interventions. The former simply provide information about anxiety through lectures or fact sheets, whereas psychological interventions attempt to change how people think, using a variety of strategies (eg, cognitive behavioral or interpersonal therapy). ~~RCTs~~ Randomized clinical trials based on medication or physical interventions (eg, sports) were excluded. The comparators allowed were care-as-usual, no intervention, **«DT6:** waiting list, attention control. To separate the effectiveness of prevention from that of therapies, baseline anxiety was required to have been discarded through standardized interviews (eg, **«DT7:** SCID>>), validated self-reports with standard cutoff points (eg, **«DT8:** BAI-II>>), or diagnosis by a mental health specialist. Outcomes included the incidence of new cases of any *DSM-IV* anxiety disorder and/or the reduction of anxiety symptoms. Outcomes were required to have been measured by standardized interviews or validated symptom scales. Posttraumatic stress disorder ~~PTSD~~ was excluded because, in this case, it is difficult to separate treatment from

prevention.[19] Participants could have any demographic characteristic (eg, age, sex~~, etc.~~) and all settings and languages were considered.

Selection of Studies

Titles and abstracts were reviewed independently by ~~two~~ 2 ~~reviewers~~ authors (P.M.-P. and S.C.-C.), who used the ~~criteria~~ abovementioned criteria to determine study eligibility. The ~~F~~full text of potentially relevant studies was reviewed for final inclusion. All discrepancies were resolved by consensus with a third study reviewer (M.R.-V. or A.F.). The degree of agreement between ~~PMP and SCC~~the initial reviewers was good (Cohen~~'s~~ κ = ~~kappa~~ 0.74; 95% CI, 0.60-0.89).[20]

Data Extraction

Data extracted from each study were recorded in an evidence table. Two independent reviewers (P.M.-P. and S.C.-C.) collected data from primary studies. Any discrepancies were solved by consensus between the reviewers. When necessary information was not reported in the study, the authors of the original article were contacted for further details.

Assessing the Risk of Bias

We used the Cochrane Collaboration ~~'~~ ~~R~~risk of bias~~'~~ tool to assess the quality of the studies included.[21] All of the studies included were assessed

and any disagreements were resolved by ~~two~~ 2 independent reviewers (P.M.-P. and S.C.-C.). ~~Disagreements were solved by the two raters.~~ The level of agreement was good (intraclass correlation coefficient, 0.83; 95% CI, 0.77-0.87).[22]

Statistical Analyses

~~We used Comprehensive Meta-Analysis (CMA version 3.0) and STATA Release 14.2 to perform analyses.~~

When the outcome was differences in anxiety symptoms between intervention and control groups, means ~~and standard deviations~~(SDs) for each arm were extracted. ~~Then, for each RCT w~~We then calculated standardized mean differences (SMDs) for each RCT by estimating the mean SMD at different follow-up times. The pooled SMDs for all RCTs and ~~its~~ their 95% ~~confidence interval (~~CIs~~)~~ were estimated. Negative SMDs represented an improvement in the reduction of anxiety symptoms~~atology~~ in the intervention group. If only new cases of anxiety were reported (incidence of anxiety), **«DT9:** Comprehensive Meta-Analysis (CMA),>> version 3.0 ~~CMA~~ was used to obtain the equivalent SMDs. Cohen**«DT10:** offered the following guidelines for interpreting the magnitude of this effect size: "an SMD of 0.2 is considered as indicating a low effect; SMD of 0.5

indicates a moderate effect and 0.8 a large effect.”~~.~~ **«DT11:** ~~23~~» We ~~have~~ inflated the ~~standard errors~~SEs of the nested comparisons in the same RCT following the suggestions of Cates.[24] We selected the random-effects model for ~~our~~ the study~~,~~ under the assumption that the studies included in ~~our~~ the meta-analysis were performed in a variety of ~~‘~~populations~~’~~ that may differ from each other.[21]

Statistical heterogeneity was evaluated using the I^2 statistic, where a value of 0% to ~~-~~40% might ~~be~~ indicate no~~t~~ important heterogeneity;~~,~~ 30% to ~~-~~60%, moderate;~~,~~ 50% to ~~-~~90%, substantial; and 75% to ~~-~~100%, considerable.[21] In addition, we calculated the *Q* statistic and its *P* value.

To detect publication bias, a funnel plot was examined by visual inspection and the Duval and Tweedie’s[25] trim-and-fill procedure, which is a test of symmetry of the funnel plot.~~[25]~~ This procedure yields an adjusted pooled effect size after accounting for missing studies due to publication bias. We also performed **«DT12:** Begg and Mazumdar rank correlation and the Egger~~’s~~ test

Since the SMD could differ at varying follow-up times, we also conducted sensitivity analyses at first and last follow-ups. Sensitivity analyses also included fixed effects and~~,~~ Hedges~~'~~ *g*, and excluded~~ing~~ some

RCTs from analysis (those ~~which~~ that caused the greatest increase in heterogeneity and those ~~which~~ that measured anxiety as a secondary outcome).

We used a mixed-effects model for sub-group analyses according to the type of prevention, type of outcome measure (symptoms scale vs standardized diagnostic interview), type of anxiety, country, population age, setting, comparator, ~~provider (the~~ professional delivering the intervention~~)~~, intervention orientation, type of intervention, intervention format, number of sessions, follow-up, sample size, and risk of bias.

Meta-regression was performed to explain the between-trial heterogeneity observed. We forced ~~two~~ 2 quantitative variables—risk of bias and sample size—in the meta-regression models for adjustment. The former is related to the quality of the RCTs and the latter to publication bias. Of the remaining covariables considered for subgroup analysis, only ~~a~~ 1 covariable was introduced in each new model. The final model was composed of the ~~two~~ 2 forced quantitative variables and dummy covariables with a significance level of $P < .15$ that were not removed from the model due to collinearity. We used the Knapp and~~&~~ Hartung method[26] to estimate ~~standard error~~SE and ~~confidence intervals~~95% CIs. We also used a Higgins and~~&~~ Thompson[27] permutation test approach to calculate *P* values, taking

into account multiplicity adjustment «DT13: (Monte Carlo approach; 20 000 permutations We used CMA, version 3.0 and Stata, version 14.2 (StataCorp) to perform analyses.

Results

Search Results

A total of 3273 abstracts were reviewed. ~~Next~~Of these, 131 articles were included for full-text review~~. Finally~~ and~~,~~ 29 RCTs met the inclusion criteria of ~~our~~ the meta-analysis (Figure 1).[28-57]

Characteristics of Included Studies

The characteristics of the 29 RCTs included are described in ~~the~~ eTable 1 in the Supplement. ~~Most~~ Twenty studies ~~(20)~~ were published in or after 2010, and only ~~three~~ 3 RCTs were published before 2005. Seven RCTs were conducted in the ~~US~~United States.

A total of 10 430 patients were enrolled. Sample sizes ranged from 24 to 2998 (median, ~~=~~ 165). A total of 9 RCTs included adults (from 18 to 65 years), 9 included children or adolescents, 4 were performed in older adults,

6 in adults and elderly individuals, and 1 in both~~,~~ adults and children. Settings included school or university in 12 RCTs.

Interventions were based on the principle of cognitive behavioral therapy ~~(CBT)~~ in 25 RCTs, whereas 4 RCTs were based on other types of interventions (2 psychoeducational, 1 acceptance and commitment therapy, and 1 biopsychosocial). Interventions were delivered in individual format in 14 RCTs. Four RCTs included interventions with a guided self-help format (computerized). The number of sessions ranged from ~~one~~ 1 to 12 (median, ~~=~~ 8). The comparator ~~employed~~ used was care-as-usual in 13 RCTs. Interventions were conducted by a mental health specialist in 13 RCTs.

Follow-up periods ranged from 7 weeks to 60 months (median, ~~=~~ 12 months). The duration of follow-up exceeded 12 months in ~~six~~ 6 RCTs.

Indicated, selective, and universal prevention were evaluated in 11, 10, and 8 RCTs, respectively. With respect to outcomes, 10 RCTs measured the reduction in anxiety symptoms and~~,~~ 10 determined the incidence of anxiety disorders; ~~and~~ 9 RCTs measured both reduction of symptoms and incidence.

Risk of Bias in Included Studies

The risk of bias for each study is ~~shown~~ reported in eTable 2 in the Supplement. Eight RCTs had a low risk ~~of bias~~ (≤4 points), 9 had a moderate risk (5-6 points), and 12 had a high risk ~~of bias~~ (≥7 points) of bias.

Effectiveness of the Interventions to Prevent Anxiety

Meta-analysis calculations were based on 36 comparisons performed in 29 RCTs (eTable 3 in the Supplement). The pooled SMD was −0.31~~05~~ (95% CI, −0.40~~0~~ to −0.21~~09~~; $P < .001$), and the equivalent pooled odds ratio (OR) was 0.57 (95% CI, 0.48 to 0.68; $P < .001$), with substantial heterogeneity ($I^2 = 61.1\%$; $Q_{35} = 90.13$~~0~~; ~~df(Q) = 35; P~~ $< .001$). This finding means that psychological and/or educational preventive interventions for anxiety had a small and statistically significant effect on anxiety prevention. Figure 2 shows the forest plot for the overall and individual effect sizes.

Publication Bias

Results of ~~T~~the Egger~~'s~~ (intercept, −1.30~~295~~; 95% CI, −2.25~~49~~ to −0.34~~1~~; $P = .01$) and Begg~~'s test~~ ($Z = −2.40$; $P = .02$) tests indicated the presence of publication bias. The SMDs adjusted for publication bias according to Duval and Tweedie's trim-and-fill procedure barely decreased

(SMD, −0.2768; 95% CI, −0.3766 to −0.171). The Ffunnel plot is shown in the eFigure 1 in the Supplement.

Sensitivity Analyses

Sensitivity analyses are shown reported in Table 1. The pooled SMDs scarcely changed little with the first or last evaluation, the fixed-effect model, or the Hedges *g*, test when the RCT [38] that most increased heterogeneity or the RCTs in which anxiety was a secondary outcome[30,38,40] were excluded.

Subgroup Analyses

«DT14: Subgroup>>analyses revealed differences in the effectiveness of psychological and/or educational interventions depending on the outcome measure, comparator, provider, sample size, risk of bias, and follow-up (eTable 4 in the Supplement).

Meta-Regression

Meta-regression is shown reported in Table 2. As many as 85.3% of total variance was attributable to within-study variability, and the remaining 14.7% was attributable to between-study variability. In total, 99.6% of between-study variance was explained by the five 5 variables included in the meta-regression model. There was a statistically significant association

between higher SMD ~~and~~ with a lower sample size~~,~~ and when the comparator was ~~“~~waiting list~~”~~. There was no association between SMD and risk of bias, type of outcome measure (standardized interview), and family physician (~~provider~~caregiver). Analysis of residuals showed a good fit of the meta-regression model (eFigure 2 in the Supplement).

Discussion

~~Summary~~

We found that psychological and/or educational interventions are effective in the prevention of anxiety. The overall effect size was small but statistically significant. This result was derived from 29 RCTs (36 comparisons)~~, which~~ that included 10 430 patients from 11 countries on 4 continents. Sensitivity analyses and adjustment for publication bias demonstrated that the overall effect size was robust. Heterogeneity was substantial and ~~completely~~ explained by a model of meta-regression including ~~five~~ 5 variables, 2 of which ~~two~~ had a statistically significant association with effect size (waiting list and sample size), whereas the other ~~three~~ 3 variables did not (risk of bias, family physician as ~~provider~~ caregiver, and standardized interview as outcome).

Strengths

To the best of our knowledge, this is the first systematic review and meta-analysis to examine the effectiveness of psychological and/or educational interventions in the prevention of anxiety in ~~all~~ varied types of populations. Our meta-analysis included~~s~~ a reasonable number of ~~RTCs~~ RCTs representing a large population of individuals with different characteristics and from diverse settings. In addition, this study involved~~s~~ a wide spectrum of interventions (any psychological and/or educational intervention) for ~~all~~ most types of anxiety disorders (except posttraumatic stress disorder~~PTSD~~) and implemented by a variety of professionals in different settings. These aspects give the study a wide scope, which supports its external validity. We ~~employed~~ used multiple complementary electronic databases with supplementary hand searching. Thus, the variety of databases ~~employed~~ utilized, combined with the broad range of search terms, ~~used~~ contributed to a highly sensitive~~ity~~ search. ~~Besides~~In addition, the strict inclusion criteria, ~~employed by which~~ analyzing only RCTs ~~including~~ with a study population free of anxiety at baseline, ~~and that~~ allowed us to distinguish prevention effectiveness from treatment effectiveness. Study selection, data extraction, and risk of bias assessment were performed by trained and independent reviewers, with good inter-observer reliability. We

performed sensitivity analyses and adjustment for publication bias, which results support the robustness of the pooled SMDs. Finally, the meta-regression model completely explained heterogeneity and enabled adjustment for confounding biases and multiple comparisons.

Limitations

Our meta-analysis had has several limitations. that must be taken into account. First, although most of the studies included had low- to- moderate risk of bias (17 RCTs), 12 had a high risk of bias. Subgroup analysis showed that the studies with a lower risk of bias had a tendency to report a lower smaller effect size (SMD, 0.15; 95% CI, **«DT15:** 0.07**»**-0.23` nevertheless, after adjusting for confounding biases, the meta-regression model clearly showed that the risk of bias was not significant. **«DT16:** Second, the duration of follow-up exceeded 12 months in only 8 RCTs **»**which tended to report a lower effect size (SMD, 0.15; 95% CI, 0.01-0.29). Although follow-up duration was clearly not significant when adjustment for sample size and risk of bias was performed, firm conclusions about long-term effectiveness cannot be drawn from our study. Third, the interventions implemented in most of the RCTs included in our the meta-analysis were aimed at preventing more than one 1 specific anxiety disorder (or simply

used non-specific anxiety symptoms as outcomes); therefore, no inferences can be made about any specific anxiety disorder. Fourth, reduction of anxiety symptoms (measured by scales) was the only outcome of 10 RCTs; although the reliability and validity of scales are widely accepted, standardized diagnostic interviews generally have greater validity. Nevertheless, the reduction of anxiety symptoms is also useful as an outcome because it has a positive and relevant impact effect on quality of life and cost.[38,58] Another related aspect is that RCTs where in which standardized diagnostic interviews were employed conducted tended to report a lower effect size («**DT17:** SMD, -0.18; 95% CI, 0.06-0.30»). Again, adjustment for confounding biases and multiple comparisons in meta-regression discarded any statistical significance. Fifth, evidence of publication bias was found, which means that it is quite likely that some RCTs with non-significant results were have not been published. Nevertheless, this limitation does not seem relevant as because the effect size scarcely decreased after adjustment ing for publication bias. Sixth, we cannot establish the superiority of an one intervention over another (eg, cognitive behavioral therapy CBT vs acceptance and commitment therapy) because it was not within the scope of our the study and we purposely excluded the few RCTs where this in which these types of comparisons were

made. Seventh, it is probable that the effect size of the anxiety prevention that we obtained was ~~really~~ smaller ~~as~~ since it was increased by the use of waiting list comparator and small samples. Finally, in some categories in specific subgroup~~-~~ analysis, the number of RCTs or comparisons was low; in these cases (eg, ~~for~~ type of anxiety), the lack of statistical power prevents ~~that~~ firm conclusions ~~are drawn~~.

Comparison With Existing Literature

The overall effect size obtained was small. Other meta-analyses on anxiety prevention report similar SMDs (range, 0.13-0.32),[11-13,16] and the same occurs with meta-analyses on the prevention of depression.[59-61]

We ~~only~~ found statistically significant associations only for sample size and waiting list as comparators when adjustment for confounding biases and multiplicity testing were performed in meta-regression. A recent meta-analysis on the effectiveness of cognitive behavioral therapy ~~CBT~~ for anxiety disorders ~~(~~and major depression~~)~~ showed that ~~effects~~ responses were large when the control condition was waiting list, but small to moderate when it was care-as-usual or pill placebo.[62] Similar results were found in a network meta-analysis on the effectiveness of treatments for depression. The authors suggest that waiting list can be a “nocebo” and may introduce negative psychological expectations in the sense of ~~‘~~waiting for the desired

active treatment', whereas patients allocated to 'non-intervention or usual care' may more actively seek other treatments, either by themselves or by others, for their ailment.[63] In a recent meta-analysis, subgroup analysis on of the prevention of anxiety in young people revealed that the studies where in which waiting list was employed used as a comparator tended to report a significantly higher effect size; nevertheless, after adjustment for confounding factors in meta-regression, this tendency disappeared.[11] Zalta (2011)[16] found no statistically significant differences between active and non-active comparators in a meta-analysis, although, in this meta-analysis, waiting list was categorized within the "non-active" category and no adjustment for confounding factors was made.

Regarding sample size, effect sizes were smaller in the RCTs with larger sample sizes after adjustment for confounding biases and multiple comparisons were performed. This effect could be due to publication bias, as evidenced in our meta-analysis, although its impact influence on the overall effect size was minimal. Studies with small samples are more likely to obtain negative results and not to be published; however, when they yield statistically significant results, their effect sizes are higher.

Effect size tended to decrease when the outcomes were assessed using standardized diagnostic interviews, although no statistically significant

associations were found in meta-regression. When RCTs had small samples, ~~it was~~they were more likely to ~~get~~ determine statistically significant effects on anxiety prevention if symptom scales (difference of means) were ~~employed~~utilized, ~~as~~ compared ~~to~~ with structured interviews (comparison of proportions). Furthermore, there was a negative correlation between risk of bias and standardized interview as outcomes (~~Rho =~~ ρ = −0.27). Therefore, the loss of statistical significance between effect size and standardized interview can be explained in part by adjustment for confounding factors with the introduction of the variables ~~‘~~sample size~~’~~ and ~~‘~~risk of bias~~’~~ in the meta-regression model. Adjustment for multiple comparisons also contributed to the loss of significance.

Regarding the professional who delivered the intervention (~~`the provider~~`caregiver), effect sizes tended to increase when the ~~provider~~ caregiver was a family physician, but this effect was attenuated after adjustments in meta-regression. The SMDs for family physician and mental health specialist were similar, but the latter was removed from meta-regression because of collinearity. Nevertheless, interventions were led by a family physician in only ~~two~~ 2 RCTs and results should therefore be interpreted with caution.

Subgroup analysis revealed statistically significant associations between low risk of bias ~~and~~ with a lower effect size~~,~~ and follow-up time (SMDs higher in RCTs <6 months). However, this effect disappeared when adjustment for confounding bias was performed. No relevant differences were observed when the first (SMD, ~~=~~ 0.30) and last ~~evaluation~~ (SMD, 0.33) evaluations were included as outcomes for sensitivity analysis. Other meta-analyses assessing studies on anxiety and depression[11,16,59,60] report that effect size seems to diminish over time. Yet, a recent meta-analysis of studies on the prevention of depression found no association between effect size and follow-up time.[61] Regarding the risk of bias, a previous meta-analysis did not ~~found~~ find any statistically significant association between risk of bias and effect size.[13]

A tendency was observed ~~in~~ for SMDs to be higher in selective prevention, followed by indicated and universal prevention, although differences were not statistically significant even when adjustment for confounding bias was not performed. Some previous meta-analyses have not found any association between type of prevention and effect size[11,12,16]; however, ~~a~~ 1 meta-analysis found that selective and indicated interventions had a greater effect size than universal prevention,[13] whereas another meta-analysis reported that universal prevention was more effective.[10]

As in the rest of the meta-analyses concerning the prevention of anxiety,[10-13,16] most of the interventions included in our study had a cognitive-behavioral orientation (31 comparisons; SMD, 0.25); the remaining six 6 comparisons had other orientations and tended to have a greater effect response (SMD, 0.52), although it was not statistically significant. Therefore, no conclusions can be drawn about orientation.

Conclusions

The pooled effect size obtained for 'prevention of anxiety' is rather modest as compared to with the sizes observed in treatments for anxiety disorders.[62] Although the preventive fraction that derived from the pooled effect size that we obtained (OR, 0.57), **«DT18:** 43%**»** reduction in the incidence of anxiety, was higher than those found in other meta-analyses,[11-13,59-61] future studies should strive to further develop and test new prevention interventions with greater effect sizes. Yet, from the perspective of public health, small effects on prevention could have a high impact, thereby improving quality of life and reducing costs. By way of illustration, prevention programs reaching a large population through extensive school[28] and primary care programs[30] or information and communication technologies can have a large cumulative effect.[64] From this point of view,

our results suggest that programs for the prevention of anxiety should be implemented. Nevertheless, there are some aspects that are not well understood and should be further investigated. There are ~~very~~ few studies that assess~~ing~~ the cost-effectiveness and cost-utility of programs for the prevention of anxiety.[58,65] In addition, long-term RCTs with larger samples and low risk of bias comparing different programs and strategies for the prevention of anxiety are needed.

Article Information

Accepted for Publication: June 29, 2017.

Corresponding Author: Patricia Moreno-Peral, PhD, **«DT19:** Unidad de Investigación, Distrito de Atención Primaria Málaga-Guadalhorce, **»**C/Sevilla 23, 3ª Planta, 29009 Málaga, Spain (predictmalaga@hotmail.com).

Author Contributions: Drs Moreno-Peral and Bellón had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Moreno-Peral, Conejo-Cerón, Rubio-Valera, Fernandez, Luna del Castillo, Bellón.

Acquisition, analysis, or interpretation of data: Moreno-Peral, Conejo-Cerón, Rubio-Valera, Fernandez, Navas-Campaña, Rodríguez-Morejón, Motrico, Rigabert, Martín-Pérez, Rodríguez-Bayón, Ballesta-Rodríguez, Luciano, Bellón.

Drafting of the manuscript: Moreno-Peral, Bellón.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Moreno-Peral, Conejo-Cerón, Luna del Castillo, Bellón.

Obtained funding: Bellón.

Administrative, technical, or material support: Moreno-Peral.

Study supervision: Rubio-Valera, Fernandez, Luna del Castillo, Bellón.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by the Spanish Ministry of Health, the Institute of Health Carlos III, and ~~the~~ European Regional Development Fund Una manera de hacer Europa ~~(~~grant ~~FIS reference:~~ PI12/02755~~)~~ and the Andalusian Council of Health ~~(~~grant ~~reference:~~ 0583/2012~~)~~; as well as the Prevention and Health Promotion Research Network ~~‘(~~redIAPP~~)’~~ ~~(~~RD16/0007~~)~~, ~~the ‘~~PRISMA group~~’~~ ~~(~~RD16/0007/0012~~)~~, and ~~the ‘~~SAMSERAP group~~’~~ ~~(~~RD16/0007/0010~~)~~. ~~The~~

~~next to last author (JVL)~~ Dr Luciano has a ~~"~~Miguel Servet~~"~~ research contract from the Institute of Health Carlos III (~~ISCIII;~~ CP14/00087).

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: ~~The authors thank~~ **«DT20:** ~~t~~The Primary Care District of Málaga provided ~~for their~~ support.**»** ~~We also thank t~~The Institute of Health Carlos III ~~(ISCIII)~~, the European Regional Development Fund, the Andalusian Council of Health, the Biomedical Research Institute of Málaga ~~(IBIMA)~~, and the Prevention and ~~Health Promotion Research Network~~ ~~(~~redIAPP~~)~~ ~~for their economic and~~provided logistical support.

References

1. Steel Z, Marnane C, Iranpour C, et al. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. *Int J Epidemiol*. 2014;43(2):476-493. Medline:24648481

2. Vos T, Allen C, Arora M, et al; GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1545-1602. Medline:27733282

3. Whiteford HA, Degenhardt L, Rehm J, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013;382(9904):1575-1586. Medline:23993280

4. Acarturk C, Cuijpers P, van Straten A, de Graaf R. Psychological treatment of social anxiety disorder: a meta-analysis. *Psychol Med*. 2009;39(2):241-254. Medline:18507874

5. Cuijpers P, Sijbrandij M, Koole S, Huibers M, Berking M, Andersson G. Psychological treatment of generalized

anxiety disorder: a meta-analysis. *Clin Psychol Rev*. 2014;34(2):130-140. Medline:24487344

6. Sánchez-Meca J, Rosa-Alcázar AI, Marín-Martínez F, Gómez-Conesa A. Psychological treatment of panic disorder with or without agoraphobia: a meta-analysis. *Clin Psychol Rev*. 2010;30(1):37-50. Medline:19775792

7. Fernández A, Haro JM, Martínez-Alonso M, et al. Treatment adequacy for anxiety and depressive disorders in six European countries. *Br J Psychiatry*. 2007;190:172-173. Medline:17267936

8. Andrews G, Issakidis C, Sanderson K, Corry J, Lapsley H. Utilising survey data to inform public policy: comparison of the cost-effectiveness of treatment of ten mental disorders. *Br J Psychiatry*. 2004;184:526-533. Medline:15172947

9. Neil AL, Christensen H. Efficacy and effectiveness of school-based prevention and early intervention

programs for anxiety. *Clin Psychol Rev*. 2009;29(3):208-215. Medline:19232805

10. Stockings EA, Degenhardt L, Dobbins T, et al. Preventing depression and anxiety in young people: a review of the joint efficacy of universal, selective and indicated prevention. *Psychol Med*. 2016;46(1):11-26. Medline:26315536

11. Werner-Seidler A, Perry Y, Calear AL, Newby JM, Christensen H. School-based depression and anxiety prevention programs for young people: a systematic review and meta-analysis. *Clin Psychol Rev*. 2017;51:30-47. Medline:27821267

12. Fisak BJ Jr, Richard D, Mann A. The prevention of child and adolescent anxiety: a meta-analytic review. *Prev Sci*. 2011;12(3):255-268. Medline:21437675

«WH21: »13. Teubert D, Pinquart M. A meta-analytic review on the prevention of symptoms of anxiety in children and adolescents. *J Anxiety Disord*. 2011;25(8):1046-1059.

14. Forneris CA, Gartlehner G, Brownley KA, et al. Interventions to prevent post-traumatic stress disorder: a systematic review. *Am J Prev Med*. 2013;44(6):635-650. Medline:23683982

15. Wessely S, Rose S, Bisson J. Brief psychological interventions ("debriefing") for trauma-related symptoms and the prevention of post traumatic stress disorder. *Cochrane Database Syst Rev*. 2000;(2):CD000560. Medline:10796724

16. Zalta AK. A meta-analysis of anxiety symptom prevention with cognitive-behavioral interventions. *J Anxiety Disord*. 2011;25(5):749-760. Medline:21698842

17. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535. Medline:19622551

18. Piantadosi S. *Clinical Trials: A Methodological Perspective*. 2nd ed. Somerset, New Jersey: John Wiley & Sons; 2005.
19. Kearns MC, Ressler KJ, Zatzick D, Rothbaum BO. Early interventions for PTSD: a review. *Depress Anxiety*. 2012;29(10):833-842. Medline:22941845
20. Fleiss JL. *Statistical Methods for Rates and Proportions*. 2nd ed. New York, NY: John Wiley; 1981.
21. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. http://handbook.cochrane.org/. Updated March 2011. Accessed May 23, 2017.
22. Fleiss JL. *The design and Analysis of Clinical Experiments*. New York, NY: John Wiley & Sons; 1986.
23. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Erlbaum; 1988.
24. Cates C. Multiple-arm trial data: using a corrected standard error for GIV analyses. Cochrane Colloquium. https://abstracts.cochrane.org/2015-vienna/multiple-

arm-trial-data-using-corrected-standard-error-giv-analyses; Published 2015. Accessed May 1, 2017.

25. Duval S, Tweedie R. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455-463. Medline:10877304

26. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. *Stat Med*. 2003;22(17):2693-2710. Medline:12939780

27. Higgins JPT, Thompson SG. Controlling the risk of spurious findings from meta-regression. *Stat Med*. 2004;23(11):1663-1682. Medline:15160401

28. Aune T, Stiles TC. Universal-based prevention of syndromal and subsyndromal social anxiety: a randomized controlled study. *J Consult Clin Psychol*. 2009;77(5):867-879. Medline:19803567

29. Balle M, Tortella-Feliu M. Efficacy of a brief school-based program for selective prevention of childhood anxiety.

Anxiety Stress Coping. 2010;23(1):71-85. Medline:19326270

30. Bellón JA, Conejo-Cerón S, Moreno-Peral P, et al. Intervention to prevent major depression in primary care: a cluster-randomized trial. *Ann Intern Med*. 2016;164(10):656-665. Medline:27019334

31. Bouchard S, Gervais J, Gagnier N, Loranger C. Evaluation of a primary prevention program for anxiety disorders using story books with children aged 9-12 years. *J Prim Prev*. 2013;34(5):345-358. Medline:23943134

32. Christensen H, Batterham P, Mackinnon A, et al. Prevention of generalized anxiety disorder using a web intervention, iChill: randomized controlled trial. *J Med Internet Res*. 2014;16(9):e199. Medline:25270886

«WH22: »33. Cukrowicz KC, Joiner TE Jr. Computer-based intervention for anxious and depressive symptoms in a non-clinical population. *Cognit Ther Res*. 2007;31(5):677-693.

34. Dadds MR, Spence SH, Holland DE, Barrett PM, Laurens KR. Prevention and early intervention for anxiety disorders: a controlled trial. *J Consult Clin Psychol*. 1997;65(4):627-635. Medline:9256564

35. Dozeman E, van Schaik DJ, van Marwijk HW, Stek ML, Beekman AT, van der Horst HE. Feasibility and effectiveness of activity-scheduling as a guided self-help intervention for the prevention of depression and anxiety in residents in homes for the elderly: a pragmatic randomized controlled trial. *Int Psychogeriatr*. 2011;23(6):969-978. Medline:21338550

36. Dozeman E, van Marwijk HW, van Schaik DJ, et al. Contradictory effects for prevention of depression and anxiety in residents in homes for the elderly: a pragmatic randomized controlled trial. *Int Psychogeriatr*. 2012;24(8):1242-1251. Medline:22436082

37. Feldner MT, Zvolensky MJ, Babson K, Leen-Feldner EW, Schmidt NB. An integrated approach to panic

prevention targeting the empirically supported risk factors of smoking and anxiety sensitivity: theoretical basis and evidence from a pilot project evaluating feasibility and short-term efficacy. *J Anxiety Disord*. 2008;22(7):1227-1243. Medline:18281190

38. Fledderus M, Bohlmeijer ET, Pieterse ME, Schreurs KM. Acceptance and commitment therapy as guided self-help for psychological distress and positive mental health: a randomized controlled trial. *Psychol Med*. 2012;42(3):485-495. Medline:21740624

«WH23: »39. Gallegos J, Linan-Thompsonb S, Starkb K, Ruvalcabac N. Preventing childhood anxiety and depression: testing the effectiveness of a school-based program in Mexico. *Psicol Educ*. 2013;19(1):37-44.

40. García-Campayo J, Arevalo E, Claraco LM, Alda M, Lopez del Hoyo Y. A prevention programme for somatoform disorders is effective for affective disorders. *J Affect Disord*. 2010;122(1-2):124-132. Medline:19619900

«WH24: »41. Gardenswartz CA, Craske MG. Prevention of panic disorder. *Behav Ther*. 2001;32:725-737.

42. Ginsburg GS, Drake KL, Tein JY, Teetsel R, Riddle MA. Preventing onset of anxiety disorders in offspring of anxious parents: a randomized controlled trial of a family-based intervention. *Am J Psychiatry*. 2015;172(12):1207-1214. Medline:26404420

43. Ginsburg GS. The Child Anxiety Prevention Study: intervention model and primary outcomes. *J Consult Clin Psychol*. 2009;77(3):580-587. Medline:19485597

44. Joling KJ, van Marwijk HW, Smit F, et al. Does a family meetings intervention prevent depression and anxiety in family caregivers of dementia patients? a randomized trial. *PLoS One*. 2012;7(1):e30936. Medline:22303473

45. Li C, Chu F, Wang H, Wang XP. Efficacy of Williams LifeSkills training for improving psychological health: a pilot comparison study of Chinese medical students.

Asia Pac Psychiatry. 2014;6(2):161-169. Medline:23857943

46. Livermore N, Sharpe L, McKenzie D. Prevention of panic attacks and panic disorder in COPD. *Eur Respir J*. 2010;35(3):557-563. Medline:19741029

«WH25: »47. Lock S, Barrett PM. A longitudinal study of developmental differences in universal preventive intervention for child anxiety. *Behav Change*. 2003;20(4):183-199.

48. Mall AK, Mehl A, Kiko S, et al. Evaluation of a DVD-based self-help program in highly socially anxious individuals—pilot study. *Behav Ther*. 2011;42(3):439-448. Medline:21658526

49. Pitceathly C, Maguire P, Fletcher I, Parle M, Tomenson B, Creed F. Can a brief psychological intervention prevent anxiety or depressive disorders in cancer patients? a randomised controlled trial. *Ann Oncol*. 2009;20(5):928-934. Medline:19126633

50. Rooney R, Hassan S, Kane R, Roberts CM, Nesa M. Reducing depression in 9-10 year old children in low SES schools: a longitudinal universal randomized controlled trial. *Behav Res Ther*. 2013;51(12):845-854. Medline:24185214

51. Schmidt NB, Eggleston AM, Woolaway-Bickel K, Fitzpatrick KK, Vasey MW, Richey JA. Anxiety Sensitivity Amelioration Training (ASAT): a longitudinal primary prevention program targeting cognitive vulnerability. *J Anxiety Disord*. 2007;21(3):302-319. Medline:16889931

52. Timpano KR, Abramowitz JS, Mahaffey BL, Mitchell MA, Schmidt NB. Efficacy of a prevention program for postpartum obsessive-compulsive symptoms. *J Psychiatr Res*. 2011;45(11):1511-1517. Medline:21764404

53. Topper M, Emmelkamp PM, Watkins E, Ehring T. Prevention of anxiety disorders and depression by targeting excessive worry and rumination in

adolescents and young adults: A randomized controlled trial. *Behav Res Ther*. 2017;90:123-136. Medline:28049069

54. van der Aa HP, van Rens GH, Comijs HC, et al. Stepped care for depression and anxiety in visually impaired older adults: multicentre randomised controlled trial. *BMJ*. 2015;351:h6127. Medline:26597263

55. van't Veer-Tazelaar PJ, van Marwijk HW, van Oppen P, et al. Stepped-care prevention of anxiety and depression in late life: a randomized controlled trial. *Arch Gen Psychiatry*. 2009;66(3):297-304. Medline:19255379

56. van't Veer-Tazelaar PJ, van Marwijk HW, van Oppen P, et al. Prevention of late-life anxiety and depression has sustained effects over 24 months: a pragmatic randomized trial. *Am J Geriatr Psychiatry*. 2011;19(3):230-239. Medline:21425519

57. Zhang DX, Lewis G, Araya R, et al. Prevention of anxiety and depression in Chinese: a randomized clinical trial

testing the effectiveness of a stepped care program in primary care. *J Affect Disord*. 2014;169:212-220. Medline:25216464

58. Simon E, Dirksen C, Bögels S, Bodden D. Cost-effectiveness of child-focused and parent-focused interventions in a child anxiety prevention program. *J Anxiety Disord*. 2012;26(2):287-296. Medline:22245700

59. Cuijpers P, van Straten A, Smit F, Mihalopoulos C, Beekman A. Preventing the onset of depressive disorders: a meta-analytic review of psychological interventions. *Am J Psychiatry*. 2008;165(10):1272-1280. Medline:18765483

60. van Zoonen K, Buntrock C, Ebert DD, et al. Preventing the onset of major depressive disorder: a meta-analytic review of psychological interventions. *Int J Epidemiol*. 2014;43(2):318-329. Medline:24760873

61. Conejo-Cerón S, Moreno-Peral P, Rodríguez-Morejón A, et al. Effectiveness of psychological and/or educational

interventions to prevent depression in primary care: a systematic review and meta analysis. *Ann Fam Med*. 2017;15(3):262-271. Medline:28483893

62. Cuijpers P, Cristea IA, Karyotaki E, Reijnders M, Huibers MJH. How effective are cognitive behavior therapies for major depression and anxiety disorders? a meta-analytic update of the evidence. *World Psychiatry*. 2016;15(3):245-258. Medline:27717254

63. Furukawa TA, Noma H, Caldwell DM, et al. Waiting list may be a nocebo condition in psychotherapy trials: a contribution from network meta-analysis. *Acta Psychiatr Scand*. 2014;130(3):181-192. Medline:24697518

64. Powell J, Hamborg T, Stallard N, et al. Effectiveness of a web-based cognitive-behavioral tool to improve mental well-being in the general population: randomized controlled trial. *J Med Internet Res*. 2012;15(1):e2. Medline:23302475

65. Mihalopoulos C, Vos T, Rapee RM, et al. The population cost-effectiveness of a parenting intervention designed to prevent anxiety disorders in children. *J Child Psychol Psychiatry*. 2015;56(9):1026-1033. Medline:26111550

«DT26: Figure »1. The PRISMA Flowchart of the Randomized Clinical Trials (RCTs) Included

«DT27: XX»

Figure 2. ~~Forest Plot of Comparison:~~ Intervention vs Control Group Comparison

Random effects model. AC indicates active website; ACE, active website with email; ACP, active website with telephone; C, control website; CP, control website with telephone; ~~; ACP, active website with telephone; ACE, active website with email; EES, acceptance and commitment therapy with extensive email support; MES, acceptance and commitment therapy with minimal email support;~~ GI, group intervention; II, internet intervention; and SMD, standardized mean difference.

Table 1. Effectiveness of Psychological and/or Educational Interventions to Prevent Anxiety

Primary Analysis	No. of Participants	SMD (95% CI)	*P* Value	I^2 «DT28: (95% CI)»
Effectiveness to prevent anxiety	36	−0.3105 (−0.400 to −0.2109)	<.001	61.1% (44% to 73%)
Sensitivity analyses				
At first evaluation	36	−0.294 (−0.3988 to −0.200)	<.001	61.8% (45% to 73%)
At last evaluation	36	−0.334 (−0.4439 to −0.230)	<.001	67.2% (54% to 77%)
Fixed effects	36	−0.233 (−0.284 to −0.182)	<.001	61.1% (44% to 73%)
Hedges *g*	36	−0.303 (−0.40398 to −0.2108)	<.001	61.0% (44% to 73%)
Fledderus et al,[38] 2012 excluded[a]	34	−0.2547 (−0.331 to −0.163)	<.001	45.6% (19% to 64%)
RCTs with anxiety as a secondary outcome excluded	32	−0.241 (−0.330 to −0.152)	<.001	42.5% (12% to 62%)

Abbreviations: RCTs, randomized control clinical trials; SMD, standardized mean difference.

[a]The RCT that most increased heterogeneity.

Table 2. Meta-Regression

Model[a]	«DT29: β» (95% CI)[b]	*P* Value	*«DT30: P* Value» (95% CI)[c]
Sample size (lg)[d]	0.15~~47~~ (0.06~~2~~ to 0.23)~~2~~	.001	.01~~1~~ (0.001 to .01~~3~~)
Risk of bias (lg)[d]	−0.09~~1~~ (−0.27~~0~~ to 0.09~~88~~)	.31	.8~~6~~7 (0.86~~2~~ to 0.87~~1~~)
Standardized interview (outcome)	0.17~~0~~ (−0.01~~2~~ to 0.35~~1~~)	.07	.35~~4~~ (0.35~~47~~ to 0.36~~0~~)
Waiting list (comparator)	−0.33~~2~~ (−0.55~~4~~ to −0.11)~~09~~	.005	.03~~1~~ (0.03~~29~~ to 0.03~~4~~)
Family physician (~~provider~~caregiver)	−0.30~~299~~ (−0.61~~08~~ to 0.01)~~0~~	.06	.34~~35~~ (0.33~~28~~ to 0.34~~1~~)

«DT31: [a]Model $F_{5,30}$ = 9.31; P < .00~~0~~1; I^2 residual, 14.7~~4~~%; **»**adjusted R^2 -= 99.6~~59~~%.

[b]Knapp and~~&~~ Hartung method for estimation of ~~standard error~~SE and ~~confidence intervals~~95% CIs.

[c]Higgins and ~~&~~ Thompson permutation test, Monte Carlo approach (20 000 permutations).

«DT32: [d]Logarithmic transformation of the sample size (S-K test for normality: χ^2_2 = 4.11; P = .13~~282~~) and risk of bias (S-K test for normality: χ^2_2 = 1.99; P = .37~~689~~).**»**

Supplement. **eAppendix.** Search Strategies

eTable 1. Characteristics of 29 Randomized Clinical Trials Included to Prevent Anxiety

eTable 2. Risk of Bias of 29 Randomized Clinical Trials Included to Prevent Anxiety

eTable 3. Data Used to Calculate SM

eTable 4. Subgroup Analysis of Effectiveness of Psychological and/or Educational Interventions to Prevent Anxiety

eFigure 1. Funnel Plot

eFigure 2. Normal Probability Plot of Standardized Shrunken Residuals