

# A Meta-Analysis of HDL Cholesterol Efflux Capacity and Concentration in Patients With Rheumatoid Arthritis

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## Research

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## Abstract

**Background:** Poor cholesterol efflux capacity (CEC) has been proposed to be an independent risk factor for cardiovascular diseases. However, the current evidences in the literature are inconsistent. This meta-analysis aimed to identify whether CEC is impaired or altered by drug therapy in individuals with rheumatoid arthritis (RA).

**Methods:** The PubMed, Embase, and Cochrane library databases were searched to identify studies on CEC in RA patients. The searches were focused on studies in human subjects that were published before 10 Sep 2020, without language restrictions. The primary outcomes were CEC and the high-density lipoprotein cholesterol (HDL-C) and C-reactive protein levels (CRP).

**Results:** A total of 11 eligible articles, including 6 observational and 5 intervention studies, were retrieved. The pooled results showed that CEC is not significantly lower in RA patients than in healthy controls (SMD: -0.34, 95% CI: -0.83 to 0.14), whereas the plasma HDL-C level is not significantly lower HDL-C levels (WMD: -3.91, 95% CI: -7.15 to -0.68). Furthermore, in the before-after studies, the CEC of RA patients (SMD: 0.20, 95% CI: 0.02 to 0.37) increased, but the plasma HDL-C level (WMD: 3.63, 95% CI: -0.13 to 7.39) remained at a similar level after anti-rheumatic treatment compared to the baseline. In addition, the funnel plot was relatively symmetric and did not suggest the presence of publication bias.

**Conclusion:** The current meta-analysis demonstrated that HDL-mediated CEC can be improved by the early control of inflammation and anti-rheumatic treatment in RA patients, which is independent of HDL-C levels. Future research is needed to determine whether therapeutic strategies to enhance CEC in RA patients have beneficial effects for preventing CVD.

## Introduction

Rheumatoid arthritis (RA), a chronic polyarthritis autoimmune disease that causes arthrosis impairment and even leads to disability [1], affects approximately 0.3%-1.0% of people worldwide [2]. RA leads to a heavy burden for both patients and society, and those living with RA have a significantly shorter life expectancy. A higher risk of cardiovascular diseases (CVDs) has been found in patients with RA than in the general population [3]. RA inflammation increases arterial stiffness, changes the lipid profile, and destabilizes plaques. Moreover, 60% of excess mortality among RA patients is attributed to CVDs [4], which is one of the most severe complications of RA and cannot be fully explained by traditional cardiovascular risk factors.

High-density lipoprotein cholesterol (HDL-C) is known as “good cholesterol” owing to its protective effects against CVDs [5]. Numerous studies have suggested that plasma HDL-C levels are also lower in the RA population than in the general population [6–8]. For example, a study noted that an average decrease by 9% in the plasma HDL-C level has been observed before the onset of symptoms among RA patients [9]. In addition, paradoxical associations among low lipid levels (i.e., total cholesterol (TC), LDL-C and HDL-C levels) and the ongoing risk of CVDs have been observed in patients with poorly controlled RA [10], while the initial reductions in these parameters have been shown to increase with anti-inflammatory treatment in patients with RA. Therefore, the European League Against Rheumatism suggested that the TC to HDL-C ratio is more appropriate for predicting the CVD risk in individuals with RA [11]. However, recent clinical trials have shown that HDL-C-raising therapies do not considerably reduce the risk of cardiovascular events in individuals at high risk [12–14]. Therefore, whether the concentrations of circulating HDL-C in patients with RA change even after anti-inflammatory treatment merits further investigation.

HDL has several key atheroprotective functions, including reverse cholesterol transport, endothelial function maintenance, anti-inflammatory activity and platelet aggregation inhibition [15]. Of these functions, reverse cholesterol transport (RCT) is an overriding process that promotes excess plasma cholesterol from the cell to the liver for catabolism [6]. Macrophage cholesterol efflux is the first critical step of RCT and is considered a key atheroprotective property [16]. The general methods for measuring cholesterol efflux capacity (CEC) include using radioisotope-labeled cholesterol that is labeled with [<sup>3</sup>H]-cholesterol (<sup>3</sup>H]-C) and fluorescence-labeled cholesterol to measure CEC [17, 18]. CEC has been proven to increase the risk of CVDs, which is independent of the plasma HDL-C level [19, 20]. However, the epidemiological data that have been used to explore the association between CEC and RA are inconsistent. Some of the previous studies have shown that the CEC is significantly lower in RA patients than in healthy controls, but others have failed to reach conclusions [21–30].

Therefore, to assess the conflicting results, the epidemiological evidence on the changes in CEC as well as HDL-C levels of RA patients were systematically reviewed and meta-analyzed.

## Methods

### Literature Search and Selection Criteria

We conduct this meta-analysis and written the manuscript according to the PRISMA guidelines. The study have been registrated in PROSPERO database and the registration number is CRD42020209010. This meta-analysis was conducted and written the manuscript according to the PRISMA guidelines. EMBASE, MEDLINE and Cochrane Library databases were searched for records reporting CEC in patients with RA. Searches were focused on human subjects with no restriction on language and published before 10 Sep 2020. To avoid missing any relevant studies, we also searched manually the bibliographies of identified studies and review papers. The following medical subject headings terms and keywords were used alone or in combination: “high density lipoprotein” or “HDL” or “HDL-C”, “rheumatoid arthritis” or “RA”, “high density lipoprotein function” or “cholesterol efflux capacity” or “CEC” or “HDL-mediated cholesterol efflux”.

### Study selection

The studies were initially assessed according to the following inclusion criteria: 1) intervention and observational studies; 2) studies including only subjects older than 18 years of age; 3) studies including RA patients who fulfilled the 1987 or 2011 the American College of Rheumatology (ACR) criteria, regardless of whether cardiovascular disease was concomitant; 4) studies including healthy control subjects without inflammatory conditions; and 5) studies in which the

outcomes of interest were CEC and HDL-C levels. The exclusion criteria were as follows: 1) studies that did not report CEC and HDL-C levels; 2) studies with a repeated study population; and 3) animal research, letters, or meeting abstracts.

Two researchers independently removed the duplicate records and screened the titles and abstracts to identify the potentially relevant articles. Two researchers independently screened the full texts to identify additional eligible studies. If the data were duplicated included in more than one study, the study with the largest dataset and population was selected for inclusion.

### **Data extraction and outcome measures**

Two reviewers independently extracted data on each eligible article by using a standardized data collection form, including the first author's name, publication year, study design, country, patient characteristics, sample size, sex distribution, CEC assay methods, plasma HDL-C levels, CEC, Disease Activity Score for 28 joints (DAS28), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), records of all medicines taken, length of the follow-up period and study outcome. Data that were reported as medians and ranges were converted to means and standard deviations using Hozo's approach [31]. Although some participants were followed-up for varying durations, the data collected after the longest period were extracted. If necessary, we contacted the authors of the studies for additional data. Disagreements between reviewers were resolved by discussion with a third author.

### **Quality and risk assessment**

Two quality rating scales were used to assess the methodological quality of the studies. First, the quality of the observational studies was evaluated by the Newcastle-Ottawa Scale (NOS) [32]. According to the guidelines, three aspects were assessed: selection, comparability and exposure. Scores of 1-4 were defined as low quality, and scores of 5-9 were defined as high quality. Second, the Downs and Black (D&B) scale was adopted to analyze the risk of bias in nonrandomized and randomized studies from a list of 27 criteria. The last question about power was replaced by a modified version that was published in previous systematic reviews [33]. Scores of 1-14 were defined as low quality, and scores of 15-32 were defined as high quality.

### **The assessment of cumulative evidence**

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was assessed quality of the evidence [34]. The GRADE assessment was performed using GRADEpro software (McMaster University, Hamilton, Canada) [35].

### **Statistical Analysis**

The data from the observational studies and intervention studies were analyzed. Means and standard deviation (SDs) were commonly used to evaluate the changes in CEC and plasma HDL-C levels in RA patients. For the continuous variables, the standardized and weighted mean differences (SMD & WMD) as well as the corresponding 95% confidence intervals (CIs) were calculated. SMD was used combining continuous data, when studies have used different instruments to measure the same construct. Otherwise, WMD was chosen to synthesize the results. For the intervention studies, the baseline data were recorded as the control data, and the data from the end of the treatment phase were collected as the experimental data. The level of heterogeneity across the eligible studies was assessed by using Cochran's Q test and  $I^2$  statistic. When heterogeneity was low ( $I^2 < 50\%$ ) and  $p < 0.05$ , the fixed effect model will be applied to synthesize the data, while  $I^2 > 50\%$  and  $p > 0.05$ , the random effect model will be used. Subgroup analysis was additionally performed to determine the sources of heterogeneity according to the mean age of participants and DAS28.

Sensitivity analysis was subsequently conducted by comparing two different models to enhance the robustness of the results. In addition, sensitivity analysis was also assessed by excluding one study at a time. The risk of publication bias was assessed visually by funnel plots and further quantified using Egger's and Begg's test, where  $P < 0.1$  indicated potential publication bias [36,37]. All analyses were performed using STATA, version 14.0 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP), and Review Manager, version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

## **Results**

### **Literature search results and study characteristics**

A total of 2270 articles were initially retrieved from the various databases. After the duplicate articles were removed and the titles and abstracts were screened, 2235 more articles were excluded. The full texts of the remaining 35 articles were reviewed according to the inclusion criteria. Eventually, only 11 articles were included. Twenty-six articles were excluded for the following reasons: 6 studies did not assess the outcome of CEC; 3 were reviews; 10 were abstracts of articles for which the full texts were not available; and 6 were animal studies. For the rest of the studies listed, there were a total of 6 observational studies and 5 intervention studies. The whole screening process is shown in the flow chart in Fig 1.

Table 1 and Table 2 show the main characteristics of the included studies. These 11 articles were published from 2012 to 2019. Of these studies, 7 were conducted in the USA, 3 were conducted in the UK, and 1 was conducted in Spain. The sample size of these studies ranged from 36 to 401; several of them had a sample size ranging from 50 to 100, which was considered a modest size, and 3 other studies had a large sample size ( $> 100$ ). The average age of the participants ranged from 42 to 65 years. Cases and controls were matched by gender, age and body mass index (BMI) in the case-control studies. According to the NOS and D&B standard criteria, the quality scores of the 6 observational studies ranged from 5 to 8, which indicated moderate to high quality. Moreover, the quality scores of the intervention studies ranged from 11 to 17, and 2 studies were considered high-quality and 3 were considered low-quality studies. Most observational studies did not report the nonresponse rate, and the D&B scores indicated that the intervention studies had weak external validity.

### **The main outcome: changes in the CEC and HDL-C levels among RA patients**

A total of 5 observational studies reported the CEC in both the case and control groups, with a total of 809 participants. The pooled results showed that the CEC of the RA patients was not significantly lower than that of the healthy controls (SMD: -0.34, 95% CI: -0.83 to 0.14;  $I^2 = 89%$ ,  $P$  for heterogeneity < 0.001). In addition, 6 studies including 845 subjects in which the plasma HDL-C levels were measured showed that patients with RA had lower HDL-C levels (WMD: -3.91, 95% CI: -7.15 to -0.68,  $I^2 = 64%$ ,  $P$  for heterogeneity = 0.020) (Fig 2). In addition, the TC and LDL-C plasma levels but not the TG level significantly differed between the two groups (see Additional file 1).

A total of 5 before-after studies that included 8 trials revealed a statistically significant elevation of CEC in RA patients who had taken anti-rheumatic medications compared to the baseline (SMD: 0.20, 95% CI: 0.02 to 0.37;  $I^2 = 0%$ ,  $P$  for heterogeneity = 0.680). In addition, only 4 intervention studies were suitable for inclusion in the analysis of the change in HDL-C levels. The plasma HDL-C levels was increased in the RA patients after anti-rheumatic drug treatment than at baseline (WMD: 3.63, 95% CI: -0.13 to 7.39). The heterogeneity was quite high ( $I^2 = 0%$ ,  $P$  for heterogeneity = 0.640) (Fig 3). Other lipid parameters, such as LDL-C, TC and TG levels, were not significantly different between the baseline and follow-up (see Additional file 2).

### The secondary outcome: the levels of CRP and ESR in RA

In the observational studies, five studies reported the CRP level as a continuous variable. The pooled analysis data showed that the CRP level was higher in the RA patients than in the healthy controls (SMD: 2.74, 95% CI: 1.13 to 4.36;  $I^2 = 98%$ ,  $P$  for heterogeneity < 0.001). (Fig 2). However, the CRP level significantly decreased after anti-rheumatic drug therapy in the intervention studies (SMD: -1.61, 95% CI: -1.89 to -1.32;  $I^2 = 2%$ ,  $P$  for heterogeneity = 0.360). A high level of ESR has been found in patients with RA (SMD: 1.22, 95% CI: 0.66 to 1.78;  $I^2 = 83%$ ,  $P$  for heterogeneity = 0.003). The pooled SMD from 5 trials revealed the level of ESR was decrease in RA patient who received anti-inflammation therapy (SMD: -1.98, 95%CI: -3.23 to -0.74;  $I^2 = 92%$ ,  $P$  for heterogeneity < 0.001) (Fig 3).

### Subgroups and sensitivity analysis

Substantial heterogeneity were observed in our meta analysis for CEC, HDL-C,CRP and ESR. Evaluation of subgroup by DAS28 provided similar results as the previous overall estimate. A heterogeneity reduction of HDL-C was significant when subgroup analysis stratified by age (< 55 years/  $\geq$  55 years) was conducted ( $I^2 = 35.0%$ ;  $I^2 = 19.6%$ , respectively). Part of the heterogeneity might be explained by the variables (see Additional file 3). The sensitivity analysis showed that the overall effect sizes of CEC, CRP and ESR obtained using the fixed-effects and random-effects models were identical, and no individual study significantly affected the pooled results. When we excluded two studies [25,26]. However, the result of HDL-C was different from the previous conclusion. (see Additional file 4 and 5). Two studies has substantial impact on the robustness of overall estimate through excluding one study at a time.

### Publication bias

Funnel plots for CEC, HDL and CRP were created to assess publication bias (Fig 4). The presence of publication bias was also evaluated by using Begg's and Egger's tests. Currently, the results of Egger's test ( $P_{CEC} = 0.201$ ;  $P_{HDL-C} = 0.699$ ;  $P_{CRP} = 0.932$ ;  $P_{ESR} = 0.475$ ) and Begg's test ( $P_{CEC} = 0.221$ ;  $P_{HDL-C} = 0.452$ ;  $P_{CRP} = 0.806$ ;  $P_{ESR} = 1.000$ ). However, the statistical power for detecting publication bias was low due to the small number of studies.

### The assessment of cumulative evidence

The GRADE rating for the quality of evidence on each outcome parameter was showed in additional file 6. The CEC, HDL-C, and CRP indexes was scored as "very low quality" because of risk of limitations, inconsistency and imprecision.

### Strength and study limitations

Several potential limitations should be taken into consideration. First, the quality of the meta- and pooled analyses largely depended on the quality of the original studies. Among the studies included, there were six observational studies that were susceptible to selection and recall bias. Second, substantial heterogeneity was reported in this meta-analysis. Therefore, sensitivity analyses were conducted to confirm the stability of the results. Third, there is currently no established gold standard for ex vivo CEC assays. In addition, the rate of cholesterol efflux was expressed in various forms, leading to slight differences among the reported CEC values. Thus, to minimize the variation, the standardized effect size was calculated. Fourth, the small number of included studies can limit the ability to interpret the funnel plot.

## Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to simultaneously evaluate whether the CEC and plasma HDL-C levels are decreased or altered by drug therapy in individuals with RA. The results did not show any significant changes in the HDL-mediated CEC, while the plasma HDL-C level was not significantly lower in the patients with RA than in the healthy subjects but was significantly decreased in the RA Patients with moderate BMI. In addition, stratified analysis did not influence the tendency of the CEC or HDL-C levels in the individuals with RA. However, it is interesting that in the intervention studies, elevated CEC was seen in RA patients who were taking their medications, as well as a reduction in the CRP level compared to the baseline level. These findings suggested that the inhibition of inflammation might improve HDL-mediated CEC. Although the plasma HDL-C levels slightly increased after RA treatment, the difference was not significant, which indirectly indicated that CEC is more sensitive than is the HDL-C level. Several potential mechanisms can thus be proposed to explain the changes in CEC, plasma HDL-C and CRP levels in patients with RA.

In 2012, Charles-Schoeman et al. first reported that there was no significant difference in CEC between RA patients and control subjects but that CEC was inversely associated with high disease activity in RA patients [26]. Subsequently, another cross-sectional study published in 2014 that analyzed different CEC efflux pathways demonstrated that ABCG1-mediated CEC was markedly impaired in individuals with RA [24]. Furthermore, in 2015, another study conducted

by Ronda et al. showed that CEC can be modified by methotrexate (MTX) but not MTX + adalimumab (ADA) in RA patients [30]. A study reported in 2016 showed that the net cholesterol efflux did not change after RA therapy [27]. Since then, 11 population-based studies have been published, reporting inconsistent results.

RA is an autoimmune disease associated with chronic inflammation, which might lead to multiple changes in the HDL structure and changes in HDL function [38]. First, most patients with RA have elevated levels of certain proinflammatory cytokines, including CRP, interleukin-6 in their blood. Many studies have indicated that HDL-C levels were dramatically reduced during inflammation, and one possible mechanism underlying these changes associated with the live phospholipid transfer protein (PLTP) expression. For example, Audo et al. showed that PLTP was overexpressed in the joints of RA patients, causing active inflammation[39]. Furthermore, Jiang et al. demonstrated that the plasma HDL apolipoproteins was obviously attenuated by reduced lasma PLTP activity, which demonstrated that the surface components of triglyceride-rich lipoproteins has a positive role in keeping normal HDL levels [40]. In subgroup analysis by BMI, the result show that the plasma HDL-C levels were significantly decreased in the RA patients compared to the healthy groups, which suggested that the inflammatory status and severity of patients with RA was inversely related to the plasma HDL-C levels. However, the plasma HDL-C levels did not change significantly after RA treatment.

Second, there is now substantial evidence suggesting that a high inflammation status can limit the capacity for HDL to promote cholesterol efflux from macrophages [41]. McGillicuddy et al. conducted a study in mice found that RCT process were impaired by acute inflammation, decreasing HDL acceptor function, cholesterol efflux capacity, and cholesterol elimination [42]. Thus, the inflammatory status in patients with RA affects not only the rate of cholesterol efflux but also other processes in RCT. Surprisingly, in the meta-analysis, CEC did not significantly differ between the RA and control subjects. It is possible that the routinely measured baseline CEC in RA patients may not be accurate due to fluctuations in the inflammatory status. Moreover, although several studies used a few different approaches to measure CEC, some of them might have underestimated the actual cholesterol efflux. However, a large quantity of population-based evidence has demonstrated that CEC is a sensitive predictor of the risk of CVD, regardless of the circulating HDL-C concentration [43, 44]. In addition, CEC significantly increases in patients with RA after medical care, followed by a reduction in the CRP level compared to the baseline level, while the HDL-C level does not significantly change after anti-rheumatoid treatment. These findings indirectly indicate that CEC might be a more sensitive indicator than the HDL-C level in the prevention of CVDs in individuals with RA. Generally, effectively controlling inflammation in individuals with RA might help improve the function of HDL. Some possible mechanisms have been proposed to determine the specific role of an increased CEC in preventing CVDs in patients with RA. Additional larger-scale population-based studies and experimental studies are needed to confirm the fundamental roles and mechanisms.

Heterogeneity poses an important challenge in conducting and interpreting the results of meta-analyses [45]. Subgroup analysis was conducted to evaluate the heterogeneity in the CEC and HDL-C levels. The analysis results showed that age is the source of statistical heterogeneity in HDL levels. Sensitivity analysis was performed to enhance the robustness and reliability of the results. The result of HDL-C levels was not significant decrease in patients with RA when excluded two studies [25, 26]. Therefore, we need to treat this result with caution.

Several potential limitations should be taken into consideration. First, the quality of the meta- and pooled analyses largely depended on the quality of the original studies. Among the studies included, there were six observational studies that were susceptible to selection and recall bias. Second, substantial heterogeneity was reported in this meta-analysis. Therefore, sensitivity analyses were conducted to confirm the stability of the results. Third, there is currently no established gold standard for ex vivo CEC assays. In addition, the rate of cholesterol efflux was expressed in various forms, leading to slight differences among the reported CEC values. Thus, to minimize the variation, the standardized effect size was calculated. Fourth, the small number of included studies can limit the ability to interpret the funnel plot.

## Conclusions

The current meta-analysis demonstrated that HDL-mediated CEC can be improved by the early control of inflammation and anti-rheumatic treatment in RA patients, which does not affect the HDL-C level. Additional studies with larger sample sizes and consensus-based methodologies are needed to determine the role of CEC in predicting CVD events in individuals with RA and whether therapeutic strategies to enhance CEC in individuals with RA have beneficial effects for preventing CVD.

## Abbreviations

RA Rheumatoid arthritis

CEC Cholesterol efflux capacity

CVD Cardiovascular diseases

OS Oxidative stress

MPO Myeloperoxidase

HDL-C High-density lipoprotein cholesterol

TC Total cholesterol

LDL-C Low-density lipoprotein cholesterol

TG Triglycerides

EULAR The European League Against Rheumatism

RCT Reverse cholesterol transport

MTX Methotrexate

ADA Adalimumab

PLTP Phospholipid transfer protein

DAS28 Disease Activity Score for 28 joints

CRP C-reactive protein

D&B Downs and Black scale

NOS Newcastle-Ottawa Scale

SMD Standardized mean differences

WMD Weighted mean differences

SD Standard deviation

95%CI 95% Confidence intervals

95%PI 95% Protective intervals

BMI Body mass index

## Declarations

### Availability of data and materials

Not applicable.

### Authors' contribution

Study concept and design: CQ-L and JH. Data extraction and analysis: B-BX, YL and TL. Manuscript drafting: B-BX and CQ-L. All authors were involved in data analysis, drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Conflict of interest

The authors declare that they have no competing interest.

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## References

1. Sangha O. Epidemiology of rheumatic diseases. *Rheumatology (Oxford)* 2000;39:3-12.
2. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. *Bull World Health Organ* 2003;81:646-56.
3. Symmons DP, Gabriel SE. Epidemiology of CVD in rheumatic disease, with a focus on RA and SLE. *Nat Rev Rheumatol* 2011;7:399-408.

4. Meune C, Touze E, Trinquart L, Allanore Y. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. *Rheumatology (Oxford)* 2009;48:1309-1313.
5. Rader DJ, Hovingh GK. HDL and cardiovascular disease. *Lancet* 2014;384:618-25.
6. Alsawalay AM, Fathi AI, Kamel RA, Ewis I. Correlation between serum osteoprotegerin and atherosclerotic vascular disorders in rheumatoid arthritis patients. *The Egyptian Rheumatologist* 2012;34:35-42.
7. Vergeer M, Holleboom AG, Kastelein JJ, Kuivenhoven JA. The HDL hypothesis: does high-density lipoprotein protect from atherosclerosis? *J Lipid Res* 2010;51:2058-73.
8. Kim J-Y, Lee E-Y, Park JK, Song YW, Kim J-R, Cho KH. Patients with Rheumatoid Arthritis Show Altered Lipoprotein Profiles with Dysfunctional High-Density Lipoproteins that Can Exacerbate Inflammatory and Atherogenic Process. *PLoS One* 2016;11:e0164564.
9. Nurmohamed MT. Atherogenic lipid profiles and its management in patients with rheumatoid arthritis. *Vasc Health Risk Manag* 2007;3:845-52.
10. Myasoedova E, Crowson CS, Kremers HM, Roger VL, Fitz-Gibbon PD, Thorneau TM, et al. Lipid paradox in rheumatoid arthritis: The impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. *Ann Rheum Dis* 2011;70:482-7.
11. Chodara AM, Wattiaux A, Bartels CM. Managing Cardiovascular Disease Risk in Rheumatoid Arthritis: Clinical Updates and Three Strategic Approaches. *Curr Rheumatol Rep* 2017;19:16.
12. Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Desvignes-Nickens P, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy *N Engl J Med* 2011;365:2255-2267.
13. Taylor AJ. Given the ENHANCE trial results, ezetimibe is still unproven. *Cleve Clin J Med* 2008;75:497-506.
14. Brown BG, Taylor AJ. Does ENHANCE diminish confidence in lowering LDL or in ezetimibe?. *N Engl J Med* 2008;358:1504-1507.
15. Rosenson RS, Brewer HB Jr, Davidson WS, Fayad ZA, Fuster V, Goldstein J, et al. Cholesterol efflux and atheroprotection: advancing the concept of reverse cholesterol transport. *Circulation* 2012;125:1905-1919.
16. Jeong SJ, Lee MN, Oh GT. The Role of Macrophage Lipophagy in Reverse Cholesterol Transport. *Endocrinol Metab (Seoul)* 2017;32:41-46.
17. Liu C, Zhang Y, Ding D, Li X, Yang Y, Li Q et al. Cholesterol efflux capacity is an independent predictor of all-cause and cardiovascular mortality in patients with coronary artery disease: A prospective cohort study. *Atherosclerosis*. 2016;249:116-124.
18. Shimizu T, Miyazaki O, Iwamoto T, Usui T, Sato R, Hiraishi C, et al. A new method for measuring cholesterol efflux capacity uses stable isotope-labeled, not radioactive-labeled, cholesterol. *J Lipid Res*. 2019;60:1959-1967.
19. Kosmas CE, Martinez I, Sourlas A, Bouza KV, Campos FN, Torres V, et al. High-density lipoprotein (HDL) functionality and its relevance to atherosclerotic cardiovascular disease. *Drugs Context* 2018;7:212525.
20. Rohatgi A, Khera A, Berry JD, Givens EG, Ayers CR, Wedin KE, et al. HDL cholesterol efflux capacity and incident cardiovascular events. *N Engl J Med* 2014;371:2383-2393.
21. Ronda N, Favari E, Borghi MO, Ingegnoli F, Gerosa M, Chighizola C, et al. Impaired serum cholesterol efflux capacity in rheumatoid arthritis and systemic lupus erythematosus. *Ann Rheum Dis* 2014;73:609-15.
22. Vivekanandan-Giri A, Slocum JL, Byun J, Tang C, Sands RL, Gillespie BW, et al. High density lipoprotein is targeted for oxidation by myeloperoxidase in rheumatoid arthritis. *Ann Rheum Dis* 2013;72:1725-31.
23. Charles-Schoeman C, Lee YY, Grijalva V, Amjadi S, FitzGerald J, Olmos JM, et al. Cholesterol efflux by high density lipoproteins is impaired in patients with active rheumatoid arthritis. *Ann Rheum Dis* 2012;71:1157-62.
24. O'Neill F, Charakida M, Topham E, McLoughlin E, Patel N, Sutill E, et al. Anti-inflammatory treatment improves high-density lipoprotein function in rheumatoid arthritis. *Heart* 2017;103:766-73.
25. Ormseth MJ, Yancey PG, Yamamoto S, Oeser AM, Gebretsadik T, Shintani A, et al. Net cholesterol efflux capacity of HDL enriched serum and coronary atherosclerosis in rheumatoid arthritis. *IJC Metab Endocr* 2016;13:6-11.
26. Tejera-Segura B, Macia-Diaz M, Machado JD, de Vera-Gonzalez A, Garcia-Dopico JA, OlmosNJM, et al. HDL cholesterol efflux capacity in rheumatoid arthritis patients: contributing factors and relationship with subclinical atherosclerosis. *Arthritis Res Ther* 2017;19:113.
27. Ronda N, Greco D, Adorni MP, Zimetti F, Favari E, Hjeltnes G, et al. Newly identified antiatherosclerotic activity of methotrexate and adalimumab: complementary effects on lipoprotein function and macrophage cholesterol metabolism. *Arthritis Rheumatol* 2015;67:1155-1164.
28. Liao KP, Playford MP, Frits M, Coblyn JS, Iannaccone C, Weinblatt ME, et al. The association between reduction in inflammation and changes in lipoprotein levels and HDL cholesterol efflux capacity in rheumatoid arthritis. *J Am Heart Assoc* 2015;4:e001588.
29. Ormseth MJ, Yancey PG, Solus JF, Bridges SL Jr, Curtis JR, Machado JD, et al. Effect of drug therapy on net cholesterol efflux capacity of high-density lipoprotein-enriched serum in rheumatoid arthritis. *Arthritis Rheumatol* 2016;68:2099-105.
30. Ferraz-Amaro I, Hernández-Hernández MV, Tejera-Segura B, Delgado-Frías E, Macía-Díaz M, Linton MF, et al. Effect of IL-6 Receptor Blockade on Proprotein Convertase Subtilisin/Kexin Type-9 and Cholesterol Efflux Capacity in Rheumatoid Arthritis Patients. *Horm Metab Res* 2019;51:200-209.
31. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005;5:13.
32. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses, 2012. Available from: [http://www.ohrica/programs/clinical\\_epidemiology/oxfordasp](http://www.ohrica/programs/clinical_epidemiology/oxfordasp).
33. Sohanpal R, Hooper R, Hames R, Priebe S, Taylor S. Reporting participation rates in studies of non-pharmacological interventions for patients with chronic obstructive pulmonary disease: a systematic review. *Syst Rev* 2012;1:66.

34. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol* 2011; 64: 380–382.
35. GRADE Working Group. GRADEpro. GRADE's software for Summary of Findings tables, Health Technology Assessment and Guidelines. Available from <https://gradepro.org/2015>.
36. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088-101.
37. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj* 1997;315:629-34.
38. Feingold KR, Grunfeld C. Effect of inflammation on HDL structure and function. *Curr Opin Lipidol* 2016;27:521-530.
39. Audo R, Deckert V, Daien CI, Che H, Elhmioui J, Lemaire S, et al. PhosphoLipid transfer protein (PLTP) exerts a direct pro-inflammatory effect on rheumatoid arthritis (RA) fibroblasts-like-synoviocytes (FLS) independently of its lipid transfer activity. *PLoS One* 2018;13:e0193815.
40. Jiang XC, Bruce C, Mar J, Lin M, Ji Y, Francone OL, et al. Targeted mutation of plasma phospholipid transfer protein gene markedly reduces high-density lipoprotein levels. *J Clin Invest* 1999;103:907-14.
41. Malik P, Berisha SZ, Santore J, Agatista-Boyle C, Brubaker G, Smith JD. Zymosan-mediated inflammation impairs in vivo reverse cholesterol transport. *J Lipid Res* 2011;52:951–957.
42. McGillicuddy FC, de la Llera Moya M, Hinkle CC, Joshi MR, Chiquoine EH, Billheimer JT, et al. Inflammation impairs reverse cholesterol transport in vivo. *Circulation* 2009;119:1135-45.
43. Anastasius M, Kockx M, Jessup W, Sullivan D, Rye KA, Kritharides L. Cholesterol efflux capacity: An introduction for clinicians. *Am Heart J* 2016;180:54-63.
44. Mortensen MB, Afzal S, Nordestgaard BG, Falk E. The high-density lipoprotein-adjusted SCORE model worsens SCORE-based risk classification in a contemporary population of 30,824 Europeans: the Copenhagen General Population Study. *Eur Heart J* 2015;36:2446-2453.
45. Threapleton DE, Greenwood DC, Evans CE, Cleghorn CL, Nykjaer C, Woodhead C, et al. Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ* 2013;347:f6879.

## Tables

Table 1  
Characteristics of observational studies in this systematic review and meta-analysis

Authors	Country	Study type	Subjects (female, %)	Duration <sup>a</sup> (month)	Assay method of CEC	Labeled-cholesterol	Quality score	Outcome summary	BMI
Ronda et al., 2013 [24]	USA	Case-control	52 (86.7)	NA <sup>c</sup>	J774, Fu5AH, CHO-k1 to ApoB-depleted serum	<sup>3</sup> H-cholesterol	5	CEC <sup>b</sup> is impaired in RA	N/A <sup>c</sup>
Vivekanandan-Giri et al., 2013 [25]	USA	Case-control	34 (58.6)	4.0	J774 to ApoB-depleted serum	<sup>3</sup> H-cholesterol	5	CEC was diminished in RA patients	Case: 27.9 ± 5.4 Control: 27.8 ± 7.4
Charles-Schoeman et al., 2015 [26]	USA	Case-control	66 (82.0)	12.8	RAW264.7 to isolated HDL	<sup>3</sup> H-cholesterol	9	no difference of CEC between RA patients and controls	Case: 28 ± 7 Control: 25 ± 4
O'Neill et al., 2016 [21]	UK	Case-control	22 (73.0)	5.0	J774 to ApoB-depleted serum	<sup>3</sup> H-cholesterol	7	-	Case: 24.42 ± 4.71 Control: 26.27 ± 2.29
Ormseth et al., 2016 [22]	USA	Case-control	144 (68.6)	3.9	THP-1 to ApoB-depleted serum	<sup>3</sup> H-cholesterol	6	CEC is not significantly altered in RA patients	Case: 28.5 (23.9, 33.3) Control: 27.2 (24.8, 32.3)
Tejera-Segura et al., 2017 [23]	Spain	Cross-sectional	295 (73.6)	7.0	J774 to ApoB-depleted serum	BODIPY-cholesterol	7	CEC is not significantly altered in RA patients	Case: 28 ± 5 Control: 28 ± 5

Data are presented as median (interquartile range) or mean ± SD unless otherwise indicated; <sup>a</sup> duration of RA; <sup>b</sup> cholesterol efflux capacity; <sup>c</sup> not available.

Table 2  
 Characteristics of interventional studies in this systematic review and meta-analysis

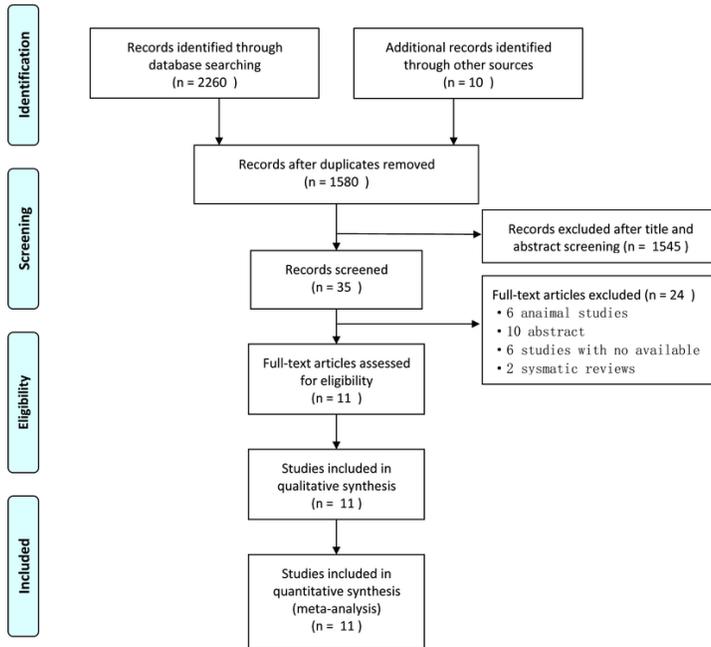
Authors	Country	Treatment	Dose of drugs	Study design	N/female (%)	Mean (age)	Duration <sup>a</sup> (year)	Length of follow-up (m)	Quality score	Outcome summary	BMI
Ronda et al., 2015 [24]	USA	MTX <sup>c</sup> , ADA <sup>d</sup> , MTX	MTX: 3–5 mg ADA: 40 mg	One-arm study	56 (NA)	57.0	2.0	6	11	CEC <sup>b</sup> was not significantly altered after RA therapy	NA <sup>i</sup>
P.Liao et al., 2015 [25]	USA	MTX, INF <sup>e</sup> , MTX + INF	NA	One-arm study	80 (88.9)	57.0	16.5	12	13	CEC was improved in CEC after therapy	Baseline: 27.0 (5.5)
O'Neill et al., 2016 [21]	UK	MTX + INF, MTX + PLA <sup>f</sup>	M + I: 5 mg/kg M + p: 2.5–25 mg/kg	Two-arm study	18 (66.7)	58.6	5.0	12	16	CEC was not significantly altered after RA treatment	Treatment: 24.98 ± 5.11 placebo: 25.88 ± 0.55
Ormseth et al., 2016 [26]	USA	MTX, TCZ <sup>g</sup> , ADA <sup>h</sup>	NA	Three-arm study	59 (84.0)	53.0	9.0	6	17	CEC was not significantly altered after RA treatment	NA
Ferraz-Amaro et al., 2019 [27]	UK	TCZ	8 mg/kg	One-arm study	24 (88)	52.0	8.0	12	12	CEC was significantly increased after RA treatment	Treatment: 29 ± 6 Baseline: 28 ± 5

Data are presented as median (interquartile range) or mean ± SD unless otherwise indicated; <sup>a</sup> duration of RA; <sup>b</sup> cholesterol efflux capacity; <sup>c</sup> methotrexate; <sup>d</sup> adalimumab; <sup>e</sup> infliximab; <sup>f</sup> placebo; <sup>g</sup> tocilizumab; <sup>h</sup> adalimumab; <sup>i</sup> not available.

## Figures



## PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. doi:10.1371/journal.pmed1000097

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

Figure 1

Flow diagram of selection process in the meta-analysis.

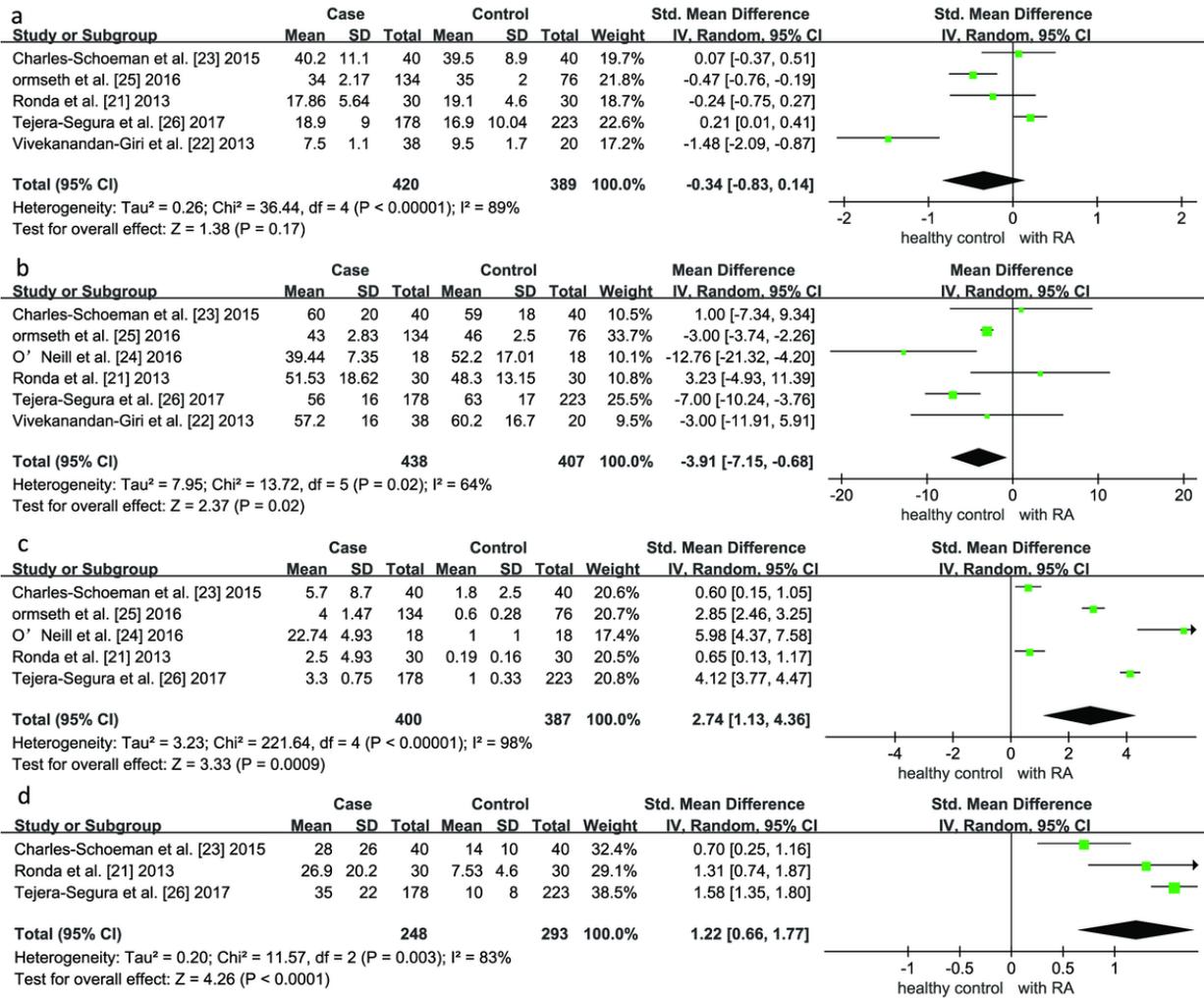


Figure 2

Forest plot of the plasma levels of CEC (a), high-density lipoprotein (b) and C-reactive protein (c) for patients with RA versus control group in observational study.

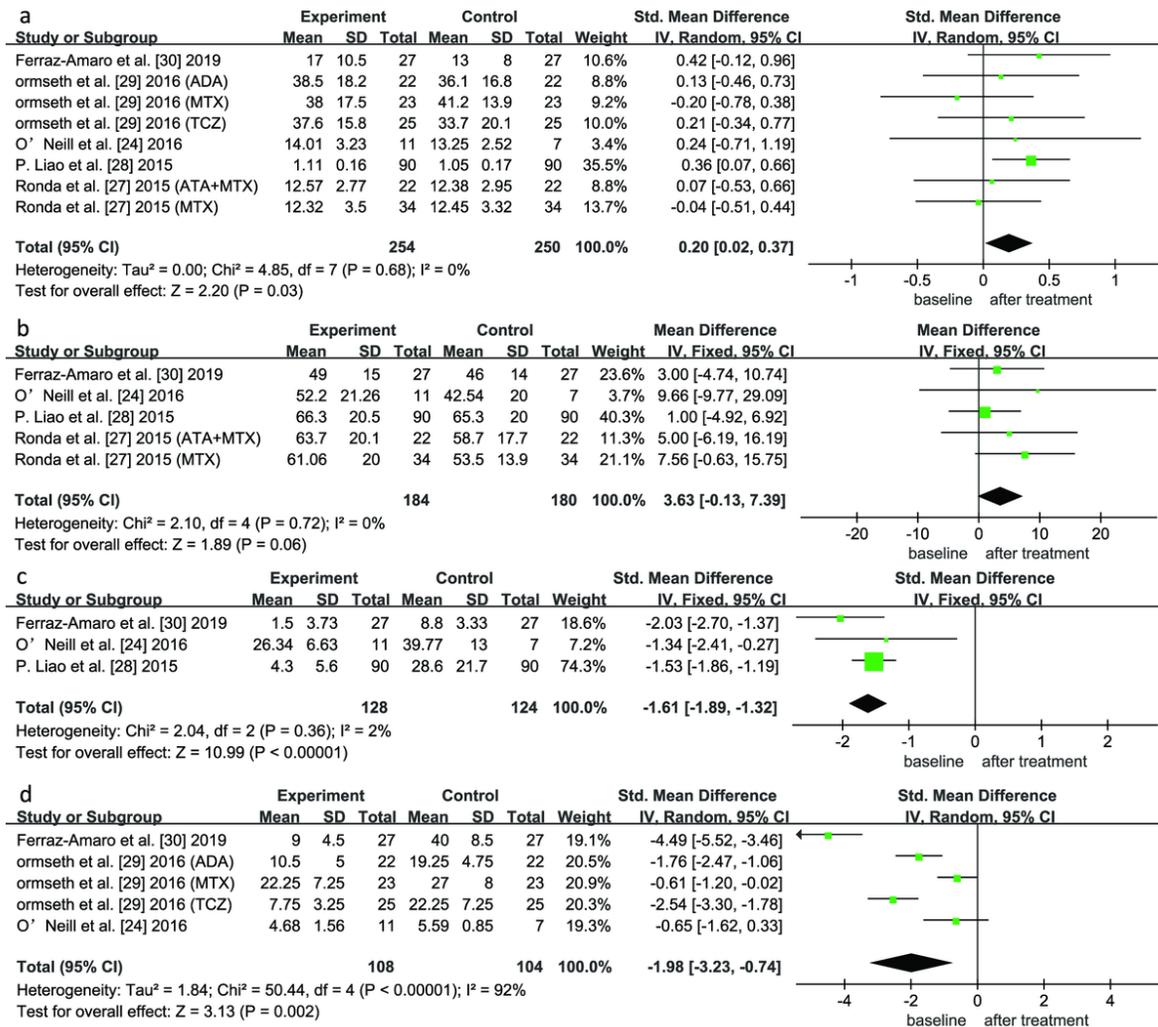
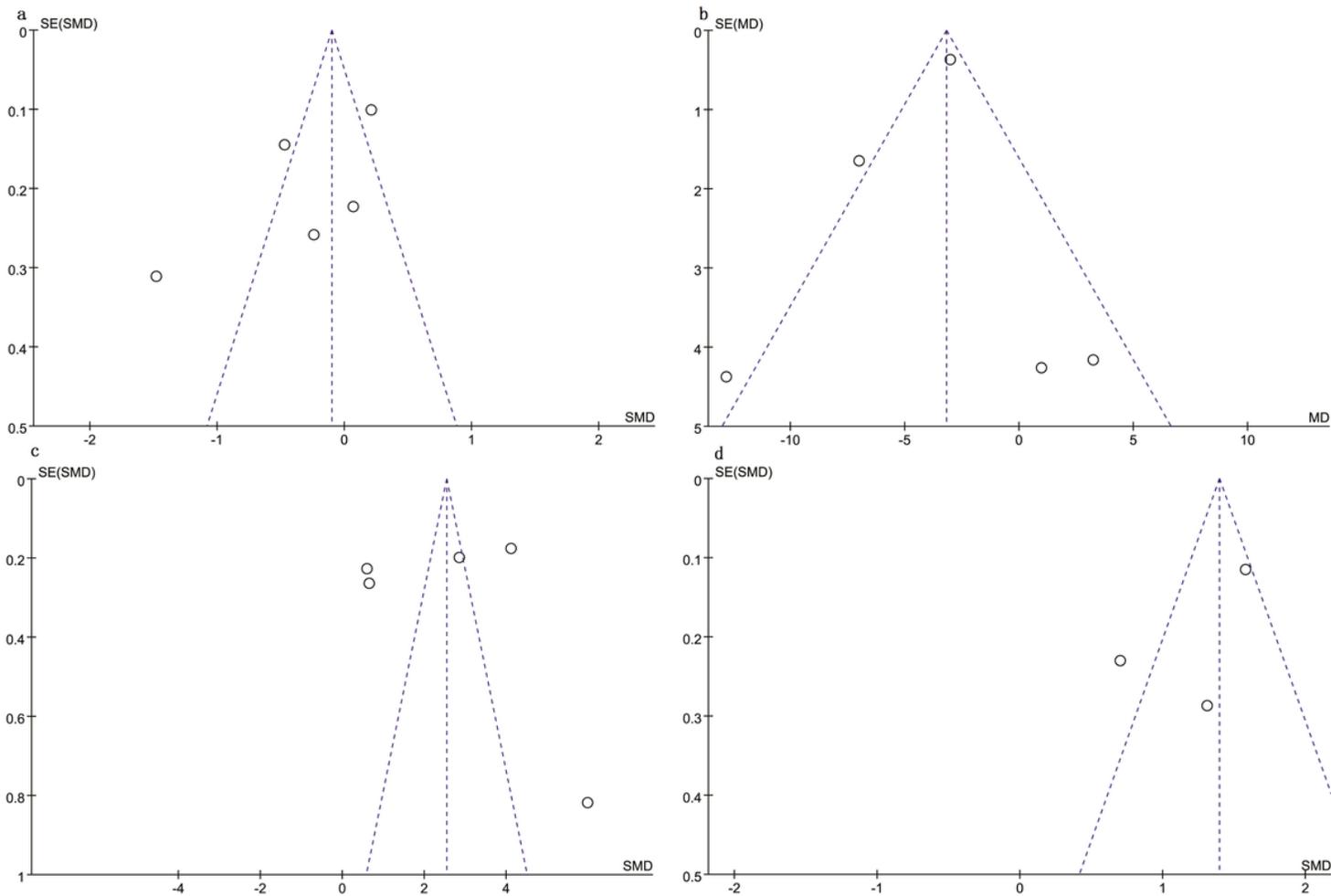


Figure 3

Forest plot of the plasma levels of CEC (a), high-density lipoprotein (b), C-reactive protein (c) and erythrocyte sedimentation rate (d) for patients with RA and control group in before-after studies



**Figure 4**  
 Funnel plots evaluating the pooled estimates for the plasma levels of CEC (a), high-density lipoprotein (b), C-reactive protein (c) and erythrocyte sedimentation rate (d) among patients with RA.

## Supplementary Files

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