Systematic Review

A Scoping Review of Evidence to Develop an Evidenced-Based Protocol on the Prevention and Treatment of Constipation in the Critically Ill

Malissa A. Mulkey, PhD, APRN, CCNS, CCRN, CNRN[1]; Anne Sorrell, MA[2]; Anya Savransky, MS[2]; D. Erik Everhart, PhD, ABPP[2]; Kelly L. Wierenga, PhD, RN[3]

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[1]University of South Carolina, College of Nursing, Columbia, South Carolina, USA
[2]East Carolina University, Psychology Department, Greenville, North Carolina, USA
[3]Indiana University-Purdue University, School of Nursing, Indianapolis, Indiana, USA
Corresponding author: Malissa A. Mulkey at malissam@mailbox.sc.edu.

ABSTRACT

Background

Depression is associated with cardiac-related events and cognitive dysfunction, contributing to poorer health outcomes and quality of life. Specifically, after cardiac surgery, broad cognitive domains are negatively affected. To address cognitive dysfunction following cardiac surgery, researchers have tested non-pharmacological interventions with varied success. Depression is associated with worse cardiac and cognitive health outcomes, yet depression's potential contribution to interventions mitigating cognitive dysfunction following cardiac surgery is poorly understood.

Aims

This review aims to examine the impact of depression on the effectiveness of non-pharmacological interventions designed to minimize cognitive dysfunction associated with cardiac surgery.

Methods

A systematic literature review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Peer reviewed articles between January 2011 and June 2023 obtained from PubMed, MEDLINE, EMBASE, Psych INFO, CINAHL, and the Web of Science databases were screened for inclusion based on predetermined criteria. Each article was screened, and two authors abstracted data.

Results

Of 8166 articles screened, 460 were assessed for eligibility, and 4 met inclusion criteria. Three of the studies did not report associated depression scale scores. The other study reported depression symptoms as mild to severe.

Conclusion

These findings suggest limited information exists regarding the relationship between depression and cognitive function among cardiac surgery patients who undergo non-pharmacologic interventions. Future studies should carefully examine symptoms of depression in relation to cognitive impairment post-cardiac surgery; such studies may further guide clinical interventions.

Keywords: Depression, cardiac surgery, cognition, non-pharmacological systemic review

INTRODUCTION

While common in the general population, depression has a higher prevalence in cardiac surgery patients, with as many as 54% being affected (Caspi-Avissar et al., 2021; Horne et al., 2013; Tully, 2012). Depression is also considered to be a leading cause of disability worldwide, a major contributor to the overall burden of disease, and damaging for people undergoing cardiac surgery. Several damaging cardiovascular mechanisms associated with depression may contribute to negative health outcomes in people undergoing cardiac surgery, including increased sympathetic tone, cortisol, catecholamines, inflammatory markers, and abnormal platelet activation. Each of these mechanisms increases the risk for cardiovascular events, postoperative delirium, and cognitive dysfunction in people undergoing cardiac surgery (Hassanabad et al., 2021). Potentially as a result of these mechanisms as well as others, depression is a well-established predictor of increased rates of recurrent cardiac events, cognitive impairment, morbidity, mortality, longer hospital length of stay, and lower quality of life, leading to increasing rates of service utilization and healthcare cost for people undergoing cardiac surgery (Blumenthal et al., 2003; Buschmann et al., 2022; Connerney et al., 2001; Flaherty et al., 2017; Goyal et al., 2005; Poole et al., 2017; Salzmann et al., 2020; Tully et al., 2009).

Following cardiac surgery, people can experience decreased function in several cognitive domains, such as processing speed, memory, and executive function (McIntyre et al., 2015). Empirical studies have tested pharmacological and non-pharmacological interventions aimed to minimize cognitive dysfunction after cardiac surgery with varied success (Brown et al., 2019; Eryomina et al., 2015; Jia & Lubetkin, 2017; Petrova et al., 2019; Stoicea et al., 2016; Wu et al., 2018). Worsening cognitive function can be attributed to depression, among other causes (American Psychiatric Association, 2013). Research suggests that up to 94% of individuals with depression report memory-related problems, and up to 44% of individuals report sustained memory-related problems with depression symptom remission (Conradi et al., 2011). While many risk factors for cognitive dysfunction following surgery are non-modifiable, depression is treatable. As such, identifying methods to reduce depression and identify the impact it may have on interventions targeting the prevention of cognitive dysfunction for people undergoing cardiac and non-cardiac surgery is needed (Buschmann et al., 2022; Oyeyemi et al., 2022). Therefore, the aim of this review was to examine the impact of depression on the effectiveness of non-pharmacological interventions designed to minimize cognitive dysfunction in people undergoing cardiac surgery.

METHODS

We conducted a systematic literature review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Ajtahed et al., 2019; Hudetz et al., 2011). All extracted variables were determined prior to conducting the literature search based on the aim presented in this article as well as an article examining overall effectiveness of non-pharmacological treatments on preserving cognitive function following cardiac surgery (Mulkey et al., 2022). Variables extracted for this review included study type, type and location of recruitment site, inclusion and exclusion criteria, sample size, sample mean (Standard deviation) age, intervention evaluated, independent and dependent variables, confounders, study limitations, recruitment methods, cognitive, anxiety and depression measures (including psychometrics), definition of outcomes and measure, timing, and results of cognitive and mood evaluations. The original review was published and registered in the International Prospective Register of Systematic Reviews [CRD42021236388] and included extracting data on all variables included in this analysis.

Search strategy

Search terms included: cardiac surgery or heart surgery or surgery, cardiovascular or coronary artery bypass or cardiopulmonary bypass, or CABG, or heart valve surgery, or heart valve repair, or heart valve replacement, and cognition or cognitive function or brain function, or memory, or brain, or cognitive impairment, or cognitive dysfunction and depression or mood or depressed (Appendix 1). The literature search, conducted by one author and verified by another author, examined results from the following electronic databases: CINAHL, MEDLINE, PubMed, EMBASE, PsycInfo, and Web of Science. With the advancements in surgical procedures such as off pump and arterial approach to valve repair and replacement and performing surgeries on higher risk patients, publications were limited to articles published between January 2011 and July 2023.

Eligibility criteria

Studies were included if they met the following eligibility criteria: 1) peer reviewed controlled intervention studies with a comparator group (e.g., non-exposed control group, group exposed to different interventions) testing a non-pharmacological intervention; 2) participant samples that were exclusively adults who were undergoing either CABG and/or valve repair/replacement; 3) outcome measures of cognitive function reported with a standardized instrument, scale, or test; and 4) depression measured with a standardized instrument, scale, or test. We excluded studies if they were 1) not written in English; 2) included non-adult or non-human participants; or 3) included participants with congenital anomalies, carcinoid tumors, or surgical procedures in addition to cardiac surgery

(e.g., cholecystectomy).

Study selection

References were managed using Covidence (www.covidence.org) (Babineau, 2014). After removal of article duplications, 2 reviewers independently screened remaining studies for inclusion based on titles and abstracts. For the articles remaining, 2 independent reviewers again evaluated inclusion with the full-text articles. If consensus was reached, articles were included or excluded with 2 reviewers, in cases without consensus, a third reviewer reviewed content and a consensus meeting was conducted. Following initial study selection, a reverse citation search was conducted on all eligible studies to identify additional relevant articles following the same eligibility and study selection protocols.

Study appraisal

To determine risk of bias, the National Heart Lung and Blood Institute (NHLBI) risk of bias assessment tool for controlled intervention studies was used, classifying each study as either good, fair, or poor (National Heart Lung and Blood Institute (NHLBI, nd). This tool provides objective characterization guidelines for randomization, treatment allocation concealment and outcome evaluation, as well as determining differences in baseline participant characteristics, dropout rate, adherence to interventions, the implementation of other interventions during the study period, measurement validity and reliability, determining sample size based on power analysis, *a priori* identification of outcomes, and original group assignment-based analysis. Repeating procedures of study selection, two reviewers independently assessed the risk of bias, with a third reviewer contributing to consensus meetings in the case of disagreement.

Reviewers' expertise includes PhD prepared faculty from nursing and psychology and two PhD psychology students. One nursing faculty reviewer is a practicing advanced practice registered nurse and one psychology faculty reviewer has a joint appointment in the school of medicine's neurology department and continues to work clinically.

Data extraction

Similarly, 2 independent reviewers extracted and recorded data from each article. A third reviewer reviewed extracted data for similarity. When data extracted was determined to have discrepancies a consensus meeting was conducted with all three reviewers for final determinations. Individual factor data extracted for this review included age, gender, and surgery type. Study factors extracted included intervention characteristics (type, timing, frequency, and delivery method), measured cognitive tests (type, domain(s) assessed, the timing of assessments), the reported operationalized definition of cognitive impairment, depression measurement (timing, frequency, and delivery method), risk factors, reported clinical outcomes, the facility type and country where the study was conducted,

study inclusion and exclusion criteria, dates of participant recruitment, and study limitations.

RESULTS

Study characteristics

The study selection process is illustrated on the PRISMA Study Flow diagram in Figure 1. A total of 8166 articles were screened with 4 assessed for eligibility. Articles were excluded for the following reasons: 1) 391 had the wrong study design or outcome; 2) 24 articles included patient populations that were not exclusively CABG and/or valve repair/replacement; 3) 28 were not empirical research. 4) 15 did not include depression measurements. Therefore, four studies met the inclusion criteria for this review.

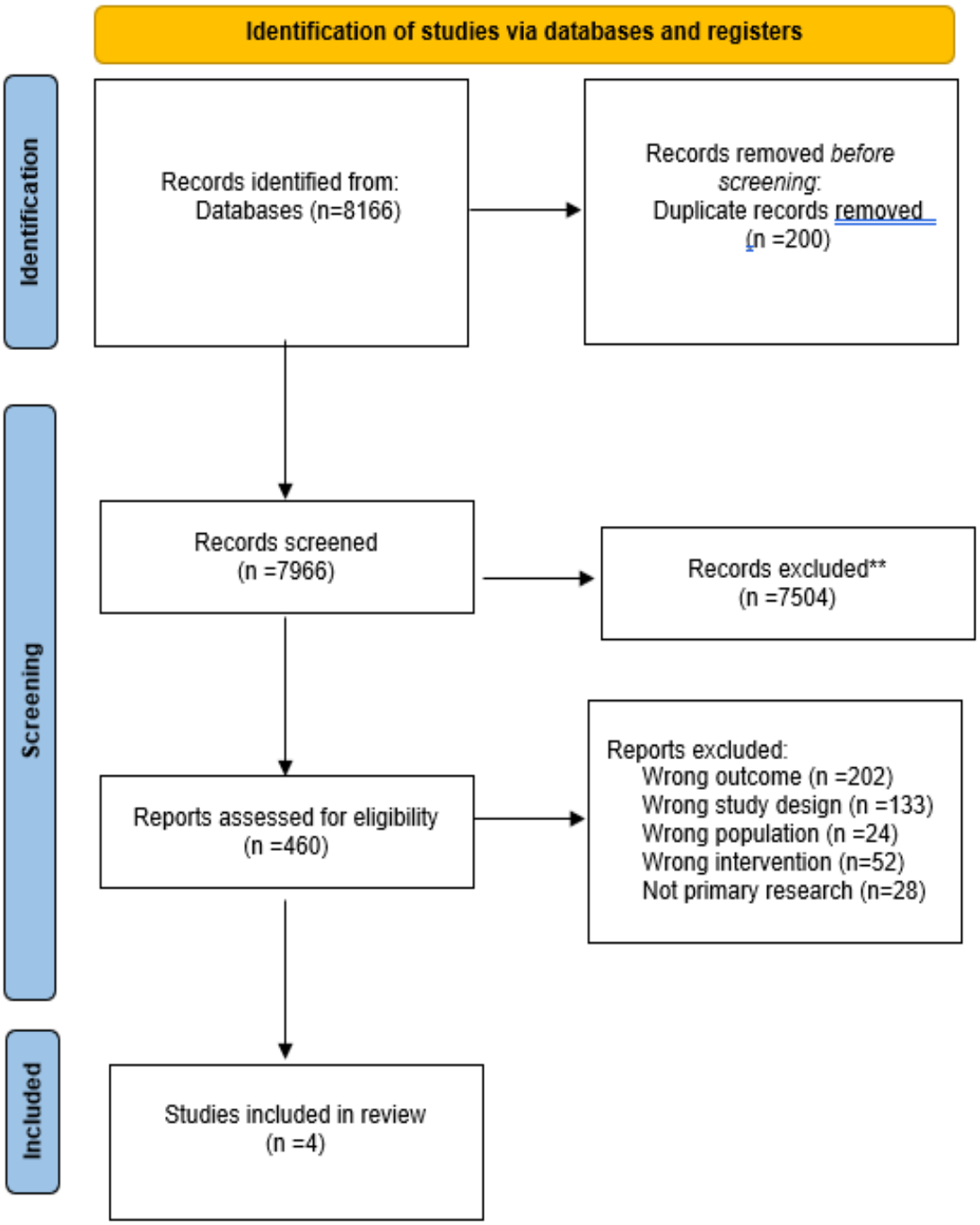
Based on the NHLBI risk of bias assessment conducted by this team, one study (Hudetz et al., 2015) was determined to be of good quality, with the least risk of bias. The other three studies (Petrova et al., 2019; Rogers et al., 2017) were fair, i.e., susceptible to some bias, yet considered sufficient for inclusion in this review. All 4 identified articles were included in the results based on this assessment. (see Table 1)

Table 2 summarizes the characteristics of the four studies included in this review. The included studies were conducted in four different countries: the United States (Ajtahed et al., 2019; Hudetz et al., 2015), United Kingdom (Rogers et al., 2017), Russia (Petrova et al., 2019), and Iran (Ajtahed et al., 2019). All 4 studies (Hudetz et al., 2015; Petrova et al., 2019; Rogers et al., 2017) were conducted at a single site. Two of the studies were described as a pilot study (Ajtahed et al., 2019; Hudetz et al., 2015). Study sample sizes were relatively small ranging from 15-90 participants. Participants in the studies were undergoing only CABG surgery in 2 studies (Ajtahed et al., 2019; Petrova et al., 2019) or both CABG and valve repair/replacement surgery in 2 studies (Hudetz et al., 2015; Rogers et al., 2017)

Interventions to mitigate cognitive dysfunction included remote ischemic limb preconditioning, cerebral oxygenation monitoring, and computerized cognitive training. Computerized cognitive training was evaluated in 2 studies (Ajtahed et al., 2019; Petrova et al., 2019). The use of remote ischemic limb preconditioning to trigger the body's natural protection against hypoperfusion injury by using a blood pressure cuff to temporarily occlude blood flow was evaluated in 1 study (Hudetz et al., 2015). Early oxygen reperfusion therapy guided by use of near-infrared spectroscopy (NIRS) based cerebral oximetry in the operating room was evaluated in 1 study (Rogers et al., 2017).

Figure 1.

PRISMA 2020 Flow Diagram for Systematic Study to Examine The Impact Of Depression On The Effectiveness Of Non-Pharmacological Interventions Designed To Minimize Cognitive Dysfunction Associated With Cardiac Surgery



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. British Medical Journal (BMJ) 2021;372:n71. doi: 10.1136/bmj.n71

Table 1.

Risk of Bias Assessment

NHLBI Risk of Bias Assessment Category	Article Citation			
	Ajtahed, Rezapour et al. 2019	Hudetz, Patterson et al. 2015	Petrova, Prokopenko et al. 2019	Rogers, Stoica et al. 2017
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	No	Yes	No	Yes
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?	Other	Yes	Other	Yes
3. Was the treatment allocation concealed (so that assignments could not be predicted)?	No	Yes	Other	Yes
4. Were study participants and providers blinded to treatment group assignment?	No	No	Other	Yes
5. Were the people assessing the outcomes blinded to the participants' group assignments?	Other	Yes	Other	Yes
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	Yes	Yes	No	
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	No	Yes	Other	Yes
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	No	Yes	Other	Yes
9. Was there high adherence to the intervention protocols for each treatment group?	Other	Yes	Other	
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	Yes	Yes	Other	
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Yes	Other	No	Yes
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main	Yes	No	No	

outcome between groups with at least 80% power?				
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	Yes	Yes	Yes	Yes
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	Yes	Yes	Yes	
Final Score	**Fair**	**Good**	**Fair**	**Fair**

Note: NHLBI – National Heart Lung and Blood Institute; Criteria are marked as Yes, No, or Other. Other indicates that the criteria cannot be determined, information is not reported, or the criteria is not applicable. Studies received an overall grading of poor, fair, or good quality based on the proportion of applicable checklist items that were met and marked as a "yes" (poor, <30% of items; fair, 30%-60%; good, >60%)

Depression measurement

Across the four studies, three self-report depression screening instruments were used including the 42-item Depression Anxiety Stress Scale (DASS), 15-item Geriatric Depression Scale (GDS), and 14-item Hospital Anxiety and Depression Scale (HADS). The DASS has three subscales including depression, anxiety, and stress while the HADS has two subscales including depression and anxiety (Hudetz et al., 2011; Moryś et al., 2016). The GDS is designed to detect only depression in older adults (Sohani & Samaan, 2012; Stafford et al., 2007).

Group differences in depressive symptoms

A limited number of studies reported group differences in depressive symptoms. Of the studies included in this review, three studies collected depressive symptoms at baseline only (Ajtahed et al., 2019; Petrova et al., 2019; Rogers et al., 2017). Two of these studies used baseline depressive scores for stratification purposes (Petrova et al., 2019; Rogers et al., 2017) . The other study used depressive symptom scores to describe the sample (Ajtahed et al., 2019). A single study conducted by Hudetz et al. (2011) evaluating the use of remote ischemic pre-conditioning reported results of depressive symptoms before and after intervention, and identified no between group differences at baseline, 1 week or hospital discharge (Ajtahed et al., 2019; Hudetz et al., 2011; Petrova et al., 2019; Rogers et al., 2017). See Table 3

Table 2.

Article Demographic Characteristics and Risk of Bias

Author Year	Country	Sample Size	Sample Mean Age (SD) in years	Intervention	Cognitive Test(s)	Cognitive Impairment Operational Definition	Depression Screening	NHLBI Risk of Bias
Ajtahed et al, 2019	Iran	N = 75 INT, n = 25 AC, n = 25 C, n = 25	INT, 57.0 (15.2) AC, 58.0 (9.8) C, 56.5 (12.7)	Computerized cognitive rehabilitation treatment	CPT Flanker Task UFOV Digit Span test	Not provided, examined effect size post-intervention to determine improvement in cognitive domains	• DASS • Prior to surgery • Results reported as normal, mild, moderate, severe	Fair
Hudetz et al, 2015	United States	N = 45 INT, n = 15 C, n = 15 NSC, n =15	INT, 66.0 (6.0) C, 65.0 (9.0) NSC, 64.0 (7.0)	Remote ischemic preconditioning	ICDSC Story Memory BVMT-R Digit Span test, backward Semantic Fluency Phonemic Fluency SCWT HIS	Decrease of 1+ SD from baseline tests post-op	• GDS • Prior to and after surgery • States no difference in depression detected • Results not reported	Good
Petrova et al, 2019	Russia	N = 87 INT, n = 50 C, n = 37	INT, 60.3 (6.8) C, 60.5 (6.4)	Computer-based simulation programs	MMSE FAB CDT Schulte Tables 5 Words	Decrease of at least 20% from baseline values in 3+ tests post-op	• HADS • Prior to surgery • Results not reported	Fair

Author Year	Country	Sample Size	Sample Mean Age (SD) in years	Intervention	Cognitive Test(s)	Cognitive Impairment Operational Definition	Depression Screening	NHLBI Risk of Bias
					Memory task Association test (semantic speech activity) · Digit Span test			
Rogers et al, 2017	United Kingdom	N = 208 INT, n = 102 C, n = 106	Full, 68.0 (11.0) INT, 65.9 (range 18.5-86.6) C, 70.0 (range 29.5-88.7)	Regional cerebral oxygen saturation monitoring	TMT – Parts A & B RAVLT WAIS block design DSST Controlled word association test GPT WTAR Color Word Test	Significant change at the 5% level in 4/6 domains post-op	• HADS • Prior to and after surgery • Results not reported	Fair

Abbreviations: AC, active control group; BVMT-R, brief visuospatial memory test – revised; C, control group; CDT, clock drawing test; CPT, continuous performance test; SCWT, Stroop Color Word Test; Depression Anxiety Stress Scale (DASS); DSST, digit symbol substitution test; FAB, frontal assessment battery; Geriatric Depression Scale (GDS); GPT, grooved pegboard test; Hospital Anxiety Depression Scale (HADS); HIS, Hachinski Ischemic Scale; ICDSC, Intensive Care Delirium Screening Checklist; INT, intervention group; NHLBI, National Heart, Lung, and Blood Institute; MMSE, Mini-Mental State Examination; NSC, non-surgical control group; RAVLT, Rey auditory verbal learning test; SD, standard deviation; TMT, trail making test; UFOV, useful field of view; WAIS, Wechsler Adult Intelligence Scale; WTAR, Wechsler test of adult reading

Table 3.
Cognitive and Depression Tests with Measurement Timing

Author, Year	Measurement Timing						Cognitive Domain								
	Pre-op	1 wk	1 mo	3 mo	6 mo	12 mo	Global	Memory	Attention	Processing Speed	Executive Function	Language	Intelligence	Delirium	Depression
Remote Ischemic Pre-Conditioning (RIPC)															
Hudetz, 2015		X						X[b, g, h]	X[g]			X[c,d]		X[e]	X[p]
Computerized Cognitive Rehabilitation Therapy															
Ajtahad, 2019	X				X				X[l,m,n]						X[q]
Petrovia, 2019	X		X		X	X	X[f]	X[s,t]				X[c]			X[r]
Near Infrared Spectroscopy (NIRS)															
Rogers, 2017	X	X		X				X[i]		X[a,o]	X[a]		X[j,k]		X[r]

Notes: Trail Making[a], Brief Visual Memory[b], Semantic Fluency[c], Phonemic Fluency[d], ICUDSC[e], MMSE[f], STROOP[g], Digit Span Test[h], Rey's Auditory Verbal Learning Test[i], Wechsler Adult Intelligence Test[j], Wechsler's Test of Adult Reading[k], Continuous Performance Test[l], Useful Field of View Test[m], Visual Memorizing, Color Trails Test[o], Depression Anxiety Stress Scale (DASS)[p], Geriatric Depression Scale (GDS)[q], Hospital Anxiety Depression Scale (HADS)[r]

DISCUSSION

The initial aim of this review was to examine the effect of depression on effectiveness of non-pharmacological interventions designed to minimize cognitive dysfunction associated with cardiac surgery. Upon review of more than 400 studies, only 4 studies met criteria for inclusion, This was largely because measures of depression were not a consideration for most of the non-pharmacological intervention studies. While measures of depression were used one study reported results as normal to severe prior to surgery only. One study reported postoperative depression as simply no difference detected. As a result, our understanding of depression's impact on effectiveness of interventions is significantly limited.

This finding was surprising given the previously reported prevalence rate for depression among cardiac patients of 20-50%, (Tully, 2012) (Moryś et al., 2016; Sohani & Samaan, 2012; Stafford et al., 2007). Research estimates that approximately 50% of individuals undergoing treatment for depression continue to report moderate cognitive impairment (e.g., executive function, attention, memory) even after depression symptoms have resolved (Moryś et al., 2016). Given the increased sympathetic and inflammatory response and platelet function associated with depression, cognitive dysfunction and cardiovascular events, it is reasonable to assume depression may have moderating effects on cognitive interventions (Fatehi Hassanabad et al., 2021). Despite known relationships amongst these variables, very few studies included both as variables of interests. As a result of this limited information, it is currently difficult to operationalize depression as related to cognitive outcome (or related factors) regarding non-pharmacologic intervention.

Overall, this review highlights the dearth of research within this area. While depression is a common feature in this patient population, to our knowledge, there is no evidence of systematic examination of the impact of depression on interventions mitigating cognitive dysfunction in this population. Literature that assists with understanding these complicated relationships is needed and warranted.

Limitations

This review was not able to provide clarity on the problem addressed due to the lack of articles written in English evaluating the impact of depressive symptoms on the effectiveness of non-pharmacological interventions for cognitive impairment after cardiac surgery. Despite depressive scores being measured in the included articles, findings on between group differences were largely lacking. Standardization of measurement methods and timing for depression screening are important to understanding the potential impact.

Implications for practice and research

At present, symptoms of depression are under studied within cardiac surgery populations where non pharmacologic cognitive interventions are used. While the

relationship between depression and its impact on interventions mitigating cognitive dysfunction is not clear, it remains important to assess patients undergoing cardiac surgeries for symptoms of depression. This is particularly important given the prevalence and previously established relationships between depression and health outcomes (Oldham et al., 2019). Research is needed to test the hypothesis that greater symptoms and severity of depression are detrimental to non-pharmacologic interventions aimed at mitigating cognitive dysfunction. If true, modifications to existing interventions such as during cardiac rehabilitation and follow-up care or simultaneous treatment of depression may be warranted. Some recommended interventions have included providing psychological interventions, postoperative physical mobilization therapy and collaborative care models including mental health providers (Buschmann et al., 2022).

Inclusion of measures of depression for pre-, peri- and post- non-pharmacologic intervention will be vital for further development and understanding of cognitive dysfunction and long-term health outcomes and will ultimately enhance understanding of these complex relationships.

CONCLUSION

In conclusion, it is well known that depression is associated with cardiac-related events and cognitive dysfunction that contribute to poorer health outcomes and quality of life. However, at present, based on this review, limited information exists concerning the relationship between depression and cognitive function among cardiac surgery patients who undergo non pharmacologic interventions. It is recommended that future studies examining cognitive functioning after cardiac surgery carefully examine symptoms of depression pre- and post-intervention as a related variable to disentangle these relationships and enhance understanding of potential clinical applications.

Author Bios:

Malissa A. Mulkey, PhD, APRN, CCNS, CCRN, CNRN, is an instructor at the University of South Carolina, College of Nursing, Columbia, South Carolina, USA.

Anne Sorrell, MA, works in the [2]East Carolina University, Psychology Department, Greenville, North Carolina, USA.

Anya Savransky, MS, works in the [2]East Carolina University, Psychology Department, Greenville, North Carolina, USA.

D. Erik Everhart, PhD, ABPP, works in the [2]East Carolina University, Psychology Department, Greenville, North Carolina, USA.

Kelly L. Wierenga, PhD, RN, is an instructor at Indiana University-Purdue University, School of Nursing, Indianapolis, Indiana, USA

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Appendix 1.

Search Terms for Systematic Review

Search	Query	Results	Time
#6	Search: (((#2) AND (#3)) AND (#4)) AND (#5) Filters: Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Observational Study, Pragmatic Clinical Trial, Randomized Controlled Trial, Twin Study, Validation Study, Humans, English, Adult: 19+ years, Young Adult: 19-24 years, Adult: 19-44 years, Middle Aged + Aged: 45+ years, Middle Aged: 45-64 years, Aged: 65+ years, 80 and over: 80+ years	160	22:07:54
#5	Search: (((cognition) OR (cognitive)) OR (cognit*)) OR (delirium)Filters: Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Observational Study, Pragmatic Clinical Trial, Randomized Controlled Trial, Twin Study, Validation Study, Humans, English, Adult: 19+ years, Young Adult: 19-24 years, Adult: 19-44 years, Middle Aged + Aged: 45+ years, Middle Aged: 45-64 years, Aged: 65+ years, 80 and over: 80+ years	64,650	22:07:06
#4	Search: (((surgery) OR (repair)) OR (replace*)) OR (replacement)Filters: Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Observational Study, Pragmatic Clinical Trial, Randomized Controlled Trial, Twin Study, Validation Study, Humans, English, Adult: 19+ years, Young Adult: 19-24 years, Adult: 19-44 years, Middle Aged + Aged: 45+ years, Middle Aged: 45-64 years, Aged: 65+ years, 80 and over: 80+ years	401,550	22:06:14
#3	Search: ((depress*) OR (depression)) OR (mood) Filters: Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Observational Study, Pragmatic Clinical Trial, Randomized Controlled Trial, Twin Study, Validation Study, Humans, English, Adult: 19+ years, Young Adult: 19-24 years, Adult: 19-44 years, Middle Aged + Aged: 45+ years, Middle Aged: 45-64 years, Aged: 65+ years, 80 and over: 80+ years	109,947	22:05:22
#2	Search: ((cardiac)) OR (heart) Filters: Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Observational Study, Pragmatic Clinical Trial, Randomized Controlled Trial, Twin Study, Validation Study, Humans, English, Adult: 19+ years, Young Adult: 19-24 years, Adult: 19-44 years, Middle Aged + Aged: 45+ years, Middle Aged: 45-64 years, Aged: 65+ years, 80 and over: 80+ years	165,420	22:04:49