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# BMJ Open

## Systematic Review of preoperative physical activity and its impact on post-cardiac surgical outcomes

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**Title: Systematic Review of preoperative physical activity and its impact on post-cardiac surgical outcomes**

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DSK was responsible for 1) analysis and interpretation of data, 2) drafting and revising the manuscript, and 3) consenting for manuscript submission. ANS, BH, NT, RF, ASH, NG, AH, JL were responsible for 1) analysis and interpretation of data, 2) revising the manuscript, and 3) consenting for manuscript submission. KM was responsible for 1) developing the systematic review literature search, 2) analysis and interpretation of data, 3) drafting and revising the manuscript, and 3) consenting for manuscript submission. RCA and TAD were responsible for 1) the conception and design, and analysis and interpretation of data, 2) revising the manuscript, and 3) consenting for manuscript submission RCA and TAD are co-senior authors.

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57

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60

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62 The authors have no conflicts of interest to declare

63

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66 **ABSTRACT:**

67 **Objectives:** The objective of this systematic review was to study the impact of preoperative physical  
68 activity levels adult cardiac surgical patients' postoperative: 1) major adverse cardiac and cerebrovascular  
69 events (MACCE), 2) adverse events within 30 days, 3) hospital length of stay (HLOS), 4) intensive care  
70 unit length of stay (ICU LOS), 5) activities of daily living (ADLs), 6) quality of life, 7) cardiac  
71 rehabilitation attendance, and 8) physical activity behavior.

72 **Methods:** A systematic search of MEDLINE, Embase, AgeLine, and Cochrane library for cohort studies  
73 was conducted.

74 **Results:** Eleven studies (n=5,733 patients) met the inclusion criteria. Only self-reported physical activity  
75 tools were used. Few studies used multivariate analyses to compare active versus inactive patients prior to  
76 surgery. When comparing patients who were active versus inactive preoperatively, there were mixed  
77 findings for MACCE, 30 day adverse events, HLOS, and ICU LOS. Of the studies which adjusted for  
78 confounding variables, five studies found a protective, independent association between physical activity  
79 and MACCE (n= 1), 30 day postoperative events (n= 2), hospital length of stay (n= 1), and ICU length of  
80 stay (n= 1), but two studies found no protective association for 30 day postoperative events (n= 1) and  
81 postoperative ADLs (n= 1). No studies investigated if activity status before surgery impacted quality of  
82 life or cardiac rehabilitation attendance postoperatively. Three studies found that active patients prior to  
83 surgery were more likely to be inactive postoperatively.

84 **Conclusion:** Due to the mixed findings, the literature does not presently support that self-reported  
85 preoperative physical activity behavior is associated with postoperative cardiac-surgical outcomes. Future  
86 studies should objectively measure physical activity, clearly define outcomes, and adjust for clinically  
87 relevant variables.

88 **Registration:** PROSPERO number CRD42015023606.

89  
90 **Keywords:** Cardiac Surgical Procedures, Exercise, Prognosis, Postoperative Complications  
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3 92 **ARTICLE SUMMARY**

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5 93 **Strengths and limitations of this study**

- 6  
7 94 - There were mixed findings regarding the impact of physical activity on post cardiac-surgical  
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9 outcomes.  
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11 95  
12 96 - Only self-reported physical activity tools were used.  
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14 97 - The multiple tools to measure physical activity and the variety of definitions of outcomes did not  
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16 98 allow for a quantitative synthesis (meta-analysis).  
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99 **INTRODUCTION**

100 Recent reports suggest that more than half of cardiac surgeries are being performed on older adults who  
101 are more likely to be frail and have multiple co-morbidities.<sup>1</sup> While cardiac surgery has been shown to  
102 improve the outcomes of these patients, more than 75% of major perioperative complications and deaths  
103 occur in older adults.<sup>2,3</sup> Before surgery, many of these patients are de-conditioned and have diminished  
104 resilience in the face of major stressors such as cardiac surgery, and it has been postulated that they could  
105 benefit from a therapeutic intervention prior to their major surgical procedure in order to reduce their  
106 operative risk. However, little information exists to evaluate the benefit of preoperative risk reduction  
107 strategies for the older cardiac surgery patient.

109 Adopting and sustaining a more physically active lifestyle is typically intended to be a part of an  
110 interdisciplinary rehabilitation plan that is instituted postoperatively and has been shown to reduce the  
111 risk of cardiac mortality and hospital admissions and improve health-related (QOL) in patients.<sup>4</sup>  
112 Importantly, older adults who sustain a physically active lifestyle after a postoperatively exercise-based  
113 rehabilitation program can continue to improve their functional walking status.<sup>5</sup> However, evidence  
114 suggests that cardiac surgery patients are highly sedentary during the preoperative period, especially in  
115 older adults.<sup>6</sup> Furthermore, few randomized controlled trials exist which evaluate the therapeutic benefit  
116 of preoperative lifestyle modification in patients undergoing cardiac surgery.<sup>7-9</sup> Information regarding the  
117 link between preoperative physical activity and postoperative health outcomes in cardiac surgery patients  
118 would be valuable for healthcare providers to assist them in selecting patients who might benefit from  
119 preoperative exercise therapy.

121 The purpose of this systematic review was to compare the following postoperative outcomes between  
122 cardiac surgery patients defined as physically active prior to surgery and those who were defined as  
123 physically inactive preoperatively: 1) major adverse cerebrovascular and cardiovascular events (MACCE)  
124 2) 30-day adverse events 3) hospital length of stay, 4) Intensive Care Unit (ICU) length of stay, 5) health-



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125 related QOL, 6) activities of daily living (ADL) 7) cardiac rehabilitation attendance and 8) physical  
126 activity levels postoperatively.

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3 128 **MATERIAL AND METHODS**

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8 130 The protocol for this systematic review has been described in PROSPERO: CRD42015023606. Note  
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10 131 the following *ad-hoc* changes to the previous protocol: ICU length of stay and postoperative physical  
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12 132 activity as additional outcomes were explored in this systematic review.  
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16 134 **Eligibility criteria**

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20 136 Eligible studies included cohort studies which examined adult (>18 years) cardiac surgery patients  
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22 137 undergoing coronary artery bypass grafting (CABG), aortic or mitral valve repair/replacement,  
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24 138 transcatheter aortic valve implantation, or combined procedures. Studies with patients undergoing  
25  
26 139 congenital cardiac surgery, heart transplantation or left ventricular assist device implantation procedures  
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28 140 were excluded. Studies could compare physically active versus inactive patients prior to cardiac surgery  
29  
30 141 on the basis of subjective (e.g., questionnaire) or objective (e.g., pedometer, accelerometry) assessments  
31  
32 142 of physical activity.  
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35  
36 144 Eligible studies had to compare at least one of the following postoperative outcomes: MACCE defined  
37  
38 145 as death, stroke, myocardial infarction, and the need for emergency cardiac surgery; 30-day adverse  
39  
40 146 events as defined by the Society of Thoracic Surgeons (STS);<sup>10</sup> Hospital length of stay; ICU length of  
41  
42 147 stay; health-related QOL with any assessment tool; ADLs using any evaluation strategy; cardiac  
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44 148 rehabilitation attendance; and physical activity behavior using either subjective or objective forms of  
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46 149 assessment.  
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3 154 **Search strategy**

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8 156 The search strategy was completed by a librarian and reviewed by a second librarian. The search  
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10 157 included keywords and controlled vocabulary. English language limits were applied. Databases used  
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12 158 included MEDLINE, Embase, AgeLine, and Cochrane Library (CDSR, CENTRAL, DARE). The  
13  
14 159 MEDLINE strategy was registered and published online in PROSPERO  
15  
16 160 ([http://www.crd.york.ac.uk/PROSPEROFILES/23606\\_STRATEGY\\_20150518.pdf](http://www.crd.york.ac.uk/PROSPEROFILES/23606_STRATEGY_20150518.pdf)). The search was  
17  
18 161 validated through a cross-check of references of studies selected for inclusion. In addition, conference  
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20 162 abstracts were hand searched using the Internet. Attempts were made to contact authors of conference  
21  
22 163 abstracts to determine if their findings were published in a peer-reviewed journal.  
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29 166 **Study selection**

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33 168 The title, abstract and full-text article screening processes were independently completed by two  
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35 169 reviewers. A training exercise for the title and abstract phase was conducted by the independent reviewers  
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37 170 using a random sample of 100 titles and abstracts. Discrepancies in studies for inclusion were resolved by  
38  
39 171 discussion of the two reviewers. The final observed agreement was 98% with a kappa statistic of 0.47 for  
40  
41 172 the title and abstract screen. One training exercise of 10 randomly selected articles was completed for the  
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43 173 full-text screen. Discrepancies for inclusion were resolved through discussion. The observed agreement  
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45 174 for the full-text screen was 96% with a kappa statistic of 0.83.  
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51 176 **Data abstraction**

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55 178 Two reviewers independently extracted relevant data for the selected outcomes described above.  
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57 179 Discrepancies in the data extraction procedure were resolved through discussion. Data abstraction items  
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3 180 included study characteristics (e.g., authors, year of publication, sample size, follow up time points if  
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5 181 relevant), patient characteristics (e.g., age, sex, surgery type), physical activity tool used, and the  
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7 182 outcomes which were measured.  
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### 11 184 **Risk of bias assessment**

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15 186 Two reviewers independently reviewed the risk of bias of each included study using the Newcastle-  
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17 187 Ottawa Scale.<sup>11</sup> Items within this tool assess the risk of bias associated with selection of participants,  
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19 188 comparability (e.g., study authors controlled for patient demographics and clinical characteristics), and  
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21 189 outcome assessment (e.g., data collection method for outcome, sufficient follow-up, and adequacy of  
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23 190 follow up of cohorts). Each study was given a score within each category (Selection: 0-4; Comparability:  
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25 191 0-2; and Outcome: 0-3) and an overall score ranging from 0-9. A score of zero suggests an increased risk  
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27 192 of bias and a higher score suggests a lower risk of bias.  
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### 33 194 **Quantitative synthesis**

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37 196 Due to the significant heterogeneity between studies in terms of physical activity assessment tools used  
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40 197 and outcomes assessed, meta-analyses were not performed.  
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198 **RESULTS**

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200 The literature search results are shown in Figure 1. After removing duplicates, 5722 articles were title  
201 and abstract screened. A total of 137 articles were then assessed in full-text. Eleven studies met the  
202 eligibility criteria for the final analysis, and they included a total of 5,733 patients.<sup>12-22</sup>

203  
204 An overview of the included studies can be viewed in Table 1. Five studies evaluated CABG only  
205 patients,<sup>12-16</sup> four evaluated both CABG and/or valve procedures,<sup>17-21</sup> and one study evaluated isolated  
206 aortic valve repair patients.<sup>22</sup> The average age of participants in different studies ranged from 60 years<sup>15,16</sup>  
207 to 75 years.<sup>17,18,21,22</sup> Six studies excluded patients with physical impairments or with New York Heart  
208 Association heart failure class IV symptoms (severe cardiac symptoms)<sup>14-19</sup> but in general exclusion  
209 criteria were not explicitly reported. Studies were conducted in the Netherlands,<sup>12,14,20,22</sup> Brazil,<sup>13,15,16</sup>  
210 Italy,<sup>17-19</sup> and the United States.<sup>21</sup> Two studies used the same patient sample, but examined different  
211 outcomes.<sup>15,16</sup> The sample size of studies ranged from 35<sup>21</sup> to 3150.<sup>20</sup>

212  
213 The physical activity assessments in each study were based on self-reported assessment tools. Four  
214 studies used the Corpus Christi Heart Project questionnaire;<sup>12,14,20,22</sup> three studies used a structured  
215 questionnaire confirmed by the Minnesota Leisure Time Physical Activity Questionnaire<sup>13</sup> or the Baecke  
216 Usual Physical Activity questionnaire;<sup>15,16</sup> two studies used the Physical Activity Scale for the  
217 Elderly;<sup>17,19</sup> one study used the Harvard Alumni Questionnaire;<sup>18</sup> and one study used The Health and  
218 Retirement Survey physical activity-related questions.<sup>21</sup>

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3 219 **MACCE**  
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7 221 Outcomes within the definition of MACCE were evaluated in four studies (Table 2).<sup>13,15,17,22</sup> The  
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10 222 follow-up periods were one,<sup>13</sup> two,<sup>15,22</sup> and five years<sup>17</sup> postoperatively. Unadjusted differences between  
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12 223 active versus inactive patients and MACCE (defined as atrial fibrillation, hospital admission, reoperation  
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14 224 and MI) were found one-year postoperatively in one study.<sup>13</sup> Another study found no differences (defined  
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16 225 as mortality, re-hospitalization, cerebrovascular accident and MI) at two years postoperatively.<sup>15</sup> One  
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18 226 study found that unadjusted rates of mortality within two years post-surgery was significantly higher in  
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20 227 the active versus inactive group.<sup>22</sup> One study found a significant and dose-response relationship between  
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22 228 physical activity and postoperative cardiac and all-cause mortality after controlling for preoperative  
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24 229 demographics, medical history, medications, and clinical characteristics.<sup>17</sup>  
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29 231 **30-day events**  
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33 233 Five studies evaluated postoperative events within 30 days of surgery (Table 2).<sup>12,16–18,20</sup> The  
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35 234 postoperative events measured varied significantly between the studies. Three studies examined if  
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37 235 physical activity was an independent protective factor against postoperative events.<sup>16,18,20</sup> Physical  
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39 236 activity was an independent protective factor against the combined outcome of mortality, MI, and  
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41 237 reoperation;<sup>16</sup> as well as postoperative atrial fibrillation;<sup>18</sup> but not for in-hospital or 30-day mortality.<sup>20</sup>  
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46 239 **Postoperative health-related QOL**  
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50 241 No studies evaluated postoperative health-related QOL.  
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57 244 **Hospital and ICU length of stay**  
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246 Three studies compared hospital length of stay between active vs. inactive cardiac surgery patients  
247 (Table 3).<sup>12,13,16</sup> Hospital length of stay was longer in the inactive group in two of three studies. One study  
248 did not report hospital length of stay summary statistics between the active vs. inactive groups.<sup>16</sup> However  
249 that study reported an independent association between the preoperative active vs. inactive group and a  
250 reduced likelihood of prolonged hospital length of stay, though “prolonged” was not defined in the study.

251  
252 Three studies compared ICU length of stay between the preoperative physical activity groups (Table  
253 3).<sup>12,19,20</sup> Two of three studies found that the inactive group had a significantly longer ICU length of stay  
254 compared to the active group.<sup>12,20</sup> One study conducted a multivariate analysis, and found that the active  
255 group was less likely to have a prolonged ICU length of stay >3 days compared to the inactive group after  
256 controlling for age, off-pump CABG, stroke, and renal failure.<sup>19</sup>

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### **Postoperative ADLs**

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260 One study examined the impact of preoperative physical activity and postoperative ADLs at the time of  
261 hospital discharge and revealed no statistically significant ( $p=0.079$ ) association between the two after  
262 adjusting for preoperative demographics and clinical variables.<sup>19</sup>

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### **Cardiac rehabilitation attendance**

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266 No studies evaluated cardiac rehabilitation attendance postoperatively.

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### **Postoperative physical activity behavior**

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3 271 The impact of preoperative physical activity on postoperative physical activity levels was examined in  
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5 272 three studies (Table 3).<sup>12,14,21</sup> These studies found that the active group preoperatively was more likely to  
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7 273 be physically inactive postoperatively. Two of three studies completed a multivariate analyses and this  
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9 274 association remained statistically significant after controlling for age, gender, and preoperative clinical  
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11 275 characteristics.<sup>12,14</sup>  
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### 16 277 **Risk of bias**

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20 279 The risk of bias assessment via the Newcastle-Ottawa Scale can be viewed in the Supplemental Digital  
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22 280 Content. Since some studies assessed multiple outcomes, the risk of bias assessments were based on their  
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24 281 highest possible score (e.g., some outcomes were assessed with a multivariable analysis, while others  
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26 282 were not in the same study). All studies scored at least 3 out of 4 for the selection of study groups. There  
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28 283 was variability across studies for the ascertainment of exposure or outcome of interest. Total risk of bias  
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30 284 scores ranged from 5 to 9, suggesting the studies were of moderate to high quality, respectively.  
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3 285 **DISCUSSION**  
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5 286 The purpose of this systematic review was to determine if physical activity before cardiac surgery was  
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7 287 associated with postoperative health outcomes. Given the different self-reported physical activity tools  
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10 288 used, the inconsistent use of adjustment for potential confounders, and the varying outcomes evaluated for  
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12 289 MACCE and 30 day postoperative events, it cannot be concluded that preoperative physical activity is  
13  
14 290 associated with postoperative outcomes in adult cardiac surgery patients. This systematic review highlight  
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16 291 important gaps within the literature on this topic. Therefore, key recommendations for examining the  
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18 292 impact of preoperative physical activity behavior on post-surgical outcomes of cardiac patients are  
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20 293 provided (Box 1).  
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24 295 The different self-reported physical activity tools used across the studies makes it difficult to compare  
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26 296 the preoperative physical activity levels of patients prior to cardiac surgery. There seems to be no  
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28 297 universally accepted tool to measure self-reported physical activity levels.<sup>23</sup> One advantage of using self-  
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30 298 reported physical activity measures in studies is their ease of administration compared to other objectively  
31  
32 299 measured physical activity tools. Furthermore, self-reported physical activity tools appear to provide  
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34 300 some value when assessing the independent association between activity levels and poor outcomes. In  
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36 301 fact, most physical activity guideline recommendations for health benefits, including those in North  
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38 302 America, are based on self-reported measures.<sup>24,25</sup> However, cardiac surgery patients and other patient  
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40 303 populations tend to misreport their physical activity levels compared to objectively measured physical  
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42 304 activity (e.g., accelerometers).<sup>6,26</sup> Nevertheless, this systematic review found no studies that evaluated  
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44 305 objectively measured physical activity before cardiac surgery and its link to postoperative health  
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46 306 outcomes. Evidence suggests there is a stronger association between objective measures of physical  
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48 307 activity and various cardiovascular and metabolic biomarkers as compared to subjective measures of  
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50 308 physical activity.<sup>27,28</sup> Therefore, future studies should use a physical activity tools such as accelerometers  
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52 309 or pedometers.  
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3 311 There were inconsistent findings across studies assessing the same outcomes, and many studies did not  
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5 312 adjust for clinically relevant variables that could influence the health outcomes of cardiac surgery  
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7 313 patients. Even so, some of the results of this systematic review are promising. Specifically, of the studies  
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9 314 which controlled for confounding variables, five studies found a protective, independent association,  
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11 315 between higher preoperative physical activity levels when assessing clinical outcomes, including  
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13 316 MACCE,<sup>17</sup> 30 day postoperative events,<sup>16,18</sup> hospital length of stay,<sup>16</sup> and ICU length of stay;<sup>19</sup> whereas,  
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15 317 only two studies found no protective association for 30 day postoperative events<sup>20</sup> and postoperative  
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17 318 ADLs.<sup>19</sup> Yet, more studies are needed to elucidate the impact of preoperative physical activity on post-  
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19 319 cardiac surgical outcomes that control for clinically relevant variables. Clinical variables included in the  
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21 320 cardiac surgical risk models (e.g., EuroSCORE, STS score) could attenuate or mitigate the relationship  
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23 321 between preoperative physical activity behavior and postoperative outcomes. Collectively, future studies  
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25 322 are needed to determine if preoperative physical activity is a protective factor for health outcomes after  
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27 323 cardiac surgery which control for clinically relevant variables known to impact cardiac surgery outcomes.  
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34 325 An unanticipated finding was that patients who were active before surgery had a higher likelihood of  
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36 326 being physically inactive postoperatively, after controlling for co-morbidities.<sup>12,14,21</sup> Healthcare providers  
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38 327 may have advised patients with more severe symptomology prior to surgery to refrain from physical  
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40 328 activity. Also, the relief of cardiac symptoms after surgery among inactive patients could have led them to  
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42 329 become more active postoperatively. However, these possibilities were not explored in the included  
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44 330 studies.  
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49 332 While outside the scope of this systematic review, future studies should investigate if changes to  
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51 333 physical activity levels prior to cardiac surgery impact long-term patient health-outcomes. Cardiac  
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53 334 rehabilitation programs are intended to support cardiac patients in becoming more physically active  
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55 335 postoperatively and it has been shown that patients who attend such programs reduce their risk for  
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57 336 cardiac-related mortality and hospitalization rates.<sup>29</sup> Evidence suggests that among those referred to  
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**Running Head:** PA and post-cardiac surgical outcomes

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3 337 cardiac rehabilitation after cardiac surgery, only 40% attend.<sup>6</sup> However, the literature is less clear on  
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5 338 whether patients who attend cardiac rehabilitation are more physically active compared to those who do  
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7 339 not attend. It is possible that patients who adopt and sustain a more physically active lifestyle on their  
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10 340 own after cardiac surgery could yield similar health benefits compared to those who attend an exercise-  
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12 341 based rehabilitation program, but this hypothesis requires further investigation.

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16 343 Previous randomized controlled trials comparing an exercise program to standard care prior to elective  
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18 344 cardiac surgery (i.e., “Prehab”) demonstrate reductions in hospital length of stay and improvements in  
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20 345 walking ability postoperatively.<sup>7-9</sup> However, there were mixed findings from this systematic review when  
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22 346 comparing preoperative physical activity behavior and hospital stay.<sup>12,16</sup> These divergent findings suggest  
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24 347 either that a medically supervised and individualized physical activity program is needed to derive the  
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26 348 health benefits of physical activity prior to cardiac surgery, or that patients are misreporting their physical  
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28 349 activity behaviors. Future cohort studies in this area should address the drawbacks of the included studies  
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30 350 in this systematic review included in Box 1, while randomized trials should focus on whether preoperative  
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32 351 exercise therapy programs are feasible and efficacious in clinical practice.

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38 353 The findings of this systematic review suggest that the literature would benefit from standardization of  
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40 354 the definition of measures such as MACCE and postoperative events within 30 days. The heterogeneity in  
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42 355 reporting of outcomes can lead to considerably different conclusions across studies.<sup>30</sup> Attempts should  
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44 356 also be made to ensure other clinically important outcomes are captured, such as the addition of 30-day  
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46 357 events. Only one study in this review compared physically active versus inactive patients preoperatively  
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48 358 and reported on the individual postoperative events within 30 days.<sup>20</sup> Collectively, uniform outcome  
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50 359 reporting and appropriate outcome definitions are recommended when examining the outcomes of cardiac  
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52 360 surgery.<sup>30</sup>

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**Running Head:** PA and post-cardiac surgical outcomes

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3 362 Patient-oriented outcomes should also be captured to ensure that cardiac surgery is improving other  
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5 363 outcomes that patients value. No studies in this review determined if there was a link between  
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7 364 preoperative physical activity behavior and postoperative health-related QOL, and only one study  
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9 365 evaluated postoperative ADLs.<sup>19</sup> QOL postoperatively tends to improve in some older patients, while  
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11 366 others tend to decline.<sup>31</sup> Importantly, the preoperatively physical activity and overall functional status of  
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13 367 cardiac surgery patients could play a role in the postoperative trajectory of these outcomes such as QOL.  
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15 368 Other patient-oriented outcomes, including postoperative pain and cardiac symptoms, could also be  
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17 369 investigated.  
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### 22 371 **Limitations**

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25 372 One limitation to consider is that the patients included across the studies evaluated in this systematic  
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27 373 review may have been different, as the recruitment criteria were not always clearly stated. A small sample  
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29 374 of studies explicitly stated that they excluded those with physical limitations and healthcare providers  
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31 375 may have advised higher risk patients to not participate in physical activity. There is also a limitation  
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33 376 associated with the methodology of this systematic review: only studies written in English were included,  
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35 377 raising the possibility that some studies were missed.  
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### 39 379 **Conclusion**

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42 380 Due to the mixed findings in this systematic review, it cannot be concluded that self-reported physical  
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44 381 activity behavior before cardiac surgery is associated with health outcomes after surgery. The mixed  
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46 382 findings could be due to the heterogeneity in physical activity tools used, definitions of outcomes, and the  
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48 383 few studies adjusting for other potentially confounding variables. These findings highlight the need for  
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50 384 more research in this area.  
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**Running Head:** PA and post-cardiac surgical outcomes

**FIGURE LEGENDS**

**Figure 1.** Study flow diagram.

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**Running Head:** PA and post-cardiac surgical outcomes

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**Table 1.** Characteristics of included studies.

First author, year	Study Population	Country	Participants at follow-up	Physical Activity Assessment	Longest follow-up	Main findings
Giaccardi, 2011 <sup>18</sup>	All patients $\geq 65$ years undergoing CABG and/or valve procedures (total sample: $74.1 \pm 5.8$ years old); 43% female	Italy	158	Harvard Alumni Questionnaire	Four weeks postoperatively	Physical activity had an independent association with postoperative atrial fibrillation within 30 days.
Markou, 2007 <sup>12</sup>	Elective CABG patients (Active: $64.4 \pm 9.4$ , Inactive: $63.8 \pm 9.0$ years old); % female not reported	Netherlands	428	The Corpus Christi Heart Project	One year	Inactive vs. Active group had significantly more peri-operative MIs, but not reoperations, ICU LOS, HLOS, or postoperative complications at one year. Inactive group was more likely than Active group to be physically active at one year.
Nery, 2007 <sup>13</sup>	All patients undergoing CABG (Active: $63 \pm 11$ , Inactive $66 \pm 14$ years old); 42% female	Brazil	55	Structured Questionnaire confirmed by Minnesota Leisure Time Physical Activity Questionnaire	One year	Inactive vs. Active group had significantly longer HLOS and more postoperative events at one year.
Markou, 2008 <sup>14</sup>	Elective CABG patients ( $64.3 \pm 9.04$ years old); 18% female	Netherlands	568	The Corpus Christi Heart Project	One year	Inactive vs. Active group were more likely to be more physically active one year postoperatively.
Martini, 2010 <sup>15</sup>	Elective CABG patients (Active: $60 \pm 10$ , Inactive: $62 \pm 10$ years old); 34% female	Brazil	185	Baecke Usual Physical Activity Questionnaire	Two years	Inactive vs. Active group did not have significantly different MACCE outcomes at two years.

**Running Head:** PA and post-cardiac surgical outcomes

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3	Nery,	Elective CABG patients (Active:	Brazil	202	Baecke Usual	Hospital	Inactive vs. Active group had
4	2010 <sup>16</sup>	60 ± 10, Inactive: 62 ± 10 years			Physical Activity	discharge	more postoperative events
5		old); 34% female			Questionnaire		within 30 days and a longer
6							HLOS.
7							
8							
9	Rengo,	Acute or elective CABG patients ≥	Italy	587	Physical Activity	Mean 44.3 ±	Physical activity had an
10	2010 <sup>17</sup>	70 years (Active: 72.3 ± 3.2,			Scale for the	21.0 months	independent and dose
11		Inactive: 76.1 ± 3.9 years old); 34%			Elderly		association with cardiac and all-
12		female					cause mortality five years
13							postoperatively.
14	Cacciatore,	All patients ≥ 65 years undergoing	Italy	250	Physical Activity	Hospital	Physical activity was
15	2012 <sup>19</sup>	CABG and/or valve procedures			Scale for the	discharge	independently associated with
16		(72.9 ± 4.8 years old); 48% female			Elderly		reduced prolonged ICU LOS.
17							Physical activity was not
18							independently associated with
19							postoperative ADLs.
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22	Noyez,	Elective CABG and/or valve	Netherlands	3150	The Corpus	30 days	Physical activity was not
23	2013 <sup>20</sup>	patients (69.7 ± 10.1 years old);			Christi Heart	postoperative	independently associated with
24					Project	ly	hospital or 30 day mortality.
25							Inactive vs. Active group had a
26							significantly longer ICU LOS.
27							
28	Min, 2015 <sup>21</sup>	Elective CABG and/or valve	United States	62	The Health and	4-6 months	Inactive vs. Active group had
29		patients ≥ 65 years (74.7 ± 5.9	of America		Retirement		significantly higher
30		years old)			Survey		postoperative physical activity
31							up to 6 months postoperatively.
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34	van Laar <sup>22</sup>	Patients ≥75 years undergoing	Netherlands	115	The Corpus	2 years	Inactive vs. Active group had
35		elective isolated aortic valve			Christi Heart	postoperative	significantly higher mortality
36		replacement (79.5 ± 2.8 years old);			Project	ly	rates 2 years postoperatively.
37		59% female					

CABG, coronary artery bypass graft surgery; HLOS, hospital length of stay; ICU LOS, intensive care unit length of stay; MI, myocardial infarction; MACCE, major adverse cerebrovascular and cardiac events; ADL, activities of daily living.

Running Head: PA and post-cardiac surgical outcomes

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**Table 2.** Major adverse and cerebrovascular events and postoperative events within 30 days

Reference	Outcome definition	Adjustment variables	Number of events per group	OR or HR and 95% CI
<b>Major adverse cerebrovascular and cardiac events</b>				
Nery, 2007 <sup>13</sup>	One year postoperative AF, hospital readmission, new CABG, PCI, MI	None	Active: 8/25 (31%); Inactive: 17/30 (57%) <sup>a</sup>	NR
Martini, 2010 <sup>15</sup>	Two year postoperative death, re-hospitalization, cerebrovascular accident, MI	None	Active: 9/66 (14%); Inactive: 31/119 (26%)	NR
Rengo, 2010 <sup>17</sup>	Five-year postoperative cardiac and all-cause mortality	Demographics, medical history, medications, and clinical findings.	NR	<u>Adjusted proportional hazard models:</u> <i>All-cause mortality:</i> Exp(B) 0.248 (95% CI 0.141-0.434) <sup>a</sup> <i>Cardiac mortality:</i> Exp(B) 0.272 (0.133-0.555) <sup>a</sup>
van Laar <sup>22</sup>	Two-year mortality	None	Active: 5/65 (13%); Inactive: 11/50 (22%) <sup>a</sup>	NR
<b>Postoperative events within 30 days</b>				
Markou, 2007 <sup>12</sup>	Perioperative MI, Re-intervention, postoperative complications (wound, renal, neurological, pulmonary, gastrointestinal)	None	<u>MI:</u> Active: 4/226 (2%); Inactive: 11/202 (5%) <sup>a</sup> <u>Reoperation:</u> Active: 15/226 (7%); Inactive: 9/202 (5%), <u>Wound infection:</u> Active: 3/226 (1%); Inactive: 7/202 (3%), <u>Renal:</u> Active: 3/226; Inactive: 7/202	NR
Nery, 2010 <sup>16</sup>	Mortality, MI, reoperation	Age, smoking, PVD, COPD, Cleveland Risk Score.	<u>Mortality:</u> Active: 0/66 (0%); Inactive: 7/136 (5%) <u>MI:</u> Active: 1/66 (2%); Inactive: 6/136 (4%) <u>Reoperation:</u> Active: 0/66 (0%); Inactive: 1/136 (0.5%)	<u>Multivariate OR for being active:</u> 0.22 (95% CI 0.09-0.51, p=0.001)

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Rengo, 2010 <sup>17</sup>	Low-output syndromes, MI, cardiac support, stroke, bleedings, mediastinitis, pneumonia, dialysis	None	<u>Any surgical complication:</u> Active: 53/267 (19.7%); Inactive: 60/320 (18.6%)	NR
Giaccardi, 2011 <sup>18</sup>	Atrial fibrillation	Age, episodes of AF one year preop, episodes of AF in the first week, $\beta$ -blockers, amiodarone, left ventricular volume, left atrial emptying fraction	<u>Postoperative atrial fibrillation:</u> Active: 6/74 (8.1%); Inactive: 27/84 (32.1%) <sup>a</sup>	<u>Multivariate OR for being inactive:</u> 4.04 (95% CI 1.16-14.14, p=0.029)
Noyez, 2013 <sup>20</sup>	Mortality, reoperation, stroke, renal insufficiency, sternal wound, ventilation	$\geq 75$ years, valve surgery, female, high operative risk, renal disease, obesity, NYHA IV, Insulin, vascular pathology, poor LVEF, lung disease, MI, neurological event	<u>Hospital mortality:</u> Active: 7/1815 (0.4%); Inactive: 15/1335 (1.1%) <sup>a</sup> <u>30 day mortality:</u> Active: 10/1815 (0.6%); Inactive: 20/1335 (1.5%) <sup>a</sup> <u>Reoperation:</u> Active: 105/1815 (5.8%); Inactive: 68/1335 (5%) <u>Stroke:</u> Active: 9/1815 (0.5%); Inactive: 12/1335 (0.9%) <u>Renal insufficiency:</u> Active: 32/1815 (1.8%); Inactive: 39/1335 (2.9%) <sup>a</sup> <u>Sternal wound:</u> Active: 10/1815 (0.6%); Inactive: 17/1335 (1.3%) <sup>a</sup> <u>Ventilation &gt;2 days:</u> Active: 31/1815 (1.7%); Inactive: 54/1335 (4.0%) <sup>a</sup>	<u>Hospital mortality multivariate OR for being inactive:</u> 1.20 (95% CI 0.4-3.5, p=0.617) <u>30 day mortality multivariate OR for being inactive:</u> 1.10 (95% CI 0.5-2.7, p=0.70)

<sup>a</sup> indicates statistical significance (P<0.05). CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; MI, myocardial infarction; NR, not reported; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; OR, odds ratio; AF, atrial fibrillation; BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.

**Running Head:** PA and post-cardiac surgical outcomes

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**Table 3.** Hospital length of stay, ICU length of stay, and postoperative activities of daily living and physical activity.

First author, year	Adjustment variables	Length of stay/number of events per group	Odds ratio (OR) or hazard ratio (HR) and 95% confidence interval (CI)
<b>Hospital length of stay</b>			
Markou, 2007 <sup>12</sup>	None	Active: 6.9 ± 8.2 days; Inactive: 7.3 ± 7.1 days	NR
Nery, 2007 <sup>13</sup>	None	Active: 12 ± 5 days, median 9 days (IQR 8-15); Inactive: 15 ± 8 days, median 12 (IQR 9-19) <sup>a</sup>	NR
Nery, 2010 <sup>16</sup>	Age, sex, Cleveland Risk Score, smoking, systemic arterial hypertension, stroke, MI, and PVD.	NR	HR: 0.67 (95% CI 0.49-0.93) <sup>a</sup>
<b>ICU length of stay</b>			
Markou, 2007 <sup>12</sup>	None	Active: 2.2 ± 5.3 days; Inactive: 2.1 ± 3.5 days	NR
Cacciatore, 2012 <sup>19</sup>	For ICU LOS >3 days: age, off-pump CABG, stroke, renal failure.	Active: 2.58 ± 1.09 days; Inactive: 3.33 ± 1.68 days <sup>a,b</sup>	<u>For ICU length of stay &gt;3 days</u> Univariate OR: 0.984 (95% CI 0.977-0.992) <sup>a</sup> Multivariate OR: 0.992 (95% CI 0.983-1.000) <sup>a</sup>
Noyez, 2013 <sup>20</sup>	None	Active: 1.3 ± 1.9 days; Inactive 3.0 ± 41.8 days <sup>a</sup>	NR
		ICU > 5 days: Active: 19/1815 (1.0%); Inactive: 46/1335 (3.4%) <sup>a</sup>	
<b>Postoperative ADLs</b>			
Cacciatore,	Age, gender, CABG, NYHA ≥3,	NR	Beta: 0.099

Running Head: PA and post-cardiac surgical outcomes

2012<sup>19</sup> ICU LOS  $\geq$ 3 days, Off-pump CABG, diabetes, renal failure, stroke, PVD, COPD, Cumulative Illness Rating Scale.

Postoperative Physical activity

Markou, 2007<sup>12</sup> Age  $\geq$ 75 years, gender, neurological disease, vascular disease, diabetes, and preoperative physical activity.

Better PA post-operatively: Active: 48/226 (21.2 %), Inactive: 129/202 (64%)<sup>a</sup>

Decreased postoperative PA OR (inactive group as reference): 8.1 (95% CI 3.5-13.5)<sup>a</sup>

Equal PA post-operatively: Active: 112/226 (49.6%), Inactive: 59/202 (29.2%)<sup>a</sup>

Worse PA post-operatively: Active: 66/226 (29.2%), Inactive: 14/202 (6.9%)<sup>a</sup>

Markou, 2008<sup>14</sup> Diabetes, vascular disease, neurological disease, renal disease, MI, preoperative activity level.

NR

For becoming physically inactive postoperatively

Male OR (inactive group as reference): 7.11 (95% CI 3.6-13.9)<sup>a</sup>

Female OR (inactive group as reference): 11.0 (95% CI 2.2-55)<sup>a</sup>

Min, 2015<sup>21</sup> None NR

Each weekly preoperative activity point was associated with a loss of 0.78 points at 6 weeks,  $p < 0.001$ , and 0.65 points at 6 months)<sup>a</sup>

<sup>a</sup> indicates statistical significance ( $P < 0.05$ ). <sup>b</sup>Unpublished data obtained from Cacciatore et al, [19]. ICU, Intensive Care Unit; ADL; activities of daily living; IQR, interquartile range; NR, not reported; MI, myocardial infarction; PVD, peripheral vascular disease; HR, hazard ratio; OR, odds ratio; CABG, coronary artery bypass graft; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; PA, physical activity.

**Running Head:** PA and post-cardiac surgical outcomes

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**Table 4.** Newcastle-Ottawa scale risk of bias scores

Reference	Selection	Comparability	Outcome	Total
Markou, 2007 <sup>12</sup>	3	2	3	8
Nery, 2007 <sup>13</sup>	3	0	2	5
Markou, 2008 <sup>14</sup>	3	2	2	7
Martini, 2010 <sup>15</sup>	3	0	2	5
Nery, 2010 <sup>16</sup>	3	2	2	7
Rengo, 2010 <sup>17</sup>	4	2	3	9
Giaccardi, 2011 <sup>18</sup>	3	2	2	7
Cacciatore, 2012 <sup>19</sup>	3	2	2	7
Noyez, 2013 <sup>20</sup>	3	2	3	8
Min, 2015 <sup>21</sup>	4	2	1	7
van Laar <sup>22</sup>	3	0	3	6
Average scores $\pm$ SD	3.18 $\pm$ 0.40	1.45 $\pm$ 0.93	2.27 $\pm$ 0.65	6.91 $\pm$ 1.22

Maximum scores are 4, 2, and 3 for selection, comparability, and outcome, respectively.  
Maximum total score is 9. A lower score within each category and for a total score indicates a higher risk of bias.



**Running Head:** PA and post-cardiac surgical outcomes

**Box 1.** Guidelines for physical activity measurement and outcome assessment in cardiac surgery patients: limitations and opportunities for future research

Drawbacks	Opportunity
<b>Physical activity</b>	
1. Heterogeneity in tools used across studies	-use of objectively measured tools (e.g., pedometers, accelerometers) which can produce data that can be compared across studies, such as step counts, intensity, and duration of physical activity.
2. Only subjective measures were used	-Capture physical activity behavior as soon as a patient is placed on a wait list, or in non-elective cases, as soon as possible prior to surgery.
3. Time of preoperative physical activity assessment was unclear in most studies	-Physical activity should be assessed ideally over a 7 day period. -Physical activity should be assessed by intensity and duration per week, and in steps per day.
<b>Outcomes</b>	
4. Heterogeneity in MACCE and postoperative events within 30 days definitions	-MACCE should be evaluated as a long-term outcome and defined as death, stroke, myocardial infarction, and the need for re-do cardiac surgery. Each outcome should be evaluated individually. -30-day postoperative events should be evaluated using the STS checklist: <sup>10</sup> along with reasons, evaluate unexpected return to the operating room, complications due to pulmonary, cardiovascular, gastrointestinal, hematological, urologic, infection, neurological, and other important miscellaneous outcomes (e.g., unexpected admission to ICU, or other events requiring admission to operating room requiring anesthesia. -re-hospitalization for any cause after cardiac surgery should also be added to outcomes.
5. No patient-oriented outcomes were assessed	-Capture postoperative health-related quality of life, mental health, pain, and cardiac symptoms using validated tools within the first 30 days and at least one-year postoperatively.
<b>Statistical procedures</b>	
6. Shortage of studies addressing confounders	-use multivariate analysis, including logistic or linear regression, or analysis of variance statistical procedures. Ensure that a power analysis is conducted prior to conducting the study.

MACCE, major adverse cerebrovascular and cardiac events. STS, Society of Thoracic Surgeons. ICU, intensive care unit.

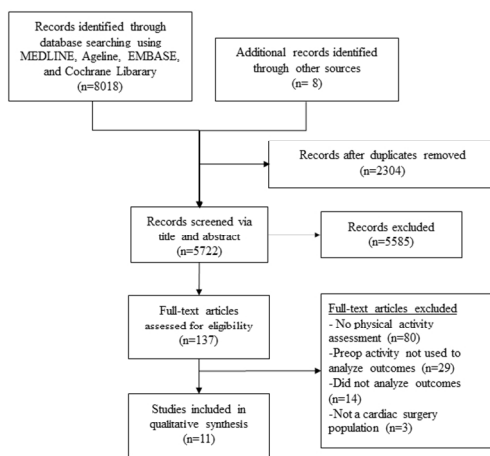


Figure 1. Study flow diagram

108x60mm (300 x 300 DPI)

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# PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5 (link provided)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	No meta-analysis



# PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	No meta-analysis
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Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7 and in Table 1 (page 20-22)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10 and in Table 4 (page 28)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-10 and in tables 2 and 3 (pages 23-27)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	No meta-analysis
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11



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Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	None. Indicated in the title page

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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# BMJ Open

## Systematic Review of preoperative physical activity and its impact on post-cardiac surgical outcomes

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-015712.R1
Article Type:	Research
Date Submitted by the Author:	31-May-2017
Complete List of Authors:	Kehler, D. Scott Stammers, Andrew N.; University of Manitoba, Tangri, Navdeep; University of Manitoba, Medicine Hiebert, Brett Fransoo, Randy; University of Manitoba, Community Health Sciences Schultz, Annette; University of Manitoba, Nursing Macdonald, Kerry Giacomontonio, Nicholas Hassan, Ansar; New Brunswick Heart Centre, Légaré, Jean-Francois Arora, Rakesh C.; University of Manitoba, Duhamel, Todd A.; University of Manitoba,
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Cardiac surgery < SURGERY, REHABILITATION MEDICINE, Exercise, Postoperative complications, Prognosis

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Manuscripts

Running Head: PA and post-cardiac surgical outcomes

1

1 **Title: Systematic Review of preoperative physical activity and its impact on post-cardiac surgical**  
2 **outcomes**

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**Running Head:** PA and post-cardiac surgical outcomes

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**Authors' Contributions:**

DSK was responsible for 1) analysis and interpretation of data, 2) drafting and revising the manuscript, and 3) consenting for manuscript submission. ANS, BH, NT, RF, ASH, NG, AH, JL were responsible for 1) analysis and interpretation of data, 2) revising the manuscript, and 3) consenting for manuscript submission. KM was responsible for 1) developing the systematic review literature search, 2) analysis and interpretation of data, 3) drafting and revising the manuscript, and 3) consenting for manuscript submission. RCA and TAD were responsible for 1) the conception and design, and analysis and interpretation of data, 2) revising the manuscript, and 3) consenting for manuscript submission RCA and TAD are co-senior authors.

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**Running Head:** PA and post-cardiac surgical outcomes

53 grant number 326290.

54

**Ethics Approval:**

56 Not applicable

57

**Systematic review registration number:**

59 PROSPERO: CRD42015023606

60

**Competing Interests:**

62 The authors have no conflicts of interest to declare

63

**Data Sharing Statement:**

65 There are no additional unpublished data to share as a part of this systematic review.

66

67 Word count (not including abstract, tables, and references): 3990

68 Figures and tables: 5

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**Running Head:** PA and post-cardiac surgical outcomes

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71 **ABSTRACT:**

72 **Objectives:** The objective of this systematic review was to study the impact of preoperative physical  
73 activity levels on adult cardiac surgical patients' postoperative: 1) major adverse cardiac and  
74 cerebrovascular events (MACCE), 2) adverse events within 30 days, 3) hospital length of stay (HLOS), 4)  
75 intensive care unit length of stay (ICU LOS), 5) activities of daily living (ADLs), 6) quality of life, 7)  
76 cardiac rehabilitation attendance, and 8) physical activity behavior.

77 **Methods:** A systematic search of MEDLINE, Embase, AgeLine, and Cochrane library for cohort studies  
78 was conducted.

79 **Results:** Eleven studies (n=5,733 patients) met the inclusion criteria. Only self-reported physical activity  
80 tools were used. Few studies used multivariate analyses to compare active versus inactive patients prior to  
81 surgery. When comparing patients who were active versus inactive preoperatively, there were mixed  
82 findings for MACCE, 30 day adverse events, HLOS, and ICU LOS. Of the studies which adjusted for  
83 confounding variables, five studies found a protective, independent association between physical activity  
84 and MACCE (n= 1), 30 day postoperative events (n= 2), hospital length of stay (n= 1), and ICU length of  
85 stay (n= 1), but two studies found no protective association for 30 day postoperative events (n= 1) and  
86 postoperative ADLs (n= 1). No studies investigated if activity status before surgery impacted quality of  
87 life or cardiac rehabilitation attendance postoperatively. Three studies found that active patients prior to  
88 surgery were more likely to be inactive postoperatively.

89 **Conclusion:** Due to the mixed findings, the literature does not presently support that self-reported  
90 preoperative physical activity behavior is associated with postoperative cardiac-surgical outcomes. Future  
91 studies should objectively measure physical activity, clearly define outcomes, and adjust for clinically  
92 relevant variables.

93 **Registration:** PROSPERO number CRD42015023606.

94  
95 **Keywords:** Cardiac Surgical Procedures, Exercise, Prognosis, Postoperative Complications  
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**Running Head:** PA and post-cardiac surgical outcomes

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3 97 **ARTICLE SUMMARY**

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5 98 **Strengths and limitations of this study**

- 6  
7 99 - There were mixed findings regarding the impact of physical activity on post cardiac-surgical  
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10 100 outcomes.  
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12 101 - Only self-reported physical activity tools were used.  
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14 102 - The multiple tools to measure physical activity and the variety of definitions of outcomes did not  
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16 103 allow for a quantitative synthesis (meta-analysis).  
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**Running Head:** PA and post-cardiac surgical outcomes

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3 104 **INTRODUCTION**  
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5 105 Recent reports suggest that more than half of cardiac surgeries are being performed on older adults who  
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7 106 are more likely to be frail and have multiple co-morbidities.<sup>1</sup> While cardiac surgery has been shown to  
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9 107 improve the outcomes of these patients, more than 75% of major perioperative complications and deaths  
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11 108 occur in older adults.<sup>2,3</sup> Before surgery, many of these patients are de-conditioned and have diminished  
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13 109 resilience in the face of major stressors such as cardiac surgery, and it has been postulated that they could  
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15 110 benefit from a therapeutic intervention prior to their major surgical procedure in order to reduce their  
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17 111 operative risk. However, little information exists to evaluate the benefit of preoperative risk reduction  
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19 112 strategies for the older cardiac surgery patient.  
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25 114 Adopting and sustaining a more physically active lifestyle is typically intended to be a part of an  
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27 115 interdisciplinary rehabilitation plan that is instituted postoperatively and has been shown to reduce the  
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29 116 risk of cardiac mortality and hospital admissions and improve health-related (QOL) in patients.<sup>4</sup>  
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31 117 Importantly, older adults who sustain a physically active lifestyle after a postoperatively exercise-based  
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33 118 rehabilitation program can continue to improve their functional walking status.<sup>5</sup> However, evidence  
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35 119 suggests that cardiac surgery patients are highly sedentary during the preoperative period, especially in  
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37 120 older adults.<sup>6</sup> Furthermore, few randomized controlled trials exist which evaluate the therapeutic benefit  
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39 121 of preoperative lifestyle modification in patients undergoing cardiac surgery.<sup>7-9</sup> Information regarding the  
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41 122 link between preoperative physical activity and postoperative health outcomes in cardiac surgery patients  
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43 123 would be valuable for healthcare providers to assist them in selecting patients who might benefit from  
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45 124 preoperative exercise therapy.  
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51 126 The purpose of this systematic review was to compare the following postoperative outcomes between  
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53 127 cardiac surgery patients defined as physically active prior to surgery and those who were defined as  
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55 128 physically inactive preoperatively: 1) major adverse cerebrovascular and cardiovascular events (MACCE)  
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57 129 2) 30-day adverse events as defined by the Society of Thoracic Surgeons (STS)<sup>10</sup> 3) hospital length of  
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**Running Head:** PA and post-cardiac surgical outcomes

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130 stay, 4) Intensive Care Unit (ICU) length of stay, 5) health-related QOL, 6) activities of daily living  
131 (ADL) 7) cardiac rehabilitation attendance and 8) physical activity levels postoperatively.  
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3 133 **MATERIAL AND METHODS**  
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8 135 The protocol for this systematic review has been described in PROSPERO: CRD42015023606. Note  
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10 136 the following *ad-hoc* changes to the previous protocol: ICU length of stay and postoperative physical  
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12 137 activity as additional outcomes were explored in this systematic review.  
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16 139 **Eligibility criteria**  
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21 141 Eligible studies included cohort studies which examined adult (>18 years) cardiac surgery patients  
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23 142 undergoing coronary artery bypass grafting (CABG), aortic or mitral valve repair/replacement,  
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25 143 transcatheter aortic valve implantation, or combined procedures. Studies with patients undergoing  
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27 144 congenital cardiac surgery, heart transplantation or left ventricular assist device implantation procedures  
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29 145 were excluded. Studies could compare physically active versus inactive patients prior to cardiac surgery  
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31 146 on the basis of subjective (e.g., questionnaire) or objective (e.g., pedometer, accelerometry) assessments  
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33 147 of physical activity.  
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38 149 Eligible studies had to compare at least one of the following postoperative outcomes: MACCE defined  
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40 150 as death, stroke, myocardial infarction, and the need for emergency cardiac surgery; 30-day adverse  
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42 151 events as defined by the STS,<sup>10</sup> including an unexpected return to the operating room, complications due  
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44 152 to pulmonary, cardiovascular, gastrointestinal, hematological, urologic, infection, and neurological  
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46 153 deficits, other important miscellaneous outcomes (e.g., unexpected admission to ICU, or other events  
47  
48 154 requiring admission to operating room requiring anesthesia; hospital length of stay; ICU length of stay;  
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50 155 health-related QOL with any assessment tool; ADLs using any evaluation strategy; cardiac rehabilitation  
51  
52 156 attendance; and physical activity behavior using either subjective or objective forms of assessment.  
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**Running Head:** PA and post-cardiac surgical outcomes

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**Search strategy**

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The search strategy was completed by a librarian and reviewed by a second librarian. The search

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included keywords and controlled vocabulary. English language limits were applied. Databases used

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included MEDLINE, Embase, AgeLine, and Cochrane Library (CDSR, CENTRAL, DARE) and articles

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18 166

were searched from inception to December 2016. The MEDLINE strategy was registered and published

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online in PROSPERO

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([http://www.crd.york.ac.uk/PROSPEROFILES/23606\\_STRATEGY\\_20150518.pdf](http://www.crd.york.ac.uk/PROSPEROFILES/23606_STRATEGY_20150518.pdf)) and is also available

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as a supplementary file. The search was validated through a cross-check of references of studies selected

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for inclusion. In addition, conference abstracts were hand searched using the Internet. Attempts were

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made to contact authors of conference abstracts to determine if their findings were published in a peer-

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reviewed journal.

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**Study selection**

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The title, abstract and full-text article screening processes were independently completed by two

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reviewers. A training exercise for the title and abstract phase was conducted by the independent reviewers

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using a random sample of 100 titles and abstracts. Discrepancies in studies for inclusion were resolved by

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discussion of the two reviewers. The final observed agreement was 98% with a kappa statistic of 0.47 for

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the title and abstract screen. One training exercise of 10 randomly selected articles was completed for the

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full-text screen. Discrepancies for inclusion were resolved through discussion. The observed agreement

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for the full-text screen was 96% with a kappa statistic of 0.83.

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Running Head: PA and post-cardiac surgical outcomes

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3 185 **Data abstraction**  
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7 187 Two reviewers independently extracted relevant data for the selected outcomes described above.  
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9  
10 188 Discrepancies in the data extraction procedure were resolved through discussion. Data abstraction items  
11  
12 189 included study characteristics (e.g., authors, year of publication, sample size, follow up time points if  
13  
14 190 relevant), patient characteristics (e.g., age, sex, surgery type), physical activity tool used, and the  
15  
16 191 outcomes which were measured.  
17

18 192  
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20 193 **Risk of bias assessment**  
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24  
25 195 Two reviewers independently reviewed the risk of bias of each included study using the Newcastle-  
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27 196 Ottawa Scale.<sup>11</sup> Items within this tool assess the risk of bias associated with selection of participants,  
28  
29 197 comparability (e.g., study authors controlled for patient demographics and clinical characteristics), and  
30  
31 198 outcome assessment (e.g., data collection method for outcome, sufficient follow-up, and adequacy of  
32  
33 199 follow up of cohorts). Each study was given a score within each category (Selection: 0-4; Comparability:  
34  
35 200 0-2; and Outcome: 0-3) and an overall score ranging from 0-9. A score of zero suggests an increased risk  
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37 201 of bias and a higher score suggests a lower risk of bias.  
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42 203 **Quantitative synthesis**  
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46 205 Due to the significant heterogeneity between studies in terms of physical activity assessment tools used  
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48 206 and outcomes assessed, meta-analyses were not performed.  
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3 207 **RESULTS**  
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7 209 The literature search results are shown in Figure 1. After removing duplicates, 5722 articles were title  
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10 210 and abstract screened. A total of 137 articles were then assessed in full-text. Eleven studies met the  
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12 211 eligibility criteria for the final analysis, and they included a total of 5,733 patients.<sup>12-22</sup>  
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16 213 An overview of the included studies can be viewed in Table 1. In the studies by Markou et al.,<sup>12,14</sup> Nery  
17  
18 214 et al.,<sup>13,16</sup> Martini et al.,<sup>15</sup> they evaluated CABG only patients. Rengo et al.,<sup>17</sup> Giaccardi et al.,<sup>18</sup>  
19  
20 215 Cacciatore et al.,<sup>19</sup> Noyez et al.,<sup>20</sup> and Min et al.<sup>21</sup> evaluated both CABG and/or valve procedures, and van  
21  
22 216 Laar et al.<sup>22</sup> evaluated isolated aortic valve repair patients. The average age of participants in different  
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24 217 studies ranged from 60 years (Martini and Nery et al.<sup>15,16</sup>) to 75 years (Rengo, Giaccardi, Min, and van  
25  
26 218 Laar et al.<sup>17,18,21,22</sup>). Rengo et al.,<sup>17</sup> Giaccardi et al.,<sup>18</sup> Min et al.,<sup>21</sup> and van Laar et al.<sup>22</sup> excluded patients  
27  
28 219 with physical impairments or with New York Heart Association heart failure class IV symptoms (severe  
29  
30 220 cardiac symptoms) but in general exclusion criteria were not explicitly reported. Studies were conducted  
31  
32 221 in the Netherlands (Markou et al.,<sup>12,14</sup> Noyez et al.,<sup>20</sup> and van Laar et al.<sup>22</sup>), Brazil (Nery et al.,<sup>13,16</sup> and  
33  
34 222 Martini et al.<sup>15</sup>), Italy (Rengo et al.,<sup>17</sup> Giaccardi et al.,<sup>18</sup> and Cacciatore et al.<sup>18</sup>), and the United States (Min  
35  
36 223 et al.<sup>21</sup>). Two studies by Nery et al.<sup>13</sup> and Martini et al.<sup>15</sup> used the same patient sample, but examined  
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38 224 different outcomes. The sample size of studies ranged from 35 in the Min et al.<sup>21</sup> study to 3150 in the  
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40 225 Noyez et al.<sup>20</sup> study  
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47 227 **Physical activity tools**  
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51 229 The physical activity assessments in each study were based on self-reported assessment tools. The  
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53 230 timing of the physical activity assessments prior to surgery was not reported by Cacciatore et al.,<sup>19</sup> Nery et  
54  
55 231 al.,<sup>13,16</sup> Markou et al.,<sup>12,14</sup> or by Martini et al.<sup>15</sup> Rengo et al.<sup>17</sup> reported the timing of their physical activity  
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57 232 assessment, which was within 35±6 days prior to surgery. Noyez et al., and van Laar et al. measured  
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**Running Head:** PA and post-cardiac surgical outcomes

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233 activity the day before surgery.<sup>20,22</sup> Min and colleagues measured physical activity four weeks prior to the  
234 patients' surgical procedure.<sup>21</sup> Finally, Giaccardi et al. measured preoperative physical activity levels  
235 approximately one week following surgery.<sup>18</sup>

236  
237 Four studies used the Corpus Christi Heart Project questionnaire<sup>12,14,20,22</sup> which asks participants about  
238 their typical physical activity behaviors over the past year during their leisure time. Participants were  
239 categorized into a sedentary group if they accumulated less than 30 minutes per day of light intensity  
240 activity, or into an active group if they accumulated at least one session per week of dynamic activity  
241 lasting  $\geq 15$  minutes marked by moderate intensity. Nery et al.,<sup>13,16</sup> and Martini et al.<sup>15</sup> used a structured  
242 questionnaire confirmed by the Minnesota Leisure Time Physical Activity Questionnaire<sup>13</sup> or the Baecke  
243 Usual Physical Activity questionnaire.<sup>15,16</sup> Both physical activity tools ask participants to recall their  
244 usual activities 12 months prior and determine the frequency, intensity, and time of activity. Participants  
245 were categorized into an inactive group if they engaged only in light intensity ( $< 3$  metabolic equivalents)  
246 activity or into an active group if they achieved  $\geq 3$  metabolic equivalents. Rengo et al.<sup>17</sup> and Cacciatore et  
247 al.<sup>19</sup> used the Physical Activity Scale for the Elderly, which is a 7-day recall of a participants' frequency,  
248 intensity, duration, and type of activity. Participants receive a total score from 0-400. Rengo et al.<sup>17</sup>  
249 separated participants by inactive and active groups using the median score, whereas Cacciatore et al.<sup>19</sup>  
250 used the continuous measure. The Harvard Alumni Questionnaire was implemented by Giaccardi and  
251 colleagues<sup>18</sup> which measures the typical weekly amount and intensity of physical activity over the past  
252 year. Participants were categorized as inactive if they participated in  $< 1$  hour per week of light activity  
253 and as active if they participated in either  $\geq 4$  hours of light or more than 1-2 hours of moderate activity  
254 per week. In the study by Min et al.,<sup>21</sup> the physical activity-related questions were used from the Health  
255 and Retirement Survey, which determines a participants' frequency and intensity of activity in a typical  
256 week. These authors used the continuous score in their study.

257

258 **MACCE**

**Running Head:** PA and post-cardiac surgical outcomes

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260 Outcomes within the definition of MACCE were evaluated in four studies (Table 2) by Nery et al.,<sup>13</sup>  
261 Martini et al.,<sup>15</sup> Rengo et al.,<sup>17</sup> and van Laar et al.<sup>22</sup> The follow-up periods were one (Nery et al.<sup>13</sup>) two  
262 (Martini et al.,<sup>15</sup> and van Laar et al.<sup>22</sup>) and five years (Rengo et al.<sup>17</sup>) postoperatively. Unadjusted  
263 differences between active versus inactive patients and MACCE (defined as atrial fibrillation, hospital  
264 admission, reoperation and MI) were found one-year postoperatively in the Nery et al.<sup>13</sup> study. The  
265 Martini et al.<sup>15</sup> study found no differences (defined as mortality, re-hospitalization, cerebrovascular  
266 accident and MI) at two years postoperatively. The unadjusted rates of mortality within two years post-  
267 surgery was significantly higher in the active versus inactive group were found in the study by van Laar  
268 and colleagues<sup>22</sup>. The study by Rengo and associates found a significant and dose-response relationship  
269 between physical activity and postoperative cardiac and all-cause mortality after controlling for  
270 preoperative demographics, medical history, medications, and clinical characteristics.<sup>17</sup>

271  
272 **30-day events**  
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274 Five studies (Markou et al.,<sup>12</sup> Nery et al.,<sup>16</sup> Rengo et al.,<sup>17</sup> Giaccardi et al.,<sup>18</sup> and Noyez et al.<sup>20</sup>)  
275 evaluated postoperative events within 30 days of surgery (Table 2). The postoperative events measured  
276 varied significantly between the studies. Three studies (Nery et al.,<sup>16</sup> Giaccardi et al.,<sup>18</sup> and Noyez et al.<sup>20</sup>)  
277 examined if physical activity was an independent protective factor against postoperative events. Physical  
278 activity was an independent protective factor against the combined outcome of mortality, MI, and  
279 reoperation in the study by Nery et al.,<sup>16</sup> as well as postoperative atrial fibrillation in the Giaccardi and  
280 associates study,<sup>18</sup> but was not significant for in-hospital or 30-day mortality in the Noyez et al.<sup>20</sup> study.

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282 **Postoperative health-related QOL**

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284 No studies evaluated postoperative health-related QOL.

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### **Hospital and ICU length of stay**

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12 289 Three studies by Markou et al.<sup>12</sup> and Nery et al.<sup>13,16</sup> compared hospital length of stay between active vs.  
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14 290 inactive cardiac surgery patients (Table 3). Hospital length of stay was longer in the inactive group in two  
15  
16 291 of three studies (both by Nery et al.<sup>13,16</sup>). One of the studies by Nery et al.<sup>16</sup> did not report hospital length  
17  
18 292 of stay summary statistics between the active vs. inactive groups. However that study reported an  
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20 293 independent association between the preoperative active vs. inactive group and a reduced likelihood of  
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22 294 prolonged hospital length of stay, though “prolonged” was not defined in the study.  
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29 297 Three studies compared ICU length of stay between the preoperative physical activity groups (Table 3)  
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31 298 (Markou et al.<sup>12</sup>, Cacciatore et al.<sup>19</sup> and Noyez et al.<sup>20</sup>). Two studies (Markou et al.<sup>12</sup> and Noyez et al.<sup>20</sup>)  
32  
33 299 found that the inactive group had a significantly longer ICU length of stay compared to the active group.  
34  
35 300 In the study by Cacciatore and colleagues, they found in their multivariate analysis that the active group  
36  
37 301 was less likely to have a prolonged ICU length of stay >3 days compared to the inactive group after  
38  
39 302 controlling for age, off-pump CABG, stroke, and renal failure.  
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### **Postoperative ADLs**

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48 306 One study by Min et al.<sup>19</sup> examined the impact of preoperative physical activity and postoperative  
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50 307 ADLs at the time of hospital discharge and revealed no statistically significant ( $p=0.079$ ) association  
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52 308 between the two after adjusting for preoperative demographics and clinical variables.  
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### **Cardiac rehabilitation attendance**

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**Running Head:** PA and post-cardiac surgical outcomes

311 No studies evaluated cardiac rehabilitation attendance postoperatively.

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314 **Postoperative physical activity behavior**

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316 The impact of preoperative physical activity on postoperative physical activity levels was examined in  
317 the two studies by Markou et al.<sup>12,14</sup> and in the other study by Min et al.<sup>21</sup>(Table 3).These studies found  
318 that the active group preoperatively was more likely to be physically inactive postoperatively. In both of  
319 the Markou et al. <sup>12,14</sup> studies, they completed a multivariate analyses and found that this association  
320 remained statistically significant after controlling for age, gender, and preoperative clinical  
321 characteristics.

322

323 **Risk of bias**

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325 The risk of bias assessment via the Newcastle-Ottawa Scale can be viewed in Table 4. Since some  
326 studies assessed multiple outcomes, the risk of bias assessments were based on their highest possible  
327 score (e.g., some outcomes were assessed with a multivariable analysis, while others were not in the same  
328 study). All studies scored at least 3 out of 4 for the selection of study groups. There was variability across  
329 studies for the ascertainment of exposure or outcome of interest. Total risk of bias scores ranged from 5 to  
330 9, suggesting the studies were of moderate to high quality, respectively.

**Running Head:** PA and post-cardiac surgical outcomes

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3 331 **DISCUSSION**

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5 332 The purpose of this systematic review was to determine if physical activity before cardiac surgery was  
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7 333 associated with postoperative health outcomes. Given the different self-reported physical activity tools  
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9 334 used that prevented comparison across studies, the inconsistent use of adjustment for potential  
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11 335 confounders, and the varying outcomes evaluated for MACCE and 30 day postoperative events, it cannot  
12  
13 336 be concluded that preoperative physical activity is associated with postoperative outcomes in adult  
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15 337 cardiac surgery patients. This systematic review highlights important gaps within the literature on this  
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17 338 topic. Therefore, key recommendations for examining the impact of preoperative physical activity  
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19 339 behavior on post-surgical outcomes of cardiac patients are provided (Box 1).  
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25 341 The different self-reported physical activity tools used across the studies makes it difficult to compare  
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27 342 the preoperative physical activity levels of patients prior to cardiac surgery. Even so, it is important to  
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29 343 note that in the studies included in this systematic review, most of the studies identified a sub-sample of  
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31 344 cardiac surgery patients who were more vulnerable to poor health outcomes by categorizing patients as  
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33 345 active or inactive prior to surgery using their self-reported physical activity measures. However, the way  
34  
35 346 the physical activity tools measured physical activity (e.g., over the past year or in the past week; see the  
36  
37 347 Methods section) could have influenced the outcomes of the study. There seems to be no universally  
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39 348 accepted tool to measure self-reported physical activity levels,<sup>23</sup> and it is unclear if any of the physical  
40  
41 349 activity tools identified by this review have been validated in the cardiac surgery patient. One advantage  
42  
43 350 of using self-reported physical activity measures in studies is their ease of administration compared to  
44  
45 351 other objectively measured physical activity tools. Furthermore, self-reported physical activity tools  
46  
47 352 appear to provide some value when assessing the independent association between activity levels and  
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49 353 poor outcomes. In fact, most physical activity guideline recommendations for health benefits, including  
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51 354 those in North America, are based on self-reported measures.<sup>24,25</sup> Another strength of using a subjective  
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53 355 physical activity tool in the preoperative cardiac surgery patient is that it would capture a patient's  
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55 356 physical activity behavior before they are placed on a waiting list, when they might refrain from being  
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**Running Head:** PA and post-cardiac surgical outcomes

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3 357 physically active in fear of making their condition worse. However, cardiac surgery patients and other  
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5 358 patient populations tend to misreport their physical activity levels compared to objectively measured  
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7 359 physical activity.<sup>6,26</sup> Nevertheless, this systematic review found no studies that evaluated objectively  
8  
9 360 measured physical activity before cardiac surgery and its link to postoperative health outcomes. Evidence  
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11 361 suggests there is a stronger association between objective measures of physical activity and various  
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13 362 cardiovascular and metabolic biomarkers as compared to subjective measures of physical activity.<sup>27,28</sup>  
14  
15 363 While it is unclear which objective measures of physical activity are most appropriate in the complex  
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17 364 cardiac surgical patients, future studies should use a physical activity tools such as accelerometers or  
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19 365 pedometers.  
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25 367 There were inconsistent findings across studies assessing the same outcomes, and many studies did not  
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27 368 adjust for clinically relevant variables that could influence the health outcomes of cardiac surgery  
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29 369 patients. It is possible that most of the included studies were not statistically powered to detect changes  
30  
31 370 between inactive and active groups. The study by Rengo et al.<sup>17</sup> had the largest sample size of the four  
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33 371 studies that assessed MACCE outcomes, which found a significant protective association between  
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35 372 preoperative physical activity and cardiac and all-cause mortality five years postoperatively after  
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37 373 controlling for clinically relevant variables (Table 2). In contrast, the largest study examined in this  
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39 374 systematic review by Noyez and colleagues<sup>20</sup> found no association between preoperative activity and  
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41 375 hospital and 30-day mortality after controlling for covariates (Table 2). It is difficult to determine if  
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43 376 patient-level factors influence outcomes (e.g., elective or acute patients, surgery type, older versus  
44  
45 377 younger, females vs. males) as the samples were somewhat heterogeneous. Even so, some of the results of  
46  
47 378 this systematic review are promising. Specifically, of the studies which controlled for confounding  
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49 379 variables, five studies found a protective, independent association, between higher preoperative physical  
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51 380 activity levels when assessing clinical outcomes, including MACCE,<sup>17</sup> 30 day postoperative events,<sup>16,18</sup>  
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53 381 hospital length of stay,<sup>16</sup> and ICU length of stay;<sup>19</sup> whereas, only two studies found no protective  
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55 382 association for 30 day postoperative events<sup>20</sup> and postoperative ADLs.<sup>19</sup> Yet, more studies are needed to  
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**Running Head:** PA and post-cardiac surgical outcomes

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3 383 elucidate the impact of preoperative physical activity on post-cardiac surgical outcomes that control for  
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5 384 clinically relevant variables. Clinical variables included in the cardiac surgical risk models (e.g.,  
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7 385 EuroSCORE, STS score) could attenuate or mitigate the relationship between preoperative physical  
8  
9 386 activity behavior and postoperative outcomes. Collectively, future studies are needed to determine if  
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11 387 preoperative physical activity is a protective factor for health outcomes after cardiac surgery which  
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13 388 control for clinically relevant variables known to impact cardiac surgery outcomes.  
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18 390 An unanticipated finding was that patients who were active before surgery had a higher likelihood of  
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20 391 being physically inactive postoperatively, after controlling for co-morbidities.<sup>12,14,21</sup> Healthcare providers  
21  
22 392 may have advised patients with more severe symptomology prior to surgery to refrain from physical  
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24 393 activity. Also, the relief of cardiac symptoms after surgery among inactive patients could have led them to  
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26 394 become more active postoperatively. However, these possibilities were not explored in the included  
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28 395 studies.  
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33 397 While outside the scope of this systematic review, future studies should investigate if changes to  
34  
35 398 physical activity levels prior to cardiac surgery impact long-term patient health-outcomes. Cardiac  
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37 399 rehabilitation programs are intended to support cardiac patients in becoming more physically active  
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39 400 postoperatively and it has been shown that patients who attend such programs reduce their risk for  
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41 401 cardiac-related mortality and hospitalization rates.<sup>29</sup> Evidence suggests that among those referred to  
42  
43 402 cardiac rehabilitation after cardiac surgery, only 40% attend.<sup>6</sup> However, the literature is less clear on  
44  
45 403 whether patients who attend cardiac rehabilitation are more physically active compared to those who do  
46  
47 404 not attend. It is possible that patients who adopt and sustain a more physically active lifestyle on their  
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49 405 own after cardiac surgery could yield similar health benefits compared to those who attend an exercise-  
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51 406 based rehabilitation program, but this hypothesis requires further investigation.  
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3 408 Previous randomized controlled trials comparing an exercise program to standard care prior to elective  
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5 409 cardiac surgery (i.e., “Prehab”) demonstrate reductions in hospital length of stay and improvements in  
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7 410 walking ability postoperatively.<sup>7-9</sup> However, there were mixed findings from this systematic review when  
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9 411 comparing preoperative physical activity behavior and hospital stay.<sup>12,16</sup> These divergent findings suggest  
10  
11 412 either that a medically supervised and individualized physical activity program is needed to derive the  
12  
13 413 health benefits of physical activity prior to cardiac surgery, or that patients are misreporting their physical  
14  
15 414 activity behaviors. Future cohort studies in this area should address the drawbacks of the included studies  
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17 415 in this systematic review included in Box 1, while randomized trials should focus on whether preoperative  
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19 416 exercise therapy programs are feasible and efficacious in clinical practice.  
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24  
25 418 The findings of this systematic review suggest that the literature would benefit from standardization of  
26  
27 419 the definition of measures such as MACCE and postoperative events within 30 days. The heterogeneity in  
28  
29 420 reporting of outcomes can lead to considerably different conclusions across studies.<sup>30</sup> Attempts should  
30  
31 421 also be made to ensure other clinically important outcomes are captured, such as the addition of 30-day  
32  
33 422 events. Only one study in this review compared physically active versus inactive patients preoperatively  
34  
35 423 and reported on the individual postoperative events within 30 days.<sup>20</sup> Collectively, uniform outcome  
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37 424 reporting and appropriate outcome definitions are recommended when examining the outcomes of cardiac  
38  
39 425 surgery.<sup>30</sup>  
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44 427 Patient-oriented outcomes should also be captured to ensure that cardiac surgery is improving other  
45  
46 428 outcomes that patients value. No studies in this review determined if there was a link between  
47  
48 429 preoperative physical activity behavior and postoperative health-related QOL, and only one study  
49  
50 430 evaluated postoperative ADLs.<sup>19</sup> QOL postoperatively tends to improve in some older patients, while  
51  
52 431 others tend to decline.<sup>31</sup> Importantly, the preoperatively physical activity and overall functional status of  
53  
54 432 cardiac surgery patients could play a role in the postoperative trajectory of these outcomes such as QOL.  
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**Running Head:** PA and post-cardiac surgical outcomes

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433 Other patient-oriented outcomes, including postoperative pain and cardiac symptoms, could also be  
434 investigated.

435  
436 If physical activity is to be assessed in the preoperative period, the extent of missing data may also be a  
437 concern, especially with objective physical activity measures. The possibility of missing data from  
438 individual studies included in this systematic review was outside the objectives of the present study, but is  
439 a salient point that should be considered for future investigations. It is also important to understand  
440 patient-level factors associated with missing data. The use of statistical techniques that address missing  
441 data, such as multiple imputation, is one approach to address missing physical activity data. Importantly,  
442 it has been shown that multiple imputation leads to precise estimates of predicting 30-day mortality risk  
443 in cardiac surgery patients when important clinical variables are missing, as compared to estimating risk  
444 with a complete case analysis.<sup>32</sup>

445

### 446 **Limitations**

447 One limitation to consider is that the patients included across the studies evaluated in this systematic  
448 review may have been different, as the recruitment criteria were not always clearly stated. A small sample  
449 of studies explicitly stated that they excluded those with physical limitations and healthcare providers  
450 may have advised higher risk patients to not participate in physical activity. There is also a limitation  
451 associated with the methodology of this systematic review: only studies written in English were included,  
452 raising the possibility that some studies were missed.

453

### 454 **Conclusion**

455 Due to the mixed findings in this systematic review, it cannot be concluded that self-reported physical  
456 activity behavior before cardiac surgery is associated with health outcomes after surgery. The mixed  
457 findings could be due to the heterogeneity in physical activity tools used, definitions of outcomes, and the

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458 few studies adjusting for other potentially confounding variables. These findings highlight the need for  
459 more research in this area.

For peer review only

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Running Head: PA and post-cardiac surgical outcomes

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3 **FIGURE LEGENDS**  
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5 **Figure 1.** Study flow diagram.  
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**Running Head:** PA and post-cardiac surgical outcomes

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**Table 1.** Characteristics of included studies.

First author, year	Study Population	Country	Participants at follow-up	Physical Activity Assessment	Longest follow-up	Main findings
Giaccardi, 2011 <sup>18</sup>	All patients $\geq 65$ years undergoing CABG and/or valve procedures (total sample: $74.1 \pm 5.8$ years old); 43% female	Italy	158	Harvard Alumni Questionnaire	Four weeks postoperatively	Physical activity had an independent association with postoperative atrial fibrillation within 30 days.
Markou, 2007 <sup>12</sup>	Elective CABG patients (Active: $64.4 \pm 9.4$ , Inactive: $63.8 \pm 9.0$ years old); % female not reported	Netherlands	428	The Corpus Christi Heart Project	One year	Inactive vs. Active group had significantly more peri-operative MIs, but not reoperations, ICU LOS, HLOS, or postoperative complications at one year. Inactive group was more likely than Active group to be physically active at one year.
Nery, 2007 <sup>13</sup>	All patients undergoing CABG (Active: $63 \pm 11$ , Inactive $66 \pm 14$ years old); 42% female	Brazil	55	Structured Questionnaire confirmed by Minnesota Leisure Time Physical Activity Questionnaire	One year	Inactive vs. Active group had significantly longer HLOS and more postoperative events at one year.
Markou, 2008 <sup>14</sup>	Elective CABG patients ( $64.3 \pm 9.04$ years old); 18% female	Netherlands	568	The Corpus Christi Heart Project	One year	Inactive vs. Active group were more likely to be more physically active one year postoperatively.
Martini, 2010 <sup>15</sup>	Elective CABG patients (Active: $60 \pm 10$ , Inactive: $62 \pm 10$ years old); 34% female	Brazil	185	Baecke Usual Physical Activity Questionnaire	Two years	Inactive vs. Active group did not have significantly different MACCE outcomes at two years.

**Running Head:** PA and post-cardiac surgical outcomes

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1 2 3 4 5 6 7 8	Nery, 2010 <sup>16</sup>	Elective CABG patients (Active: 60 ± 10, Inactive: 62 ± 10 years old); 34% female	Brazil	202	Baecke Usual Physical Activity Questionnaire	Hospital discharge	Inactive vs. Active group had more postoperative events within 30 days and a longer HLOS.
9 10 11 12 13	Rengo, 2010 <sup>17</sup>	Acute or elective CABG patients ≥ 70 years (Active: 72.3 ± 3.2, Inactive: 76.1 ± 3.9 years old); 34% female	Italy	587	Physical Activity Scale for the Elderly	Mean 44.3 ± 21.0 months	Physical activity had an independent and dose association with cardiac and all- cause mortality five years postoperatively.
14 15 16 17 18 19 20 21	Cacciatore, 2012 <sup>19</sup>	All patients ≥ 65 years undergoing CABG and/or valve procedures (72.9 ± 4.8 years old); 48% female	Italy	250	Physical Activity Scale for the Elderly	Hospital discharge	Physical activity was independently associated with reduced prolonged ICU LOS. Physical activity was not independently associated with postoperative ADLs.
22 23 24 25 26 27	Noyez, 2013 <sup>20</sup>	Elective CABG and/or valve patients (69.7 ± 10.1 years old);	Netherlands	3150	The Corpus Christi Heart Project	30 days postoperative ly	Physical activity was not independently associated with hospital or 30 day mortality. Inactive vs. Active group had a significantly longer ICU LOS.
28 29 30 31 32 33	Min, 2015 <sup>21</sup>	Elective CABG and/or valve patients ≥ 65 years (74.7 ± 5.9 years old)	United States of America	62	The Health and Retirement Survey	4-6 months	Inactive vs. Active group had significantly higher postoperative physical activity up to 6 months postoperatively.
34 35 36 37	van Laar <sup>22</sup>	Patients ≥75 years undergoing elective isolated aortic valve replacement (79.5 ± 2.8 years old); 59% female	Netherlands	115	The Corpus Christi Heart Project	2 years postoperative ly	Inactive vs. Active group had significantly higher mortality rates 2 years postoperatively.

CABG, coronary artery bypass graft surgery; HLOS, hospital length of stay; ICU LOS, intensive care unit length of stay; MI, myocardial infarction; MACCE, major adverse cerebrovascular and cardiac events; ADL, activities of daily living.

Table 2. Major adverse and cerebrovascular events and postoperative events within 30 days

Reference	Outcome definition	Adjustment variables	Number of events per group	OR or HR and 95% CI
<b>Major adverse cerebrovascular and cardiac events</b>				
Nery, 2007 <sup>13</sup>	One year postoperative AF, hospital readmission, new CABG, PCI, MI	None	Active: 8/25 (31%); Inactive: 17/30 (57%) <sup>a</sup>	NR
Martini, 2010 <sup>15</sup>	Two year postoperative death, re-hospitalization, cerebrovascular accident, MI	None	Active: 9/66 (14%); Inactive: 31/119 (26%)	NR
Rengo, 2010 <sup>17</sup>	Five-year postoperative cardiac and all-cause mortality	Demographics, medical history, medications, and clinical findings.	NR	<u>Adjusted proportional hazard models:</u> <i>All-cause mortality:</i> Exp(B) 0.248 (95% CI 0.141-0.434) <sup>a</sup> <i>Cardiac mortality:</i> Exp(B) 0.272 (0.133-0.555) <sup>a</sup>
van Laar 2015 <sup>22</sup>	Two-year mortality	None	Active: 5/65 (13%); Inactive: 11/50 (22%) <sup>a</sup>	NR
<b>Postoperative events within 30 days</b>				
Markou, 2007 <sup>12</sup>	Perioperative MI, Re-intervention, postoperative complications (wound, renal, neurological, pulmonary, gastrointestinal)	None	<u>MI:</u> Active: 4/226 (2%); Inactive: 11/202 (5%) <sup>a</sup> <u>Reoperation:</u> Active: 15/226 (7%); Inactive: 9/202 (5%), <u>Wound infection:</u> Active: 3/226 (1%); Inactive: 7/202 (3%), <u>Renal:</u> Active: 3/226; Inactive: 7/202	NR
Nery, 2010 <sup>16</sup>	Mortality, MI, reoperation	Age, smoking, PVD, COPD, Cleveland Risk Score.	<u>Mortality:</u> Active: 0/66 (0%); Inactive: 7/136 (5%) <u>MI:</u> Active: 1/66 (2%); Inactive: 6/136 (4%) <u>Reoperation:</u> Active: 0/66 (0%); Inactive: 1/136 (0.5%)	<u>Multivariate OR for being active:</u> 0.22 (95% CI 0.09-0.51, p=0.001)

Running Head: PA and post-cardiac surgical outcomes

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4	Rengo, 2010 <sup>17</sup>	Low-output syndromes, MI, cardiac support, stroke, bleedings, mediastinitis, pneumonia, dialysis	None	<u>Any surgical complication:</u> Active: 53/267 (19.7%); Inactive: 60/320 (18.6%)	NR
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10	Giaccardi, 2011 <sup>18</sup>	Atrial fibrillation	Age, episodes of AF one year preop, episodes of AF in the first week, $\beta$ -blockers, amiodarone, left ventricular volume, left atrial emptying fraction	<u>Postoperative atrial fibrillation:</u> Active: 6/74 (8.1%); Inactive: 27/84 (32.1%) <sup>a</sup>	<u>Multivariate OR for being inactive:</u> 4.04 (95% CI 1.16-14.14, p=0.029)
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21	Noyez, 2013 <sup>20</sup>	Mortality, reoperation, stroke, renal insufficiency, sternal wound, ventilation	$\geq 75$ years, valve surgery, female, high operative risk, renal disease, obesity, NYHA IV, Insulin, vascular pathology, poor LVEF, lung disease, MI, neurological event	<u>Hospital mortality:</u> Active: 7/1815 (0.4%); Inactive: 15/1335 (1.1%) <sup>a</sup> <u>30 day mortality:</u> Active: 10/1815 (0.6%); Inactive: 20/1335 (1.5%) <sup>a</sup> <u>Reoperation:</u> Active: 105/1815 (5.8%); Inactive: 68/1335 (5%) <u>Stroke:</u> Active: 9/1815 (0.5%); Inactive: 12/1335 (0.9%) <u>Renal insufficiency:</u> Active: 32/1815 (1.8%); Inactive: 39/1335 (2.9%) <sup>a</sup> <u>Sternal wound:</u> Active: 10/1815 (0.6%); Inactive: 17/1335 (1.3%) <sup>a</sup> <u>Ventilation &gt;2 days:</u> Active: 31/1815 (1.7%); Inactive: 54/1335 (4.0%) <sup>a</sup>	<u>Hospital mortality multivariate OR for being inactive:</u> 1.20 (95% CI 0.4-3.5, p=0.617) <u>30 day mortality multivariate OR for being inactive:</u> 1.10 (95% CI 0.5-2.7, p=0.70)
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<sup>a</sup> indicates statistical significance (P<0.05). CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; MI, myocardial infarction; NR, not reported; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; OR, odds ratio; AF, atrial fibrillation; BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.

**Running Head:** PA and post-cardiac surgical outcomes

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**Table 3.** Hospital length of stay, ICU length of stay, and postoperative activities of daily living and physical activity.

First author, year	Adjustment variables	Length of stay/number of events per group	Odds ratio (OR) or hazard ratio (HR) and 95% confidence interval (CI)
<b>Hospital length of stay</b>			
Markou, 2007 <sup>12</sup>	None	Active: 6.9 ± 8.2 days; Inactive: 7.3 ± 7.1 days	NR
Nery, 2007 <sup>13</sup>	None	Active: 12 ± 5 days, median 9 days (IQR 8-15); Inactive: 15 ± 8 days, median 12 (IQR 9-19) <sup>a</sup>	NR
Nery, 2010 <sup>16</sup>	Age, sex, Cleveland Risk Score, smoking, systemic arterial hypertension, stroke, MI, and PVD.	NR	HR: 0.67 (95% CI 0.49-0.93) <sup>a</sup>
<b>ICU length of stay</b>			
Markou, 2007 <sup>12</sup>	None	Active: 2.2 ± 5.3 days; Inactive: 2.1 ± 3.5 days	NR
Cacciatore, 2012 <sup>19</sup>	For ICU LOS >3 days: age, off-pump CABG, stroke, renal failure.	Active: 2.58 ± 1.09 days; Inactive: 3.33 ± 1.68 days <sup>a,b</sup>	<u>For ICU length of stay &gt;3 days</u> Univariate OR: 0.984 (95% CI 0.977-0.992) <sup>a</sup> Multivariate OR: 0.992 (95% CI 0.983-1.000) <sup>a</sup>
Noyez, 2013 <sup>20</sup>	None	Active: 1.3 ± 1.9 days; Inactive 3.0 ± 41.8 days <sup>a</sup>	NR
		ICU > 5 days: Active: 19/1815 (1.0%); Inactive: 46/1335 (3.4%) <sup>a</sup>	
<b>Postoperative ADLs</b>			
Cacciatore,	Age, gender, CABG, NYHA ≥3,	NR	Beta: 0.099

**Running Head:** PA and post-cardiac surgical outcomes

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2012<sup>19</sup> ICU LOS  $\geq$ 3 days, Off-pump CABG, diabetes, renal failure, stroke, PVD, COPD, Cumulative Illness Rating Scale.

### Postoperative Physical activity

Markou, 2007<sup>12</sup> Age  $\geq$ 75 years, gender, neurological disease, vascular disease, diabetes, and preoperative physical activity.

Better PA post-operatively: Active: 48/226 (21.2 %), Inactive: 129/202 (64%)<sup>a</sup>

Decreased postoperative PA OR (inactive group as reference): 8.1 (95% CI 3.5-13.5)<sup>a</sup>

Equal PA post-operatively: Active: 112/226 (49.6%), Inactive: 59/202 (29.2%)<sup>a</sup>

Worse PA post-operatively: Active: 66/226 (29.2%), Inactive: 14/202 (6.9%)<sup>a</sup>

Markou, 2008<sup>14</sup> Diabetes, vascular disease, neurological disease, renal disease, MI, preoperative activity level.

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For becoming physically inactive postoperatively

Male OR (inactive group as reference): 7.11 (95% CI 3.6-13.9)<sup>a</sup>

Female OR (inactive group as reference): 11.0 (95% CI 2.2-55)<sup>a</sup>

Min, 2015<sup>21</sup> None

NR

Each weekly preoperative activity point was associated with a loss of 0.78 points at 6 weeks,  $p < 0.001$ , and 0.65 points at 6 months)<sup>a</sup>

<sup>a</sup> indicates statistical significance ( $P < 0.05$ ). <sup>b</sup>Unpublished data obtained from Cacciatore et al, [19]. ICU, Intensive Care Unit; ADL; activities of daily living; IQR, interquartile range; NR, not reported; MI, myocardial infarction; PVD, peripheral vascular disease; HR, hazard ratio; OR, odds ratio; CABG, coronary artery bypass graft; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; PA, physical activity.

**Running Head:** PA and post-cardiac surgical outcomes

**Table 4.** Newcastle-Ottawa scale risk of bias scores

Reference	Selection	Comparability	Outcome	Total
Markou, 2007 <sup>12</sup>	3	2	3	8
Nery, 2007 <sup>13</sup>	3	0	2	5
Markou, 2008 <sup>14</sup>	3	2	2	7
Martini, 2010 <sup>15</sup>	3	0	2	5
Nery, 2010 <sup>16</sup>	3	2	2	7
Rengo, 2010 <sup>17</sup>	4	2	3	9
Giaccardi, 2011 <sup>18</sup>	3	2	2	7
Cacciatore, 2012 <sup>19</sup>	3	2	2	7
Noyez, 2013 <sup>20</sup>	3	2	3	8
Min, 2015 <sup>21</sup>	4	2	1	7
van Laar <sup>22</sup>	3	0	3	6
Average scores $\pm$ SD	3.18 $\pm$ 0.40	1.45 $\pm$ 0.93	2.27 $\pm$ 0.65	6.91 $\pm$ 1.22

Maximum scores are 4, 2, and 3 for selection, comparability, and outcome, respectively.  
Maximum total score is 9. A lower score within each category and for a total score indicates a higher risk of bias.

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**Box 1.** Guidelines for physical activity measurement and outcome assessment in cardiac surgery patients: limitations and opportunities for future research

Drawbacks	Opportunity
<b>Physical activity</b>	
1. Heterogeneity in tools used across studies	-use of objectively measured tools (e.g., pedometers, accelerometers) accompanied by a questionnaire which can produce data that can be compared across studies, such as step counts, intensity, and duration of physical activity.
2. Only subjective measures were used	-Capture physical activity behavior as soon as a patient is placed on a wait list, or in non-elective cases, as soon as possible prior to surgery. -Physical activity should be assessed ideally over a 7 day period.
3. Time of preoperative physical activity assessment was unclear in most studies	-Physical activity should be assessed by intensity and duration per week, and in steps per day.
<b>Outcomes</b>	
4. Heterogeneity in MACCE and postoperative events within 30 days definitions	-MACCE should be evaluated as a long-term outcome and defined as death, stroke, myocardial infarction, and the need for re-do cardiac surgery. Each outcome should be evaluated individually. -30-day postoperative events should be evaluated using the STS checklist: <sup>10</sup> along with reasons, evaluate unexpected return to the operating room, complications due to pulmonary, cardiovascular, gastrointestinal, hematological, urologic, infection, neurological, and other important miscellaneous outcomes (e.g., unexpected admission to ICU, or other events requiring admission to operating room requiring anesthesia. -re-hospitalization for any cause after cardiac surgery should also be added to outcomes.
5. No patient-oriented outcomes were assessed	-Capture postoperative health-related quality of life, mental health, pain, and cardiac symptoms using validated tools within the first 30 days and at least one-year postoperatively.
<b>Statistical procedures</b>	
6. Shortage of studies addressing confounders	-use multivariate analysis, including logistic or linear regression, or analysis of variance statistical procedures. Ensure that a power analysis is conducted prior to conducting the study.

MACCE, major adverse cerebrovascular and cardiac events. STS, Society of Thoracic Surgeons. ICU, intensive care unit.



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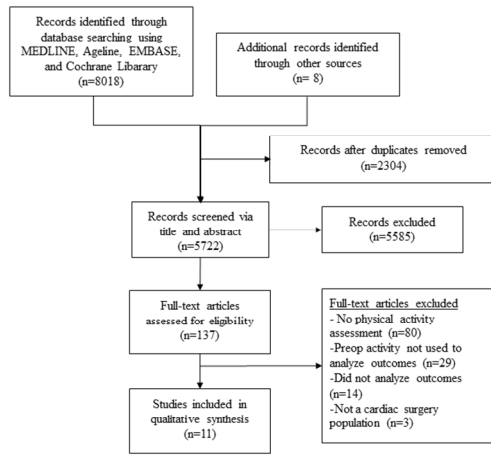


Figure 1. Study flow diagram

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review only

**MEDLINE search strategy.**

1. Sedentary Lifestyle/
2. physical endurance/ or physical fitness/
3. exercis\*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. motor activit\*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5. accelerometry.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6. sedentary.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
7. inactive.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8. (inactivity or physical inactivity or physical activity or active lifestyle or inactive lifestyle or physically active or physically inactive).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9. physical therapy modalities/ or exp exercise therapy/ or physiotherapy.mp. or physical therapy.mp. or motor activity/ or exp Exercise/ or physical exertion/ or physical endurance/ or anaerobic threshold/ or exercise tolerance/ or physical fitness/
10. (physical adj5 function\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
11. physical\* mobil\*.mp.
12. \*"Quality of Life"/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. cardiac surger\*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
15. cardiovascular surger\*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
16. coronary artery bypass.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
17. heart bypass.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

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- 4 18. ((aortic or aorta or mitral) adj7 (replacement or repair)).mp. [mp=title, abstract, original title,
- 5 name of substance word, subject heading word, keyword heading word, protocol supplementary
- 6 concept word, rare disease supplementary concept word, unique identifier]
- 7 19. cardiovascular surgical procedures/ or cardiac surgical procedures/ or cardiac valve
- 8 annuloplasty/ or heart bypass, right/ or exp heart valve prosthesis implantation/ or myocardial
- 9 revascularization/ or coronary artery bypass/ or coronary artery bypass, off-pump/ or vascular
- 10 surgical procedures/
- 11 20. 14 or 15 or 16 or 17 or 18 or 19
- 12 21. (postoperative\* or postoperative period or post surgical or post surgery).mp. or Postoperative
- 13 Period/ or exp Postoperative Complications/
- 14 22. perioperative\*.mp. or Perioperative Period/ or peroperative\*.mp.
- 15 23. preoperative\*.mp. or Preoperative Period/
- 16 24. Time Factors/
- 17 25. (after adj7 (surgery or bypass)).mp. [mp=title, abstract, original title, name of substance
- 18 word, subject heading word, keyword heading word, protocol supplementary concept word, rare
- 19 disease supplementary concept word, unique identifier]
- 20 26. (inpatient\* or in hospital or hospitali\* or discharge\*).mp. [mp=title, abstract, original title,
- 21 name of substance word, subject heading word, keyword heading word, protocol supplementary
- 22 concept word, rare disease supplementary concept word, unique identifier]
- 23 27. 21 or 22 or 23 or 24 or 25 or 26
- 24 28. (pediatric\* or paediatric\* or child\* or adolescen\* or youth).mp. [mp=title, abstract, original
- 25 title, name of substance word, subject heading word, keyword heading word, protocol
- 26 supplementary concept word, rare disease supplementary concept word, unique identifier]
- 27 29. 13 and 20 and 27
- 28 30. 29 not 28
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# PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6-7
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	8
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	No meta-analysis



# PRISMA 2009 Checklist

Page 1 of 2

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	No meta-analysis
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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A

## RESULTS

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11 and in Table 1 (page 27-28)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	15 and in Table 4 (page 33)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-10 and in tables 2 and 3 (pages 23-27)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	No meta-analysis
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A

## DISCUSSION

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-20
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Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-21
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2-3

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

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