Roles of cholesterol efflux capacity in the occurrence and prognosis coronary artery disease

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Research article

Keywords: cholesterol efflux capacity, coronary artery disease, risk, prognosis

Posted Date: November 13th, 2019

DOI: https://doi.org/10.21203/rs.2.17179/v1

Abstract

Background The association between cholesterol efflux capacity (CEC) with the occurrence and prognosis of coronary artery disease (CAD) remains unrevealed. In our study, a systematic review was performed to quantitively analyze the association between CEC and the risk of CAD and follow-up endpoint events of the patients with CAD.

Methods A systematic search of electronic databases (PubMed, EMBASE, OVID, Web of Science and Cochrane Library) for studies published until September 2019 was performed. Cohort, case-control studies, and randomized controlled trials that examined the effect of CEC on risk and prognosis of CAD were included.

Results Eighteen studies involving a total of 12615 subjects that met the inclusion criteria were included. Among them, 14 studies reported the CEC levels in control and CAD group and 8 of them analyzed the association of CEC with risk of CAD. Four studies reported the prognosis of CAD or acute coronary syndrome (ACS). From the pooled analyses, significantly decreased CEC level was shown in patients with stable CAD in comparison with the control. It was also true in subgroup analysis of the patients with ACS. The decreased CEC was significantly associated with increased risk of CAD (OR=0.65, 95% CI: 0.55-0.75, P<0.001). Decreased CEC level predicted higher all-cause (OR= 0.39, 95% CI: 0.20-0.77, P=0.007) and cardiovascular related mortality (OR= 0.34, 95% CI: 0.13-0.90, P=0.03) risk in patients with CAD. However, CEC levels failed to predict the occurrence of stroke and myocardial infraction in patients with CAD.

Conclusions Decreased cholesterol efflux capacity is an independent risk factor for the occurrence of CAD patients, and its level predicts all-cause and cardiovascular related mortality risk in patients with CAD. Prospective studies should further investigate whether CEC control might improve outcomes in CAD patients.

Introduction

Coronary artery disease (CAD) represents the leading cause of death across the world and its morbidity is persistently increasing globally. It is estimated that approximately 35~60% of deaths worldwide would be attributed to cardiovascular diseases by 2025[1]. Generally, CVD is consisted with a wide spectrum of heart diseases, ranging from asymptomatic ischemia to chronic stable angina pectoris, acute coronary syndrome, unstable angina, acute myocardial infarction, ischemic cardiomyopathy and sudden death. CAD is a multi-factorial disease, a series of risk factors, including dysregulated cholesterol, hypertension, diabetes and smoking are accounted for its onset and progression. In addition to these traditional identified risks, infection, inflammatory and chronic diseases are suggested to be risk factors of cardiovascular diseases.

Multiple epidemiological studies documented that CAD patients presented reduced high density lipoprotein-cholesterol (HDL-C) and HDL-C level negatively predicted the occurrence of CAD, which proposed a rational for raising HDL-C for the treatment of CAD [2]. Unfortunately, the clinical trials for

evaluating the clinical efficacy of HDL-C raising therapeutics have ceased for not observing the priority of these drugs in reducing cardiovascular events [3]. Furthermore, it is considered that in normal healthy states, HDL exhibits anti-inflammatory, anti-oxidative and reverse cholesterol transport effects to resist atherosclerosis. However, the anti-atherogenic properties of HDL could be reversed in case of the pathological conditions, such as inflammation, diabetes, and oxidative stress [4]. Therefore, given that HDL-C content may not an independent protective factor for CVS and it is modifiable under certain circumstance, more interest has been gradually shifted from raising HDL-C to improving HDL function.

Recent studies demonstrate that HDL function may serve as a better predictor of atherosclerotic risk than HDL-C concentrations[5]. Among the functions exerted by HDL, promoting reverse cholesterol transport from the periphery to the liver for further use is one of key anti-atherogenic function of HDL, and cholesterol efflux from macrophages to HDL act the first crucial step for reverse cholesterol transport. Macrophage-specific cholesterol efflux capacity (CEC) has been reported to be directly associated with the alleviation of murine atherosclerosis[6]. Meanwhile, CEC was confirmed to be reduced in patients with CAD and heart failure [7, 8]. CEC is inversely associated with carotid intima-media thickness in patients with end-stage renal disease, independent of HDL-C concentrations[9]. A prospective cohort study showed that CEC may serve as an independent measure for predicting all-cause and cardiovascular mortality in patients with coronary artery disease[10]. However, not all studies investigating the association between CEC and CVD reached a consensus. Li et al found that higher cholesterol efflux capacity was paradoxically associated with increased risk of non-fatal MI or stroke and major adverse cardiovascular events[11]. Study by Ormseth et al showed that net cholesterol efflux capacity is not significantly altered in patients with relatively well-controlled RA nor is it significantly associated with coronary artery calcium score[5]. Therefore, whether CEC is independent of HDL-C as a biomarker for CAD risk and prediction of prognosis are unanswered. To comprehensively analyze the association between CEC and CAD, we summarized the data and performed a systematic review to explore the indicative importance of CEC in the risk prediction and prognosis of CAD.

Materials And Methods

Databases and search strategy

Published studies were retrieved by two independent authors from the electronic databases (Medline, PubMed, EMBASE, OVID, Web of Science, The Cochrane Library) from Jan 1970 to Sep 2019. The following key words in combination as both MeSH terms and text words were used: “cholesterol efflux capacity” AND “coronary artery disease” OR “coronary heart disease” OR “myocardial infarction” OR “acute coronary syndrome” OR “unstable angina”. Only publications in English were included. In addition, bibliographies of included articles and pertinent reviews were also manually performed to identify any additional relevant studies. Reporting of this meta-analysis is adhere to the PRISMA statement as described [12]. Titles and abstracts were screened by two independent reviewers and full articles were retrieved in cases of missing abstracts.

Study selection

Eligible studies were enrolled based on the following inclusion and exclusion criteria. Inclusion criteria: (1) case-control, cohort and randomized controlled trails as study design; (2) cholesterol efflux capacity detection method and baseline level of CEC were described; (3) patients with CAD and aged over 18 years; (4) reporting the risk of CAD in low and high CEC groups; (5) reporting the follow-up occurrence of MACE (death, myocardial infarction, and cerebrovascular events including stroke and transient ischemic attacks) or restenosis. Exclusion criteria: (1) Detecting the CEC level using unreported method; (2) heart failure not directly preceded by a CAD diagnosis; (3) conference abstract, reviews or letter to editor as study design. Full text data extraction was conducted by two independent evaluators.

Data abstraction and study quality assessment

Two authors independently screened the titles or abstracts, and got access to full-text of eligible articles. Following information were extracted from the included studies: (1) publication information: name of the first author, year of publication, geographical location; (2) baseline characteristics: type of CAD diseases, number of patients, mean age of patients, gender; CEC detection method, absolute level, cut-off point of CEC (3) follow-up information: definition of cardiac event, number of each event, follow-up time, fully adjusted risk estimate, adjustment for confounders, and study quality score. A nine-star Newcastle-Ottawa Scale (NOS) was applied to assess the quality and risk of bias of the included publications involving selection of study groups, comparability of groups, and ascertainment of outcomes. Studies that scored ≥7 stars are considered of high quality. Two independent evaluators executed the NOS assessment and any discrepancies were resolved by discussion with a third reviewer and reached an agreement.

Statistical analyses

All analyses were performed using Review Manager (RevMan) 5.3 (Cochrane Collection, Copenhagen, Denmark) or STATA 12.0 (StataCorp, TX, USA). CEC levels were compared between patients with or without CAD either as absolute values or dichotomized as high *vs.* low. The multivariate-adjusted RR and 95% CI for all-cause mortality, cardiac death, and cardiac events were pooled by comparing the high with the low CEC level group. Heterogeneity among the included studies was indicated by the I^2 statistic and Cochrane Q test. In case of I^2 statistic> 50% or p-value of Cochrane Q test< 0.1, a random effect model was applied. Otherwise, a fixed-effect model was selected. Subgroup analyses were conducted by the type of CAD (stable CAD or ACS). Sensitivity analysis was performed by a leave-one-out study approach in order to observe the reliability of the pooling risk summary. A visual funnel plot and the Egger's linear regression test were performed to examine the publication bias when the outcomes included at least 5 studies.

Results

Study selection and characteristics of the included studies

The study selection process is delineated in a flow chart of Fig.1. A total of 665 studies were potentially identified from the electronic database search and reference lists checking using our search strategy, and 458 studies were excluded because of their repetition after an overall review of the titles and abstracts. After excluding 166 other studies designed as case reports, letters to editor, review articles, in vitro studies, animal studies, 41 articles in full-text article were assessed for eligibility. Finally, 18 articles reporting outcomes of interest were included in the meta-analysis[2, 3, 7, 8, 10, 13–25]. Of them, 12 studies were designed as case-control studies and 6 were cohort studies. Thirteen studies reported the CEC levels in control and case group[3, 7, 8, 13–16, 18, 20–24]. Eight of them analyzed the association between CEC and the risk of stable CAD or ACS [7, 8, 16, 18, 19, 21–23]. Four studies reported the prognosis of stable CAD or ACS [2, 10, 17, 25].

A total number of 12,685 subjects were included, with sample sizes varying from 40 to 3,494 in individual study. Five studies enrolled ACS patients and eleven studies enrolled patients with stable CAD. An *ex vivo* detection system using J774 cells for measuring the CEC levels was applied in 11 of the included studies, and a THP–1 macrophage/monocyte system was use in 5 studies. Total NOS score of individual studies ranged from 6 to 8 stars. The main characteristics of the selected studies for comparing CEC levels and estimating the effect of CEC on the occurrence of heart diseases are summarized in Table 1. The characteristics of the studies reported the prognosis of CAD or ACS are summarized in Table 2.

Comparison of cholesterol efflux capacity level between CAD and non-CAD subjects

Thirteen studies presented data and comparison of the CEC levels in control and case group. As shown in Fig.2, a total of 3,334 patients with CAD or ACS were included with 3,336 control subjects. Twelve studies showed decreased CEC in CAD or ACS patients. A pooled mean difference between case and control group was −0.44 [95% CI: −0.63- −0.25] and a significant difference was indicated between the two groups with regarding to the comparison on CEC levels ($Z = 4.58$, $P < 0.001$). We then performed a subgroup analysis on stable CAD patients and ACS patients, and the results showed that CEC levels were significantly lower either in stable CAD ($Z = 3.50$, $P = 0.0005$) or ACS ($Z = 8.90$, $P<0.001$) patients comparing to the control (Fig.2a and 2b). Furthermore, we performed subgroup analysis considering the difference in presenting the values of CEC level. The data revealed the substantial difference between the case and groups, either expressed in arbitrary units (Fig.3a) or as a percentage of change (Fig.3b).

Baseline cholesterol efflux capacity and the occurrence risk of CAD

The association between baseline CEC levels with the risk of CAD or ACS were evaluated in 8 of the included studies. As shown in Fig.4a, the pooled odds ratios of the included studies were 0.65 [95% CI: 0.55–0.75]. When removing one study on ACS, the pooled odds ratio had no substantial changes [0.70, 95% CI: 0.64–0.76] (Fig.4b). We found there were significant associations between baseline CEC level and risk of CAD/ACS ($Z = 5.56$, $P<0.001$) or stable CAD ($Z = 7.84$, $P<0.001$).

Baseline cholesterol efflux capacity and the prognosis of CAD

Four cohort studies reporting the long-term follow up outcome of the CAD and ACS were included. The media follow-up time ranged from 3 years to 10.8 years. The pooled ORs of all-cause mortality were 0.39 [95%CI:0.20–0.77], and increase of CEC levels was significantly associated with the decrease of risk of death in these patients ($Z = 2.72$, $P = 0.007$) (Fig.5a). Besides, the combined ORs for cardiovascular mortality between higher and lower CEC groups were 0.34 [95% CI: 0.13–0.90], and significant association was suggested ($Z = 2.17$, $P = 0.03$) (Fig.5b). No significant associations between CEC levels with the risk of stroke or myocardial infarction were indicated in the pooled studies (Fig.5c and 5d).

Evaluation for publication bias

Funnel plot to evaluate publication bias is shown in Figure 6. The graph is fairly symmetric and only mild publication bias is suggested.

Discussion

Cardiovascular diseases rank the leading cause of death and global medical burden a in both developed and developing countries. However, the exact mechanisms for the occurrence and development of cardiovascular diseases are unrevealed. In this systematic review and meta-analysis, we pooled the cholesterol efflux capacity data for 12,685 subjects from 18 eligible published studies. The pooled data suggested that CEC levels were largely decreased in patients with stable CAD or ACS, and the decreased CEC levels were associated the poor prognosis of all-cause mortality and cardiovascular mortality in these patients. However, no exact correlation was found between CEC levels with the occurrence of stable CAD.

Numerous epidemiological studies revealed that decreased levels of high-density lipoprotein cholesterol (HDL-C) was associated with increased cardiovascular risk. However, pharmacological intervention aiming to raise serum HDL-C levels failed to reduce the incidence of cardiovascular disease events as assessed in several randomized controlled trials. Study by Hafiane et al. supposed that HDL-C mass did not reflect HDL functionality and macrophage-specific cholesterol efflux to apo A-I particles binding to the ABCA1 is considered the most relevant to atherosclerosis [26]. Cholesterol efflux from macrophages is considered a crucial step of reverse cholesterol transport that is responsible for maintaining normal

cholesterol balance. Previous study revealed that RCT had a strong inverse association with carotid intima-media thickness and CAD likelihood independent of HDL-C level [3]. Therefore, cholesterol efflux capacity reflects the global ability of cholesterol efflux from macrophages.

Our meta study included 11 case-control studies and 2 cohort studies for comparing the levels of CEC between non-CAD subjects and patients with stable CAD or ACS. The pooled data showed that almost all studies reported decrease of CEC in CAD patients except that described in study by Asztalos [14]. The controversy was explained by the authors for the influence of preβ–1 concentration and differences in the study populations or in lipid-modifying interventions. We further divided the whole sample into stable CAD and ACS, and significant decrease of CEC was found in these two subgroups. Besides, we noticed that the values of CEC were expressed either in percentage or activity in arbitrary units. It was also true for the significant lower levels of CEC in patient group in spite of the difference in data presentation.

Emerging evidence demonstrated that CEC had an inverse relationship with incidence of cardiovascular events in population-based studies and CEC improve cardiovascular disease risk prediction beyond conventional risk factors [26]. It was also concluded that measures of HDL function might be a better marker of cardiovascular risk and, possibly, of recurrent events than are HDL cholesterol levels [27]. In this meta-analysis, 8 studies detailed the association between CEC levels and occurrence risk of cardiovascular diseases. The combined studies showed that decreased CEC was significantly associated with the risk of coronary heart disease, and this association also existed in stable CAD. However, whether CEC level correlated with the occurrence of ACS was unexamined because only one study fulfilled this analysis.

Finally, we explored the relations between baseline CEC levels with the prognosis of CAD, and endpoints events including all-cause mortality, cardiovascular mortality, stroke and myocardial infarction were extracted and analyzed. A large-scale prospective cohort study by Liu *et al* [10] demonstrated a relationship between cholesterol efflux capacity and risk of all-cause and cardiovascular mortality in patients with CAD. Meanwhile, adding CEC to a model containing traditional cardiovascular risk factors significantly increased discriminatory power and predictive value of all cause and cardiovascular mortality in patients with CAD. Rohatgi et al. did not find an association between cholesterol efflux capacity and cardiovascular death because of small numbers of events [2]. In this pooled study, CEC was confirmed to be a predictor for all-cause and cardiovascular mortality for patients with CAD. However, no association was indicated between CEC and stroke or myocardial infarction.

In conclusion, our study revealed that cholesterol efflux capacity was significantly lower in patients with stable coronary artery diseases and acute coronary syndrome compared with the control subjects. Cholesterol efflux capacity levels was associated with the incidence of CAD and could serve as a predictor for all-cause and cardiovascular mortality. These findings support implementation of cholesterol efflux capacity into clinical practice and stress the need to establish reference values.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Competing interests All authors declare that they have no conflicts of interest.

Funding: None

Authors' contributions: HMY and JJP concepted and designed the study. HMY drafted of the manuscript. HMY, GYX and HLR collected the data. GYX and HLR analyzed and interpreted the data. HMY and JJP revised the manuscript for important content. All authors checked and approved the submission.

Acknowledgements: None

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article.

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Tables

Table 1 Summary of the characteristics of the included studies for cholesterol efflux capacity level comparison

Author	Region	Study design	Control	Case	Sample size	Ages(years)	CHD types	Ex vivo cells
Agarwala, 2015[13]	USA	case-control	120	55	175	69 ± 12 vs. 64 ±11	CAD	J774
Asztalos, 2018[14]	USA	case-control	100	100	200	55±16 vs.61±7	stable CAD	J774
Attia, 2007[15]	Tunisia	case-control	35	35	70	52.74 ± 7.81 vs. 56.75 ± 5.83	CAD	Fu5AH cells
Ebtehaj, 2019[16]	Sweden	case-control	354	351	705	59.0 ±10.9 vs. 59.1 ± 10.7	incident cardiovascular event	THP-1 macrophages
Ishikawa, 2015[18]	Japan	case-control	72	182	254	64.3 ± 9.8 vs. 66.2 ± 10.3	CAD	J774
Khera, 2011[19]	USA	nested case-control	314	314	628	51±8 vs.-62±9	CAD	J774
Luo, 2018[20]	China	case-control	90	120	210	63.09±8.25 vs. 63.96± 7.85	ACS	THP-1 monocytes
Luo, 2017[3]	China	case-control	99	140	239	62.81 ± 8.01 vs. 63.10 ± 8.42	ACS	THP-1 monocytes
Norimatsu, 2017[7]	Japan	prospective cohort	146	58	204	65(59-72)	stable angina	J774
Patel, 2013[8]	USA	nested case–control	46	23	69	57.8± 8 vs. 58.2± 10	angiographic CAD	J774
Saleheen, 2015[21]	UK	case-control study	1749	1745	3494	65±7.8 vs. 66·1 ±7·48	CAD	J774
Shao, 2014[22]	China	case-control	20	20	40		ACS	BHK cells
Stein, 2019 [23]	USA	cohort	465	465	930	45-85	baseline healthy	THP-1 monocytes
Wang, 2018[24]	China	cross-sectional case-control study	40	40	80	NA	CAD	J774

Table 2 Summary of the characteristics of the included studies for prognosis analysis

Author	Region	Study design	Sample size	Ages(years)	CHD types	Methods
Guerin, 2018[17]	France-Europe	prospective cohort	1609	63.4±14.1	acute MI	THP-1 macrophages
Liu, 2016[10]	China	prospective cohort	1737	40-75	CAD	J774
Rohatgi, 2014[2]	USA	cohort	2416	42 (36-51)	CAD	J774
Zhang, 2016[25]	China	prospective cohort	330	65±11	ACS	J774

Figures

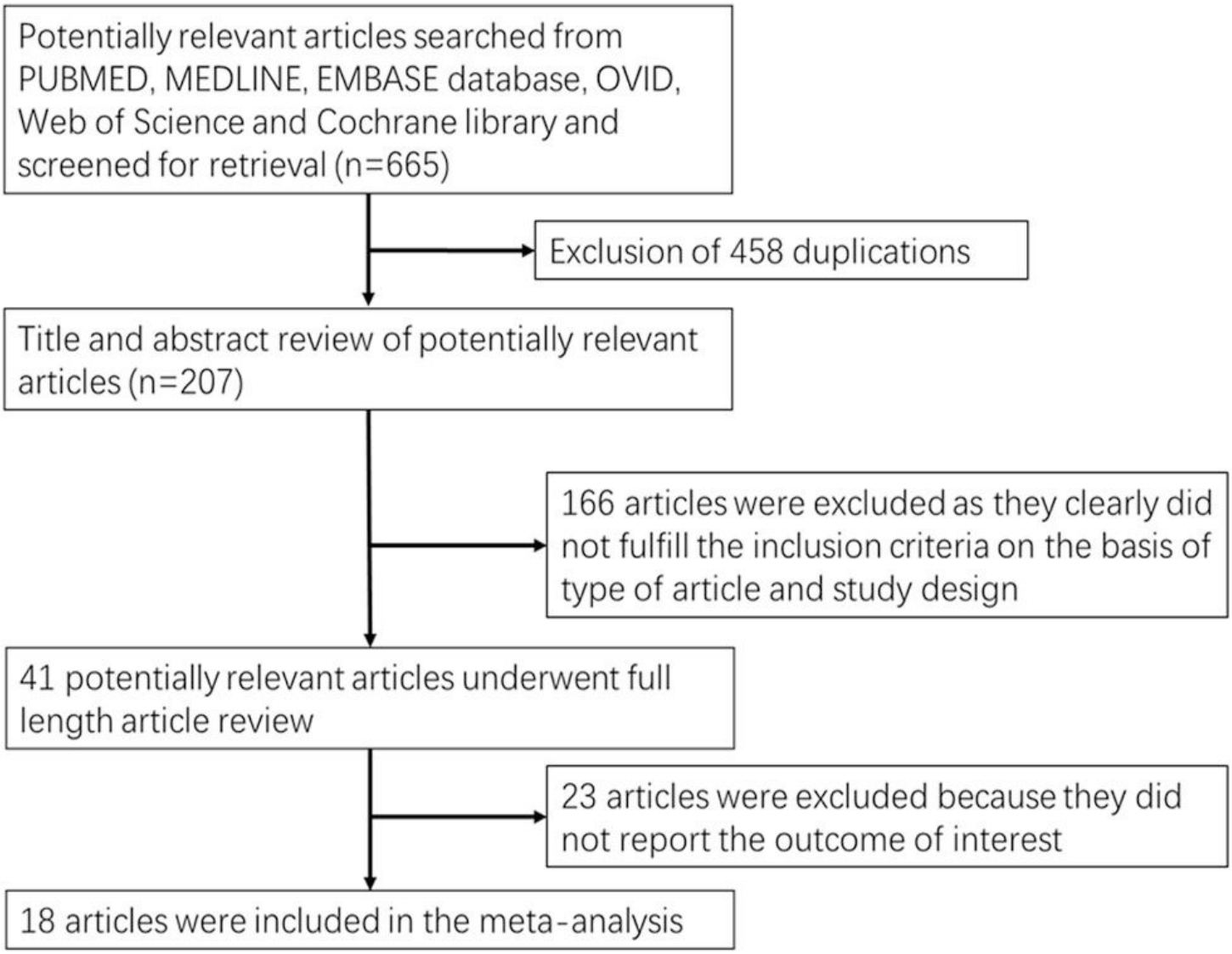

Figure 1

Flow chart of the included cholesterol efflux capacity studies for meta-analysis.

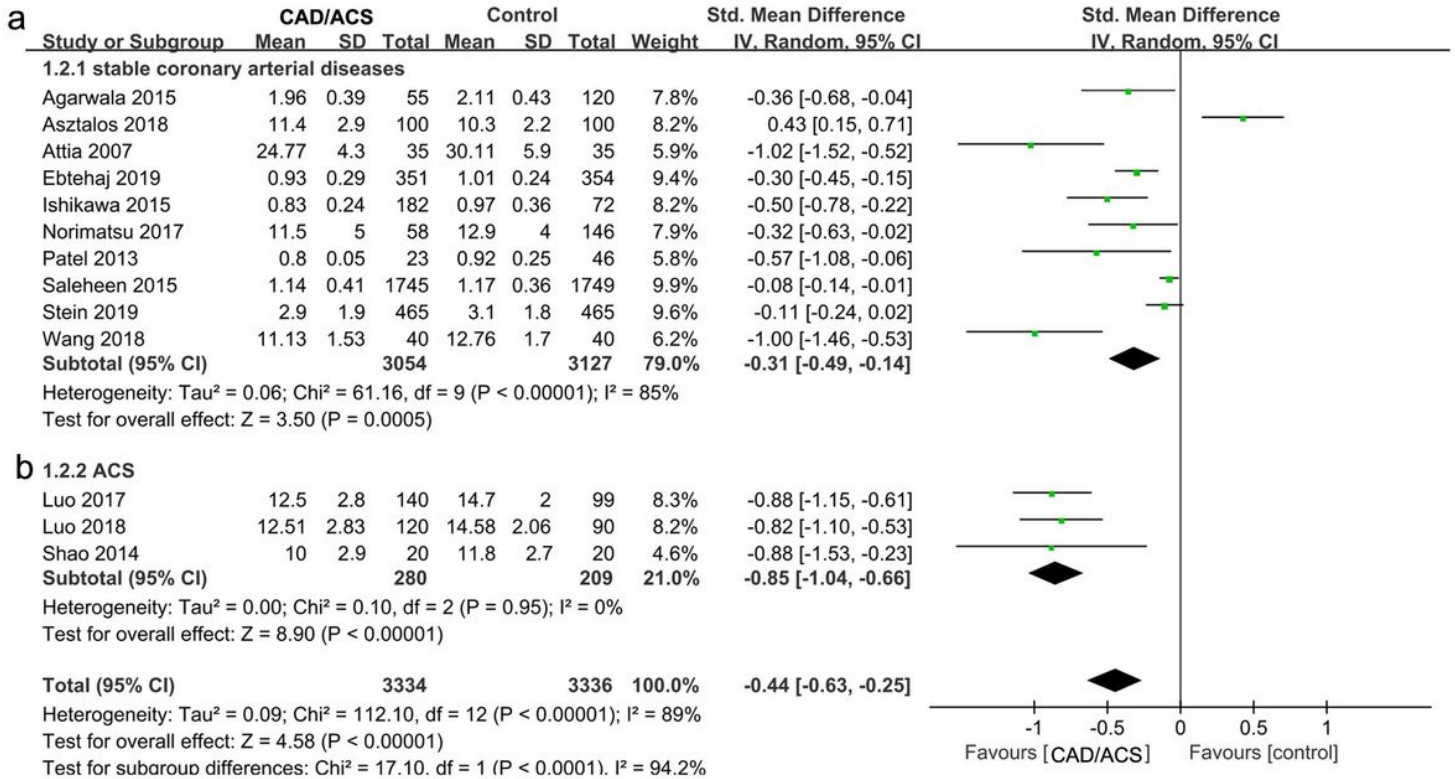

Figure 2

Comparison of mean cholesterol efflux capacity in patients with coronary heart diseases and control patients. (a) Mean cholesterol efflux capacity in patients with stable coronary artery diseases (b) Mean cholesterol efflux capacity in patients with acute coronary syndrome. Data are expressed as a mean difference and analyzed using a random effects model.

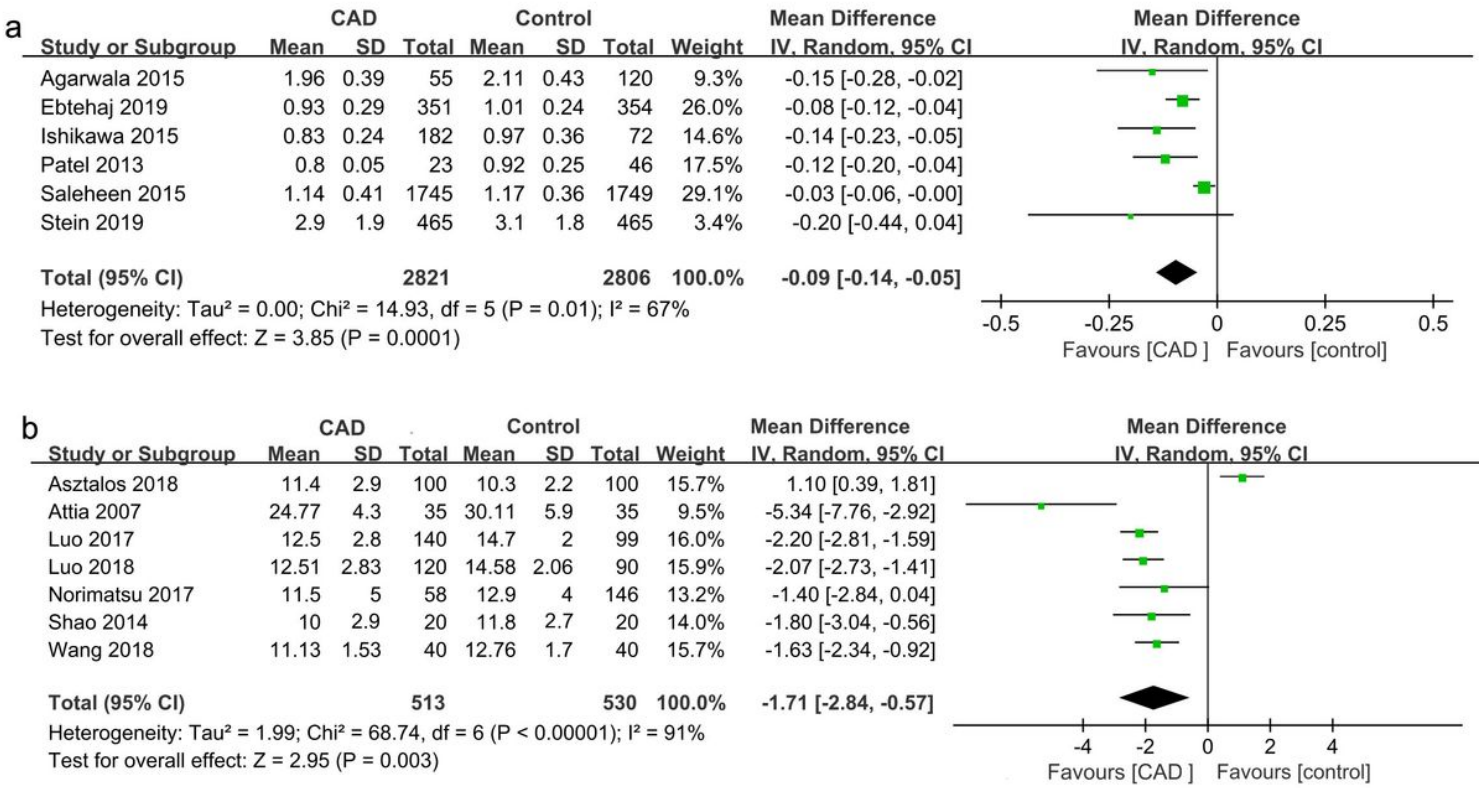

Figure 3

Subgroup analysis of mean cholesterol efflux capacity in patients and control patients. Data is expressed as a mean difference and analyzed using a random effects model. (a) Comparison of cholesterol efflux capacity expressed in arbitrary units. (b) Comparison of cholesterol efflux capacity expressed as a percentage.

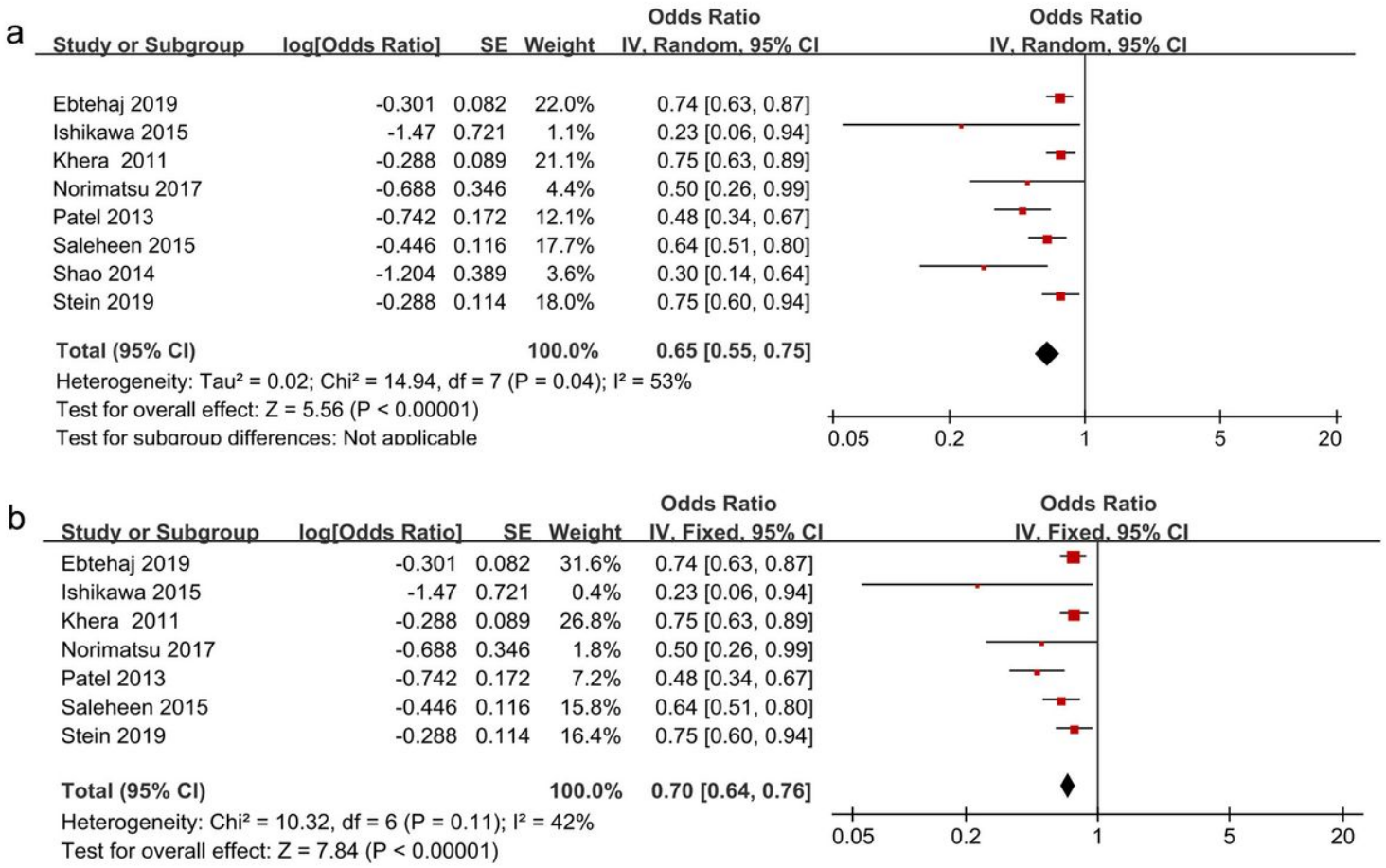

Figure 4

Effects of cholesterol efflux capacity on the risk of cardiovascular heart diseases. Data is expressed as a risk ratio and analyzed using a random effects model. (a) stable CAD and ACS; (b) ACS.

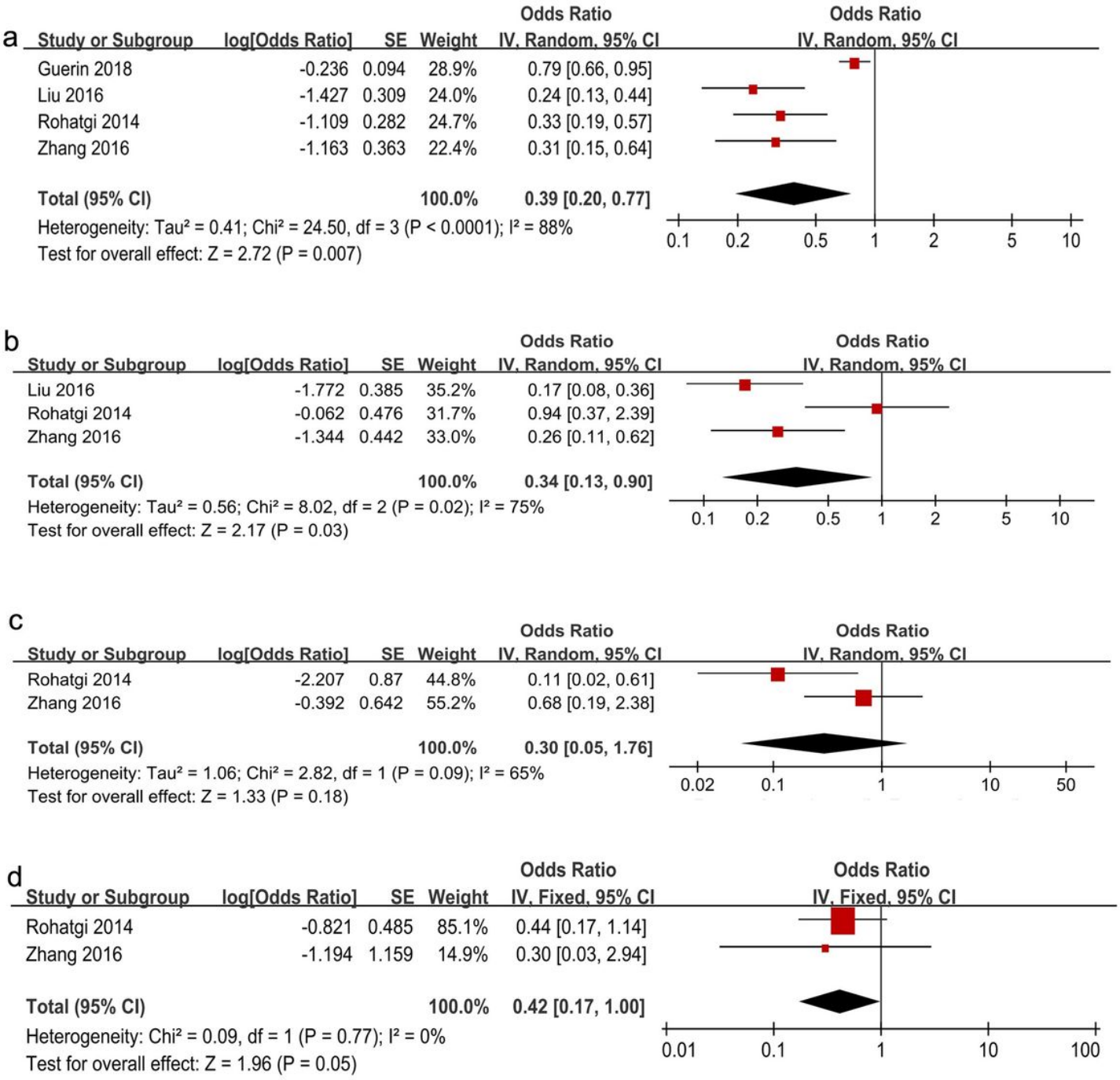

Figure 5

The predictive efficiency of cholesterol efflux capacity on the prognosis of CAD. (a) all-cause mortality; (b) cardiovascular mortality; (c) stroke and (d) myocardial infarction.

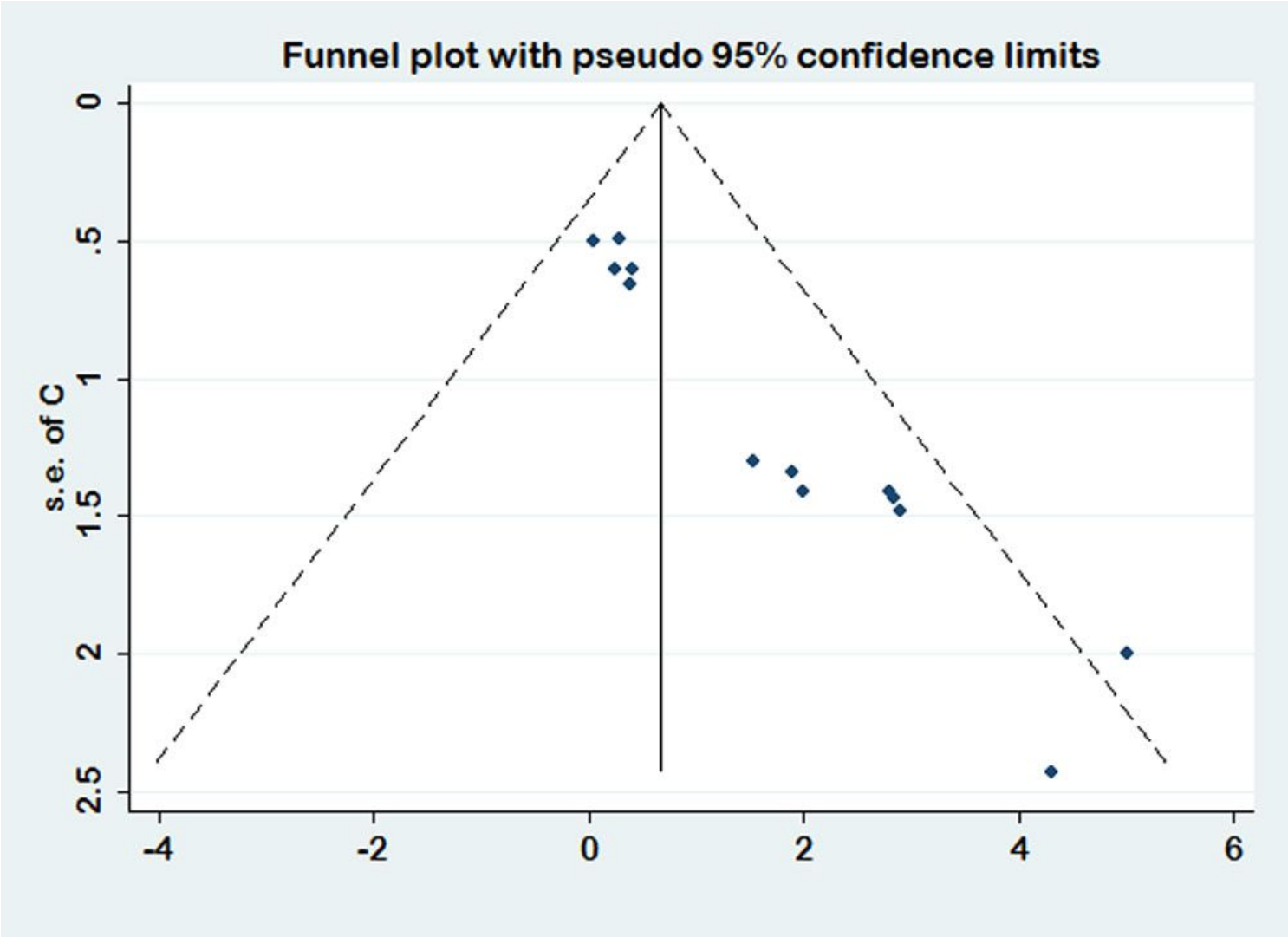

Figure 6

Funnel plot of the publication bias for studies involving the comparison of cholesterol efflux capacity