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REVIEW ARTICLE

Health-Related Quality of Life after Coronary Revascularization: A systematic review with meta-analysis

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Abstract *Objective:* To conduct a systematic review and meta-analysis to summarize evidence and determine the impact of coronary revascularization (CR) on cardiac patients' Health-Related Quality of Life (HRQoL), highlighting factors that may affect this outcome in patients.
Methods: A systematic search of Medline (Pubmed), EMBASE, Cochrane Library, Sciverse (Science Direct and Scopus) and PsycInfo was conducted to identify studies published from January 2000 to December 2012. Data were analyzed using MIX 2.0 Pro and SPSS 20.
Results: Thirty-four longitudinal studies met the inclusion criteria; these studies included 15,992 patients, of whom 8,027 had undergone PCI, 6,348 had undergone CABG and 1,617 had received medication treatment. Moderate long-term effect sizes were revealed for both CR procedures. Both percutaneous coronary interventions (PCI) and coronary artery bypass graft surgery (CABG) had significantly greater effects on HRQoL than did medication; however, the CR procedures did not differ significantly from each other. Moderators included the type of instrument used to assess HRQoL and the study quality. Benefits related to physical functioning were greater than those related to psychosocial functioning in patients treated with CABG.

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Conclusions: Empirical research highlights the positive effect of CR on patient HRQoL. Researchers should carefully select the instrument they use to measure HRQoL, as this may affect the results and thus conclusions. More RCTs and between-group studies employing pre-post designs should be conducted before clear conclusions can be drawn.

1. Introduction

The field of coronary heart disease has advanced considerably in the last decade. Through the use of interventional (percutaneous coronary interventions; PCI) and surgical (coronary artery bypass graft surgery; CABG) procedures, symptom relief and survival rates have increased globally.[1]

The comparative effectiveness of CABG versus PCI in patients who are eligible for either procedure is poorly understood,[2] although a recent review suggested that older patients and patients with diabetes treated with CABG had increased survival rates relative to patients treated with PCI.[3]

In addition to survival and symptom relief, health-related quality of life (HRQoL) among patients with cardiovascular disease is a critical issue.[4] Based on the World Health Organization's definition, health is not only a biomedical but also a biopsychosocial issue.[5] Although no consensus definition exists, HRQoL includes physical, psychological and social well-being.[6,7] Enhancing coronary patients' HRQoL should be a component of the priorities of a medical team.

Few systematic reviews over the past ten years have examined the effect of coronary interventions on HRQoL. Jokinen and colleagues[8] reviewed 21 randomized control trials (RCT) evaluating CABG and concluded that post-surgical patients experienced improved HRQoL regardless of which procedure they had undergone (On- vs Off-Pump CABG), especially when the procedure was performed by experienced surgeons. Furthermore, the results of a RCT conducted by Jokinen and colleagues (2010) suggested that preoperative HRQoL predicted posttreatment HRQoL, with long-lasting beneficial effects and HRQoL increasing to a level comparable to that of the general population post-treatment. Noyez et al. (2011)[9] reviewed 29 articles addressing the effects of cardiac surgery. They concluded that many studies had presented only postoperative QoL data, which limited the derivation of conclusions concerning the beneficial effect of heart surgery on QoL. They also highlighted the need for good clinical trials with longer follow-up periods (periods greater than one year). Sun et al. (2012)[10] and Cormack et al. (2012)[11] reviewed 13 RCTs and 28 longitudinal studies, respectively, that had investigated CABG. Both reviews concluded that CABG patients may experience a decline in cognitive functioning during the weeks immediately following treatment but that this decline reversed at twelve months postsurgery. Finally, Blankenship et al.[12] reviewed 25 studies and concluded that the effect of PCI on QoL was greater than that of medical (drug) treatment; however, this benefit decreased over time. Moreover, the effect of PCI on QoL during the month immediately following treatment was greater than that of CABG; however, in the long-term, both procedures lead to similar improvements in QoL. Blankenship et al.[12] also suggested that patients of all ages benefited equally regardless of which revascularization procedure was performed, although they found that women reported lower HRQoL than men following PCI. Unemployment status, smoking and medical comorbidities were associated with lower QoL following PCI.[12]

Soo Hoo et al. (2014)[13] reviewed 18 studies of PCI and supported Blankenship et al.'s (2013)[12] conclusion that all individuals, regardless of age, reported improvements in HRQoL and that age, therefore, could not be considered as a moderator, especially when other comorbidities were taken into consideration.

Abah and colleagues (2015)[14] reviewed 44 mostly retrospective studies on the influence of heart surgery (CABG, PCI, Valve) on HRQoL on older patients. The results showed that the majority of patients demonstrated improvement, while 8-19% demonstrated a decline, in HRQoL following heart surgery.

Although these reviews may provide insights into the effect of CR on HRQoL in cardiac patients, a number of issues need to be addressed prior to making recommendations for clinical practice. For instance, Sun et al. (2012)[10] and Cormack et al. (2012)[11] focused only on one aspect of HRQoL, cognitive functioning; thus, a clear conclusion about the effect of CR on other aspects of HRQoL cannot be drawn. Blankenship et al.'s (2012)[12] study, while of good quality, was solely a literature review and lacked rigorous systematic methodology (e.g., many studies included were of low quality and/or provided only posttreatment data for the effect of CR on HRQoL); thus, conclusions from this study may be biased. Noyez et al.'s (2011)[9] and Abah et al.'s (2015)[14] work focused on surgical treatment of various heart problems (e.g., aortic or mitral valve surgery) instead of only on treatment of coronary artery disease. Hence, further investigations are needed to establish clear conclusions regarding the effect of CR on HRQoL. Finally, no prior reviews have provided effect sizes for the association between CR on HRQoL, as they did not use meta-analytic techniques to illustrate the extent of the effect of CR and its moderators. Thus, a systematic review and meta-analysis was needed update the literature and, due to the nature of these methodologies, simultaneously provide a more complete understanding of the impact of CR and its potential moderators on HRQoL.

The main aim of the present systematic review was to determine the impact of CR on HRQoL and identify factors that may influence this outcome. The secondary aim was to develop recommendations for both future research and clinical practice. The objectives of this study were as follows: a) to estimate the size of the overall effect of coronary revascularization on HRQoL in patients, b) to detect any differences in the effects of two types of CR (PCI and CABG) on HRQoL, and c) to identify factors moderating HRQoL following coronary revascularization.

2. Methods

The methodology used in the present study followed the Centre for Reviews and Dissemination[15] guidance for systematic reviews and the Cochrane Collaboration[16] and Field and Gillett's[17] suggestions for systematic reviews with meta-analysis.

2.1. Systematic literature search

The literature search was conducted from December 2012 to January 2013 using five online databases: Medline (Pubmed), EMBASE, Cochrane Library, Sciverse (Science Direct and Scopus) and PsycInfo. Keywords used in all searches were "quality of life (QoL) or health-related quality of life (HRQoL) or health status and heart surgery or coronary bypass or CABG or PCI or PTCA or coronary angioplasty or coronary percutaneous interventions not adolescent not children". Terms were searched for in the titles, abstracts and keywords. The search included studies published in the 13-year period from January 2000 to December 2012. In addition, "snowball" techniques[18] were used; through this technique, reference lists of primary studies and reviews were searched manually to detect studies that may fulfil inclusion criteria. Abstracts written in English were also considered, even if the research paper was written in another language. When an abstract seemed relevant to the topic under investigation and the paper was published in a language other than English, Greek, French, German, and Spanish, the authors were contacted to determine whether a full English version or results section were available. Authors were also contacted when their papers seemed eligible for inclusion but not all information needed for the analysis was presented.

Studies were included if they fulfilled the following criteria: (1) participants should be $\geq$ 19 years of age; (2) HRQoL was the target outcome; (3) study design was randomized, non-randomized or observational; (4) at least two interval times were reported, including pretreatment (baseline) and postoperation; (5) data were collected after 1996; (6) published in a peer-reviewed journal; and (7) published in various languages at which the present authors were proficient (i.e., English, Greek, French, Spanish, and German).

A cut-off point of 1996 was selected to reduce heterogeneity in outcomes resulting from "old" medical procedures not commonly used today. According to the cardiology literature, in the last fifteen years, new methods have been developed for both interventional and surgical coronary revascularization.[19,20]

Studies were excluded when (1) they used a questionnaire that did not measure all subdomains of HRQoL (based on the WHO definition) or that had poor/unknown psychometric properties, (2) they used a qualitative or case study design, (3) available data were not sufficient for effect size estimation even after contacting the corresponding author, (4) only norm-based summary scores were presented and (5) they were psychometric studies testing the properties of a QoL instrument.

2.2. Screening identified studies

A total of 1123 citations were identified in the initial searches. Details about the exclusion procedure are shown in the flow diagram below (Figure 1).

In total, 34 papers fulfilled the criteria for inclusion in this review. Of these, 29 were written in English, 2 in German, 2 in Spanish and 1 in Greek.

2.3. Data extraction

Studies were coded for the following: year of publication; country; type of CR; study design; sample size at baseline and follow-up(s); mean age; sex distribution; smoking status; body mass index (BMI); diagnosis of hypertension; diagnosis of diabetes (I or II); intervention duration; number of follow-up assessments; QoL measurement tool; data collection method (e.g., face-to-face, email, or phone); pre- and post-intervention QoL score (raw mean score for

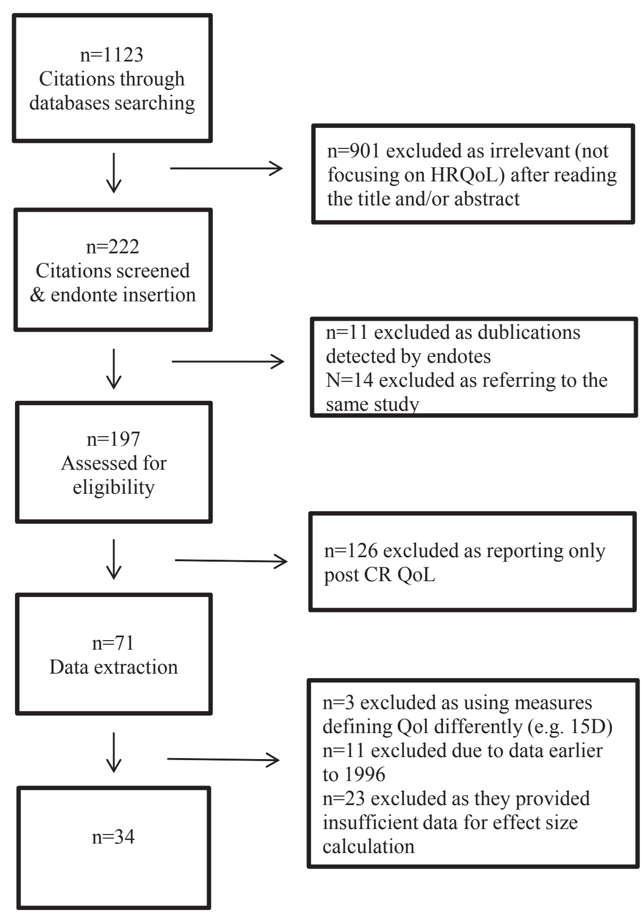

Figure 1 Flow diagram for selection of studies.

each subscale at baseline and last follow up and their standard deviations or mean difference, confidence intervals (CI), standard error (SE), and *p* values); effect size (when provided); and the authors' main findings. An SPSS data sheet was created for each included study to facilitate *d* conversions and avoid hand calculation errors.

2.4. Studies' quality assessment

Studies were assessed for quality using a combination of the Downs and Black[21] checklist for methodological quality (examining reporting, external validity, and bias); Noyez et al.'s[9] requirements for a 'good' study; and the Critical Appraisal Skills Programme[22] instrument for assessing the overall quality of cohort studies. Ten total criteria were applied: (Does the study address a clearly defined issue? Are patient characteristics clearly described? Were the main outcome measures used accurate (valid, reliable and disease-specific)? Were confounding factors taken into consideration? Have the characteristics of patients lost to follow-up been described? Were losses of patients to follow-up taken into account? Is the procedure described? Were the statistical tests used to assess the main outcomes appropriate? Are the main findings of the study clearly described? Was the follow-up period sufficiently long (i.e., $>$ 12 months)?). Studies were scored 0 when a criterion was not met, 0.5 when a criterion was partially met and 1 when a criterion was totally met. Scores could, therefore, range from 0 to 10.

2.5. Analysis

Standardized mean differences (SMDs) were generated to estimate effect sizes (ESs) for each study in accordance with recommended guidelines.[17,23] For within group analysis of pre-and post-intervention HRQoL scores, *d* indicated the difference between the mean pre- and post-test scores divided by the pre-test standard deviation. For between group comparisons, *d* indicated the average change in one group before and after the intervention minus the mean change of the other group divided by the pre-intervention pooled standard deviation.[24–26] ESs were corrected for biases due to small sample size using Hedges' *g* index.[26] Similar to Cohens' *d*, Hedges' *g* pools standard deviations assuming equal population variances. However, unlike *d*, *g* factors n-1 instead of n into the pooling, and therefore provides a better estimation, especially when sample size is small. The overall effect size was estimated both with fixed-effects models (assuming one true effect and any variation is due to random error) and random-effects models (assuming that there is not one true effect due to variations among studies as each study represents a "unique" population). The random-effects model was selected for subgroup analyses due to the assumption that individual studies estimated different effects. Homogeneity analyses of ES variances were conducted using *Q*, I^2 and τ^2 statistics. The *Q* index represented the weighted sum of the squared differences between the studies' means and fixed-effect estimations; however, it could be influenced by the number of studies included. When *Q* was significant, heterogeneity was assumed. I^2 measured the heterogeneity based on the *Q* index taking into account sample sizes. I^2 values of 0-40 indicated no important heterogeneity, while a value of approximately 50 indicated medium and approximately 75 indicated considerable heterogeneity. τ^2 assessed the between study variances without being influenced by the number of studies included in the analyses. When $\tau^2 > 1$, then substantial heterogeneity is assumed. Potential publication biases were examined using *Begg's z* (rank correlation between standardized effect size and the variance of these effects) and *Egger's t* indices[27] (*Egger's t* is similar to *Begg's z* but uses the values of effects sizes and their variances rather than their ranks). Sensitivity analyses was conducted by excluding outliers and poorer quality studies.[28] Analyses were performed using MIX 2.0 Pro,[29,30] Excel (MS office Excel, 2007) and SPSS 20.[31]

3. Results

Of the 34 studies identified, 8 evaluated the effects of only PCI, 20 evaluated the effects of only CABG and 6 evaluated the effects of both PCI and CABG on HRQoL. Therefore, 14 studies examined PCI, and 26 studies examined CABG. The majority of studies ($k = 26$) had a moderate to good quality, ranging from 5 to 7.5 points, while a few studies ($k = 8$) had a low quality, ranging from 3.5 to 4.5 points.

In total, 15,992 patients were included in these studies (8,027 had undergone PCI, 6,348 had undergone CABG and 1,617 had received medication treatment). Patient demographic and clinical characteristics for each study are summarized in Table 1. Among these patients, mean age was 63.0 years ($SD = 4.2$) and, on average, samples were 23% female and 32% smokers, with 59% of the patients having hypertension and 24% of the patients having diabetes (see Table 1).

The majority of studies ($k = 22$) used the SF-36 for measuring HRQoL. Other measurements of Quality of Life used were SAQ ($k = 2$), NHP ($k = 3$), Rand-36 ($k = 1$), WHOQoL ($k = 1$), MacNew ($k = 3$), and EQ-5D ($k = 1$).

Most studies ($k = 15$) assessed HRQoL up to 1 year after CR.[32–47] Fourteen studies ($k = 14$) had a shorter follow-up, ranging from 1 to 6 months.[48–60] and only five studies ($k = 5$) had a follow-up period longer than 12 months, ranging from 24 to 96 months.[61–65]

Table 2 displays additional characteristics, such as number of follow-ups and summaries of the main findings of each study.

3.1. CR Overall Effect on HRQoL

The size of the overall effect on HRQoL after treatment is displayed in Table 3. The relative contribution of each study on the overall effect of coronary revascularization (using random-effects assumptions) on patient HRQoL can been observed in Figure 2. Analyses were conducted using both random- and fixed-effects models, which suggested a moderate to low improvement in HRQoL after all types of treatments, even after controlling for length of follow up. Univariate analysis of variances showed a significant difference between different treatment types [$F(2,44)=4.57$, $p < .05$]. Weighted multiple comparisons (Bonferroni post hoc test) revealed that patients who underwent CABG or

Table 1 Baseline demographic and clinical characteristics of studies included in the review

	Study (year)	Country	Sample size at baseline[†]		Instrument[‡]	Female %	Mean age	Smoking %	Hypertension %	Diabetes %
			PCI	CABG						
1	Benzer (2003)	Austria	64	33	MAcNew	35.3	64.5	44.3	NR	NR
2	Cohen (2011)	USA	903	897	SF-36	22.5	65.2	18.5/21.9	NR	38.1/28.9
3	Hofer (2006;2005)	Austria	60	121	MAcNew	24.1	61.8	28.3/33.9	50/69.4	15/19.8
4	Lukkarinen (2006)	Finland	100	100	NHP	32.5	57.2/61.8	4	NR	NR
5	Škodová (2011)	Slovakia	37	41	SF-36	15.1	55.8/59.4	NR	NR	NR
6	Zang (2003)	Eur & Can.	488	500	SAQ	21	61.4	NR	45.2	14.4
7	de Quadros (2011)	Brazil	110		SAQ	38	62.8	24	90	32
8	Denvir (2006)	UK	1346		EQ-5D	32.5	60.9	38.6	32.5	11.1
9	Melberg (2010)	Norway	427		SF-36	20.3	58.4	29.9	23.9	6.1
10	Li (2010;2012)	China	287		SF-36	26.2	64	31	58	30
11	Viswanathan (2011)	UK	2935		NHP	29.3	58.1	26.7	30.7	6.4
12	Weilu (2011)	China	223		SF-36	14.3	60.6	51.6	52.9	13.9
13	Weintraub (2008)	USA & Can.	969		RAND-36	15	62	29	67	34
14	Wong (2007)	Hong Kong	78		SF-36	24.6	66	15.4	42.9	29.2
15	Azzopardi (2009)	Australia		87	SF-36	14.6	66.6	24.2	97.9	42
16	Barolia (2012)	Pakistan		65	WHOQOL-Brief	15.3	59.7	20.0	72.0	51.0
17	Colak (2008)	Croatia		111	SF-36	12.6	61.1	NR	87	28.2
18	Damgaard (2011)	Denmark		331	SF-36	11.8	59	46.5	47.6	25.3
19	Gjeilo (2008;2012)	Norway		534	SF-36	22.7	NR	NR	NR	NR
20	Houlind (2012)	Denmark		900	SF-36	23.0	75	25.5	71.0	20.0
21	Hunt (2000)	Australia		123	SF-36	22	64	NR	NR	NR
22	Jensen (2006)	Denmark		120	SF-36	40	76	18.3	60.8	18.3
23	Kiebzak (2002)	USA		85	SF-36	21.2	62	NR	NR	NR
24	Krecki, (2010)	Poland		55	SF-36	25	61.5	36	96	49
25	Krannich (2007)	Germany		142	SF-36	19.0	65.1	NR	NR	NR
26	Lie (2009)	Norway		185	SF-36	10.3	62	29	NR	16.2
27	Martin (2012)	USA		495	SF-12	17.1	63.9	44.0	78.0	32.0
28	Mathisen (2005)	Norway		120	SF-36	21.6	64.4	NR	40	14.2
29	Merkouris (2009)	Greece		63	MAcNew	23.8	72.9	64	62	35
30	Peric (2010; 2006)	Serbia		243	NHP	20	58.7	43	70	19
31	Pfaffenberger (2010)	German		55	SF-36	14.8	64.8	35.2	66.7	NR
32	Pirraglia (2003)	USA		590	SF-36	28	65.1	68.3	52.4	25.6
33	Puskas (2004)	USA		200	SF-36	22.5	62.3	29.4	63.8	33
34	Rothenhäusler (2010)	German		147	SF-36	16.5	60.8	NR	NR	NR

[†] baseline= pre-revascularization.
[‡] instrument used for ES calculations.

Table 2 Additional characteristics and main findings of studies included in the review

ID	Author	QoL Focus	N (prior to treatment)	Study Design	*N* (and duration) of Follow-Ups	Main findings
Both interventions						
1	Benzer, 2003	PCI vs CABG vs MED	64 33 109	Prospective, cross-sectional	1 (12 m)	Greater improvement in QoL 1 year after CABG and PCI compared to medical therapy were identified.
2	Cohen, 2011	PCI vs CABG	903 897	Prospective, cross-sectional	3 (1 m, 6 m, 12 m)	The PCI group scored higher on physical aspects of QoL compared to the CABG group. NS differences between treatment groups at were observed at 12 months.
3	Hofer, 2006	PCI vs CABG vs MED	60 121 96	Prospective cross-sectional	2 (1 m, 3 m)	The CR groups demonstrated greater changes in QoL compared to the MED groups. The PCI group experienced a significant increase in QoL 1 month posttreatment, with a slight further increase at 3 months. The CABG group experienced a significant increase at 3 m. Depression and anxiety scores accounted for most of the change in HRQoL (64-69%), whereas treatment accounted for less than 1% of the changes in HRQoL at 3 m post treatment.
4	Lukkarinen, 2006	PCI vs CABG vs MED	100 100 80	Prospective, cross-sectional	2 (12 m, 96 m)	PCI & CABG pts had higher QoL after 12 and 96 m compared to MED patients. CABG pts scored significantly better on mobility, energy and pain. PCI pts had significantly better HRQoL in emotional reactions, pain, mobility and energy at 96 m posttreatment.
5	Škodová, 2011	PCI vs CABG vs MED	37 41 28	Prospective, cross-sectional	2 (12 m, 24 m)	Significantly better QoL was observed after all types of treatment. The PCI and CABG groups demonstrated significantly greater mean changes in physical QoL aspects than the MED group, while the CABG and MED groups demonstrate significantly greater mean change at mental QoL aspects.
6	Zang,2003	PCI vs CABG	488 500	Prospective, cross-sectional	2 (6 m, 12 m)	Both the CABG and PCI groups demonstrated improvement in cardiac-related health status.
PCI interventions						
7	de Quadros, 2011	PCI + pred	110	Prospective, repeated measures	2 (6 m,12 m)	Pts demonstrated a significant improvement after treatment. Male gender and QoL at baseline were significant predictors of posttreatment QoL level.

8	Denvir, 2006	PCI High vs low SES	1346	Prospective, repeated measures	1 (12 m)	Pts demonstrated a significant improvement after treatment. Pts with low SES demonstrated significantly lower mean HRQoL scores at baseline and 12 m posttreatment compared to those with high SES.
9	Melberg, 2010	PCI + non surg vs surg hospital	427	Prospective, repeated measures	1 (6 m)	Significant improvement of QoL after treatment. Similar improvements observed in both hospital types.
10	Li, 2012	PCI vs MED	287 298	Prospective, cross-sectional	1 (6 m)	PCI pts score higher in QOL 6 m posttreatment compared to MED pts. PCI elderly patients, especially those $\geq$80 years of age, experienced the greatest benefit in QoL 6 m posttreatment.
11	Viswanathan, 2011	PCI with & without prior CABG	2935	Prospective, repeated measures	3 (3 m, 12 m, 24 m)	Pts with previous CABG had less improvement in HRQOL after PCI. At 24 m, patients with prior CABG demonstrated worse physical functioning than was reported at baseline.
12	Weilu, 2011	PCI stent effect	223	Prospective, repeated measures	1 (6 m)	At 6 m after intervention, HRQoL increased in all 8 domains. Factors negatively associated with 6 m QoL scores were as follows: gender, age and activity were associated with bodily pain; activity was associated with physical functioning; and age and activity were associated with mental health and general health.
13	Weintraub, 2008	PCI vs MED	969 958	Prospective, cross-sectional	7 (1 m, 3 m, 6 m, 12 m, 24 m, 36 m)	At 12 m posttreatment, pts that underwent PCI demonstrated greater mean changes in HRQoL compared to those receiving medication. At 36 m after treatment, NS differences between groups existed.
14	Wong, 2007	PCI	78	Prospective, repeated measures	2 (1 m, 3 m)	Increased scores were observed after treatment. NS changes in physical and social functioning were identified.
CABG interventions						
15	Azzopardi,2009	CABG	87	Prospective, repeated measures	3 (6 m, 12 m, 24 m)	Increased scores at 24 m and NS differences between pts and normative Australian individuals were observed.
16	Barolia, 2011	CABG + gender & age dif	65	Prospective, repeated measures	1 (1 m)	Significant improvements in all domains were observed. One m postsurgery, females had significantly lower psychological health, while patients >60 yrs of age had significantly greater social satisfaction.
17	Colak, 2008	Cabg & comparison with norm	111	Prospective, repeated measures	1 (12 m)	Twelve m post treatment, pts demonstrated improvements in all 6 domains of QoL. NS mean changes in all subdomains were observed.

(*continued on next page*)

Table 2 (*continued*)

ID	Author	QoL Focus	N (prior to treatment)	Study Design	*N* (and duration) of Follow-Ups	Main findings
18	Damgaard, 2011	CABQ vs CABG	170 161	Prospective, cross-sectional	2 (3 m, 11 m)	Significant improvements at 11 m posttreatment and NS differences between the two groups were observed.
19	Gjeilo, 2012	CABG + Gender & age effect	413	Prospective, repeated measures	2 (6 m, 12 m)	Female pts scored lower compared to male pts at all measured time points. However, the mean changes in most subscales favored women (except the GH and ER scales). Pts ≥75 years of age demonstrated lower general health and physical, social, role, and emotional functioning compared to younger patients. At 12 m posttreatment, pts had almost equal HRQoL to non-cardiac populations with the exception of role and physical functioning, on which pts ≥75 years of age scored relatively lower.
20	Houlind, 2012	CABG on vs off	900	Prospective, repeated measures	1 (6 m)	Pts demonstrated a significant improvement in all domains. NS differences between groups were observed.
21	Hunt, 2000	CABG	123	Prospective, repeated measures	1 (12 m)	Pts demonstrated a significant improvement. NS gender differences were observed.
22	Jensen, 2006	CABG on vs off	120	Prospective, repeated measures	1 (3 m)	Pts demonstrated a significant improvement in all domains. NS difference between groups were observed.
23	Kiebzak, 2002	CABG	85	Prospective, repeated measures	1 (12 m)	Improvement at 1 yr and NS changes in role, emotional and general health subscales were observed.
24	Krannich, 2007	CABG	142	Prospective, repeated measures	2 (10 d, 12 m)	Pts demonstrated a significant improvement in all domains. At 1 yr post CABG, pts demonstrated almost equal HRQoL to the non-cardiac population.
25	Krecki, 2010	CABG vs MED	55 52	Prospective, cross-sectional	1 (12 m)	CABG pts demonstrated significant improvements in all domains, while MED pts demonstrated significant improvements only in pain and limitations due to emotional problems.
26	Lie, 2009	CABG Rehabilitation effects	185	Prospective, repeated measures	2 (6 w, 6 m)	Improvement in QoL level and NS differences between groups were observed.
27	Martin, 2012	CABG + gender effect	495	Prospective, repeated measures	1 (6 m)	Improvement in all domains was observed. Women significantly score lower at baseline and 6 m posttreatment compared to men.

28	Mathisen, 2005	CABG on vs off	120	Prospective, cross-sectional	3 (3 m, 6 m, 12 m)	QoL improved in both groups. NS differences between groups were observed.
29	Merkouris, 2009	CABG + age effect	63	Prospective, repeated measures	2 (4 m, 12 m)	Pts demonstrated a significant improvement in all domains except cognitive. Almost 1/3 of pts reported cognitive decline. At 12 months posttreatment, women scored significantly lower than men.
30	Peric, 2010	CABG + gender effect	243	Prospective, repeated measures	1 (6 m)	Pts demonstrated improvement after treatment. Women scored worse preoperatively and postoperatively than men.
31	Pfaffenberger, 2010	CABG + anxiety, depression effect	54	Prospective, repeated measures	2 (4 w, 3 m)	Pts demonstrated significant improvement after treatment Anxiety was a sig predictor for scores in all QoL subdomains when the MacNew is used as the outcome measure but only the Mental Health domain when the SF-36 was used. Depression was a significant predictor of only mental health.
32	Pirraglia, 2003	CABG	590	Prospective, repeated measures	1 (6 m)	Pts demonstrated significant improvement posttreatment.
33	Puskas, 2004	CABG on vs off	200	Prospective, repeated measures	4 (4w, 6w, 6 m, 12 m)	Pts demonstrate significant improvement posttreatment. NS differences between groups were observed.
34	Rothenhäusler, 2010	CABG + depression, PTSD	147	Prospective, repeated measures	1 (6 m)	Pts demonstrated significant improvement posttreatment. Clinical depression and PTSD were associated with lower levels of improvement.

PCI = percutaneous coronary intervention, CABG = coronary bypass graft surgery, MED = pharmacotherapy, d = days, w = weeks, m = months, pts = patients, NS = nonsignificant, PTSD = posttraumatic stress disorder.

Table 3 Central tendency and variability in the impact of coronary treatment on health-related quality of life.

Groups	*k*	*N* (pre/last follow-up)	Hedge's *g* (95% CI)		Homogeneity of effect sizes	
			Fixed-effects assumptions	Random-effects assumptions	I^2 †	τ^2 ‡
Prior to sensitivity analysis						
All studies (CR)	34	14375/12502	0.53 (0.51, 0.56)	0.59 (0.48, 0.69)	93.02 (91.21, 94.45)	0.08
PCI groups	14	8027/6857	0.43 (0.39, 0.46)	0.55 (0.40, 0.69)	93.01 (89.93, 95.15)	0.06
CABG groups	26	6348/5645	0.67 (0.64, 0.71)	0.60 (0.48, 0.72)	89.95 (86.59, 92.47)	0.08
MED groups	7	1617/1039	0.25 (0.18, 0.33)	0.25 (0.18, 0.33)	0.00 (0.00, 70.81)	0.00
After exclusions of outliers						
All studies (CR)	19	5431/4656	0.54 (0.49, 0.57)	0.53 (0.47, 0.59)	29.92 (0.00, 59.85)	0.01
PCI groups	6	1955/1742	0.50 (0.44, 0.57)	0.48 (0.38, 0.59)	52.02 (0.00, 79.58)	0.01
CABG groups	15	3476/2914	0.54 (0.49, 0.59)	0.54 (0.47, 0.60)	25.42 (0.00, 0.45)	0.01
MED groups	3	390/290	0.32 (0.17,0.43)	0.32 (0.17,0.43)	0.00 (0.00, 89.60)	0.00

As I^2 increases from 0, the presence of heterogeneity can be assumed ($I^2 = 25$ defined minor heterogeneity, $I^2 = 50$ defined moderate heterogeneity, and $I^2 = 75$ defined considerable heterogeneity). Presence of heterogeneity represented inconsistencies among individual study results.
As τ^2 *increases from 0, the presence of heterogeneity was assumed* ($\tau^2 > 1$, considerable heterogeneity is present).
† based on precision.
‡ based on variance.

PCI experienced a significantly greater improvement of HRQoL over patients treated with medicines (MED) while patients treated with PCI and CABG did not differ significantly from each other (CABG > MED, md = 0.35, $p < .005$; PCI > MED, md = 0.32, $p < .05$; CABG > PCI, md = 0.03, $p = 0.72$). Furthermore, when considering only the six studies that included both PCI and CABG patients, the difference in improvement of HRQoL was also nonsignificant ($p = 0.12$).

Additionally, when the t^2 index was used to detect the level of heterogeneity in CR effect size, all studies seemed to be homogeneous ($t^2 = 0.08$), while when the I^2 estimate was used, a high level of heterogeneity ($I^2 = 93\%$) was identified, suggesting that there were studies that should be excluded as outliers.

In the examination of publications biases, *Begg's* test ($z = 0.03$, $p = 0.98$) and *Egger's* test [$t = 4.98$ (CI = 0.25,0.61), $p = 0.19$] results rejected the probability of a significant publication bias.

Sensitivity analyses demonstrated that 15 studies should be excluded as outliers. Table 3 and Figure 3 demonstrate the number of studies retained. Even after their exclusion, the combined effect size on HRQoL remained moderate for both types of coronary revascularization and low for MED. Overall, the mean difference became slightly lower but no essential changes were detected, [$F(2,32) = 10.42$, $p < 0.001$, CABG > MED, md = 0.27, $p < 0.001$; PCI > MED, md = 0.20, $p < 0.001$, CABG > PCI, md = 0.07, $p = 0.28$).

The forest plots (Figures 2 and 3) provide graphical representations of effects sizes and CIs before and after sensitivity analysis.

3.2. Moderator analysis

Including all 34 studies, three factors were associated with the outcome: type of instrument, time (study duration) and study quality. Multiple linear regression analysis of mean difference weighted by the inverse variance demonstrated that these moderators accounted for 96.5% of the outcome variability. In fact, 13% of the variance was accounted for by study quality [$F(1,38) = 6.69$, $p < 0.05$], and 83.6% of the variance could be attributed to type of instrument [$F(7,31) = 109.98$, $p < 0.001$], while time (study duration) accounted for a small but significant 1% of the variability [$F(2,29) = 4.29$, $p < 0.05$]. Specifically, analysis indicated that these variables had larger effects in lower quality studies ($b = -2.69$, $t(33) = -2.36$, $p = 0.025$), in studies with short-term follow-ups ($b = -0.52$, $t(33) = -2.87$, $p = 0.007$) and for disease-specific measures of HRQoL (e.g., a larger effect for the disease-specific measure SAQ)($b = 20.83$, $t(33) = 10.25$, $p < 0.001$) than for the generic SF-36 ($b = 11.91$, $t(33) = 14.66$, $p < 0.001$)).

When analyses were repeated with 19 studies (after excluding outliers and poorer quality studies), the effect of CR on HRQoL was still significant (Table 3). However, study quality and study duration were no longer significant predictors, and the effect of HRQoL measurement type could be not analyzed, as the majority of remaining studies (89%) used the SF-36.

3.3. Subgroup analysis: Psychosocial vs Physical domains

Subgroup analysis was conducted among the studies using the SF-36 to assess HRQoL following CR to detect any differences in the effect of CR on HRQoL within the psychosocial and physical subdomains. In 21 studies (participant $n = 5{,}232$), findings revealed that patients reported greater mean changes in the physical than the psychosocial domains (ES = 4.45, 95% CI, 3.93 to 5.20; $p < 0.05$).

However, the mean difference (md) between the physical and psychosocial domains were significant for CABG but not PCI (Figure 4). Meta-regression analysis for the influence of potential moderators on the differences in CABG effect sizes between the physical and psychosocial dimensions did not reveal any significant results.

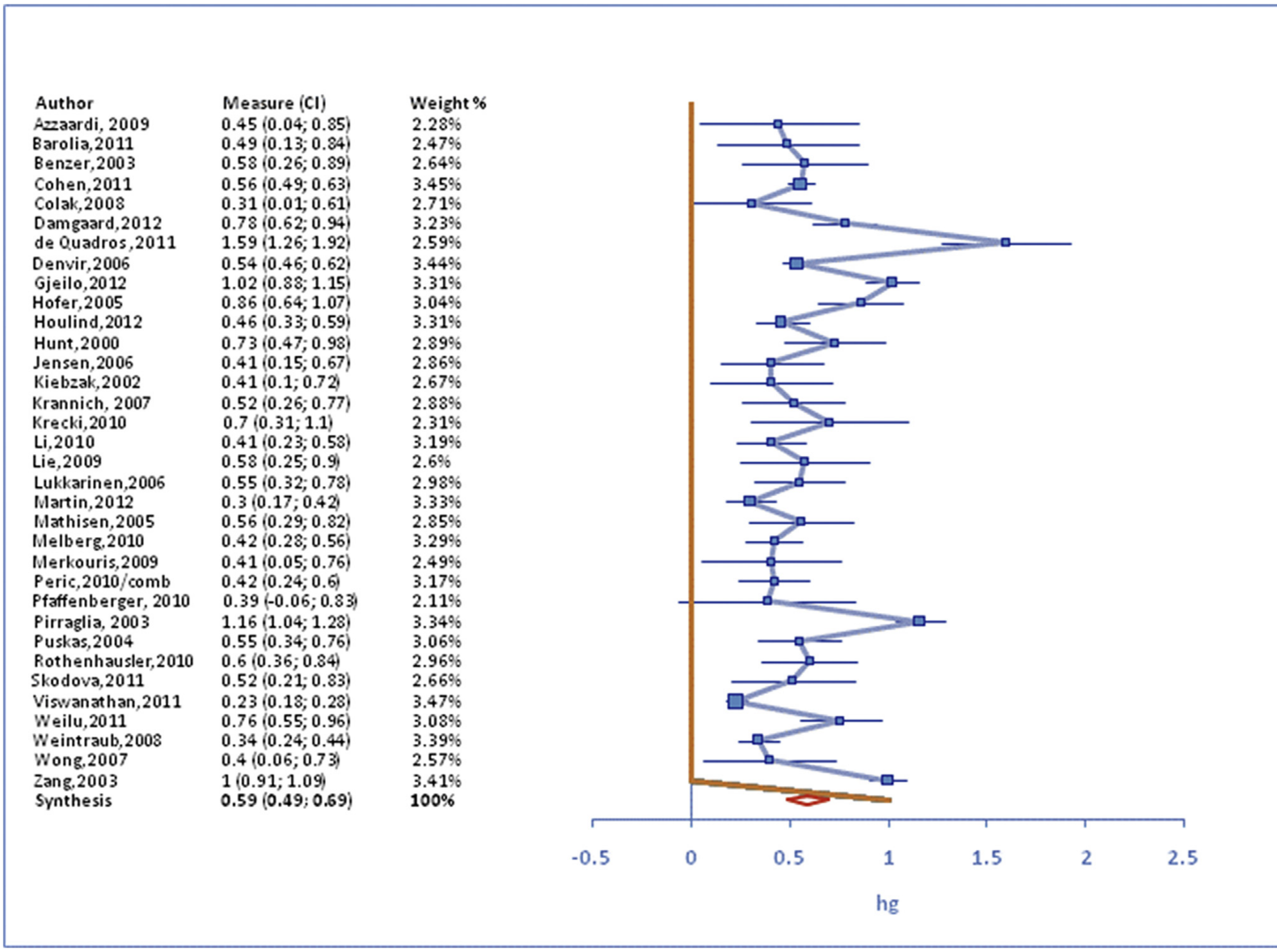

Figure 2 Forest plot diagram showing the effect (hg) of CR within each study and the overall effect ($k = 34$) after synthesis of overall pooled effect. CI = confidence interval. $Q = 472.67$, $p < 0.005$, $I^2 = 93.02\%$.

4. Discussion

The present systematic review and meta-analysis identified 34 studies evaluating the effect of CR on improvements in HRQoL to compare the effects of PCI and CABG on and to identify factors moderating improvements in HRQoL following CR.

PCI and CABG had moderate effects on improving HRQoL. Both were significantly better than medication treatment but did not differ from each other. These findings were consistent with those of Blankenship et al. (2013)[12] and Jokinen et al. (2010),[8] although these authors examined only PCI and only CABG, respectively. The present study is the first to examine both procedures simultaneously.

Regarding the duration of improved HRQoL, the effect size was slightly greater at 12 months than at 36 or 48 months after CR (data not presented). This evidence is in line with Blankenship et al.'s (2013)[12] conclusions.

For both CR procedures, type of instrument used to measure HRQoL and study quality were strong moderators of the outcome. A discussion exists in the literature regarding the instruments used in HRQoL research. In the current paper, all studies used valid and reliable measures; however, the majority used generic rather than disease-specific measures. Studies using a disease-specific instrument reported a greater effect size than studies using generic measures. As there has been no consensus definition of QoL, results produced by various measurements may vary significantly, as each instrument may include common as well as different domains dependent upon the theoretical framework used by the authors.[66] While generic measures such as the SF-36[67] are valid and reliable, some items are likely to be less sensitive in detecting treatment effects[68,69] for specific health conditions[70] such as a coronary revascularization.[71] For example, in a rehabilitation program, the results of a generic measure led to the conclusion that the program did not improve QoL, while the results of a disease-specific measurement did demonstrate significant improvement.[72]

Neither age nor sex predicted HRQoL, although fewer women than men had undergone CR in the included studies. These findings are in line with Lansky et al.'s[73,74] conclusions that the seemingly worse outcomes in women may be associated with higher risk profiles in women undergoing CR and differences in mortality or health outcomes that have been observed in some studies were related to risks factors other than sex. In short, the findings of the present study imply that neither age nor gender need be considered as risk factors for lower HRQoL when treatment decisions for coronary artery disease are made.

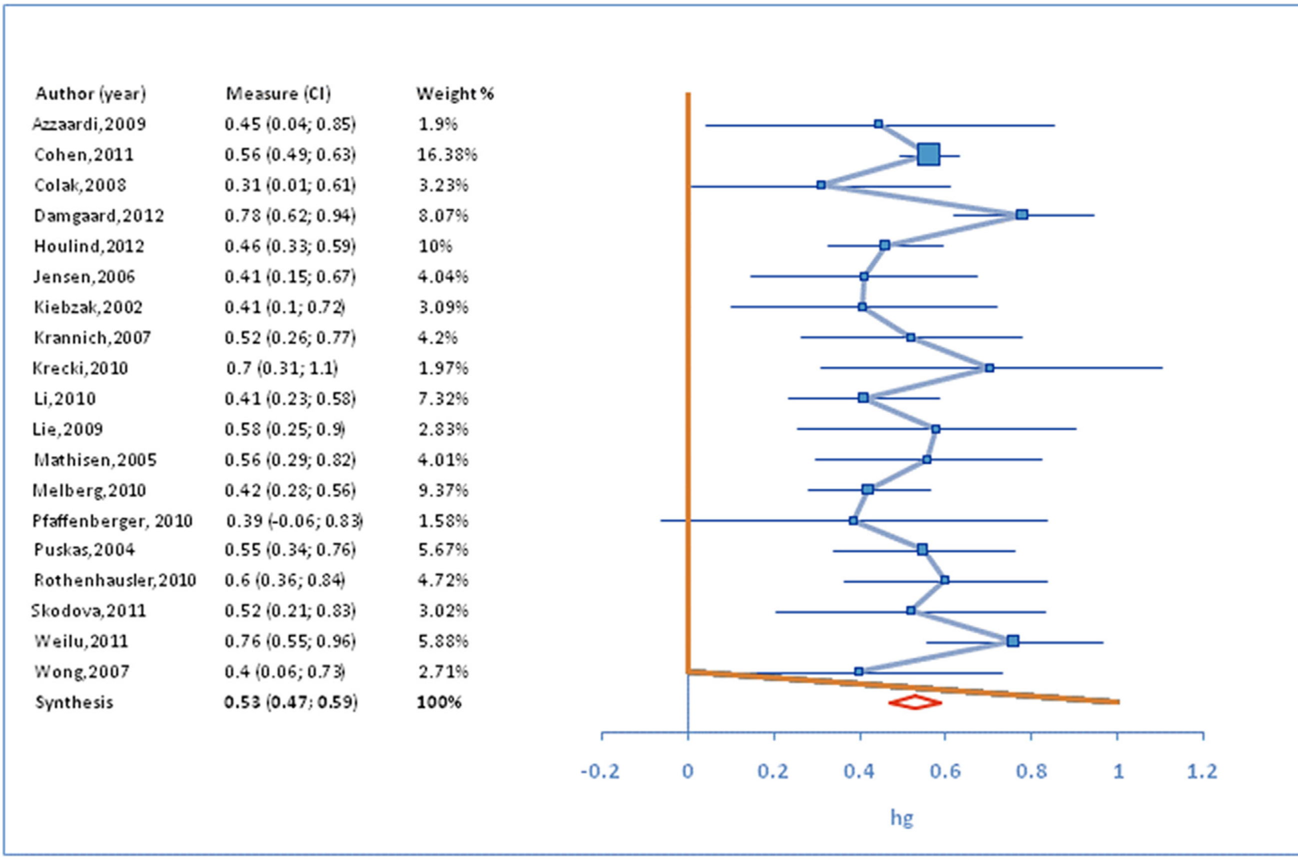

Figure 3 Forest plot diagram showing the effect (hg) of CR within each study and the overall effect ($k = 19$) after excluding outliers. CI = confidence interval. $Q = 40.35$, $p < 0.005$, $I^2 = 50.44\%$.

Subgroups analyses showed a greater effect of CR on physical functioning compared to psychosocial functioning regardless of the procedure completed. However, the post intervention mean score was similar for all subdomains of HRQoL, suggesting that the beneficial effects in the psychosocial domain may be due to patients demonstrating greater dysfunction in physical rather than psychosocial functioning prior to CR treatment. This implies that it is vital that researchers consider pre-post scores and not just compare the outcome (post) scores to draw conclusions, a point also highlighted by Noyez et al. (2011).[9]

A large body of literature has been published addressing the debate over the appropriate index for detecting heterogeneity in continuous data. Findings may change dramatically depending on the index chosen. The findings in the present study highlight this difference. When the τ index was used, homogeneity among studies was revealed and type of instrument and female sex appeared to moderate the effect of CR on improvements in HRQoL. However, when the I^2 index was employed, 15 studies were identified as outliers. With a subsequent decrease in heterogeneity after their exclusion, the effects of CABG and PCI on improvement in HRQoL were maintained; however, none of the variables examined had a significant moderating effect. This highlights two basic issues: a) that statisticians should focus on resolving this issue to allow reviewers to detect genuine heterogeneity levels and b) that findings from heterogeneous studies should be considered carefully before any recommendations are made.

Several limitations are present in this study. First, only a few studies examined the severity of angina prior to treatment or provided data for complex coronary lesions. As a result, these important variables were not included in the analysis, raising questions about the precision of the estimates for the effect of CR on HRQoL. Similarly, stressful events, depression, personality traits,[75] changes in lifestyle, adherence to medical advice and other potentially relevant factors were not considered because these were not routinely measured in the studies reviewed. Second, the majority of studies did not include control groups or alternative treatments. Only 30% of the studies reviewed presented comparisons between types of CR treatment, which may lead reviewers to a misleading conclusions. Studies using between-group designs generally demonstrated lower effect sizes for HRQoL changes compared to single group designs, a difference that may be due to the manner in which effect size was estimated.[26] Third, although in many cases the type of medication patients used wasn't reported, when it was described, it differed dramatically between treatment groups, suggesting methodological biases that could not be controlled. Fourth, the majority of studies had a follow-up period of less than 12 months, which may not be considered a sufficient period of time to reflect the true long-term effects of a treatment. Finally, the study's overall sample and its potential effect

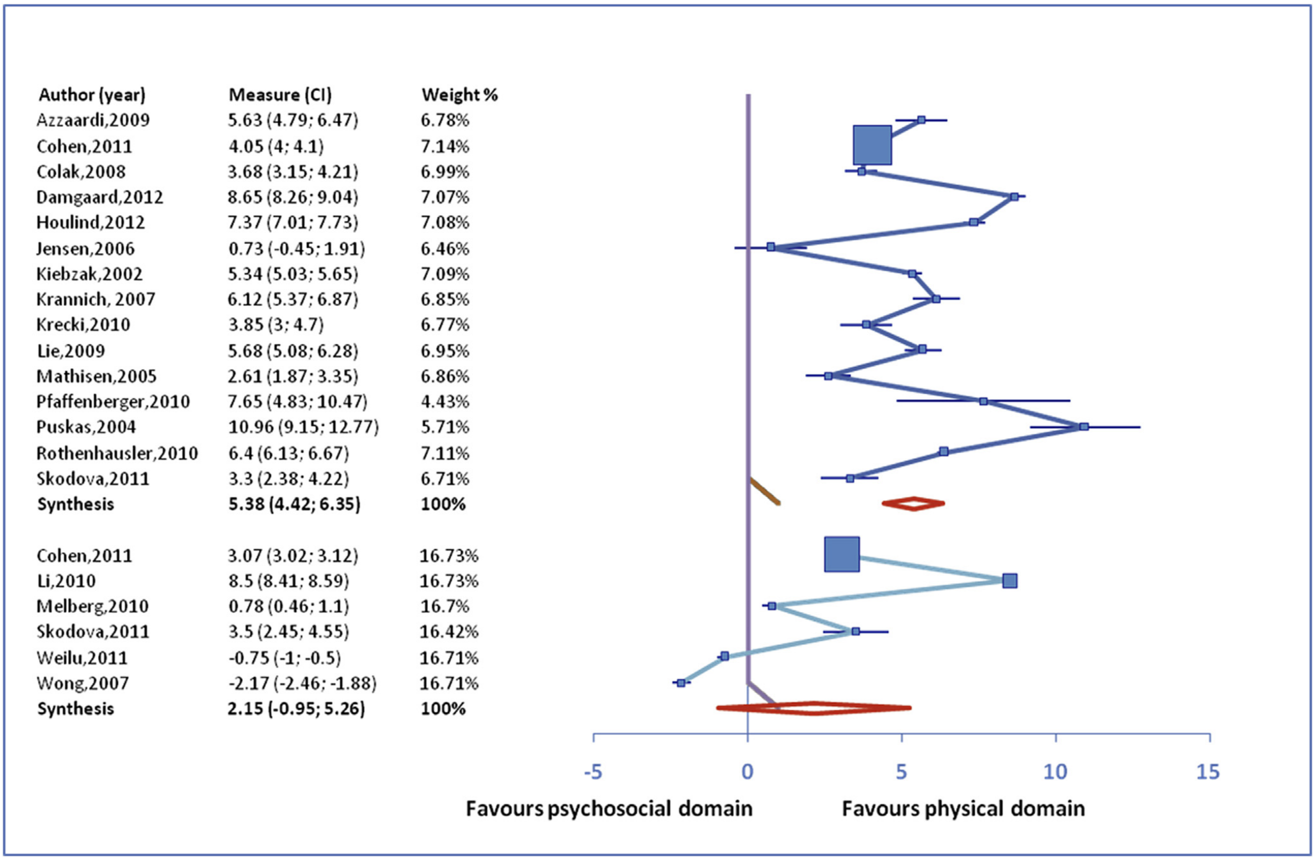

Figure 4 Forest plot diagram showing the mean difference (md) between physical and psychosocial domains per CR type; the first part repots CABG md ($p < 0.01$) and the second PCI md ($p = 0.17$). CI = confidence interval.

on the assessed moderators may not be considered ideal. For instance, sex may be a moderator; however, relatively few women were included in the studies reviewed. Thus, results should be considered cautiously until more studies with more women participants are published.

Measurement of HRQoL should be included in the routine assessment of coronary patients in order to have a complete picture of their condition and augment conclusions about the effectiveness of treatment. Additionally, cardiothoracic surgeons should pay attention to their patients' psychosocial functioning and, if necessary, advise them to seek professional guidance and support to maximize well-being.

Further high-quality research should be developed to enable the scientific community to establish rigorous conclusions about factors that influence CR's effect on patients' HRQoL. Specifically, more RCTs and between-group designs are needed to inform health care professionals about the beneficial aspects of each treatment. More variables should be included in each study to examine additional issues such as medical (e.g., angina), environmental/behavioral (e.g., adherence to medication, diabetes management, obesity, and alcohol use) and psychological (e.g., stressful life events, emotional distress, and personality) factors and identify relevant predictors. Studies should also measure HRQoL at multiple time points and place a greater emphasis on female recruitment to come to a more concrete conclusion regarding the issue of gender. More studies using disease-specific HRQoL instruments should also be conducted, as the literature suggests disease-specific instruments may allow clearer and more accurate conclusions than those derived from general instruments. Studies should also report all HRQoL subdomains, not just totals, and all relevant indices should be presented (e.g., pre-post mean scores and *p* values) to avoid transformations and calculations by reviewers that might lead to misleading results.[16]

This meta-analysis provides empirical evidence of the beneficial impact of coronary procedures on patients' HRQoL. This information may help physicians not only to justify their decision on which procedure to use but also to inform patients about the pros and cons of each procedure in terms of HRQoL. Determination of best practices in research requires careful methodological consideration to maximize study quality and produce trustworthy conclusions. Despite the advancements that have been achieved, considerable challenges and questions remain to be addressed.

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