EFFICACY OF PSYCHOLOGICAL INTERVENTIONS ON PSYCHOLOGICAL OUTCOMES IN CORONARY ARTERY DISEASE: SYSTEMATIC REVIEW AND META-ANALYSIS

Brief title: Meta-analysis of psychological interventions in CAD

Inés Magán, PhD[a]; Laura Casado, MS[a]; Rosa Jurado-Barba, PhD[a, b]; Haley Barnum, PharmD[c]; Marta M. Redondo, PhD[a]; Adrian V. Hernandez, MD, PhD[c, d]; Héctor Bueno, MD, PhD[b, e, f]

[a]Department of Psychology, Facultad de Educación y Salud, Universidad Camilo José Cela, Madrid, Spain; [b]Instituto de Investigación Biomédica del Hospital 12 de Octubre (Imas12), Madrid, Spain, [c]Health Outcomes, Policy, and Evidence Synthesis (HOPES) Group, University of Connecticut School of Pharmacy, Storrs, CT, USA; [d]Vicerrectorado de Investigacion, Universidad San Ignacio de Loyola (USIL), Lima, Peru; [e]Department of Cardiology, Hospital Universitario 12 de Octubre, Madrid, Spain; [f]Multidisciplinary Translational Cardiovascular Research Group, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain.

Corresponding author: Inés Magán. Universidad Camilo José Cela. Education and Health Faculty. Department of Psychology. C/ Castillo de Alarcón, 49. Urb. Villafranca del Castillo. 28962 – Madrid (Spain). Phone: +34 918153131. E-mail: imagan@ucjc.edu

Total word count (Intro to Discussion): 4708

ABSTRACT

Background: The benefits of cognitive-behavioral treatment (CBT) and positive psychology therapy (PPT) in patients with cardiovascular disease are still not well defined. We assessed the efficacy of CBT and PPT on psychological outcomes in coronary artery disease (CAD) patients.
Methods: Randomized controlled trials evaluating CBT or PPT in CAD patients published until May 2018 were systematically analyzed. Primary outcomes were depression, stress, anxiety, anger, happiness and vital satisfaction. Random effects meta-analyses using the inverse variance method were performed. Effects were expressed as standardized mean difference (SMD) or mean differences (MD) with their 95% confidence intervals (CIs); risk of bias was assessed with the Cochrane tool.
Results: Nineteen trials were included (n=1956); sixteen evaluated CBT (n=1732), and three PPT (n=224). Compared with control groups, depressive symptoms (13 trials; SMD -0.80; 95%CI, -1.33, -0.26) and anxiety (11 trials; SMD -1.26; 95%CI, -2.11, -0.41) improved after the PI, and depression (6 trials; SMD -2.08; 95%CI, -3.22, -0.94), anxiety (5 trials; SMD -1.33; 95%CI, -2.38, -0.29), and stress (3 trials; SMD -3.72; 95%CI, -5.91, -1.52) improved at the end of follow-up. Vital satisfaction was significantly increased at follow-up (MD 1.30, 0.27, 2.33). Non-significant effects on secondary outcomes were found. Subgroup analyses were consistent with overall analyses.
Conclusion: CBT and PPT improve several psychological outcomes in CAD patients. Depression and anxiety improved immediately after the intervention while stress and vital satisfaction improve in the mid-term. Future research should assess the individual role of CBT and PPT in CAD populations.

Keywords: Psychological intervention, cognitive-behavioral treatment, positive psychology therapy, coronary artery disease, psychological outcomes, meta-analysis.

Abbreviations list: PIs = psychological interventions; CBT = cognitive-behavioral treatment; PPT = positive psychology therapy; CAD = coronary artery disease; IHD = ischemic heart disease; RCTs = randomized controlled trials; SMD = standardized mean difference; MD = mean differences; 95%CI = 95% Confidence Interval; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Introduction

The optimal care for patients with acute or chronic coronary artery disease (CAD) needs a multi-disciplinary approach to reduce morbidity and mortality, improve symptoms and quality of life. There is reasonable evidence for the beneficial effect of a variety of interventions, including medical therapies, coronary revascularization, cardiac rehabilitation programs or lifestyle changes, such as quit smoking, healthy diet and physical activity (Fihn et al., 2014; Knuuti et al., 2020).

A comprehensive approach to improving the care for these patients should consider the psychological impact of the disease, including behavioral and several psychological factors, such as depression, anxiety, stress or anger, which have been empirically linked to increases in cardiovascular risk (Chida & Steptoe, 2009; Nicholson, Kuper, & Hemingway, 2006; Roest, Martens, de Jonge, & Denollet, 2010; Rozanski, 2014) and lower quality of life (Appels et al., 2006). Several psychological interventions (PIs) have been tested in this context and positive results have been described in narrative reviews (Linden, 2000, 2013) and meta-analyses (Linden *et al.* 2007; Dickens *et al.* 2013; Rutledge *et al.* 2013; Richards *et al.* 2018).

However, the routine use of PIs in cardiac rehabilitation programs remains controversial because, while these are recommended (Knuuti et al., 2020) and implemented in high income countries (Abreu et al., 2019; Supervia et al., 2019), this is not the case everywhere (Moghei, Oh, Chessex, & Grace, 2019; Poffley et al., 2017). Controversies, such as which specific treatment components should be included, the type and duration of interventions, professional involved, duration of follow-up, and specific endpoints, may contribute to the limited inclusion of PIs in cardiac rehabilitation programs (Linden, 2013), and may explain in part why PIs have shown beneficial effects in CAD patients but with modest effects (Dickens et al., 2013; Linden, 2000,

2013; Linden et al., 2007; Richards et al., 2018; Rutledge et al., 2013). This may also be due to the use of different definitions or types of PIs. Although cognitive-behavioral treatment (CBT)-based PIs have been suggested as the most effective for CAD patients (Linden, 2013), with two exceptions (Dickens et al., 2013; Linden et al., 2007), a number of meta-analyses included broader categories of PIs, such as those based on not well-established paradigms, mixed PIs, and psychopharmacological treatments (Richards et al., 2018; Rutledge et al., 2013). Finally, only negative psychological outcomes were assessed (Dickens et al., 2013; Linden, 2000, 2013; Linden et al., 2007; Richards et al., 2018; Rutledge et al., 2013).

Cardiovascular positive health (Labarthe et al., 2016), a new concept based on the positive psychology paradigm (Seligman, Steen, Park, & Peterson, 2005) has emerged recently. It focuses on positive psychological factors, mainly dispositional optimism, happiness, positive emotions, sense of purpose or vital satisfaction, as potentially having a role in reducing cardiovascular risk (Boehm & Kubzansky, 2012; DuBois et al., 2015; Labarthe et al., 2016). Positive effects have been reported for some PIs based on the positive psychology therapy paradigm (PPT) in cardiac rehabilitation patients (Bolier et al., 2013; Huffman et al., 2016) but only in small trials, not considered in prior meta-analyses (Dickens et al., 2013; Linden, 2000, 2013; Linden et al., 2007; Richards et al., 2018; Rutledge et al., 2013).

The aim of this systematic review and meta-analysis was to evaluate the evidence supporting the efficacy of PIs on improving negative psychological outcomes (depression, anxiety, stress, and anger) as well as positive outcomes (happiness and vital satisfaction), specifically in patients with CAD, including only studies testing the efficacy of empirically supported psychological techniques based on CBT and/or PPT.

Methods

This systematic review was conducted in accordance to the Cochrane Handbook for systematic reviews of interventions (Higgins & Green, 2011) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (Moher, Liberati, Tetzlaff, & Altman, 2009).

Study search and selection criteria

We searched PubMed, PsycInfo, Scopus, The Web of Science, and Cochrane Library for randomized controlled trials (RCTs) evaluating PIs in patients with coronary artery disease (CAD) or ischemic heart disease (IHD). The keywords used were *coronary artery disease*, *ischemic heart disease*, *acute coronary syndrome, psychological treatment, psychological intervention, cognitive-behavioral therapy and positive psychology intervention*. The search strategy for all databases is available in the Supplementary material. No language limitations were imposed. In addition, we also searched reference lists of papers. The searches were done twice: First on May 2017 and an update in May 2018. We excluded case reports, editorials, meta-analyses, narrative reviews and proceeding studies. Studies were eligible for inclusion if they met the following criteria: RCTs in humans including patients with CAD or IHD; the PIs and psychological techniques used in these therapies were based on CBT or PPT; and at least one of the psychological endpoints considered in this meta-analysis was reported. Exclusion criteria were: studies in which patient assignation to treatment conditions were not randomized or where there was not control group; PIs based on any treatment approach different to CBT or PPT; studies not describing the specific techniques used in their PIs; and when the treatment strategy only included physical exercise and educational or counselling programs. Selected studies were

saved and screened using Mendeley (Reference Management Software & Researcher Network). Titles and abstracts of the citations identified from the searches were examined by three reviewers independently (IM, RJ and LC) and disagreements were resolved by discussion.

Types of interventions

Two different types of PIs were considered: CBT and PPT paradigm. Both were PIs done in cardiac rehabilitation programs delivered by health professionals, including only adults diagnosed with CAD or IHD. We defined CBT as empirically supported PI based on the idea that learning principles and cognitions play a key role in human behavior and affective experience (Blagys & Hilsenroth, 2002), with an aim to reduce psychological distress and promoting an adaptive behavior in daily living by developing skills to manage physiological arousal and negative emotions, modifying dysfunctional beliefs and/or coping; CBT involves techniques such as relaxation training, emotion regulation, cognitive restructuring, problem-solving therapy, and/or relapse prevention (Blagys & Hilsenroth, 2002). PPT were defined as PIs focused on intervening on positive psychological dimensions and traits, such as positive emotions, vital satisfaction, dispositional optimism, happiness, or purposes of life and their link to well-being, and therefore aimed at developing individual strengths and not just correcting weaknesses through specific empirically supported positive techniques, such as gratitude training, three good things in life, developing you at your best or identifying and using signature strengths among others (Lee Duckworth, Steen, & Seligman, 2005; Seligman et al., 2005). PIs based on other psychological paradigms (e.g. psychodynamic, social learning theory, etc.) were excluded. Control groups were defined as those receiving usual cardiac rehabilitation, which could only include specific educational and/or physical activity training programs and medical treatment.

Psychological outcomes

Primary outcomes were depression, anxiety, stress, anger, vital satisfaction and happiness. Secondary outcomes included negative affect, positive affect, hostility, daily activities, quality of life, and dispositional hope. These psychological outcomes were assessed by psychological self-report questionnaires designed specifically to quantify these psychological factors with adequate psychometric criteria. Outcomes were measured at the end of intervention (post-treatment) and/or at the end of the pre-specified follow-up time when this was longer than the intervention.

Data extraction

Three reviewers carried out data extraction independently and recorded on a Microsoft Excel® spreadsheet. Extracted data included year of publication, reference, patient population, study design, total patients, number of groups, type, techniques and description of PIs, intervention duration, timing of intervention after coronary event, follow-up time, and primary and secondary outcomes (as reported by authors) per intervention arm. After data extraction, two investigators (AVH and HBa) checked for the accuracy of extractions.

Risk of bias assessment

We used the Cochrane Collaboration's risk of bias assessment tool (Higgins & Green, 2011). The risk of bias was evaluated with the following items: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. Four reviewers (IM, RJ, LC, HBa) evaluated risk of bias independently and labeled each study of having low, high, or unclear

risk of bias. Trials with high risk of bias in any of the items of randomization or blinding were rated as having high risk of bias. Any disagreement was resolved by a senior investigator (AVH).

Statistical analysis

For studies reporting medians (m) and interquartile ranges (IQR), means were estimated by x=(a+2m+b)/4, where m is median and a and b are P25 and P75, respectively (Higgins & Green, 2011). SDs were estimated using SD=IQR/1.35. When median and ranges were provided, the mean was estimated by x=(a+2m+b)/4 using the values of the median (m), the smallest and largest value (a and b, respectively); SD was estimated by SD=range/4 if sample size was <70 and SD=range/6 if sample size was >70 (Higgins & Green, 2011).

In our analyses, both CBT and PPT were combined as one PI arm. We used random effects meta-analyses and the inverse variance method. The DerSimonian and Laird method was used to calculate the tau estimator of heterogeneity. Effects of PIs vs controls on primary and secondary psychological outcomes were expressed as mean difference (MD) or standardized mean difference (SMD) and its 95% confidence interval (95%CI). SMDs were used as we anticipated different scales to measure primary and secondary outcomes across studies. To interpret SMD we used the guidelines of Cohen (Cohen, 1988): 0.2 was a small, 0.5 moderate, and 0.8 large difference. The analyses of outcomes were adjusted for baseline characteristics.

The degree of statistical heterogeneity was quantified with the inconsistency (I^2) metric (Higgins, Thompson, Deeks, & Altman, 2003). A low, moderate and high degree of heterogeneity was defined as I^2 proportion of <30%, 30-60%, and >60%, respectively. We performed a number of pre-specified subgroup analyses per outcome: type of PI (CBT vs PPT), type intervention provider (psychologist vs unknown), post-treatment assessment (<10-12 weeks vs >10-12 weeks) and follow-up assessment time (< 6 months vs > 6 months), session type

(group vs individual), type of CAD patient (acute coronary syndrome –ACS– vs any CAD, i.e. both acute and chronic CAD), and risk of bias (high vs low/unclear). Small study effects were evaluated with the funnel plot, and tested with the Egger's test of funnel plot asymmetry (Higgins & Green, 2011). Statistical analyses were conducted using Review Manager (RevMan 5.3; Cochrane Collaboration).

Results

Selection of studies

We identified 2556 publications. After removing duplicates and screening titles and abstracts, 395 articles were selected for full text evaluation (**Figure 1**). Forty-four trials potentially had relevant information, and finally 19 trials (n=1956) were found to have outcomes of interest. These 19 trials were reported in 20 studies (**Table 1**) (Bishop et al., 2005; Blumenthal et al., 2005; Dao et al., 2011; del Pino et al., 2005; Fernandes et al., 2017; Freedland et al., 2009; Karlsson et al., 2007; Lv et al., 2016; Merswolken et al., 2011; Michalsen et al., 2005; Mohammadi et al., 2018; Murphy et al., 2013; Nikrahan et al., 2016; Nyklíček et al., 2014; O'Neil et al., 2015, 2014; Rakowska, 2015; Sanjuan et al., 2016; Sebregts et al., 2005; Trzcieniecka-Green & Steptoe, 1996). The results of one trial were reported separately in two publications (O'Neil et al., 2015, 2014).

Characteristics of included studies

Table 1 summarizes the main characteristics of included studies. Studies were published between 1996 and 2018. Mean patient's age was generally older than 50 years old. Most of studies had small populations, <100 patients per arm in most cases. Trials included patients after

an ACS event or were chronic CAD patients or had a combination of acute and chronic CAD patients. No studies included only chronic CAD patients. CBT interventions were heterogeneous across trials, mostly multicomponent and in person with the only exception of the trials by O´Neil et al. (2014, 2015) where the PIs were performed by telephone. Three trials evaluated PPTs (Mohammadi et al., 2018; Nikrahan et al., 2016; Sanjuan et al., 2016) and there was also heterogeneity of this type of intervention among studies. Interventions lasted between one week (Fernandes et al., 2017) and 12 months (Karlsson et al., 2007). Depression, anxiety and stress were the outcomes more frequently reported, both after the intervention and at the end of follow-up. The time intervals defining post-treatment (at the end of the intervention) and end of follow-up showed high variability across RCTs, with post-treatment time ranging from 2-3 days (Fernandes et al., 2017) to one year (Karlsson et al., 2007; Michalsen et al., 2005), and follow-up assessment ranging from 3-4 weeks (Dao et al., 2011) to 2.5 years (Rakowska, 2015).

Risk of bias assessment

Sixteen trials had high risk of bias due to lack of blinding of patients or personnel, or due to the used of wrong randomization methods (**Online Figure 1**). Only three RCTs (Michalsen et al., 2005; Mohammadi et al., 2018; Trzcieniecka-Green & Steptoe, 1996) had an overall low risk of bias. About 55% of trials had incomplete outcome data, and about 20% had selective reporting of outcomes.

Effect of psychological interventions on primary outcomes

Meta-analyses assessing depression showed that, compared with controls, PIs significantly decrease depressive symptoms not only immediately after the intervention (13 trials, n=1543; SMD -0.80, 95%CI -1.33, -0.26, p=0.003) but also at the end of follow-up (6 trials,

n=719; and SMD -2.08, 95%CI -3.22, -0.94, p=0.0004) (**Figures 2A and 3A**). Similarly, anxiety significantly decreased both immediately after the PIs and at the end of follow-up (11 trials, n=1230; SMD -1.26, 95%CI -2.11, -0.41, p=0.004; and 5 trials, n=445; SMD -1.33, 95%CI -2.38, -0.29, p=0.01) (**Figures 2B and 3B**). However, although PIs did not decrease stress after the intervention (5 trials, n=461; SMD -1.61, 95%CI -4.04, 0.83, p=0.2) (**Figure 2C**), there was a significant reduction in stress levels at the end of follow-up (3 trials, n=256; SMD -3.72, 95%CI -5.91, -1.52, p=0.0009) (**Figure 3C**). No reduction in anger after PIs was found (3 trials, n=743; SMD -0.07, 95%CI -0.29, 0.14, p=0.5) (**Figure 2D**).

In relation to positive outcomes, although increases in vital satisfaction were not significant immediately after the two PIs (n=116; MD 1.23 points, 95%CI -1.80, 4.26, p=0.4), the improvement was significant at the end of follow-up (MD 1.30 points, 95%CI 0.27, 2.33, p=0.01) (**Figures 2E and 3D**). On the contrary, meta-analyses of the same two trials showed no effect on happiness after treatment or follow-up (MD 0.97 points, 95%CI -10.79, 12.73, p=0.9; MD 7.35 points, 95%CI -5.59, 20.29, p=0.3, respectively) (**Figures 2F and 3E**).

Effect of psychological interventions on secondary outcomes

PIs did not reduce negative affect or increased positive affect immediately after the intervention (2 trials, n=169; SMD -0.34, 95%CI -0.71, 0.03, p=0.07; and SMD 0.24, 95%CI -0.13, 0.61, p=0.2, respectively) (**Online Figures 2A and 2B**). In three trials (n=314), PIs significantly decreased hostility after the intervention (SMD -0.32, 95%CI -0.60, -0.03, p=0.03, **Online Figure 2C**), and in four trials (n=374), PIs significantly improved quality of life after the intervention (SMD 0.50, 95%CI 0.07, 0.93, p=0.02, **Online Figure 2D**). PIs did not improve daily activities (**Online Figure 3A**) or quality of life at the end of follow-up (**Online Figure 3B**),

or dispositional hope at any time (**Online Figures 2E and 3C**). For most outcomes, heterogeneity of effects was high.

Subgroup analyses

The effects of PIs on main outcomes were similar across most of pre-specified subgroups. In particular, for depression, anxiety and stress, both after treatment and at the end of follow-up (**Online Figures 4 to 9**). However, the improvement of anxiety after treatment was higher in ACS patients (5 trials, n=549; SMD -3.29, 95%CI -4.96, -1.611; p=0.0001) compared with chronic or mixed CAD patients (7 trials, n=681; SMD -0.29, 95%CI -1.34, 0.76; p=0.59; chi^2=8.85, p=0.003, **Online Figure 6A**), and in trials at high risk of bias (9 trials, n=928; SMD –1,98, 95%CI -2.92, -1.04; p=0.0001) vs. at low or unclear risk of bias (3 trials, n=302; SMD 0.99, 95%CI -1.10, 3.08, p=0.35; chi^2=6.44, p=0.01, **Online Figure 6B**). Subgroups analysis by post-treatment and follow-up assessment time, showed a larger reduction in anxiety at the end of treatment for treatment durations <10 weeks (6 trials, n=404; SMD -4.24, 95%CI -6.24, -2.23; p=0.0001) than those with a duration ≥10 weeks (7 trials, n=826; SMD 0.08, 95%CI -0.77, 0.92; p=0.004; chi^2=15.11, p=0.0001, **Online Figure 6C**). Also, larger reduction in depression were found when follow-ups were developed in the first 6 months after the intervention (4 trials, n=330; SMD -3.76, 95%CI -6.43, -1.10; p=0.006) vs. >6 months (3 trials, n=389; SMD -0.45, 95%CI -1.05, 0.15; p=0.14; chi^2=5.67, p=0.02, **Online Figure 5C**). While CBT significantly reduced depression at post-treatment (13 trials, n=302; SMD -0.94, 95%CI -1.53, -0.35; p=0.02), PPT showed a neutral effect (2 trials, n=148; SMD 0.17, 95%CI -0.17, 0.51; p=0.003; chi^2=10.14, p=0.001, **Online Figure 4C**). The improvement in depression after therapy was higher when PIs were provided by psychologists (11 trials, n=1047; SMD -1.07, 95%CI -1.78, -0.37, p=0.003) in comparison to PIs provided by undisclosed professionals (4 trials, n=496; SMD

-0.01, 95%CI -0.36, 0.33; p=0.94; chi^2=7.07, p=0.008, **Online Figure 4A**). Finally, no differences according to session type (group vs. individual) were found at any moment (**Online Figures 4E, 6D, 8C and 9**).

Discussion

Our study showed that different types of PIs can improve a number of psychological outcomes relevant for the patient´s global health and wellbeing in patients with CAD in the short- and in the mid-term. In particular, depression and anxiety improved immediately after PIs, and depression, anxiety, stress, and vital satisfaction scores significantly improved at the end of follow-up after these interventions.

Despite the relatively low number of patients and the heterogeneity of interventions, our findings show that PIs based on CBT and/or PPT are helpful in improving the patient´s psychological health, that is, improving their health in a broader way. The aims of medical therapy for CAD are improving prognosis, reducing symptoms and improving quality of life (Knuuti et al., 2020). All established interventions —i.e. medical therapy, coronary revascularization, cardiac rehabilitation— have been tested for the improvement of clinical or biological outcomes (mortality, non-fatal clinical outcomes, symptoms, such angina presentation or functional capacity) (Ponikowski et al., 2016). However, although fostering quality of life is a central target in cardiac rehabilitation interventions as it might have a positive effect on perceived wellbeing as well as on promoting treatment adherence, only a few interventions have evaluated their impact on quality of life (Riccioni et al., 2013; Stenvall et al., 2017; Weintraub et al., 2008; Zhang et al., 2018). Therefore, improving psychological outcomes is a key step for a comprehensive management of CAD from the patient´s perspective.

According to our data, PIs seemed to have positive and important effects on improving depression, anxiety and stress not only immediately after the intervention, but also at the end of follow-up. Others meta-analyses (Dickens et al., 2013; Linden, 2000, 2013; Linden et al., 2007; Richards et al., 2018; Rutledge et al., 2013) had previously shown significant effects, although of a smaller magnitude. Indeed, our results are especially relevant because the effects on the three primary psychological outcomes (depression, anxiety and stress) are not only significant but large after the intervention but the benefits increase at the end of follow-up, showing that PIs have long-lasting and robust beneficial effects, which are not explained by the mere course of time, when patients become more functional in their daily living and the cardiac event turns into something of the past. The implications of these results may be clinically relevant since depressive symptoms, anxiety or stress are considered risk factors for recurrent cardiac events or increased mortality risk (Arnold, Smolderen, Buchanan, Li, & Spertus, 2012; Carney & Freedland, 2017; Ossola, Gerra, De Panfilis, Tonna, & Marchesi, 2018; Tully et al., 2015). In addition, cardiac patients with depression or anxiety may be particularly compromised in their recovery (Nicholson et al., 2006; Roest et al., 2010; Rozanski, 2014).

Regarding positive psychological outcomes, this meta-analysis may be supporting the recently defined positive behavioral cardiology paradigm (Labarthe et al., 2016), as happiness and vital satisfaction showed large improvements after de intervention and at the end of follow-up, although only vital satisfaction was statistically significant at the end follow-up. The low statistical power probably explains the lack of significant effects. Nevertheless, these results should encourage psychologists and cardiologists to dedicate more energy and resources to the investigation of the effect of PPTs on psychological and clinical outcomes in CAD patients.

As noted above, compared to other narrative reviews (Linden 2000, 2013) and meta-analyses (Linden et al. 2007; Dickens et al. 2013; Rutledge et al. 2013; Richards et al. 2018), our

results show a larger magnitude of effects of PIs for improving psychological outcomes, which may be explained by the selection of only RCTs in which PIs were clearly based on empirically-based therapies, that is, the CBT paradigm (Linden, 2013), only done by Linden et al. (2007) and Dickens et al. (2013). The inclusion of the positive behavioral cardiology paradigm (Labarthe et al., 2016) as a well-established therapy paradigm specifically designed to improve positive psychological dimensions (Bolier et al. 2013; Lee Duckworth et al. 2005; Huffman et al. 2016; Seligman et al. 2005) is also new. Our meta-analysis, focusing specifically on the efficacy of PIs in improving psychological outcomes, both negative and positive, in CAD patients, clearly differentiates from previous studies focusing on quantifying the benefits of PIs on morbidity and mortality outcomes (Linden et al. 2007; Dickens et al. 2013; Rutledge et al. 2013; Richards et al. 2018), or their differential effects depending on distress reduction (Linden et al. 2007) or depression reduction (Rutledge et al. 2013). Only Richards et al. (2018) and Dickens et al. (2013) analyze their effects on some psychological outcomes. As PIs are specifically targeted to improve psychological outcomes, finding larger effects is no surprise, although this would not explain the differences found with the last Cochrane systematic review (Richards et al. 2018), where smaller but significant benefits on depression, anxiety and stress reduction were reported. This difference may be explained by the inclusion of all kinds of PIs, while our meta-analysis selected only RCTs based on empirically supported PIs.

Although CBT- and PPT-based PIs are specifically designed to improve negative and positive psychological outcomes, respectively, the magnitude effect of PIs might be greater in CAD patients, in whom improving psychological health and wellbeing by reducing stress and negative emotions and fostering positive psychological factors could be an important target as these are linked, respectively, to a higher (Chida & Steptoe, 2009; Nicholson et al., 2006; Roest et al., 2010; Rozanski, 2014) and lower (Boehm & Kubzansky, 2012; DuBois et al., 2015; Labarthe et

al., 2016) CV risk, as well as to a better quality of life (Appels et al., 2006). Therefore, CBT- and PPT-based PIs may have a positive impact on all-cause and CV morbidity and mortality, as changes in negative (Hamer & Malan 2010; Lovallo & Gerin 2003; Rozansky 2014; Schwartz et al. 2003; Steptoe & Kivimäki 2013; Wirtz & von Känel 2017) and positive psychological factors (Labarthe et al. 2016; Rozansky, Bavishi, Kubzansky & Cohen 2019; Steptoe, Wardle & Marmot 2005) may contribute modifying some clinical and CV parameters, according to Linden, 2013. Although the mechanisms by which changes on psychological factors may improve clinical outcomes remains unclear, it is likely that these may have a direct effect by improving CV risk factors and, indirectly, by facilitating enjoying healthier lifestyles, social and psychological functioning (Labarthe et al. 2016; Rozanski 2014; Rozanski et al. 2019; Steptoe & Kivimäki 2013; Steptoe, Wardle & Marmot 2005; Wirtz & von Känel 2017; Lovallo & Gerin 2003; Schwartz et al. 2003; Hamer & Malan 2010), and improving adherence.

Compared with PPT, CBT seems to improve depression after the intervention, which could be explained by the fact that CBT is a treatment package specifically designed to modify negative psychological factors (Blagys & Hilsenroth, 2002), such as depression, whereas PPTs are specifically aimed at improving positive psychological dimensions (Lee Duckworth et al., 2005; Seligman et al., 2005). Therefore, PPT may not be able to improve depression by itself. Unfortunately, the information is scarce and analyses could only be done for depression. Future research is needed to clarify the differential effect of CBT and PPT on CAD patients.

Furthermore, not only its role but the way PIs should be given and by whom are relevant questions. Although weak, our results show some evidence suggesting that PIs developed by well-trained health psychologists may have stronger effects. This seems to be particularly true in the effect on post-treatment depression benefits, a prevalent complication after myocardial

infarction (Pino, Zuo, Borba, Henderson, & Kalesan, 2018; Smolderen et al., 2017, 2015), what is logical as they are professionals specifically trained for it. Unfortunately, and despite its relevance, this information was lacking in a majority of the studies reviewed, which may explain the weakness of the association found. The role of the incorporation of trained health psychologists to cardiovascular care teams to improve both psychological and clinical outcomes for CAD and other high-risk patients needs further attention and prospective and rigorous evaluation.

Acute CAD patients seem to have greater benefits in anxiety reduction after PIs. This is logical as ACS is associated with acute increases in the levels of anxiety and stress after the acute phase (Xu et al., 2017). However, the benefit was observed only immediately after the intervention with no persistence at the end of follow-up. Whether this is due to the described spontaneous time-dependent improvement of these psychological situations after ACS (Xu et al., 2015) or the lack of durability of the effects of PIs needs further study.

Finally, PIs in which the follow-up assessment occurred <6 months after the intervention showed significant benefits in depression compared with those with longer follow-ups. Reductions in anxiety were also larger when the intervention duration was <10 weeks, which is consistent with the findings by Linden et al (2013), where the beneficial effects of PIs fade away with time. This points out the importance of maintenance of the benefits as one important target for PIs.

Our meta-analysis is the first one to analyze the effects of PIs on positive psychology outcomes, including only empirically-supported PIs for CAD patients (Linden et al., 2013), an inclusion criterion only in a minority of prior studies (Linden et al., 2007; Dickens et al., 2013). Our meta-analysis is also new on its exclusive focus on psychological outcomes in CAD patients while the majority of prior publications mainly focused on morbidity and mortality or on the

differential effects on these outcomes depending on distress reduction (Linden et al, 2007) or depression reduction (Rutledge et al., 2013). Only Richards et al. (2018) specifically evaluated the effects of PIs on stress, anxiety and depression, and Dickens et al. (2013) on depression, but they did not study positive psychological outcomes.

A number of limitations should be acknowledged. First, the number of studies and the absolute number of patients enrolled is small. Second, PIs included a large variety of interventions with important differences in types, methods, professionals involved and duration as well as differences in outcomes and methods to measure the results. This information is not only diverse but is often lacking. Therefore, conclusions apply to a heterogeneous group in which differences in results may be explained by a variety of reasons. Third, our study confirms the important risk of bias to which these studies are subjected due to the impossibility of blinding patients or researchers to the intervention. This limitation can only be partially overcome by the analysis of results blinded to the intervention received by each group, a technique that should be mandatory in this kind of studies. And fourth, this meta-analysis does not address the efficacy of PIs on clinical outcomes, which will be the aim of a future analysis.

Conclusion. This systematic review and meta-analysis shows that PIs are effective in improving depression and anxiety immediately after the intervention, and may have a positive impact at the end of follow-up improving also stress and the level of vital satisfaction. However, much more research is needed in the field, with higher methodological standards in the trials, including detailed information of the type of intervention, professionals involved, timing and duration. Our results suggest that there is a role of clinical and health psychology for improving the care of patients with CAD and this option should be considered in cardiology departments.

Financial support: None.

Conflicts of interest: None of the authors have conflicts of interests with public or private entities related to the content of this manuscript. Dr. Bueno receives research funding from the *Instituto de Salud Carlos III, Spain (PIE16/00021 &PI17/01799), Astra-Zeneca, BMS, Janssen and Novartis; has received consulting fees from Astra-Zeneca, Bayer, BMS-Pfizer, Novartis*; and speaking fees or support for attending scientific meetings from *Astra-Zeneca, Bayer, BMS-Pfizer, Novartis, and MEDSCAPE-theheart.org*. Dr. Jurado receives research funding from the *Ministerio de Ciencia, Innovación y Universidades, Spain (PSI2015-68851-P)*. Dr. Magán, Dr. Jurado, Dr. Redondo and Dr. Bueno have received funding from *Universidad Camilo José Cela, Madrid – Spain (2015-18)*. Dr. Hernandez receives funding from the *Agency Health Care Research and Quality (AHRQ) (HHSA290201500012I)*.

Acknowledgement: The CNIC is supported by the Instituto de Salud Carlos III (ISCIII), the Ministerio de Ciencia e Innovación and the Pro CNIC Foundation, and is a Severo Ochoa Center of Excellence (SEV-2015-0505).

References

Abreu, A., Pesah, E., Supervia, M., Turk-Adawi, K., Bjarnason-Wehrens, B., Lopez-Jimenez, F., … Grace, S. L. (2019). Cardiac rehabilitation availability and delivery in Europe: How does it differ by region and compare with other high-income countries? *European Journal of Preventive Cardiology*, *26*(11), 1131–1146. https://doi.org/10.1177/2047487319827453

Appels, A., Van, E. T., Bar, F., van der Pol, G., Erdman, R. A., Assman, M., … Pedersen, S. S. (2006). Effects of a behavioural intervention on quality of life and related variables in angioplasty patients: results of the Exhaustion Intervention Trial. *J Psychosom Res*, *61*(0022-3999 (Print)), 1–7.

Arnold, S. V., Smolderen, K. G., Buchanan, D. M., Li, Y., & Spertus, J. A. (2012). Perceived Stress in Myocardial Infarction. *Journal of the American College of Cardiology*, *60*(18), 1756–1763. https://doi.org/10.1016/j.jacc.2012.06.044

Bishop, G., Kaur, D., Tan, V., Chua, Y., Liew, S., & Mak, K. (2005). Effects of a psychosocial skills training workshop on psychophysiological and psychosocial risk in patients undergoing coronary artery bypass grafting. *American Heart Journal*, *150*(3), 602–609. Retrieved from https://doi.org/10.1016/j.ahj.2004.10.015

Blagys, M. D., & Hilsenroth, M. J. (2002). Distinctive activities of cognitive-behavioral therapy: A review of the comparative psychotherapy process literature. *Clinical Psychology Review*. https://doi.org/10.1016/S0272-7358(01)00117-9

Blumenthal, J. A., Sherwood, A., Babyak, M. A., Watkins, L. L., Waugh, R., Georgiades, A., … Hinderliter, A. (2005). Effects of Exercise and Stress Management Training on Markers of Cardiovascular Risk in Patients With Ischemic Heart Disease. *JAMA*, *293*(13), 1626.

https://doi.org/10.1001/jama.293.13.1626

Boehm, J. K., & Kubzansky, L. D. (2012). The heart's content: The association between positive psychological well-being and cardiovascular health. *Psychological Bulletin*. https://doi.org/10.1037/a0027448

Bolier, L., Haverman, M., Westerhof, G. J., Riper, H., Smit, F., & Bohlmeijer, E. (2013). Positive psychology interventions: a meta-analysis of randomized controlled studies. *BMC Public Health*, *13*(1), 119. https://doi.org/10.1186/1471-2458-13-119

Carney, R. M., & Freedland, K. E. (2017). Depression and coronary heart disease. *Nature Reviews Cardiology*, *14*(3), 145–155. https://doi.org/10.1038/nrcardio.2016.181

Chida, Y., & Steptoe, A. (2009). The Association of Anger and Hostility With Future Coronary Heart Disease. A Meta-Analytic Review of Prospective Evidence. *Journal of the American College of Cardiology*, *53*(11), 936–946. https://doi.org/10.1016/j.jacc.2008.11.044

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates. Lawrence Earlbaum Associates*. https://doi.org/http://dx.doi.org/10.1016/B978-0-12-179060-8.50008-6

Dao, T. K., Youssef, N. A., Armsworth, M., Wear, E., Papathopoulos, K. N., & Gopaldas, R. (2011). Randomized controlled trial of brief cognitive behavioral intervention for depression and anxiety symptoms preoperatively in patients undergoing coronary artery bypass graft surgery. *The Journal of Thoracic and Cardiovascular Surgery*, *142*(3), e109–e115. https://doi.org/10.1016/j.jtcvs.2011.02.046

del Pino, A., Gaos, M. T., Dorta, R., & Garcia, M. (2005). Modification of coronary-prone behaviors in coronary patients of low socio-economic status. *The Spanish Journal of*

Psychology, *8*(1), 68–78. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=15875459

Dickens, C., Cherrington, A., Adeyemi, I., Roughley, K., Bower, P., Garrett, C., … Coventry, P. (2013). Characteristics of psychological interventions that improve depression in people with coronary heart disease: A systematic review and meta-regression. *Psychosomatic Medicine*. https://doi.org/10.1097/PSY.0b013e31827ac009

DuBois, C. M., Lopez, O. V., Beale, E. E., Healy, B. C., Boehm, J. K., & Huffman, J. C. (2015). Relationships between positive psychological constructs and health outcomes in patients with cardiovascular disease: A systematic review. *International Journal of Cardiology*. https://doi.org/10.1016/j.ijcard.2015.05.121

Fernandes, A. C., McIntyre, T., Coelho, R., Prata, J., & Maciel, M. J. (2017). Brief psychological intervention in phase I of cardiac rehabilitation after acute coronary syndrome. *Revista Portuguesa de Cardiologia*, *36*(9), 641–649. https://doi.org/10.1016/j.repc.2017.01.005

Fihn, S. D., Blankenship, J. C., Alexander, K. P., Bittl, J. A., Byrne, J. G., Fletcher, B. J., … Smith, P. K. (2014). 2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease. *Journal of the American College of Cardiology*, *64*(18), 1929–1949. https://doi.org/10.1016/j.jacc.2014.07.017

Freedland, K. E., Skala, J. A., Carney, R. M., Rubin, E. H., Lustman, P. J., Davila-Roman, V. G., … Hogue, C. W. J. R. (2009). Treatment of depression after coronary artery bypass surgery: a randomized controlled trial. *Archives of General Psychiatry*, *66*(4), 387–396.

https://doi.org/10.1001/archgenpsychiatry.2009.7

Higgins, J. P., & Green, S. (2011). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]* (5.0.1). Retrieved from www.cochrane-handbook.org

Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *Bmj*, *327*(7414), 557–60. https://doi.org/10.1136/bmj.327.7414.557.

Huffman, J. C., Millstein, R. A., Mastromauro, C. A., Moore, S. V., Celano, C. M., Bedoya, C. A., … Januzzi, J. L. (2016). A Positive Psychology Intervention for Patients with an Acute Coronary Syndrome: Treatment Development and Proof-of-Concept Trial. *Journal of Happiness Studies*. https://doi.org/10.1007/s10902-015-9681-1

Karlsson, M. R., Edström-Plüss, C., Held, C., Henriksson, P., Billing, E., & Wallén, N. H. (2007). Effects of expanded cardiac rehabilitation on psychosocial status in coronary artery disease with focus on type D characteristics. *Journal of Behavioral Medicine*, *30*(3), 253–261. https://doi.org/10.1007/s10865-007-9096-5

Knuuti, J., Wijns, W., Saraste, A., Capodanno, D., Barbato, E., Funck-Brentano, C., … Clapp, B. (2020). 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *European Heart Journal*, *41*(3), 407–477. https://doi.org/10.1093/eurheartj/ehz425

Labarthe, D. R., Kubzansky, L. D., Boehm, J. K., Lloyd-Jones, D. M., Berry, J. D., & Seligman, M. E. P. (2016). Positive Cardiovascular Health: A Timely Convergence. *Journal of the American College of Cardiology*. https://doi.org/10.1016/j.jacc.2016.03.608

Lee Duckworth, A., Steen, T. A., & Seligman, M. E. P. (2005). Positive Psychology in Clinical

Practice. *Annual Review of Clinical Psychology*, *1*(1), 629–651. https://doi.org/10.1146/annurev.clinpsy.1.102803.144154

Linden, W. (2000). Psychological treatments in cardiac rehabilitation: Review of rationales and outcomes. *Journal of Psychosomatic Research*. https://doi.org/10.1016/S0022-3999(99)00094-X

Linden, W. (2013). How many meta-analyses does it take to settle a question? *Psychosomatic Medicine*, *75*(4), 332–334. https://doi.org/10.1097/PSY.0b013e318295e046

Linden, W., Phillips, M. J., & Leclerc, J. (2007). Psychological treatment of cardiac patients: A meta-analysis. *European Heart Journal*, *28*(24), 2972–2984. https://doi.org/10.1093/eurheartj/ehm504

Lv, J., Zhang, X., Ou, S., Gu, S., Su, Z., Tong, S., & Liu, BSong Z, C. L. (2016). Influence of Cognitive Behavioral Therapy on Mood and Quality of Life After Stent Implantation in Young and Middle-Aged Patients With Coronary Heart Disease. *International Heart Journal Association*, *56*(2), 167–172. https://doi.org/10.1536/ihj.15-259. Epub 2016 Mar 11.

Merswolken, M., Siebenhuener, S., Orth-Gomér, K., Zimmermann-Viehoff, F., & Deter, H. C. (2011). Treating anxiety in patients with coronary heart disease: A randomized controlled trial. *Psychotherapy and Psychosomatics*, *80*(6), 365–370. https://doi.org/10.1159/000329177

Michalsen, A., Grossman, P., Lehmann, N., Knoblauch, N. T., Paul, A., Moebus, S., … Dobos, G. J. (2005). Psychological and quality-of-life outcomes from a comprehensive stress reduction and lifestyle program in patients with coronary artery disease: results of a randomized trial. *Psychother Psychosom*, *74*(6), 344–352.

https://doi.org/10.1159/000087781

Moghei, M., Oh, P., Chessex, C., & Grace, S. L. (2019). Cardiac Rehabilitation Quality Improvement: A NARRATIVE REVIEW. *Journal of Cardiopulmonary Rehabilitation and Prevention*. https://doi.org/10.1097/HCR.0000000000000396

Mohammadi, N., Aghayousefi, A., Nikrahan, G. R., Adams, C. N., Alipour, A., Sadeghi, M., … Huffman, J. C. (2018). A randomized trial of an optimism training intervention in patients with heart disease. *General Hospital Psychiatry*, *51*, 46–53. https://doi.org/10.1016/j.genhosppsych.2017.12.004

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine*, *6*(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097

Murphy, B. M., Worcester, M. U. C., Higgins, R. O., Elliott, P. C., Le Grande, M. R., Mitchell, F., … Goble, A. J. (2013). Reduction in 2-Year Recurrent Risk Score and Improved Behavioral Outcomes After Participation in the "Beating Heart Problems" Self-management Program. *Journal of Cardiopulmonary Rehabilitation and Prevention*, *33*(4), 220–228. https://doi.org/10.1097/HCR.0b013e31828c7812

Nicholson, A., Kuper, H., & Hemingway, H. (2006). Depression as an aetiologic and prognostic factor in coronary heart disease: A meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *European Heart Journal*, *27*(23), 2763–2774. https://doi.org/10.1093/eurheartj/ehl338

Nikrahan, G. R., Suarez, L., Asgari, K., Beach, S. R., Celano, C. M., Kalantari, M., … Huffman, J. C. (2016). Positive Psychology Interventions for Patients With Heart Disease: A

Preliminary Randomized Trial. *Psychosomatics*, *57*(4), 348–358. https://doi.org/10.1016/j.psym.2016.03.003

Nyklíček, I., Dijksman, S. C., Lenders, P. J., Fonteijn, W. A., & Koolen, J. J. (2014). A brief mindfulness based intervention for increase in emotional well-being and quality of life in percutaneous coronary intervention (PCI) patients: The MindfulHeart randomized controlled trial. *Journal of Behavioral Medicine*, *37*(1), 135–144. https://doi.org/10.1007/s10865-012-9475-4

O'Neil, A., Taylor, B., Hare, D. L., Sanderson, K., Cyril, S., Venugopal, K., … Oldenburg, B. (2015). Long-term efficacy of a tele-health intervention for acute coronary syndrome patients with depression: 12-month results of the MoodCare randomized controlled trial. *European Journal of Preventive Cardiology*, *22*(9), 1111–1120. https://doi.org/10.1177/2047487314547655

O'Neil, A., Taylor, B., Sanderson, K., Cyril, S., Chan, B., Hawkes, A. L., … Oldenburg, B. (2014). Efficacy and Feasibility of a Tele-health Intervention for Acute Coronary Syndrome Patients with Depression: Results of the "MoodCare" Randomized Controlled Trial. *Annals of Behavioral Medicine*, *48*(2), 163–174. https://doi.org/10.1007/s12160-014-9592-0

Ossola, P., Gerra, M. L., De Panfilis, C., Tonna, M., & Marchesi, C. (2018). Anxiety, depression, and cardiac outcomes after a first diagnosis of acute coronary syndrome. *Health Psychology*, *37*(12), 1115–1122. https://doi.org/10.1037/hea0000658

Pino, E. C., Zuo, Y., Borba, C. P., Henderson, D. C., & Kalesan, B. (2018). Clinical depression and anxiety among ST-elevation myocardial infarction hospitalizations: Results from Nationwide Inpatient Sample 2004–2013. *Psychiatry Research*, *266*, 291–300.

https://doi.org/10.1016/j.psychres.2018.03.025

Poffley, A., Thomas, E., Grace, S. L., Neubeck, L., Gallagher, R., Niebauer, J., & O'Neil, A. (2017). A systematic review of cardiac rehabilitation registries. *European Journal of Preventive Cardiology*, *24*(15), 1596–1609. https://doi.org/10.1177/2047487317724576

Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G. F., Coats, A. J. S., … van der Meer, P. (2016). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution . *European Journal of Heart Failure*, *18*(8), 891–975. https://doi.org/10.1002/ejhf.592

Rakowska, J. M. (2015). Brief strategic therapy in first myocardial infarction patients with increased levels of stress: a randomized clinical trial. *Anxiety, Stress, & Coping*, *28*(6), 687–705. https://doi.org/10.1080/10615806.2015.1004323

Riccioni, G., Prencipe, G., Benvenuto, A., Masciocco, L., Ventra, S., Rizzo, U., … Speziale, G. (2013). Ivabradine Improves All Aspects of Quality of Life Assessed with the 36-Item Short Form Health Survey in Subjects with Chronic Ischemic Heart Disease Compared with Beta-Blockers. *Pharmacology*, *91*(1–2), 35–38. https://doi.org/10.1159/000343631

Richards, S. H., Anderson, L., Jenkinson, C. E., Whalley, B., Rees, K., Davies, P., … Taylor, R. S. (2018). Psychological interventions for coronary heart disease: Cochrane systematic review and meta-analysis. *European Journal of Preventive Cardiology*, *25*(3), 247–259. https://doi.org/10.1177/2047487317739978

Roest, A. M., Martens, E. J., de Jonge, P., & Denollet, J. (2010). Anxiety and Risk of Incident

Coronary Heart Disease. A Meta-Analysis. *Journal of the American College of Cardiology*. https://doi.org/10.1016/j.jacc.2010.03.034

Rozanski, A. (2014). Behavioral cardiology: Current advances and future directions. *Journal of the American College of Cardiology*. https://doi.org/10.1016/j.jacc.2014.03.047

Rutledge, T., Redwine, L. S., Linke, S. E., & Mills, P. J. (2013). A Meta-Analysis of Mental Health Treatments and Cardiac Rehabilitation for Improving Clinical Outcomes and Depression Among Patients With Coronary Heart Disease. *Psychosomatic Medicine*, *75*(4), 335–349. https://doi.org/10.1097/PSY.0b013e318291d798

Sanjuan, P., Montalbetti, T., Pérez-García, A. M., Bermúdez, J., Arranz, H., & Castro, A. (2016). A Randomised Trial of a Positive Intervention to Promote Well-Being in Cardiac Patients. *Applied Psychology: Health and Well-Being*, *8*(1), 64–84. https://doi.org/10.1111/aphw.12062

Sebregts, E. H., Falger, P. R., Appels, A., Kester, A. D., & Bär, F. W. (2005). Psychological effects of a short behavior modification program in patients with acute myocardial infarction or coronary artery bypass grafting. A randomized controlled trial. *Journal of Psychosomatic Research*. https://doi.org/10.1016/j.jpsychores.2004.02.021

Seligman, M. E. P., Steen, T. A., Park, N., & Peterson, C. (2005). Positive psychology progress: empirical validation of interventions. *The American Psychologist*, *60*(5), 410–421. https://doi.org/10.1037/0003-066X.60.5.410

Smolderen, K. G., Spertus, J. A., Gosch, K., Dreyer, R. P., D'Onofrio, G., Lichtman, J. H., … Krumholz, H. M. (2017). Depression Treatment and Health Status Outcomes in Young Patients With Acute Myocardial Infarction. *Circulation*, *135*(18), 1762–1764.

https://doi.org/10.1161/CIRCULATIONAHA.116.027042

Smolderen, K. G., Strait, K. M., Dreyer, R. P., D'Onofrio, G., Zhou, S., Lichtman, J. H., … Spertus, J. A. (2015). Depressive Symptoms in Younger Women and Men With Acute Myocardial Infarction: Insights From the VIRGO Study. *Journal of the American Heart Association*, *4*(4). https://doi.org/10.1161/JAHA.114.001424

Stenvall, H., Tierala, I., Räsänen, P., Laine, M., Sintonen, H., & Roine, R. P. (2017). Long-term clinical outcomes, health-related quality of life, and costs in different treatment modalities of stable coronary artery disease. *European Heart Journal - Quality of Care and Clinical Outcomes*, *3*(1), 74–82. https://doi.org/10.1093/ehjqcco/qcw024

Supervia, M., Turk-Adawi, K., Lopez-Jimenez, F., Pesah, E., Ding, R., Britto, R. R., … Grace, S. L. (2019). Nature of Cardiac Rehabilitation Around the Globe. *EClinicalMedicine*. https://doi.org/10.1016/j.eclinm.2019.06.006

Trzcieniecka-Green, A., & Steptoe, A. (1996). The effects of stress management on the quality of life of patients following acute myocardial infarction or coronary bypass surgery. *Eur Heart J*, *17*(11), 1663–1670.

Tully, P. J., Winefield, H. R., Baker, R. A., Denollet, J., Pedersen, S. S., Wittert, G. A., & Turnbull, D. A. (2015). Depression, anxiety and major adverse cardiovascular and cerebrovascular events in patients following coronary artery bypass graft surgery: a five year longitudinal cohort study. *BioPsychoSocial Medicine*, *9*(1), 14. https://doi.org/10.1186/s13030-015-0041-5

Turner, A., Hambridge, J., Baker, A., Bowman, J., & McElduff, P. (2013). Randomised controlled trial of group cognitive behaviour therapy versus brief intervention for depression

in cardiac patients. *The Australian and New Zealand Journal of Psychiatry*, *47*(3), 235–243. https://doi.org/10.1177/0004867412460592

Weintraub, W. S., Spertus, J. A., Kolm, P., Maron, D. J., Zhang, Z., Jurkovitz, C., … Boden, W. E. (2008). Effect of PCI on Quality of Life in Patients with Stable Coronary Disease. *New England Journal of Medicine*, *359*(7), 677–687. https://doi.org/10.1056/NEJMoa072771

Xu, X., Bao, H., Strait, K. M., Edmondson, D. E., Davidson, K. W., Beltrame, J. F., … Krumholz, H. M. (2017). Perceived Stress After Acute Myocardial Infarction: A Comparison Between Young and Middle-Aged Women Versus Men. *Psychosomatic Medicine*, *79*(1), 50–58. https://doi.org/10.1097/PSY.0000000000000429

Xu, X., Bao, H., Strait, K., Spertus, J. A., Lichtman, J. H., D'Onofrio, G., … Krumholz, H. M. (2015). Sex differences in perceived stress and early recovery in young and middle-aged patients with acute myocardial infarction. *Circulation*, *131*(7), 614–623. https://doi.org/10.1161/CIRCULATIONAHA.114.012826

Zhang, Z., Jones, P., Weintraub, W. S., Mancini, G. B. J., Sedlis, S., Maron, D. J., … Spertus, J. A. (2018). Predicting the Benefits of Percutaneous Coronary Intervention on 1-Year Angina and Quality of Life in Stable Ischemic Heart Disease. *Circulation: Cardiovascular Quality and Outcomes*, *11*(5). https://doi.org/10.1161/CIRCOUTCOMES.117.003971

FIGURE LEGENDS

Figure 1. Flowchart of study selection

Figure 2. Efficacy of psychological interventions on psychological outcomes immediately after the intervention

Forest-plot showing the efficacy of psychological interventions compared with control groups on predefined psychological outcomes immediately after the intervention:

2A: Effect on depression

2B: Effect on anxiety

2C: Effect on stress

2D: Effect on anger

2E: Effect on vital satisfaction

2F: Effect on happiness

Figure 3: Effect of psychological interventions at the end of follow-up

Forest-plot showing the efficacy of psychological interventions compared with control groups at the end of follow-up on the predefined psychological outcomes:

3A: Effect on depression (average follow-up, 4.5 months)

3B: Effect on anxiety (average follow-up, 5.6 months)

3C: Effect on stress (average follow-up, 13 months)

3D: Effect on vital satisfaction (average follow-up, 3.8 months)

3E: Effect on happiness (average follow-up, 3.8 months)

Table 1. Study and patient characteristics of included randomized controlled trials

Author, year	Number of patients	Patient population. Diagnosis at entry	Age, mean (SD)	Description of interventions	Intervention duration	Outcomes	Evaluation at the end of treatment	Evaluation at the end of follow-up
Trzcieniecka-Green & Steptoe 1996	Experimental group: N= 50, Control group: N=50	ACS (+bypass)	Experimental group: 59.4 (7.7), Control group: 61 (6.7)	CBT Psychologist: Yes Multicomponent Group sessions In person Description: Experimental group: Psychoeducation, Behavioral techniques for life style modification.	10 weeks	Depression Anxiety Daily activities Physical Well-being	12 weeks	6 months
Bishop *et al.* 2005	Experimental group: N= 29, Control group: N=29	Others (CABG). Unspecified if acute or programmed	Only men. Experimental group: 54.7 (1.4), Control group: 53.3 (7.3)	CBT Psychologist: Unknown Multicomponent Group sessions In person Description: Experimental group: Behavioral techniques for life style modification, Cognitive techniques.	6 weeks	Depression Stress Anxiety Anger	6 weeks	3 months
Blumenthal *et al.* 2005	Exercise group: N=44, Stress management: N=44, Control group: N=42	IHD diagnosis (+ event or intervention)	Experimental group: 63 (9), Control group: 62 (10.5)	CBT Psychologist: Unknown Multicomponent Group sessions In person Description: Experimental group: Psychoeducation, Behavioral techniques for life style modification and Cognitive techniques.	Unknown	Depression Anxiety Hostility Physical Well-being	16 weeks	No

Author, year	Number of patients	Patient population. Diagnosis at entry	Age, mean (SD)	Description of interventions	Intervention duration	Outcomes	Evaluation at the end of treatment	Evaluation at the end of follow-up
del Pino *et al.* 2005	Experimental group: N=33, Educational group: N= 33, Control group: N= 32	CHD	Only men Experimental group: 49.65 (8.22), Control group: 58.09 (5.45)	CBT Psychologist: Yes Multicomponent Group sessions In person Description: Experimental group: Psychoeducation, Relaxation techniques, Behavioral techniques for life style modification, Cognitive techniques.	9 months	Depression Anger Type A personality	9 months	12 and 24 months
Michalsen *et al.* 2005	Experimental group: N= 48, Control group: N=53	CAD (in medical treatment, excluded ACS)	Experimental group: 59.8 (7), Control group: 59.8 (8.6)	CBT Psychologist: Unknown Multicomponent Group sessions In person Description: Experimental group: Psychoeducation, Relaxation techniques, Relapse prevention, Mindfulness.	12 months	Depression Stress Anxiety Quality of life Anger	12 months	No
Sebregts *et al.* 2005	Experimental group: N= 94, Control group: N=90	ACS (MI) or CABG. Unspecified if acute or programmed	Experimental group: 55.6 (8), Control group: 55.2 (9.7)	CBT Psychologist: Yes Multicomponent Group sessions In person Description: Experimental group: Psychoeducation, Relaxation techniques, Behavioral techniques for life style modification, Relapse prevention.	8 weeks	Depression Hostility	8 weeks	9 months

Author, year	Number of patients	Patient population. Diagnosis at entry	Age, mean (SD)	Description of interventions	Intervention duration	Outcomes	Evaluation at the end of treatment	Evaluation at the end of follow-up
Karlsson *et al.* 2007	Experimental group: N= 111, Control group: N=113	CAD (included ACS and intervention but not ACS)	Experimental group: 63.8 (7.2), Control group: 63.3 (7.3)	CBT Psychologist: Unknown Unicomponent Group sessions In person Description: Experimental group: Stress management program, 5-day stay at the patient hotel, Behavioral techniques for life style modification.	12 months	Depression Stress Anxiety Anger Quality of life	12 months	No
Freedland *et al.* 2009	Experimental group: CBT: N= 41, SSM: N=42, Control group: N=40	CABG surgery	Experimental group:59 (10), Control group: 61 (9)	CBT Psychologist: Yes Multicomponent Group sessions In person Description: Experimental group: CBT Group: Psychoeducation, Relaxation techniques, Behavioral techniques for life style modification, Relapse prevention	12 weeks	Depression Stress Anxiety	3 months	6 and 9 months
Dao *et al.* 2011	Experimental group: N =50, Control group: N = 50)	CAD (+ CABG and also depression or anxiety diagnosis)	Experimental group: 62.8 (11.8), Control group: 64.2 (11.9)	CBT Psychologist: Yes Multicomponent Group sessions In person Description: Experimental group: Managing Anxiety and Depression using Education and Skills	1-2 weeks	Stress Depression Anxiety Quality of life Hopeless Vitally Mindfulness Positive and negative affect Adherence to	At least five days after surgery	3-4 weeks

Author, year	Number of patients	Patient population. Diagnosis at entry	Age, mean (SD)	Description of interventions	Intervention duration	Outcomes	Evaluation at the end of treatment	Evaluation at the end of follow-up
						psychological treatment		
Merswolken *et al.* 2011	Experimental group: N= 25, Control group: N =27	ACS (+ CHD diagnosis)	Experimental group: 62.5 (8.3), Control group: 59.8 (7.5)	CBT Psychologist: Yes Multicomponent Group sessions In person <u>Description:</u> <u>Experimental group:</u> Psychoeducation, Relaxation, Behavioral techniques for life style modification (stress management), Cognitive restructuring and Social components	6 months	Depression Anxiety	6 months	No
Turner *et al.* 2013	Experimental group: N= 25 and Control group: N= 32	ACS (other possible diagnosis)	Experimental group: 61 (11), Control group: 62 (9)	CBT Psychologist: Yes Multicomponent Group sessions In person <u>Description:</u> <u>Experimental group:</u> Psychoeducation, Behavioral techniques for life style modification, Cognitive techniques, Motivational techniques, Relapse prevention	6 weeks	Depression Anxiety Adherence to psychological treatment	No	2, 6 and 12 months

Author, year	Number of patients	Patient population. Diagnosis at entry	Age, mean (SD)	Description of interventions	Intervention duration	Outcomes	Evaluation at the end of treatment	Evaluation at the end of follow-up
Nyklíček *et al.* 2014	Experimental group: N = 55 Control group: N = 52	Others: PCI - unspecified if acute or programmed	Experimental group: 55.4 (7.3), Control group: 56.3 (7.3)	CBT Psychologist: Yes Unicomponent Group sessions In person Description: Experimental group: Minfulness-Based Stress Reduction (MBSR) Control group:self-help intervention bases on a booklet about group training written by the same psychologist	4 weeks	Stress Drug Use Positive and negative affect	4 weeks	No
O'Neil *et al.* 2014	Experimental group: N=61, Control group: N =60	ACS: MI or unstable angina with clinical significant depressive symptomato-logy during hospitalize-tion	Unknown	CBT Psychologist: Yes Multicomponent Individual Telephone Description: Experimental group: Relaxation techniques, Behavioral techniques for life style modification, Cognitive restructuring, Motivational interviewing	6 months	Depression Quality of life	6 months	No
O'Neil *et al.* 2015	The same as O´Neil 2014	The same as O´Neil 2014	The same as O´Neil 2014	The same as O´Neil 2014	The same as O´Neil 2014	Depression Stress Quality of life	No	12 months

Author, year	Number of patients	Patient population. Diagnosis at entry	Age, mean (SD)	Description of interventions	Intervention duration	Outcomes	Evaluation at the end of treatment	Evaluation at the end of follow-up
Rakowska, 2015	Experimental group: N= 41, Control group: N= 40	ACS (infarction)	Experimental group: 53.56 (4.58), Control group: 53.40 (4.27)	CBT Psychologist: Yes Multicomponent Individual In person Description: Experimental group: Problem solving, Relapse prevention	10 weeks	Stress Quality of life	10 weeks	1 year and 2,5 year
Sanjuan *et al.* 2016	Experimental group: N = 57, Control Group N=51	ACS (+ CHD diagnosis)	Experimental group:54.3 (9.5) Control group: 54.5 (8.7)	PPT Psychologist: Yes Multicomponent Group sessions In person Description: Experimental group: Psychoeducation, Relaxation, Performance of acts of kindness, Awareness of acts of gratitude, Prioritizing positive thoughts and feelings	8 weeks	Depression Hostility Positive and negative affect	8 weeks	No
Lv *et al.* 2016	Experimental group: N = 38, Control group: N = 37	CHD + PCI, no events.	Experimental group: 52.4 (6.3), Control group: 52 (6.2)	CBT Psychologist: Yes Multicomponent Individual In person Description: Experimental group: Psychoeducation, Behavioral techniques for life style modification (Identify and confirm treatment goals, develop plans for daily activities and track feedbacks,	8 weeks	Depression Anxiety Quality of life	8 weeks	No

Author, year	Number of patients	Patient population. Diagnosis at entry	Age, mean (SD)	Description of interventions	Intervention duration	Outcomes	Evaluation at the end of treatment	Evaluation at the end of follow-up
				manage emotional and behavioral activation). Cognitive restructuring.				
Nikrahan *et al.* 2016	Seligman group: N =13, Lyubomirsky group: N = 13, Fordyce group: N=15, Control group: N=14	Group 1: CAD (+ CABG or PCI)	Seligman group:55,8 (5,3), Lyubomirsky group: 59.2 (11.5), Fordyce group: 54.7 (10.1), Control group: 56.9 (6.7)	PPT Psychologist: Yes Multicomponent In group In person Description: Experimental group: Lyubomirsky Group: Mindfulness, Gratitude Expression, Forgiveness, Commitment to goals Seligman Group: Positive Emotions, Optimism and Happiness, Strength, Values and virtues, meaning of life, Prioritizing positive thoughts and feelings Fordyce Group: Optimism, Behavioral and Social activation (increasing activity and social relationship, productivity and organizations), Focusing on present, Prioritizing positive thoughts and feelings	6 weeks	Depression Vital Satisfaction Dispositional Hope Happiness	7 weeks	15 weeks
Fernandes *et al.* 2017	Experimental group: N=65, Control group: N =56	ACS	Experimental group: 61.77 (12.11), Control group: 66.11 (12.11)	CBT Psychologist: Yes Multicomponent Group sessions In person Description: Experimental group:	1 week	Depression Anxiety	2-3 days (hospital discharge)	1 and 2 months

Author, year	Number of patients	Patient population. Diagnosis at entry	Age, mean (SD)	Description of interventions	Intervention duration	Outcomes	Evaluation at the end of treatment	Evaluation at the end of follow-up
				Psychoeducation, Behavioral techniques for life style modification (Promotion of psychosocial adjustment in post-ACS rehabilitation), Cognitive techniques, Relapse prevention				
Mohammadi *et al.* 2018	Experimental group: N = 31, Control group: N= 30	Group 2: ACS (and clear diagnosis CHD)	Experimental group: 52.7 (5.0), Control group: 52.4 (5.9)	PPT Psychologist: Yes Multicomponent Group sessions In person Description: Experimental group: Optimism and happiness, Posttraumatic Growth	8 weeks	Depression Anxiety Dispositional Optimism Vital satisfaction Dispositional Hope Happiness Positive and negative affect	8 weeks	16 weeks

Figure_1

Click here to access/download;Figure(s);Figure_1_meta-analysis_of_psychological_interventions_in_CAD.pdf

Figure 1. Flow chart

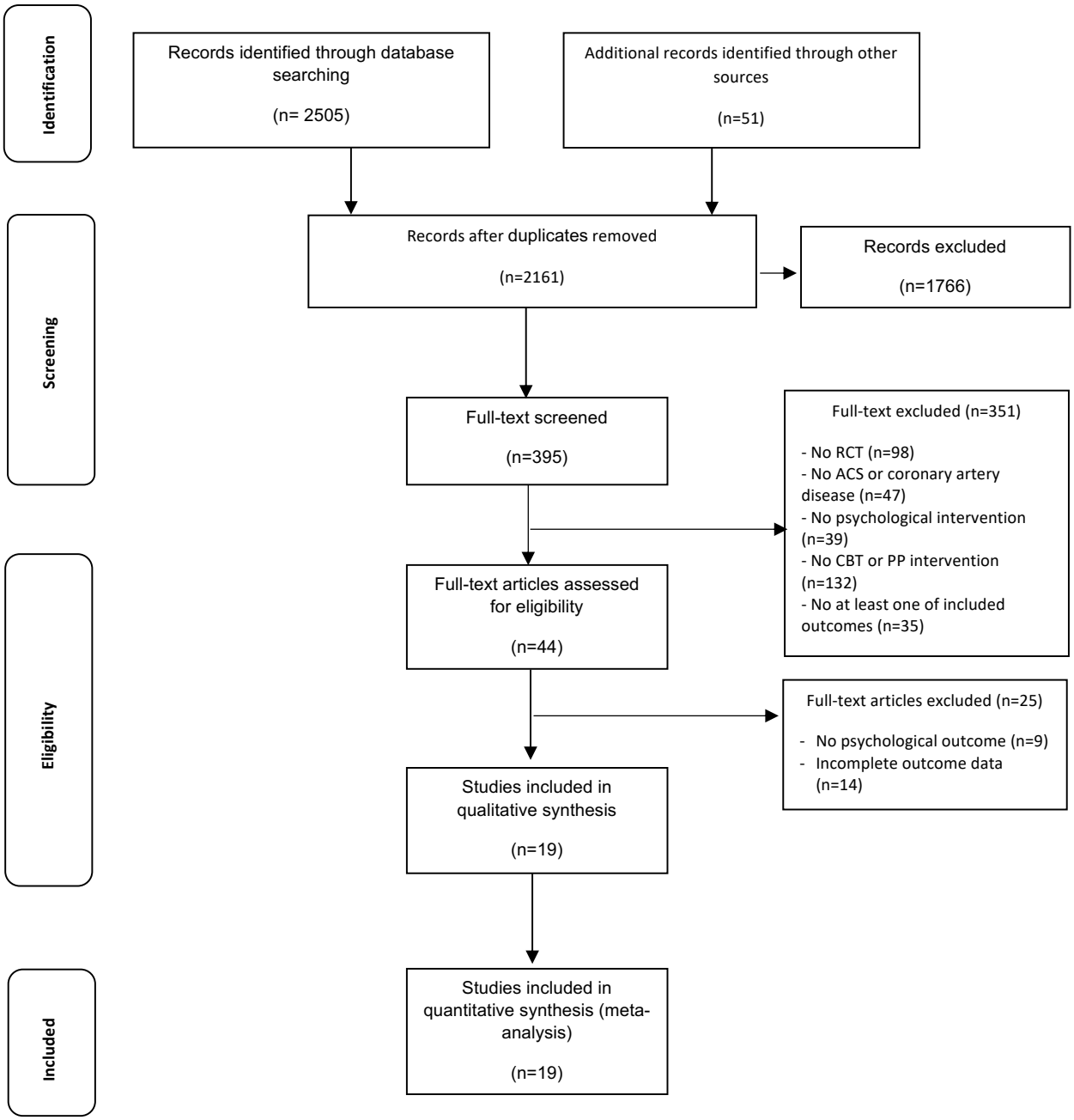


Figure_2

Click here to access/download;Figure(s);Figure_2_meta-analysis_psychological_interventions_in_CAD.pdf

Figure 2

Figure 2A

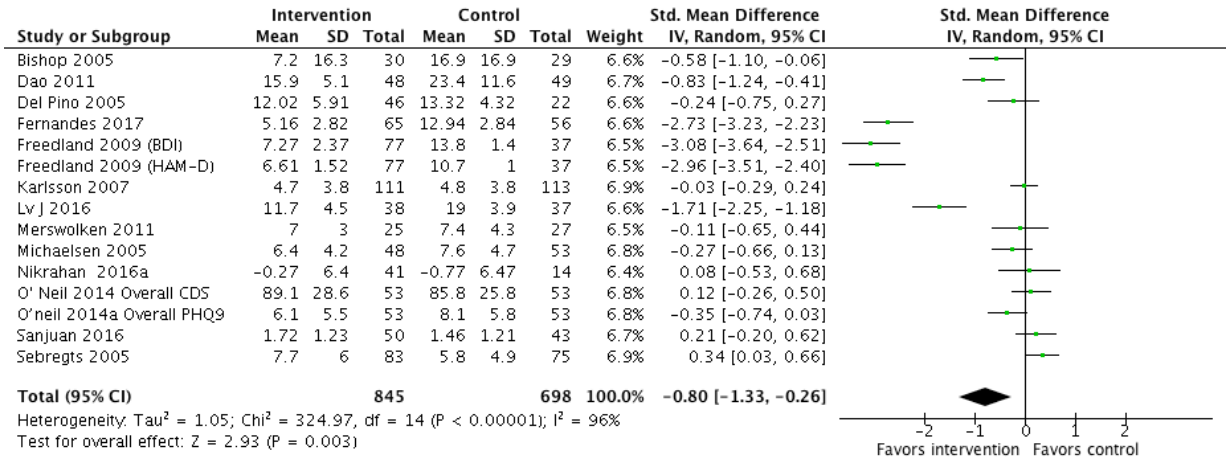


Figure 2B

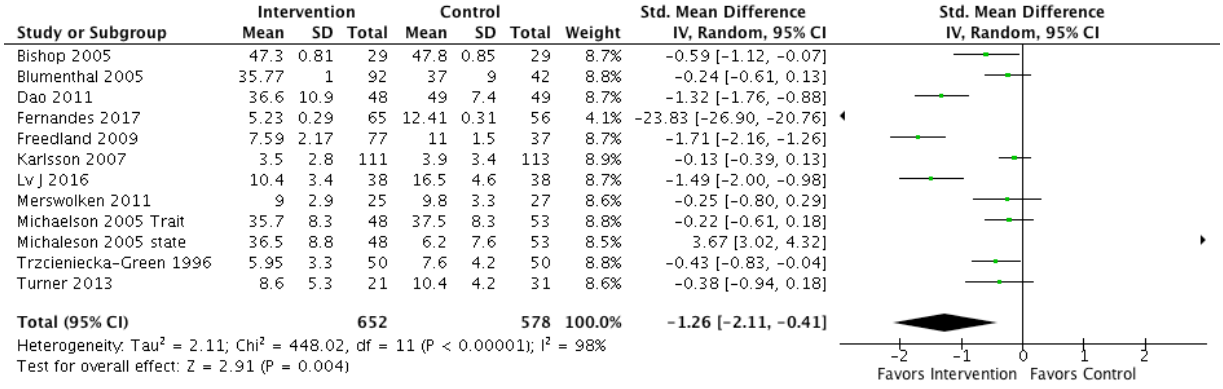


Figure 2C

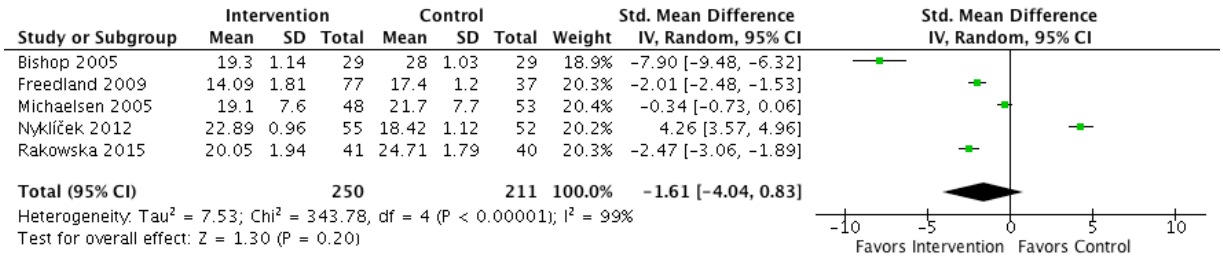


Figure 2D

Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bishop 2005	20	1.09	29	21	0.68	29	8.5%	-1.09 [-1.64, -0.53]
Del Pino 2005 Anger Arousal	29.26	9.61	23	28.09	10.1	22	8.0%	0.12 [-0.47, 0.70]
Del Pino 2005 Anger IN	21.35	4.15	23	20.54	5.78	22	8.0%	0.16 [-0.43, 0.74]
Del Pino 2005 Anger OUT	13.39	3.47	23	12.41	3.32	22	7.9%	0.28 [-0.30, 0.87]
Del Pino 2005 Total Anger	79.65	18.57	23	76.54	19.2	22	8.0%	0.16 [-0.42, 0.75]
MIchaelsen 2005 Anger Control	24.5	4.2	48	24.4	4.5	53	12.0%	0.02 [-0.37, 0.41]
Michaelsen 2005 Anger IN	17.1	4.7	48	16.8	4.9	53	12.0%	0.06 [-0.33, 0.45]
Michaelsen 2005 Anger OUT	11.6	2.7	48	11.5	3.1	53	12.0%	0.03 [-0.36, 0.42]
Michaelsen 2005 Anger State	10.9	2.3	48	11.7	2.6	53	11.9%	-0.32 [-0.72, 0.07]
Michalesen 2005 Anger Trait	17.4	4.2	48	18	4.8	53	12.0%	-0.13 [-0.52, 0.26]
Total (95% CI)			**361**			**382**	**100.0%**	**-0.07 [-0.29, 0.14]**

Heterogeneity: Tau² = 0.06; Chi² = 18.49, df = 9 (P = 0.03); I² = 51%
Test for overall effect: Z = 0.69 (P = 0.49)

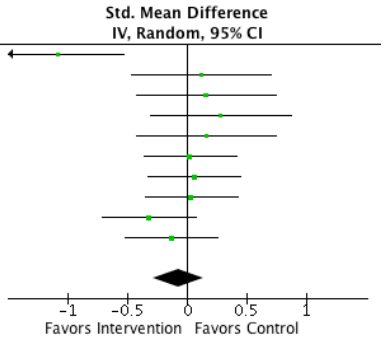


Figure 2E

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
Mohammadi 2018	2.58	0.65	56.6%	2.58 [1.31, 3.85]
Nikrahan 2016a	-0.54	1.31	43.4%	-0.54 [-3.11, 2.03]
Total (95% CI)			**100.0%**	**1.23 [-1.80, 4.26]**

Heterogeneity: Tau² = 3.80; Chi² = 4.55, df = 1 (P = 0.03); I² = 78%
Test for overall effect: Z = 0.79 (P = 0.43)

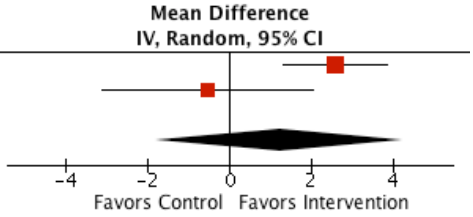


Figure 2F

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
Mohammadi 2018	6.99	2.96	49.8%	6.99 [1.19, 12.79]
Nikrahan 2016a	-5.01	2.88	50.2%	-5.01 [-10.65, 0.63]
Total (95% CI)			**100.0%**	**0.97 [-10.79, 12.73]**

Heterogeneity: Tau² = 63.47; Chi² = 8.44, df = 1 (P = 0.004); I² = 88%
Test for overall effect: Z = 0.16 (P = 0.87)

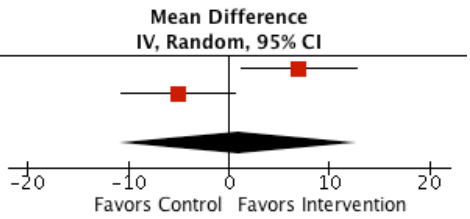


Figure_3

Click here to access/download;Figure(s);Figure_3_meta-analysis_psychological_interventions_in_CAD.pdf

Figure 3

Figure 3A

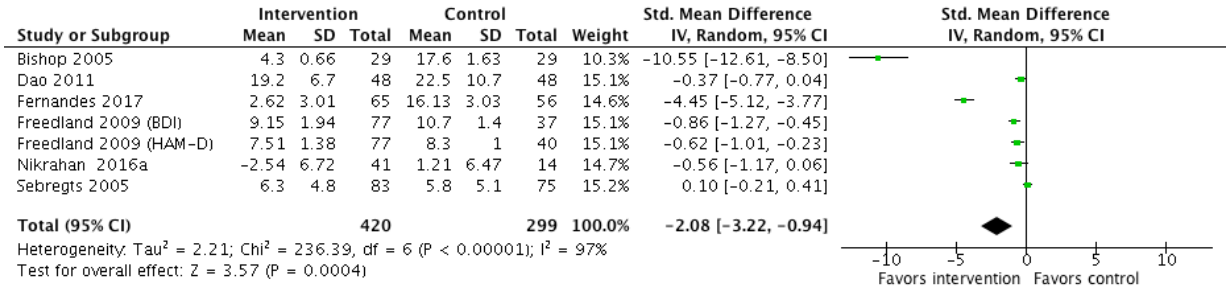


Figure 3B

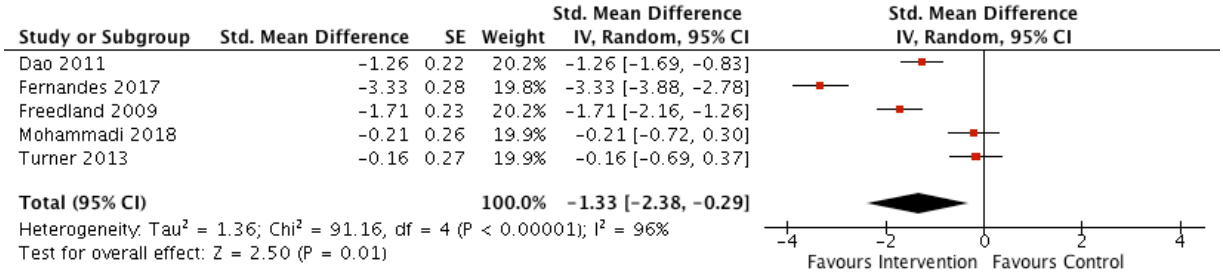


Figure 3C

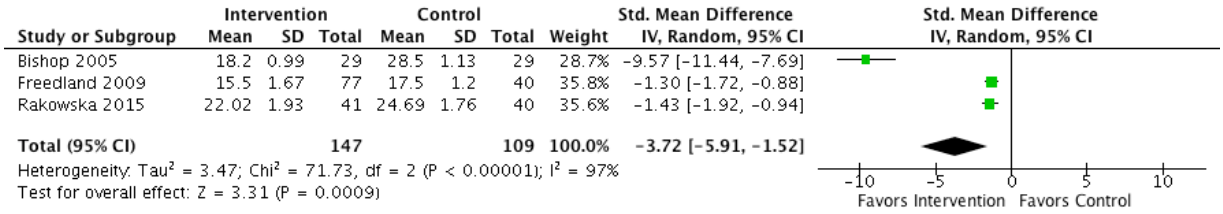


Figure 3D

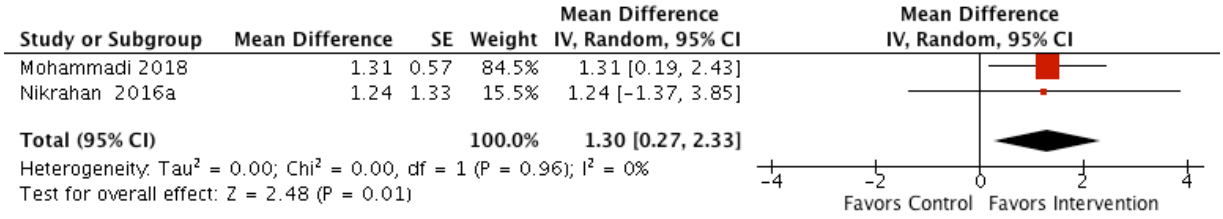
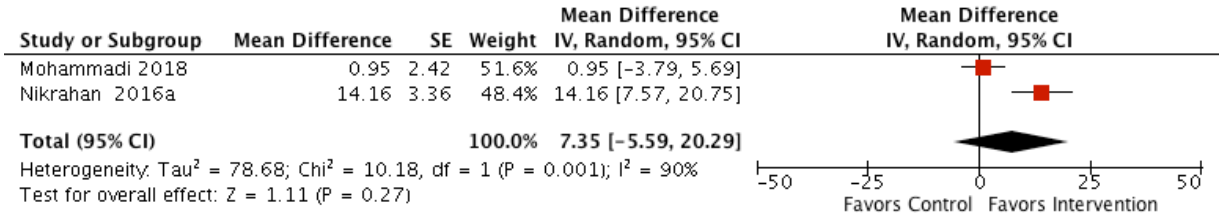


Figure 3E



Supplemental material

EFFICACY OF PSYCHOLOGICAL INTERVENTIONS ON PSYCHOLOGICAL OUTCOMES IN CORONARY ARTERY DISEASE: SYSTEMATIC REVIEW AND META-ANALYSIS

Brief title: Meta-analysis of psychological interventions in CAD

Inés Magán, PhD[a]; Laura Casado, MS[a]; Rosa Jurado-Barba, PhD[a, b]; Haley Barnum, PharmD[c]; Marta M. Redondo, PhD[a]; Adrian V. Hernandez, MD, PhD[c, d]; Héctor Bueno, MD, PhD[b, e, f]

[a]Department of Psychology, Facultad de Educación y Salud, Universidad Camilo José Cela, Madrid, Spain; [b]Instituto de Investigación Biomedica del Hospital 12 de Octubre (Imas12), Madrid, Spain, [c]Health Outcomes, Policy, and Evidence Synthesis (HOPES) Group, University of Connecticut School of Pharmacy, Storrs, CT, USA; [d]Vicerrectorado de Investigacion, Universidad San Ignacio de Loyola (USIL), Lima, Peru; [e]Department of Cardiology, Hospital Universitario 12 de Octubre, Madrid, Spain; [f]Multidisciplinary Translational Cardiovascular Research Group, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain.

February 24, 2020

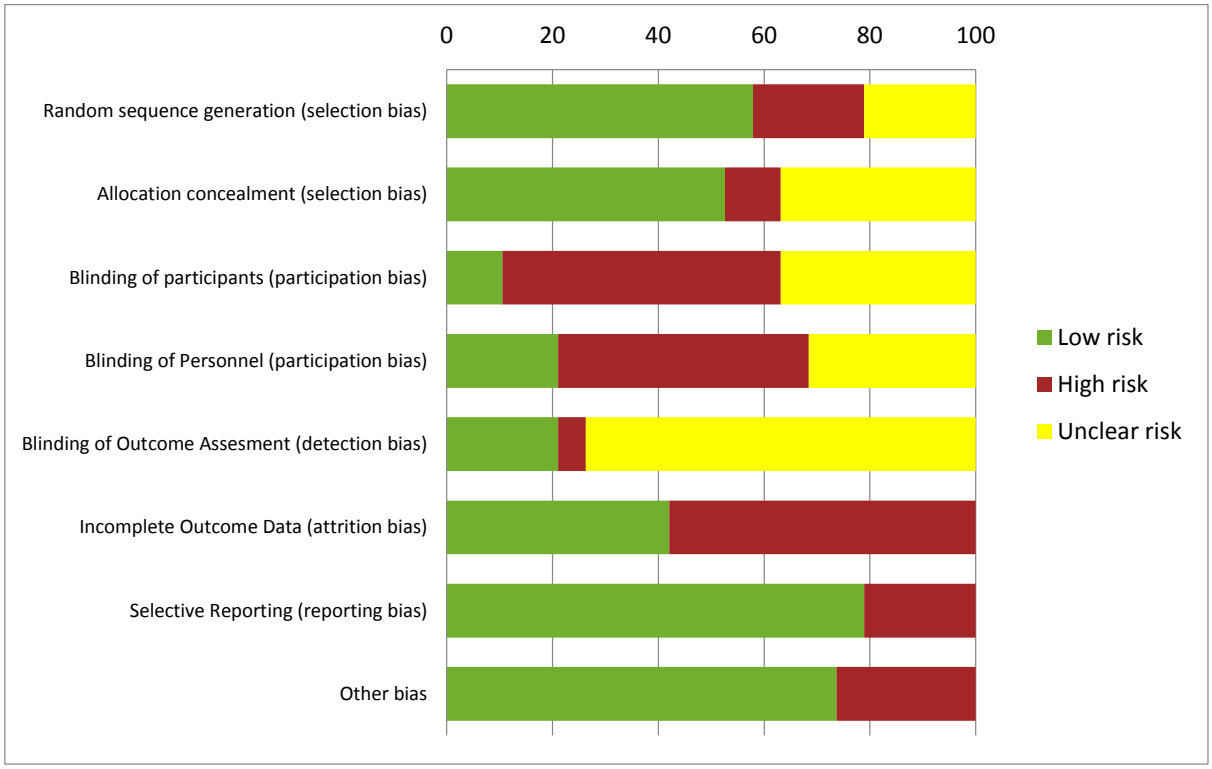
Contents of supplementary files

Search strategy for all data bases

We searched PubMed, PsycInfo, Scopus, The Web of Science, and Cochrane Library for randomized controlled trials (RCTs). Searches were undertaken from 1980 to May 2018. References were also checked to add studies. The search strategy for PubMed was: ((“coronary artery disease” [All Fields] OR “ischemic heart disease” [All Fields] OR “acute coronary syndrome” [All Fields] AND “psychological treatment” [All Fields]) OR “psychological intervention” [All Fields] OR “cognitive behavioral therapy” [All Fields] OR (“cognitive behavioral” [All Fields] AND “therapy”) OR “positive psychology intervention” [All Fields] OR (“positive psychology” [All Fields] AND “intervention” [All Fields])) AND (“randomized controlled trial” [Publication Type] OR “randomized controlled trials” [All Fields]).

Online Figure 1: Risk of bias of included trials

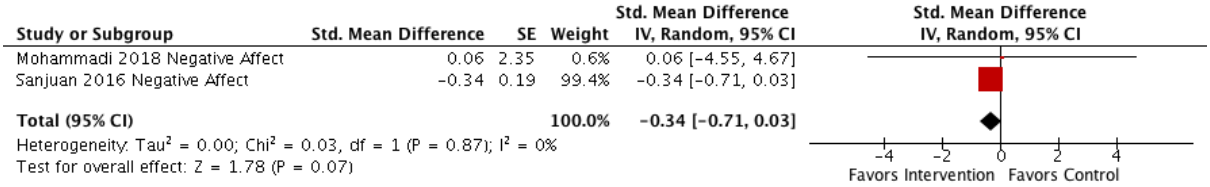
Online figure 1 shows risk of bias assessment of the included trials in this meta-analysis, following the Cochrane Collaboration's risk of bias assessment tool. The risk of bias was evaluated with the following items: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias.



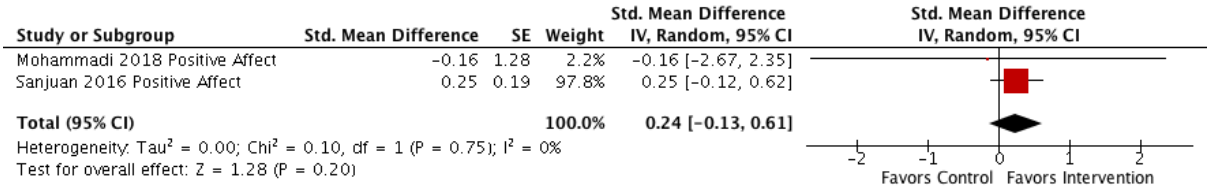
Online Figure 2: Effect of psychological interventions at the end of the intervention on secondary outcomes

Online figure 2 includes forest-plot showing the effect of psychological intervention on negative affect (online figure 2A), positive affect (online figure 2B), hostility (online figure 2C), quality of life (online figure 2D), and dispositional hope (online figure 2E) immediately at the end of the intervention.

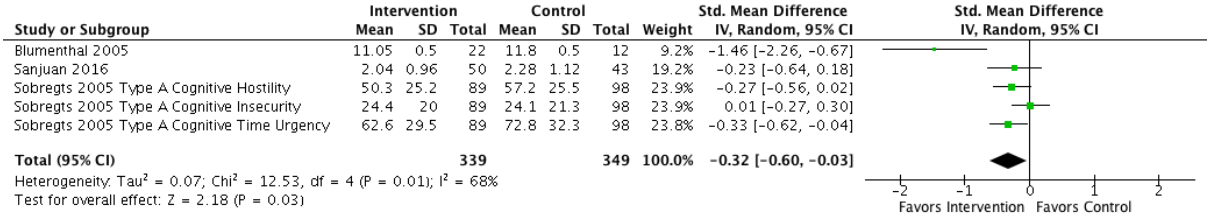
Online Figure 2A: Negative affect at the end of the intervention



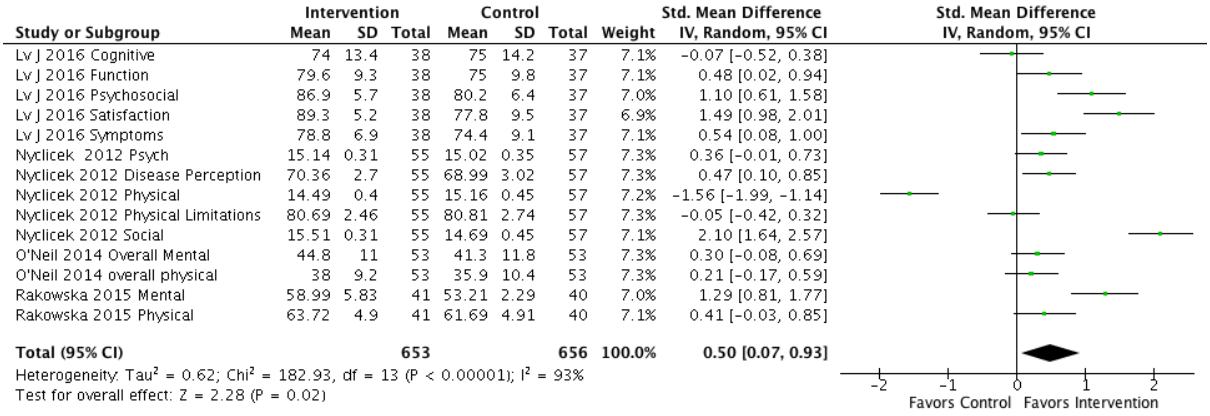
Online Figure 2B: Positive affect at the end of the intervention



Online Figure 2C: Hostility at the end of the intervention



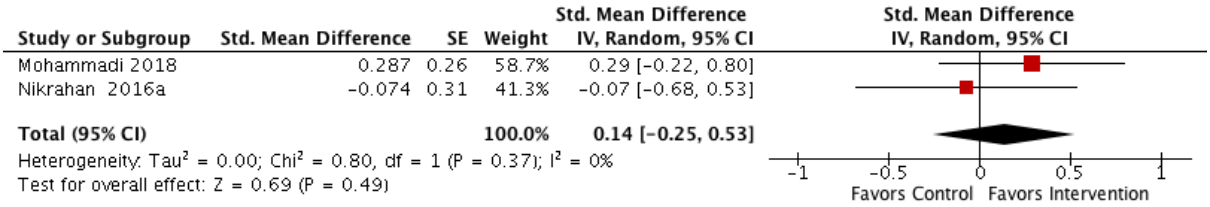
Online Figure 2D: Quality of life at the end of the intervention



Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Lv J 2016 Cognitive	74	13.4	38	75	14.2	37	7.1%	-0.07 [-0.52, 0.38]
Lv J 2016 Function	79.6	9.3	38	75	9.8	37	7.1%	0.48 [0.02, 0.94]
Lv J 2016 Psychosocial	86.9	5.7	38	80.2	6.4	37	7.0%	1.10 [0.61, 1.58]
Lv J 2016 Satisfaction	89.3	5.2	38	77.8	9.5	37	6.9%	1.49 [0.98, 2.01]
Lv J 2016 Symptoms	78.8	6.9	38	74.4	9.1	37	7.1%	0.54 [0.08, 1.00]
Nyclicek 2012 Psych	15.14	0.31	55	15.02	0.35	57	7.3%	0.36 [-0.01, 0.73]
Nyclicek 2012 Disease Perception	70.36	2.7	55	68.99	3.02	57	7.3%	0.47 [0.10, 0.85]
Nyclicek 2012 Physical	14.49	0.4	55	15.16	0.45	57	7.2%	-1.56 [-1.99, -1.14]
Nyclicek 2012 Physical Limitations	80.69	2.46	55	80.81	2.74	57	7.3%	-0.05 [-0.42, 0.32]
Nyclicek 2012 Social	15.51	0.31	55	14.69	0.45	57	7.1%	2.10 [1.64, 2.57]
O'Neil 2014 Overall Mental	44.8	11	53	41.3	11.8	53	7.3%	0.30 [-0.08, 0.69]
O'Neil 2014 overall physical	38	9.2	53	35.9	10.4	53	7.3%	0.21 [-0.17, 0.59]
Rakowska 2015 Mental	58.99	5.83	41	53.21	2.29	40	7.0%	1.29 [0.81, 1.77]
Rakowska 2015 Physical	63.72	4.9	41	61.69	4.91	40	7.1%	0.41 [-0.03, 0.85]
Total (95% CI)			**653**			**656**	**100.0%**	**0.50 [0.07, 0.93]**

Heterogeneity: $Tau^2 = 0.62$; $Chi^2 = 182.93$, df = 13 ($P < 0.00001$); $I^2 = 93\%$
Test for overall effect: Z = 2.28 (P = 0.02)

Online Figure 2E: Dispositional hope at the end of the intervention



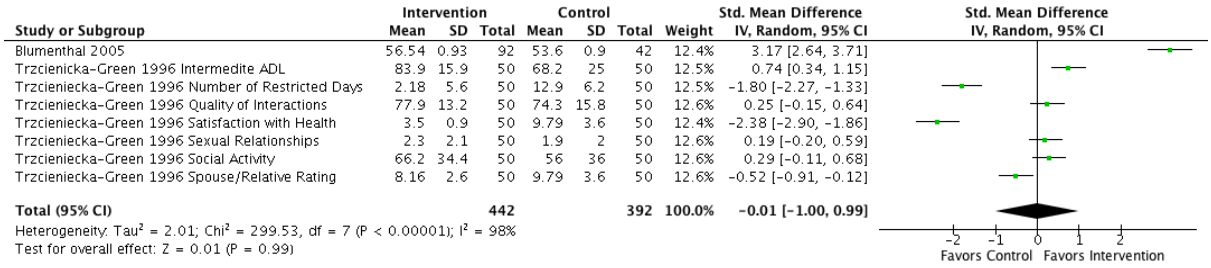
Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
Mohammadi 2018	0.287	0.26	58.7%	0.29 [-0.22, 0.80]
Nikrahan 2016a	-0.074	0.31	41.3%	-0.07 [-0.68, 0.53]
Total (95% CI)			**100.0%**	**0.14 [-0.25, 0.53]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.80$, df = 1 ($P = 0.37$); $I^2 = 0\%$
Test for overall effect: Z = 0.69 (P = 0.49)

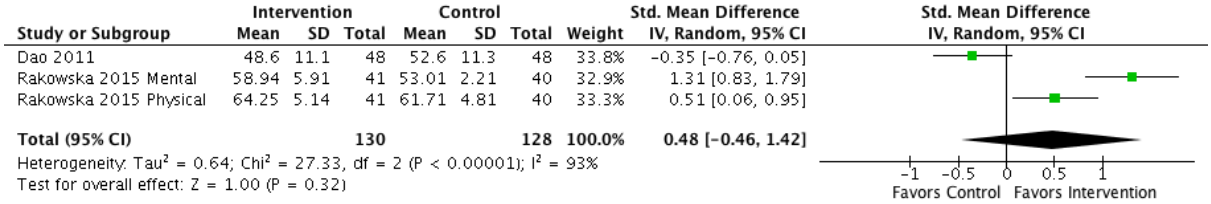
Online Figure 3: Effect of psychological interventions at the end of follow-up on secondary outcomes

Online figure 3 includes forest-plots showing the effect of psychological intervention on daily activities (online figure 3A), quality of life (online figure 3B), and dispositional hope (online figure 3C) at the end of follow-up.

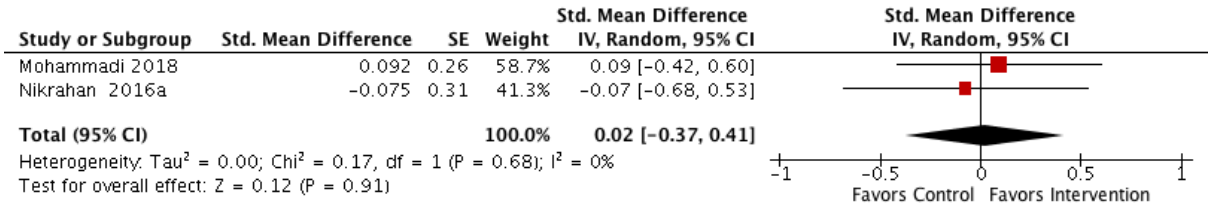
Online Figure 3A: Daily activities at the end of follow-up



Online Figure 3B: Quality of life at the end of follow-up



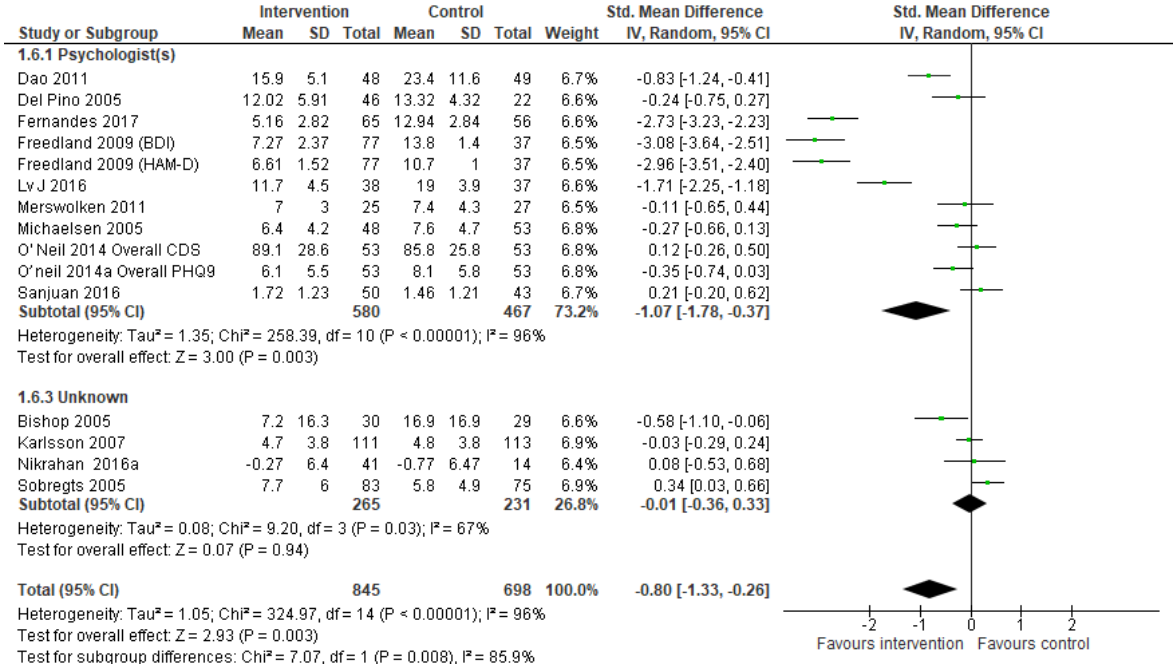
Online Figure 3C: Dispositional hope at the end of follow-up



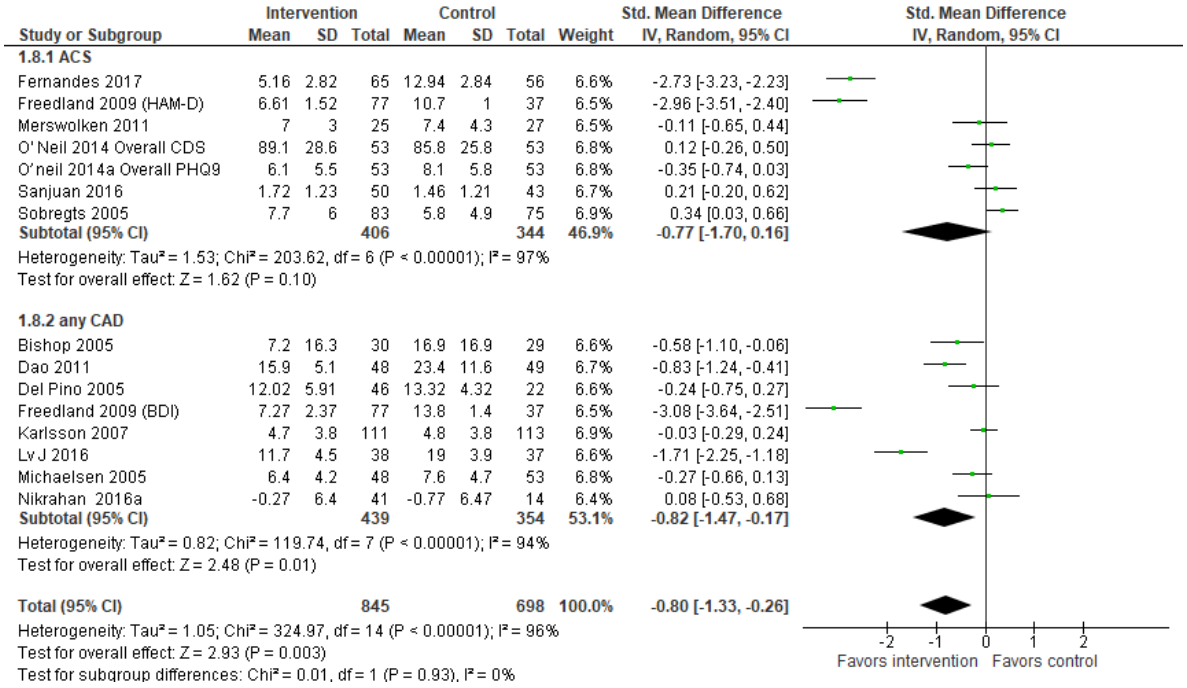
Online Figure 4: Subgroups analyses of depression at the end of the intervention

Online figure 4 includes forest-plots showing the effects of psychological interventions compared to control groups on depression immediately after treatment across the two pre-specified subgroups analyses: provider of intervention (online figure 4A), type of population (online figure 4B), type of PI (CBT and PPT (online figure 4C), post-treatment assessment time (online figure 4D), and session type (online figure 4E).

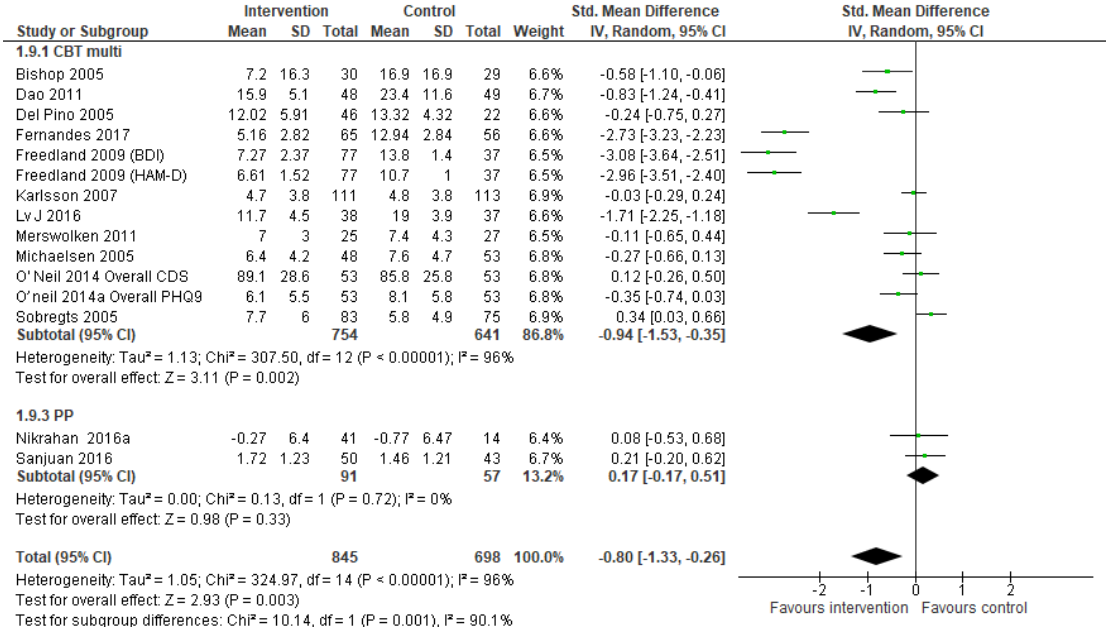
Online Figure 4A: Depression at the end of the intervention subgroup by provider of intervention (psychologist and unknown)



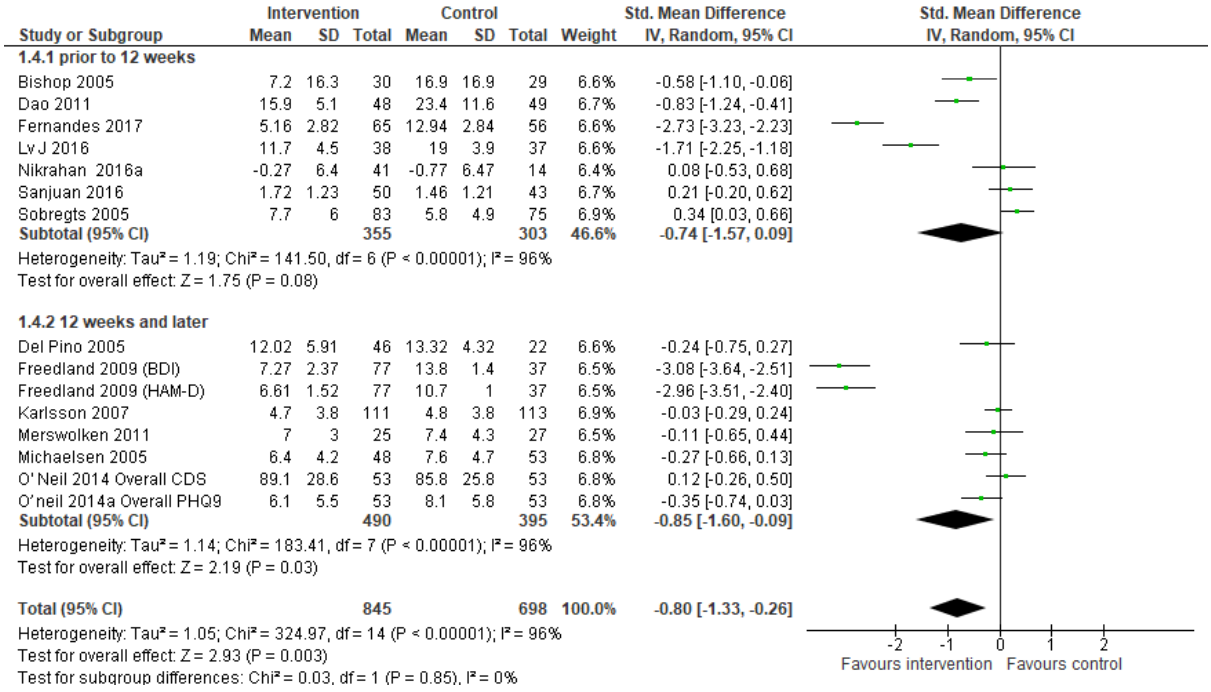
Online Figure 4B: Depression at the end of the intervention subgroup by type of population (any CAD included both chronic and acute CAD patients)



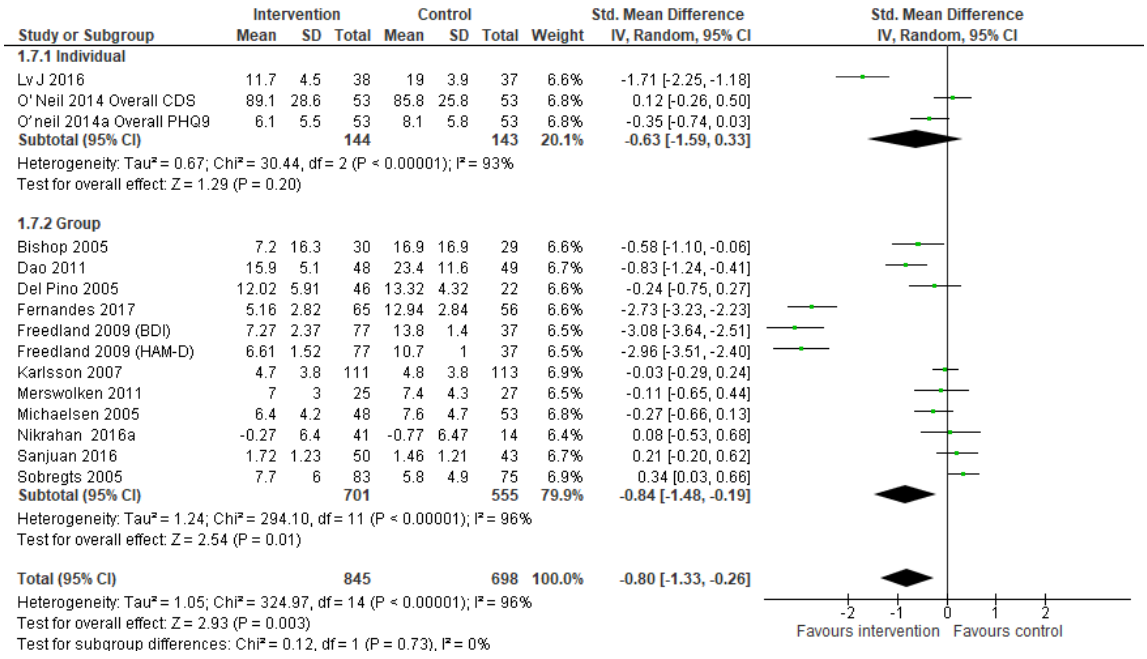
Online Figure 4C: Depression at the end of the intervention subgroup by type of PI (CBT vs. PPT)



Online Figure 4D: Depression at the end of the intervention subgroup by post-treatment assessment time (>12 weeks and <12 weeks)



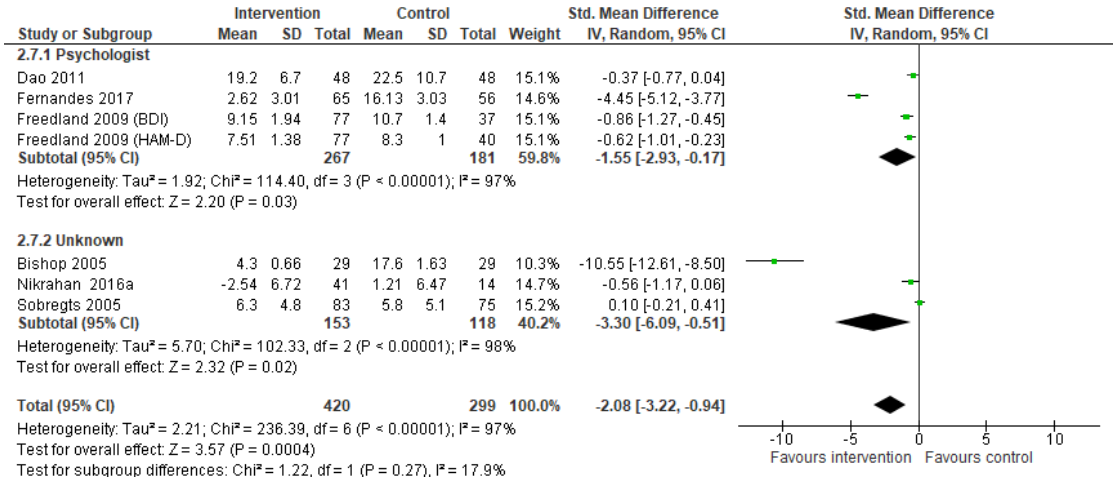
Online Figure 4E: Depression at the end of the intervention subgroup by session type (individual and group)



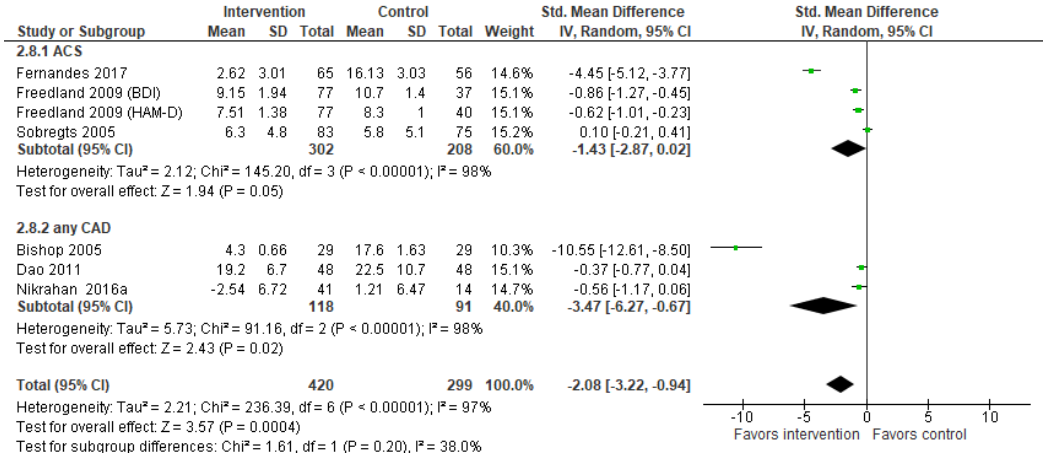
Online Figure 5: Subgroups analyses of depression at the end of follow-up

Online figure 5 includes forest-plots showing the effects of psychological interventions compared to control groups on depression at the end of follow-up across the two pre-specified subgroups analyses: provider of intervention (online figure 5A), type of population (online figure 5B), and follow-up assessment time (online figure 5C).

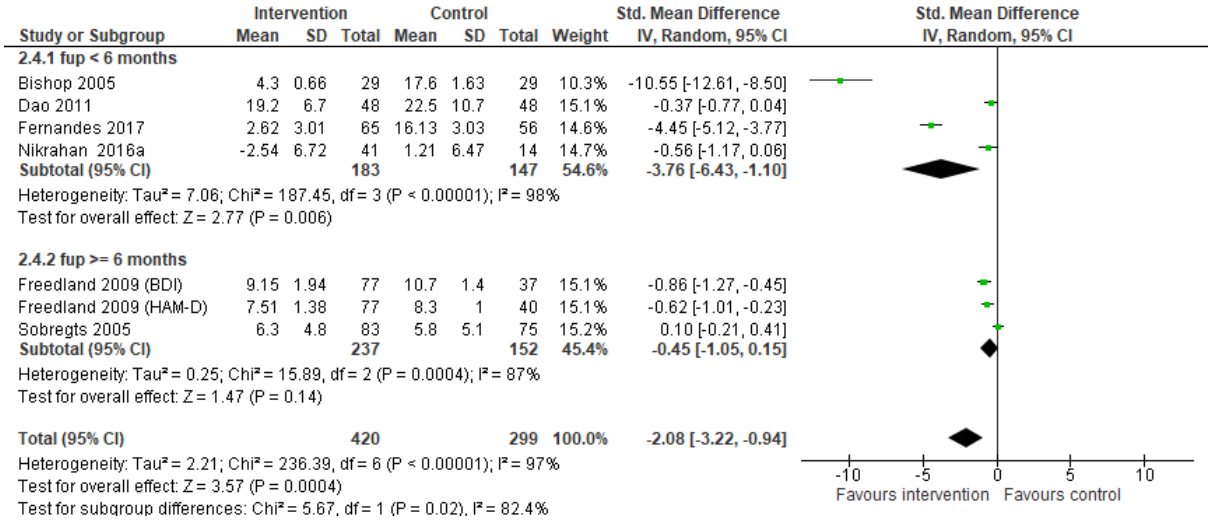
Online Figure 5A: Depression at the end follow-up subgroup by provider of intervention (psychologist and unknown)



Online Figure 5B: Depression at the end of follow-up subgroup by type of population (any CAD included both chronic and acute CAD patients)



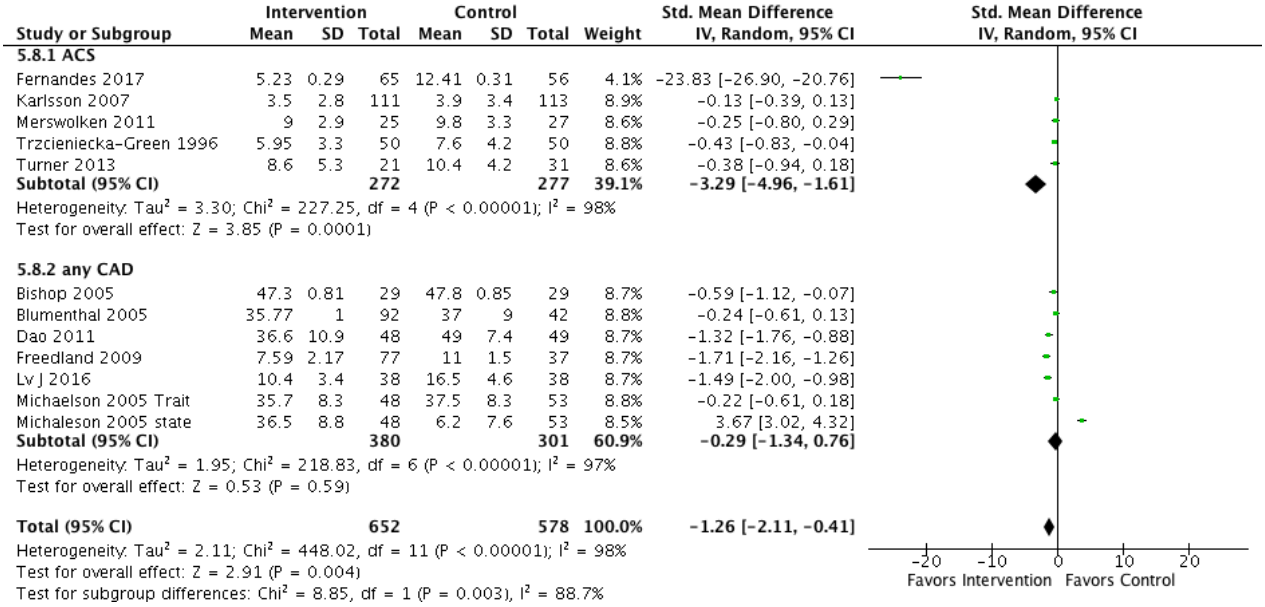
Online Figure 5C: Depression at the end of follow-up subgroup follow-up assessment time (<6 months and >6 months)



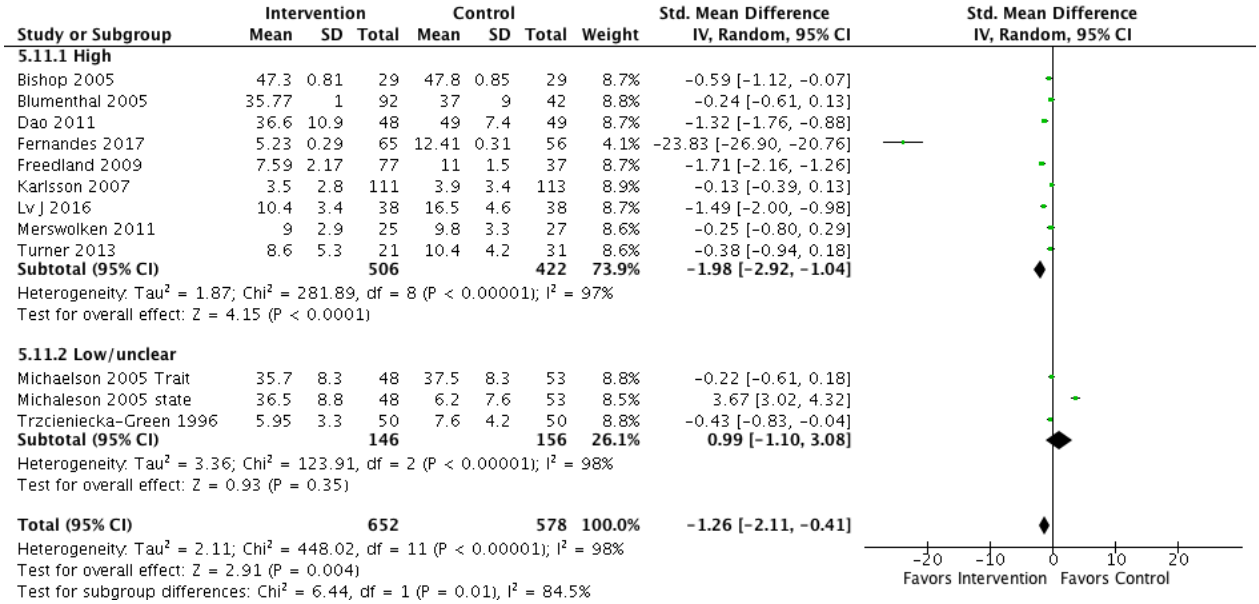
Online Figure 6: Subgroups analyses of anxiety at the end of the intervention

Online figure 6 includes forest-plots showing the effects of psychological interventions compared to control groups on anxiety immediately after treatment across the two pre-specified subgroups analyses: type of population (online figure 6A), risk of bias (online figure 6B), post-treatment assessment time (online figure 6C), and session type (online figure 6D).

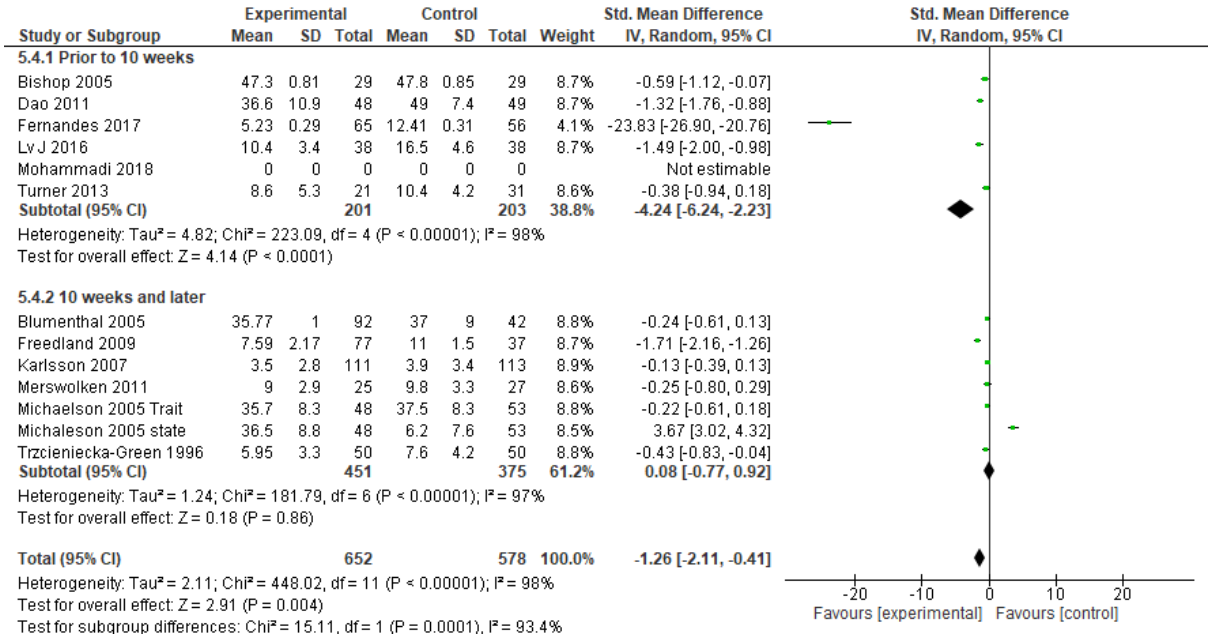
Online Figure 6A: Anxiety at the end of the intervention subgroup by type of population (any CAD included both chronic and acute CAD patients)



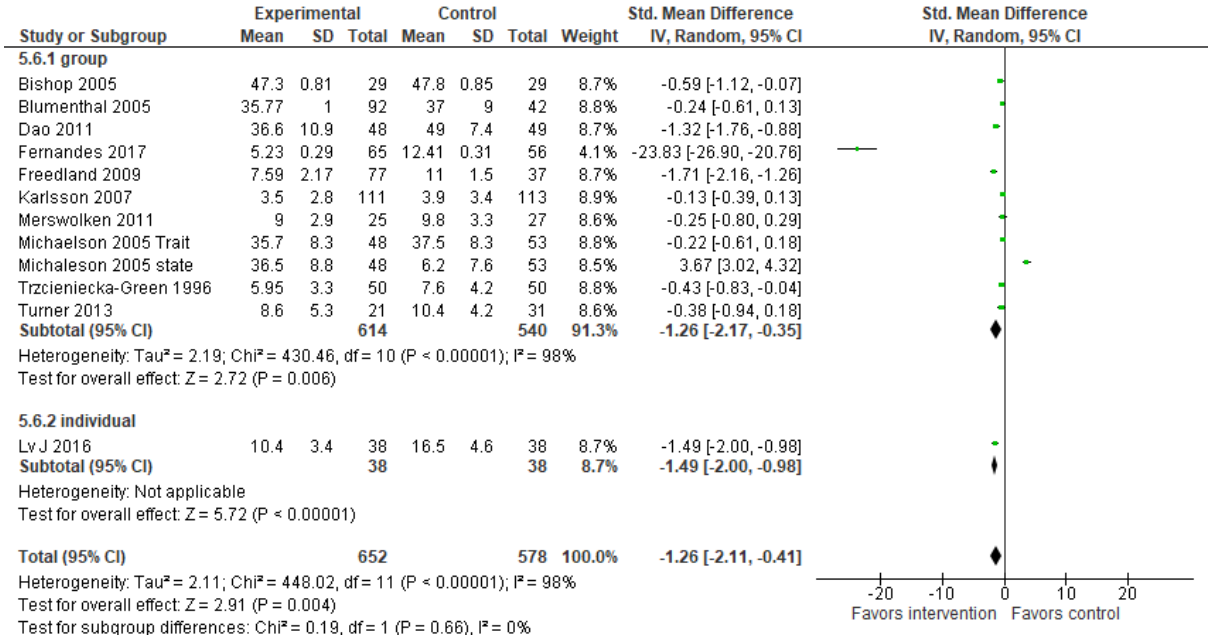
Online Figure 6B: Anxiety at the end of the intervention subgroup by risk of bias (low and high or unclear risk of bias)



Online Figure 6C: Anxiety at the end of the intervention subgroup by post-treatment assessment time (>10 weeks and <10 weeks)



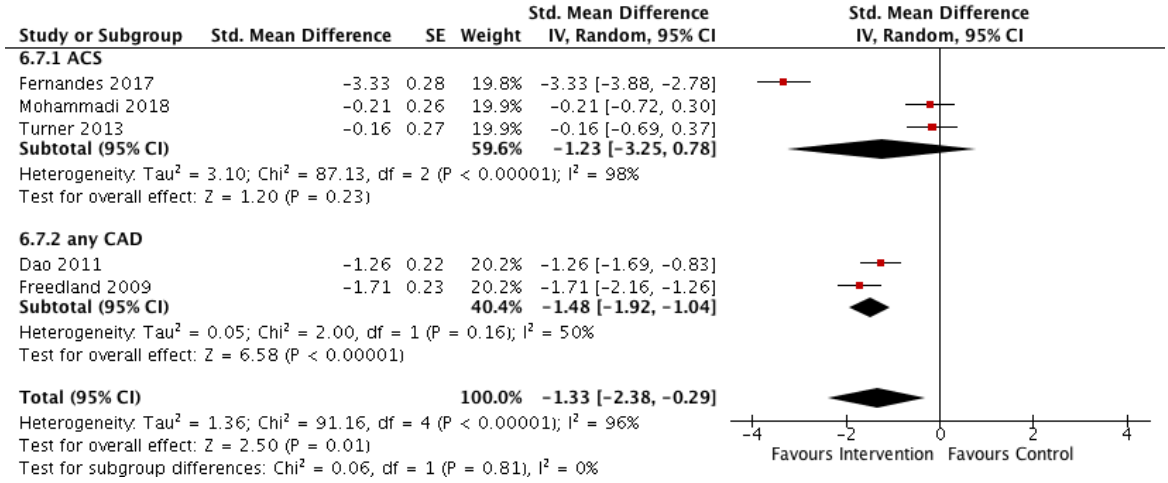
Online Figure 6D: Anxiety at the end of the intervention subgroup by session type (group and individual)



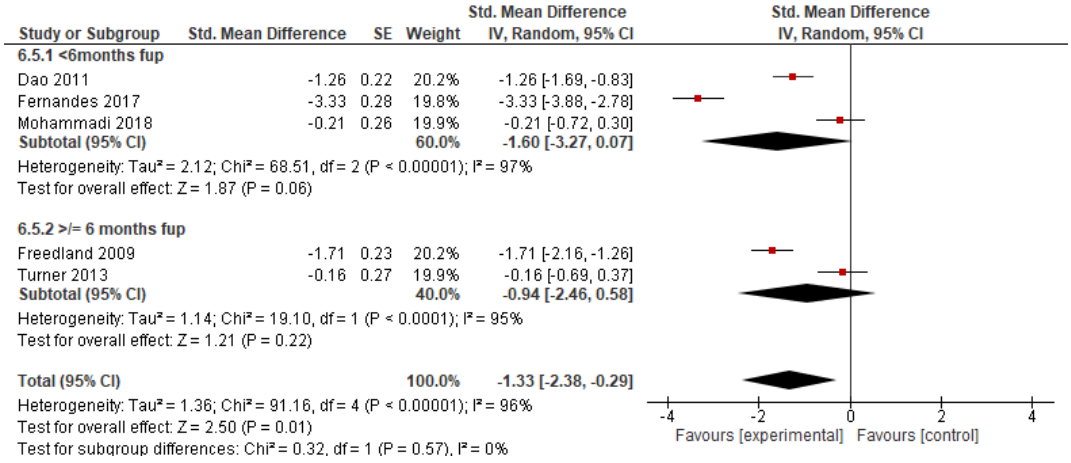
Online Figure 7: Subgroup analysis of anxiety at the end of follow-up

Online figure 7 includes forest-plot showing the effects of psychological interventions compared to control groups on anxiety at the end of follow-up across the pre-specified subgroup analysis by type of population (online figure 7A), and assessment follow-up time (online figure 7B).

Online Figure 7A: Anxiety at the end of follow-up subgroup by type of population (any CAD included both chronic and acute CAD patients)



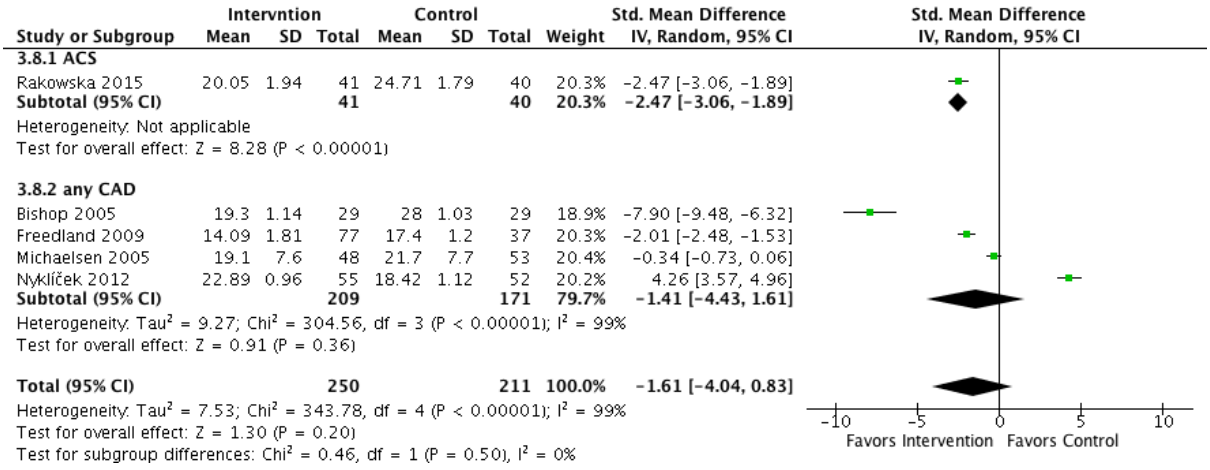
Online Figure 7B: Anxiety at the end of follow-up subgroup by assessment follow-up time (<6 months and >6 months)



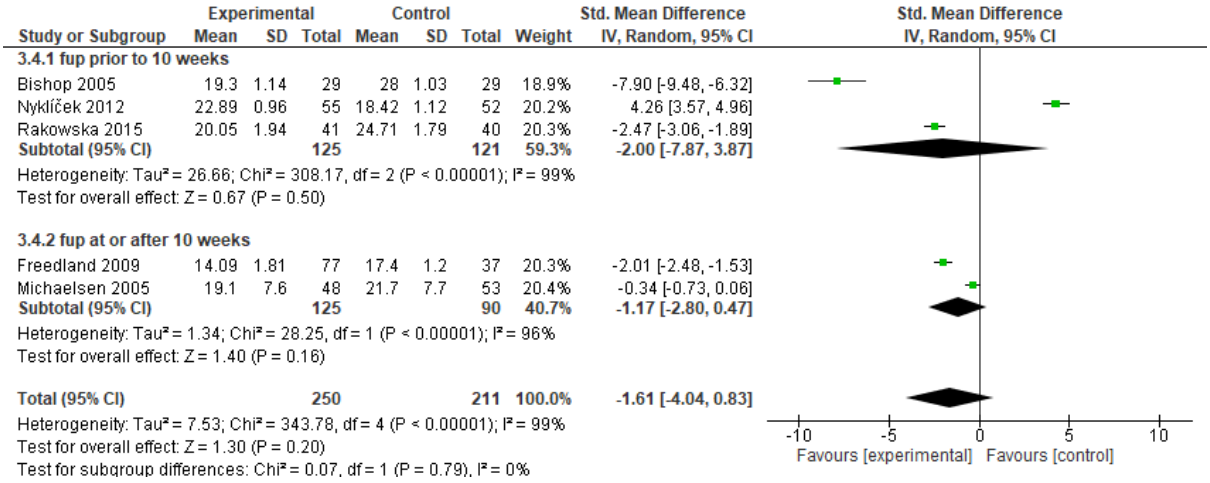
Online Figure 8: Subgroup analysis of stress at the end of post-treatment

Online figure 8 includes forest-plot showing the effects of psychological interventions compared to control groups on stress at the end of treatment across the pre-specified subgroup analysis by type of population (online figure 8A), post-treatment assessment time (online figure 8B), and session type (online figure 8C).

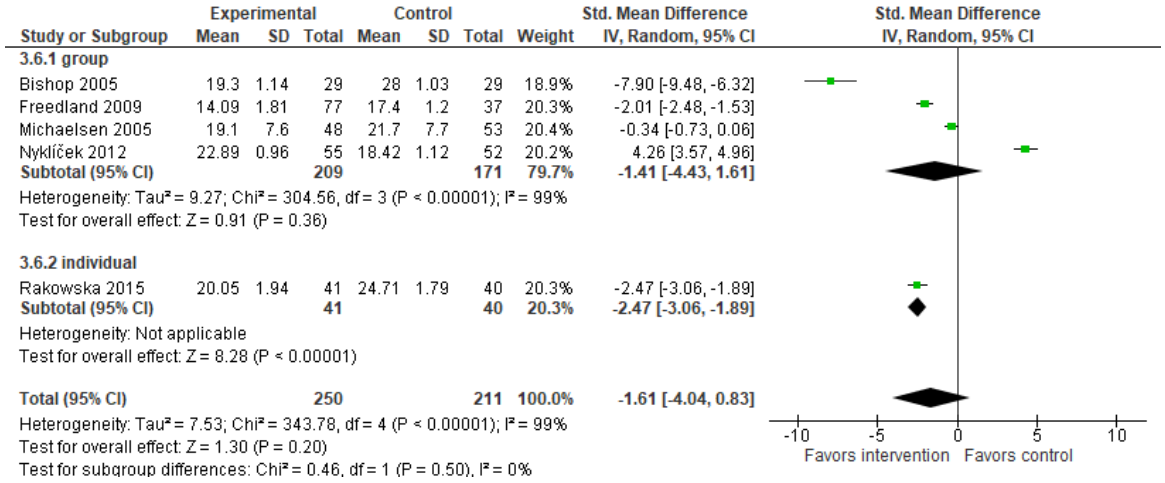
Online Figure 8A: Subgroup analysis of stress at the end treatment by type of population (any CAD included both chronic and acute CAD patients)



Online Figure 8B: Subgroup analysis of stress at the end of treatment by post-treatment assessment time (<10 weeks and >10 weeks)

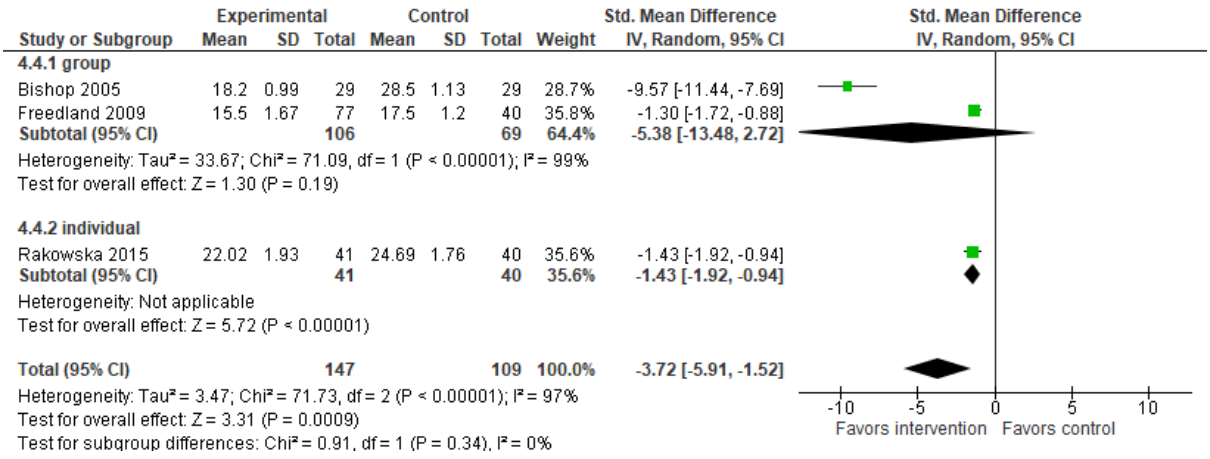


Online Figure 8C: Subgroup analysis of stress at the end by session type (group and individual)



Online Figure 9: Subgroup analysis of stress at the end of follow-up by session type (group and individual)

Online figure 9 includes forest-plot showing the effects of psychological interventions compared to control groups on stress at the end of follow-up across the pre-specified subgroup analysis by session type.



Supplemental material

EFFICACY OF PSYCHOLOGICAL INTERVENTIONS ON PSYCHOLOGICAL OUTCOMES IN CORONARY ARTERY DISEASE: SYSTEMATIC REVIEW AND META-ANALYSIS

Brief title: Meta-analysis of psychological interventions in CAD

Inés Magán, PhD[a]; Laura Casado, MS[a]; Rosa Jurado-Barba, PhD[a, b]; Haley Barnum, PharmD[c]; Marta M. Redondo, PhD[a]; Adrian V. Hernandez, MD, PhD[c, d]; Héctor Bueno, MD, PhD[b, e, f]

[a]Department of Psychology, Facultad de Educación y Salud, Universidad Camilo José Cela, Madrid, Spain; [b]Instituto de Investigación Biomedica del Hospital 12 de Octubre (Imas12), Madrid, Spain, [c]Health Outcomes, Policy, and Evidence Synthesis (HOPES) Group, University of Connecticut School of Pharmacy, Storrs, CT, USA; [d]Vicerrectorado de Investigacion, Universidad San Ignacio de Loyola (USIL), Lima, Peru; [e]Department of Cardiology, Hospital Universitario 12 de Octubre, Madrid, Spain; [f]Multidisciplinary Translational Cardiovascular Research Group, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain.

February 24, 2020

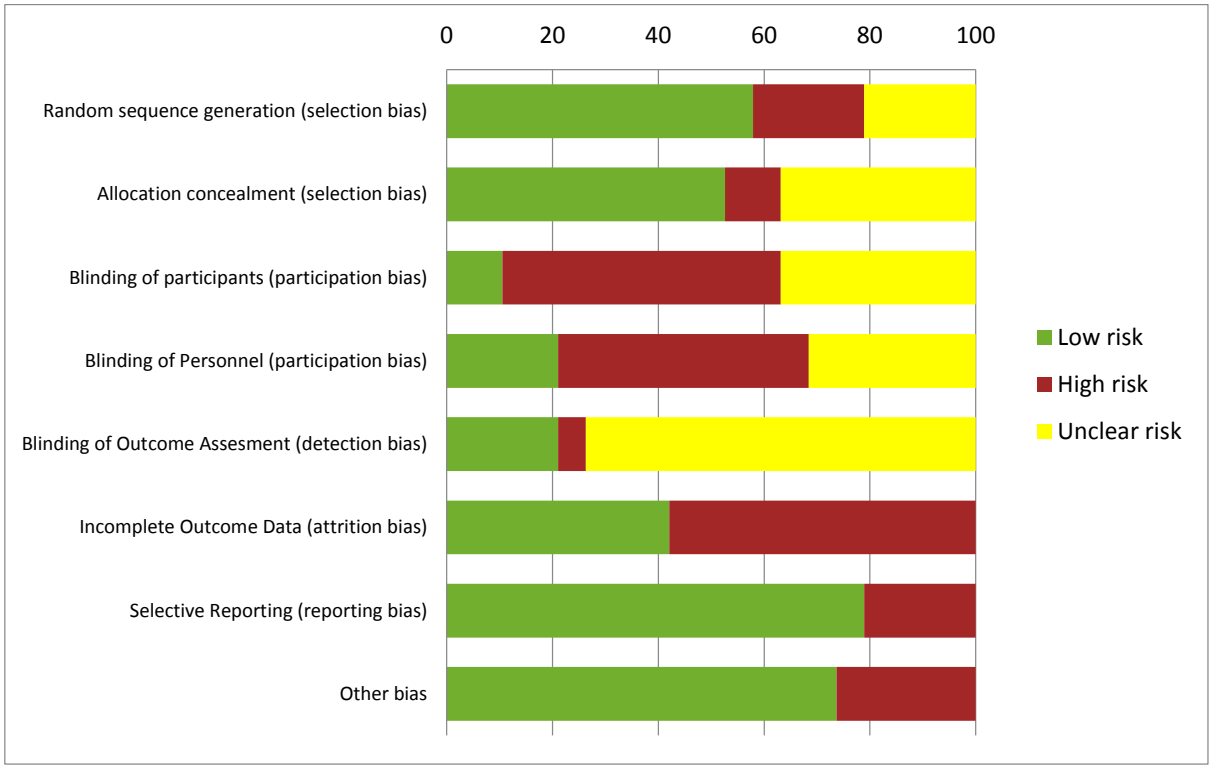
Contents of supplementary files

Search strategy for all data bases

We searched PubMed, PsycInfo, Scopus, The Web of Science, and Cochrane Library for randomized controlled trials (RCTs). Searches were undertaken from 1980 to May 2018. References were also checked to add studies. The search strategy for PubMed was: ((“coronary artery disease” [All Fields] OR “ischemic heart disease” [All Fields] OR “acute coronary syndrome” [All Fields] AND “psychological treatment” [All Fields]) OR “psychological intervention” [All Fields] OR “cognitive behavioral therapy” [All Fields] OR (“cognitive behavioral” [All Fields] AND “therapy”) OR “positive psychology intervention” [All Fields] OR (“positive psychology” [All Fields] AND “intervention” [All Fields])) AND (“randomized controlled trial” [Publication Type] OR “randomized controlled trials” [All Fields]).

Online Figure 1: Risk of bias of included trials

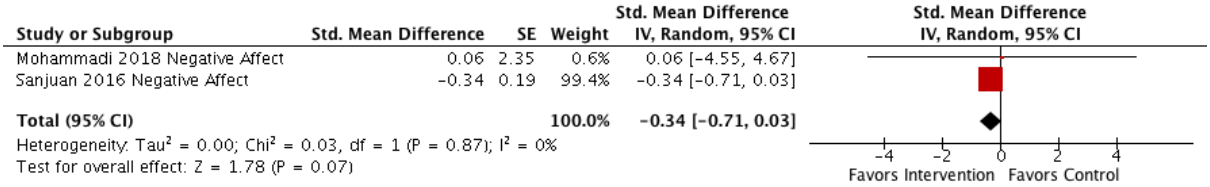
Online figure 1 shows risk of bias assessment of the included trials in this meta-analysis, following the Cochrane Collaboration's risk of bias assessment tool. The risk of bias was evaluated with the following items: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias.



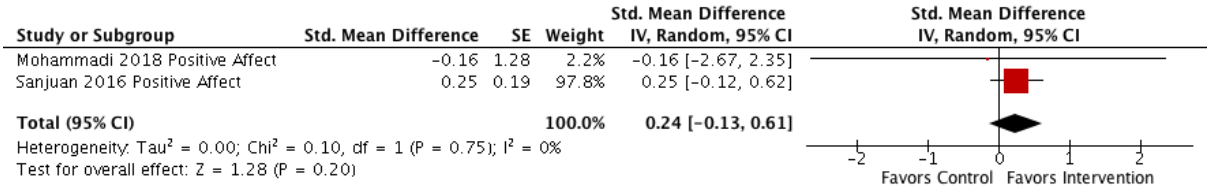
Online Figure 2: Effect of psychological interventions at the end of the intervention on secondary outcomes

Online figure 2 includes forest-plot showing the effect of psychological intervention on negative affect (online figure 2A), positive affect (online figure 2B), hostility (online figure 2C), quality of life (online figure 2D), and dispositional hope (online figure 2E) immediately at the end of the intervention.

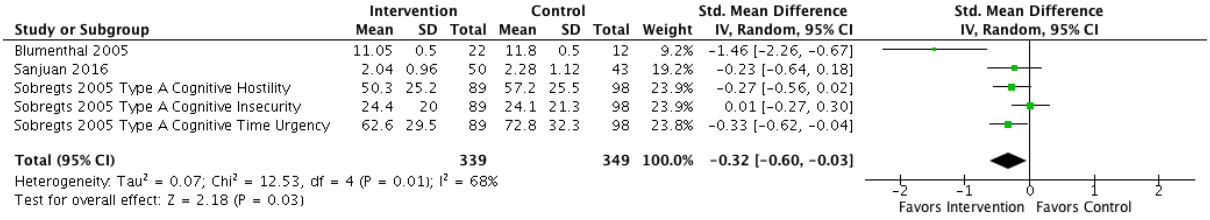
Online Figure 2A: Negative affect at the end of the intervention



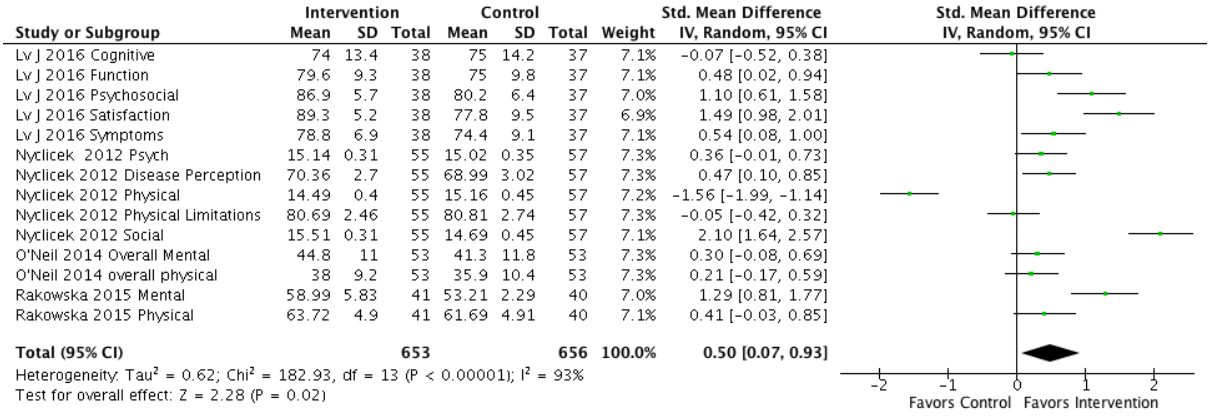
Online Figure 2B: Positive affect at the end of the intervention



Online Figure 2C: Hostility at the end of the intervention



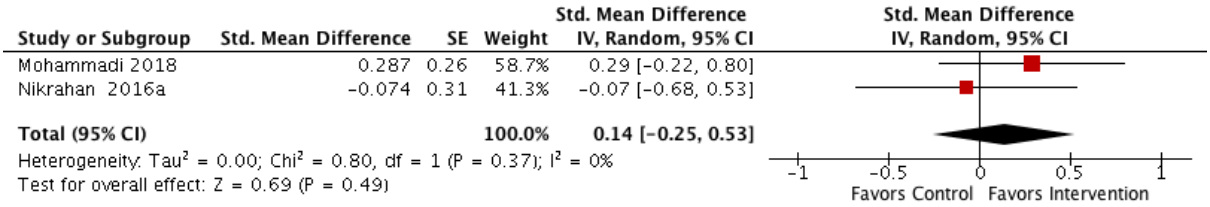
Online Figure 2D: Quality of life at the end of the intervention



Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Lv J 2016 Cognitive	74	13.4	38	75	14.2	37	7.1%	-0.07 [-0.52, 0.38]
Lv J 2016 Function	79.6	9.3	38	75	9.8	37	7.1%	0.48 [0.02, 0.94]
Lv J 2016 Psychosocial	86.9	5.7	38	80.2	6.4	37	7.0%	1.10 [0.61, 1.58]
Lv J 2016 Satisfaction	89.3	5.2	38	77.8	9.5	37	6.9%	1.49 [0.98, 2.01]
Lv J 2016 Symptoms	78.8	6.9	38	74.4	9.1	37	7.1%	0.54 [0.08, 1.00]
Nyclicek 2012 Psych	15.14	0.31	55	15.02	0.35	57	7.3%	0.36 [-0.01, 0.73]
Nyclicek 2012 Disease Perception	70.36	2.7	55	68.99	3.02	57	7.3%	0.47 [0.10, 0.85]
Nyclicek 2012 Physical	14.49	0.4	55	15.16	0.45	57	7.2%	-1.56 [-1.99, -1.14]
Nyclicek 2012 Physical Limitations	80.69	2.46	55	80.81	2.74	57	7.3%	-0.05 [-0.42, 0.32]
Nyclicek 2012 Social	15.51	0.31	55	14.69	0.45	57	7.1%	2.10 [1.64, 2.57]
O'Neil 2014 Overall Mental	44.8	11	53	41.3	11.8	53	7.3%	0.30 [-0.08, 0.69]
O'Neil 2014 overall physical	38	9.2	53	35.9	10.4	53	7.3%	0.21 [-0.17, 0.59]
Rakowska 2015 Mental	58.99	5.83	41	53.21	2.29	40	7.0%	1.29 [0.81, 1.77]
Rakowska 2015 Physical	63.72	4.9	41	61.69	4.91	40	7.1%	0.41 [-0.03, 0.85]
Total (95% CI)			**653**			**656**	**100.0%**	**0.50 [0.07, 0.93]**

Heterogeneity: $Tau^2 = 0.62$; $Chi^2 = 182.93$, df = 13 ($P < 0.00001$); $I^2 = 93\%$
Test for overall effect: Z = 2.28 (P = 0.02)

Online Figure 2E: Dispositional hope at the end of the intervention



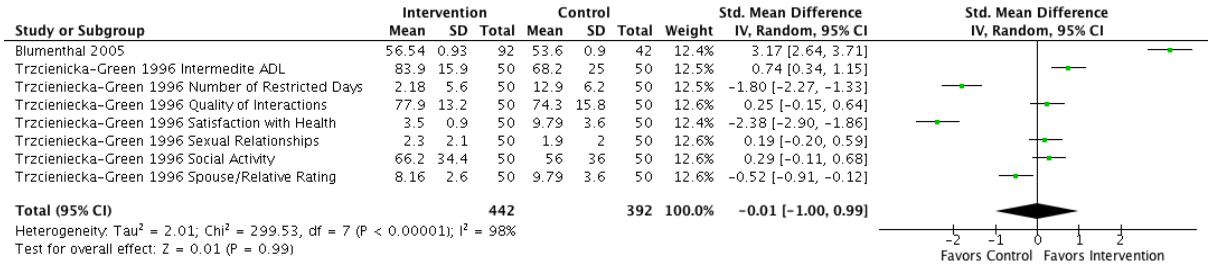
Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
Mohammadi 2018	0.287	0.26	58.7%	0.29 [-0.22, 0.80]
Nikrahan 2016a	-0.074	0.31	41.3%	-0.07 [-0.68, 0.53]
Total (95% CI)			**100.0%**	**0.14 [-0.25, 0.53]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.80$, df = 1 ($P = 0.37$); $I^2 = 0\%$
Test for overall effect: Z = 0.69 (P = 0.49)

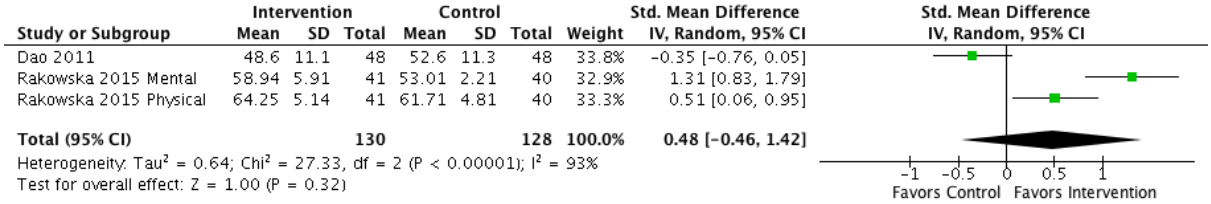
Online Figure 3: Effect of psychological interventions at the end of follow-up on secondary outcomes

Online figure 3 includes forest-plots showing the effect of psychological intervention on daily activities (online figure 3A), quality of life (online figure 3B), and dispositional hope (online figure 3C) at the end of follow-up.

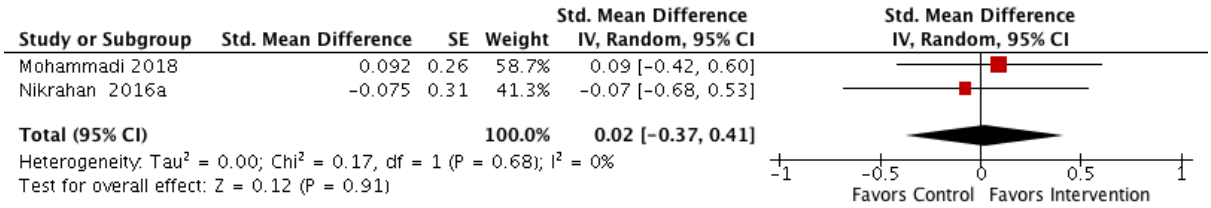
Online Figure 3A: Daily activities at the end of follow-up



Online Figure 3B: Quality of life at the end of follow-up



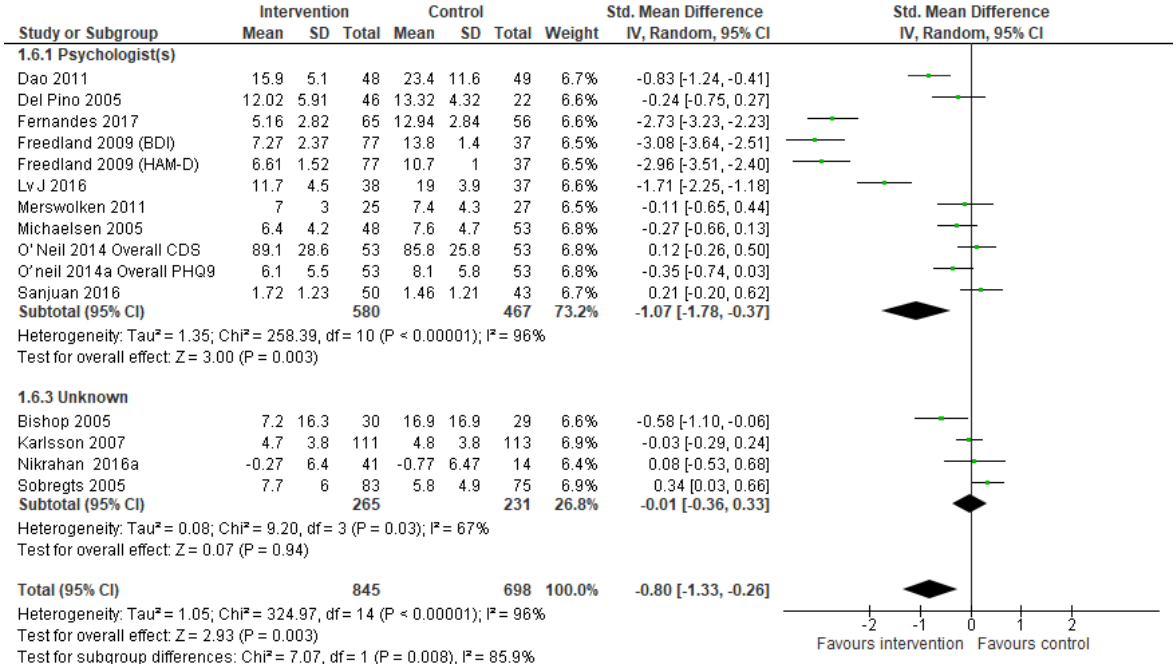
Online Figure 3C: Dispositional hope at the end of follow-up



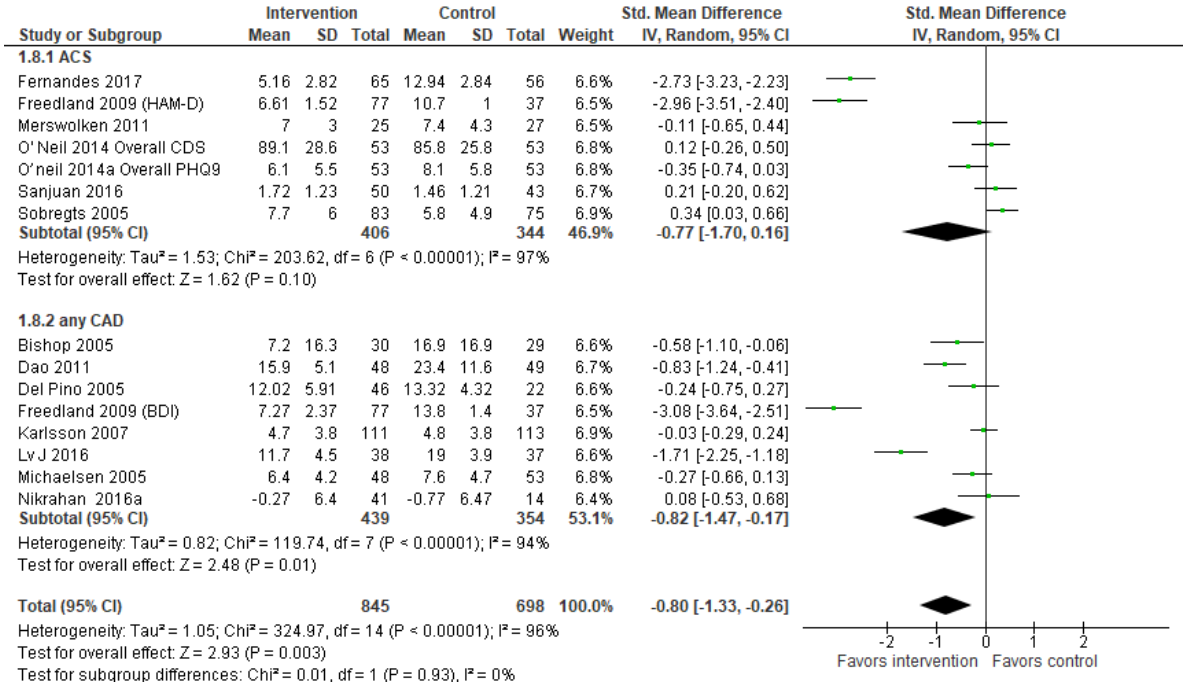
Online Figure 4: Subgroups analyses of depression at the end of the intervention

Online figure 4 includes forest-plots showing the effects of psychological interventions compared to control groups on depression immediately after treatment across the two pre-specified subgroups analyses: provider of intervention (online figure 4A), type of population (online figure 4B), type of PI (CBT and PPT (online figure 4C), post-treatment assessment time (online figure 4D), and session type (online figure 4E).

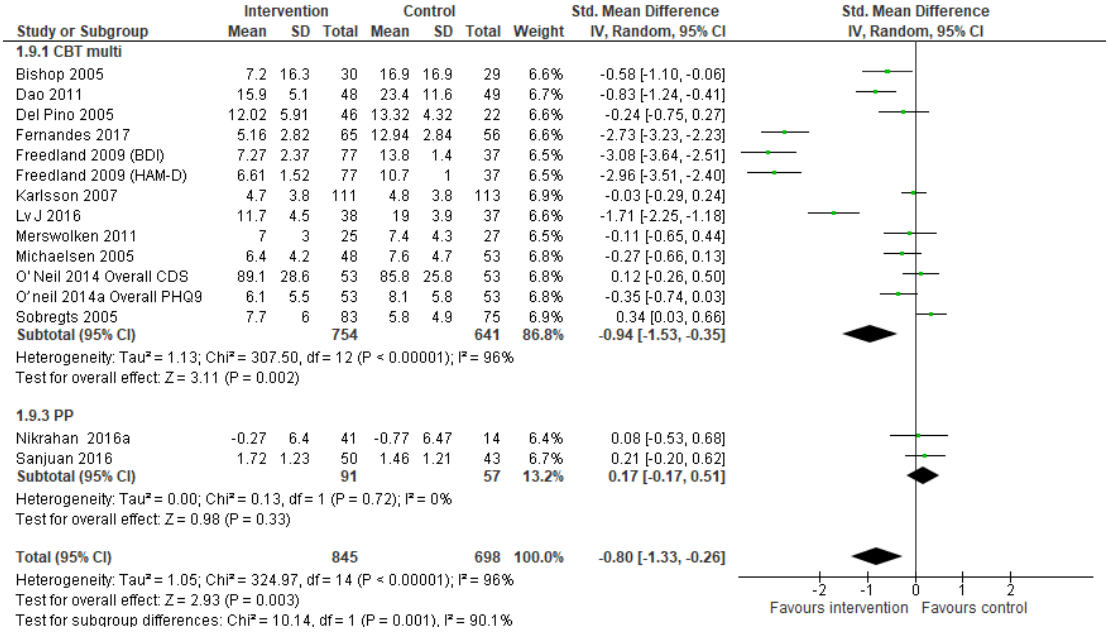
Online Figure 4A: Depression at the end of the intervention subgroup by provider of intervention (psychologist and unknown)



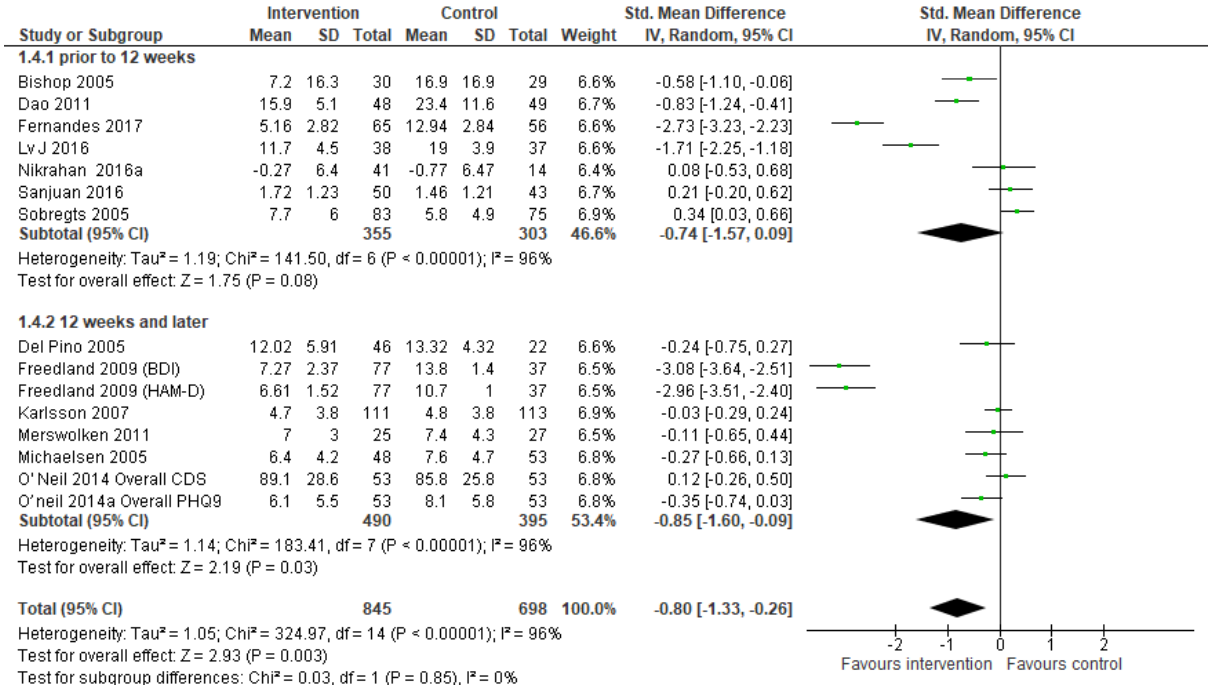
Online Figure 4B: Depression at the end of the intervention subgroup by type of population (any CAD included both chronic and acute CAD patients)



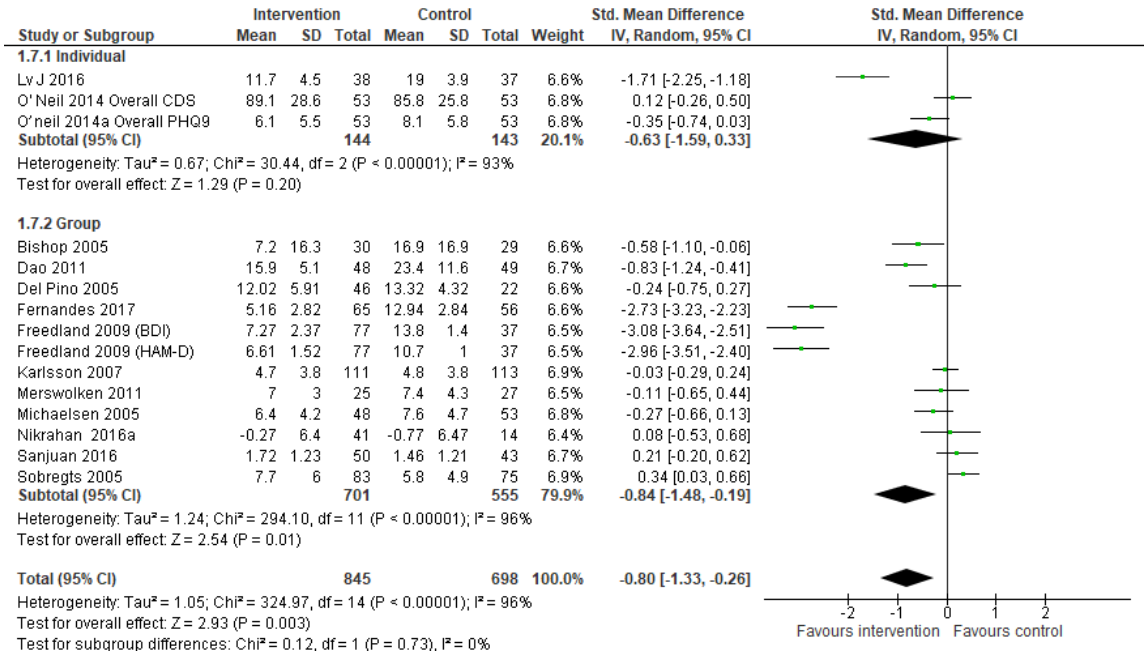
Online Figure 4C: Depression at the end of the intervention subgroup by type of PI (CBT vs. PPT)



Online Figure 4D: Depression at the end of the intervention subgroup by post-treatment assessment time (>12 weeks and <12 weeks)



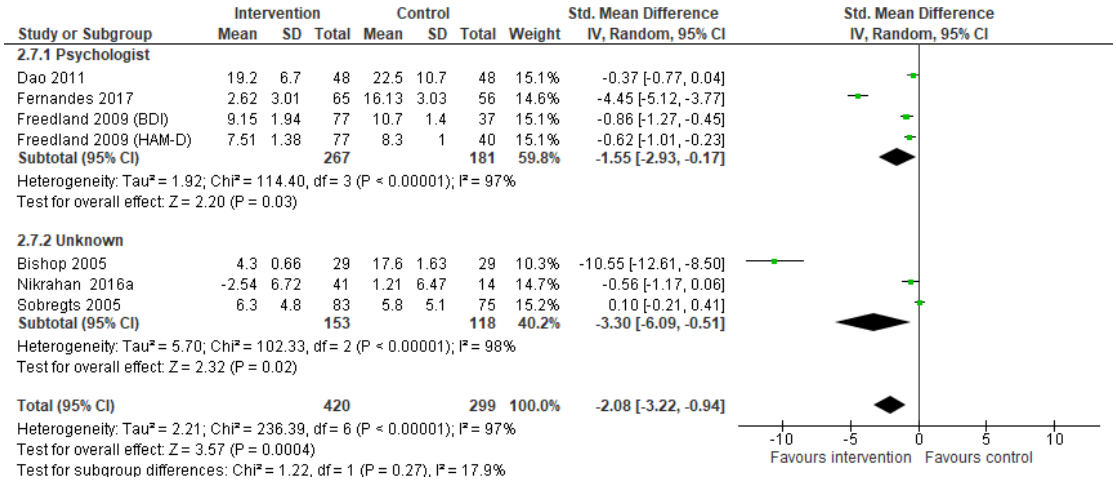
Online Figure 4E: Depression at the end of the intervention subgroup by session type (individual and group)



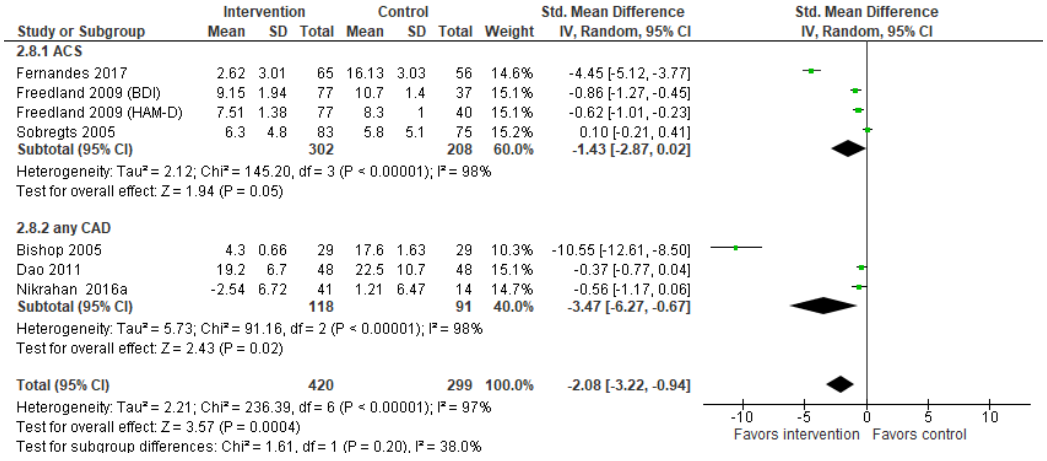
Online Figure 5: Subgroups analyses of depression at the end of follow-up

Online figure 5 includes forest-plots showing the effects of psychological interventions compared to control groups on depression at the end of follow-up across the two pre-specified subgroups analyses: provider of intervention (online figure 5A), type of population (online figure 5B), and follow-up assessment time (online figure 5C).

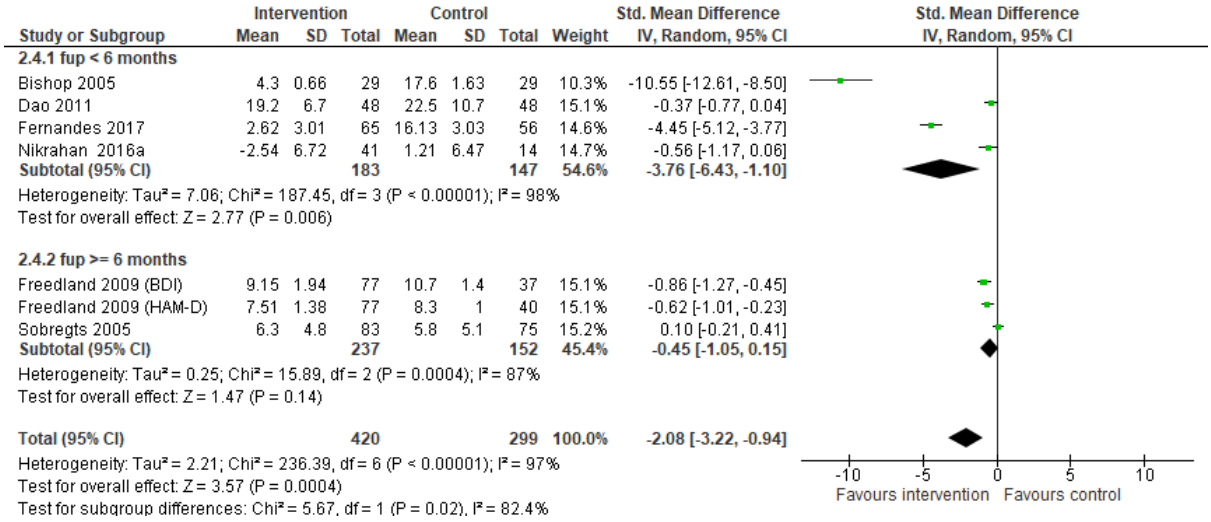
Online Figure 5A: Depression at the end follow-up subgroup by provider of intervention (psychologist and unknown)



Online Figure 5B: Depression at the end of follow-up subgroup by type of population (any CAD included both chronic and acute CAD patients)



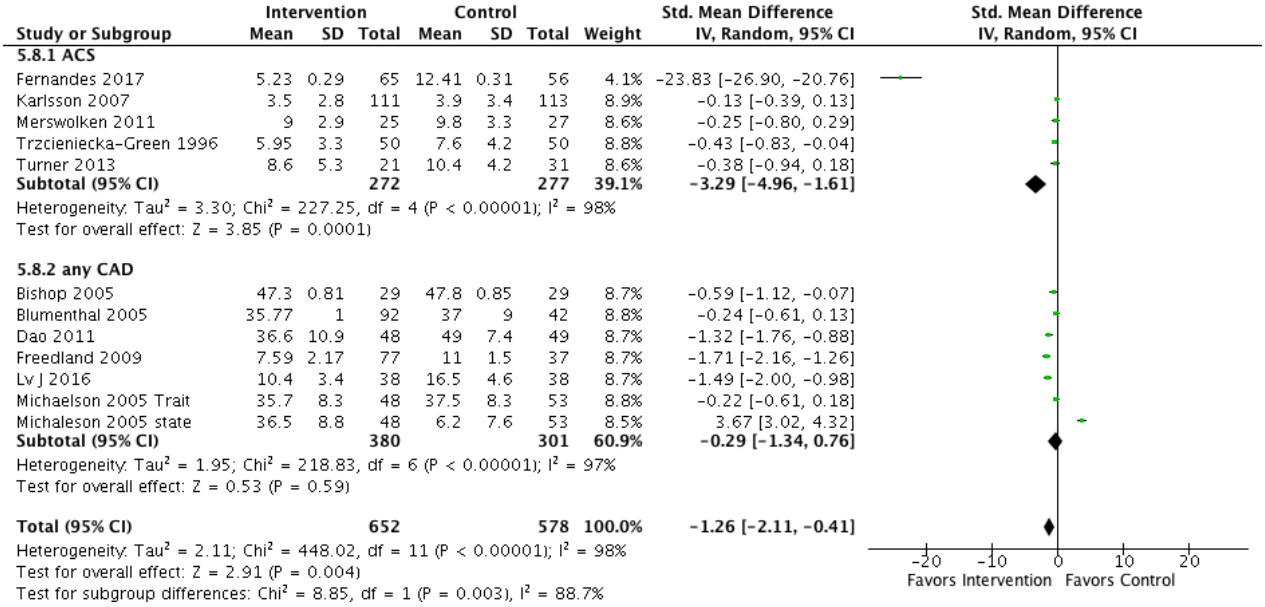
Online Figure 5C: Depression at the end of follow-up subgroup follow-up assessment time (<6 months and >6 months)



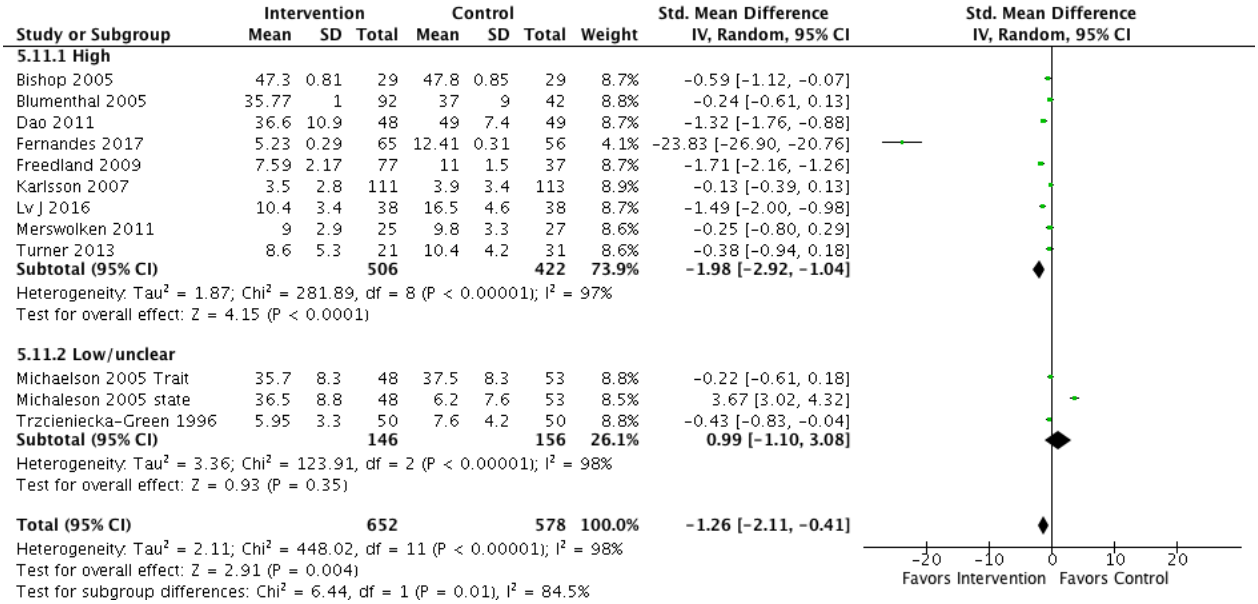
Online Figure 6: Subgroups analyses of anxiety at the end of the intervention

Online figure 6 includes forest-plots showing the effects of psychological interventions compared to control groups on anxiety immediately after treatment across the two pre-specified subgroups analyses: type of population (online figure 6A), risk of bias (online figure 6B), post-treatment assessment time (online figure 6C), and session type (online figure 6D).

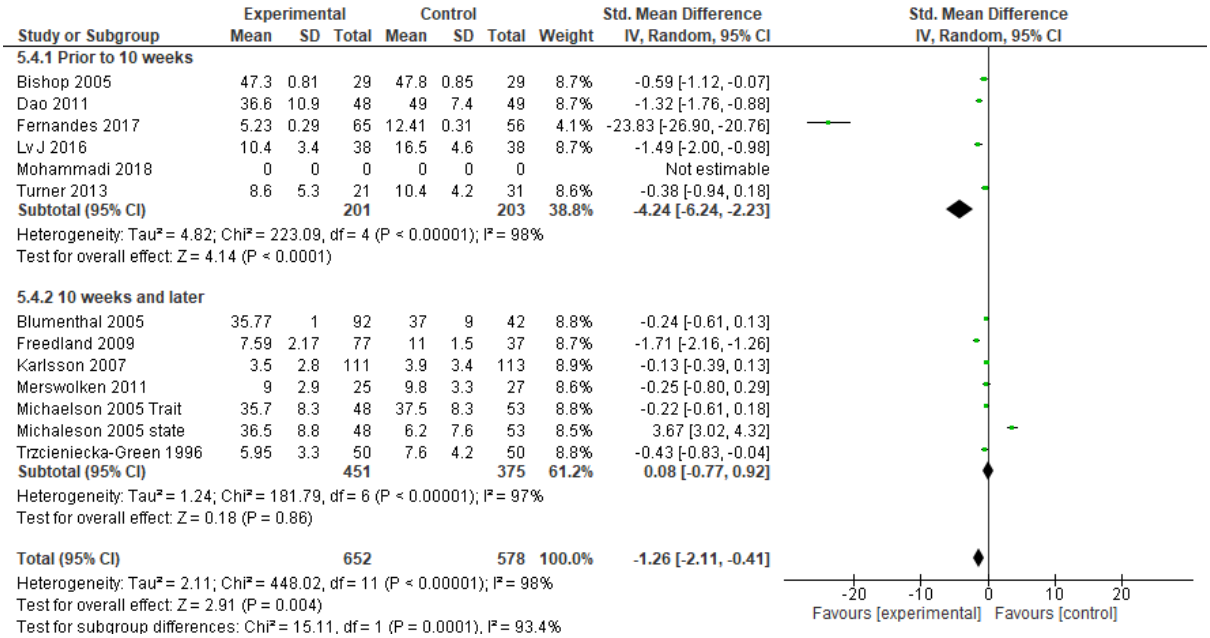
Online Figure 6A: Anxiety at the end of the intervention subgroup by type of population (any CAD included both chronic and acute CAD patients)



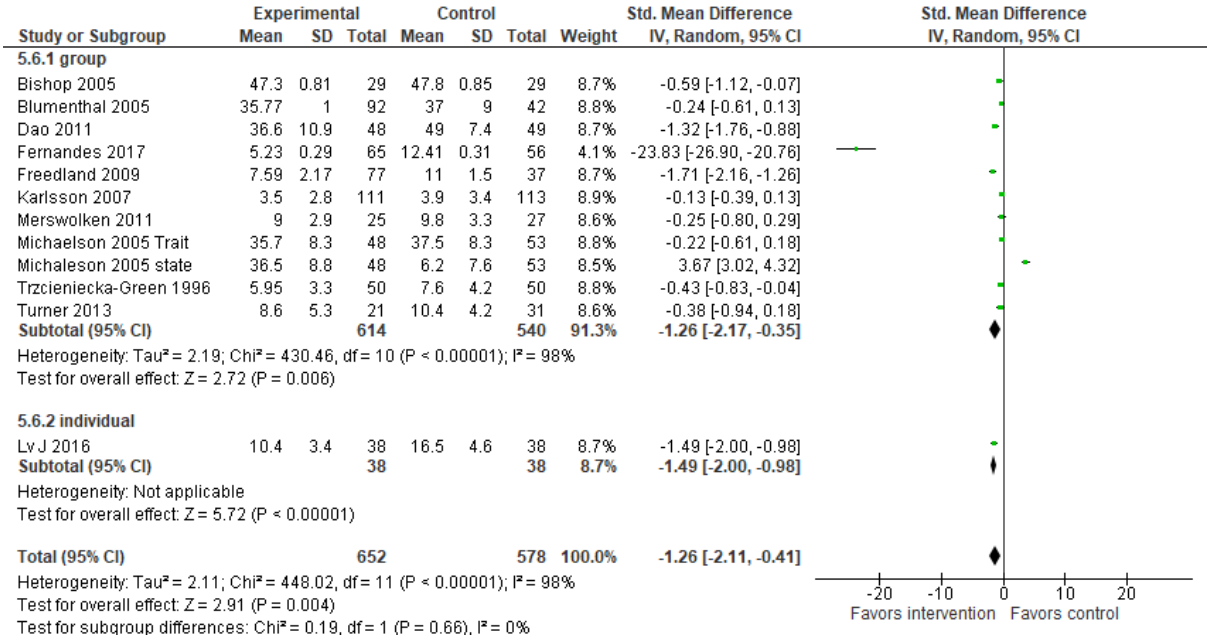
Online Figure 6B: Anxiety at the end of the intervention subgroup by risk of bias (low and high or unclear risk of bias)



Online Figure 6C: Anxiety at the end of the intervention subgroup by post-treatment assessment time (>10 weeks and <10 weeks)



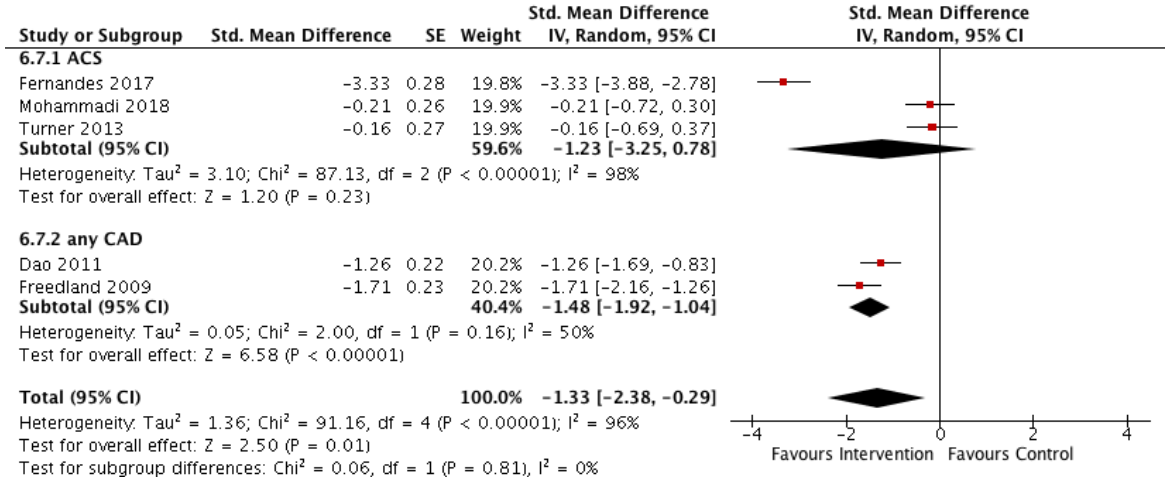
Online Figure 6D: Anxiety at the end of the intervention subgroup by session type (group and individual)



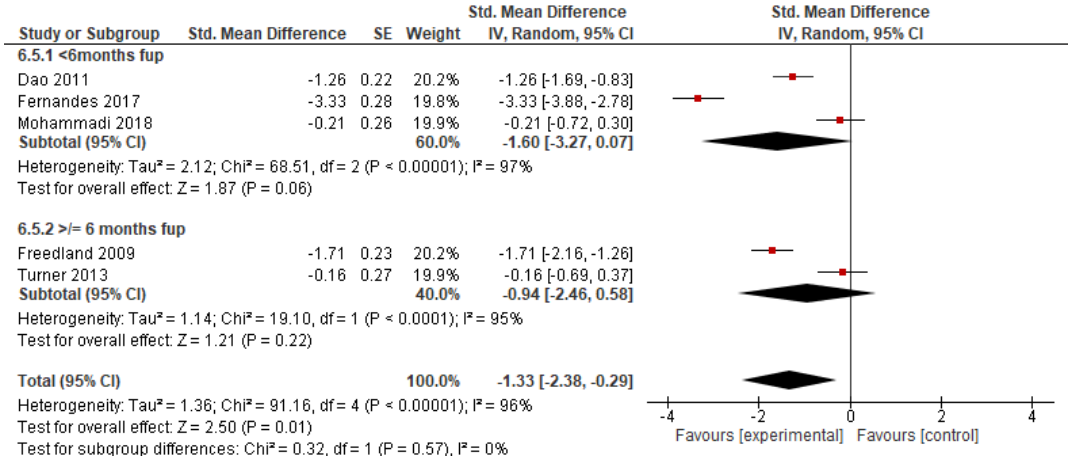
Online Figure 7: Subgroup analysis of anxiety at the end of follow-up

Online figure 7 includes forest-plot showing the effects of psychological interventions compared to control groups on anxiety at the end of follow-up across the pre-specified subgroup analysis by type of population (online figure 7A), and assessment follow-up time (online figure 7B).

Online Figure 7A: Anxiety at the end of follow-up subgroup by type of population (any CAD included both chronic and acute CAD patients)



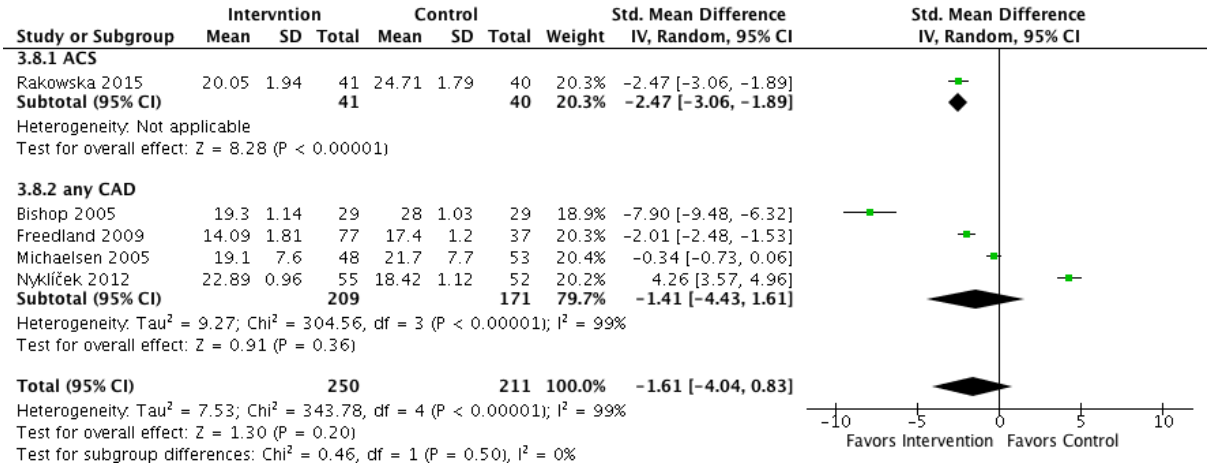
Online Figure 7B: Anxiety at the end of follow-up subgroup by assessment follow-up time (<6 months and >6 months)



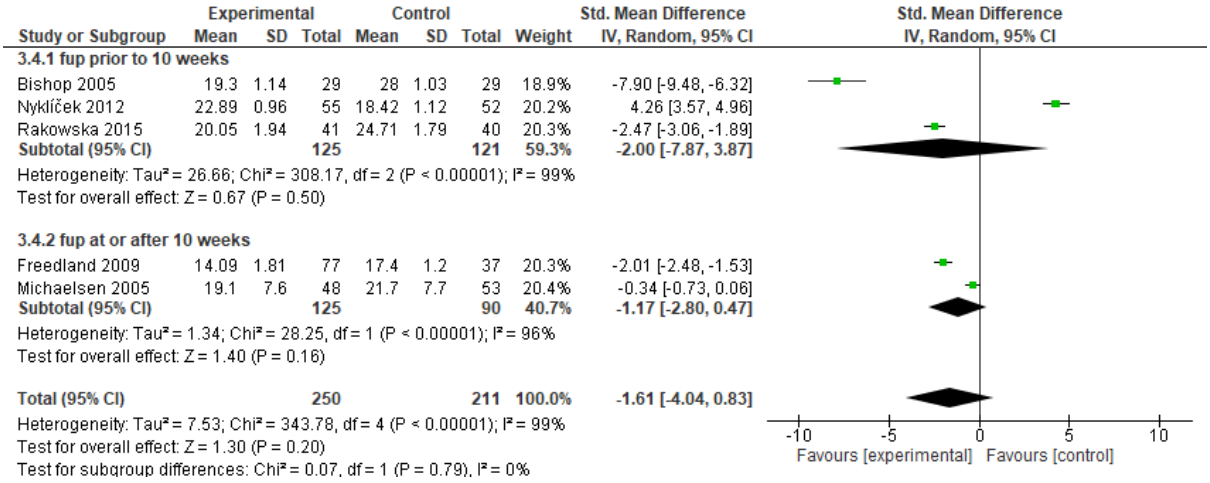
Online Figure 8: Subgroup analysis of stress at the end of post-treatment

Online figure 8 includes forest-plot showing the effects of psychological interventions compared to control groups on stress at the end of treatment across the pre-specified subgroup analysis by type of population (online figure 8A), post-treatment assessment time (online figure 8B), and session type (online figure 8C).

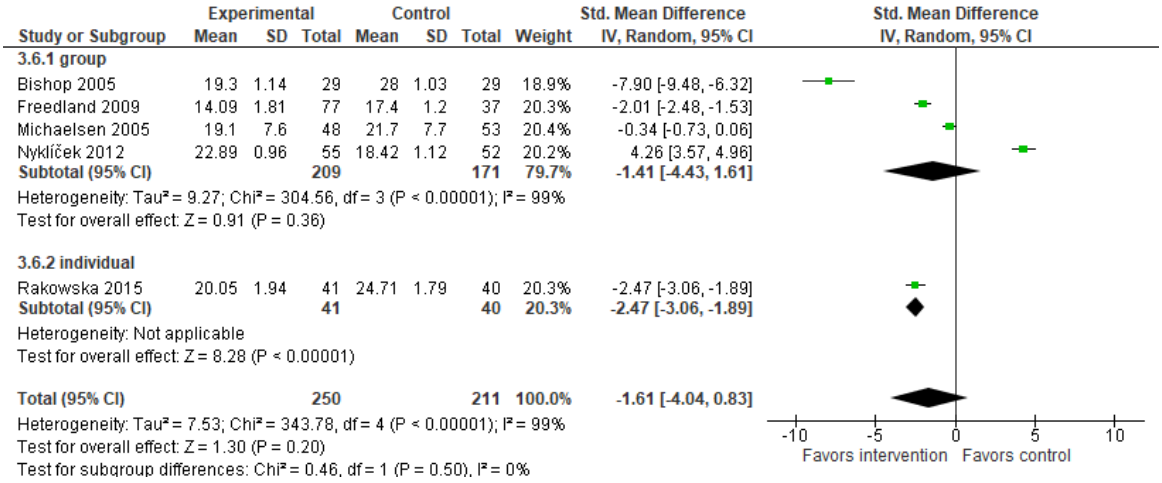
Online Figure 8A: Subgroup analysis of stress at the end treatment by type of population (any CAD included both chronic and acute CAD patients)



Online Figure 8B: Subgroup analysis of stress at the end of treatment by post-treatment assessment time (<10 weeks and >10 weeks)

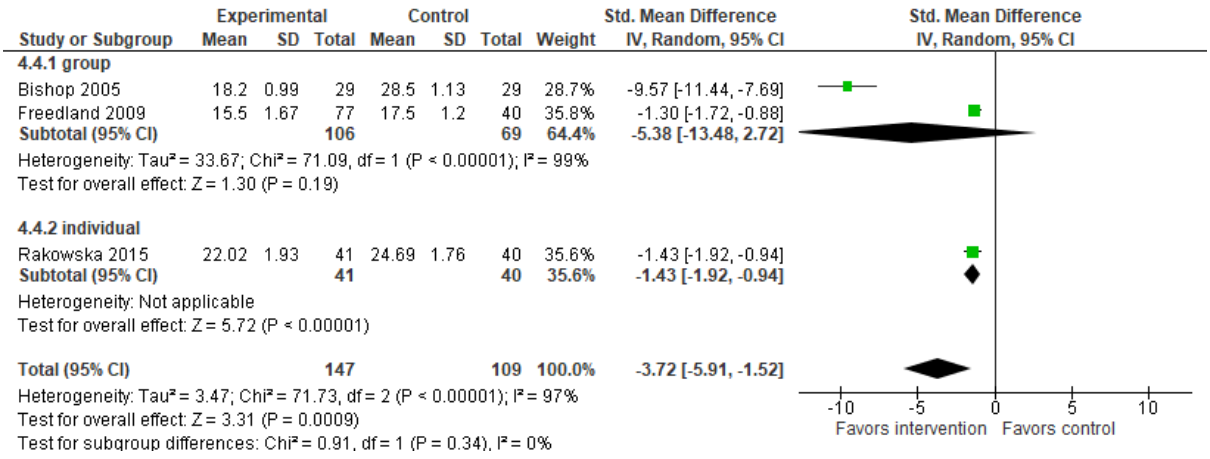


Online Figure 8C: Subgroup analysis of stress at the end by session type (group and individual)



Online Figure 9: Subgroup analysis of stress at the end of follow-up by session type (group and individual)

Online figure 9 includes forest-plot showing the effects of psychological interventions compared to control groups on stress at the end of follow-up across the pre-specified subgroup analysis by session type.



EFFICACY OF PSYCHOLOGICAL INTERVENTIONS ON PSYCHOLOGICAL OUTCOMES IN CORONARY ARTERY DISEASE: SYSTEMATIC REVIEW AND META-ANALYSIS

Brief title: Meta-analysis of psychological interventions in CAD

Inés Magán, PhD[a]; Laura Casado, MS[a]; Rosa Jurado-Barba, PhD[a, b]; Haley Barnum, PharmD[c]; Marta M. Redondo, PhD[a]; Adrian V. Hernandez, MD, PhD[c, d]; Héctor Bueno, MD, PhD[b, e, f]

[a]Department of Psychology, Facultad de Educación y Salud, Universidad Camilo José Cela, Madrid, Spain; [b]Instituto de Investigación Biomédica del Hospital 12 de Octubre (Imas12), Madrid, Spain, [c]Health Outcomes, Policy, and Evidence Synthesis (HOPES) Group, University of Connecticut School of Pharmacy, Storrs, CT, USA; [d]Vicerrectorado de Investigacion, Universidad San Ignacio de Loyola (USIL), Lima, Peru; [e]Department of Cardiology, Hospital Universitario 12 de Octubre, Madrid, Spain; [f]Multidisciplinary Translational Cardiovascular Research Group, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain.

Corresponding author: Inés Magán. Universidad Camilo José Cela. Education and Health Faculty. Department of Psychology. C/ Castillo de Alarcón, 49. Urb. Villafranca del Castillo. 28962 – Madrid (Spain). Phone: +34 918153131. E-mail: imagan@ucjc.edu

Total word count (Intro to Discussion): 4708

ABSTRACT

Background: The benefits of cognitive-behavioral treatment (CBT) and positive psychology therapy (PPT) in patients with cardiovascular disease are still not well defined. We assessed the efficacy of CBT and PPT on psychological outcomes in coronary artery disease (CAD) patients.

Methods: Randomized controlled trials evaluating CBT or PPT in CAD patients published until May 2018 were systematically analyzed. Primary outcomes were depression, stress, anxiety, anger, happiness and vital satisfaction. Random effects meta-analyses using the inverse variance method were performed. Effects were expressed as standardized mean difference (SMD) or mean differences (MD) with their 95% confidence intervals (CIs); risk of bias was assessed with the Cochrane tool.

Results: Nineteen trials were included (n=1956); sixteen evaluated CBT (n=1732), and three PPT (n=224). Compared with control groups, depressive symptoms (13 trials; SMD -0.80; 95%CI, -1.33, -0.26) and anxiety (11 trials; SMD -1.26; 95%CI, -2.11, -0.41) improved after the PI, and depression (6 trials; SMD -2.08; 95%CI, -3.22, -0.94), anxiety (5 trials; SMD -1.33; 95%CI, -2.38, -0.29), and stress (3 trials; SMD -3.72; 95%CI, -5.91, -1.52) improved at the end of follow-up. Vital satisfaction was significantly increased at follow-up (MD 1.30, 0.27, 2.33). Non-significant effects on secondary outcomes were found. Subgroup analyses were consistent with overall analyses.

Conclusion: CBT and PPT improve several psychological outcomes in CAD patients. Depression and anxiety improved immediately after the intervention while stress and vital satisfaction improve in the mid-term. Future research should assess the individual role of CBT and PPT in CAD populations.

Keywords: Psychological intervention, cognitive-behavioral treatment, positive psychology therapy, coronary artery disease, psychological outcomes, meta-analysis.

Abbreviations list: PIs = psychological interventions; CBT = cognitive-behavioral treatment; PPT = positive psychology therapy; CAD = coronary artery disease; IHD = ischemic heart disease; RCTs = randomized controlled trials; SMD = standardized mean difference; MD = mean differences; 95%CI = 95% Confidence Interval; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Introduction

The optimal care for patients with acute or chronic coronary artery disease (CAD) needs a multi-disciplinary approach to reduce morbidity and mortality, improve symptoms and quality of life. There is reasonable evidence for the beneficial effect of a variety of interventions, including medical therapies, coronary revascularization, cardiac rehabilitation programs or lifestyle changes, such as quit smoking, healthy diet and physical activity (Fihn et al., 2014; Knuuti et al., 2020).

A comprehensive approach to improving the care for these patients should consider the psychological impact of the disease, including behavioral and several psychological factors, such as depression, anxiety, stress or anger, which have been empirically linked to increases in cardiovascular risk (Chida & Steptoe, 2009; Nicholson, Kuper, & Hemingway, 2006; Roest, Martens, de Jonge, & Denollet, 2010; Rozanski, 2014) and lower quality of life (Appels et al., 2006). Several psychological interventions (PIs) have been tested in this context and positive results have been described in narrative reviews (Linden, 2000, 2013) and meta-analyses (Linden *et al.* 2007; Dickens *et al.* 2013; Rutledge *et al.* 2013; Richards *et al.* 2018).

However, the routine use of PIs in cardiac rehabilitation programs remains controversial because, while these are recommended (Knuuti et al., 2020) and implemented in high income countries (Abreu et al., 2019; Supervia et al., 2019), this is not the case everywhere (Moghei, Oh, Chessex, & Grace, 2019; Poffley et al., 2017). Controversies, such as which specific treatment components should be included, the type and duration of interventions, professional involved, duration of follow-up, and specific endpoints, may contribute to the limited inclusion of PIs in cardiac rehabilitation programs (Linden, 2013), and may explain in part why PIs have shown beneficial effects in CAD patients but with modest effects (Dickens et al., 2013; Linden, 2000,

2013; Linden et al., 2007; Richards et al., 2018; Rutledge et al., 2013). This may also be due to the use of different definitions or types of PIs. Although cognitive-behavioral treatment (CBT)-based PIs have been suggested as the most effective for CAD patients (Linden, 2013), with two exceptions (Dickens et al., 2013; Linden et al., 2007), a number of meta-analyses included broader categories of PIs, such as those based on not well-established paradigms, mixed PIs, and psychopharmacological treatments (Richards et al., 2018; Rutledge et al., 2013). Finally, only negative psychological outcomes were assessed (Dickens et al., 2013; Linden, 2000, 2013; Linden et al., 2007; Richards et al., 2018; Rutledge et al., 2013).

Cardiovascular positive health (Labarthe et al., 2016), a new concept based on the positive psychology paradigm (Seligman, Steen, Park, & Peterson, 2005) has emerged recently. It focuses on positive psychological factors, mainly dispositional optimism, happiness, positive emotions, sense of purpose or vital satisfaction, as potentially having a role in reducing cardiovascular risk (Boehm & Kubzansky, 2012; DuBois et al., 2015; Labarthe et al., 2016). Positive effects have been reported for some PIs based on the positive psychology therapy paradigm (PPT) in cardiac rehabilitation patients (Bolier et al., 2013; Huffman et al., 2016) but only in small trials, not considered in prior meta-analyses (Dickens et al., 2013; Linden, 2000, 2013; Linden et al., 2007; Richards et al., 2018; Rutledge et al., 2013).

The aim of this systematic review and meta-analysis was to evaluate the evidence supporting the efficacy of PIs on improving negative psychological outcomes (depression, anxiety, stress, and anger) as well as positive outcomes (happiness and vital satisfaction), specifically in patients with CAD, including only studies testing the efficacy of empirically supported psychological techniques based on CBT and/or PPT.

Methods

This systematic review was conducted in accordance to the Cochrane Handbook for systematic reviews of interventions (Higgins & Green, 2011) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (Moher, Liberati, Tetzlaff, & Altman, 2009).

Study search and selection criteria

We searched PubMed, PsycInfo, Scopus, The Web of Science, and Cochrane Library for randomized controlled trials (RCTs) evaluating PIs in patients with coronary artery disease (CAD) or ischemic heart disease (IHD). The keywords used were *coronary artery disease*, *ischemic heart disease*, *acute coronary syndrome, psychological treatment, psychological intervention, cognitive-behavioral therapy and positive psychology intervention*. The search strategy for all databases is available in the Supplementary material. No language limitations were imposed. In addition, we also searched reference lists of papers. The searches were done twice: First on May 2017 and an update in May 2018. We excluded case reports, editorials, meta-analyses, narrative reviews and proceeding studies. Studies were eligible for inclusion if they met the following criteria: RCTs in humans including patients with CAD or IHD; the PIs and psychological techniques used in these therapies were based on CBT or PPT; and at least one of the psychological endpoints considered in this meta-analysis was reported. Exclusion criteria were: studies in which patient assignation to treatment conditions were not randomized or where there was not control group; PIs based on any treatment approach different to CBT or PPT; studies not describing the specific techniques used in their PIs; and when the treatment strategy only included physical exercise and educational or counselling programs. Selected studies were

saved and screened using Mendeley (Reference Management Software & Researcher Network). Titles and abstracts of the citations identified from the searches were examined by three reviewers independently (IM, RJ and LC) and disagreements were resolved by discussion.

Types of interventions

Two different types of PIs were considered: CBT and PPT paradigm. Both were PIs done in cardiac rehabilitation programs delivered by health professionals, including only adults diagnosed with CAD or IHD. We defined CBT as empirically supported PI based on the idea that learning principles and cognitions play a key role in human behavior and affective experience (Blagys & Hilsenroth, 2002), with an aim to reduce psychological distress and promoting an adaptive behavior in daily living by developing skills to manage physiological arousal and negative emotions, modifying dysfunctional beliefs and/or coping; CBT involves techniques such as relaxation training, emotion regulation, cognitive restructuring, problem-solving therapy, and/or relapse prevention (Blagys & Hilsenroth, 2002). PPT were defined as PIs focused on intervening on positive psychological dimensions and traits, such as positive emotions, vital satisfaction, dispositional optimism, happiness, or purposes of life and their link to well-being, and therefore aimed at developing individual strengths and not just correcting weaknesses through specific empirically supported positive techniques, such as gratitude training, three good things in life, developing you at your best or identifying and using signature strengths among others (Lee Duckworth, Steen, & Seligman, 2005; Seligman et al., 2005). PIs based on other psychological paradigms (e.g. psychodynamic, social learning theory, etc.) were excluded. Control groups were defined as those receiving usual cardiac rehabilitation, which could only include specific educational and/or physical activity training programs and medical treatment.

Psychological outcomes

Primary outcomes were depression, anxiety, stress, anger, vital satisfaction and happiness. Secondary outcomes included negative affect, positive affect, hostility, daily activities, quality of life, and dispositional hope. These psychological outcomes were assessed by psychological self-report questionnaires designed specifically to quantify these psychological factors with adequate psychometric criteria. Outcomes were measured at the end of intervention (post-treatment) and/or at the end of the pre-specified follow-up time when this was longer than the intervention.

Data extraction

Three reviewers carried out data extraction independently and recorded on a Microsoft Excel® spreadsheet. Extracted data included year of publication, reference, patient population, study design, total patients, number of groups, type, techniques and description of PIs, intervention duration, timing of intervention after coronary event, follow-up time, and primary and secondary outcomes (as reported by authors) per intervention arm. After data extraction, two investigators (AVH and HBa) checked for the accuracy of extractions.

Risk of bias assessment

We used the Cochrane Collaboration's risk of bias assessment tool (Higgins & Green, 2011). The risk of bias was evaluated with the following items: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. Four reviewers (IM, RJ, LC, HBa) evaluated risk of bias independently and labeled each study of having low, high, or unclear

risk of bias. Trials with high risk of bias in any of the items of randomization or blinding were rated as having high risk of bias. Any disagreement was resolved by a senior investigator (AVH).

Statistical analysis

For studies reporting medians (m) and interquartile ranges (IQR), means were estimated by x=(a+2m+b)/4, where m is median and a and b are P25 and P75, respectively (Higgins & Green, 2011). SDs were estimated using SD=IQR/1.35. When median and ranges were provided, the mean was estimated by x=(a+2m+b)/4 using the values of the median (m), the smallest and largest value (a and b, respectively); SD was estimated by SD=range/4 if sample size was <70 and SD=range/6 if sample size was >70 (Higgins & Green, 2011).

In our analyses, both CBT and PPT were combined as one PI arm. We used random effects meta-analyses and the inverse variance method. The DerSimonian and Laird method was used to calculate the tau estimator of heterogeneity. Effects of PIs vs controls on primary and secondary psychological outcomes were expressed as mean difference (MD) or standardized mean difference (SMD) and its 95% confidence interval (95%CI). SMDs were used as we anticipated different scales to measure primary and secondary outcomes across studies. To interpret SMD we used the guidelines of Cohen (Cohen, 1988): 0.2 was a small, 0.5 moderate, and 0.8 large difference. The analyses of outcomes were adjusted for baseline characteristics.

The degree of statistical heterogeneity was quantified with the inconsistency (I^2) metric (Higgins, Thompson, Deeks, & Altman, 2003). A low, moderate and high degree of heterogeneity was defined as I^2 proportion of <30%, 30-60%, and >60%, respectively. We performed a number of pre-specified subgroup analyses per outcome: type of PI (CBT vs PPT), type intervention provider (psychologist vs unknown), post-treatment assessment (<10-12 weeks vs >10-12 weeks) and follow-up assessment time (< 6 months vs > 6 months), session type

(group vs individual), type of CAD patient (acute coronary syndrome –ACS– vs any CAD, i.e. both acute and chronic CAD), and risk of bias (high vs low/unclear). Small study effects were evaluated with the funnel plot, and tested with the Egger's test of funnel plot asymmetry (Higgins & Green, 2011). Statistical analyses were conducted using Review Manager (RevMan 5.3; Cochrane Collaboration).

Results

Selection of studies

We identified 2556 publications. After removing duplicates and screening titles and abstracts, 395 articles were selected for full text evaluation (**Figure 1**). Forty-four trials potentially had relevant information, and finally 19 trials (n=1956) were found to have outcomes of interest. These 19 trials were reported in 20 studies (**Table 1**) (Bishop et al., 2005; Blumenthal et al., 2005; Dao et al., 2011; del Pino et al., 2005; Fernandes et al., 2017; Freedland et al., 2009; Karlsson et al., 2007; Lv et al., 2016; Merswolken et al., 2011; Michalsen et al., 2005; Mohammadi et al., 2018; Murphy et al., 2013; Nikrahan et al., 2016; Nyklíček et al., 2014; O'Neil et al., 2015, 2014; Rakowska, 2015; Sanjuan et al., 2016; Sebregts et al., 2005; Trzcieniecka-Green & Steptoe, 1996). The results of one trial were reported separately in two publications (O'Neil et al., 2015, 2014).

Characteristics of included studies

Table 1 summarizes the main characteristics of included studies. Studies were published between 1996 and 2018. Mean patient's age was generally older than 50 years old. Most of studies had small populations, <100 patients per arm in most cases. Trials included patients after

an ACS event or were chronic CAD patients or had a combination of acute and chronic CAD patients. No studies included only chronic CAD patients. CBT interventions were heterogeneous across trials, mostly multicomponent and in person with the only exception of the trials by O´Neil et al. (2014, 2015) where the PIs were performed by telephone. Three trials evaluated PPTs (Mohammadi et al., 2018; Nikrahan et al., 2016; Sanjuan et al., 2016) and there was also heterogeneity of this type of intervention among studies. Interventions lasted between one week (Fernandes et al., 2017) and 12 months (Karlsson et al., 2007). Depression, anxiety and stress were the outcomes more frequently reported, both after the intervention and at the end of follow-up. The time intervals defining post-treatment (at the end of the intervention) and end of follow-up showed high variability across RCTs, with post-treatment time ranging from 2-3 days (Fernandes et al., 2017) to one year (Karlsson et al., 2007; Michalsen et al., 2005), and follow-up assessment ranging from 3-4 weeks (Dao et al., 2011) to 2.5 years (Rakowska, 2015).

Risk of bias assessment

Sixteen trials had high risk of bias due to lack of blinding of patients or personnel, or due to the used of wrong randomization methods (**Online Figure 1**). Only three RCTs (Michalsen et al., 2005; Mohammadi et al., 2018; Trzcieniecka-Green & Steptoe, 1996) had an overall low risk of bias. About 55% of trials had incomplete outcome data, and about 20% had selective reporting of outcomes.

Effect of psychological interventions on primary outcomes

Meta-analyses assessing depression showed that, compared with controls, PIs significantly decrease depressive symptoms not only immediately after the intervention (13 trials, n=1543; SMD -0.80, 95%CI -1.33, -0.26, p=0.003) but also at the end of follow-up (6 trials,

n=719; and SMD -2.08, 95%CI -3.22, -0.94, p=0.0004) (**Figures 2A and 3A**). Similarly, anxiety significantly decreased both immediately after the PIs and at the end of follow-up (11 trials, n=1230; SMD -1.26, 95%CI -2.11, -0.41, p=0.004; and 5 trials, n=445; SMD -1.33, 95%CI -2.38, -0.29, p=0.01) (**Figures 2B and 3B**). However, although PIs did not decrease stress after the intervention (5 trials, n=461; SMD -1.61, 95%CI -4.04, 0.83, p=0.2) (**Figure 2C**), there was a significant reduction in stress levels at the end of follow-up (3 trials, n=256; SMD -3.72, 95%CI -5.91, -1.52, p=0.0009) (**Figure 3C**). No reduction in anger after PIs was found (3 trials, n=743; SMD -0.07, 95%CI -0.29, 0.14, p=0.5) (**Figure 2D**).

In relation to positive outcomes, although increases in vital satisfaction were not significant immediately after the two PIs (n=116; MD 1.23 points, 95%CI -1.80, 4.26, p=0.4), the improvement was significant at the end of follow-up (MD 1.30 points, 95%CI 0.27, 2.33, p=0.01) (**Figures 2E and 3D**). On the contrary, meta-analyses of the same two trials showed no effect on happiness after treatment or follow-up (MD 0.97 points, 95%CI -10.79, 12.73, p=0.9; MD 7.35 points, 95%CI -5.59, 20.29, p=0.3, respectively) (**Figures 2F and 3E**).

Effect of psychological interventions on secondary outcomes

PIs did not reduce negative affect or increased positive affect immediately after the intervention (2 trials, n=169; SMD -0.34, 95%CI -0.71, 0.03, p=0.07; and SMD 0.24, 95%CI -0.13, 0.61, p=0.2, respectively) (**Online Figures 2A and 2B**). In three trials (n=314), PIs significantly decreased hostility after the intervention (SMD -0.32, 95%CI -0.60, -0.03, p=0.03, **Online Figure 2C**), and in four trials (n=374), PIs significantly improved quality of life after the intervention (SMD 0.50, 95%CI 0.07, 0.93, p=0.02, **Online Figure 2D**). PIs did not improve daily activities (**Online Figure 3A**) or quality of life at the end of follow-up (**Online Figure 3B**),

or dispositional hope at any time (**Online Figures 2E and 3C**). For most outcomes, heterogeneity of effects was high.

Subgroup analyses

The effects of PIs on main outcomes were similar across most of pre-specified subgroups. In particular, for depression, anxiety and stress, both after treatment and at the end of follow-up (**Online Figures 4 to 9**). However, the improvement of anxiety after treatment was higher in ACS patients (5 trials, n=549; SMD -3.29, 95%CI -4.96, -1.611; p=0.0001) compared with chronic or mixed CAD patients (7 trials, n=681; SMD -0.29, 95%CI -1.34, 0.76; p=0.59; chi^2=8.85, p=0.003, **Online Figure 6A**), and in trials at high risk of bias (9 trials, n=928; SMD –1,98, 95%CI -2.92, -1.04; p=0.0001) vs. at low or unclear risk of bias (3 trials, n=302; SMD 0.99, 95%CI -1.10, 3.08, p=0.35; chi^2=6.44, p=0.01, **Online Figure 6B**). Subgroups analysis by post-treatment and follow-up assessment time, showed a larger reduction in anxiety at the end of treatment for treatment durations <10 weeks (6 trials, n=404; SMD -4.24, 95%CI -6.24, -2.23; p=0.0001) than those with a duration ≥10 weeks (7 trials, n=826; SMD 0.08, 95%CI -0.77, 0.92; p=0.004; chi^2=15.11, p=0.0001, **Online Figure 6C**). Also, larger reduction in depression were found when follow-ups were developed in the first 6 months after the intervention (4 trials, n=330; SMD -3.76, 95%CI -6.43, -1.10; p=0.006) vs. >6 months (3 trials, n=389; SMD -0.45, 95%CI -1.05, 0.15; p=0.14; chi^2=5.67, p=0.02, **Online Figure 5C**). While CBT significantly reduced depression at post-treatment (13 trials, n=302; SMD -0.94, 95%CI -1.53, -0.35; p=0.02), PPT showed a neutral effect (2 trials, n=148; SMD 0.17, 95%CI -0.17, 0.51; p=0.003; chi^2=10.14, p=0.001, **Online Figure 4C**). The improvement in depression after therapy was higher when PIs were provided by psychologists (11 trials, n=1047; SMD -1.07, 95%CI -1.78, -0.37, p=0.003) in comparison to PIs provided by undisclosed professionals (4 trials, n=496; SMD

-0.01, 95%CI -0.36, 0.33; p=0.94; chi^2=7.07, p=0.008, **Online Figure 4A**). Finally, no differences according to session type (group vs. individual) were found at any moment (**Online Figures 4E, 6D, 8C and 9**).

Discussion

Our study showed that different types of PIs can improve a number of psychological outcomes relevant for the patient´s global health and wellbeing in patients with CAD in the short- and in the mid-term. In particular, depression and anxiety improved immediately after PIs, and depression, anxiety, stress, and vital satisfaction scores significantly improved at the end of follow-up after these interventions.

Despite the relatively low number of patients and the heterogeneity of interventions, our findings show that PIs based on CBT and/or PPT are helpful in improving the patient´s psychological health, that is, improving their health in a broader way. The aims of medical therapy for CAD are improving prognosis, reducing symptoms and improving quality of life (Knuuti et al., 2020). All established interventions —i.e. medical therapy, coronary revascularization, cardiac rehabilitation— have been tested for the improvement of clinical or biological outcomes (mortality, non-fatal clinical outcomes, symptoms, such angina presentation or functional capacity) (Ponikowski et al., 2016). However, although fostering quality of life is a central target in cardiac rehabilitation interventions as it might have a positive effect on perceived wellbeing as well as on promoting treatment adherence, only a few interventions have evaluated their impact on quality of life (Riccioni et al., 2013; Stenvall et al., 2017; Weintraub et al., 2008; Zhang et al., 2018). Therefore, improving psychological outcomes is a key step for a comprehensive management of CAD from the patient´s perspective.

According to our data, PIs seemed to have positive and important effects on improving depression, anxiety and stress not only immediately after the intervention, but also at the end of follow-up. Others meta-analyses (Dickens et al., 2013; Linden, 2000, 2013; Linden et al., 2007; Richards et al., 2018; Rutledge et al., 2013) had previously shown significant effects, although of a smaller magnitude. Indeed, our results are especially relevant because the effects on the three primary psychological outcomes (depression, anxiety and stress) are not only significant but large after the intervention but the benefits increase at the end of follow-up, showing that PIs have long-lasting and robust beneficial effects, which are not explained by the mere course of time, when patients become more functional in their daily living and the cardiac event turns into something of the past. The implications of these results may be clinically relevant since depressive symptoms, anxiety or stress are considered risk factors for recurrent cardiac events or increased mortality risk (Arnold, Smolderen, Buchanan, Li, & Spertus, 2012; Carney & Freedland, 2017; Ossola, Gerra, De Panfilis, Tonna, & Marchesi, 2018; Tully et al., 2015). In addition, cardiac patients with depression or anxiety may be particularly compromised in their recovery (Nicholson et al., 2006; Roest et al., 2010; Rozanski, 2014).

Regarding positive psychological outcomes, this meta-analysis may be supporting the recently defined positive behavioral cardiology paradigm (Labarthe et al., 2016), as happiness and vital satisfaction showed large improvements after de intervention and at the end of follow-up, although only vital satisfaction was statistically significant at the end follow-up. The low statistical power probably explains the lack of significant effects. Nevertheless, these results should encourage psychologists and cardiologists to dedicate more energy and resources to the investigation of the effect of PPTs on psychological and clinical outcomes in CAD patients.

As noted above, compared to other narrative reviews (Linden 2000, 2013) and meta-analyses (Linden et al. 2007; Dickens et al. 2013; Rutledge et al. 2013; Richards et al. 2018), our

results show a larger magnitude of effects of PIs for improving psychological outcomes, which may be explained by the selection of only RCTs in which PIs were clearly based on empirically-based therapies, that is, the CBT paradigm (Linden, 2013), only done by Linden et al. (2007) and Dickens et al. (2013). The inclusion of the positive behavioral cardiology paradigm (Labarthe et al., 2016) as a well-established therapy paradigm specifically designed to improve positive psychological dimensions (Bolier et al. 2013; Lee Duckworth et al. 2005; Huffman et al. 2016; Seligman et al. 2005) is also new. Our meta-analysis, focusing specifically on the efficacy of PIs in improving psychological outcomes, both negative and positive, in CAD patients, clearly differentiates from previous studies focusing on quantifying the benefits of PIs on morbidity and mortality outcomes (Linden et al. 2007; Dickens et al. 2013; Rutledge et al. 2013; Richards et al. 2018), or their differential effects depending on distress reduction (Linden et al. 2007) or depression reduction (Rutledge et al. 2013). Only Richards et al. (2018) and Dickens et al. (2013) analyze their effects on some psychological outcomes. As PIs are specifically targeted to improve psychological outcomes, finding larger effects is no surprise, although this would not explain the differences found with the last Cochrane systematic review (Richards et al. 2018), where smaller but significant benefits on depression, anxiety and stress reduction were reported. This difference may be explained by the inclusion of all kinds of PIs, while our meta-analysis selected only RCTs based on empirically supported PIs.

Although CBT- and PPT-based PIs are specifically designed to improve negative and positive psychological outcomes, respectively, the magnitude effect of PIs might be greater in CAD patients, in whom improving psychological health and wellbeing by reducing stress and negative emotions and fostering positive psychological factors could be an important target as these are linked, respectively, to a higher (Chida & Steptoe, 2009; Nicholson et al., 2006; Roest et al., 2010; Rozanski, 2014) and lower (Boehm & Kubzansky, 2012; DuBois et al., 2015; Labarthe et

al., 2016) CV risk, as well as to a better quality of life (Appels et al., 2006). Therefore, CBT- and PPT-based PIs may have a positive impact on all-cause and CV morbidity and mortality, as changes in negative (Hamer & Malan 2010; Lovallo & Gerin 2003; Rozansky 2014; Schwartz et al. 2003; Steptoe & Kivimäki 2013; Wirtz & von Känel 2017) and positive psychological factors (Labarthe et al. 2016; Rozansky, Bavishi, Kubzansky & Cohen 2019; Steptoe, Wardle & Marmot 2005) may contribute modifying some clinical and CV parameters, according to Linden, 2013. Although the mechanisms by which changes on psychological factors may improve clinical outcomes remains unclear, it is likely that these may have a direct effect by improving CV risk factors and, indirectly, by facilitating enjoying healthier lifestyles, social and psychological functioning (Labarthe et al. 2016; Rozanski 2014; Rozanski et al. 2019; Steptoe & Kivimäki 2013; Steptoe, Wardle & Marmot 2005; Wirtz & von Känel 2017; Lovallo & Gerin 2003; Schwartz et al. 2003; Hamer & Malan 2010), and improving adherence.

Compared with PPT, CBT seems to improve depression after the intervention, which could be explained by the fact that CBT is a treatment package specifically designed to modify negative psychological factors (Blagys & Hilsenroth, 2002), such as depression, whereas PPTs are specifically aimed at improving positive psychological dimensions (Lee Duckworth et al., 2005; Seligman et al., 2005). Therefore, PPT may not be able to improve depression by itself. Unfortunately, the information is scarce and analyses could only be done for depression. Future research is needed to clarify the differential effect of CBT and PPT on CAD patients.

Furthermore, not only its role but the way PIs should be given and by whom are relevant questions. Although weak, our results show some evidence suggesting that PIs developed by well-trained health psychologists may have stronger effects. This seems to be particularly true in the effect on post-treatment depression benefits, a prevalent complication after myocardial

infarction (Pino, Zuo, Borba, Henderson, & Kalesan, 2018; Smolderen et al., 2017, 2015), what is logical as they are professionals specifically trained for it. Unfortunately, and despite its relevance, this information was lacking in a majority of the studies reviewed, which may explain the weakness of the association found. The role of the incorporation of trained health psychologists to cardiovascular care teams to improve both psychological and clinical outcomes for CAD and other high-risk patients needs further attention and prospective and rigorous evaluation.

Acute CAD patients seem to have greater benefits in anxiety reduction after PIs. This is logical as ACS is associated with acute increases in the levels of anxiety and stress after the acute phase (Xu et al., 2017). However, the benefit was observed only immediately after the intervention with no persistence at the end of follow-up. Whether this is due to the described spontaneous time-dependent improvement of these psychological situations after ACS (Xu et al., 2015) or the lack of durability of the effects of PIs needs further study.

Finally, PIs in which the follow-up assessment occurred <6 months after the intervention showed significant benefits in depression compared with those with longer follow-ups. Reductions in anxiety were also larger when the intervention duration was <10 weeks, which is consistent with the findings by Linden et al (2013), where the beneficial effects of PIs fade away with time. This points out the importance of maintenance of the benefits as one important target for PIs.

Our meta-analysis is the first one to analyze the effects of PIs on positive psychology outcomes, including only empirically-supported PIs for CAD patients (Linden et al., 2013), an inclusion criterion only in a minority of prior studies (Linden et al., 2007; Dickens et al., 2013). Our meta-analysis is also new on its exclusive focus on psychological outcomes in CAD patients while the majority of prior publications mainly focused on morbidity and mortality or on the

differential effects on these outcomes depending on distress reduction (Linden et al, 2007) or depression reduction (Rutledge et al., 2013). Only Richards et al. (2018) specifically evaluated the effects of PIs on stress, anxiety and depression, and Dickens et al. (2013) on depression, but they did not study positive psychological outcomes.

A number of limitations should be acknowledged. First, the number of studies and the absolute number of patients enrolled is small. Second, PIs included a large variety of interventions with important differences in types, methods, professionals involved and duration as well as differences in outcomes and methods to measure the results. This information is not only diverse but is often lacking. Therefore, conclusions apply to a heterogeneous group in which differences in results may be explained by a variety of reasons. Third, our study confirms the important risk of bias to which these studies are subjected due to the impossibility of blinding patients or researchers to the intervention. This limitation can only be partially overcome by the analysis of results blinded to the intervention received by each group, a technique that should be mandatory in this kind of studies. And fourth, this meta-analysis does not address the efficacy of PIs on clinical outcomes, which will be the aim of a future analysis.

Conclusion. This systematic review and meta-analysis shows that PIs are effective in improving depression and anxiety immediately after the intervention, and may have a positive impact at the end of follow-up improving also stress and the level of vital satisfaction. However, much more research is needed in the field, with higher methodological standards in the trials, including detailed information of the type of intervention, professionals involved, timing and duration. Our results suggest that there is a role of clinical and health psychology for improving the care of patients with CAD and this option should be considered in cardiology departments.

Financial support: None.

Conflicts of interest: None of the authors have conflicts of interests with public or private entities related to the content of this manuscript. Dr. Bueno receives research funding from the *Instituto de Salud Carlos III, Spain (PIE16/00021 &PI17/01799), Astra-Zeneca, BMS, Janssen and Novartis; has received consulting fees from Astra-Zeneca, Bayer, BMS-Pfizer, Novartis*; and speaking fees or support for attending scientific meetings from *Astra-Zeneca, Bayer, BMS-Pfizer, Novartis, and MEDSCAPE-theheart.org*. Dr. Jurado receives research funding from the *Ministerio de Ciencia, Innovación y Universidades, Spain (PSI2015-68851-P)*. Dr. Magán, Dr. Jurado, Dr. Redondo and Dr. Bueno have received funding from *Universidad Camilo José Cela, Madrid – Spain (2015-18)*. Dr. Hernandez receives funding from the *Agency Health Care Research and Quality (AHRQ) (HHSA290201500012I)*.

Acknowledgement: The CNIC is supported by the Instituto de Salud Carlos III (ISCIII), the Ministerio de Ciencia e Innovación and the Pro CNIC Foundation, and is a Severo Ochoa Center of Excellence (SEV-2015-0505).

References

Abreu, A., Pesah, E., Supervia, M., Turk-Adawi, K., Bjarnason-Wehrens, B., Lopez-Jimenez, F., … Grace, S. L. (2019). Cardiac rehabilitation availability and delivery in Europe: How does it differ by region and compare with other high-income countries? *European Journal of Preventive Cardiology*, *26*(11), 1131–1146. https://doi.org/10.1177/2047487319827453

Appels, A., Van, E. T., Bar, F., van der Pol, G., Erdman, R. A., Assman, M., … Pedersen, S. S. (2006). Effects of a behavioural intervention on quality of life and related variables in angioplasty patients: results of the Exhaustion Intervention Trial. *J Psychosom Res*, *61*(0022-3999 (Print)), 1–7.

Arnold, S. V., Smolderen, K. G., Buchanan, D. M., Li, Y., & Spertus, J. A. (2012). Perceived Stress in Myocardial Infarction. *Journal of the American College of Cardiology*, *60*(18), 1756–1763. https://doi.org/10.1016/j.jacc.2012.06.044

Bishop, G., Kaur, D., Tan, V., Chua, Y., Liew, S., & Mak, K. (2005). Effects of a psychosocial skills training workshop on psychophysiological and psychosocial risk in patients undergoing coronary artery bypass grafting. *American Heart Journal*, *150*(3), 602–609. Retrieved from https://doi.org/10.1016/j.ahj.2004.10.015

Blagys, M. D., & Hilsenroth, M. J. (2002). Distinctive activities of cognitive-behavioral therapy: A review of the comparative psychotherapy process literature. *Clinical Psychology Review*. https://doi.org/10.1016/S0272-7358(01)00117-9

Blumenthal, J. A., Sherwood, A., Babyak, M. A., Watkins, L. L., Waugh, R., Georgiades, A., … Hinderliter, A. (2005). Effects of Exercise and Stress Management Training on Markers of Cardiovascular Risk in Patients With Ischemic Heart Disease. *JAMA*, *293*(13), 1626.

https://doi.org/10.1001/jama.293.13.1626

Boehm, J. K., & Kubzansky, L. D. (2012). The heart's content: The association between positive psychological well-being and cardiovascular health. *Psychological Bulletin*. https://doi.org/10.1037/a0027448

Bolier, L., Haverman, M., Westerhof, G. J., Riper, H., Smit, F., & Bohlmeijer, E. (2013). Positive psychology interventions: a meta-analysis of randomized controlled studies. *BMC Public Health*, *13*(1), 119. https://doi.org/10.1186/1471-2458-13-119

Carney, R. M., & Freedland, K. E. (2017). Depression and coronary heart disease. *Nature Reviews Cardiology*, *14*(3), 145–155. https://doi.org/10.1038/nrcardio.2016.181

Chida, Y., & Steptoe, A. (2009). The Association of Anger and Hostility With Future Coronary Heart Disease. A Meta-Analytic Review of Prospective Evidence. *Journal of the American College of Cardiology*, *53*(11), 936–946. https://doi.org/10.1016/j.jacc.2008.11.044

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates. Lawrence Earlbaum Associates*. https://doi.org/http://dx.doi.org/10.1016/B978-0-12-179060-8.50008-6

Dao, T. K., Youssef, N. A., Armsworth, M., Wear, E., Papathopoulos, K. N., & Gopaldas, R. (2011). Randomized controlled trial of brief cognitive behavioral intervention for depression and anxiety symptoms preoperatively in patients undergoing coronary artery bypass graft surgery. *The Journal of Thoracic and Cardiovascular Surgery*, *142*(3), e109–e115. https://doi.org/10.1016/j.jtcvs.2011.02.046

del Pino, A., Gaos, M. T., Dorta, R., & Garcia, M. (2005). Modification of coronary-prone behaviors in coronary patients of low socio-economic status. *The Spanish Journal of*

Psychology, *8*(1), 68–78. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=15875459

Dickens, C., Cherrington, A., Adeyemi, I., Roughley, K., Bower, P., Garrett, C., … Coventry, P. (2013). Characteristics of psychological interventions that improve depression in people with coronary heart disease: A systematic review and meta-regression. *Psychosomatic Medicine*. https://doi.org/10.1097/PSY.0b013e31827ac009

DuBois, C. M., Lopez, O. V., Beale, E. E., Healy, B. C., Boehm, J. K., & Huffman, J. C. (2015). Relationships between positive psychological constructs and health outcomes in patients with cardiovascular disease: A systematic review. *International Journal of Cardiology*. https://doi.org/10.1016/j.ijcard.2015.05.121

Fernandes, A. C., McIntyre, T., Coelho, R., Prata, J., & Maciel, M. J. (2017). Brief psychological intervention in phase I of cardiac rehabilitation after acute coronary syndrome. *Revista Portuguesa de Cardiologia*, *36*(9), 641–649. https://doi.org/10.1016/j.repc.2017.01.005

Fihn, S. D., Blankenship, J. C., Alexander, K. P., Bittl, J. A., Byrne, J. G., Fletcher, B. J., … Smith, P. K. (2014). 2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease. *Journal of the American College of Cardiology*, *64*(18), 1929–1949. https://doi.org/10.1016/j.jacc.2014.07.017

Freedland, K. E., Skala, J. A., Carney, R. M., Rubin, E. H., Lustman, P. J., Davila-Roman, V. G., … Hogue, C. W. J. R. (2009). Treatment of depression after coronary artery bypass surgery: a randomized controlled trial. *Archives of General Psychiatry*, *66*(4), 387–396.

https://doi.org/10.1001/archgenpsychiatry.2009.7

Higgins, J. P., & Green, S. (2011). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]* (5.0.1). Retrieved from www.cochrane-handbook.org

Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *Bmj*, *327*(7414), 557–60. https://doi.org/10.1136/bmj.327.7414.557.

Huffman, J. C., Millstein, R. A., Mastromauro, C. A., Moore, S. V., Celano, C. M., Bedoya, C. A., … Januzzi, J. L. (2016). A Positive Psychology Intervention for Patients with an Acute Coronary Syndrome: Treatment Development and Proof-of-Concept Trial. *Journal of Happiness Studies*. https://doi.org/10.1007/s10902-015-9681-1

Karlsson, M. R., Edström-Plüss, C., Held, C., Henriksson, P., Billing, E., & Wallén, N. H. (2007). Effects of expanded cardiac rehabilitation on psychosocial status in coronary artery disease with focus on type D characteristics. *Journal of Behavioral Medicine*, *30*(3), 253–261. https://doi.org/10.1007/s10865-007-9096-5

Knuuti, J., Wijns, W., Saraste, A., Capodanno, D., Barbato, E., Funck-Brentano, C., … Clapp, B. (2020). 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *European Heart Journal*, *41*(3), 407–477. https://doi.org/10.1093/eurheartj/ehz425

Labarthe, D. R., Kubzansky, L. D., Boehm, J. K., Lloyd-Jones, D. M., Berry, J. D., & Seligman, M. E. P. (2016). Positive Cardiovascular Health: A Timely Convergence. *Journal of the American College of Cardiology*. https://doi.org/10.1016/j.jacc.2016.03.608

Lee Duckworth, A., Steen, T. A., & Seligman, M. E. P. (2005). Positive Psychology in Clinical

Practice. *Annual Review of Clinical Psychology*, *1*(1), 629–651. https://doi.org/10.1146/annurev.clinpsy.1.102803.144154

Linden, W. (2000). Psychological treatments in cardiac rehabilitation: Review of rationales and outcomes. *Journal of Psychosomatic Research*. https://doi.org/10.1016/S0022-3999(99)00094-X

Linden, W. (2013). How many meta-analyses does it take to settle a question? *Psychosomatic Medicine*, *75*(4), 332–334. https://doi.org/10.1097/PSY.0b013e318295e046

Linden, W., Phillips, M. J., & Leclerc, J. (2007). Psychological treatment of cardiac patients: A meta-analysis. *European Heart Journal*, *28*(24), 2972–2984. https://doi.org/10.1093/eurheartj/ehm504

Lv, J., Zhang, X., Ou, S., Gu, S., Su, Z., Tong, S., & Liu, BSong Z, C. L. (2016). Influence of Cognitive Behavioral Therapy on Mood and Quality of Life After Stent Implantation in Young and Middle-Aged Patients With Coronary Heart Disease. *International Heart Journal Association*, *56*(2), 167–172. https://doi.org/10.1536/ihj.15-259. Epub 2016 Mar 11.

Merswolken, M., Siebenhuener, S., Orth-Gomér, K., Zimmermann-Viehoff, F., & Deter, H. C. (2011). Treating anxiety in patients with coronary heart disease: A randomized controlled trial. *Psychotherapy and Psychosomatics*, *80*(6), 365–370. https://doi.org/10.1159/000329177

Michalsen, A., Grossman, P., Lehmann, N., Knoblauch, N. T., Paul, A., Moebus, S., … Dobos, G. J. (2005). Psychological and quality-of-life outcomes from a comprehensive stress reduction and lifestyle program in patients with coronary artery disease: results of a randomized trial. *Psychother Psychosom*, *74*(6), 344–352.

https://doi.org/10.1159/000087781

Moghei, M., Oh, P., Chessex, C., & Grace, S. L. (2019). Cardiac Rehabilitation Quality Improvement: A NARRATIVE REVIEW. *Journal of Cardiopulmonary Rehabilitation and Prevention*. https://doi.org/10.1097/HCR.0000000000000396

Mohammadi, N., Aghayousefi, A., Nikrahan, G. R., Adams, C. N., Alipour, A., Sadeghi, M., … Huffman, J. C. (2018). A randomized trial of an optimism training intervention in patients with heart disease. *General Hospital Psychiatry*, *51*, 46–53. https://doi.org/10.1016/j.genhosppsych.2017.12.004

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine*, *6*(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097

Murphy, B. M., Worcester, M. U. C., Higgins, R. O., Elliott, P. C., Le Grande, M. R., Mitchell, F., … Goble, A. J. (2013). Reduction in 2-Year Recurrent Risk Score and Improved Behavioral Outcomes After Participation in the "Beating Heart Problems" Self-management Program. *Journal of Cardiopulmonary Rehabilitation and Prevention*, *33*(4), 220–228. https://doi.org/10.1097/HCR.0b013e31828c7812

Nicholson, A., Kuper, H., & Hemingway, H. (2006). Depression as an aetiologic and prognostic factor in coronary heart disease: A meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *European Heart Journal*, *27*(23), 2763–2774. https://doi.org/10.1093/eurheartj/ehl338

Nikrahan, G. R., Suarez, L., Asgari, K., Beach, S. R., Celano, C. M., Kalantari, M., … Huffman, J. C. (2016). Positive Psychology Interventions for Patients With Heart Disease: A

Preliminary Randomized Trial. *Psychosomatics*, *57*(4), 348–358. https://doi.org/10.1016/j.psym.2016.03.003

Nyklíček, I., Dijksman, S. C., Lenders, P. J., Fonteijn, W. A., & Koolen, J. J. (2014). A brief mindfulness based intervention for increase in emotional well-being and quality of life in percutaneous coronary intervention (PCI) patients: The MindfulHeart randomized controlled trial. *Journal of Behavioral Medicine*, *37*(1), 135–144. https://doi.org/10.1007/s10865-012-9475-4

O'Neil, A., Taylor, B., Hare, D. L., Sanderson, K., Cyril, S., Venugopal, K., … Oldenburg, B. (2015). Long-term efficacy of a tele-health intervention for acute coronary syndrome patients with depression: 12-month results of the MoodCare randomized controlled trial. *European Journal of Preventive Cardiology*, *22*(9), 1111–1120. https://doi.org/10.1177/2047487314547655

O'Neil, A., Taylor, B., Sanderson, K., Cyril, S., Chan, B., Hawkes, A. L., … Oldenburg, B. (2014). Efficacy and Feasibility of a Tele-health Intervention for Acute Coronary Syndrome Patients with Depression: Results of the "MoodCare" Randomized Controlled Trial. *Annals of Behavioral Medicine*, *48*(2), 163–174. https://doi.org/10.1007/s12160-014-9592-0

Ossola, P., Gerra, M. L., De Panfilis, C., Tonna, M., & Marchesi, C. (2018). Anxiety, depression, and cardiac outcomes after a first diagnosis of acute coronary syndrome. *Health Psychology*, *37*(12), 1115–1122. https://doi.org/10.1037/hea0000658

Pino, E. C., Zuo, Y., Borba, C. P., Henderson, D. C., & Kalesan, B. (2018). Clinical depression and anxiety among ST-elevation myocardial infarction hospitalizations: Results from Nationwide Inpatient Sample 2004–2013. *Psychiatry Research*, *266*, 291–300.

https://doi.org/10.1016/j.psychres.2018.03.025

Poffley, A., Thomas, E., Grace, S. L., Neubeck, L., Gallagher, R., Niebauer, J., & O'Neil, A. (2017). A systematic review of cardiac rehabilitation registries. *European Journal of Preventive Cardiology*, *24*(15), 1596–1609. https://doi.org/10.1177/2047487317724576

Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G. F., Coats, A. J. S., … van der Meer, P. (2016). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution . *European Journal of Heart Failure*, *18*(8), 891–975. https://doi.org/10.1002/ejhf.592

Rakowska, J. M. (2015). Brief strategic therapy in first myocardial infarction patients with increased levels of stress: a randomized clinical trial. *Anxiety, Stress, & Coping*, *28*(6), 687–705. https://doi.org/10.1080/10615806.2015.1004323

Riccioni, G., Prencipe, G., Benvenuto, A., Masciocco, L., Ventra, S., Rizzo, U., … Speziale, G. (2013). Ivabradine Improves All Aspects of Quality of Life Assessed with the 36-Item Short Form Health Survey in Subjects with Chronic Ischemic Heart Disease Compared with Beta-Blockers. *Pharmacology*, *91*(1–2), 35–38. https://doi.org/10.1159/000343631

Richards, S. H., Anderson, L., Jenkinson, C. E., Whalley, B., Rees, K., Davies, P., … Taylor, R. S. (2018). Psychological interventions for coronary heart disease: Cochrane systematic review and meta-analysis. *European Journal of Preventive Cardiology*, *25*(3), 247–259. https://doi.org/10.1177/2047487317739978

Roest, A. M., Martens, E. J., de Jonge, P., & Denollet, J. (2010). Anxiety and Risk of Incident

Coronary Heart Disease. A Meta-Analysis. *Journal of the American College of Cardiology*. https://doi.org/10.1016/j.jacc.2010.03.034

Rozanski, A. (2014). Behavioral cardiology: Current advances and future directions. *Journal of the American College of Cardiology*. https://doi.org/10.1016/j.jacc.2014.03.047

Rutledge, T., Redwine, L. S., Linke, S. E., & Mills, P. J. (2013). A Meta-Analysis of Mental Health Treatments and Cardiac Rehabilitation for Improving Clinical Outcomes and Depression Among Patients With Coronary Heart Disease. *Psychosomatic Medicine*, *75*(4), 335–349. https://doi.org/10.1097/PSY.0b013e318291d798

Sanjuan, P., Montalbetti, T., Pérez-García, A. M., Bermúdez, J., Arranz, H., & Castro, A. (2016). A Randomised Trial of a Positive Intervention to Promote Well-Being in Cardiac Patients. *Applied Psychology: Health and Well-Being*, *8*(1), 64–84. https://doi.org/10.1111/aphw.12062

Sebregts, E. H., Falger, P. R., Appels, A., Kester, A. D., & Bär, F. W. (2005). Psychological effects of a short behavior modification program in patients with acute myocardial infarction or coronary artery bypass grafting. A randomized controlled trial. *Journal of Psychosomatic Research*. https://doi.org/10.1016/j.jpsychores.2004.02.021

Seligman, M. E. P., Steen, T. A., Park, N., & Peterson, C. (2005). Positive psychology progress: empirical validation of interventions. *The American Psychologist*, *60*(5), 410–421. https://doi.org/10.1037/0003-066X.60.5.410

Smolderen, K. G., Spertus, J. A., Gosch, K., Dreyer, R. P., D'Onofrio, G., Lichtman, J. H., … Krumholz, H. M. (2017). Depression Treatment and Health Status Outcomes in Young Patients With Acute Myocardial Infarction. *Circulation*, *135*(18), 1762–1764.

https://doi.org/10.1161/CIRCULATIONAHA.116.027042

Smolderen, K. G., Strait, K. M., Dreyer, R. P., D'Onofrio, G., Zhou, S., Lichtman, J. H., … Spertus, J. A. (2015). Depressive Symptoms in Younger Women and Men With Acute Myocardial Infarction: Insights From the VIRGO Study. *Journal of the American Heart Association*, *4*(4). https://doi.org/10.1161/JAHA.114.001424

Stenvall, H., Tierala, I., Räsänen, P., Laine, M., Sintonen, H., & Roine, R. P. (2017). Long-term clinical outcomes, health-related quality of life, and costs in different treatment modalities of stable coronary artery disease. *European Heart Journal - Quality of Care and Clinical Outcomes*, *3*(1), 74–82. https://doi.org/10.1093/ehjqcco/qcw024

Supervia, M., Turk-Adawi, K., Lopez-Jimenez, F., Pesah, E., Ding, R., Britto, R. R., … Grace, S. L. (2019). Nature of Cardiac Rehabilitation Around the Globe. *EClinicalMedicine*. https://doi.org/10.1016/j.eclinm.2019.06.006

Trzcieniecka-Green, A., & Steptoe, A. (1996). The effects of stress management on the quality of life of patients following acute myocardial infarction or coronary bypass surgery. *Eur Heart J*, *17*(11), 1663–1670.

Tully, P. J., Winefield, H. R., Baker, R. A., Denollet, J., Pedersen, S. S., Wittert, G. A., & Turnbull, D. A. (2015). Depression, anxiety and major adverse cardiovascular and cerebrovascular events in patients following coronary artery bypass graft surgery: a five year longitudinal cohort study. *BioPsychoSocial Medicine*, *9*(1), 14. https://doi.org/10.1186/s13030-015-0041-5

Turner, A., Hambridge, J., Baker, A., Bowman, J., & McElduff, P. (2013). Randomised controlled trial of group cognitive behaviour therapy versus brief intervention for depression

in cardiac patients. *The Australian and New Zealand Journal of Psychiatry*, *47*(3), 235–243. https://doi.org/10.1177/0004867412460592

Weintraub, W. S., Spertus, J. A., Kolm, P., Maron, D. J., Zhang, Z., Jurkovitz, C., … Boden, W. E. (2008). Effect of PCI on Quality of Life in Patients with Stable Coronary Disease. *New England Journal of Medicine*, *359*(7), 677–687. https://doi.org/10.1056/NEJMoa072771

Xu, X., Bao, H., Strait, K. M., Edmondson, D. E., Davidson, K. W., Beltrame, J. F., … Krumholz, H. M. (2017). Perceived Stress After Acute Myocardial Infarction: A Comparison Between Young and Middle-Aged Women Versus Men. *Psychosomatic Medicine*, *79*(1), 50–58. https://doi.org/10.1097/PSY.0000000000000429

Xu, X., Bao, H., Strait, K., Spertus, J. A., Lichtman, J. H., D'Onofrio, G., … Krumholz, H. M. (2015). Sex differences in perceived stress and early recovery in young and middle-aged patients with acute myocardial infarction. *Circulation*, *131*(7), 614–623. https://doi.org/10.1161/CIRCULATIONAHA.114.012826

Zhang, Z., Jones, P., Weintraub, W. S., Mancini, G. B. J., Sedlis, S., Maron, D. J., … Spertus, J. A. (2018). Predicting the Benefits of Percutaneous Coronary Intervention on 1-Year Angina and Quality of Life in Stable Ischemic Heart Disease. *Circulation: Cardiovascular Quality and Outcomes*, *11*(5). https://doi.org/10.1161/CIRCOUTCOMES.117.003971

FIGURE LEGENDS

Figure 1. Flowchart of study selection

Figure 2. Efficacy of psychological interventions on psychological outcomes immediately after the intervention

Forest-plot showing the efficacy of psychological interventions compared with control groups on predefined psychological outcomes immediately after the intervention:

2A: Effect on depression

2B: Effect on anxiety

2C: Effect on stress

2D: Effect on anger

2E: Effect on vital satisfaction

2F: Effect on happiness

Figure 3: Effect of psychological interventions at the end of follow-up

Forest-plot showing the efficacy of psychological interventions compared with control groups at the end of follow-up on the predefined psychological outcomes:

3A: Effect on depression (average follow-up, 4.5 months)

3B: Effect on anxiety (average follow-up, 5.6 months)

3C: Effect on stress (average follow-up, 13 months)

3D: Effect on vital satisfaction (average follow-up, 3.8 months)

3E: Effect on happiness (average follow-up, 3.8 months)

Table 1. Study and patient characteristics of included randomized controlled trials

Author, year	Number of patients	Patient population. Diagnosis at entry	Age, mean (SD)	Description of interventions	Intervention duration	Outcomes	Evaluation at the end of treatment	Evaluation at the end of follow-up
Trzcieniecka-Green & Steptoe 1996	Experimental group: N= 50, Control group: N=50	ACS (+bypass)	Experimental group: 59.4 (7.7), Control group: 61 (6.7)	CBT Psychologist: Yes Multicomponent Group sessions In person Description: Experimental group: Psychoeducation, Behavioral techniques for life style modification.	10 weeks	Depression Anxiety Daily activities Physical Well-being	12 weeks	6 months
Bishop *et al.* 2005	Experimental group: N= 29, Control group: N=29	Others (CABG). Unspecified if acute or programmed	Only men. Experimental group: 54.7 (1.4), Control group: 53.3 (7.3)	CBT Psychologist: Unknown Multicomponent Group sessions In person Description: Experimental group: Behavioral techniques for life style modification, Cognitive techniques.	6 weeks	Depression Stress Anxiety Anger	6 weeks	3 months
Blumenthal *et al.* 2005	Exercise group: N=44, Stress management: N=44, Control group: N=42	IHD diagnosis (+ event or intervention)	Experimental group: 63 (9), Control group: 62 (10.5)	CBT Psychologist: Unknown Multicomponent Group sessions In person Description: Experimental group: Psychoeducation, Behavioral techniques for life style modification and Cognitive techniques.	Unknown	Depression Anxiety Hostility Physical Well-being	16 weeks	No

Author, year	Number of patients	Patient population. Diagnosis at entry	Age, mean (SD)	Description of interventions	Intervention duration	Outcomes	Evaluation at the end of treatment	Evaluation at the end of follow-up
del Pino *et al.* 2005	Experimental group: N=33, Educational group: N= 33, Control group: N= 32	CHD	Only men Experimental group: 49.65 (8.22), Control group: 58.09 (5.45)	CBT Psychologist: Yes Multicomponent Group sessions In person Description: Experimental group: Psychoeducation, Relaxation techniques, Behavioral techniques for life style modification, Cognitive techniques.	9 months	Depression Anger Type A personality	9 months	12 and 24 months
Michalsen *et al.* 2005	Experimental group: N= 48, Control group: N=53	CAD (in medical treatment, excluded ACS)	Experimental group: 59.8 (7), Control group: 59.8 (8.6)	CBT Psychologist: Unknown Multicomponent Group sessions In person Description: Experimental group: Psychoeducation, Relaxation techniques, Relapse prevention, Mindfulness.	12 months	Depression Stress Anxiety Quality of life Anger	12 months	No
Sebregts *et al.* 2005	Experimental group: N= 94, Control group: N=90	ACS (MI) or CABG. Unspecified if acute or programmed	Experimental group: 55.6 (8), Control group: 55.2 (9.7)	CBT Psychologist: Yes Multicomponent Group sessions In person Description: Experimental group: Psychoeducation, Relaxation techniques, Behavioral techniques for life style modification, Relapse prevention.	8 weeks	Depression Hostility	8 weeks	9 months

Author, year	Number of patients	Patient population. Diagnosis at entry	Age, mean (SD)	Description of interventions	Intervention duration	Outcomes	Evaluation at the end of treatment	Evaluation at the end of follow-up
Karlsson *et al.* 2007	Experimental group: N= 111, Control group: N=113	CAD (included ACS and intervention but not ACS)	Experimental group: 63.8 (7.2), Control group: 63.3 (7.3)	CBT Psychologist: Unknown Unicomponent Group sessions In person Description: Experimental group: Stress management program, 5-day stay at the patient hotel, Behavioral techniques for life style modification.	12 months	Depression Stress Anxiety Anger Quality of life	12 months	No
Freedland *et al.* 2009	Experimental group: CBT: N= 41, SSM: N=42, Control group: N=40	CABG surgery	Experimental group:59 (10), Control group: 61 (9)	CBT Psychologist: Yes Multicomponent Group sessions In person Description: Experimental group: CBT Group: Psychoeducation, Relaxation techniques, Behavioral techniques for life style modification, Relapse prevention	12 weeks	Depression Stress Anxiety	3 months	6 and 9 months
Dao *et al.* 2011	Experimental group: N =50, Control group: N = 50)	CAD (+ CABG and also depression or anxiety diagnosis)	Experimental group: 62.8 (11.8), Control group: 64.2 (11.9)	CBT Psychologist: Yes Multicomponent Group sessions In person Description: Experimental group: Managing Anxiety and Depression using Education and Skills	1-2 weeks	Stress Depression Anxiety Quality of life Hopeless Vitally Mindfulness Positive and negative affect Adherence to	At least five days after surgery	3-4 weeks

Author, year	Number of patients	Patient population. Diagnosis at entry	Age, mean (SD)	Description of interventions	Intervention duration	Outcomes	Evaluation at the end of treatment	Evaluation at the end of follow-up
						psychological treatment		
Merswolken *et al.* 2011	Experimental group: N= 25, Control group: N =27	ACS (+ CHD diagnosis)	Experimental group: 62.5 (8.3), Control group: 59.8 (7.5)	CBT Psychologist: Yes Multicomponent Group sessions In person <u>Description:</u> <u>Experimental group:</u> Psychoeducation, Relaxation, Behavioral techniques for life style modification (stress management), Cognitive restructuring and Social components	6 months	Depression Anxiety	6 months	No
Turner *et al.* 2013	Experimental group: N= 25 and Control group: N= 32	ACS (other possible diagnosis)	Experimental group: 61 (11), Control group: 62 (9)	CBT Psychologist: Yes Multicomponent Group sessions In person <u>Description:</u> <u>Experimental group:</u> Psychoeducation, Behavioral techniques for life style modification, Cognitive techniques, Motivational techniques, Relapse prevention	6 weeks	Depression Anxiety Adherence to psychological treatment	No	2, 6 and 12 months

Author, year	Number of patients	Patient population. Diagnosis at entry	Age, mean (SD)	Description of interventions	Intervention duration	Outcomes	Evaluation at the end of treatment	Evaluation at the end of follow-up
Nyklíček *et al.* 2014	Experimental group: N = 55 Control group: N = 52	Others: PCI - unspecified if acute or programmed	Experimental group: 55.4 (7.3), Control group: 56.3 (7.3)	CBT Psychologist: Yes Unicomponent Group sessions In person Description: Experimental group: Minfulness-Based Stress Reduction (MBSR) Control group:self-help intervention bases on a booklet about group training written by the same psychologist	4 weeks	Stress Drug Use Positive and negative affect	4 weeks	No
O'Neil *et al.* 2014	Experimental group: N=61, Control group: N =60	ACS: MI or unstable angina with clinical significant depressive symptomato-logy during hospitalize-tion	Unknown	CBT Psychologist: Yes Multicomponent Individual Telephone Description: Experimental group: Relaxation techniques, Behavioral techniques for life style modification, Cognitive restructuring, Motivational interviewing	6 months	Depression Quality of life	6 months	No
O'Neil *et al.* 2015	The same as O´Neil 2014	The same as O´Neil 2014	The same as O´Neil 2014	The same as O´Neil 2014	The same as O´Neil 2014	Depression Stress Quality of life	No	12 months

Author, year	Number of patients	Patient population. Diagnosis at entry	Age, mean (SD)	Description of interventions	Intervention duration	Outcomes	Evaluation at the end of treatment	Evaluation at the end of follow-up
Rakowska, 2015	Experimental group: N= 41, Control group: N= 40	ACS (infarction)	Experimental group: 53.56 (4.58), Control group: 53.40 (4.27)	CBT Psychologist: Yes Multicomponent Individual In person Description: Experimental group: Problem solving, Relapse prevention	10 weeks	Stress Quality of life	10 weeks	1 year and 2,5 year
Sanjuan *et al.* 2016	Experimental group: N = 57, Control Group N=51	ACS (+ CHD diagnosis)	Experimental group:54.3 (9.5) Control group: 54.5 (8.7)	PPT Psychologist: Yes Multicomponent Group sessions In person Description: Experimental group: Psychoeducation, Relaxation, Performance of acts of kindness, Awareness of acts of gratitude, Prioritizing positive thoughts and feelings	8 weeks	Depression Hostility Positive and negative affect	8 weeks	No
Lv *et al.* 2016	Experimental group: N = 38, Control group: N = 37	CHD + PCI, no events.	Experimental group: 52.4 (6.3), Control group: 52 (6.2)	CBT Psychologist: Yes Multicomponent Individual In person Description: Experimental group: Psychoeducation, Behavioral techniques for life style modification (Identify and confirm treatment goals, develop plans for daily activities and track feedbacks,	8 weeks	Depression Anxiety Quality of life	8 weeks	No

Author, year	Number of patients	Patient population. Diagnosis at entry	Age, mean (SD)	Description of interventions	Intervention duration	Outcomes	Evaluation at the end of treatment	Evaluation at the end of follow-up
				manage emotional and behavioral activation). Cognitive restructuring.				
Nikrahan *et al.* 2016	Seligman group: N =13, Lyubomirsky group: N = 13, Fordyce group: N=15, Control group: N=14	Group 1: CAD (+ CABG or PCI)	Seligman group:55,8 (5,3), Lyubomirsky group: 59.2 (11.5), Fordyce group: 54.7 (10.1), Control group: 56.9 (6.7)	PPT Psychologist: Yes Multicomponent In group In person Description: Experimental group: Lyubomirsky Group: Mindfulness, Gratitude Expression, Forgiveness, Commitment to goals Seligman Group: Positive Emotions, Optimism and Happiness, Strength, Values and virtues, meaning of life, Prioritizing positive thoughts and feelings Fordyce Group: Optimism, Behavioral and Social activation (increasing activity and social relationship, productivity and organizations), Focusing on present, Prioritizing positive thoughts and feelings	6 weeks	Depression Vital Satisfaction Dispositional Hope Happiness	7 weeks	15 weeks
Fernandes *et al.* 2017	Experimental group: N=65, Control group: N =56	ACS	Experimental group: 61.77 (12.11), Control group: 66.11 (12.11)	CBT Psychologist: Yes Multicomponent Group sessions In person Description: Experimental group:	1 week	Depression Anxiety	2-3 days (hospital discharge)	1 and 2 months

Author, year	Number of patients	Patient population. Diagnosis at entry	Age, mean (SD)	Description of interventions	Intervention duration	Outcomes	Evaluation at the end of treatment	Evaluation at the end of follow-up
				Psychoeducation, Behavioral techniques for life style modification (Promotion of psychosocial adjustment in post-ACS rehabilitation), Cognitive techniques, Relapse prevention				
Mohammadi *et al.* 2018	Experimental group: N = 31, Control group: N= 30	Group 2: ACS (and clear diagnosis CHD)	Experimental group: 52.7 (5.0), Control group: 52.4 (5.9)	PPT Psychologist: Yes Multicomponent Group sessions In person Description: Experimental group: Optimism and happiness, Posttraumatic Growth	8 weeks	Depression Anxiety Dispositional Optimism Vital satisfaction Dispositional Hope Happiness Positive and negative affect	8 weeks	16 weeks

Response to Editors and Reviewers

PSM-D-19-01144. EFFICACY OF PSYCHOLOGICAL INTERVENTIONS ON PSYCHOLOGICAL OUTCOMES IN CORONARY ARTERY DISEASE: SYSTEMATIC REVIEW AND META-ANALYSIS Psychological Medicine

A) You must now complete and return to the Editorial Office the Author Publishing Agreement (see instructions for authors for full details). You can upload this with your other manuscript files - the dropdown list gives options for various submission items and Author Publishing Agreement is amongst them: https://www.cambridge.org/core/journals/psychological-medicine/information/author-publishing-agreement

Response: Done

B) Abstract must be structured using our standard subheadings only (Background, Methods, Results, Conclusions), not to exceed 250 words (including the 4 subheadings). NB: Review articles only may have an unstructured abstract not exceeding 250 words. Editorials and correspondence do not require an abstract but may include one at authors' discretion.

Response: The abstract has been structured and sized accordingly

C) Figures, which must be uploaded only as a separate file and not combined with any other element of the submission, should be produced using size 8 point Arial font for the legend. Any wording within a figure should ideally be in Arial - 8 point size is standard, but this may vary depending on space limitations within individual figures. Wherever possible figures for print should be monochrome although colour figures are acceptable for online. You will be asked to pay for unnecessary colour printing. If you wish you may have colour online and black-and-white in print at no charge, in which case you should submit two copies of the figures, identical in every respect other than the colour. Figures should NOT be embedded or included in the main text tile.

Response: Done

D) We are now adopting the APA* referencing format, listing all authors up to 7 in number, or the first 6 authors plus the last author, date, article title, journal title in full, volume, page numbers and/or DOI.

Response: References are now presented with the APA referencing format

E) Appendices and supplementary material also should be submitted as a separate file from the main text. These will be published online exactly as they are received, so a clean version without track changes showing, etc, must be submitted. Authors may upload two *clearly labelled* versions of supplementary material, one clean and one showing changes if they feel this appropriate.

Response: Done

F) Text files (and tables) should be uploaded in editable form (ie word processor files, not pdf).

Response: Done

G) A clean copy of ALL files will be required prior to final acceptance. If you send a tracked changes copy of your revised manuscript (useful for editors and reviewers to see where you have made changes), you MUST also send a clean copy. The clean copy should be indicated as the main document, with the TRACKED copy as "RESPONSE TO REVIEWERS". You can have more than one file for each designation so it is possible to have both a tracked copy of the manuscript and a letter explaining your changes both indicated as response to reviewers. The tracked copy should NEVER be the main document.

Response: Done

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Please indicate clearly what changes you have made, and where they occur within the revised manuscript. If you have not made any changes in respect of any point raised by the reviewers, please also state this clearly in your response. ***It would be best if you included the full comments of the reviewers and your response to their concerns, point by point.***

Response: Done

Response to Reviewer #1:

This Ms describes a MA of psychological interventions (PIs), namely cognitive behavioral treatment (CBT) and positive psychology therapy (PPT) in patients with cardiovascular disease; N=19 trials were identified.
Quote from abstract : "the benefits of PT for CAD patents are not well defined" (I disagree given that previous meta-analyses on the topic largely agree in their conclusions especially when it comes to reduction of negative affect.

Response: In relation with your comments, this sentence has been changed for "*The benefits of cognitive-behavioral treatment (CBT) and positive psychology therapy (PPT) in patients with cardiovascular disease are still not well defined*".

Strengths
There are many strengths to this work. The review process and steps are well described; the quality of the lit review process, study selection, data extraction, analysis and documentation is very good and follows industry standard guidelines.
I congratulate the authors on not limiting themselves to English language articles only. They do worry appropriately about bias in reporting results and methodological quality of trials. They are aware of relevant MAs in the existing literature.

Response: Thank you for the positive comments.

The weaknesses of this work lie in what is missing:
[1] The lit review and rationale building for this Ms is a mere 1.5 pages long which gives no opportunity to even touch on controversies and contradictions in the field (as described by Linden , 2013 which the authors appropriately cite but the content of which is largely ignored even though it has major implications for the current MA).
We are not told why was this meta analysis done when they are multiple previous ones (which the authors are aware of and cite) ; what is innovative here? At first glance it seemed to me that what's new here is [a] to distinguish CBT from PPT and [b] adds studies with positive psychology concepts as outcomes . If this is meant to be an addition to the literature , then it will have to carry all the way in the lit selection and analyses but… The authors don't follow through on these points
A direct quote from p. 1 of the lit review highlight some of the problems with the Introduction and rationale building: "However, cardiac rehabilitation usual care programs rarely include PIs, maybe because of the important differences in methods, type and duration of interventions, professional involved, duration of follow-up and specific endpoints; therefore these reasons could also be explaining why PIs, although beneficial for patients with CAD, have showed small magnitude effects" . This three-part sentence is problematic because I do believe that most cardiac rehab programs don't have a distinct psychol therapy component but this is not referenced or documented; it is just stated. The second part of the phrase beginning with 'maybe' is not a logical sequitur to the first nor does it explain why effects may be small (i.e., the third part of the phrase).

Response: Thank you for the thorough review and the suggestions. It is true that the Introduction section was short, so we have modified it according to your comments (page 3-4).

> "*However, the routine use of PIs in cardiac rehabilitation programs remains controversial because, while these are recommended (Knuuti et al., 2020) and implemented in high income countries (Abreu et al., 2019; Supervia et al.,*

2019), this is not the case everywhere (Moghei, Oh, Chessex, & Grace, 2019; Poffley et al., 2017).”

Also, a more specific paragraph have been added at page 4 to explain why previous meta-analyses showed positive but small effect of PIs for CAD patients

“Controversies, such as which specific treatment components should be included, the type and duration of interventions, professional involved, duration of follow-up, and specific endpoints, may contribute to the limited inclusion of PIs in cardiac rehabilitation programs (Linden, 2013), and may explain in part why PIs have shown beneficial effects in CAD patients but with modest effects (Dickens et al., 2013; Linden, 2000, 2013; Linden et al., 2007; Richards et al., 2018; Rutledge et al., 2013). This may also be due to the use of different definitions or types of PIs. Although cognitive-behavioral treatment (CBT)-based PIs have been suggested as the most effective for CAD patients (Linden, 2013), with two exceptions (Dickens et al., 2013; Linden et al., 2007), a number of meta-analyses included broader categories of PIs, such as those based on not well-established paradigms, mixed PIs, and psychopharmacological treatments (Richards et al., 2018; Rutledge et al., 2013). Finally, only negative psychological outcomes were assessed (Dickens et al., 2013; Linden, 2000, 2013; Linden et al., 2007; Richards et al., 2018; Rutledge et al., 2013).”

“ (…) some PIs based on positive psychology therapy paradigm (PPT) (…), not considered in prior meta-analyses (Dickens et al., 2013; Linden, 2000, 2013; Linden et al., 2007; Richards et al., 2018; Rutledge et al., 2013).”

This has also been commented on Discussion section at pages 14-15:

“As noted above, compared to other narrative reviews (Linden 2000, 2013) and meta-analyses (Linden et al. 2007; Dickens et al. 2013; Rutledge et al. 2013; Richards et al. 2018), our results show a larger magnitude of effects of PIs for improving psychological outcomes, which may be explained by the selection of only RCTs in which PIs were clearly based on empirically-based therapies, that is, the CBT paradigm (Linden, 2013), only done by Linden et al. (2007) and Dickens et al. (2013). The inclusion of the positive behavioral cardiology paradigm (Labarthe et al. 2016) as a well-established therapy paradigm specifically designed to improve positive psychological dimensions (Bolier et al. 2013; Lee Duckworth et al. 2005; Huffman et al. 2016; Seligman et al. 2005) is also new. Our meta-analysis, focusing specifically on the efficacy of PIs in improving psychological outcomes, both negative and positive, in CAD patients, clearly differentiates from previous studies focusing on quantifying the benefits of PIs on morbidity and mortality outcomes (Linden et al. 2007; Dickens et al. 2013; Rutledge et al. 2013; Richards et al. 2018), or their differential effects depending on distress reduction (Linden et al. 2007) or depression reduction (Rutledge et al. 2013). Only Richards et al. (2018) and Dickens et al. (2013) analyze their effects on some psychological outcomes. As PIs are specifically targeted to improve psychological outcomes, finding larger effects is no surprise, although this would not explain the differences found with the last Cochrane systematic review (Richards et al. 2018), where smaller but significant benefits on depression, anxiety and stress reduction were reported. This difference may be explained by the inclusion of all kinds of PIs, while our meta-analysis selected only RCTs based on empirically supported PIs.”

The innovations and contributions of our study are now explained in a new paragraph in the Discussion (page 17-18):

> *"Our meta-analysis is the first one to analyze the effects of PIs on positive psychology outcomes, including only empirically-supported PIs for CAD patients (Linden et al., 2013), an inclusion criterion only in a minority of prior studies (Linden et al., 2007; Dickens et al., 2013). Our meta-analysis is also new on its exclusive focus on psychological outcomes in CAD patients while the majority of prior publications mainly focused on morbidity and mortality or on the differential effects on these outcomes depending on distress reduction (Linden et al, 2007) or depression reduction (Rutledge et al., 2013). Only Richards et al. (2018) specifically evaluated the effects of PIs on stress, anxiety and depression, and Dickens et al. (2013) on depression, but they did not study positive psychological outcomes."*

Regarding your comment if the innovations are differentiating the effect of CBT and PPT on both negative and positive psychological outcomes in CAD patients and the importance of following this scheme in the Results section, please note that the effect of PIs on negative (depression, anxiety, stress, anger, negative affect) and positive outcomes (vital satisfaction, happiness, dispositional hope) have been separately analyzed. However, given the small numbers, unfortunately our results do not allow differentiating separately the effect of CBT and PPT on each of the psychological outcomes considered in this study, with the only exception of depression immediately after the intervention. This information was not included in the original paper for consistency as it is only possible with one of the outcomes but has now been included in the Supplementary material and commented on the Results section (page 13) and the Discussion (page 16):

> *"Compared with PPT, CBT seems to improve depression after the intervention, which could be explained by the fact that CBT is a treatment package specifically designed to modify negative psychological factors (Blagys & Hilsenroth 2002), such as depression, whereas PPTs are specifically aimed at improving positive psychological dimensions (Lee Duckworth et al. 2005; Seligman et al. 2005). Therefore, PPT may not be able to improve depression by itself. Unfortunately, the information is scarce and analyses could only be done for depression. Future research is needed to clarify the differential effect of CBT and PPT on CAD patients."*

[2] No coverage is offered on the issue of different outcomes for men and women although a number of the references cited by the authors deal with this topic. I also recommend the following excellent reading: Humphries KH, Izadnegadar M, Sedlak T, Saw J, Johnston N, Schenck-Gustafsson K, Shah RU, Regitz-Zagrosek V, Grewal J, Vaccarino V, Wei J, Bairey Merz CN. Sex Differences in Cardiovascular Disease - Impact on Care and Outcomes. Frontiers Neuroendocrin 2017: 46: 46-70Hum phries et al, 2017 for a read)

Response: We think this is an important issue but, unfortunately, expanding it with specific results and comments is beyond the scope of this manuscript so we have decided to eliminate this point and leave it for future work.

[3] No mention is made of previous reviews that deal with mortality and cardiac event recurrence. These are hard endpoints that, if benefitting from PT , provide powerful arguments for implementation of psychol tx in all clinics. I do agree that improving quality of life and reducing negative affect are worthwhile targets in and of themselves but in the world of psychol factors in physical disease the physical disease itself is always a target, too

Response: We fully agree with this comment, as morbidity and mortality are the main targets on CVD. As it has been also discussed at comment one, this meta-analysis specifically aimed at testing PIs effect on both negative and positive psychological factors as they have been empirically supported as mediational dimensions to increase or reduce CV risk (Nicholson et al. 2006; Chida & Steptoe, 2009; Roest et al., 2010; Rozanski, 2014; Labarthe et al., 2016; Bohem & Kubzansky, 2012; DuBois et al., 2015), so their improvement could be, by themselves, an important benefit for patients with CAD and their quality of life. In fact, our research group have just finished another meta-analysis that is complementary to this one, focused on the effect of PIs on mortality, morbidity and biological outcomes. It was not possible to unify all this information on one paper, so we decided to split it into two publications.

Nevertheless, as we agree with your comment, we mention it in a specific paragraph at Discussion section has been done at page 16:

> *"Although CBT- and PPT-based PIs are specifically designed to improve negative and positive psychological outcomes, respectively, the magnitude effect of PIs might be greater in CAD patients, in whom improving psychological health and wellbeing by reducing stress and negative emotions and fostering positive psychological factors could be an important target as these are linked, respectively, to a higher (Chida & Steptoe, 2009; Nicholson et al., 2006; Roest et al., 2010; Rozanski, 2014) and lower (Boehm & Kubzansky, 2012; DuBois et al., 2015; Labarthe et al., 2016) CV risk, as well as to a better quality of life (Appels et al., 2006). Therefore, CBT- and PPT-based PIs may have a positive impact on all-cause and CV morbidity and mortality, as changes in negative (Hamer & Malan 2010; Lovallo & Gerin 2003; Rozansky 2014; Schwartz et al. 2003; Steptoe & Kivimäki 2013; Wirtz & von Känel 2017) and positive psychological factors (Labarthe et al. 2016; Rozansky, Bavishi, Kubzansky & Cohen 2019; Steptoe, Wardle & Marmot 2005) may contribute modifying some clinical and CV parameters, according to Linden, 2013. Although the mechanisms by which changes on psychological factors may improve clinical outcomes remains unclear, it is likely that these may have a direct effect by improving CV risk factors and, indirectly, by facilitating enjoying healthier lifestyles, social and psychological functioning (Labarthe et al. 2016; Rozanski 2014; Rozanski et al. 2019; Steptoe & Kivimäki 2013; Steptoe, Wardle & Marmot 2005; Wirtz & von Känel 2017; Lovallo & Gerin 2003; Schwartz et al. 2003; Hamer & Malan 2010), and improving adherence."*

[4] It is not clarified how long follow ups were although the author report outcomes separately for immediate vs delayed treatment

Response: Table 1 now specifies this information for each study included in the meta-analysis and specified in the Statistical Analysis section on page 8-9, and in the Characteristics of included studies section (page 10):

> *"The time intervals defining post-treatment (at the end of the intervention) and end of follow-up showed high variability across RCTs, with post-treatment time*

ranging from 2-3 days (Fernandes et al., 2017) to one year (Karlsson et al., 2007; Michalsen et al., 2005), and follow-up assessment ranging from 3-4 weeks (Dao et al., 2011) to 2.5 years (Rakowska, 2015).”

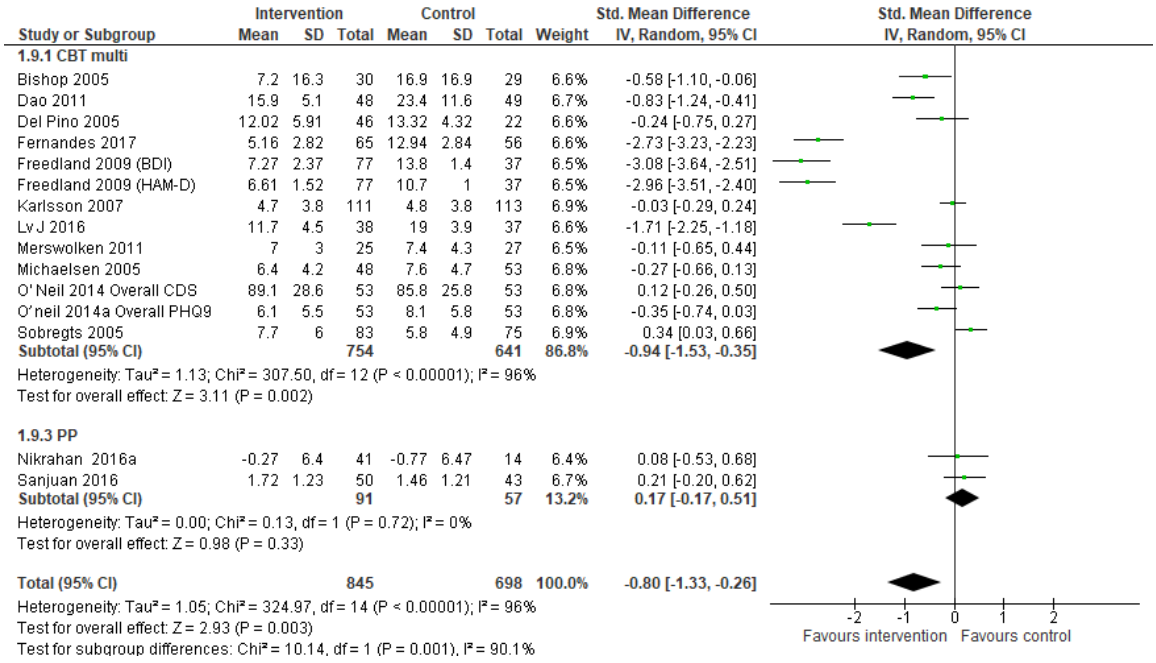
[5] It is not clear whether only those studies were extracted that included both pos and negative affect concepts. If so, this would make this MA original but my reading suggested that only a minority of the trials measured both types of outcomes.

Response: It is true that RCTs including both type of psychological outcomes were a minority among the studies that tested the efficacy of CBT. Only Dao et al. (2001) and Nyklíček *et al.* (2014) assessed psychological negative factors and positive ones. However, the RCTs testing the efficacy of PPT always assessed positive and negative psychological outcomes (San Juan et al., 2016; Nikraham et al., 2016; Mohammadi et al., 2018).

[6] In the Intro and Method section the authors differentiate CBT from PPT which is great but don't tell us what the inter-reliability was for making this distinction and, oddly, immediately collapse these 2 tx classes when it comes to computing outcomes! Why identify these two types of different txs if you don't deal with this distinction? Even if the cell sizes are very uneven (n=3 for PPT) I want to know whether these 3 PPT trials produced outlier results in one direction or the other.

Response: Thanks for the comment. We pre-specified analyses by type of treatment (CBT vs PPT); however, available outcome data was very scarce for PPT. We had enough information only to run the analysis for depression at the end of the intervention (see figure below). CBT significantly reduced depression after the intervention in contrast to a neutral effect of PPT (p for interaction =0.001). This information has been included now in the Supplemental material, as well as in the Results section (page 12) and the Discussion (page 16):

“Compared with PPT, CBT seems to improve depression after the intervention, which could be explained by the fact that CBT is a treatment package specifically designed to modify negative psychological factors (Blagys & Hilsenroth 2002), such as depression, whereas PPTs are specifically aimed at improving positive psychological dimensions (Lee Duckworth et al. 2005; Seligman et al. 2005). Therefore, PPT may not be able to improve depression by itself. Unfortunately, the information is scarce and analyses could only be done for depression. Future research is needed to clarify the differential effect of CBT and PPT on CAD patients.”

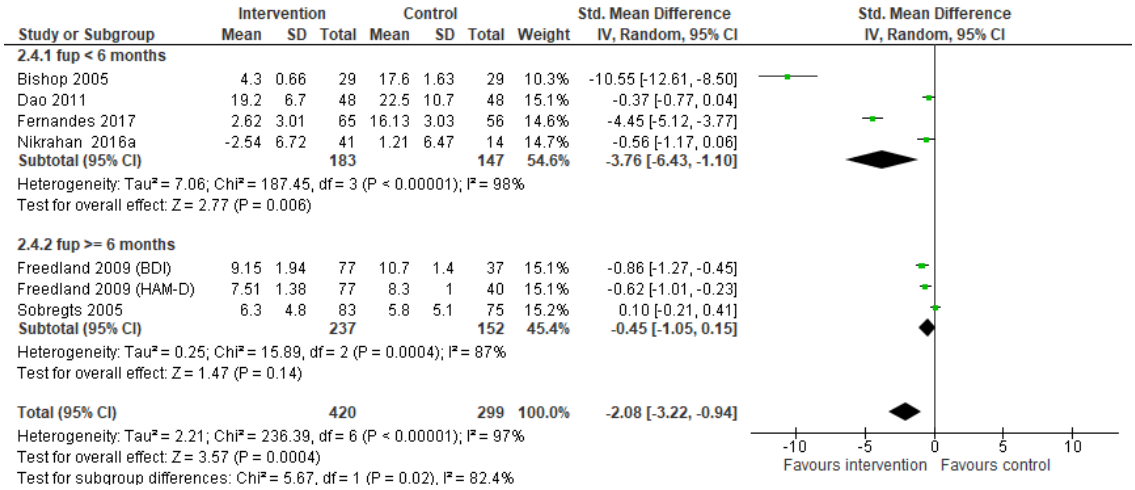


[7] Figs 2c and 3c speak to changes in outcomes over time and are compared with each other but these are apples and oranges comparisons because they are not the same exact studies.

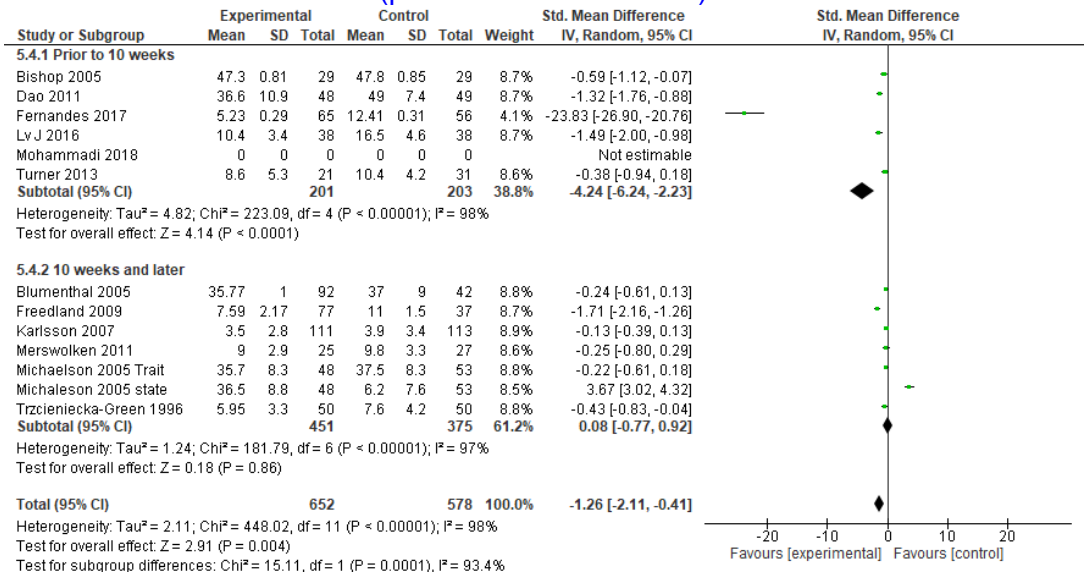
Response: It is true that they did not include the same studies, but they have been compared because they refer to the same endpoint -stress-, Figure 2c immediately after the intervention and Figure 3c figure at the end of follow-up, so we thought it was interesting to compare what happened with similar psychological endpoints at the end of the treatment, and at the end of follow-up assessments in order to clarify if there were a maintenance of the changes between post-treatment and at follow-up, or they were smaller or bigger. In our opinion, this is interesting because one of weakness of PIs is the long-term maintenance of the improvements achieved immediately after the interventions.

[8] I want to know to what degree length of tx (i.e., dosage) affects positive outcomes. This is very important for health care planners.

Response: We stratified the analyses by time of treatment and time to follow-up for all outcomes. We also pre-specified subgroup analyses by the median time of treatment and follow-up, respectively. Again, due to the scarcity of data, we could only perform analyses for depression (both, for time of treatment and follow-up time), stress (only time for treatment), and anxiety (both, for time of treatment and time of follow-up). Interventions produced a larger reduction in depression at the end of follow up for those with <6months of follow up (p for interaction=0.02)



Interventions produced a larger reduction in anxiety at the end of treatment for those with <10 weeks of treatment (p for interaction=0.0001)



Other subgroups did not show differences by times of treatment or by follow up times. This data has been added to the Supplemental material and commented on Results section at page 12-13 and at Discussion section on page 17:

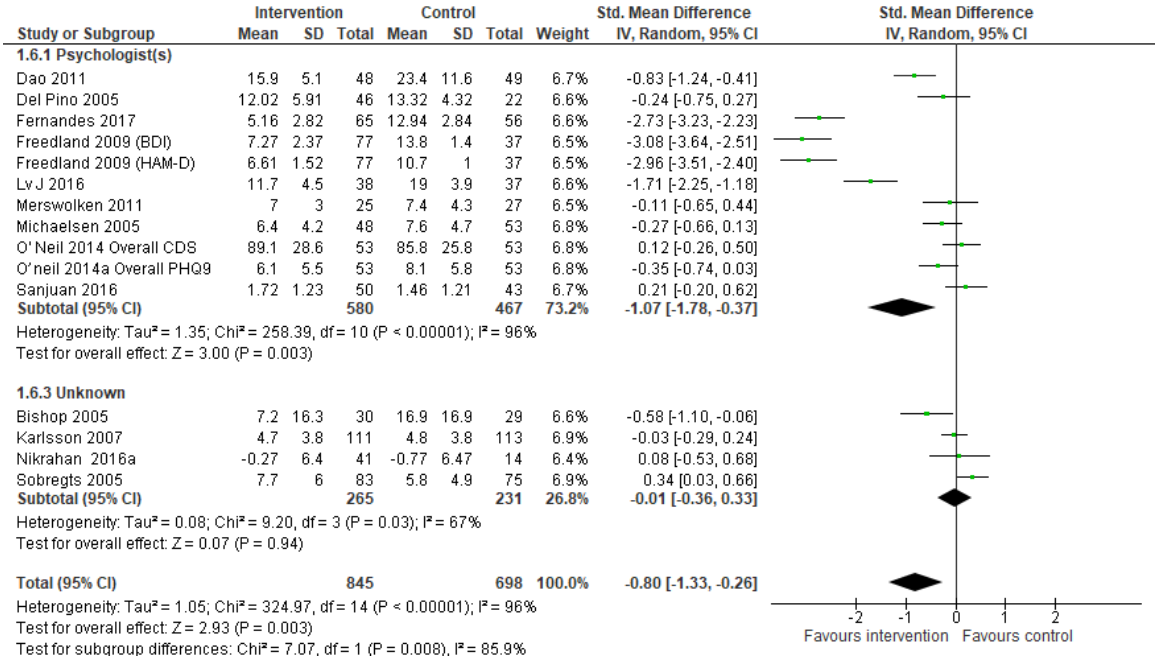
> *"Finally, PIs in which the follow-up assessment occurred <6 months after the intervention showed significant benefits in depression compared with those with longer follow-ups. Reductions in anxiety were also larger when the intervention duration was <10 weeks, which is consistent with the findings by Linden et al (2013), where the beneficial effects of PIs fade away with time. This points out the importance of maintenance of the benefits as one important target for PIs."*

Indeed, according to your comment, also subgroup analysis by session type (group vs. individual) has been included as this may be useful for treatment planner. This data has been added at Supplemental material and commented on Results section at page 12-13.

[9] The last sentence of the results section throws in a little surprise, but only in a singular phrase are we told that tx offered by psychologists was more effective. As much as I want to hear this (I am a psychologist after all), how large was this difference and which types of professions/therapist are being compared here?

Response: Subgroup analysis by the professional provided the intervention was also pre-specified. Again, the scarcity of outcome data only allowed us to run this subgroup analysis for depression. Interventions provided by psychologists produced a larger effect on depression at the end of treatment in comparison to interventions provided by undisclosed professionals (p for interaction=0.008). These results have been added to the Supplemental material and commented on Results section at page 12-13 and at Discussion section on page 16-17; it is specified why this result could have emerged:

> "*what is logical as they are professional specifically trained for it*".



There was no difference on the effect of interventions provided by psychologists on depression at the end of follow up in comparison to interventions provided by undisclosed professionals (p for interaction=0.27)

[10] The discussion offers no serious coverage of the surprisingly large ESs (i.e. 3-4 times as large as in the previous MAs which were cited in the Ms. We must be told for example to what degree the studies selected here were already analysed in previous meta analyses; and if there is large overlap, then the larger, here-observed, benefits are especially puzzling.

Response: Thank you for the comment. The reasons why our results show larger ESs are now discussed. These differences may be explained by different reasons as it has been specified in the Discussion section (page 14-15) and noted above:

> *"As noted above, compared to other narrative reviews (Linden 2000, 2013) and meta-analyses (Linden et al. 2007; Dickens et al. 2013; Rutledge et al. 2013; Richards et al. 2018), our results show a larger magnitude of effects of PIs for improving psychological outcomes, which may be explained by the selection of*

only RCTs in which PIs were clearly based on empirically-based therapies, that is, the CBT paradigm (Linden, 2013), only done by Linden et al. (2007) and Dickens et al. (2013). The inclusion of the positive behavioral cardiology paradigm (Labarthe et al. 2016) as a well-established therapy paradigm specifically designed to improve positive psychological dimensions (Bolier et al. 2013; Lee Duckworth et al. 2005; Huffman et al. 2016; Seligman et al. 2005) is also new. Our meta-analysis, focusing specifically on the efficacy of PIs in improving psychological outcomes, both negative and positive, in CAD patients, clearly differentiates from previous studies focusing on quantifying the benefits of PIs on morbidity and mortality outcomes (Linden et al. 2007; Dickens et al. 2013; Rutledge et al. 2013; Richards et al. 2018), or their differential effects depending on distress reduction (Linden et al. 2007) or depression reduction (Rutledge et al. 2013). Only Richards et al. (2018) and Dickens et al. (2013) analyze their effects on some psychological outcomes. As PIs are specifically targeted to improve psychological outcomes, finding larger effects is no surprise, although this would not explain the differences found with the last Cochrane systematic review (Richards et al. 2018), where smaller but significant benefits on depression, anxiety and stress reduction were reported. This difference may be explained by the inclusion of all kinds of PIs, while our meta-analysis selected only RCTs based on empirically supported PIs."

It has been specifically noted in Introduction section at page 3-4:

"Controversies, such as which specific treatment components should be included, the type and duration of interventions, professional involved, duration of follow-up, and specific endpoints, may contribute to the limited inclusion of PIs in cardiac rehabilitation programs (Linden, 2013), and may explain in part why PIs have shown beneficial effects in CAD patients but with modest effects (Dickens et al., 2013; Linden, 2000, 2013; Linden et al., 2007; Richards et al., 2018; Rutledge et al., 2013). This may also be due to the use of different definitions or types of PIs. Although cognitive-behavioral treatment (CBT)-based PIs have been suggested as the most effective for CAD patients (Linden, 2013), with two exceptions (Dickens et al., 2013; Linden et al., 2007), a number of meta-analyses included broader categories of PIs, such as those based on not well-established paradigms, mixed PIs, and psychopharmacological treatments (Richards et al., 2018; Rutledge et al., 2013). Finally, only negative psychological outcomes were assessed (Dickens et al., 2013; Linden, 2000, 2013; Linden et al., 2007; Richards et al., 2018; Rutledge et al., 2013)."

"(…) some PIs based on positive psychology therapy paradigm (PPT) (…), not considered in prior meta-analyses (Dickens et al., 2013; Linden, 2000, 2013; Linden et al., 2007; Richards et al., 2018; Rutledge et al., 2013)."

Reviewer #2: This is a well conducted and presented systematic review and meta-analysis of psychological interventions in coronary heart disease. The authors have done a great job simplifying a complex field.

Response: Thank you for the positive comments.

However, the authors may have over-simplified the results. They have taken a very mixed range of interventions and pooled them and there may be significant differences between them. This is important as there is high heterogeneity which could be explored.
1. Please give explicit inclusion criteria for trials - these are reported as study search and selection, but you need to provide a list of exactly what the inclusion and exclusion criteria for studies were. Please state explicitly whether you limited these studies to people with symptoms of distress at baseline or whether this was for all patients with CHD, I assume the latter, but this distinction is important and might also be raised more in the introduction.

Response: Thank you for your recommendation. The inclusion and exclusion criteria are now specified on the Study search and selection criteria section in page 5:

> *"Studies were eligible for inclusion if they met the following criteria: RCTs in humans including patients with CAD or IHD; the PIs and psychological techniques used in these therapies were based on CBT or PPT; and at least one of the psychological endpoints considered in this meta-analysis was reported. Exclusion criteria were: studies in which patient assignation to treatment conditions were not randomized or where there was not control group; PIs based on any treatment approach different to CBT or PPT; studies not describing the specific techniques used in their PIs; and when the treatment strategy only included physical exercise and educational or counselling programs."*

2. Please describe the interventions in more depth - from the table, you don't say the intensity of the intervention but give duration - 1 week to 12 months - it would be helpful to know how many sessions were involved where that is possible. Was cCBT or other online methods eligible? Again the eligibility criteria need to be more specific here.

Response: Due to constrains in the number of words by the journal guidelines, the PIs paradigms considered in this meta-analysis (CBT and PPT) briefly described in page 6. The characteristics of the PIs form all studies are mentioned in page 9-10, and the specific and detailed information of the PI from each RCT are shown in Table 1, i.e. type of PI (CBT or PPT), PI provider (psychologist, health provider or unknown), if PI were multicomponent or single component, group or individual treatment, as well as the specific techniques included in the experimental PI condition and treatment modality (in-person vs. on-line). Also, more information related to treatment sessions periodicity and/or duration has been added to Table 1.

There were no restrictions related to the methodology of PI application, as the inclusion criteria was that treatment included cognitive-behavioral and/or positive psychology techniques. However, all the studies included in this meta-analysis were developed in person treatment, except for the studies by O´Neil et al. (2014 and 2015) where the PIs were developed by telephone. This information is now mentioned in the "Characteristics of included studies" section in page 10:

"*CBT interventions were heterogeneous across trials, mostly multicomponent and in person with the only exception of the trials by O´Neil et al. (2014, 2015) where PIs were performed by telephone*".

3. Please provide information where available on baseline mental health scores - differences in the baseline scores may be an important source of heterogeneity, and as far as I can see the analyses only take account of endpoint scores, not baseline.

Response: The information on baseline mental health scores is not mentioned in the manuscript due to extension constrains. However, differences between baseline and post-treatment or follow-up scores were analyzed and adjusted for in multivariate analyses, as described in the Methods ("The analyses of outcomes were adjusted for baseline characteristics").

4. P12 - the authors' English is excellent, but "the short statistical power" isn't quite right - suggest substitute "low" for "short".

Response: Thank you for your recommendation. This has been changed in page 14.

Héctor Bueno, MD, PhD, FESC, FAHA
Centro Nacional de Investigaciones Cardiovasculares (CNIC)
Department of Cardiology, Hospital Universitario 12 de Octubre
Madrid, Spain

Inés Magán, PhD
Department of Psychology. Universidad Camilo José Cela
Madrid, Spain

Robert M. Murray
Editor, Psychological Medicine, UK Office

February 24, 2020

Dear Dr. Murray,

Thank you very much for the opportunity to revise and resubmit our manuscript entitled "***"Efficacy of psychological interventions on psychological outcomes in coronary artery disease: Systematic review and meta-analysis***" (Manuscript ID PSM-D-19_01144) to *Psychological Medicine*. We would also like to thank the reviewers for their insightful and helpful comments. We have carried out a revision of the manuscript according to your recommendations, addressing each comment from all reviewers.

We thank you in advance for your time and look forward to receiving a positive response from you.

Yours sincerely,

Héctor Bueno, MD, PhD

Inés Magan, PhD