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STRESS MANAGEMENT ON THE INCIDENCE OF MAJOR CARDIOVASCULAR EVENTS: PROTOCOL OF A SYSTEMATIC REVIEW

MANEJO DO ESTRESSE NA INCIDÊNCIA DE EVENTOS CARDIOVASCULARES MAIORES: PROTOCOLO DE UMA REVISÃO SISTEMÁTICA

MANEJO DEL ESTRÉS EN LA INCIDENCIA DE EVENTOS CARDIOVASCULARES MAYORES: PROTOCOLO DE UNA REVISIÓN SISTEMÁTICA

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ABSTRACT

This is a Systematic review of randomized controlled trials to To evaluate the effect of psychological interventions for stress management on the incidence of major adverse cardiovascular events in individuals with coronary artery diasease. The primary outcome will be a combination of major adverse cardiovascular events endpoints including cardiovascular death, nonfatal acute myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, nonfatal stroke, and cardiovascular hospitalization. Outcomes will be presented as Risk Ratio (RR) and related 95% confidence

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intervals (95% CIs). Data will be pooled using a random-effects model to account for clinical heterogeneity in psychological interventions. Heterogeneity of results will be tested using the Higgins inconsistency test (I^2). Univariate meta-regression will be used to assess heterogeneity of studies and the level of significance will be set at $p < 0.05$. We will use Cochrane Risk of Bias 2 (RoB 2) tool to assess the risk of individual bias and GRADE tool to evaluate the quality of individual studies in the systematic review. Statistical analyses will be performed using RStudio for Windows (v1.3.959). The protocol of this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42021275198)

Keywords: Psychological Distress. Stress. Psychological. Cardiovascular Diseases. Cardiovascular Events. Systematic Review.

RESUMO

Esta é uma revisão sistemática de ensaios clínicos randomizados para avaliar o efeito de intervenções psicológicas para o gerenciamento do estresse na incidência de eventos cardiovasculares adversos maiores em indivíduos com doença arterial coronária. O desfecho primário será uma combinação de desfechos de eventos cardiovasculares adversos maiores, incluindo morte cardiovascular, infarto agudo do miocárdio não fatal, intervenção coronária percutânea, cirurgia de revascularização do miocárdio, acidente vascular cerebral não fatal e hospitalização cardiovascular. Os desfechos serão apresentados como razão de risco (RR) e intervalos de confiança de 95% relacionados (ICs de 95%). Os dados serão agrupados usando um modelo de efeitos aleatórios para levar em conta a heterogeneidade clínica em intervenções psicológicas. A heterogeneidade dos resultados será testada usando o teste de inconsistência de Higgins (I^2). Metarregressão univariada será usada para avaliar a heterogeneidade dos estudos e o nível de significância será estabelecido em $p < 0,05$. Utilizaremos a ferramenta Cochrane Risk of Bias 2 (RoB 2) para avaliar o risco de viés individual e a ferramenta GRADE para avaliar a qualidade de cada estudo na revisão sistemática. As análises estatísticas serão realizadas no RStudio para Windows (v1.3.959). O protocolo desta revisão foi registrado no Registro Prospectivo Internacional de Revisões Sistemáticas (PROSPERO) (CRD42021275198).

Palavras-chave: Sofrimento Psicológico. Estresse Psicológico. Doenças Cardiovasculares. Eventos Cardiovasculares. Revisão Sistemática.

RESUMEN

Esta es una revisión sistemática de ensayos controlados aleatorios para evaluar el efecto de las intervenciones psicológicas para el manejo del estrés sobre la incidencia de eventos cardiovasculares adversos mayores en individuos con enfermedad de la arteria coronaria. El resultado primario será una combinación de puntos finales de eventos cardiovasculares adversos mayores que incluyen muerte cardiovascular, infarto agudo de miocardio no fatal, intervención coronaria percutánea, cirugía de injerto de derivación de la arteria coronaria, accidente cerebrovascular no fatal y hospitalización cardiovascular. Los resultados se presentarán como razón de riesgos (RR) e intervalos de confianza del 95% relacionados (IC del 95%). Los datos se agruparán utilizando un modelo de efectos aleatorios para tener en cuenta la heterogeneidad clínica en las intervenciones psicológicas. La heterogeneidad de los resultados se probará utilizando la prueba de inconsistencia de Higgins (I^2). Se utilizará metarregresión univariante para evaluar la heterogeneidad de los estudios y el

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nivel de significancia se establecerá en p <0,05. Utilizaremos la herramienta Cochrane de Riesgo de Sesgo 2 (RoB 2) para evaluar el riesgo de sesgo individual y la herramienta GRADE para evaluar la calidad de los estudios individuales en la revisión sistemática. Los análisis estadísticos se realizarán con RStudio para Windows (v1.3.959). El protocolo de esta revisión se registró en el Registro Prospectivo Internacional de Revisiones Sistemáticas (PROSPERO) (CRD42021275198).

Palabras clave: Distrés psicológico. Estrés psicológico. Enfermedades cardiovasculares. Eventos cardiovasculares. Revisión sistemática.

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INTRODUCTION

Our understanding of the pathophysiology of coronary artery disease (CAD) has evolved greatly over the years. Stable CAD is a clinical categorization that has been reconsidered and more clearly defined as chronic coronary vascular disease including groups of patients with significant risk of future major coronary events [1]. The probability of the occurrence of major adverse cardiovascular events (MACE) within 5 years of the onset of apparently stable angina is up to 35% depending on risk-related clinical variables[2]. This risk range points to the need of identifying those individuals who are at higher risk and further optimize their disease management. The risk of cardiovascular events is increased in patients with chronic CAD when there is a combination of systemic and specific cardiovascular risk factors. Recent developments show that chronic cardiovascular risk factors are modifiable and can lead to clinically significant gains in those who are at high risk. New improved clinical concepts and approaches have been developed for managing the chronic and acute phases of CAD particularly focusing on mostly modifiable psychological aspects such as psychological stress[1,3].

Stress has been associated to the development of atherosclerosis and subclinical CAD. It has also been identified as a determinant of clinical outcomes and prognosis in patients with preexisting cardiovascular or cerebrovascular disease, and can trigger acute cardiovascular events in people with advanced CAD [3,4]. A meta-analysis of the effect of perceived stress and its association with CAD found a 27% increase in the rate of cardiovascular disease in those with high perceived stress [5]. Another meta-analysis of mental stress-induced myocardial ischemia showed that mental stress was associated with a twofold increase in the risk of combined cardiovascular events or total deaths[6].

Nonpharmacological psychological interventions for stress management aim to promote adaptive responses to stress situations. Behavior change is a complex process involving individual, cultural and environmental aspects, among others. It is thus crucial to use simple effective approaches, including multimodal behavioral therapy, and as well as effective simple communication strategies[7]. Psychological interventions targeted to patients with cardiovascular conditions include individual and group counseling on psychological risk factors and coping strategies; cognitive behavioral therapy; stress management programs such as meditation; autogenic training; biofeedback; and breathing and muscle relaxation techniques[8,9].

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Several clinical practice guidelines include recommendations of stress management for patients with cardiovascular diseases. The *2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult* suggested that health care providers could explore stress management techniques with patients with acute myocardial infarction (MI) and depression to optimize their quality of life. The 2021 updated recommendations include stress management for pregnant women with hypertensive conditions[10,11].

The *2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice* recommend investigating stress at work and in family life as key for the assessment of psychological risk factors in clinical practice. Addressing psychological risk factors can help improving quality of life and prognosis in patients with cardiovascular diseases. Categorized as class I of recommendation and level of evidence A, multimodal interventions, including stress management and counseling on psychological risk factors, are recommended for individuals at very high cardiovascular risk[12]. Similarly, the *Brazilian Heart Society First Guideline for Cardiovascular Prevention* assgins a class I of recommendation and level of evidence A rating to addressing psychological factors for primary prevention and stress management in individuals at high risk of cardiovascular disease[7].

Though some guidelines recommend stress management, the *American Heart Association/American College of Cardiology (AHA/ACC) 2013 Guideline on the Assessment of Cardiovascular Risk* and the *2014 Update* does not clearly recommend stress management interventions, which may in part suggest that evidence available on this topic is not robust enough to fully support clinical recommendations and further investigations are needed[13,14]. Thus, this systematic review and meta-analysis of randomized clinical trials (RCTs) aim to put together evidence available concerning the effect of stress management interventions on the incidence of MACE in patients with CAD.

METHODS AND ANALYSIS

Our study will follow the guideline of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[15].

STUDY DESIGN

Protocol of systematic review and meta-analysis of RCTs.

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RESEARCH DATA AVAILABILITY

The dataset generated in this meta-analysis will be available in an open-access research data repository, the Mendeley Data Repository (data.mendeley.com/).

SELECTION CRITERIA

This systematic review will include RCTs evaluating the effect of nonpharmacological psychological interventions for stress management on the incidence of MACE in patients with CAD.

The primary outcome will be a combination of MACE endpoints, including cardiovascular death, nonfatal MI, revascularization procedures (coronary artery bypass graft surgery [CABG] or percutaneous coronary intervention [PCI]), nonfatal stroke and cardiovascular hospitalization. The secondary outcomes will be total deaths and a separate analysis for each event in the combination of MACE endpoints.

We will use the PICOS framework to develop the study design and research question for our review, as follows: ***P****opulation* – adult patients (aged 18 years or more) with CAD; ***I****ntervention* – nonpharmacological psychological intervention for stress management defined like psychological techniques employed to support patients in reducing emotional or physiological responses resulting from stressful events [16] without the use of associated drug therapy to stress management; ***C****omparison* – no intervention for stress management (standard clinical care only and/or other psychological intervention that was not specific to stress management); ***O****utcome* – MACE (cardiovascular death; nonfatal MI; revascularization procedures including CABG or PCI; nonfatal stroke; and cardiovascular hospitalization) and total deaths; ***S***tudy – RCTs.

The inclusion criteria will include RCTs; adult patients (aged 18 years or more); CAD; use of nonpharmacological psychological techniques for stress management; studies with information on stress management and other techniques; and studies using a control group.

The exclusion criteria will include studies evaluating interventions for the treatment of stress-related conditions, i.e., in patients with clinically established stress-related psychological disorders, including post-traumatic stress disorder, obsessive compulsive disorder (OCD), borderline disorder and substance abuse; studies involving interventions using plant chemicals (floral teas and others, aromatherapy, and herbal medicines) or drug therapy for stress management; and studies involving patients with congenital heart disease (Figure 1).

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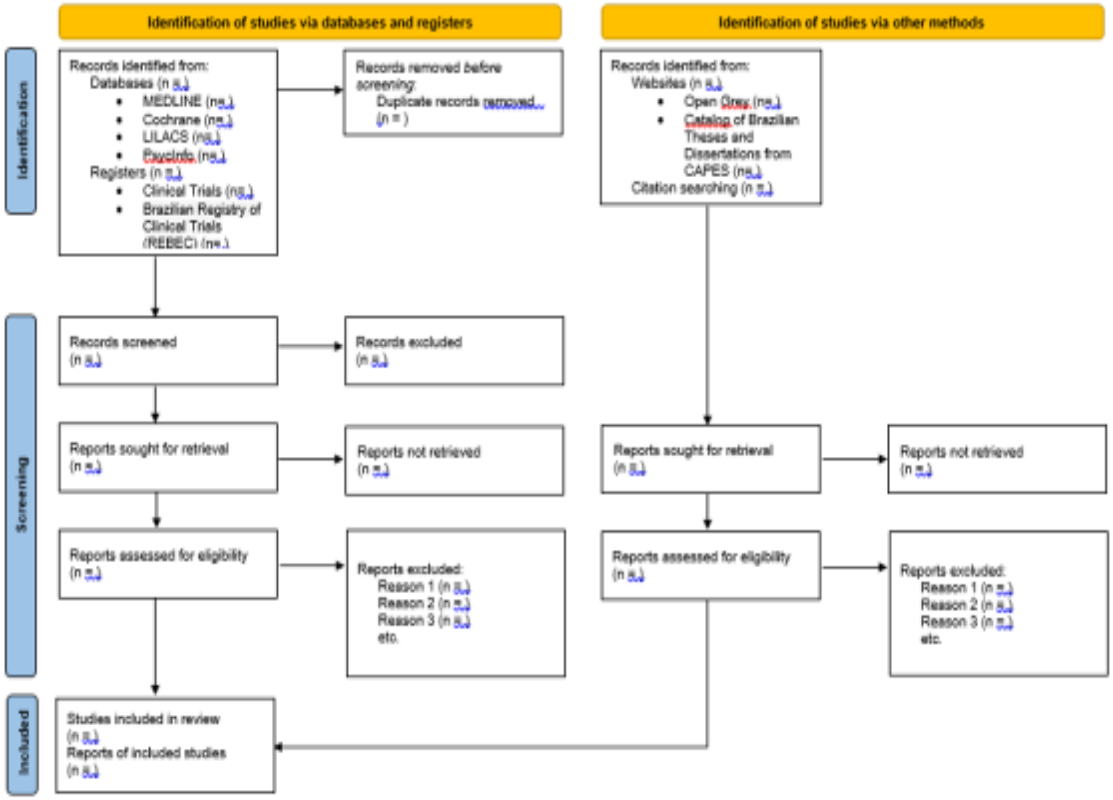
Figure 1: *Search Strategy Flowchart*



SEARCH STRATEGY AND STUDY SELECTION

We will conduct searches in the following electronic databases: Medline (via PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), Latin American and Caribbean Health Sciences Literature (LILACS) and PsycINFO. We will manually check reference lists from published studies. Duplicate studies will be excluded in the first stage of study selection. There will no restrictions to language and status of publication. Search words will be defined based on health sciences descriptors (DeCS), and medical subject headings (MeSH) terms and related keywords as well as common expressions found in the literature (Table 1). To complement our search and to minimize any publication bias, we will also conduct searches on online gray literature, including OpenGrey and the Brazilian Coordination for the Improvement of Higher Education Personnel (CAPES) Bank of Theses and Dissertations. For unpublished clinical trials, our searches will be undertaken in the Brazilian Clinical Trials Registry – ReBEC, ClinicalTrial. Two reviewers (KESS and AMS) will independently screen the articles retrieved based on their titles and abstracts. When there will be not sufficient information available in the abstract to apply the study inclusion

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and exclusion criteria, they will conduct full-text evaluations. In the second stage, both reviewers will independently review full-text articles and make their selection after applying the eligibility criteria. Disagreements between reviewers will be resolved by consensus or by decision of a third independent reviewer (MMS).

Table 1. Search strategy via databases and registries

Medline database (via PubMed) ((((((((((((((((((((((((Psychological Distress[MeSH Terms]) OR (Stress, Psychological[MeSH Terms])) OR (stress management[Text Word])) AND (Psychological Techniques[MeSH Terms])) OR (Orientation[MeSH Terms])) OR (Handling, Psychological[MeSH Terms])) OR (Practice, Psychological[MeSH Terms])) OR (Cognitive Behavioral Therapy[MeSH Terms])) OR (behavior therapy[MeSH Terms])) OR (Cognitive Remediation[MeSH Terms])) OR (Emotion-Focused Therapy[MeSH Terms])) OR (Psychotherapy, Brief[MeSH Terms])) OR (Psychotherapy, Group[MeSH Terms])) OR (Relaxation Therapy[MeSH Terms])) OR (Mind-Body Therapies[MeSH Terms])) OR (relaxation[MeSH Terms])) OR (Meditation[MeSH Terms])) OR (Imagery, Psychotherapy[MeSH Terms])) OR (Biofeedback, Psychology[MeSH Terms])) OR (Mindfulness[MeSH Terms])) AND (Cardiovascular Diseases[MeSH Terms])) OR (cardiovascular events[Text Word])) *Filters applied: Clinical Trial, Interview, Randomized Controlled Trial, Humans, Adult: 19+ years.*
Cochrane Central Register of Controlled Trials Database (CENTRAL) Title abstract keyword: Psychological Distress OR Stress, Psychological OR stress management AND Title abstract keyword: Psychological Techniques OR Orientation OR Handling, Psychological OR Practice, Psychological OR Cognitive Behavioral Therapy OR behavior therapy OR Cognitive Remediation OR Emotion-Focused Therapy OR Psychotherapy, Brief OR Psychotherapy, Group OR Relaxation Therapy OR Mind-Body Therapies OR relaxation OR Meditation OR Imagery, Psychotherapy OR Biofeedback, Psychology OR Mindfulness AND Title abstract keyword: Cardiovascular Diseases OR cardiovascular events in Trials (Word variations have been searched)
LILACS database **Portuguese:** Angústia Psicológica OR Estresse Psicológico OR manejo do estresse [Palavras] and Técnicas Psicológicas OR Orientação OR Manobra Psicológica OR Prática Psicológica OR terapia cognitivo-comportamental OR Remediação Cognitiva OR Terapia Focada em Emoções OR Psicoterapia Breve OR Psicoterapia de Grupo OR Terapia de Relaxamento OR Terapias Mente-Corpo OR Relaxamento OR Meditação OR Imagens, Psicoterapia OR Biorretroalimentação Psicológica OR Atenção Plena [Palavras] and Doenças Cardiovasculares OR eventos cardiovasculares [Palavras] **English:** Psychological Distress OR Stress, Psychological OR stress management [Words] and Psychological Techniques OR Orientation OR Handling, Psychological OR Practice, Psychological OR Cognitive Behavioral Therapy OR behavior therapy OR Cognitive Remediation OR Emotion-Focused Therapy OR Psychotherapy, Brief OR Psychotherapy, Group OR Relaxation Therapy OR Mind-Body Therapies OR relaxation OR Meditation OR Imagery, Psychotherapy OR Biofeedback, Psychology OR Mindfulness [Words] and Cardiovascular Diseases OR cardiovascular events [Words] **Spanish:** Distrés Psicológico OR Estrés Psicológico OR manejo del estrés [Palabras] and Técnicas Psicológicas OR Orientación OR Manobra Psicológica OR Práctica Psicológica OR Terapia Cognitivo-Conductual OR Remediación Cognitiva OR Terapia Centrada en la Emoción OR Psicoterapia Breve OR Psicoterapia de Grupo OR Terapia por Relajación OR Terapias Mente-Cuerpo OR Relajación OR Meditación OR Imágenes en Psicoterapia OR Biorretroalimentación Psicológica OR Atención Plena [Palabras] and Enfermedades Cardiovasculares OR eventos cardiovasculares [Palabras]

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PsycInfo database (PsycArticles) Accessed at: psycnet.apa.org/search/advanced **MeSH**: Psychological Distress *OR* **MeSH**: Stress, Psychological *OR* **Abstract**: stress management *AND* **MeSH**: Psychological Techniques *OR* **MeSH**: Orientation *OR* **MeSH**: Handling, Psychological *OR* **MeSH**: Practice, Psychological *OR* **MeSH**: Cognitive Behavioral Therapy *OR* **MeSH**: behavior therapy *OR* **MeSH**: Cognitive Remediation *OR* **MeSH**: Emotion-Focused Therapy *OR* **MeSH**: Psychotherapy, Brief *OR* **MeSH**: Psychotherapy, Group *OR* **MeSH**: Relaxation Therapy *OR* **MeSH**: Mind-Body Therapies *OR* **MeSH**: relaxation *OR* **MeSH**: Meditation *OR* **MeSH**: Imagery, Psychotherapy *OR* **MeSH**: Biofeedback, Psychology *OR* **MeSH**: Mindfulness *AND* **MeSH**: Cardiovascular Diseases *OR* **Abstract**: cardiovascular events *OR* **MeSH**: Coronary disease *OR* **MeSH**: Heart diseases *AND* **Age Group**: Adulthood (18 yrs & older) *AND* **Methodology**: Treatment Outcome *AND* **Population Group**: Human *Pesquisar bancos de dados:* APA PsycInfo, APA PsycArticles, APA PsycBooks, APA PsycExtra
Clinical Trials CONDITION OR DISEASE: Psychological Distress OR Stress, Psychological AND Cardiovascular Diseases OR cardiovascular events Filters: **Status** Recruitment: • Suspended • Terminated • Completed • Withdrawn Expanded Access: • Available • Approved for marketing **Eligibility Criteria** Age: • Adult (18–64) • Older Adult (65+) Sex: • All **Study Type** • Interventional (Clinical Trial) **Study Results** • With Results
ReBEC registry **Search text:** Psychological Distress OR Stress, Psychological AND Cardiovascular Diseases OR cardiovascular events

DATA EXTRACTION

Event rate data will be extracted for dichotomous outcomes of total deaths, cardiovascular death, and cardiovascular morbidity (nonfatal acute MI; revascularization procedures [CABG and PCI]; nonfatal stroke; and cardiovascular hospitalization). Two blinded reviewers (KESS and AMS) will independently extract data using a pre-structured form in Microsoft Excel including participants' characteristics, description of interventions and primary outcome of cardiovascular events. Disagreements will be resolved by consensus, or in consultations with a third independent reviewer (MMS). Authors will be contacted by email for clarifications or to obtain missing information if needed. In case of no

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response, the option of missing data imputation will be discussed[17]. For the extraction of data from RCTs with the outcomes of interest presented in graphs, we will use GetDate Graph Digitizer 2.26 to extract the data of interest.

RISK OF BIAS ASSESSMENT OF INCLUDED STUDIES

Each study will be rated based on previously established methodological criteria in order to identify selection bias, misclassification bias and confounding bias using the Cochrane Risk of Bias 2 (RoB 2) tool[18]. The assessment is based on a set of six domains of bias: 1) randomization sequence generation; 2) allocation sequence concealment; 3) blinding of participants and personnel; 4) blinding of outcome evaluators; 5) incomplete outcome data; and 6) selective outcome reporting. The studies will be rated as low risk of bias (in all domains for this outcome); some concerns of bias (in at least one domain for this outcome, but not at high risk of bias in any domain); or high risk of bias (in at least one domain for this outcome, or the study is judged to be at some concerns for several domains in a way that significantly reduces confidence in the outcome). No study will be excluded based on the risk of bias assessment. The risk of bias will be assessed for the primary and secondary outcomes of interest in our review.

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

It was not possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

DATA ANALYSIS

Data on cardiovascular events will be described as dichotomous and presented as risk ratio (RR) and related 95% confidence interval (95% CIs). If the studies do not have sufficient similarities to warrant a fixed-effects model, RRs will be pooled using a random-effects model and the Mantel-Haenszel method. Since the 95% CI from random effect refers to uncertainty in the location of the mean of different effects in the studies, we will include the calculated values for a 95% prediction interval (PI) as they reflect the interval uncertainty of effects to be expected in future clinical trials[19]. We will use the DerSimonian-Laird method to estimate the heterogeneity of results. The degree of heterogeneity will be tested using the Higgins inconsistency test (I^2) (0% to 40%, might not be important; 30% to 60%, may represent moderate heterogeneity; 50% to 90%, may represent substantial

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heterogeneity; 75% to 100%, considerable heterogeneity)[18,20]. To explore the heterogeneity ($p < 0.05$), we will conduct subgroup analyses and meta-regression (≥10 studies) for effect modifiers with normal distribution in a quartile-quartile plot (qq-plot) and confirm it with Shapiro-Wilk test ($p > 0.05$). To remove discrepant data from the meta-analysis, forest plots will be constructed to visually identify the effect estimate and no CI overlapping that is due to heterogeneity[21]. If there is significant heterogeneity between the studies that cannot be explained, we will not perform a meta-analysis and results will be presented individually instead. We will carry out the Egger's test or Begg's test using a funnel plot to assess potential publication bias if applicable (≥10 studies; one or more studies with significant statistical data; and studies with different sample sizes). If publication bias is detected ($p < 0.1$), the trim-and-fill method will be used to identify and correct the funnel plot asymmetry by adding information about the bias-corrected data to the original data. Data will be analyzed with RStudio (version 1.3.959) using the "meta" package for Windows (version 3.6.1). After the review is complete, we will perform additional searches for inclusion of more recent studies. Update analyses will be carried out before submission. Table 3 shows the script to conduct the meta-analysis using the RStudio program.

DISCUSSION AND CONCLUSION

Psychological stress causes several physiological changes in the human body. The hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathetic-adrenomedullary axis are the main pathways activated during stress response[22-24]. Stressful situations are characterized by elevated levels of adrenaline and noradrenaline, increased heart rate, increased peripheral vasoconstriction, vasovagal (parasympathetic) withdrawal and increased energy mobilization. Components of the stress response that can plausibly contribute to CAD include increased blood pressure, reduced insulin sensitivity and endothelial dysfunction[22,24].

For those patients with preexisting CAD, acute cardiovascular events following emotional stress may arise from increased shear stress in a weak atherosclerotic plaque (with subsequent plaque rupture) or from regional myocardial ischemia distal to a stenotic vessel leading to ventricular dysrhythmias[22,25].

Considering that psychological stress is associated with harmful cardiovascular effects, particularly in individuals at high risk, such as those with established CAD, stress management interventions have been proposed to educate patients on avoiding stressful

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situations and improving their coping skills to mitigate the physiological response to these stressors[26]. RCTs have sought to assess whether behavioral interventions could effectively reduce the risk of a cardiovascular event in response to psychological factors[27-29]. However, since a large sample of patients is required to assess challenging clinical outcomes in RCTs, cardiovascular events have been mainly reported as secondary outcomes, and most studies are not originally designed to assess these outcomes. We propose a systematic review that will allow us to summarize this body of evidence and assess the actual impact of nonpharmacological psychological interventions for stress management on the incidence of MACE in patients with CAD.

ETHICS AND DISSEMINATION

The protocol of this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (www.crd.york.ac.uk/PROSPERO/, CRD42021275198, registered on August 24, 2021). The databases that will be analyzed will be inserted and can be freely consulted on Mendeley Data (https://data.mendeley.com/).

AUTHORS' CONTRIBUTIONS

KESS, ASQ and MMS were involved in conception and design of the study. KESS and GW were involved in data analysis plans. KESS and AMS will be involved in data collection and extraction. GW will be responsible for data analysis. GW, ASQ and MMS were involved in critical review of the article. KESS and MMS was involved in writing, drafting and editing the final document for publication. All authors read and approved the final manuscript.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

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