# HDL cholesterol efflux capacity and concentration in patients with rheumatoid arthritis: a systematic review and meta-analysis

**Binbin Xie**
Jinan university
**Jiang He**
Southern Medical University
**Yong Liu**
Anhui Medical University
**Ting Liu**
Jinan University
**Chaoqun Liu** ( lcqun1987@126.com )
Jinan University https://orcid.org/0000-0001-8322-3290

**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 June 2020, without language restrictions. The primary outcomes were CEC and the high-density lipoprotein cholesterol (HDL-C) and C-reactive protein levels (CRP) levels.

**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: -0.22, 95% CI: -0.65 to 0.20), whereas the plasma HDL-C level is not significantly (WMD: -3.98, 95% CI: -8.32 to 0.37, $I^2$ = 54%, $P$ for heterogeneity = 0.050) but is significantly decreased in the RA patients with moderate body mass index (BMI) (WMD: -5.46, 95% CI: -9.40 to -1.52, $I^2$ = 37%, $P$ for heterogeneity = 0.175). Furthermore, in the before-after studies, the CEC of RA patients (SMD: 0.20, 95% CI: 0.03 to 0.38) increased, but the plasma HDL-C level (WMD: 3.26, 95% CI: -0.17 to 6.69) remained at a similar level after anti-rheumatic treatment compared to the baseline. In addition, stratified analysis suggested that the Disease Activity Score for 28 joints could be a potential source of heterogeneity for CEC. 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]. However, studies have shown that dyslipidemia involving low HDL-C levels and high low-density lipoprotein cholesterol (LDL-C) levels is a major risk factor for cardiovascular events [6-8]. Furthermore, numerous studies have suggested that plasma HDL-C levels are also lower in the RA population than in the general population [9-11]. 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 [12]. 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 [13], 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 [14]. 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 [15-17]. 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 [18]. Of these functions, reverse cholesterol transport (RCT) is an overriding process that promotes excess plasma cholesterol from the cell to the liver for catabolism [9]. Macrophage cholesterol efflux is the first critical step of RCT and is considered a key atheroprotective property [19]. The general methods for measuring cholesterol efflux capacity (CEC) include using radioisotope-labeled cholesterol that is labeled with [$^3$H]-cholesterol ([$^3$H]-C) and fluorescence-labeled cholesterol to measure CEC [20,21]. CEC has been proven to increase the risk of CVDs, which is independent of the plasma HDL-C level [22,23]. 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 [24-33].

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

This meta-analysis was conducted and written the manuscript according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. EMBASE, MEDLINE and Cochrane Library databases were searched for records reporting CEC in patients with RA. The searches were focused on studies in human subjects that were published before 10 June 2020, without language restrictions. 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), 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 [34]. 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) [35]. 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 [36]. 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 [37]. The GRADE assessment was performed using GRADEpro software (McMaster University, Hamilton, Canada) [38].

### 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 choosed 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 . The 95% predictive intervals (PIs) were calculated to assess the influence of heterogeneity when the outcomes had high heterogeneity [39,40]. Subgroup analysis was additionally performed to determine the sources of heterogeneity. By comparing random- and fixed-effects models, a sensitivity analysis was subsequently conducted, and the influence of each individual study on the overall outcome was 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' test, where $P < 0.1$ indicated potential publication bias [41,42]. 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: -0.22, 95% CI: -0.65 to 0.20; 95% PI: -2.35 to 0.63; $I^2$ = 86%, $P$ 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 was not significantly lower (WMD: -3.98, 95% CI: -8.32 to 0.37, $I^2$ = 54%, $P$ for heterogeneity = 0.050) (Fig 2) but was significantly decreased in the RA patients with moderate or high BMI (WMD: -5.46, 95% CI: -9.40 to -1.52, $I^2$ = 37%, $P$ for heterogeneity = 0.175). 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: 0.03 to 0.38; $I^2$= 0%, $P$ for heterogeneity = 0.650). In addition, only 4 intervention studies were suitable for inclusion in the analysis of the change in HDL-C levels. In contrast, the plasma HDL-C levels were slightly higher in the RA patients after anti-rheumatic drug treatment than at baseline, but the difference was not significant (WMD: 3.26, 95% CI: -0.17 to 6.69). 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). Five studies reported the CRP level as a continuous variable. Accordingly, in the observational studies, the pooled analysis data showed that the CRP level was higher in the RA patients than in the healthy controls (SMD: 1.25, 95% CI: 0.34 to 2.17; 95% PI: -2.44 to 5.68; $I^2$ = 96%, $P$ for heterogeneity < 0.001). However, the CRP level significantly decreased after anti-rheumatic drug therapy in the intervention studies (SMD: -0.46, 95% CI: -0.71 to -0.21; $I^2$ = 0%, $P$ for heterogeneity = 0.830).

### Subgroups and sensitivity analysis

The results showed that DAS28 had a significant impact on the heterogeneity of CEC ($I^2$ = 22.6%). In addition, the heterogeneity in the HDL-C level significantly decreased when subgroup analysis stratified by BMI and age was conducted ($I^2$ = 36.9%; $I^2$ = 19.6%, respectively) (see Additional file 3). The sensitivity analysis showed that the overall effect sizes of CEC and CRP obtained using the fixed-effects and random-effects models were identical, and no individual study significantly affected the pooled results. The results of the random-effects and fixed-effects models as well as the subgroup analysis were similar (see Additional file 4). After a single article [18] was excluded, low heterogeneity was found after remerging ($I^2$ = 36.9%), and the results of the random-effects model were consistent with the results of the fixed-effects model (fixed-effects model: WMD: -6.07, 95% CI: -8.67 to -3.64; random-effects model: WMD: -5.45, 95% CI: -9.40 to -1.51) (see Additional file 5).

### 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. The presence of publication bias was also evaluated by using the Begg's and Egger's tests. Currently, the results of Egger's test ($P_{CEC}$ = 0.106; $P_{HDL\text{-}C}$ = 0.342; $P_{CRP}$ = 0.721) and Begg's test ($P_{CEC}$ = 0.086; $P_{HDL\text{-}C}$ = 0.707; $P_{CRP}$ = 0.462) . 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 waswas 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. Fifth, this review protocol was not published in the PROSPERO database. However, we performed this study by strictly following the protocol.

## 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-meditated CEC, while the plasma HDL-C level were 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 [43]. First, most patients with RA have elevated levels of certain proinflammatory cytokines, including CRP, and interleukin-6 in their blood. Many studies have indicated that HDL-C levels, dramatically decreases during inflammation, and one possible mechanism underlying these changes is 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 [44]. 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 [45]. In subgroup analysis by BMI, the results show that the plasma HDL-C levels are significantly lower in the RA patients than in the healthy individuals, which suggests that the inflammatory status and severity of RA are 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 [46]. 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 [47]. Thus, the inflammatory status in patients with RA affects not only the rate of cholesterol efflux but also other processes in RCT. Studies have indicated that the circulating level is positively associated with the levels of oxidative stress and inflammation [48,49]. Furthermore, Vivekanandan-Giri reported that the myeloperoxidase-oxidized HDL levels are increased and CEC is diminished in individuals with RA due to inflammation and oxidative stress [25]. 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 [50,51]. 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 [52]. Subgroup analysis was conducted to evaluate the heterogeneity in the CEC and HDL-C levels. The analysis results showed that DAS28 is the source of statistical heterogeneity. For the HDL levels, BMI and age, not DAS28, were the sources of heterogeneity. Sensitivity analysis was performed to enhance the robustness and reliability of the results. The effect size of the HDL-C level does not significantly change with a random-effects model, when a study performed by Ronda, et al. [30], which may be due to the younger age of the RA patients and the fact that they were not allowed to take statins; both of these factors can lead to a marked increase in the plasma HDL-C level. Furthermore, nearly half of the included studies were case-control studies, which have comparatively low quality. Given that recall bias and selection bias can exist in case-control studies, more large-scale prospective cohort studies with models fully adjusted for potential confounding factors are urgently needed to confirm the inverse association between the CEC and CRP levels.

## 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.

# Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Availability of data and material

All data generated or analysed during this study are available from the corresponding author on request.

### Conflict of interest

The authors declare that they have no competing interest.


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### 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.


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# Abbreviations

RA Rheumatoid arthritis

CEC Cholesterol efflux capacity

CVD Cardiovascular diseases

HDL-C High-density lipoprotein cholesterol

TC Total cholesterol

LDL-C Low-density lipoprotein cholesterol

TG Triglycerides

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

SDs Standard deviation

95%CIs 95% Confidence intervals

95%PI 95% Pretective intervals

BMI Body mass index

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## Tables

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

| Authors | Country | Study type | Subjects (female, %) | Duration[a] (month) | Assay method of CEC | Labeled-cholesterol | Quality score | Outcome summary | BMI[d] |
|---|---|---|---|---|---|---|---|---|---|
| Ronda et al., 2013 [24] | USA | Case-control | 52 (86.7) | N/A[c] | J774, Fu5AH, CHO-k1 to ApoB-depleted serum | $^{3}$H-cholesterol | 5 | CEC[b] is impaired in RA | 24.4±4.7 |
| Vivekanandan-Giri et al., 2013 [25] | USA | Case-control | 34 (58.6) | 4.0 | J774 to ApoB-depleted serum | $^{3}$H-cholesterol | 5 | CEC was diminished in RA patients | 27.9±5.4 |
| Charles-Schoeman et al., 2015 [26] | USA | Case-control | 66 (82.0) | 12.8 | RAW264.7 to isolated HDL | $^{3}$H-cholesterol | 9 | no difference of CEC between RA patients and controls | 28.0±7.0 |
| O'Neill et al., 2016 [21] | UK | Case-control | 22 (73.0) | 5.0 | J774 to ApoB-depleted serum | $^{3}$H-cholesterol | 7 | - | 24.4±4.7 |
| Ormseth et al.,2016 [22] | USA | Case-control | 144 (68.6) | 3.9 | THP-1 to ApoB-depleted serum | $^{3}$H-cholesterol | 6 | CEC is not significantly altered in RA patients | 28.5 (23.9, 33.3) |
| 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 | 28.0±5.0 |

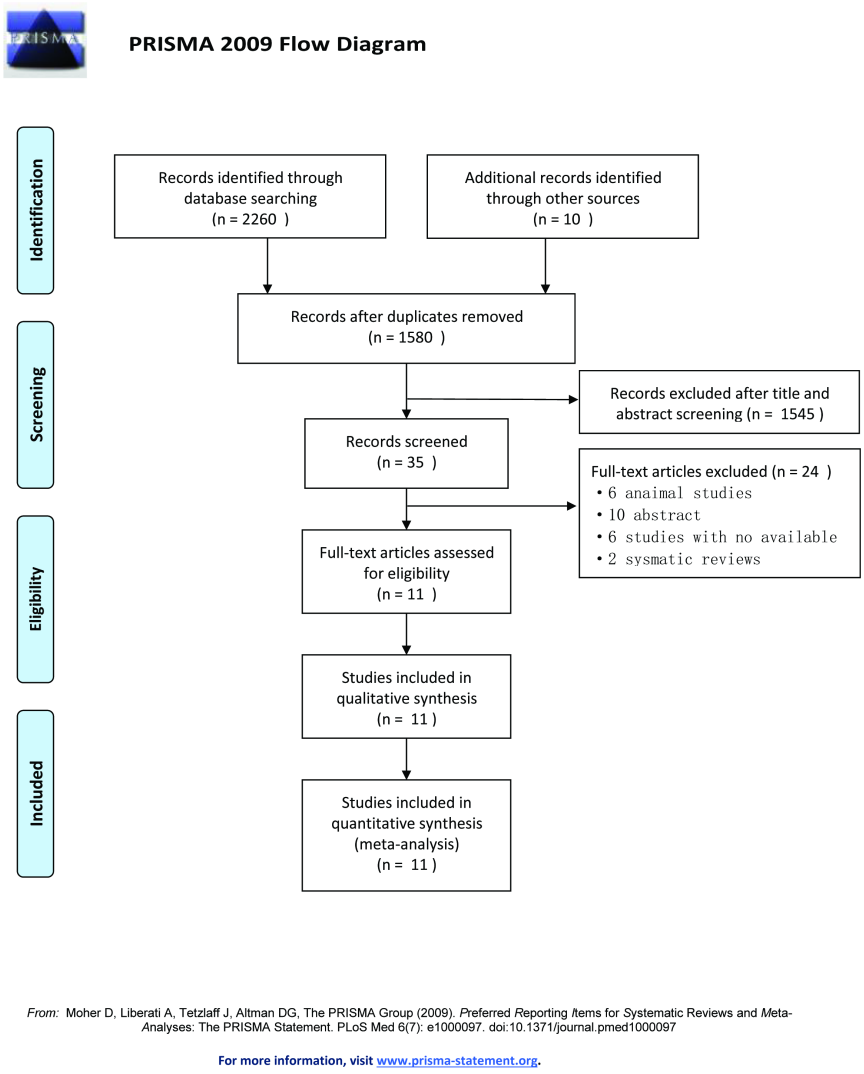
Data are presented as median (interquartile range) or mean ± SD unless otherwise indicated; [a] duration of RA; [b] cholesterol efflux capacity; [c] not available; [d] body mass index.

| Authors | Country | Treatment | Dose of drugs | Study design | N/female (%) | Mean (age) | Duration[a] (year) | Length of follow-up (m) | Quality score | Outcome summary | BMI[j] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ronda et al., 2015 [24] | USA | MTX[c], ADA[d],MTX | MTX: 3-5 mg ADA: 40 mg | One-arm study | 56 (N/A) | 57.0 | 2.0 | 6 | 11 | CEC[b] was not significantly altered after RA therapy | N/A[c] |
| P.Liao et al., 2015 [25] | USA | MTX, INF[e], MTX + INF | NA[i] | One-arm study | 80 (88.9) | 57.0 | 16.5 | 12 | 13 | CEC was improved in CEC after therapy | 27.0±5.5 |
| O'Neill et al., 2016 [21] | UK | MTX+INF, MTX+PLA[f] | 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 | 24.98±5.11 |
| Ormseth et al., 2016 [26] | USA | MTX, TCZ[g], ADA[h] | NA | Three-arm study | 59 (84.0) | 53.0 | 9.0 | 6 | 17 | CEC was not significantly altered after RA treatment | N/A[c] |
| 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 | 29 ± 6 |

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

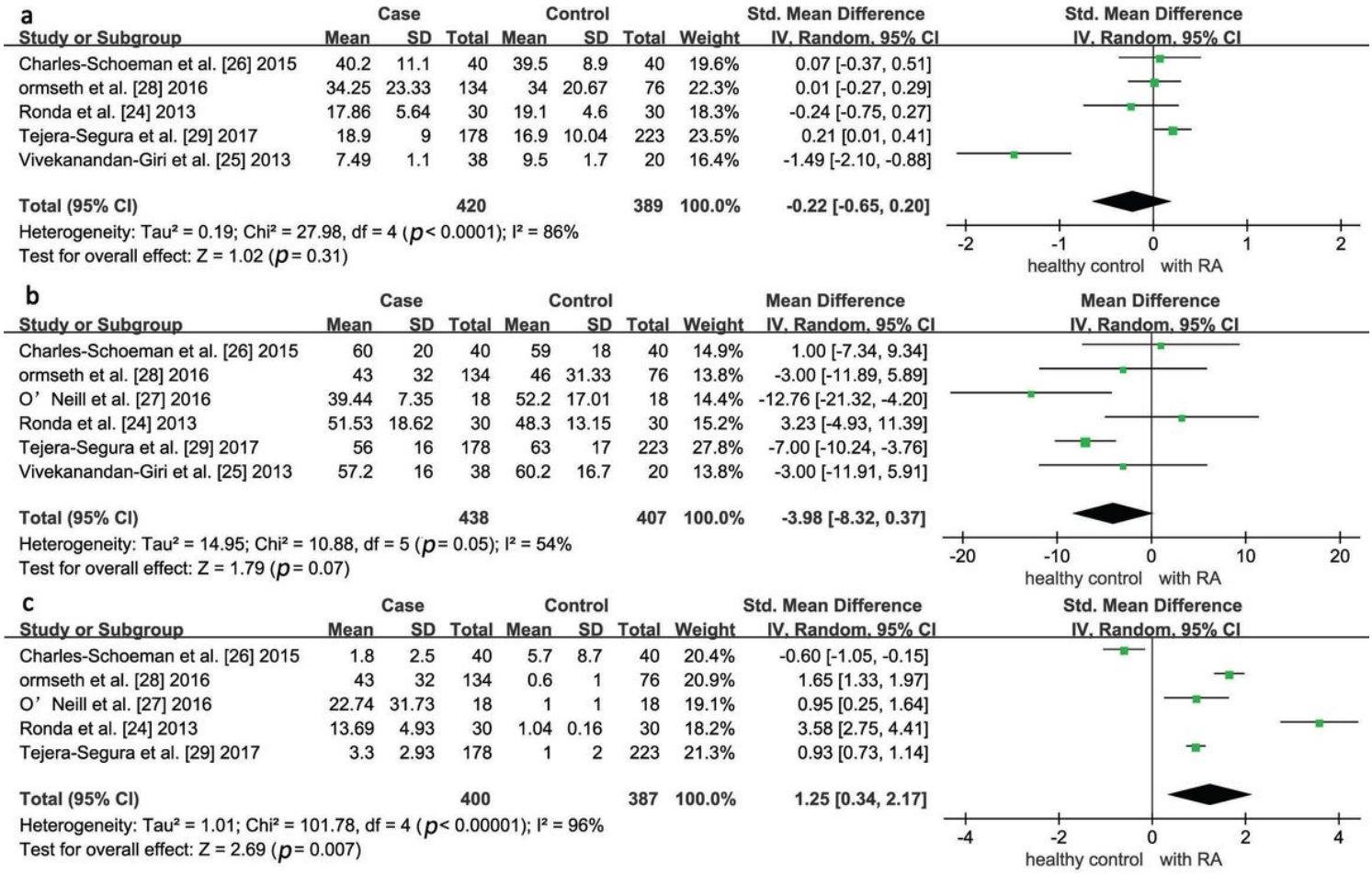
Data are presented as median (interquartile range) or mean ± SD unless otherwise indicated; [a] duration of RA; [b] cholesterol efflux capacity; [c] methotrexate; [d] adalimumab; [e] inflixximab; [f] placebo; [g] tocilizumab; [h] adalimumab; [i] not available; [j] body mass index.

# Figures




## 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-reaction protein (c) for patients with RA versus control group in observational study.

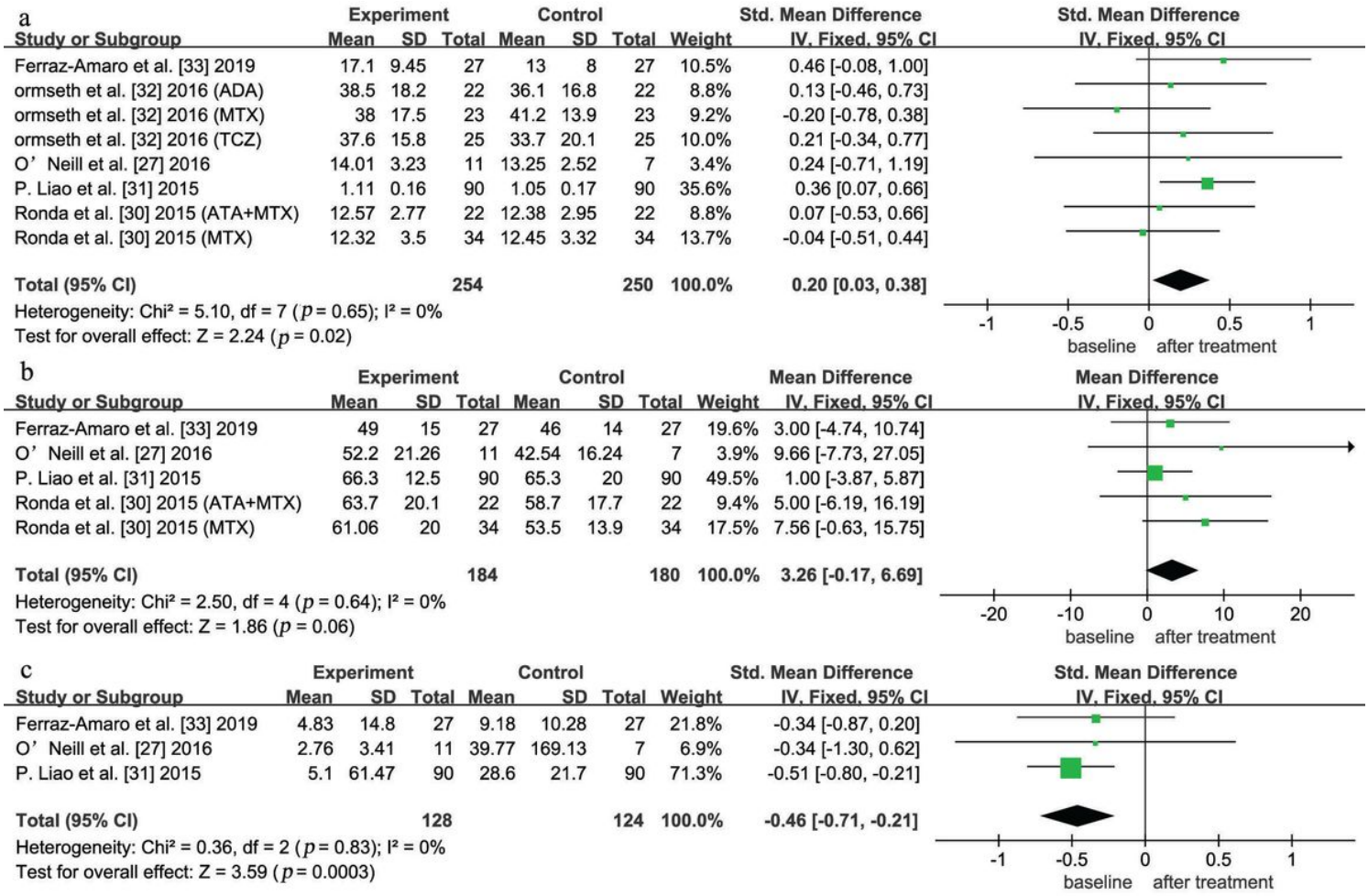



**Figure 3**

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

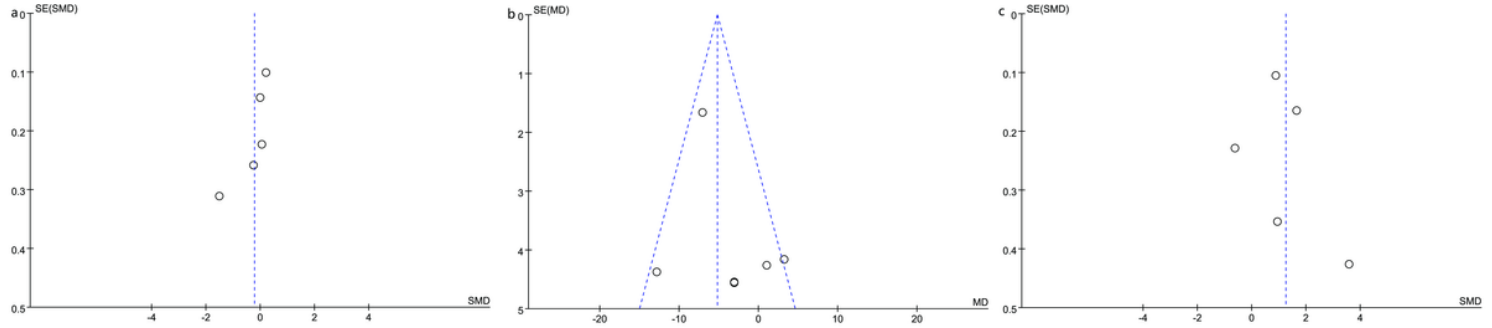



**Figure 4**

Funnel plots evaluating the pooled estimates for the plasma levels of CEC (a), high-density lipoprotein (b) and C-reaction protein (c) among patients with RA.

## Supplementary Files

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- Additionalfile6.docx