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Effect of a nonpharmacological psychological stress management intervention on major cardiovascular events and mortality in patients with coronary artery disease: a systematic review and meta-analysis of randomized clinical trials Effect of a psychological stress management intervention on cardiovascular events and mortality in patients with coronary artery disease

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Research Article

Keywords: Psychological Stress, Mortality, Cardiovascular Diseases, Systematic Review, Meta-Analysis

Posted Date: January 19th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2487764/v1

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Abstract

Introduction: Psychological stress is associated with major adverse cardiovascular events (MACE). The objective of this systematic review (SR) is to evaluate the effect of nonpharmacological psychological stress management interventions on MACE and mortality in patients with coronary artery disease (CAD).

Methods: SR and meta-analysis of randomized clinical trials (RCTs) of adult patients with CAD undergoing nonpharmacological psychological stress management interventions. MEDLINE, Cochrane, LILACS, PsycInfo, Clinical Trials databases and gray literature were used for the search. There were no limits regarding publication status, year, or language. The analyzed outcome was a combination of MACE (cardiovascular mortality, nonfatal infarction, revascularization, nonfatal stroke, and cardiovascular hospitalization). The secondary outcomes were total mortality. Results were expressed as risk ratio (RR) with their 95% confidence interval (CI95%). The random effects model was used for the analyses, the RoB2 tool to risk of bias and RStudio for the statistical analyses. Prospective International Register of Systematic Reviews (CRD42021275198).

Results: This SR included seven RCTs (n = 1908). There was no effect attributable to the intervention on reducing MACE (34.54% *vs* 39.05%*;* RR= 0.84 [CI95% 0.63–1.12], p = 0.24; PI95% 0.35–2.02; I^2 = 74.7%, p = 0.001) or on the analysis of isolated events. The intervention reduced the risk of total mortality by 37% (8.58% vs 13.62%; RR= 0.63 [CI95% CI 0.42– 0.95], p = 0.03; PI95% 0.18–2.25; I^2 = 23.8%, p = 0.27).

Conclusion: This meta-analysis showed no significant decrease in psychological intervention for stress management in MACE, but a significant decrease in mortality.

Introduction

Psychological stress is a cardiovascular risk factor and contributes through different mechanisms to the occurrence of major adverse cardiovascular events (MACE) and mortality (Dar et al., 2019; Kivimäki & Steptoe, 2018). Acute stress can cause left ventricular dysfunction and arrhythmias and trigger cardiovascular events through sympathetic activation and rupture of preexisting atherosclerotic plaques (Dar et al., 2019; Kivimäki & Steptoe, 2018). Chronic stress has an inflammatory effect on endothelial function and is linked to the development and progression of coronary artery disease (CAD), culminating in cardiovascular events and mortality (Fioranelli et al., 2018). Patients with established CAD have a higher risk of cardiovascular events secondary to stress than patients without CAD, which makes this population especially vulnerable (Dar et al., 2019; Fioranelli et al., 2018; Kivimäki & Steptoe, 2018). Therefore, several psychological interventions for stress management have been proposed (Blumenthal et al., 2016; Gulliksson et al., 2011; Schneider et al., 2012). However, evidence is still scarce and individual results of studies are not robust enough to define the effects of treating this risk factor on mortality and MACE. Thus, the objective of this study was to perform a systematic review (SR) of randomized clinical trials (RCTs) that evaluated the effect of nonpharmacological psychological interventions for stress management on mortality and MACE in patients with CAD.

Methods

SR with meta-analysis of RCTs. The protocol of this review was registered in the International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/PROSPERO/, CRD42021275198 registration date 8/24/2021). The review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019; Moher et al., 2015). A detailed description of the protocol was provided in a separate article.

Study search and selection strategy

The MEDLINE (accessed through PubMed), Cochrane Central, LILACS, and PsycINFO electronic databases were searched. Unpublished studies (gray literature) were searched in the ClinicalTrials.gov, Brazilian Registry of Clinical Trials (REBEC),

OpenGrey, and CAPES Brazilian Dissertations and Theses databases. Studies cited in the RCTs eligible for our SR were also reviewed. The words to structure the search grid were derived from the Health Sciences Descriptors (DeCS), Medical Subject Headings (MeSH, PubMed), keywords of articles on the topic and usual expressions found in the literature (Tables 1 and 2 of the Online Resource). The articles were searched and selected in duplicate (AMS and KESS) and cases of disagreement or doubt were first resolved in consensus between the two reviewers. Cases of permanent indecision had the final analysis of a third reviewer (MMS).

Selection criteria

This SR included only RCTs that evaluated the effect of nonpharmacological psychological stress management intervention and reported as clinical outcome MACE and/or total mortality. There were no restrictions regarding language, follow-up time, or study size.

The primary outcome assessed was a MACE combination including cardiovascular mortality, nonfatal infarction, revascularization (coronary artery bypass graft and percutaneous coronary intervention), nonfatal stroke, and cardiovascular hospitalization. Secondary outcomes were total mortality and assessment of each of the events that composed the MACE combination. The events were classified according to the description of the study authors. Fatal infarctions were considered cardiovascular mortality events.

Data extraction

The data were extracted by two blinded investigators (AMS and KESS) using a pre-specified data-collection form in a Microsoft Office Excel 2010 spreadsheet, and included study characteristics, clinical variables of the samples, details of stress assessment instruments, interventions applied, and cardiovascular event rates. Cases of discrepant data were resolved through double review and consensus between reviewers. The WebPlotDigitizer software (version 4.5, August 2021) (Rohatgi, 2017) was used to extract data from the stress scale expressed in graphs, and the standard deviation (SD) of the mean was calculated through the minimum and maximum values (Higgins et al., 2019). The difference between means (▲= Post-Pre-intervention or control) and its respective dispersion were extracted when available).

Assessment of the risk of bias

The studies were judged regarding selection, measurement, and confounding biases according to the six domains of the Cochrane Risk of Bias 2 (RoB2) (Higgins et al., 2019) and classified as “low risk of bias” (all domains for this outcome), “some concerns” (a few questions in at least one domain for this outcome, but not high risk of bias in any domain), or “high risk of bias” (high risk of bias in at least one domain for this outcome, or a few concerns in several domains in a way that substantially reduces confidence in the outcome). Risk of bias will be assessed for the primary outcome. No studies were excluded based on the risk of bias outcome.

Data analysis

All data were described as risk ratio (RR) and 95% confidence interval (CI95%). Owing to the known clinical and methodological heterogeneity of psychological intervention studies, effect estimates were pooled using the random model(Cornell et al., 2014) and Mantel-Haenszel method. As the CI95% described for the random effect refers to uncertainty in the location of mean effects in different studies, values calculated for a 95% prediction interval (PI95%) were included for better interpretation (IntHout et al., 2016). Result heterogeneity was estimated using the DerSimonian-Laird method and its magnitude by the Higgins inconsistency test (I^2) (0–40%: may not be important; 30–60%: may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity; 75–100%: considerable heterogeneity) (Dias et al., 2013; Higgins et al., 2019). Heterogeneity ($p < 0.05$) was tested using subgroup or meta-regression analyses for effect modifiers normally distributed on QQ-plots and verified by the Shapiro-Wilk test (Dias et al., 2013). Potential effect modifiers including age, body mass index (BMI), sex, and year of publication were separately analyzed. Imprecise effect estimates due to heterogeneity were visually identified when their CI95% did not overlap in the forest plot to remove discrepant data from the meta-analysis(Dias et al., 2013). To identify potential *outliers*, analyses with and without each study were performed as part of

the sensitivity analysis (Boutron et al., 2019). Dispersion measures expressed as CI or standard errors (SE) were converted into SD (SE = upper limit - lower limit/1.96 x 2; SD = SE * √n) prior to analysis. The data were analyzed with the RStudio software (version 1.3.959) using the “meta” package (version 3.6.1 for Windows). The Script used for RStudio analyses is shown in Table 3 of the Online Resource. The analyzed databases can be freely checked at Mendeley Data (https://data.mendeley.com/).

Results

Study selection

A total of 6,687 studies were identified through the search strategy up to December 2021, of which 6,285 were from databases and registries, and 402 from gray literature. Of the studies from databases and registries, 42 duplicates were excluded, leaving 6,243 scanned articles, of which 5,980 were excluded by title and 244 were not selected for full reading. Nineteen articles were accessed for eligibility, of which 13 were excluded and six were included in the SR. Of the 402 studies screened from websites and bibliographic citations, 10 were selected for abstract review and, of these, two were accessed for eligibility and one was included in the SR. Therefore, seven studies were included in the SR(Appels et al., 2005; Blumenthal et al., 2016; Claesson et al., 2005; Gulliksson et al., 2011; Orth-Gomér et al., 2009; Rakowska, 2015; Schneider et al., 2012) (Fig. 1).

Study characterization

The seven studies included (Appels et al., 2005; Blumenthal et al., 2016; Claesson et al., 2005; Gulliksson et al., 2011; Orth-Gomér et al., 2009; Rakowska, 2015; Schneider et al., 2012) totaled 1,908 patients (intervention: 966, control: 942). The mean follow-up time was 4.2 years. Table 4 of the Online Resource presents the clinical characteristics of the patients of the studies by intervention and control groups. Two studies included only women (Claesson et al., 2005; Orth-Gomér et al., 2009) and the others had mostly men (Appels et al., 2005; Blumenthal et al., 2016; Gulliksson et al., 2011; Rakowska, 2015; Schneider et al., 2012). The mean age ranged from 53.4 to 61.5 years.

Assessment of risk of bias

Risk of bias was assessed for the primary outcome MACE and included six studies (Appels et al., 2005; Blumenthal et al., 2016; Claesson et al., 2005; Gulliksson et al., 2011; Rakowska, 2015; Schneider et al., 2012). These studies were assessed regarding the attribution to the intervention (the “intention-to-treat” effect) and the bias due to the randomization process was classified as low in the six studies (Appels et al., 2005; Blumenthal et al., 2016; Claesson et al., 2005; Gulliksson et al., 2011; Rakowska, 2015; Schneider et al., 2012). The bias due to intervention deviations was classified as low in two studies (Appels et al., 2005; Blumenthal et al., 2016) and high in four (Claesson et al., 2005; Gulliksson et al., 2011; Rakowska, 2015; Schneider et al., 2012) because of the impossibility of patient blinding due to the psychological intervention. Bias due to lack of outcome data was low in two studies (Appels et al., 2005; Blumenthal et al., 2016) and high in four studies (Claesson et al., 2005; Gulliksson et al., 2011; Rakowska, 2015; Schneider et al., 2012), considering that the missing outcome data because of losses were not similarly distributed between groups. Risk of bias for outcome measurement was rated as low in the six studies (Appels et al., 2005; Blumenthal et al., 2016; Claesson et al., 2005; Gulliksson et al., 2011; Rakowska, 2015; Schneider et al., 2012); for selection of the reported result, it was low in five studies (Appels et al., 2005; Blumenthal et al., 2016; Gulliksson et al., 2011; Rakowska, 2015; Schneider et al., 2012) and classified as some concern in one (Claesson et al., 2005), in which outcome analysis was performed per protocol. In general, the RoB2 characterized the assessment of the quality of the studies in this SR as presenting high risk (66.67%) and low risk (33.33%). The assessment of the risk of bias of the studies is summarized in Fig. 2.

Stress management intervention and control group

Table 5 of the Online Resource presents data on stress management interventions for each study selected. In four studies, the stress management intervention used psychoeducation that included themes such as traditional risk factors, cardiovascular system, stress, and the relationship among these components, also seeking to promote self-care and adherence to clinical

guidelines (Blumenthal et al., 2016; Claesson et al., 2005; Gulliksson et al., 2011; Orth-Gomér et al., 2009). Cognitive-behavioral therapy was the most used, aiming at reducing demands and stressors, developing management skills, and coping with stress and cognitive restructuring (Blumenthal et al., 2016; Claesson et al., 2005; Gulliksson et al., 2011; Orth-Gomér et al., 2009). Two studies (Claesson et al., 2005; Gulliksson et al., 2011) used the same standardized Cognitive-Behavioral Therapy Program (Burell & Granlund, 2002) comprising education, self-monitoring, skill training, cognitive restructuring, and spiritual development, emphasizing stress management and coping to reduce the experience of daily stress and negative affectivity, with a focus on hostility and search for emotional and spiritual balance.

One study (Rakowska, 2015) used the brief strategic therapy, which identified the problems that generated stress while avoiding ineffective solutions responsible for maintaining this problem by adopting an opposite behavior. Group therapy focused on reducing stressors that cause exhaustion and on supporting recovery was used in one study (Appels et al., 2005). Another study (Schneider et al., 2012) used transcendental meditation as a mind–body intervention because of its influence on the physiological effects of stress and cardiovascular outcomes, considering its standardization, reproducibility, and validity. Muscle relaxation techniques (Appels et al., 2005; Blumenthal et al., 2016; Orth-Gomér et al., 2009), incentive to rest (Appels et al., 2005), breathing training, use of images (Blumenthal et al., 2016), self-monitoring diaries (Claesson et al., 2005), and homework assignments (Appels et al., 2005; Blumenthal et al., 2016; Gulliksson et al., 2011) were also employed.

As for intervention modalities, most studies used group interventions (Appels et al., 2005; Blumenthal et al., 2016; Claesson et al., 2005; Gulliksson et al., 2011; Orth-Gomér et al., 2009) with four–nine patients—one of them encouraging familial follow-up(Appels et al., 2005). In one study, the groups were separated by sex (Gulliksson et al., 2011) and in two studies this separation was not necessary because they comprised only women (Claesson et al., 2005; Orth-Gomér et al., 2009). Of the selected studies, only one performed the intervention individually (Rakowska, 2015). The modality of individual intervention associated with group intervention was used in one study (Schneider et al., 2012).

A for the number and duration of sessions, one study conducted 14 two-hour sessions (Appels et al., 2005), two studies conducted 20 two-hour sessions (Claesson et al., 2005; Gulliksson et al., 2011), and another had the same number of sessions but lasting 2–2.5 hours (Orth-Gomér et al., 2009). The study that used transcendental meditation taught the technique in a seven-step course comprising six meetings of 1.5–2 hours. Thereafter, follow-up and maintenance meetings were held weekly in the first month, biweekly in the following two months, and monthly thereafter (Schneider et al., 2012). Finally, one study held 10 one-hour sessions (Rakowska, 2015) and another held 12 sessions of 1.5 hours each (Blumenthal et al., 2016).

In the control group, six of the seven studies performed usual clinical treatment, which included routine cardiologist visits, clinical heart disease treatment, and traditional risk factor optimization (Appels et al., 2005; Blumenthal et al., 2016; Claesson et al., 2005; Gulliksson et al., 2011; Orth-Gomér et al., 2009; Rakowska, 2015). In two studies, the researchers chose to refer control group patients to conventional cardiac rehabilitation (Appels et al., 2005; Blumenthal et al., 2016). In one study (Schneider et al., 2012), the control intervention was a cardiovascular health education program designed to match the experimental intervention format with instructional time, instructor attention, participant expectancy, social support, and other nonspecific factors.

As for stress measurement, 12 different assessment scales were used. The Maastricht Questionnaire was the most used (Appels et al., 2005; Claesson et al., 2005; Gulliksson et al., 2011), followed by the Everyday Life Stress Scale (Claesson et al., 2005; Orth-Gomér et al., 2009), and the Perceived Stress Scale (Blumenthal et al., 2016; Rakowska, 2015). Four studies used a single scale (Appels et al., 2005; Gulliksson et al., 2011; Orth-Gomér et al., 2009; Rakowska, 2015) and three studies assessed stress through combined scales (Blumenthal et al., 2016; Claesson et al., 2005; Schneider et al., 2012). In four studies, the scales were reapplied after the end of the intervention (Appels et al., 2005; Blumenthal et al., 2016; Claesson et al., 2005; Rakowska, 2015), although in one of these studies (Appels et al., 2005) the stressed patients were categorized by exhaustion level and post-intervention scale values were not directly reported.

Stress management intervention effect on cardiovascular events

In MACE analysis, no stress management intervention effect was demonstrated in reducing event risk (34.54% *vs* 39.05%; RR = 0.84 [CI95% 0.63–1.12], p = 0.24; PI95% 0.35–2.02; I^2 = 74.7%, p = 0.001) (Fig. 3).

Sensitivity analysis, removing the studies individually, determine no significant changes in the summarized result or in heterogeneity (Fig. 1 of the Online Resource). Meta-regression for the effect modifiers age, BMI, and sex, showed no interference in the summarized data for cardiovascular events. However, when the analysis was directed to year of publication, it showed a strong potential to explain the heterogeneity (I^2 = 74.7%, p = 0.001) found for the outcome (R^2 = 86.9, p = 0.003; Shapiro-Wilk normality test, p = 0.25) (Fig. 2 of the Online Resource).

As for the analysis of isolated events, the psychological stress management intervention showed no effect in modifying the risk of cardiovascular mortality (0.77% *vs* 2.15%; RR = 0.38 [CI95% 0.12–1.19], p = 0.10; PI95% 0.00–5,984.93; I^2 = 21.9%, p = 0.28) (Fig. 4a), nonfatal stroke (1.57% *vs* 2.28%; RR = 0.69 [CI95% 0.19–2.46], p = 0.57; PI95% 0.00–2,599.58; I^2 = 0.00%, p = 0.87) (Fig. 4b), nonfatal acute myocardial infarction (AMI) (8.43% *vs* 10.28%; RR = 0.70 [CI95% 0.35–1.40], p = 0.32; PI95% 0.11–4.28; I^2 = 55.3%, p = 0.05) (Fig. 4c), revascularization (17.55% *vs* 15.65%; RR = 1.10 [CI95% 0.86–1.41], p = 0.44; 95% PI 0.64 to 1.90]; I^2 = 0.00%, p = 0.89) (Fig. 4d), and cardiovascular hospitalization (23.27% *vs* 27.25%; RR = 0.82 [CI95% 0.66–1.01], p = 0.06; PI95% 0.51–1.30; I^2 = 0.00%, p = 0.80) (Fig. 4e).

For the outcome nonfatal AMI (Fig. 4c), which showed moderate heterogeneity, when removing the studies individually, sensitivity analysis determined no significant change in the summarized result or heterogeneity (Fig. 3 of the Online Resource). Meta-regression for the effect modifiers age, BMI, and year of publication showed no potential to interfere in the summarized result. However, when the analysis was performed by sex, the higher number of men in the sample was a strong potential to moderate the summarized outcome for nonfatal AMI (intervention: R^2 = 92.0, p = 0.016; control: R^2 = 84.8, p = 0.026) (Shapiro-Wilk normality test, p = 0.063). The bubble plots are shown in Fig. 4 of the Online Resource.

Effect of stress management intervention on total mortality

The psychological stress management intervention demonstrated a decreased risk of total mortality (8.58% *vs* 13.62%; RR = 0.63 [CI95% 0.42–0.95], p = 0.03; PI95% 0.18–2.25; I^2 = 23.8%, p = 0.27) (Fig. 5).

Discussion

This meta-analysis of RCTs verified the effects of psychological stress management intervention on cardiovascular events and mortality. Although other meta-analyses have already investigated the benefits of nonpharmacological psychological interventions on psychological (Klainin-Yobas et al., 2016; Magán et al., 2021; Zou et al., 2021), physical (Abbott et al., 2014; Rainforth et al., 2007), and hard outcomes (Richards et al., 2018) in patients with cardiovascular disease, to the best of our knowledge, this is the first study specifically investigating the effects of stress management intervention on MACE and mortality. Although this SR did not show that psychological interventions reduce cardiovascular events and mortality, they can reduce the risk of total mortality by 37%.

The evolution of pharmacotherapy in recent years is noteworthy, associated with CAD management and device technologies, which widely reflected in the understanding of pathophysiological mechanisms of CAD and in reducing procedure- and device-related adverse events(Cao et al., 2021). Additionally, other nonpharmacological interventions were developed, such as physical exercise and eating habit changes to reduce cardiovascular morbidity and mortality (Cao et al., 2021; Olin et al., 2016). All of this certainly interfered in the lower effect of psychological treatment on MACE in the most recent studies. Other aspects that may have interfered with this result are the number of studies and patients included and the heterogeneity of the interventions used.

From the clinical perspective, there is a trend toward lower rates in the intervention group for all isolated events except revascularization. One of the probable causes for this may be the imbalance between sexes. For the outcome nonfatal AMI, for example, which showed moderate heterogeneity, meta-regression analysis showed that the higher number of men in the sample was a strong potential to moderate the summarized outcome for nonfatal AMI. Differences by sex in symptomatology and incidence risk of AMI from coronary heart disease are well-documented in the literature (Khamis et al., 2016; Liakos & Parikh, 2018; Regitz-Zagrosek & Kararigas, 2017), as well as differences in etiology, presentations, and forms of coping with stress (Lee & Dik, 2017; Matud, 2004; Möller-Leimkühler, 2022). Although none of the studies was conducted exclusively with male patients, these meta-regression data suggest a possible treatment benefit in the approach by sex. However, there is a lack of studies designed by sex characteristics both in cardiovascular pathophysiology and in stress presentations, especially with male patients, to allow attributing a better effect of stress management intervention, if applied, considering these differences.

Another hypothesis for the lack of treatment effect on event reduction may be the higher prevalence of risk factors in the patients analyzed in more recent studies, especially dyslipidemia and hypertension. Considering that risk factors interact and jointly affect CAD and cardiovascular risk (Malakar et al., 2019; Said et al., 2019), a more intensified treatment would be required to optimize the treatment of stress in patients with more comorbidities, with more and/or longer sessions (Gillespie et al., 2002), as the last studies had fewer sessions with reduced time (10 and 12 sessions of 1–1.5 hours each) compared to the initial studies (20 sessions of 2–2.5 hours each).

The association between stress and different causes of mortality has already been documented (Taouk et al., 2020; Wei et al., 2014), being explained through the several mechanisms of stress that influence these outcomes (Bahri et al., 2019; Kruk et al., 2019; Wei et al., 2014). One assumption is that this result is due to the immune system suppression as a consequence of stress, which leads to oxidative stress, accelerating aging and accumulating oncogenic cell mutations that predispose to cancer (Bahri et al., 2019; Kruk et al., 2019). The effect of stress on the hypothalamic-pituitary-adrenal axis increases cortisol and inhibits antineoplastic activity (Bahri et al., 2019; Kruk et al., 2019). Additionally, stress impacts intermediate outcomes such as inflammatory markers, interleukins and cytokines—the latter, when imbalanced, may suppress immune system function and lead to several disorders, including infection or neoplastic growth (Bahri et al., 2019; Steptoe et al., 2007). Thus, the reduced mortality risk after stress management interventions indicates that the techniques used help improve stress in such a manner that there is an improvement in oxidative stress, immunity, and aggressiveness, as one of the symptoms of stress is irritability. The techniques can also affect the patients' self-regulation.

Self-regulation is the organism's effort to change its own responses and includes overcoming impulses to behave in a certain manner and replacing them with more adaptive behaviors (Roberton et al., 2012). The patients may have acquired this ability through the several interventions used, which may have contributed to the adoption of better regulated behaviors in general in their lives, reducing risky behaviors such as dangerous driving, alcohol abuse, etc., consequently reflecting in less involvement in traffic accidents and conflict situations with knife or firearm injuries, for example (Bogdan et al., 2016; Hofmann et al., 2012; Zhang & Chan, 2016). This relationship should be investigated in future studies, especially by verifying whether the reduced total mortality risk is also reproduced in the general population and not only in patients with cardiovascular diseases, and the mechanisms through which these effects are achieved.

This study has a few limitations. We identified lower event rates in the intervention group; however, considering the number of patients required for the evaluation of hard cardiovascular outcomes, the total sample of patients and studies included may have been insufficient to demonstrate the relationship between stress management intervention and MACE, also considering the different characteristics of the populations and interventions involved. Therefore, this issue requires further investigation. Moreover, this meta-analysis demonstrated the effect of stress management intervention in reducing mortality; however, we could not elucidate through which mechanisms this result occurs. Therefore, this relationship be investigated in future studies. Given the considerable PI95% reported and the small number of studies, the results of this meta-analysis should be cautiously interpreted.

Conclusion

This meta-analysis showed no significant decrease in psychological intervention for stress management in MACE patients with preexisting cardiovascular disease, but a significant decrease in mortality.

Declarations

Competing Interests:

The authors have no competing interests to declare that are relevant to the content of this article. There are no financial interests or non-financial interests that are directly or indirectly related to the work submitted for publication.

Author contributions

Karine Elisa Schwarzer Schmidt, Alexandre Schaan de Quadros and Marcia Moura Schmidt contributed to the study conception and design. The literature search and data collection were performed by Karine Elisa Schwarzer Schmidt and Adriane Marinês dos Santos. The data analysis were performed by Gustavo Waclawovsky. Gustavo Waclawovsky, Alexandre Schaan de Quadros and Marcia Moura Schmidt critically revised the work. The first draft of the manuscript was written by Karine Elisa Schwarzer Schmidt and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Tables

Tables 1 to 5 are available in the Supplementary Files section.

Figures

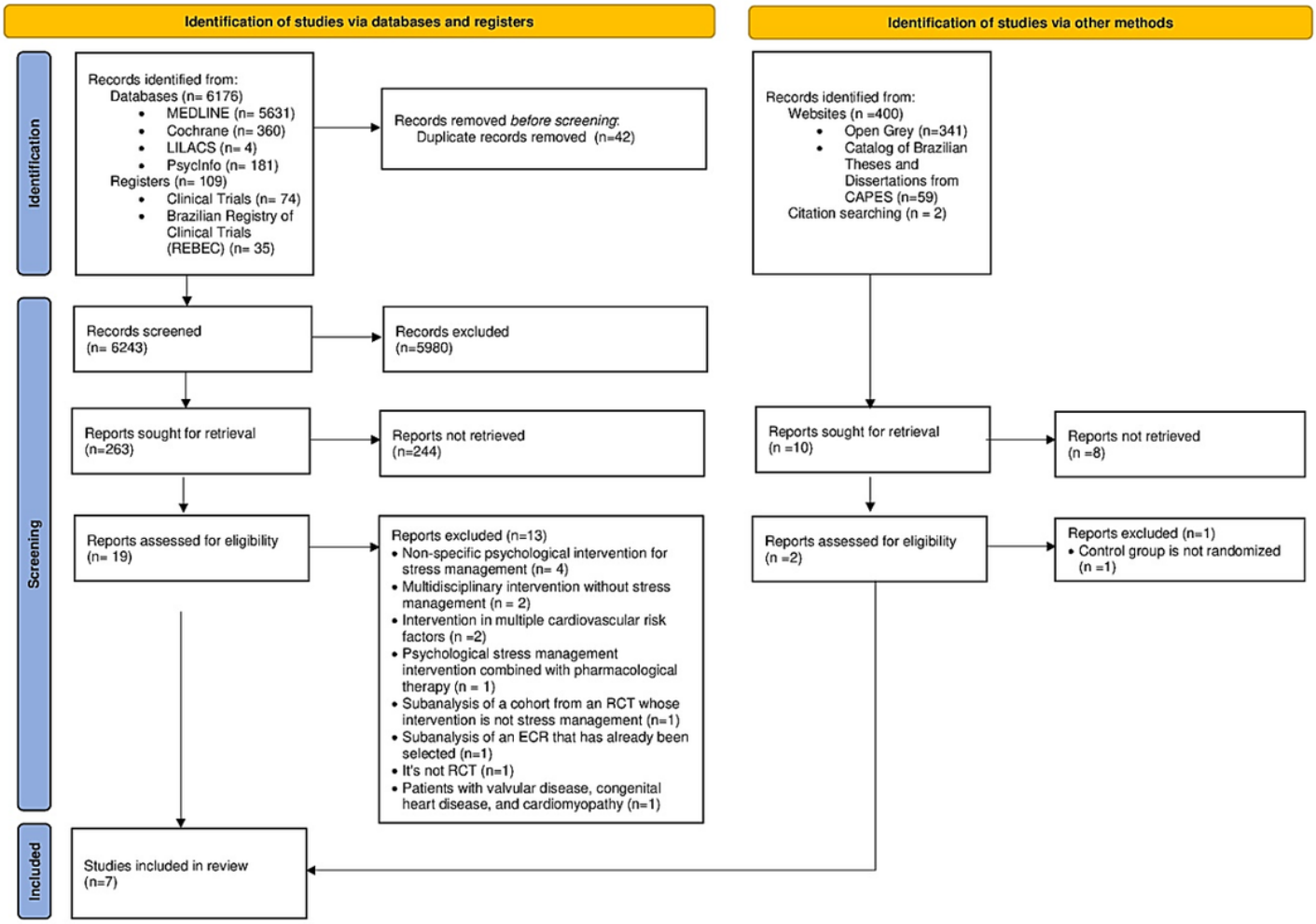


Figure 1

Flowchart.

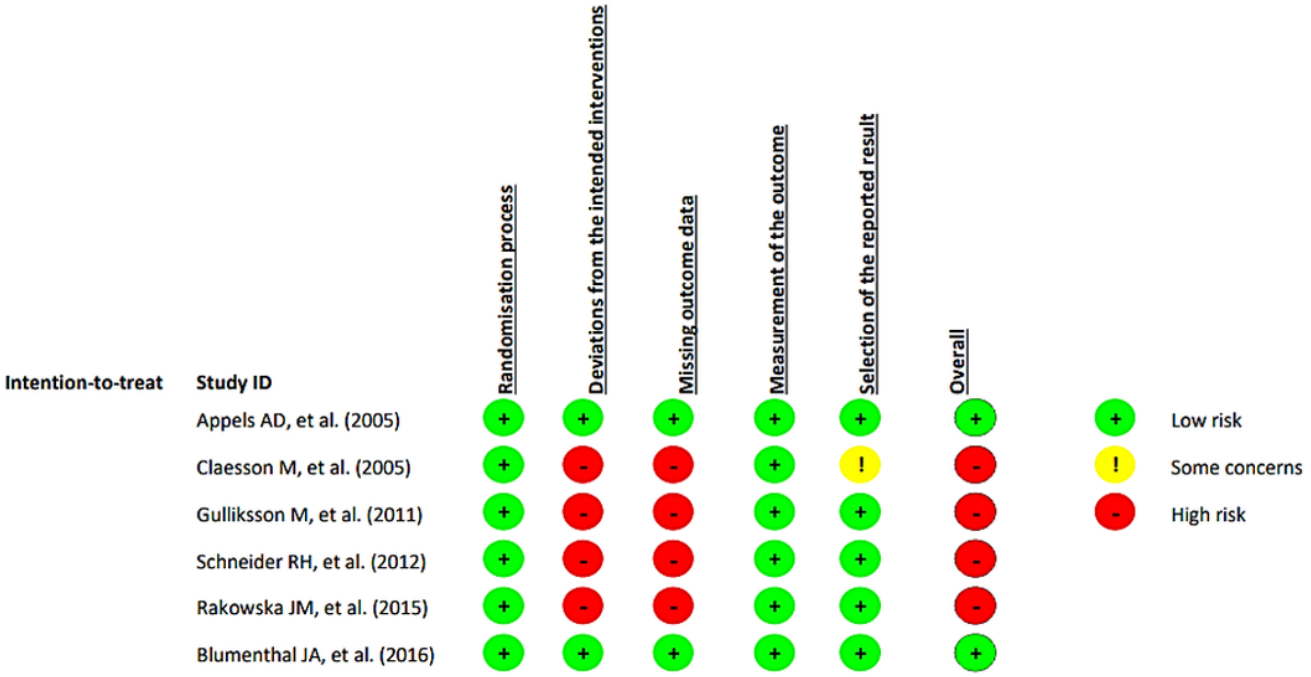


Figure 2

Analysis of the risk of bias by the RoB2 with the intention-to-treat effect.

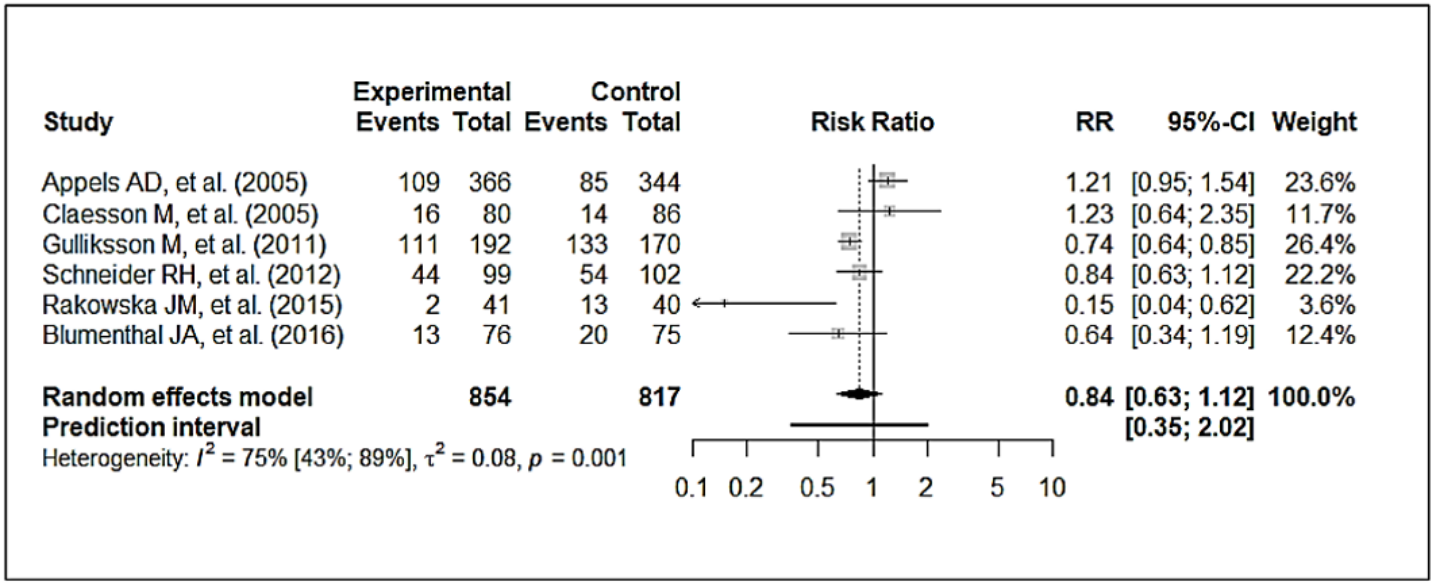


Figure 3

Effect of psychological stress management intervention on MACE.

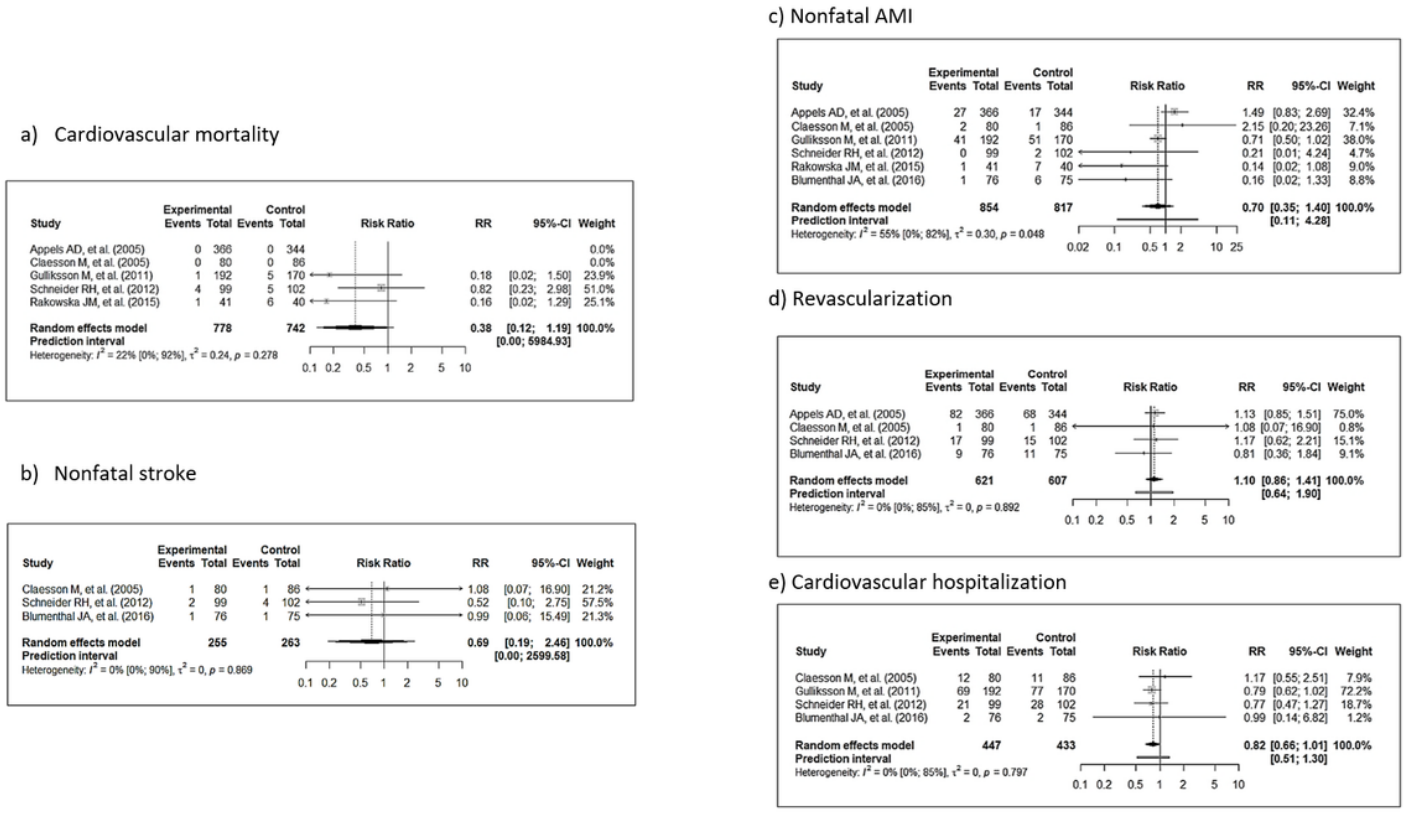


Figure 4

Effect of psychological stress management intervention on isolated cardiovascular events.

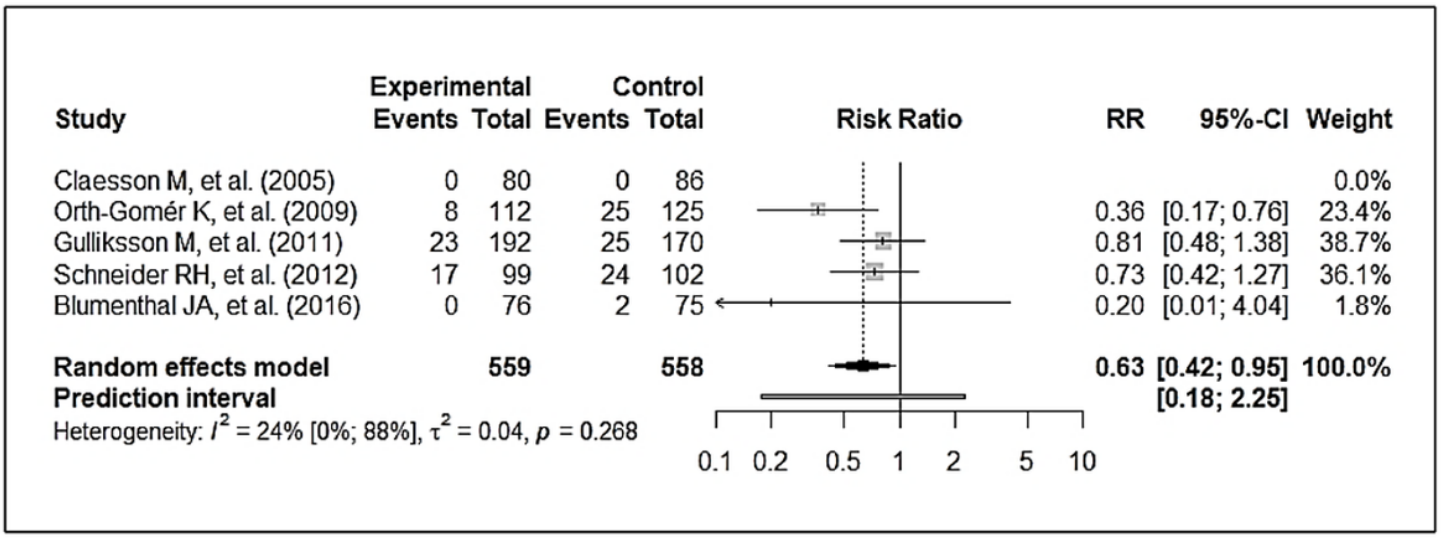


Figure 5

Effect of psychological stress management intervention on total mortality.

Supplementary Files

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