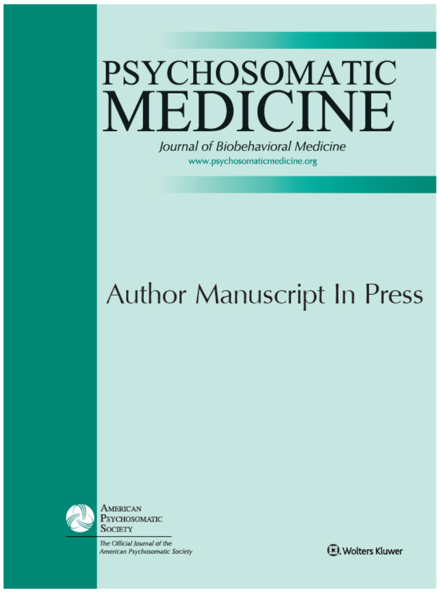
DOI:
10.1097/PSY.0000000000000872

Citation for published version (APA):
Rosson, S., Monaco, F., Miola, A., Cascino, G., Stubbs, B., Correll, C. U., Firth, J., Ermis, C., Perrotti, A., Marciello, F., Carvalho, A. F., Brunoni, A. R., Fusar-Poli, P., Fornaro, M., Gentile, G., Granziol, U., Pigato, G., Favaro, A., & Solmi, M. (2021). Longitudinal course of depressive, anxiety, and posttraumatic stress disorder symptoms after heart surgery: A meta-analysis of 94 studies. *Psychosomatic Medicine*, *83*(1), 85-93. https://doi.org/10.1097/PSY.0000000000000872



Psychosomatic Medicine
Author's Accepted Manuscript

Article Title: Longitudinal course of depressive, anxiety, and post-traumatic stress disorder symptoms after heart surgery: a meta-analysis of 94 studies

Authors: Stella Rosson, Francesco Monaco, Alessandro Miola, Giammarco Cascino, Brendon Stubbs, Christoph U. Correll, Joseph Firth, Cagatay Ermis, Andrea Perrotti, Francesca Marciello, Andrè F. Carvalho, Andre R Brunoni, Paolo Fusar-Poli, Michele Fornaro, Giovanni Gentile, Umberto Granziol, Giorgio Pigato, Angela Favaro, and Marco Solmi

DOI: 10.1097/PSY.0000000000000872

Received Date: March 17, 2020
Revised Date: July 13, 2020

Psychosomatic Medicine Publish Ahead of Print
DOI: 10.1097/PSY.0000000000000872

Longitudinal course of depressive, anxiety and post-traumatic stress disorder symptoms after heart surgery: a meta-analysis of 94 studies

Stella Rosson, MD[1], Francesco Monaco, MD[2], Alessandro Miola, MD[1], Giammarco Cascino, MD[3], Brendon Stubbs, PhD[4,5], Christoph U. Correll, MD, PhD[6,7,8,9], Joseph Firth, MD, PhD[10,11,12], Cagatay Ermis, MD[13], Andrea Perrotti, MD, PhD[14,15], Francesca Marciello, MD[3], Andrè F. Carvalho, MD, PhD[16,17], Andre R Brunoni, MD, PhD[18,19,20], Paolo Fusar-Poli, MD, PhD[21,22,23,24], Michele Fornaro, MD, PhD[25], Giovanni Gentile, PhD[26], Umberto Granziol, PhD[27], Giorgio Pigato, MD[28], Angela Favaro, MD, PhD[1,26], Marco Solmi, MD, PhD[1,21,26]

[1] Neurosciences Department, University of Padua, Padua, Italy

[2] Department of Mental Health, Residential Eating Disorder Unit "Mariconda", ASL Salerno, Salerno, Italy

[3] Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", Section of Neurosciences, University of Salerno, Salerno, Italy

[4] Physiotherapy Department, South London and Maudsley National Health Services Foundation Trust, London, UK.

[5] Department of Psychological Medicine, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK.

[6] The Zucker Hillside Hospital, Department of Psychiatry, Northwell Health, Glen Oaks, NY, USA.

[7] Zucker School of Medicine at Hofstra/Northwell, Department of Psychiatry and Molecular Medicine, Hempstead, NY, USA.

[8] The Feinstein Institute for Medical Research, Center for Psychiatric Neuroscience, Manhasset, NY, USA.

[9] Charité Universitätsmedizin Berlin, Department of Child and Adolescent Psychiatry, Berlin, Germany.

[10] Division of Psychology and Mental Health, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom.

[11] NICM Health Research Institute, School of Science and Health, University of Western Sydney, Sydney, Australia

[12] Centre for Youth Mental Health, University of Melbourne, Melbourne, Australia.

[13] Dokuz Eylul University, Department of Child and Adolescent Psychiatry

[14] Cardio-Thoracic Surgery Department, University Hospital Jean Minjoz, Boulevard Fleming, 25000, Besançon, France.

[15] EA 3920, University of Franche-Comté, 25000, Besançon, France.

[16] Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada

[17] Department of Psychiatry, University of Toronto, Toronto, ON, Canada.

[18] Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany;

[19] Service of Interdisciplinary Neuromodulation, Department of Psychiatry, Laboratory of Neurosciences (LIM-27) and National Institute of Biomarkers in Neuropsychiatry (INBioN), Institute of Psychiatry, University of Sao Paulo, Sao Paulo, Brazil;

[20] Hospital Universitario, Departamento de Clínica Médica, Faculdade de Medicina da USP, São Paulo, Brazil.

[21] Early Psychosis: Interventions and Clinical-detection (EPIC) lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology& Neuroscience, King's College London, London, UK.

[22] OASIS service, South London and Maudsley NHS Foundation Trust, London, UK.

[23] Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy.

[24] National Institute for Health Research, Maudsley Biomedical Research Centre, South London and Maudsley NHS Foundation Trust, London, UK.

[25] Neuroscience, Reproductive Science and Odontostolmatology, Section of Psychiatry, University School of Medicine Federico II, Naples, Italy

[26] Neuroscience Centre, University of Padua, Padua, Italy.

[27] Department of General Psychology, University of Padua, Padua, Italy

[28] Padua University Hospital, Psychiatry Unit, Padua, Italy

Corresponding author

Dr. Marco Solmi, PhD, MD

Neurosciences Department, University of Padua, Padua, Italy

Via Giustiniani, 5, 35100, Padua, Italy

Marco.solmi83@gmail.com – 00390498213830

Conflicts of Interest and Source of Funding

Stella Rosson, Francesco Monaco, Alessandro Miola, Giammarco Cascino, Brendon Stubbs, Joseph Firth, Andrea Perrotti, Francesca Marciello, Andrè F. Carvalho, Andre R. Brunoni, Michele Fornaro, Giovanni Gentile, Umberto Granziol, Giorgio Pigato, Angela Favaro, Marco Solmi, have no conflict of interest to declare.

Christoph U. Correll has been a consultant and/or advisor to or has received honoraria from: Alkermes, Allergan, Angelini, Gedeon Richter, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, MedAvante-ProPhase, Medscape, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva. He has provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Rovi, Supernus, and Teva. He received royalties from UpToDate and grant support from Janssen and Takeda. He is also a stock option holder of LB Pharma. Cagatay Ermis was supported by a grant from The Scientific and Technological Research Council of Turkey (TUBITAK). Paolo Fusar-Poli has received honoraria from Lundbeck and Menarini and grant support from Lundbeck.

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Abstract

Objective: To analyze the longitudinal course of depression, anxiety and post-traumatic stress disorder (PTSD) symptoms in cardiac patients following heart surgery (HS).

Methods: We conducted a systematic review and random-effects meta-analysis of cohort studies on patients undergoing HS, measuring anxiety, depressive, and PTSD symptoms before and at least 30 days after. Subgroup and meta-regression analyses, investigation of publication bias, and quality assessment were undertaken.

Results: We included 94 studies relating to 15,561 patients. HS included coronary artery bypass graft surgery, valve replacement, implantable cardioverter defibrillator placement, left ventricular assist device placement, heart transplantation, and other types of HS. Across studies, symptoms of depression ($g=0.32$; 95%CI=0.25,0.39; $p<0.001$) and anxiety improved after HS ($g=0.52$; 95%CI=0.43,0.62; $p<0.001$), while PTSD symptoms worsened ($g=-0.42$; 95%CI=-0.80,-0.04; $p=0.032$). The reduction of depression and anxiety levels was more pronounced for patients with underlying coronary artery disease and heart failure, and persisted over one year after HS, whereas the increase in PTSD symptoms returned to baseline after 6 months. Depression improvement was inversely associated with older age, diabetes, hypertension and dyslipidemia, and positively with baseline heart failure. No additional clinical or demographic variables were associated with the course of anxiety symptoms. Quality of included studies was low overall. Publication bias was non-significant.

Conclusions: Depressive and anxiety symptoms improve over one-year after HS, while PTSD symptoms might worsen. Older patients, those with metabolic comorbidities, valve disease or ventricular arrhythmias are at higher risk for continued depressive and anxiety symptoms and should be monitored closely.

Key words: Depression, Anxiety, Cardiovascular diseases, Heart surgery, Post-traumatic stress disorder

Abbreviations: CABG = coronary artery bypass graft; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; DSM= Diagnostic and Statistical Manual of Mental Disorders; HF = heart failure; HS = heart surgery; HT = heart transplantation; ICD = implantable cardioverter defibrillator; ICU = intensive care unit; MDD = Major Depressive Disorder; MetS = metabolic syndrome; NOS = Newcastle-Ottawa Scale; PRISMA = Reporting Items for Systematic Reviews and Meta-Analyses; PTSD = post-traumatic stress disorder; PTSS = post-traumatic stress symptoms; SCA = sudden cardiac arrest; VAD = ventricular assist device.

Introduction

It is estimated that over 290,000 heart surgery (HS) procedures are performed annually just in the United States of America (1). The most frequent procedures among adults involve coronary artery bypass graft (CABG) surgery, isolated aortic valve replacement, and a combination of these two (1). These surgical interventions are performed for life-threatening and disabling cardiac conditions, including coronary heart disease (CHD) and heart valve disease. Surgical interventions also encompass life-saving treatments, such as heart transplantations (HT), that are performed in few specialized centers worldwide.

There is a strong association between cardiovascular disease (CVD) and mental disorders, with data showing that patients with severe mental illness have an increased risk of both having (cross-sectional data) or developing (longitudinal data) CVD, compared to the general population (2). The association between CVD and mental disorders also holds true in the opposite direction (3). For instance, in the case of full-threshold Major Depressive Disorder (MDD), a condition mainly characterized by depressed mood and/or decreased interest or pleasure, depression affects up to one out of five patients with CHD or heart failure (HF), and an even higher proportion for subthreshold depression. (4,5)

Patients with CVD can also suffer from anxiety disorders, including Generalized Anxiety Disorder, a condition identified by pervasive worry or anxiety, and Panic Disorder, that is defined by recurrent panic attacks. (5) Additionally, depressive and anxiety disorders frequently co-occur and share common features, like alterations in the sleeping pattern and impaired concentration. (5) The prevalence of any anxiety disorder in CHD patients has been estimated to be around 15%, and the comorbidity with depression has been reported for nearly half of the patients. (6,7)

Moreover, PTSD symptoms, such as heightened state of arousal, intrusive memories, and avoidant behavior related to a traumatic experience, are not rare in patients with cardiac disease. (5) Among these patients, the prevalence of PTSD has been reported as high as 12%, which is actually consistent with the lifetime prevalence of PTSD in the general population. (8–11)

Depressive and anxiety disorders can also affect the prognosis of patients with CHD, in terms of occurrence of major adverse cardiac events and, ultimately, mortality for those undergoing HS. (12–14) For instance, it has been reported that poor mental health impacts on adherence to the complex medication schedule required, with subsequent long-term complications and mortality. (14–18)

Although the outcome of CVDs can be dramatically modified by specific surgical operations in this population, the course of anxiety, depressive, and PTSD symptoms following HS has been less extensively explored. Some studies suggest that individuals undergoing HS suffer from symptoms of depression and anxiety more frequently than the average population, and that can develop PTSD in the post-operative period. (19–21) However, the rates reported are variable and mainly related to CABG surgery alone.

Given the limited evidence on effects of HS on mental health, the bidirectional relationship between cardiac and psychiatric disorders, and the potential consequences of impaired mental health on physical outcomes after HS, it is important to understand how HS impacts on mental health. However, the current evidence on the course of mental health in patients undergoing HS is equivocal, with no prior meta-analysis performing any evidence synthesis on this clinically relevant topic.

Therefore, we conducted a systematic review and meta-analysis to determine the impact of HS on mental health outcomes. Due to the link between cardiac health and depression and anxiety, we firstly hypothesized that HS would improve depressive and anxiety symptoms. Second, we hypothesized HS could trigger PTSD symptoms because of the exposure to potentially traumatic experiences such as the Intensive Care Unit (ICU) stay and the surgery itself. (22,23). Finally, we aimed to identify specific moderators of such improvements.

Material and methods

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (24). It followed a predetermined but unpublished protocol that can be found in the study protocol, Supplemental Digital Content, http://links.lww.com/PSYMED/A690.

Search and selection strategy

Two authors (SR, FMo) independently conducted a systematic literature search in two electronic databases (PubMed and Scopus), until 07/31/2019, using the following keywords: ("implantable cardiac defibrillator" OR "cardiac operation" OR "heart surgery" OR "cardiac surgery" OR "coronary artery bypass" OR "open heart surgery" OR "valve surgery" OR “heart transplant*”)

AND ((("depression" OR "depressive") AND "episode") OR "major depressive disorder" OR "anxiety" OR "PTSD" OR "post-traumatic stress disorder" OR "acute stress-reaction" OR "quality of life"). Search results were collected on a spreadsheet and duplicates were removed. Six reviewers in blind couples (SR, FMo, AP, FMa, AM, GG) then conducted the study selection. According to PRISMA guidelines, a first screening based on title and abstract assessment was followed by the full-text evaluation of potentially eligible articles. (24) Only studies fulfilling all the predefined criteria were finally included. Any disagreement among authors was resolved by consensus with a third investigator (MS).

Inclusion and exclusion criteria

We included peer-reviewed articles reporting on cohort studies that a) involved cardiac patients scheduled to undergo HS, b) measured depression, anxiety, or PTSD symptoms with validated scales, c) reported symptom measures before and at least 1 month after surgery. This time window was set a-priori to collect information regarding sustained depressive, anxiety and post-traumatic symptoms, rather than transient disturbances attributable to an acute stress disorder, according to the DSM criteria (5).

We excluded articles in languages other than English, editorials, case reports, interventional studies, review articles, meta-analyses, and conference abstracts. Considering the evolution of diagnostic systems, as well as HS techniques, we opted to exclude articles published before 1980, when PTSD was first described among mental disorders. (25)

Data extraction

The same six reviewers in blind couples conducted the data extraction from the included studies. The following data were extracted in a pre-defined spreadsheet: i) bibliographic information (DOI, authors, country, year of publication); ii) sample size, demographics, follow-up duration; iii) medical information (heart disease, severity markers, type of HS, and medical comorbidities); iv) psychometric information (assessed psychiatric diagnoses at baseline, symptom measures and instruments, and values at baseline and at the longest follow-up); v) information to rate quality (see below). Whereas outcomes of the study population had been reported for subgroups by the authors, we extracted additional information regarding the partition criteria for the cohort.

Outcomes

The primary outcome was the magnitude of change in depressive, anxiety, and PTSD symptoms in cardiac patients following HS. The secondary outcomes were the duration of such changes, and the identification of demographic and clinical variables predictive of improvement in mental health after HS.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was applied to assess the quality of cohort studies based on cohort selection, comparability and evaluation. The possible score ranges from 0 to 9, with higher scores indicating a better methodological conduction. (26) We set a threshold of 7 points to identify high quality investigations, as previously done in medical literature (27,28).

Data analyses

This meta-analysis was performed by using the software Comprehensive Meta-Analysis, version 2.0. (29)

Analyses were run separately for depressive, anxiety, and PTSD symptoms. Given that we anticipated considerable heterogeneity across included studies, we performed a random-effects meta-analysis. (30,31) To maximize the number of included studies (k), we calculated standardized effect size Hedge's g for outcomes reported either in a continuous or dichotomous fashion and pooled them together. We assumed a conservative pre-post correlation coefficient of 0.5, if not otherwise specified by the authors. Heterogeneity was assessed with the I^2 statistics for each analysis (with significant heterogeneity being indicated by $I^2 \geq 50\%$).(32) Publication bias was assessed via visual inspection of funnel plots and Egger bias test. (33,34)

We conducted subgroup analyses to investigate if there was any difference among studies that included patients with psychiatric disorders at baseline or not, among regions, type of heart surgery, among individuals undergoing HS for the first time or more, and among follow-up duration ranges (1-3 months, ≥3-6 months, ≥6-12 months , >1 year). A subgroup analysis was also conducted for modalities of reporting the outcome, to investigate a potential bias introduced from pooling effect sizes of binary and continuous data together.

Finally, we performed meta-regression analyses of continuous variables, including mean age, % married, % white, % males, % with specific medical comorbidities, and % smoking. Meta-regression analyses were performed on moderator variables which included data from ≥10 studies, according to Cochrane guidelines. (35)

Results

Search results

The study selection process is outlined in **Figure 1**. Overall, from initially 13,315 hits, 717 full-text articles were retrieved (the list of excluded studies with reason is reported in Supplementary table 4, http://links.lww.com/PSYMED/A690), of which finally 94 prospective studies were eligible for inclusion.

Characteristics of included studies and participants

The analyzed 94 studies involved 15,561 individuals undergoing cardiac surgery. Supplementary Table 1, http://links.lww.com/PSYMED/A690 reports detailed characteristics of the included studies. Mean age of the study population was 62.9 years. Participants were 73.8% male and 71.7% white. Investigations were conducted in 24 different countries, with the highest number conducted in Europe (43.6%) and North America (40.4%), followed by Asia (9.6%), Oceania (4.3%), and South America (2.1%). The year of publication ranged from 1982 to 2019. The patients reported across the studies underwent CABG (60.6%), heart transplant (3.6%), isolated valve surgery (0.8%), ventricular assist device (VAD) implantation (0.4%), implantable cardioverter defibrillator (ICD) implantation (0.2%), or were reported to have a mixture of different surgical operations (34.4%), such as combined procedures and congenital heart disease surgery. The mean follow-up was 11.4 months.

Main and subgroup meta-analyses of cohort studies

Detailed results of main and subgroup meta-analyses are reported in **Tables 1-3.** Forest and funnel plots can be found as Supplementary figures 1-6, http://links.lww.com/PSYMED/A690.

The overall effect size for reducing depressive symptoms was Hedge' g=0.32 (k= 81; 95%CI= 0.25, 0.39; p<0.001; I^2=86%), without evidence for publication bias (p=0.060). Subgroup analyses identified differences among regions, with a significant improvement only for Asia, Europe and North America, and for type of surgical procedures, with amelioration for CABG, HT, VAD implantation, and mixed procedures, but not for isolated valve surgery or ICD implantation. No difference was found for groups defined by baseline inclusion of psychiatric disorders, first time/second time or more prior HS procedures, or follow-up duration. There was a difference for outcome measurement (p=0.005), with a higher effect size for continuous rather than binary assessments (yet both were significant).

The overall effect size for the decrease in anxiety symptoms was 0.52 (k=53; 95%CI= 0.43, 0.62; p<0.001; I^2=89%), without evidence for publication bias (p=0.35). The subgroup analyses confirmed the same differences among regions and surgical procedures observed for depressive symptoms. No difference in improvement was found for inclusion of psychiatric disorders at baseline, selection of first-time intervention, outcome measurement, or follow-up duration.

Post-traumatic stress symptoms (PTSS) worsened after HS (k=7; g=-0.42; 95%CI= -0.80, -0.04; p=0.032; I^2=76%), without evidence for publication bias (p=0.060). A subgroup analysis revealed a difference for follow-up duration (p=0.002), with significant aggravation of PTSS only during the first 6 months after surgery. Among regions, a significant worsening was detected for studies conducted in North America, but not in Asia and Europe. There was also significant worsening among underlying disease for CAD, but not for HF or mixed conditions. No difference was found for the other variables explored.

Meta-regression

Detailed results of meta-regression analyses are reported in Supplementary table 2, http://links.lww.com/PSYMED/A690.

For depressive symptoms, a moderator of improvement was having heart failure at baseline, while age, comorbid diabetes, hypertension, and dyslipidemia worsened the outcome. The only severity marker reported in at least 10 investigations was the left ventricular ejection fraction (LVEF), whose value did not seem to affect this psychiatric outcome.

Regarding the course of anxiety symptoms, no clinical or demographic variable proved to be influential. No severity index of cardiac disease was reported in enough studies to perform a meta-regression.

Meta-regression analysis could not be performed for PTSS because of the small number of studies.

Quality of included studies

Among studies, the median NOS score was 5 (range: 4 - 8), indicating that quality was overall unsatisfactory. The main criteria lowering the NOS score was the lack of a non-exposed cohort as a comparison in the vast majority of the studies. Only 4 studies reached the threshold of 7 (3 for depression, 1 for anxiety, 1 for PTSS), not allowing us to perform a sensitivity analysis based on high-quality investigations. NOS score details can be found in Supplementary table 3, http://links.lww.com/PSYMED/A690.

Discussion

To the best of our knowledge, this study is the first large-scale meta-analysis investigating the evolution of depressive, anxiety and PTSD symptoms in cardiac patients exposed to HS.

Evidence from cohort studies showed that patients undergoing HS had a mild to moderate and long-lasting improvement of depressive and anxiety symptoms. This change depended on the surgical procedure, with the greatest improvements following VAD implantation and HT, small but significant effects for CABG and mixed interventions, and non-significant improvement following valve surgery and ICD implantation. The amelioration of depressive symptoms was hindered by older age, hypertension, diabetes, and dyslipidemia. PTSS worsened after HS, but only temporarily in the first 6 post-operative months, thereafter resuming to pre-surgical levels.

Despite the high prevalence of depression in patients with HF (7,18), our analysis demonstrated that patients with end-stage HF undergoing this intervention experienced the largest improvement in observational studies. Such improvement of depressive symptoms in individuals undergoing HS with terminal HF could be related to the dramatic physical and life-expectancy improvement for these patients compared to the pre-HS severity. (36) Regarding the negatively moderating effects of hypertension, diabetes, and dyslipidemia on depressive symptoms, results are consistent in indicating an adverse role of metabolic syndrome (MetS), rather than its individual components. (37–40) MetS has indeed been shown to have a bidirectional association with depression. (41) Unfortunately, there were insufficient data to perform a meta-regression analysis testing obesity as a potential moderator to assess all the individual components of MetS. LVEF, the objective marker of severity we analyzed, did not seem to be associated with this psychiatric outcome, in line with previous evidence for patients with HF, even though the reasons remain unclear. (42,43) It is possible that subjective indicators, such as the New York Heart Association class, could predict depressive symptoms, as a connection has been found among patients diagnosed with HF. (42,43) However, the latter was not possible to investigate with a meta-regression, and further studies are required to establish this potential relationship in HS patients.

Individuals undergoing HS also displayed moderate improvement of anxiety symptoms, that lasted over time. Similar to our findings for depressive symptoms, improvement was dependent from the underlying cardiac disease, being highest for patients with end-stage HF requiring VAD implantation or HT, whereas patients undergoing ICD implantation or valve surgery did not show a significant decrease in anxiety symptoms. Improved anxiety was not related to demographic variables. It is interesting to notice that the cardiometabolic conditions that worsened depression did not show a significant impact on anxiety symptoms. Actually, a previous meta-analysis investigating the relationship between MetS and anxiety demonstrated a link between the two conditions in cross-sectional data, but could not prove a reciprocal influence in longitudinal data. (44) Although anxiety symptoms are suspected to increase the risk of MetS through alterations such as decreased heart rate variability, the opposite relationship has been less in-depth investigated. (45–47)

In contrast with the amelioration of depressive and anxiety symptoms, there was a mild worsening of PTSS after heart surgery. Differently from the first two disturbances, PTSD is classified as a stress-related disorder because of its distinctive feature of being triggered by a traumatic experience, like a surgical procedure and the ICU stay can be perceived. (5) Moreover, the underlying pathophysiological mechanisms of these clinical conditions only partially overlap. For instance, even though all these different disorders share an HPA axis dysregulation, depressive and anxiety disorders have been linked with increased levels of cortisol, while the development of PTSD seems associated with lower cortisol levels. (22,48,49) Our subgroup analysis revealed that the population at higher risk for PTSS were patients undergoing CABG. The severity of PTSS was highest during the first 6 months post-HS, becoming non-significant thereafter. This finding is consistent with previous evidence of the longitudinal course of PTSD, suggesting maximum prevalence soon after the traumatic experience with a decline over time. (50) However, the limited number of available studies and the frequent use of PTSS assessments as continuous measure of severity rather than categorical diagnosis suggest a cautious interpretation of these results.

Several limitations should be taken into account when interpreting our results. First, the variability of assessment tools to detect anxiety, PTSD and depression, and within the same rating scales the use of different cut-offs to identify a clinically relevant condition, might have influenced the heterogeneity of the measured symptoms. Second, only few studies referred to international systems, such as the DSM, when reporting the diagnoses. Third, based on the ratings, it was impossible to distinguish to what degree depressive symptoms and anxiety were related to the CVD and its burden/consequences or to concerns about the impending HS itself. Last, it would have been of great interest to confirm our results with a sensitivity analysis based on high-quality studies, that was not possible to perform due to the small number of investigations meeting our high-quality standards.

The present study has also several strengths. First, this is the largest evidence synthesis to date reporting on the longitudinal course of depressive and anxiety symptoms after HS. Second, by comprehensively assessing the evidence with quantitative meta-analytic methods we were able to generate new evidence that has clinical implications, indicating that depressive and anxiety symptoms improve after HS, and that PTSS are generally time limited. Third, we were able to identify subgroups of cardiac patients that should be better monitored for psychological wellbeing in the post-operative period, since at risk for persistent depressive or anxiety symptoms. Finally, our results highlight the need of customized interventions for patients undergoing HS whom depressive symptoms and anxiety do not improve; specifically, calling for future randomized controlled trials testing mental health outcomes of pharmacological, psychotherapeutic, and rehabilitative interventions in this population.

In conclusion, our results suggest a positive course of depressive and anxiety symptoms in cardiac patients following HS, and that arising PTSS commonly vanish after 6 months.

Individuals undergoing valve surgery and ICD implantation are less susceptible to a reduction in depression and anxiety post-HS. Older patients with cardiometabolic conditions are the most vulnerable to continue with depressive symptoms. Clinical trials targeting depressive, anxiety, and PTSD symptoms in this specific population are needed to identify effective adjunctive treatments for those cases in whom the expected improvement of depressive symptoms and anxiety does not occur after HS, and in whom clinically relevant PTSS persist.

Acknowledgements

None.

References

1. D'Agostino RS, Jacobs JP, Badhwar V, Paone G, Rankin JS, Han JM, McDonald D, Edwards FH, Shahian DM. The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2017 Update on Outcomes and Quality. Ann. Thorac. Surg. [Internet]. 2017 [cited 2019 Apr 1];103:18–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27884412
2. Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P, Thapa-Chhetri N, Fornaro M, Gallicchio D, Collantoni E, Pigato G, Favaro A, Monaco F, Kohler C, Vancampfort D, Ward PB, Gaughran F, Carvalho AF, Stubbs B. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry. 2017;16:163–80.
3. Firth J, Siddiqi N, Koyanagi A, Siskind D, Rosenbaum S, Galletly C, Allan S, Caneo C, Carney R, Carvalho AF, Chatterton M Lou, Correll CU, Curtis J, Gaughran F, Heald A, Hoare E, Jackson SE, Kisely S, Lovell K, Maj M, McGorry PD, Mihalopoulos C, Myles H, O'Donoghue B, Pillinger T, Sarris J, Schuch FB, Shiers D, Smith L, Solmi M, Suetani S, Taylor J, Teasdale SB, Thornicroft G, Torous J, Usherwood T, Vancampfort D, Veronese N, Ward PB, Yung AR, Killackey E, Stubbs B. The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. The Lancet Psychiatry. 2019;6:675–712.
4. Huffman JC, Celano CM, Beach SR, Motiwala SR, Januzzi JL. Depression and Cardiac Disease: Epidemiology, Mechanisms, and Diagnosis. Cardiovasc. Psychiatry Neurol. 2013;2013:695925.
5. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC: Author; 2013.
6. Tully PJ, Cosh SM, Baumeister H. The anxious heart in whose mind? A systematic review and

meta-regression of factors associated with anxiety disorder diagnosis, treatment and morbidity risk in coronary heart disease. Journal of Psychosomatic Research. 6: 439-448; 2014. p. 77.

7. Fusar-Poli P, Martinelli V, Klersy C, Campana C, Callegari A, Barale F, Viganò M, Politi P. Depression and quality of life in patients living 10 to 18 years beyond heart transplantation. J. Hear. Lung Transplant. 2005;24:2269–78.

8. Vilchinsky N, Ginzburg K, Fait K, Foa EB. Cardiac-disease-induced PTSD (CDI-PTSD): A systematic review. Clin. Psychol. Rev. 2017;55:92–106.

9. Lane-Fall MB, Kuza CM, Fakhry S, Kaplan LJ. The Lifetime Effects of Injury: Postintensive Care Syndrome and Posttraumatic Stress Disorder. Vol. 37, Anesthesiology Clinics. W.B. Saunders; 2019. p. 135–50.

10. Schelling G. Post-traumatic stress disorder in somatic disease: lessons from critically ill patients. Vol. 167, Progress in Brain Research. 2008. p. 229–37.

11. Meentken MG, van Beynum IM, Legerstee JS, Helbing WA, Utens EMWJ. Medically Related Post-traumatic Stress in Children and Adolescents with Congenital Heart Defects. Front. Pediatr. 2017;5.

12. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and Risk of Incident Coronary Heart Disease. A Meta-Analysis. J. Am. Coll. Cardiol. 2010;56:38–46.

13. Frasure-Smith N, Lespérance F. Depression and Anxiety as Predictors of 2-Year Cardiac Events in Patients With Stable Coronary Artery Disease. Arch Gen Psychiatry. 2008;65:62–71.

14. Takagi H, Ando T, Umemoto T. Perioperative depression or anxiety and postoperative mortality in cardiac surgery: a systematic review and meta-analysis. Heart Vessels. 2017;32:1458–68.

15. Ghoneim MM, O'Hara MW. Depression and postoperative complications: An overview Visceral and general surgery. Vol. 16, BMC Surgery. BioMed Central Ltd.; 2016.

16. Politi P, Piccinelli M, Poli PF, Klersy C, Campana C, Goggi C, Viganò M, Barale F. Ten years of “extended” life: quality of life among heart transplantation survivors. Transplantation. 2004;78:257–63.

17. Fusar-Poli P, Picchioni M, Martinelli V, Bhattacharyya S, Cortesi M, Barale F, Politi P. Anti-depressive Therapies After Heart Transplantation. Vol. 25, Journal of Heart and Lung Transplantation. 2006. p. 785–93.

18. Martinelli V, Fusar-Poli P, Emanuele E, Klersy C, Campana C, Barale F, Viganò M, Politi P. Getting Old With a New Heart: Impact of Age on Depression and Quality of Life in Long-term Heart Transplant Recipients. J. Hear. Lung Transplant. 2007;26:544–48.

19. Hata M, Yagi Y, Sezai A, Niino T, Yoda M, Wakui S, Soeda M, Nohata I, Shiono M MK. Risk analysis for depression and patient prognosis after open heart surgery. Circ. J. 2006;Apr;70:389–92.

20. Pignay-Demaria V, Lespé Rance F, Demaria RG, Frasure-Smith N, Perrault LP. Depression and Anxiety and Outcomes of Coronary Artery Bypass Surgery Overview of Epidemiology of Depression and Anxiety in Coronary Artery Disease. Vol. 75, Ann Thorac Surg. 2003. Available from: www.ncbi.nlm.nih.gov/PubMed

21. Tully PJ, Baker RA. Depression, anxiety, and cardiac morbidity outcomes after coronary artery bypass surgery: A contemporary and practical review. Vol. 9, Journal of Geriatric Cardiology. 2012. p. 197–208.

22. Porhomayon J, Kolesnikov S, Nader ND. The Impact of Stress Hormones on Post-traumatic Stress Disorders Symptoms and Memory in Cardiac Surgery Patients. J. Cardiovasc. Thorac. Res. 2014;6:79–84.

23. Al-Bitar ZB, Al-Ahmad HT. Anxiety and post-traumatic stress symptoms in orthognathic

surgery patients. Eur. J. Orthod. 2017;39:92–97.

24. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. In: J. Clin. Epidemiol. 2009. p. e1–34.

25. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (Third Edition). Washington, DC: APA Press.; 1980.

26. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Al. E. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Ottawa Hospital Research Institute, editor. Ottawa; Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp2017.

27. Lyngsø J, Ramlau-Hansen CH, Bay B, Ingerslev HJ, Hulman A, Kesmodel US. Association between coffee or caffeine consumption and fecundity and fertility: A systematic review and dose-response meta-analysis. Vol. 9, Clinical Epidemiology. Dove Medical Press Ltd; 2017. p. 699–719.

28. He YK, Li HZ, Lu HD. Is blood transfusion associated with an increased risk of infection among spine surgery patients?: A meta-Analysis. Vol. 98, Medicine (United States). Lippincott Williams and Wilkins; 2019.

29. Biostat. Comprehensive Meta-Analysis. Available from: http://www.meta-analysis.com

30. DerSimonian R, Laird N. Meta-Analysis in Clinical Trials. Control. Clin. Trials. 1986;7:177–88.

31. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: An update. Contemp. Clin. Trials. 2007;28:105–14.

32. Higgins J, Thompson S, Deeks J, Altman D. Measuring inconsistency in meta-analyses. Br. Med.

J. 2003;327:557–60.

33. Begg CB, Mazumdar M. Operating Characteristics of a Rank Correlation Test for Publication Bias. Biometrics. 1994;50:1088–1101.

34. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Br. Med. J. 1997;315:629–34.

35. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, Welch V. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane; 2019. Available from: www.training.cochrane.org/handbook

36. Alraies MC, Eckman P. Adult heart transplant: Indications and outcomes. J. Thorac. Dis. 2014;6:1120–28.

37. Meng L, Chen D, Yang Y, Zheng Y, Hui R. Depression increases the risk of hypertension incidence: A meta-analysis of prospective cohort studies. Vol. 30, Journal of Hypertension. 2012. p. 842–51.

38. Roy T, Lloyd CE. Epidemiology of depression and diabetes: A systematic review. Vol. 142, Journal of Affective Disorders. 2012.

39. Moulton CD, Pickup JC, Ismail K. The link between depression and diabetes: The search for shared mechanisms. Vol. 3, The Lancet Diabetes and Endocrinology. Lancet Publishing Group; 2015. p. 461–71.

40. Parekh A, Smeeth D, Milner Y, Thuret S. The Role of Lipid Biomarkers in Major Depression. Healthcare. 2017;5:5.

41. Pan A, Keum N, Okereke OI, Sun Q, Kivimaki M, Rubin RR, Hu FB. Bidirectional Association Between Depression and Metabolic Syndrome: A systematic review and meta-analysis of epidemiological studies. Diabetes Care [Internet]. 2012;35:1171–80. Available from:

http://care.diabetesjournals.org/cgi/doi/10.2337/dc11-2055

42. Lossnitzer N, Feisst M, Wild B, Katus HA, Schultz JH, Frankenstein L, Stock C. Cross-lagged analyses of the bidirectional relationship between depression and markers of chronic heart failure. Depress. Anxiety. 2020;

43. Feola M, Garnero S, Vallauri P, Salvatico L, Vado A, Leto L, Testa M. Relationship Between Cognitive Function, Depression/Anxiety and Functional Parameters in Patients Admitted for Congestive Heart Failure. Open Cardiovasc Med J . . 2013;7:54–60.

44. Tang F, Wang G, Lian Y. Association between anxiety and metabolic syndrome: A systematic review and meta-analysis of epidemiological studies. Psychoneuroendocrinology. 2017;77:112–21.

45. Hu MX, Lamers F, De Geus EJC, Penninx BWJH. Differential autonomic nervous system reactivity in depression and anxiety during stress depending on type of stressor. Psychosom. Med. 2016;78:562–72.

46. Hillebrand S, Gast KB, De Mutsert R, Swenne CA, Jukema JW, Middeldorp S, Rosendaal FR, Dekkers OM. Heart rate variability and first cardiovascular event in populations without known cardiovascular disease: Meta-analysis and dose-response meta-regression. Europace. 2013;15:742–49.

47. Stuckey MI, Tulppo MP, Kiviniemi AM, Petrella RJ. Heart rate variability and the metabolic syndrome: A systematic review of the literature. Diabetes. Metab. Res. Rev. 2014;30:784–93.

48. Furtado M, Katzman MA. Neuroinflammatory pathways in anxiety, posttraumatic stress, and obsessive compulsive disorders. Vol. 229, Psychiatry Research. Elsevier Ireland Ltd; 2015. p. 37–48.

49. Joseph JJ, Golden SH. Cortisol dysregulation: the bidirectional link between stress, depression,

and type 2 diabetes mellitus. Vol. 1391, Annals of the New York Academy of Sciences. Blackwell Publishing Inc.; 2017. p. 20–34.

50. Santiago PN, Ursano RJ, Gray CL, Pynoos RS, Spiegel D, Lewis-Fernandez R, Friedman MJ, Fullerton CS. A Systematic Review of PTSD Prevalence and Trajectories in DSM-5 Defined Trauma Exposed Populations: Intentional and Non-Intentional Traumatic Events. PLoS One. 2013;8:e59236.

Figure caption:

Figure 1. PRISMA study selection process

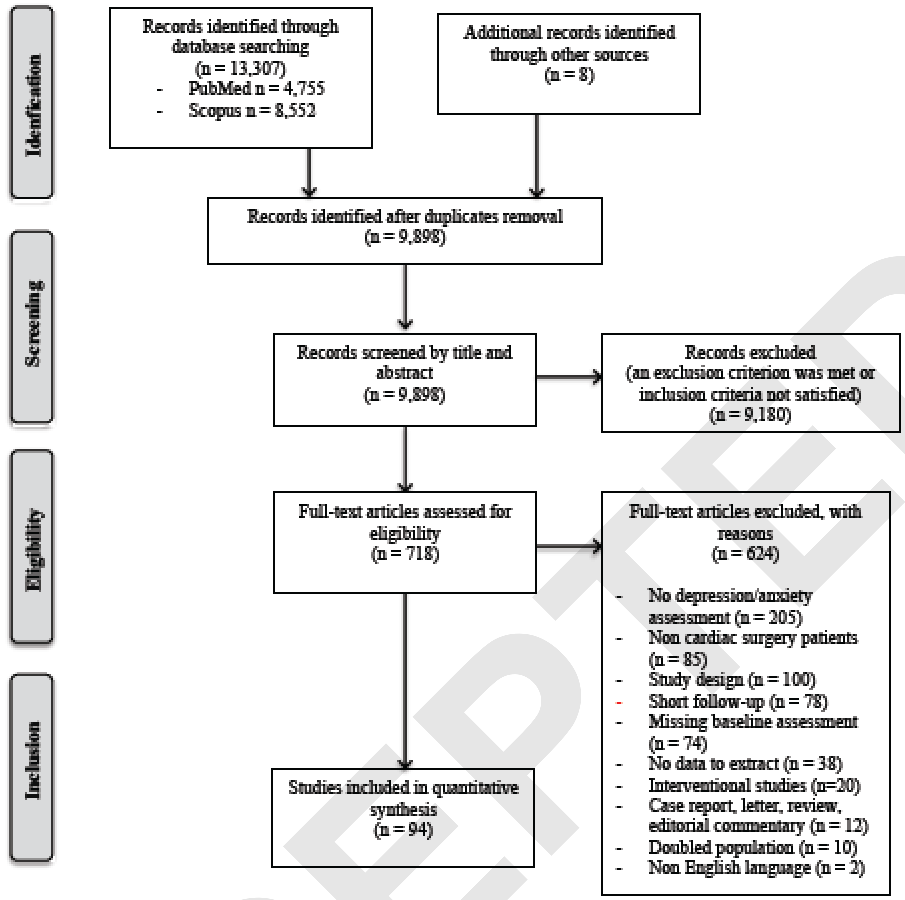


Figure 1. PRISMA study selection process.

Table 1. Random-effects meta-analysis of depressive symptoms before and after heart surgery in cohort studies, with subgroup analyses

		K of studies (subpopulations)	Hedge's g (95%CI)	*p* value	Heterogeneity (I^2%)	Publication bias – Subgroup difference *
Main analysis		**81 (102)**	**0.32 (0.25 – 0.39)**	**<0.001**	**86%**	**0.06**
Psychiatric disorder included at baseline	Yes	59 (72)	0.35 (0.27 – 0.43)	<0.001	87%	0.206
	No	24 (30)	0.26 (0.15 – 0.38)	<0.001	85%	
Region	Asia	7 (7)	0.51 (0.18 – 0.84)	0.002	95%	0.708
	Europe	33 (43)	0.29 (0.22 – 0.37)	<0.001	72%	
	North America	35 (46)	0.34 (0.24 – 0.44)	<0.001	89%	
	Oceania	4 (4)	0.32 (-0.27 – 0.91)	0.290	92%	
	South America	2 (2)	0.13 (-0.48 – 0.75)	0.672	80%	
Type of heart surgery (Cardiac condition)	CABG (CAD)	48 (60)	0.28 (0.21 – 0.36)	<0.001	88%	**<0.001**
	Heart Transplant (HF)	11 (11)	0.82 (0.51 – 1.13)	<0.001	72%	
	ICD Implantantion (SCA/Ventricular Arrhythmias)	1 (1)	0.42 (-0.08 – 0.91)	0.097	0%	
	Mixed (Mixed)	19 (26)	0.23 (0.12 – 0.34)	<0.001	78%	
	VAD implantation (HF)	2 (2)	1.05 (0.74 – 1.36)	<0.001	0%	
	Valve Surgery (Valve disease)	2 (2)	0.28 (-0.22 – 0.78)	0.279	72%	
First time intervention only	yes	26 (32)	0.32 (0.20 – 0.45)	<0.001	88%	0.960
	no	55 (70)	0.32 (0.25 – 0.40)	<0.001	85%	

Outcome measurement	Binary	38 (44)	0.21 (0.10 – 0.32)	<0.001	86%	**0.005**
	Continuous	43 (58)	0.40 (0.32 – 0.48)	<0.001	87%	
FU duration class	1-3 months	20 (25)	0.26 (0.16 – 0.37)	<0.001	82%	0.511
	3 - 6 months	29 (42)	0.31 (0.20 – 0.43)	<0.001	88%	
	6 months - 1 year	19 (21)	0.38 (0.27 – 0.48)	<0.001	81%	
	> 1 year	13 (14)	0.34 (0.07 – 0.62)	0.015	87%	

Legend. 95% CI, 95% confidence interval; * Egger's test p value for main analysis, subgroup difference *p* value for subgroup analyses

Table 2. Random-effects meta-analysis of anxiety symptoms before and after heart surgery in cohort studies, with subgroup analyses

		K of studies (subpopulations)	Hedge's g (95%CI)	*p* value	Heterogeneity (I^2%)	Publication bias – Subgroup difference *
Main analysis		**53 (66)**	**0.52 (0.43-0.62)**	**<0.001**	**89%**	**0.35**
Psychiatric disorder included at baseline	Yes	39 (49)	0.49 (0.37 – 0.60)	<0.001	90%	0.136
	No	14 (17)	0.60 (0.51 – 0.69)	<0.001	69%	
Region	Asia	5 (6)	0.41 (0.07 – 0.74)	0.016	94%	0.377
	Europe	28 (38)	0.48 (0.37 – 0.60)	<0.001	86%	
	North America	16 (18)	0.62 (0.49 – 0.74)	<0.001	87%	
	Oceania	4 (4)	0.65 (0.05 – 1.25)	0.033	87%	
Type of heart surgery (Cardiac condition)	CABG (CAD)	30 (36)	0.54 (0.45 - 0.64)	<0.001	86%	**0.001**
	Heart Transplant (HF)	7 (7)	0.57 (0.25 – 0.89)	<0.001	74%	
	ICD Implantation (SCA/Ventricular Arrhythmias)	1 (1)	0.49 (-0.83 – 1,81)	0.733	0%	
	Mixed (Mixed)	14 (19)	0.46 (0.29-0.62)	<0.001	91%	
	VAD Implantation (HF)	1 (1)	1.45 (0.82 – 2.07)	<0.001	0%	
	Valve surgery (Valve disease)	2 (2)	0.13 (-0.08- 0.34)	0.229	0%	

First time intervention only	Yes	14 (16)	0.54 (0.33 – 0.74)	<0.001	92%	0.822
	No	39 (50)	0.51 (0.42 – 0.61)	<0.001	88%	
Outcome measurement	Binary	17 (20)	0.43 (0.24 – 0.61)	<0.001	91%	0.230
	Continuous	36 (46)	0.55 (0.47 – 0.64)	<0.001	83%	
Follow-up duration	1-3 months	14 (16)	0.50 (0.30 – 0.69)	<0.001	89%	0.910
	3 - 6 months	20 (30)	0.73 (0.42 – 0.63)	<0.001	80%	
	6 months - 1 year	11 (12)	0.57 (0.38 – 0.77)	<0.001	94%	
	> 1 year	8 (8)	0.45 (0.12 – 0.78)	0.007	85%	

Legend. 95% CI, 95% confidence interval; * Egger's test p value for main analysis, subgroup difference *p* value for subgroup analyses

Table 3. Random-effects meta-analysis of PTSD symptoms before and after heart surgery in cohort studies, with subgroup analyses

		K of studies (subpopulations)	Hedge's g (95%CI)	*p* value	Heterogeneity (I^2%)	Publication bias – Subgroup difference*
Main analysis		**7 (7)**	**-0.42 (-0.80 – -0.04)**	**0.032**	**76%**	**0.06**
Psychiatric disorder included at baseline	Yes	5 (5)	-0.48 (-1.04– 0.09)	0.097	78%	0.649
	No	2 (2)	-0.92 (-2.71 – 0.88)	0.318	85%	
Region	Asia	1 (1)	-0.16 (-0.44 – 0.12)	0.266	0%	0.137
	Europe	5 (5)	-0.51 (-1.06 – 0.04)	0.069	81%	
	North America	1 (1)	-1.40 (-2.74 – -0.05)	0.043	0%	
Type of heart surgery (Cardiac condition)	CABG (CAD)	1 (1)	-1.10 (-1.88 - -0.33)	0.005	0%	0.056
	Heart Transplant (HF)	1 (1)	-1.24 (-2.59 - 0.10)	0.069	0%	
	Mixed (Mixed)	5 (5)	-0.20 (-0.57 – 0.16)	0.274	75%	
First time intervention only	Yes	3 (3)	-0.86 (-2.40 – 0.68)	0.275	85%	0.537
	No	4 (4)	-0.36 (-0.72 – 0.00)	0.050	67%	
Outcome measurement	Binary	3 (3)	-0.86 (-2.40 – 0.68)	0.275	85%	0.537
	Continuous	4 (4)	-0.36 (-0.72 – 0.00)	0.050	67%	
FU duration class	1-3 months	1 (1)	-1.40 (-2.74 – -0.05)	0.043	0%	**0.002**
	3 - 6 months	4 (4)	-0.45 (-0.87 – -0.02)	0.038	75%	
	6 months - 1	1	0.30	0.081	0%	

	year	(1)	(-0.04 – 0.64)			
	> 1 year	1 (1)	-1.24 (-2.59 - 0.10)	0.069	0%	

Legend. 95% CI, 95% confidence interval; * Egger's test p value for main analysis, subgroup difference *p* value for subgroup analyses