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# Effects of Exercise-Based Cardiac Rehabilitation in Patients with Acute Coronary Syndrome: A Meta-Analysis

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
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**Background:** Acute coronary syndrome (ACS) has become an important cause of death from cardiovascular disease. Cardiac rehabilitation (CR) plays an essential role in ACS patients after treatment. Therefore, in order to detect the impact of CR on mortality and major adverse cardiac events in patients with ACS, we conducted this meta-analysis.




**Material/Methods:** We searched PubMed, Web of science, and EMBASE databases to obtain published research results from 2010 to August 2018 to determine the relevant research. Random-effects model or fixed-effects model were used to calculate relative risk (RR) and 95% confidence interval (CI).

**Results:** Overall, a total of 25 studies with 55 035 participants were summarized in our meta-analysis. The results indicated that the hazard ratio (HR) of mortality significantly lower in the CR group than in the non-CR group (HR=-0.47; 95% CI=(-0.56 to -0.39; P<0.05). Fourteen studies on mortality rate showed exercise was associated with reduced cardiac death rates (RR=0.40; 95% CI=0.30 to 0.53; P<0.05). We found the risk of major adverse cardiac events (MACE) was lower in the rehabilitation group (RR=0.49; 95% CI=0.44 to 0.55; P<0.05). In 11 articles on CR including 8098 participants, the benefit in the CR group was greater than in the control group concerning revascularization (RR=0.69, 95% CI: 0.53 to 0.88; P=0.003). The recurrence rate of MI was reported in 13 studies, and the risk was lower in the CR group (RR=0.63, 95% CI: 0.57-0.70; P<0.05).

**Conclusions:** Our meta-analysis results suggest that CR is clearly associated with reductions in cardiac mortality, recurrence of MI, repeated PCI, CABG, and restenosis.

**MeSH Keywords:** **Acute Coronary Syndrome • Meta-Analysis • Rehabilitation**

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## Background

Cardiovascular disease (CVD) is one of the world's most well-known health problems. Over the course of the decades, the overall incidence of CVD, particularly in acute coronary syndrome (ACS), has risen rapidly [1]. ACS has become an important cause of death from cardiovascular disease, especially in elderly ACS patients [2]. The mortality rate of patients with ACS has declined due to advances in medical technology [3]. However, improper treatment of ACS patients not only seriously endangers national health, but also imposes a heavy public health and economic burden.

ACS is a group of clinical syndromes based on the rupture or invasion of coronary atherosclerotic plaque, followed by complete or incomplete occlusive thrombosis, including acute ST-segment elevation myocardial infarction (STEMI), acute non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA). For the treatment of ACS, cardiologists have a very important sentence: "time is the heart muscle and time is life" [4]. ACS, especially acute ST-segment elevation myocardial infarction, treatment emphasizes the opening of blocked blood vessels as soon as possible, restores blood perfusion of the heart, and protects the viable myocardium to maximize the protection of cardiac function and improve long-term prognosis. The treatment of ACS mainly includes: (1) conservative treatment of drugs, (2) interventional therapy, and (3) surgical treatment [5]. ACS treatment is not a single treatment, but rather requires a comprehensive treatment strategy, including short-term anticoagulant therapy, long-term antiplatelet therapy, combined use of lipids and other drugs, and appropriate application of interventional or surgical treatment. Overall, 30-day mortality rates for ACS patients have decreased significantly over the past 10 years due to improved antithrombotic therapy and early revascularization. Therefore, the epidemiology of ACS has also undergone profound changes: more patients with ACS survive from the initial ischemic event, and then recurrent ischemic events, heart failure, atrial fibrillation or non-cardiac disease (such as cancer), and longer survival time [1]. Therefore, long-term care for ACS patients will receive more and more attention, and cardiac rehabilitation will be an important component.

Cardiac rehabilitation (CR) is a comprehensive method that includes exercise training, risk factor education, psychological support, lifestyle and behavior changes, and reducing common risk factors [6-8]. Exercise is the best medicine [9]. In the past few decades, many epidemiological studies have shown that exercise is good for human health by reducing the risk of dementia, providing protection against metabolic disorders, and improving quality of life. CR after PCI has become very popular, especially during the rehabilitation of PCI, which helps to alleviate the symptoms of the patient; exercise often was used

in combination with conventional treatment. The American Heart Association (AHA) guidelines [10] recommend training as a core element of exercise-based cardiac rehabilitation [11]. Cardiac rehabilitation aims to improve health and outcomes after ACS. There are several meta-analyses that have been published before, such as Anderson et al's study [12] and Yang et al's study [13]. Anderson et al's study included 63 studies, and the results showed that CR reduced heart mortality in patients with coronary heart disease, but had no significant effect on myocardial infarction and revascularization. Yang et al's study showed that exercise was not obviously associated with cardiac death reductions, MI recurrence, repetitive PCI, CABG, or restenosis. No meta-analysis focused on the relationship between ACS and CR based on exercise. Therefore, in order to detect the influence of CR on mortality and major adverse cardiac events (MACE, which were defined as a composite of all-cause death, non-fatal acute myocardial infarction, or target vessel revascularization [14]) in ACS patients, we conducted this meta-analysis.

## Material and Methods

### Information source and search strategy

We conducted a systematic search in PubMed, Cochrane Central Register of Controlled Trials, and EMBASE from 2010 to August 2018 to assess the relevant research. The following terms were used to search related research in the database without language restrictions: "Acute myocardial infarction" or "Unstable angina" and "Coronary heart disease" and "Cardiac rehabilitation". The list of references for searched articles were filtered to determine other eligible references.

### Inclusion and exclusion criteria

Two researchers independently reviewed the title and abstract of the results. Disagreements were resolved by discussion with another author and the included articles needed to meet the following inclusion criteria: (1) Research population includes ACS patients of all ages; (2) If the study is a randomized controlled with follow-up for more than 6 months or retrospective study, we considered it to be compliant; and (3) Patients needed to participate in any form of exercise program or included comprehensive cardiac rehabilitation combined with education of improved lifestyle; and comprised a control group that did not accept any form of structural exercise training but included medical treatment. The following studies were excluded: (1) The patients had severe cardiac complications such as heart failure, or mitral valve prolapse; (2) The patients who has a malignant tumor. (3) Cardiovascular mortality or hazard ratio (HR) or incidence of MACE (non-fatal myocardial infarction, revascularization) have not been reported or cannot

be calculated based on available data; and (4) Full texts were not published in English.

### Data extraction

The required data were extracted from all eligible studies, including the first author's last name, publication time, number of patients in all studies, method of rehabilitation, and follow-up time. We obtained 4 tables of mortality and MACE incidence directly from the article to calculate RR and 95% CI. In addition, we directly obtained the HR and 95% CI of mortality.

### Statistical analysis

Statistical analysis was conducted using STATA 14.0 software.  $\chi^2$  and I-squared ( $I^2$ ) tests were used to evaluate the heterogeneity. If  $p \leq 0.10$  and  $I^2 \geq 50\%$ , which means there is heterogeneity between the studies, a random-effects model was used; otherwise, a fixed-effects model was used. Bilateral  $p < 0.05$  was regarded as statistically significant. We use forest plots to present the results of the meta-analysis.

## Results

### Selected studies and characteristics

We initially retrieved 2071 original studies, with and 1820 remaining after removing 251 duplicate articles. By screening the title and abstract in these 1820 articles, we found that 1784 did not match the topic. We reviewed 34 selected studies to determine their compliance with inclusion criteria. After screening full texts, 7 articles did not contain specific data for death or MACE, 1 was a review article, and 1 was not published in English, so these articles were excluded. Thus, a total of 25 studies with 55035 participants were summarized in our systematic review. The search and selection processes are shown in Figure 1. The characteristics and data of all 25 studies [15–39] are described in Table 1.

### Meta-analysis

#### Cardiac rehabilitation and cardiovascular mortality

Ten articles were included that analyzed the relationship between cardiac rehabilitation and hazard ratio (HR) of cardiovascular mortality. We summarized the results of HR by fixed-effects models, and the analysis indicated cardiovascular mortality was significantly lower in the cardiac rehabilitation group than in the non-cardiac rehabilitation group (HR = -0.47; 95% CI = (-0.56, -0.39);  $P < 0.05$ ) (Figure 2). Fourteen studies reported the relationship between cardiovascular mortality rate and cardiac rehabilitation. Significant heterogeneity

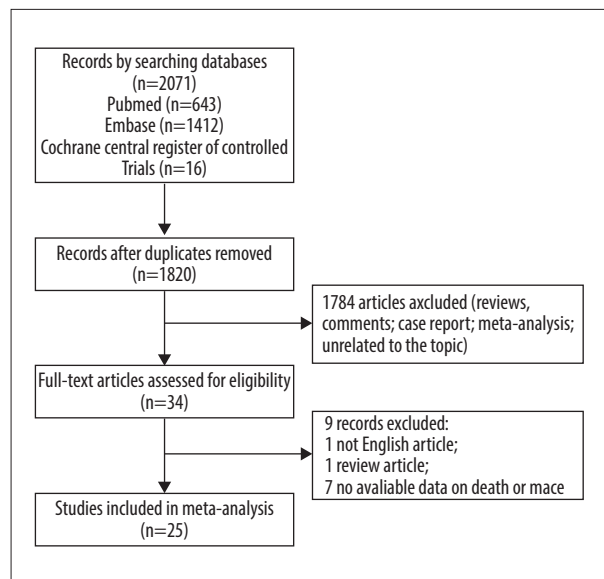


Figure 1. Results of the studies search.

in the cardiovascular mortality rate of the pooled estimates was observed ( $I^2 = 87.3\%$ ). Thus, we used a random-effects model. The results showed exercise was associated with significantly reduced cardiac death rates (RR = 0.40; 95% CI = 0.30–0.53;  $P < 0.05$ ) (Figure 3).

Because of the greater heterogeneity of the included articles, we conducted a subgroup analysis. Meta-analysis with a follow-up of less than 2 years showed that cardiac rehabilitation exercise was not associated with cardiac death. However, meta-analysis with a follow-up of 2–4 years, 4.1–6 years, 6.1–10 years showed a positive correlation between exercise and decreased cardiac death (Figure 4).

#### Cardiac rehabilitation and major adverse cardiovascular events

We included 15 articles about cardiac rehabilitation and MACE, and fixed-effects models showed that the risk of MACE was lower in the rehabilitation group (RR = 0.49; 95% CI = 0.44–0.55;  $P < 0.05$ ) (Figure 5).

#### Cardiac rehabilitation and revascularization (re-PCI or CABG)

In the 11 articles on CR, which included 8098 participants, we found that the benefit in the CR group was greater than in the control group (RR = 0.69, 95% CI: 0.53–0.88;  $P = 0.003$ ) by random-effects model ( $p = 0.000$ ,  $I^2 = 69.9\%$ ) (Figure 6).

We performed a subgroup analysis based on whether PCI/CABG was performed before the rehabilitation exercise, and the results showed that CR was not associated with revascularization in the AMI group. We could not confirm whether

**Table 1.** Characteristics of the studies included in the meta-analysis.

Year	Author	Country	Type of Study	Participants	Rehabilitation method and duration	Follow-up time (month)
2018	Sara Doimo	United States	Retrospective research	ACS patients (PCI or CABG)	Stationary bicycle training for 45 min, 2 time per week for 5 weeks, and gym training for 45 min, 3 times per week for 6 weeks; counseling about lifestyle; 5M	60
2018	Yong Zhang	China	Randomized controlled study	AMI patients (PCI)	Exercise for 3 phases; 6M	6
2018	Madoka Sunamura	Netherlands	Retrospective research	Patients with PCI	Exercise for 1.5h, twice per week; 12 W	120
2017	Manuel F. Jimenez-Navarro	United States	Retrospective research	Patients with PCI	Multidisciplinary rehabilitation for 3 h per week; 12W	120
2017	A. J. Hautala	Netherlands	Cohort design	ACS patients	Exercise for once per week; 6M	12
2016	Marion Pouche	French	Cohort design	AMI patients	N/A	60
2016	Jong-Young Lee	Korea	Retrospective research	Patients with PCI	Multidisciplinary rehabilitation for 3 times per week; 3M	85
2015	Han de Vries	Netherlands	Retrospective research	ACS patients (PCI or CABG)	Exercise for 30min, 2-3 times per week; relaxation therapy consists of 4–6 sessions lasting 60–90 min; 6-12W	48
2015	Hui-Ming Chen	Taiwan	Retrospective research	AMI patients (PCI)	Range of motion, muscle strengthening, breathing, and chest expansion exercises	60
2014	Roser Coll-Fernandez	Spanish	Cohort design	AMI <3 months	N/A	18
2014	Hee Eun Choi	Korea	Retrospective research	Patients with PCI	Main exercise for 30 min, 3 times per week; 8W	9
2014	Shannon M. Dunlay	United States	Retrospective research	AMI patients	N/A	91
2014	Bernhard Rauch	Germany	Randomized controlled study	AMI patients	Physiotherapy (3h per week), motivation, information, and education (7.2 and 7.0 h per week), social support service (0.9 and 1.1 hours per week), psychological support and supervision (2.3 and 3.4 h per week), and nursing (3.5 and 2.5 hours per week); –4W	12
2013	Quinn R. Pack	United States	Retrospective research	Patients with CABG	Exercise for 30-45 min, 3 times per week;	120
2010	Tomo Onishi	Japan	Cohort design	AMI patients (PCI)	Exercise for 1h, twice per week; dietary and education program; 6M	30
2009	Dominique Hansen	Belgium	Cohort design	AMI patients (PCI or CABG)	Exercise for 1 h, 3 times per week; psychological and dietary counseling; 3M	24
2008	Paul Dendale	Belgium	Cohort design	Patients with PCI	Exercise for 1 h, 3 times per week; psychological and dietary counseling consisted of 8 education sessions; 3M	54

**Table 1 continued.** Characteristics of the studies included in the meta-analysis.

Year	Author	Country	Type of Study	Participants	Rehabilitation method and duration	Follow-up time (month)
2008	David A. Alter	Canada	Retrospective research	ACS patients	36 supervised exercise sessions; 1Y	62
2008	Kirsten M. Nielsen	Denmark	Cohort design	ACS patients (PCI or CABG)	Exercise, twice per week; 4 individual consultations; 6W	24
2005	Paul Dendale	Belgium	Retrospective research	ACS patients (PCI)	Exercise for 1 h, 3 times per week; psychological and dietary counseling consisted of 8 education sessions; 3M	15
2005	Jan Lisspers	Sweden	Randomized controlled study	Patients with PCI	Multidisciplinary rehabilitation-based health education and training activities; 1M	60
2002	Maria Teresa La Rovere	Italy	Randomized controlled study	ACS patients	Exercise for 30min, 5 times per week; 4W	120
2001	Romualdo Belardinelli	Italy	Randomized controlled study	Patients with PCI or PTCA	Exercise for 1h, 3 times per week; 6M	33
2001	Johan Denollet	Belgium	Cohort design	Patients with CABG	Exercise for 36 sessions. The first 24 sessions (3 times per week) included ECG-monitored aerobic exercise. The last 12 sessions (2 times per week) were performed without ECG monitoring; psychosocial group intervention comprised 6 sessions (2 hours, 1 time per week); 3W	108
2001	Bo Hedback	Sweden	Cohort design	Patients with CABG	Exercise for 30-40 min, twice per week; psychosocial support; 3M	120

the intervention was PCI/CABG (RR=0.94, 95% CI: 0.70–1.26; P>0.05). Moreover, CR significantly reduced the incidence of vascular remodeling in the PCI/CABG group (RR=0.69, 95% CI: 0.53–0.88; P<0.05) (Figure 7).

#### Cardiac rehabilitation and non-fatal myocardial infarction

Based on heterogeneity studies, we use fixed-effects models to analyze CR and non-fatal myocardial infarction. The recurrence rate of myocardial infarction was reported in 13 studies that included 9626 participants. In terms of the comparison between the CR groups and control groups, there was a significant difference in risk (RR=0.63, 95% CI: 0.57–0.70; P<0.05) (Figure 8).

#### Publication bias

Funnel plots were used to assess possible publication bias. Priorities for positive findings were found in articles about CR and more patients or longer follow-up time needed to reduce publication bias (Figure 9).

#### Sensitivity analysis

Because of the high degree of heterogeneity between the meta-analysis of CR and cardiac death and the meta-analysis of CR and revascularization, we performed a sensitivity analysis to assess the reliability of the results. The results indicate that the reliability of the results may have been affected by the short follow-up time [26,32,35] and large [22] or small [39] sample numbers (Figure 10).

#### Discussion

To the best of our knowledge, this is the first a meta-analysis on the effects of cardiac rehabilitation in ACS patients. Our review contained 25 studies and 55 035 participants who presented with ACS. The purpose of our meta-analysis was to determine if endpoint events could be reduced or survival could be improved by exercise in patients with ACS. In this analysis of studies, we found that CR was obviously related to decrease in cardiac death, recurrence of MI, repeated PCI, CABG, and restenosis.

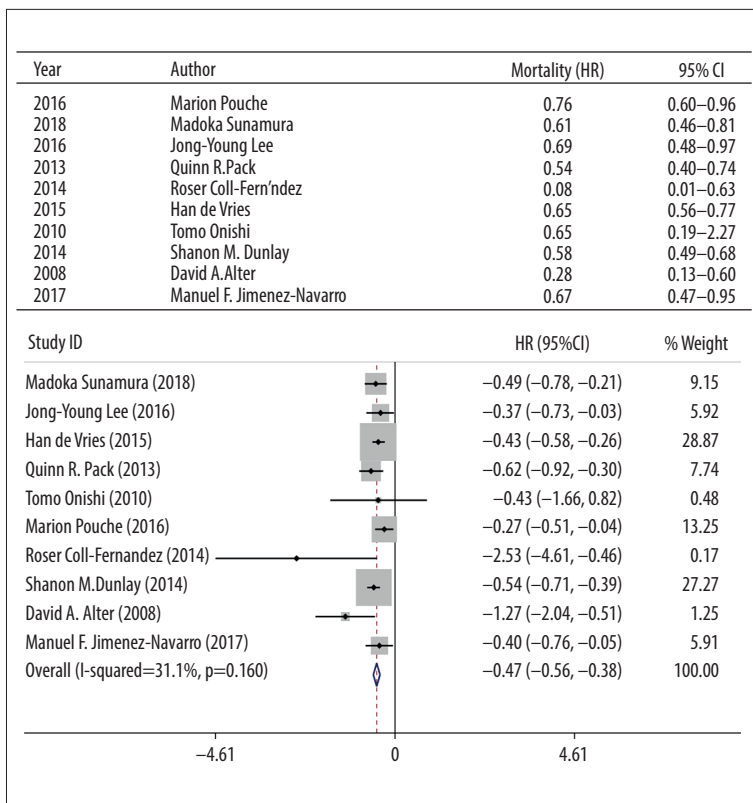


Figure 2. Meta-analysis for the association between CR and HR of cardiovascular mortality.

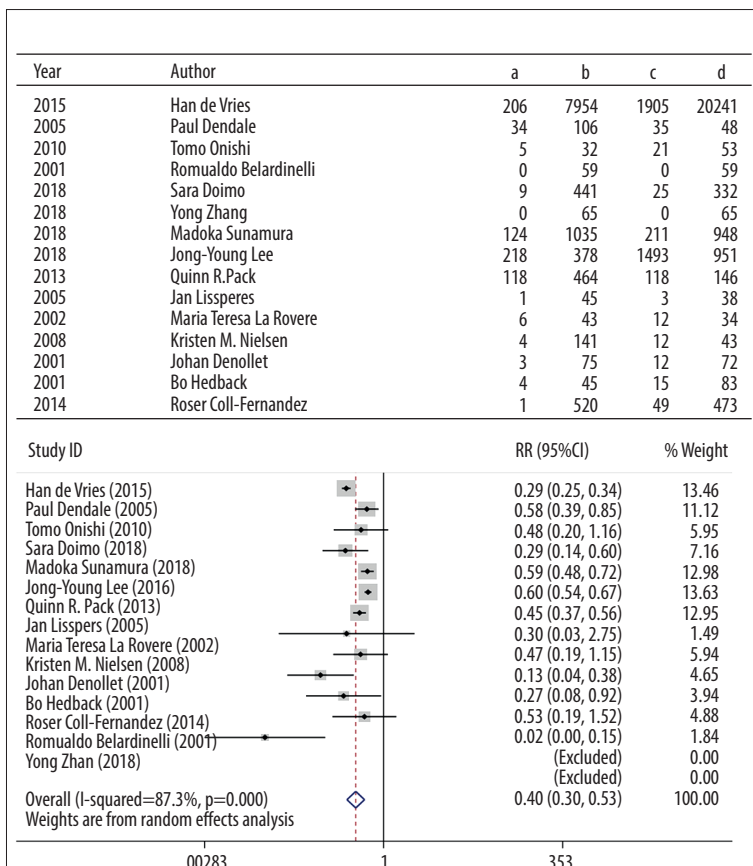
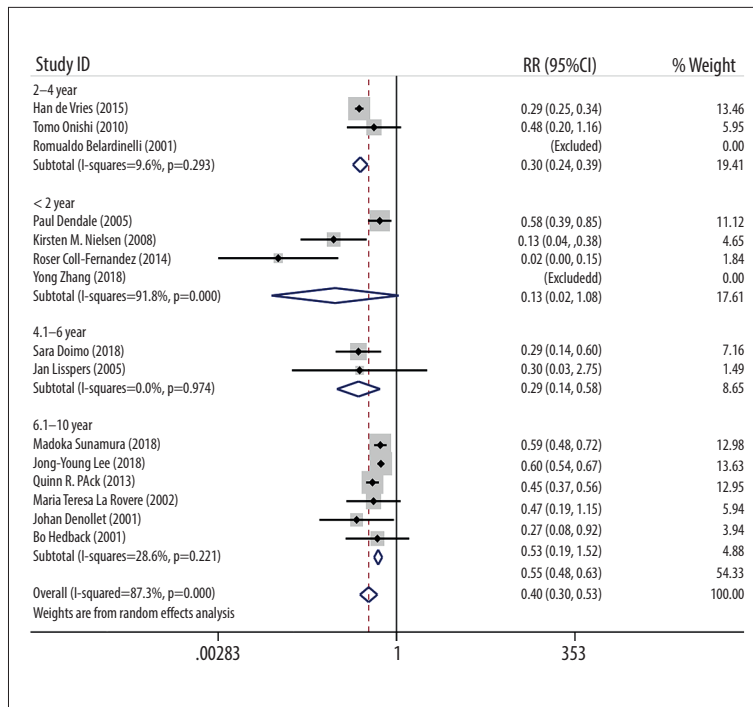
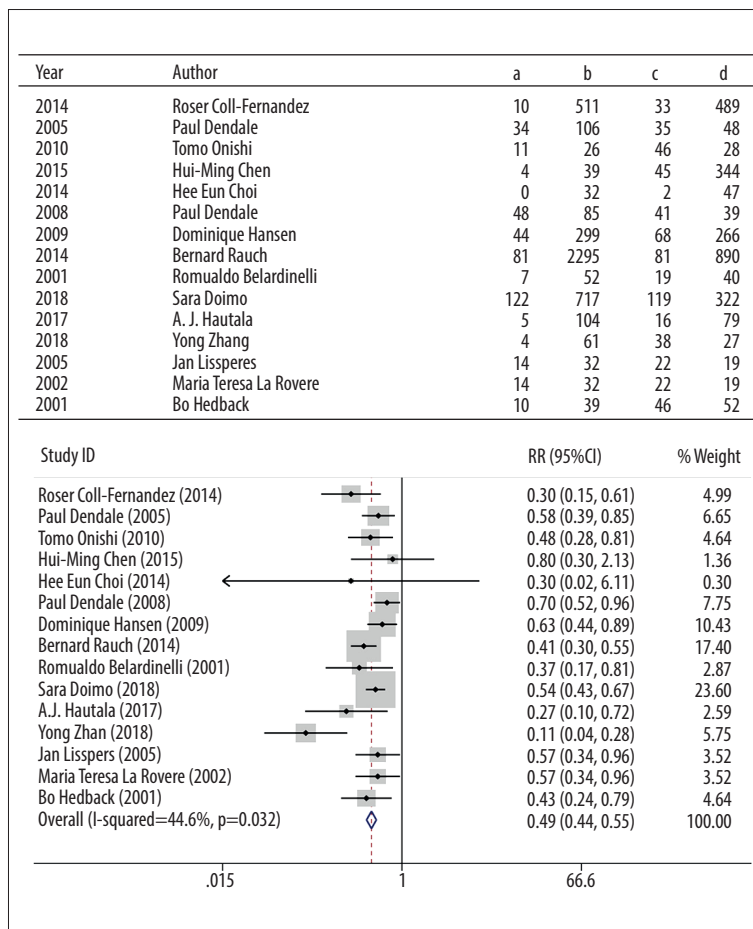


Figure 3. Meta-analysis for the association between CR and cardiac death rates.



**Figure 4.** Subgroup meta-analysis based on follow-up time between CR and cardiac death rates.



**Figure 5.** Meta-analysis for the association between CR and MACE.

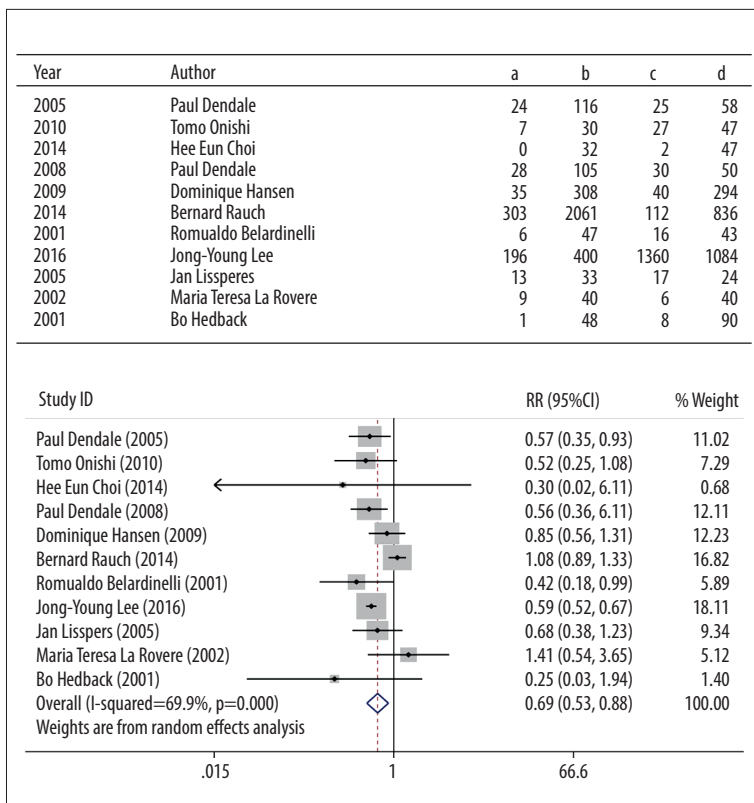


Figure 6. Meta-analysis for the association between CR and revascularization.

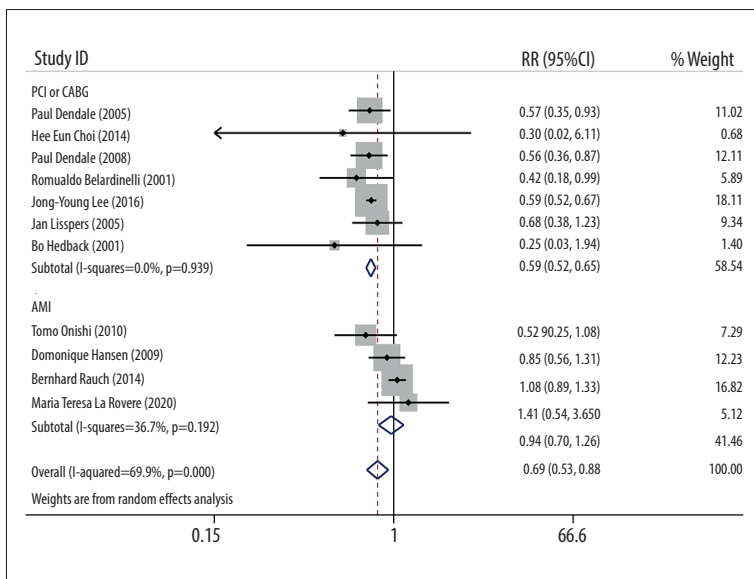


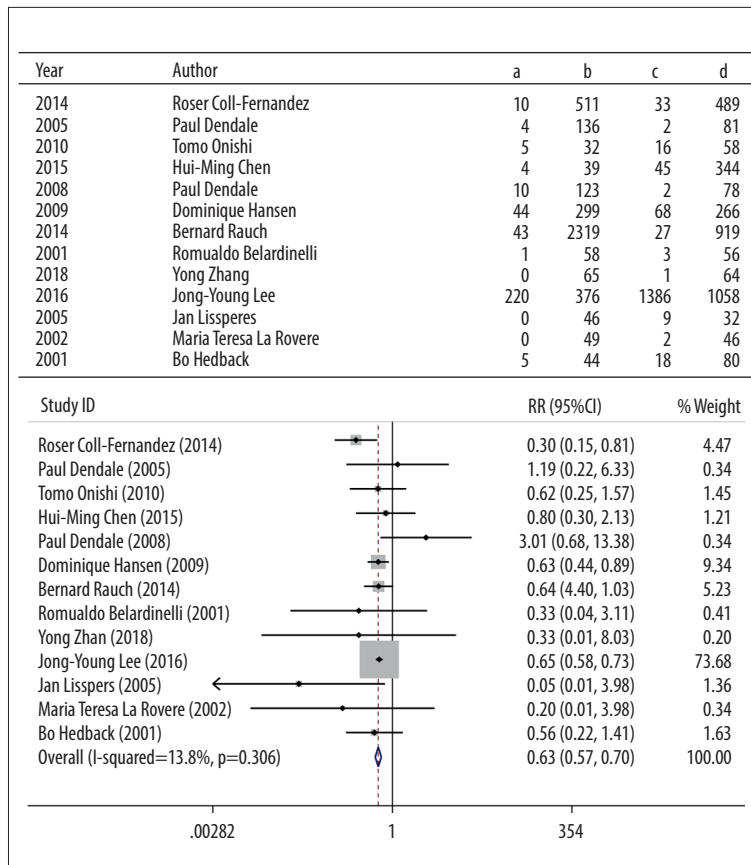
Figure 7. Subgroup meta-analysis based on treatment before CR between CR and revascularization.

In the past few years, CR has evolved from a simple plan to monitor patients' safe physical activity into a comprehensive discipline program that includes post-operative patient care, drug therapy optimization, nutritional counseling, smoking cessation, risk stratification, stress management, and lifestyle improvement [40], and different projects have different rehabilitation plans.

CR has several beneficial effects, including improvement of exercise capacity, muscle strength, cardiac risk factors, and health-related quality of life, as well as reducing mortality in ACS patients. Our analysis and others have shown that these benefits of CR even affect elderly patients with ACS [41–45].

The exact mechanism by which CR improves the prognosis of patients with ACS has not been fully elucidated [46]. In past





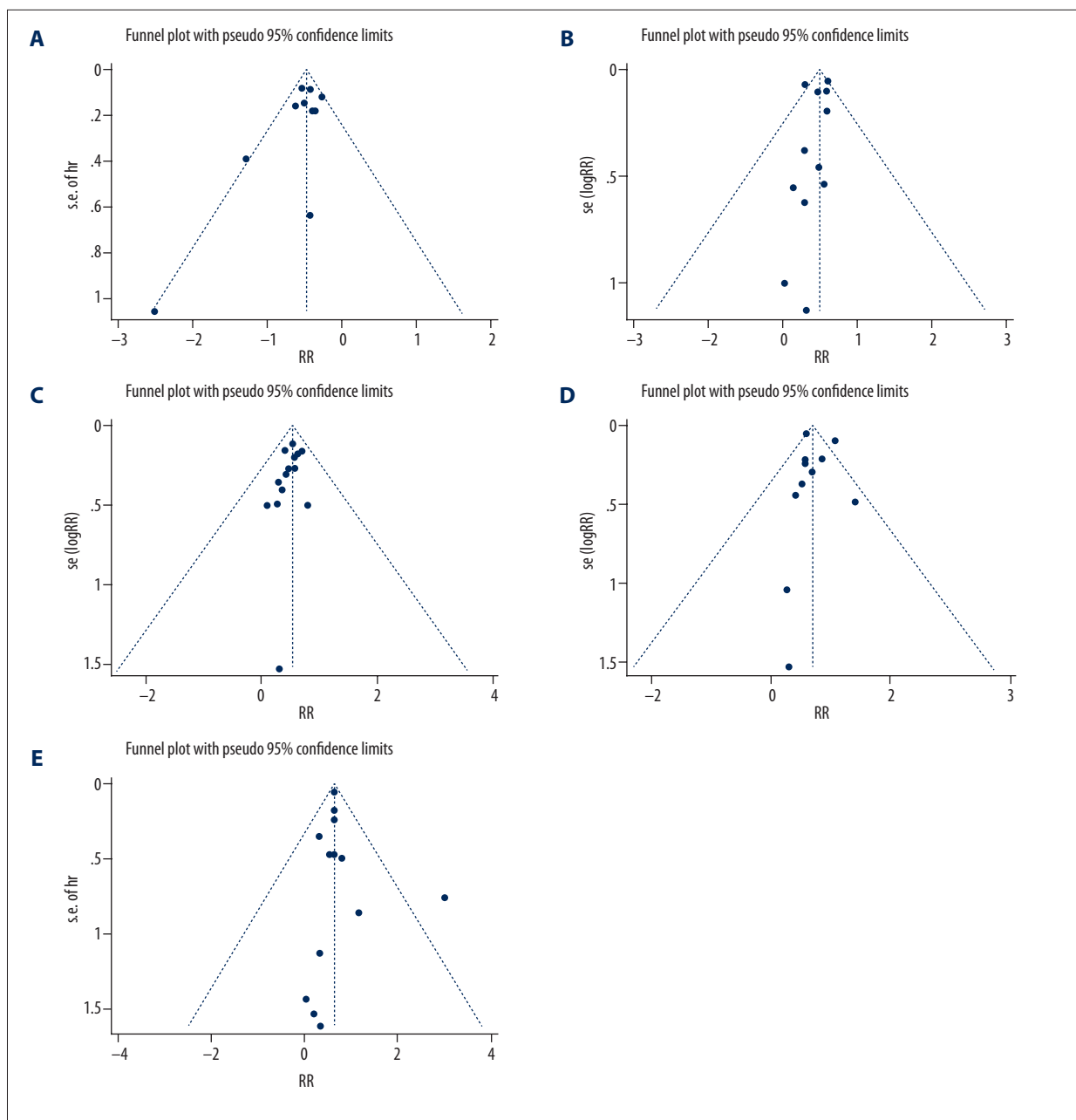
**Figure 8.** Meta-analysis for the association between CR and non-fatal myocardial infarction.

clinical practice and experiments, CR has been shown to have many direct benefits for the cardiovascular system, such as enhancing myocardial oxygen supply, endothelial function, autonomic nervous tone, coagulation factors, inflammatory markers, and development of coronary collateral vessels [47,48]. However, this may also be regulated by the indirect effects of exercise by improving the risk factors for atherosclerotic disease [49]. In Onishi's study, the BMI of the CR group was significantly lower, and the levels of TG and fasting blood glucose levels in the CR group were significantly lower than those in the control group [29]. Indeed, a randomized study showed that CR reduced fat weight without a reduction in lean body weight, and also reduced the levels of TC in older patients with CAD [41]. These direct and indirect effects may have led to the reduction in cardiovascular events, and these effects can predict MACE in ACS patients, such as neurogenic mechanism and CRP [50,51].

We found that randomized controlled trials and observational studies [28,49,52–55] showed that, after participating in CR, the mortality rate after MI was reduced in the patients. The difference observed in the randomized controlled trial was less than the crude difference in mortality in the observational study [52,56]. To some extent, this can be ascribed to the non-random nature of the intervention, i.e., older patients with

more severe conditions are less likely to participate in CR, but are more likely to have poor outcomes. Older patients with comorbidities that are common in clinical practice will generally be excluded from trial registration and their response to interventions such as CR may vary. In addition, the mortality rates of various trends involved in CR continue to decrease, indicating that even the highest-risk events involved in CR have a lower mortality rate for MI survivors than those who do not participate in CR.

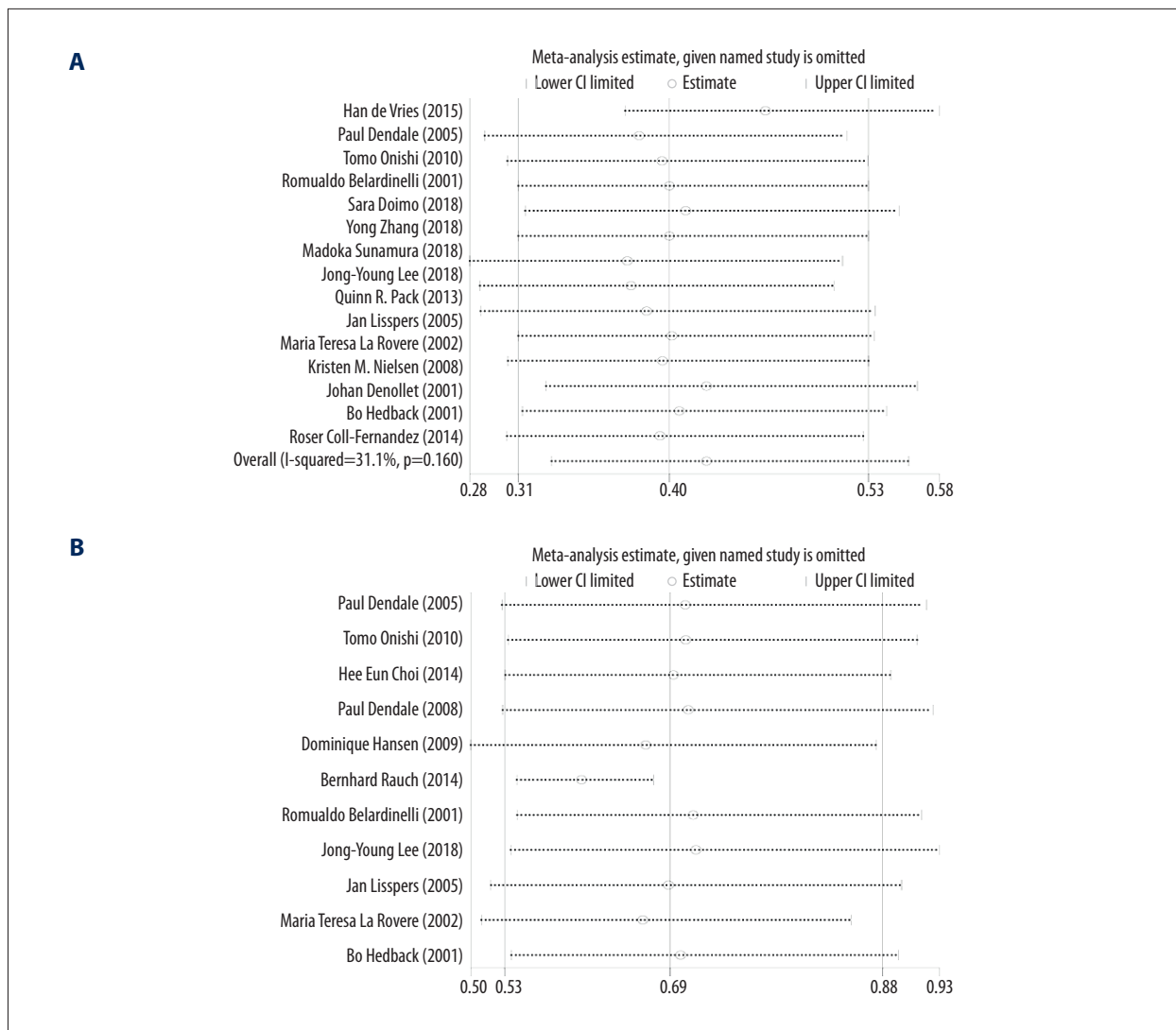
We conducted an updated meta-analysis of exercise-based CR in people with existing ACS. Due to inconsistent follow-up time, the meta-analysis was heterogeneous; therefore, we conducted a subgroup analysis and we still came to the conclusion that CR can reduce the cardiac death rate. In addition, Dendale et al's studies found that non-fatal myocardial infarction in the rehabilitation group increased [33], which may be because exercise increased the instability of pre-existing coronary plaque. However, our meta-analysis combined all the literature to conclude that exercise reduces non-fatal myocardial infarction. Our meta-analysis was based on a large sample size with long follow-up times, and we performed sensitivity analysis and subgroup analysis, so our results showing that CR can reduce cardiac death and MACE reliability in patients with ACS are reliable.



**Figure 9.** Funnel plot for the meta-analysis ((A) HR of cardiovascular mortality; (B) cardiac death rates; (C) MACE; (D) revascularization; (E) non-fatal myocardial infarction).

Although it has long been recognized that CR can improve prognosis, the participation rate of CR has not been high. In Pouche’s study [20], the 22.1% participation rate for CR is comparatively low, and the 1998 PREVENIR study had similar conclusions (23.3%) [57]. Another study reported similar results, with 13.9% of patients who had ACS and 31% who had a coronary artery bypass grafting [58]. In Europe, less than half the patients eligible for CR actually attend the programs [59].

The factors that determine the restrictions on participation or compliance with CR [60] may include: personal barriers (thinking that CR is not useful, patients have low control of cardiovascular risk factors, negative perceptions of those involved in rehabilitation, language barriers); barriers related to medical staff (they may provide information that is contradictory or provided at inappropriate times, inadequate understanding of CR objectives, and exclusion criteria); environmental and socio-professional barriers (inconvenient planning, incompatible timing); economic barriers; family barriers (lack of family



**Figure 10.** Sensitivity analysis results ((A) cardiac death rates; (B) revascularization).

involvement in rehabilitation); and physical barriers, including lack of transport or transport difficulties. Gaining a better understand of these barriers will be very important in improving CR compliance [61].

## Conclusions

This meta-analysis showed that CR was clearly associated with reductions in cardiac death, recurrence of MI, repeated PCI, CABG, and restenosis. Expanding the sample size and improving the quality of studies will be very important in future research.

## Conflict of interest

None.

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