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A COMPREHENSIVE SYSTEMATIC REVIEW AND META-ANALYSIS INVESTIGATING THE RELATIONSHIP BETWEEN CHOLESTEROL EFFLUX CAPACITY AND CARDIOVASCULAR RISK

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ЦЯЛОСТЕН СИСТЕМАТИЧЕН ПРЕГЛЕД И МЕТААНАЛИЗ, ИЗСЛЕДВАЩ ВРЪЗКАТА МЕЖДУ КАПАЦИТЕТА ЗА ЕФЛУКС НА ХОЛЕСТЕРОЛА И СЪРДЕЧНО-СЪДОВИЯ РИСК

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Abstract. **Background:** HDL is decisive for reverse cholesterol transport, enabling the removal of cholesterol from macrophages in atherosclerotic plaques. Although HDL-C has long been allied to CVS protection, recent evidence suggests that CEC may more accurately reflect HDL's functional efficacy. However, studies exploring the relationship between CEC and CAD risk have produced inconsistent results. **Objectives:** The association between CEC and CAD risk was assessed, along with its potential to predict MACE, including cardiac mortality, all-cause mortality, and non-fatal MI, in this systematic review and meta-analysis. **Material and methods:** A comprehensive search of PubMed, Scopus, Web of Science, and The Cochrane Library was conducted to identify studies published up to January 2025. Observational studies comparing CEC levels between individuals with and without CAD were included. **Results:** Twenty-three studies met the inclusion criteria. The pooled SMD of – 0.40 (95% CI: -0.53−-0.26), with a p-value < 0.0001, revealed significantly lower CEC levels in CAD patients compared to non-CAD individuals. Higher CEC was strongly allied with a reduced risk of CAD – OR = 0.57; 95% CI: 0.48−0.67, P < 0.00001, and a pooled risk ratio (RR) of 0.64; 95% CI: 0.48−0.86, p = 0.003. Impaired CEC was associated with an increased risk of cardiac mortality – OR = 3.94; 95% CI: 2.63−5.90, p < 0.00001, and all-cause mortality – OR = 2.84; 95% CI: 2.01−4.00, p < 0.00001. However, insignificant association was found between CEC and non-fatal MI (OR = 3.47; 95% CI: 0.41−29.22, p = 0.25). **Conclusion:** This meta-analysis underscores the probability of CEC as a biomarker for the assessment of CVS risk. Higher CEC levels are linked to a reduced risk of CAD, cardiac mortality, and all-cause mortality, but no significant relationship was observed with non-fatal MI. Future research should prioritize standardizing CEC measurement methods and investigating its therapeutic potential for preventing atherosclerotic CVS disease.

Key words: cholesterol efflux capacity; cardiovascular risk; high-density lipoprotein; low-density lipoprotein

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Резюме.

Въведение: Липопротеините с висока плътност (HDL) са от решаващо значение за обратния транспорт на холестерола, като позволяват отстраняването на холестерола от макрофагите в атеросклеротичните плаки. Въпреки че HDL холестерола (HDL-C) отдавна се свързва със защитата на сърдечно-съдовата система, последните данни сочат, че способността за извеждане на холестерола (cholesterol efflux capacity – CEC) може да отразява по-точно функционалната ефикасност на HDL. Проучванията, изследващи връзката между CEC и риска от коронарна артериална болест (КАБ), обаче дават противоречиви резултати. **Цел:** В този систематичен преглед и метаанализ беше оценена връзката между CEC и риска от КАБ, както и потенциалът му да предсказва MACE, включително сърдечна смъртност, смъртност от всички причини и нефатален миокарден инфаркт (МИ). **Материал и методи:** Беше проведено изчерпателно търсене в базите PubMed, Scopus, Web of Science и The Cochrane Library, за да се идентифицират проучвания, публикувани до януари 2025 г. Бяха включени наблюдателни проучвания, сравняващи нивата на CEC между лица със и без КАБ. **Резултати:** Двадесет и три проучвания отговаряха на критериите за включване. Общото SMD от – 0,40 (95% CI: -0,53—0,26), с p-стойност < 0,0001, показа значително по-ниски нива на CEC при пациенти с CAD в сравнение с лица без CAD. По-високите CEC бяха силно свързани с намален риск от CAD – OR = 0,57; 95% CI: 0,48–0,67, p < 0,00001 и обединено съотношение на риска (RR) от 0,64; 95% CI: 0,48–0,86, p = 0,003. Нарушената CEC беше свързана с повишен риск от сърдечна смъртност – OR = 3,94; 95% CI: 2,63–5,90, p < 0,00001, и смъртност от всички причини – OR = 2,84; 95% CI: 2,01–4,00, p < 0,00001. Въпреки това не беше установена значима корелация между CEC и нефаталния МИ (OR = 3,47; 95% CI: 0,41–29,22, p = 0,25). **Заключение:** Този метаанализ подчертава вероятността CEC да бъде биомаркер за оценка на риска от ССЗ. По-високите нива на CEC са свързани с намален риск от ИБС, сърдечна смъртност и смъртност от всички причини, но не е наблюдавана значима връзка с нефатален МИ. Бъдещите изследвания трябва да дадат приоритет на стандартизирането на методите за измерване на CEC и проучването на терапевтичния му потенциал за превенция на атеросклеротичните сърдечно-съдови заболявания.

Ключови думи: способност за извеждане на холестерол, сърдечно-съдов риск, липопротеини с висока плътност, липопротеини с ниска плътност

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Introduction

High-density lipoprotein (HDL) is essential in protecting against atherosclerosis by promoting cholesterol clearance from macrophages embedded in arterial plaques [1]. Although reduced HDL levels and increased low-density lipoprotein (LDL) concentrations are recognized as key contributors to coronary artery disease (CAD), interventions aimed at lipid regulation remain a focal point of ongoing research [2, 3]. Notably, reducing LDL levels has only been effective in preventing approximately one-third of cardiovascular (CVS) events in CAD patients. Although reduced HDL cholesterol (HDL-C) levels are indicated as an autonomous risk aspect for atherosclerotic cardiovascular disease (ASCVD), evolving evidence advocates that merely increasing HDL-C concentrations does not consistently confer protection against atherosclerosis [4]. Data from multiple cohort studies have indicated that HDL-C levels may display a plateau effect or, in some cases, an amplified risk association with CAD at higher concentrations [5-7]. Several clinical and observational articles have recognized a contrary relation between HDL-C and ASCVD [8, 9]. The main atheroprotective role of HDL is intermediating reverse cholesterol transport, which enables the extraction of cholesterol from macrophages within atherosclerotic plaques and its subsequent delivery to the liver for processing. This process reduces foam cell formation, a critical factor in atherosclerosis progression.

Cholesterol efflux capacity (CEC) is defined as the ability of HDL particles to accept cholesterol from macrophages during the initial step of reverse cholesterol transport. It reflects HDL's functional quality rather than its circulating quantity. CEC is therefore considered a functional biomarker of HDL, providing insight into its protective role in reducing atherosclerotic burden. Importantly, rather than HDL-C levels alone, improved CEC and overall HDL functionality are believed to play a more critical role in reducing ASCVD risk [10].

Studies on patients with genetically higher levels of HDL-C and apolipoprotein A-I (apoA-I) have yielded inconsistent findings regarding CVS disease risk reduction [11, 12, 13]. Additionally, clinical articles examining therapies aimed at increasing HDL-C levels, e.g. niacin and cholesteryl ester transfer protein (CETP) inhibitors in combination with statins, have failed to show substantial CVS advantages [5]. The relationship between CEC and future CVS events remains inconsistent, with some studies reporting a positive correlation and others indicating an inverse association. Li et al. [14] detected a direct association between CEC and CVS risk in patients with stable CAD, while Rohatgi et al. [15] found an inverse correlation in individuals without CAD. Also, a case-control study demonstrated that higher CEC was allied to a reduced likelihood of developing coronary heart disease. [16] Given these conflicting findings, this systematic review and meta-analysis aim to comprehensively assess the association between CEC and CVS outcomes, as well as its possible role as a therapeutic aim in ASCVD prevention.

Material and methods

Databases search and study selection

A comprehensive search of the literature was accomplished across Scopus, PubMed, The Cochrane Library, and Web of Science to identify articles available until January 2025. The search strategy incorporated both MeSH terms and keyword variations, including (‘cholesterol efflux capacity’ OR CEC) combined with (‘coronary artery disease’ OR CAD OR ‘myocardial infarction’ OR MI OR ‘acute coronary syndrome’). Only studies published in English were included. Additionally, reference lists of relevant articles were examined for supplementary studies. The meta-analysis was conducted following PRISMA guidelines [17]. Study eligibility was determined through a two-stage screening process by independent reviewers. Initially, the titles and abstracts of all retrieved citations were screened to determine their relevance. Subsequently, full-text articles were evaluated for eligibility according to predefined criteria. Any disagreements among reviewers were addressed and resolved through mutual consensus. Studies were included if they were comparative observational studies or randomized controlled trials, provided details on baseline CEC levels, involved patients with CAD and/or diabetes, examined CAD risk concerning low and high CEC arms, and reported major adverse cardiovascular events (MACE), including death, stroke, myocardial infarction (MI), or transient ischemic attack. Exclusion criteria included non-English publications, lack of full-text availability, conference abstracts, case reports, review articles, and editorials, as well as articles that did not line up with the research aims.

Data Extraction and Quality Appraisal

Extracted data included study population characteristics, key findings, risk of bias evaluations, and article outcomes related to MACE. Any disagreements were settled through consultation with a third assessor. The included observational studies were evaluated for quality using the Newcastle-Ottawa Scale (NOS) [18], ensuring that methodological rigor was maintained.

Data synthesis and statistical analyses

For continuous variables, standardized mean differences (SMD) were calculated from baseline to endpoint along with their standard deviations (SD) and total sample sizes. The data were examined utilizing the inverse variance approach within a random-effects framework. Dichotomous outcomes were assessed using odds ratios (OR), also employing a random-effects model. The assessment of study heterogeneity involved both a visual examination of forest plots and the application of statistical measures, specifically the Cochrane Q test and the I^2 statistic. A P-value below 0.1 and an I^2 value exceeding 50% were used as thresholds to identify significant heterogeneity. Statistical analyses were performed utilizing RevMan 5.3 software on a Windows operating system.

Publication bias

Publication bias was evaluated for outcomes that included more than [10] studies, as recommended by the Cochrane Handbook. Funnel plots were constructed to visually assess asymmetry, with the standard error (SE) plotted against the standardized mean difference (SMD) for continuous outcomes and the logarithm of the odds ratio (log OR) for dichotomous outcomes.

Results

Literature search

Our literature search initially identified 2,481 records. Following the screening of titles and abstracts and the removal of duplicates, 39 full-text articles were evaluated for inclusion. Among these, 23 studies [14, 16, 19-39] fulfilled the inclusion criteria and were included in our study. The PRISMA flow diagram (Fig. 1) illustrates the study assortment process, while Table 1 provides an overview of the characteristics of the included articles and the baseline demographics of the participants.

Quality of the included articles

The quality evaluation of the 23 included articles, conducted via NOS, revealed that 21 studies were of high methodological quality, scoring above 7, suggesting a low risk of bias. In contrast, two studies 23, 38 scored below 7, indicating potential limitations in study design or data reliability. Detailed risk of bias assessments for each article are presented in Table 1.

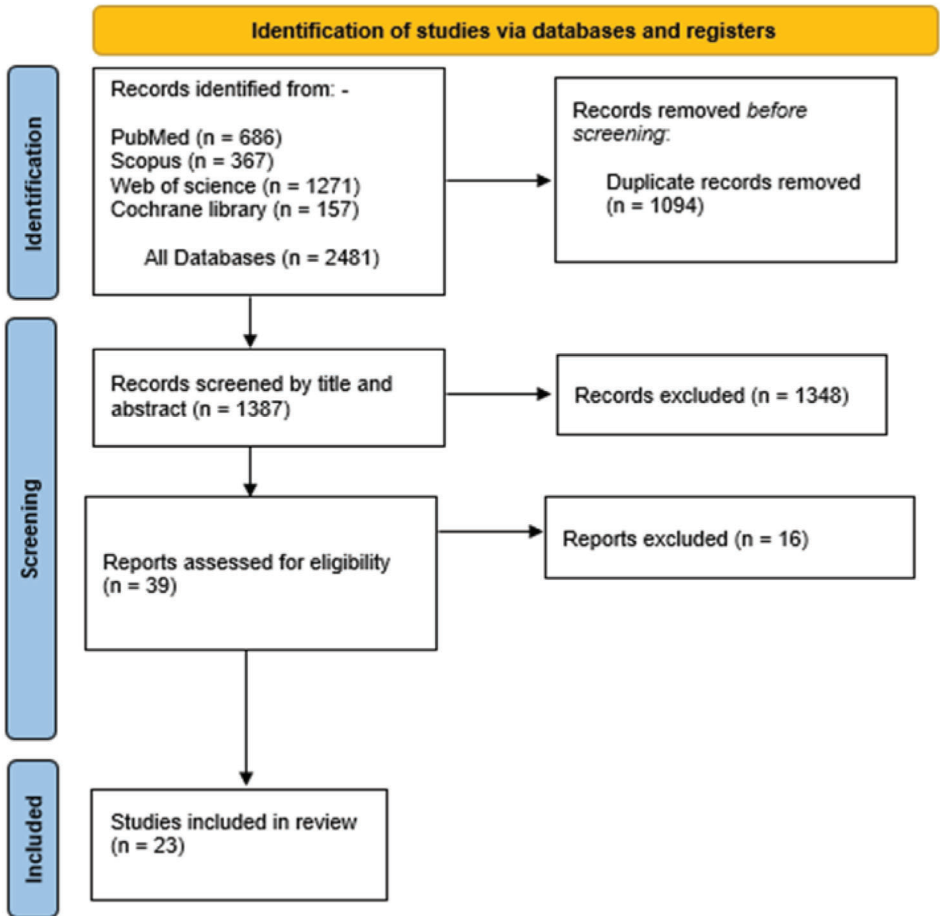

Fig. 1. Flow diagram of the included articles

Table 1. Overview of the characteristics of the included articles and the baseline demographics of the participants

Study ID	Country	Study design	Number of Population	Age (mean)	Male n (%)	Diabetes n (%)	HDL-C (mean); mg/dl	Criteria of the included population	Main findings
Patel 2013 [1]	USA	Case-Control	69	58	40 (57.97)	11 (15.94)	0.79	Patients undergoing cardiac catheterization for evaluation of angina	Reduced EF in ischemia is linked to impaired HDL, exacerbating heart failure.
Li, 2013 [2]	USA	Case-Control	1727	61.25	226 (13.09)	73 (4.23)	42.67	Patients underwent elective diagnostic CAG for evaluation of CAD.	Increased cholesterol efflux to apoB-depleted serum is paradoxically linked to higher cardiovascular risk, likely involving non-HDL pathways.
Shao, 2014 [3]	USA	Case-Control	60	61	41 (68.33)	12 (20)	50	Patients with stable CAD or ACS	Chlorotyrosine and oxidized methionine in HDL may serve as independent cardiovascular risk biomarkers beyond HDL-C levels.
Ishikawa, 2015 [4]	Japan	Case-Control	254	65.25	198 (77.95)	113 (44.5)	53.45	Patients undergoing elective CAG, PCI, or MSCT.	Cholesterol efflux capacity is a key clinical predictor of CAD beyond traditional risk factors.
Saleheen, 20155	UK	Case-Control	3494	65.55	2254 (64.51)	357 (10.22)	1.35 (mmol/L)	Participants were classified as having CHD if hospitalized or died from CHD during follow-up.	Enhancing HDL efflux capacity offers a therapeutic strategy to reduce coronary heart disease risk.
Agarwala, 2015 [6]	USA	Case-Control	175	66.5	107 (61.14)	NR	86	Subjects with HDL-C > 90th percentile and coronary heart disease.	High HDL-C with reduced phospholipids and impaired efflux capacity is linked to unexpected CAD.

Continuation table 1

Study ID	Country	Study design	Number of Population	Age (mean)	Male n (%)	Diabetes n (%)	HDL-C (mean); mg/dl	Criteria of the included population	Main findings
Luo, 2017 [7]	China	Case-Control	230	62.96	147 (63.91)	41 (17.83)	1.07 (mmol/L)	Patients with CAD	ApoCIII in HDL may impact cholesterol efflux, linking it to atherosclerosis development.
Ebtehaj, 2019 [8]	Sweden	Case-Control	705	59	502 (71.2)	40 (5.7)	1.16 (mmol/l)	Participants who had experienced a new cardiovascular event.	Baseline CEC predicts future CVD events independent of HDL-C and apoA-I levels.
Cahill, 2019 [9]	USA	Case-Control	1397	63	1397 (100)	79 (5.65)	44.65	Participants who had an incident MI or fatal CHD.	CEC's predictive value for CHD may be influenced by HDL-C levels in healthy men.
Soria-Florido, 2020 [10]	Spain	Case-Control	1000	67.4	670 (67)	NR	48.98	Type 2 diabetes or multiple cardiovascular risk factors increase CHD susceptibility.	Impaired cholesterol efflux, pro-inflammatory HDL, and low S1P and apoA-I are linked to higher acute coronary syndrome risk.
Attia, 2007 [11]	France	Cohort	94	54.63	58 (61.7)	59 (62.77)	0.86 (mmol/l)	Tunisian diabetic patients, with and without CAD.	Elevated PLTP activity in Type 2 diabetes may impair cholesterol clearance and accelerate atherosclerosis.
Khera, 2011 [12]	USA	Cohort	996	56.67	583 (58.53)	147 (14.76)	50	Patients undergoing cardiac catheterization with >50% luminal stenosis in a major artery.	Macrophage cholesterol efflux inversely correlates with CIMT and CAD risk, independent of HDL-C levels.
Liu, 2016 [13]	China	Cohort	1737	63.55	1132 (65.17)	690 (39.7)	41.75	Patients aged 40–85 years diagnosed with CAD.	Cholesterol efflux capacity independently predicts all-cause and cardiovascular mortality in CAD patients.
Zhang, 2016 [14]	China	Cohort	313	67	235 (75)	66 (21)	1.1 (mmol/l)	Patients with a primary complaint of angina pectoris who underwent CAG	Cholesterol efflux capacity independently predicts plaque stability and CAD prognosis.
Guerin, 2018 [15]	France	Cohort	1609	63.4	1218 (75.7)	298 (18.5)	0.35 g/l	Patients treated for an acute STEMI who underwent primary PCI.	Serum cholesterol efflux inversely predicts all-cause mortality in MI patients, independent of HDL-C.
Shea, 2019 [16]	USA	Cohort	1744	65.33	948 (54.36)	57 (3.27)	50.2	Patients aged 45–85 years with no clinical CVD at baseline.	HDL-mediated cholesterol efflux protects against CHD but not stroke.
Hisauchi, 2020 [17]	Japan	Cohort	180	66.85	147 (81.67)	99 (55)	51.85	Patients with CAD undergo elective CAG, elective PCI, or MSCT.	CEC >1 in CAD patients predicts better outcomes, highlighting its prognostic and therapeutic value.
Ritsch, 2020 [18]	Austria	Cohort	2468	62.8	1681 (68.1)	713 (28.9)	39	Patients with acute coronary syndrome	Cholesterol efflux, linked to HDL composition and inflammation, inversely predicts cardiovascular mortality independently of HDL-C.
Magnoni, 2022 [19]	Italy	Cohort	525	60.48	305 (58.1)	65 (12.38)	49.55	Patients aged 45–75 years without ACS, normal LVEF, stratified by risk factors and CAD status.	Reduced SR-BI-mediated cholesterol efflux in diffuse CAD predicts poorer outcomes, independent of plaque characteristics.

Continuation table 1

Study ID	Country	Study design	Number of Population	Age (mean)	Male n (%)	Diabetes n (%)	HDL-C (mean); mg/dl	Criteria of the included population	Main findings
Sato, 2023 [20]	Sweden	Cohort	100	59.7	77 (77)	18 (18)	50.65	Patients with CAD.	HDL-SPE may become a standard test for cardiovascular risk assessment and drug development.
Norimatsu, 2016 [21]	Japan	Cross-Sectional	204	65.33	114 (56)	53 (26)	50.67	Patients with CAD.	Fixed HDL cholesterol efflux showed no CAD link, but total efflux capacity correlated with CAD presence.
Wang, 2018 [22]	China	Cross-Sectional	80	60.04	44 (55)	NR	2.76 (mmol/l)	CAD patients with low or high HDL.	Chinese CAD patients with low HDL showed reduced CEC and HDL dysfunction despite stable proteome and MPO levels.
Luo, 2018 [23]	China	Cross-Sectional	210	63.53	128 (60.95)	NR	42.34	Patients with CAD	ANGPTL8 impairs HDL-mediated cholesterol efflux by disrupting cholesterol removal.

CAD – coronary artery disease, HDL – High-Density Lipoprotein, CAG – coronary angiography, PCI – percutaneous coronary intervention, or MSCT – multi-slice coronary computed tomography, STEMI – ST-segment elevation myocardial infarction, MI – myocardial infarction, EF – Ejection Fraction, ANGPTL8 – angiopoietin-like protein 8, HDL-SPE – High-Density Lipoprotein-Specific Protein Enrichment, SR-BI – scavenger receptor class B type I, PLTP – Phospholipid Transfer Protein

Outcomes of meta-analysis

Main Outcomes

CEC

• **Overall analysis.** CEC was evaluated across fifteen studies(). The analysis included a total of [8], [483] patients, comprising [4], [163] in the CAD arm and [4], [320] in the non-CAD arm (Figure [2]. The pooled standardized mean difference (SMD) was – [0]. [40] – [95]% CI: – [0]. [53], – [0]. [26]], with a P-value < [0]. [0001], demonstrating a statistically significant reduction in CEC levels among CAD patients compared to those without CAD. The analysis revealed substantial heterogeneity (I^2 = [85]%, P < [0]. [00001], which persisted despite sensitivity analyses, suggesting variability across studies that could not be fully accounted for.

• **Association of CEC with CHD risks.** This pooled analysis examined the link between CEC and the risk of CAD across 16 studies (Fig. 3). The combined OR of 0.57 (95% CI: 0.48−0.67, $p < 0.00001$) revealed that higher CEC is significantly associated with a reduced risk of CAD. The analysis revealed moderate heterogeneity ($I^2 = 49\%$, $p = 0.03$) (Fig. 3A). In addition, the pooled risk ratio (RR) is 0.64 (95% CI: 0.48−0.86), indicating that higher CEC is significantly related to a 36% reduced risk of CAD ($p = 0.003$). However, significant heterogeneity was noticed among the studies ($I^2 = 80\%$, $p = 0.0004$) (Fig. 3B).

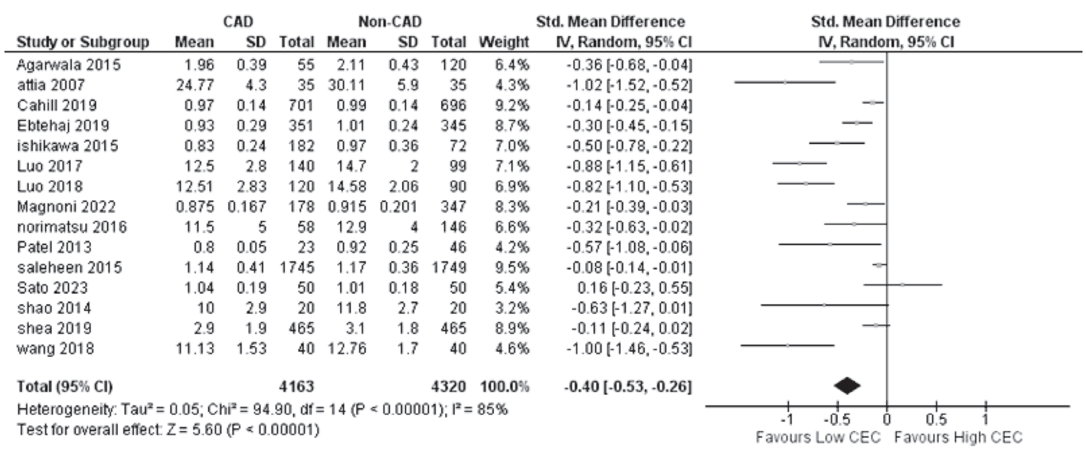

Fig. 2. The overall analysis of CEC

• **Publication bias.** The publication bias is illustrated in the funnel plots in Fig. 4, which display an asymmetrical distribution of studies around the vertical reference line, indicating a potential risk of publication bias.

Other Outcomes

• **Cardiac death.** This pooled analysis evaluated the association between CEC and cardiac mortality across three studies (Fig. 5). The pooled OR of 3.94 (95% CI: 2.63−5.90), with a p-value < 0.00001, demonstrated that individuals with reduced CEC face a substantially greater risk of cardiac death compared to those with higher CEC levels. The heterogeneity among the studies is negligible (I^2 = [0]%, P = [0]. [91].

• **All causes of death.** This analysis evaluated the link between CEC and all-cause death based on two studies (Fig. 6). An OR of 2.84 (95% CI: 2.01-4.00), $p < 0.00001$ suggests that individuals with diminished CEC have a substantially greater likelihood of all-cause death compared to those with improved CEC. The analysis demonstrated moderate heterogeneity (I^2 = 53%, p = 0.14.

• **Non-fatal MI.** This analysis evaluated the relationship between CEC and non-fatal MI based on two studies (Fig. 7). The pooled OR of 3.47 (95% CI: 0.41-29.22), p = 0.25 indicated a statistically insignificant association between impaired CEC and non-fatal MI risk. The analysis showed no heterogeneity (I^2 = 0%, p = 0.50).

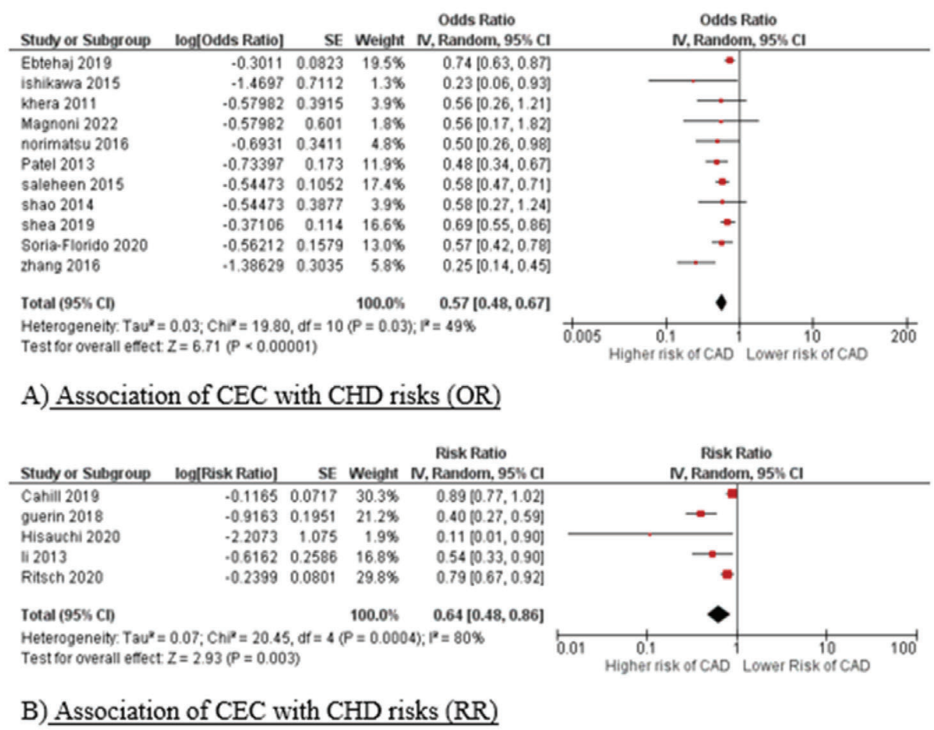

Fig. 3. Association of CEC with CHD risk

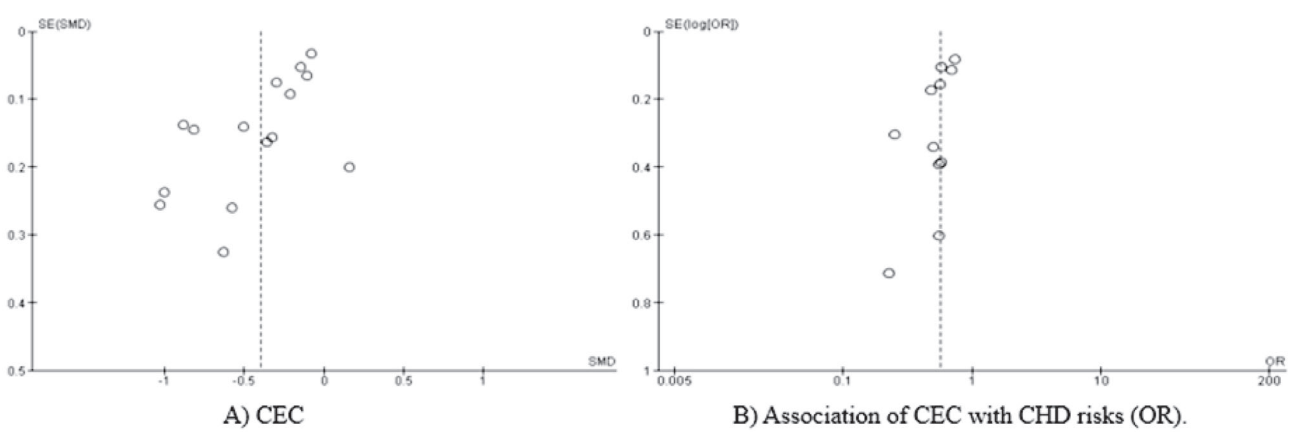

Fig. 4. Funnel plots for publication bias of main outcomes

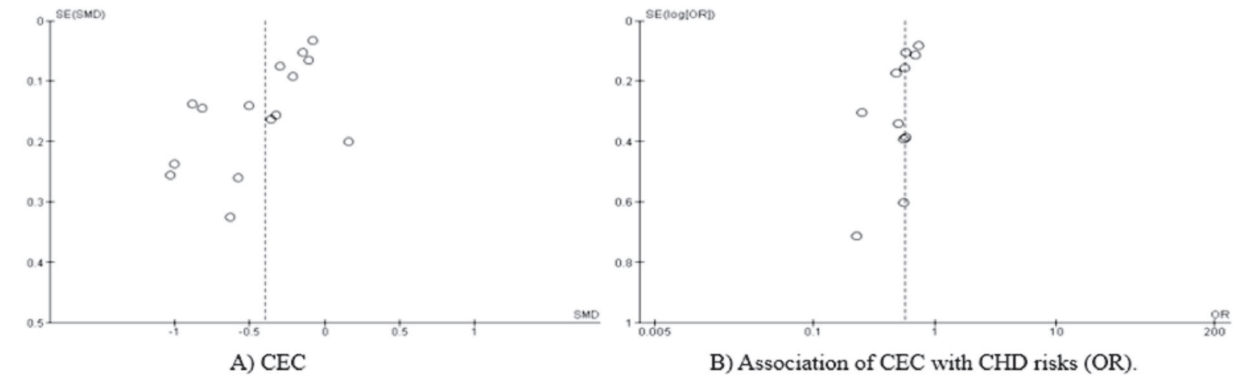

Fig. 5. The overall analysis of cardiac death

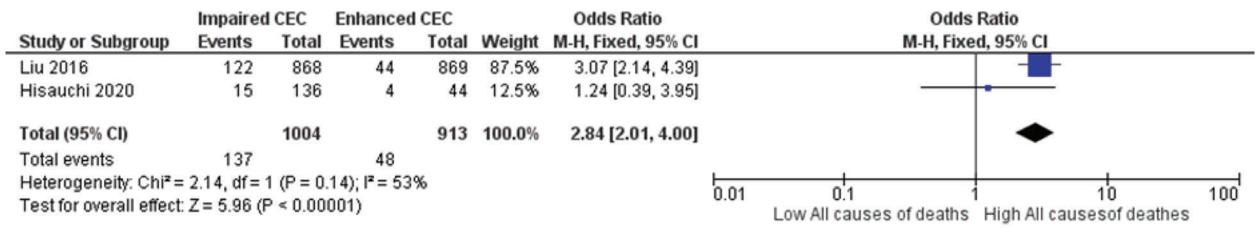

Fig. 6. The overall analysis of All causes of death

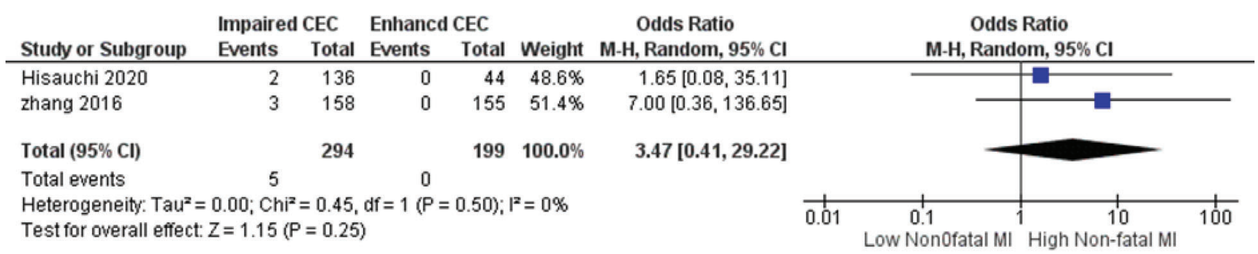

Fig. 7. The overall analysis of non-fatal MI

Discussion

CEC is generally measured using in vitro assays that assess the ability of a patient's HDL to promote cholesterol efflux from radiolabeled or fluorescently tagged macrophage foam cells. The most commonly employed methods include efflux assays based on cultured macrophages (e.g., J 774, THP-1 cells) that quantify cholesterol transfer to apoB-depleted plasma or isolated HDL fractions. Variations exist depending on the efflux pathway being evaluated, such as ABCA 1-mediated efflux, ABCG 1, or passive diffusion. Recently, cell-free assays targeting HDL-specific phospholipid efflux have also been developed for improved reproducibility.

In real-life clinical practice, while CEC measurement is still largely research-based, its integration into cardiovascular risk prediction models could help refine patient stratification. By combining CEC with traditional risk markers such as LDL-C, blood pressure, and diabetes status, clinicians may better identify high-risk individuals who may not be adequately captured by standard lipid profiles. Furthermore, therapeutic interventions aimed at enhancing HDL functionality, rather than simply raising HDL-C levels, could provide new treatment avenues. Thus, standardization of CEC measurement and validation in large-scale clinical settings remain essential steps toward its adoption in routine practice.

Our meta-analysis, encompassing 23 studies, provides robust evidence on the relationship between CEC and CVS risk. Consistently lower CEC levels were observed in CAD patients, reinforcing the hypothesis that impaired cholesterol efflux contributes to disease progression. The negative relationship between CEC and CAD risk, along with its ability to predict both cardiac and all-cause mortality, underscores the probable utility of CEC as a biomarker for evaluating CVS risk. However, our findings also reveal inconsistencies, particularly regarding the relationship between CEC and myocardial infarction, where no significant association was detected. These discrepancies may stem from variations in study populations, methodologies, and CEC measurement techniques, emphasizing the need for standardized assessment protocols.

HDL contributes to slowing the progression of atherosclerotic plaque formation through multiple biological processes. However, research indicates that genetic variations influencing HDL-C levels do not always correspond with CAD risk, and therapeutic strategies designed to elevate HDL concentrations have not consistently led to a reduction in CVS events among CAD patients. As a result, assessing HDL levels alone does not provide a comprehensive evaluation of its functionality. On the other hand, CEC is essential for reverse cholesterol transport, aiding in the removal of cholesterol from macrophages within arterial walls and transferring it to the liver for metabolism. This process is a key mechanism through which HDL contributes to preventing the buildup of plaque. Therefore, HDL-CEC is suggested as a key marker of plasma HDL functionality and a potential biomarker for assessing CVS risk. Cheng et al. demonstrated significantly lower CEC in CAD patients, a finding that aligns with the results reported by Ye et al. and those of our study. Moreover, individuals with high CEC exhibit a significantly reduced risk of CAD, as highlighted by Cheng et al., and Ye et al., and consistently supported by our findings.

Similar to CAD, CVS mortality is driven by a complex interplay of conventional risk factors and genetic predisposition. While CEC is one of many contributing factors, a study by Cheng et al. reported an insignificant correlation between CEC and the risk of CVS death, contradicting both our findings and those of Ye et al. This discrepancy highlights the need for further investigation. Furthermore, changes in HDL-CEC may play a bidirectional role, acting both as a driving force and a result of CAD onset and progression. Ye et al. established an association between CEC and the risk of all-cause death in CAD patients. Our pooled analysis further confirmed CEC as a reliable prognosticator of all-cause death in this population. However, both Ye et al.() and our study revealed an insignificant association between CEC and myocardial infarction, reinforcing the consistency of these findings.

Despite these promising findings, this study has certain limitations. High heterogeneity was observed across the pooled studies, likely due to differences in experimental methodologies and patient characteristics. Furthermore, the number of studies included in the all-cause mortality, cardiac death, and non-fatal MI analyses was relatively small, limiting the statistical power of our conclusions. Another important limitation is the inability to assess other protective functions of HDL, such as its antioxidative, anti-inflammatory, and antidiabetic effects, which may also influence CVS outcomes.

Future perspectives

Future studies should focus on refining CEC measurement techniques to improve reproducibility and comparability across research settings. Comprehensive, large-scale prospective studies are essential to determine whether causal links exist between CEC and the occurrence of CVS events. Furthermore, integrating CEC into established risk prediction models alongside traditional biomarkers may enhance the accuracy of CVS risk stratification. Investigating the molecular pathways underlying CEC's cardioprotective effects and its interactions with other HDL functions could provide novel therapeutic targets for atherosclerosis prevention.

Conclusion

This meta-analysis underscores the significance of CEC as a potential biomarker for CVS risk assessment. Our findings confirm that individuals with CAD exhibit significantly lower CEC levels and that higher CEC is allied with a lower risk of CAD, cardiac mortality, and all-cause mortality. However, an insignificant association was observed between CEC and non-fatal MI. Given the heterogeneity among studies, further research is essential to validate CEC as a predictive tool and explore its role in CVS disease prevention and management.

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References

1. von Eckardstein A, Nordestgaard BG, Remaley AT, Catapano AL. High-density lipoprotein revisited: biological functions and clinical relevance. Eur Heart J. 2023;44(16):1394-1407. https://doi.org/10.1093/eurheartj/ehac605

2. Collins R, Armitage J, Parish S, Sleight P, Peto R, Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. Lancet. 2004;363(9411):757-767. https://doi.org/10.1016/S0140-6736(04)15690-0

3. Reiner Z. Managing the residual cardiovascular disease risk associated with HDL-cholesterol and triglycerides in statin-treated patients: a clinical update. Nutr Metab Cardiovasc Dis. 2013;23(9):799-807. https://doi.org/10.1016/j.numecd.2013.05.002

4. Lüscher TF, Landmesser U, von Eckardstein A, Fogelman AM. High-density lipoprotein: vascular protective effects, dysfunction, and potential as a therapeutic target. Circ Res. 2014;114(1):171-182. https://doi.org/10.1161/CIRCRESAHA.114.300935

5. Pownall HJ, Gotto AM. New insights into the high-density lipoprotein dilemma. Trends Endocrinol Metab. 2016;27(1):44-53. https://doi.org/10.1016/j.tem.2015.11.004

6. Glomset JA. The plasma lecithins: cholesterol acyltransferase reaction. J Lipid Res. 1968;9(2):155-167.

7. Rader DJ, Alexander ET, Weibel GL et al. The role of reverse cholesterol transport in animals and humans and its relationship to atherosclerosis. J Lipid Res. 2009;50 Suppl(Suppl):S189-S194. https://doi.org/10.1194/jlr.R800088-JLR200

8. Kappelle PJWH, Gansevoort RT, Hillege JL et al, PREVEND study group. Apolipoprotein B/A-I and total cholesterol/high-density lipoprotein cholesterol ratios both predict cardiovascular events in the general population independently of nonlipid risk factors, albuminuria and C-reactive protein. J Intern Med. 2011;269(2):232-242. https://doi.org/10.1111/j.1365-2796.2010.02323.x

9. Nicholls SJ, Tuzcu EM, Sipahi I, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. JAMA. 2007;297(5):499-508. https://doi.org/10.1001/jama.297.5.499

10. Lee JJ, Chi G, Fitzgerald C, et al. Cholesterol efflux capacity and its association with adverse cardiovascular events: a systematic review and meta-analysis. Front Cardiovasc Med. 2021;8:774418. https://doi.org/10.3389/fcvm.2021.774418

11. Winkelmann BR, März W, Boehm BO, et al. Rationale and design of the LURIC study—a resource for functional genomics, pharmacogenomics, and long-term prognosis of cardiovascular disease. Pharmacogenomics. 2001;2(1 Suppl 1):S1-S73. https://doi.org/10.1517/14622416.2.1.S1

12. Simera I, Moher D, Hoey J et al. A catalog of reporting guidelines for health research. Eur J Clin Invest. 2010;40(1):35-53. https://doi.org/10.1111/j.1365-2362.2009.02234.x

13. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2935-2959. https://doi.org/10.1016/j.jacc.2013.11.005

14. Li X-M, Tang WHW, Mosior MK, et al. Paradoxical association of enhanced cholesterol efflux with increased incident cardiovascular risks. Arterioscler Thromb Vasc Biol. 2013;33(7):1696-1705. https://doi.org/10.1161/ATVBAHA.113.301373

15. Rohatgi A, Khera A, Berry JD, et al. HDL cholesterol efflux capacity and incident cardiovascular events. N Engl J Med. 2014;371(25):2383-2393. https://doi.org/10.1056/NEJMoa1409065

16. Saleheen D, Scott R, Javad S, et al. Association of HDL cholesterol efflux capacity with incident coronary heart disease events: a prospective case-control study. Lancet Diabetes Endocrinol. 2015;3(7):507-513. https://doi.org/10.1016/S2213-8587(15)00126-6

17. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100. https://doi.org/10.1371/journal.pmed.1000100

18. Ottawa Hospital Research Institute. Accessed February 5, 2025. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

19. Soria-Florido MT, Castañer O, Lassale C, et al. Dysfunctional High-Density Lipoproteins Are Associated With a Greater Incidence of Acute Coronary Syndrome in a Population at High Cardiovascular Risk: A Nested Case-Control Study. Circulation. 2020;141(6):444-453. doi:10.1161/CIRCULATIONAHA.119.041658

20. Zhang J, Xu J, Wang J, et al. Prognostic usefulness of serum cholesterol efflux capacity in patients with coronary artery disease. Am J Cardiol. 2016;117(4):508-514. doi:10.1016/j.amjcard.2015.11.033

21. Wang G, Mathew AV, Yu H, et al. Myeloperoxidase-mediated HDL oxidation and HDL proteome changes do not contribute to dysfunctional HDL in Chinese subjects with coronary artery disease. PLoS ONE. 2018;13(3):e0193782. doi:10.1371/journal.pone.0193782

22. Shea S, Stein JH, Jorgensen NW, et al. Cholesterol mass efflux capacity, incident cardiovascular disease, and progression of carotid plaque. Arterioscler Thromb Vasc Biol. 2019;39(1):89-96. doi:10.1161/ATVBAHA.118.311366

23. Shao B, Tang C, Sinha A, et al. Humans with atherosclerosis have impaired ABCA1 cholesterol efflux and enhanced high-density lipoprotein oxidation by myeloperoxidase. Circ Res. 2014;114(11):1733-1742. doi:10.1161/CIRCRESAHA.114.303454

24. Sato M, Neufeld EB, Playford MP, et al. Cell-free, high-density lipoprotein-specific phospholipid efflux assay predicts incident cardiovascular disease. J Clin Invest. 2023;133(18). doi:10.1172/JCI165370

25. Ritsch A, Duerr A, Kahler P, et al. Cholesterol efflux capacity and cardiovascular disease: the Ludwigshafen risk and cardiovascular health (LURIC) study. Biomedicines. 2020;8(11). doi:10.3390/biomedicines8110524

26. Patel PJ, Khera AV, Wilensky RL, Rader DJ. Anti-oxidative and cholesterol efflux capacities of high-density lipoprotein are reduced in ischaemic cardiomyopathy. Eur J Heart Fail. 2013;15(11):1215-1219. doi:10.1093/eurjhf/hft084

27. Norimatsu K, Kuwano T, Miura S-I, et al. Significance of the percentage of cholesterol efflux capacity and total cholesterol efflux capacity in patients with or without coronary artery disease. Heart Vessels. 2017;32(1):30-38. doi:10.1007/s00380-016-0837-7

28. Magnoni M, Andreini D, Pirillo A, et al. Predictive value of HDL function in patients with coronary artery disease: relationship with coronary plaque characteristics and clinical events. Ann Med. 2022;54(1):1036-1046. doi:10.1080/07853890.2022.2063374

29. Luo M, Zhang Z, Peng Y, Wang S, Peng D. The negative effect of ANGPTL8 on HDL-mediated cholesterol efflux capacity. Cardiovasc Diabetol. 2018;17(1):142. doi:10.1186/s12933-018-0785-x

30. Luo M, Liu A, Wang S, et al. ApoCIII enrichment in HDL impairs HDL-mediated cholesterol efflux capacity. Sci Rep. 2017;7(1):2312. doi:10.1038/s41598-017-02601-7

31. Liu C, Zhang Y, Ding D, 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. doi:10.1016/j.atherosclerosis.2015.10.111

32. Khera AV, Cuchel M, de la Llera-Moya M, et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. N Engl J Med. 2011;364(2):127-135. doi:10.1056/NEJMoa1001689

33. Ishikawa T, Ayaori M, Uto-Kondo H et al. High-density lipoprotein cholesterol efflux capacity as a relevant predictor of atherosclerotic coronary disease. Atherosclerosis. 2015;242(1):318-322. doi:10.1016/j.atherosclerosis.2015.06.028

34. Hisauchi I, Ishikawa T, Ayaori M, et al. High-Density Lipoprotein Cholesterol Efflux Capacity as a Novel Prognostic Surrogate for Coronary Artery Disease. J Atheroscler Thromb. 2021;28(7):696-702. doi:10.5551/jat.59279

35. Guerin M, Silvain J, Gall J, et al. Association of Serum Cholesterol Efflux Capacity With Mortality in Patients With ST-Segment Elevation Myocardial Infarction. J Am Coll Cardiol. 2018;72(25):3259-3269. doi:10.1016/j.jacc.2018.09.080

36. Ebtehaj S, Gruppen EG, Bakker SJL et al. HDL (High-Density Lipoprotein) Cholesterol Efflux Capacity Is Associated With Incident Cardiovascular Disease in the General Population. Arterioscler Thromb Vasc Biol. 2019;39(9):1874-1883. doi:10.1161/ATVBAHA.119.312645

37. Cahill LE, Sacks FM, Rimm EB, Jensen MK. Cholesterol efflux capacity, HDL cholesterol, and risk of coronary heart disease: a nested case-control study in men. J Lipid Res. 2019;60(8):1457-1464. doi:10.1194/jlr.P093823

38. Attia N, Nakbi A, Smaoui M, et al. Increased phospholipid transfer protein activity associated with the impaired cellular cholesterol efflux in type 2 diabetic subjects with coronary artery disease. Tohoku J Exp Med. 2007;213(2):129-137. doi:10.1620/tjem.213.129

39. Agarwala AP, Rodrigues A, Risman M, et al. High-density lipoprotein (HDL) Phospholipid Content and Cholesterol Efflux Capacity Are Reduced in Patients With Very High HDL Cholesterol and Coronary Disease. Arterioscler Thromb Vasc Biol. 2015;35(6):1515-1519. doi:10.1161/ATVBAHA.115.305504

40. Rye K-A, Bursill CA, Lambert G et al. The metabolism and anti-atherogenic properties of HDL. J Lipid Res. 2009;50 Suppl(Suppl): S195-200. doi:10.1194/jlr.R800034-JLR200

41. Rader DJ, Hovingh GK. HDL and cardiovascular disease. Lancet. 2014;384(9943):618-625. doi:10.1016/S0140-6736(14)61217-4

42. Fogacci F, Borghi C, Cicero AFG. New evidence on the association between high-density lipoprotein cholesterol and cardiovascular risk: a never-ending research story. Eur J Prev Cardiol. 2022;29(5):842-843. doi:10.1093/eurjpc/zwac015

43. Cuchel M, Rader DJ. Macrophage reverse cholesterol transport: a key to the regression of atherosclerosis? Circulation. 2006;113(21):2548-2555. doi:10.1161/CIRCULATIONAHA.104.475715

44. Koekemoer AL, Codd V, Masca NGD, et al. Large-scale analysis of determinants, stability, and heritability of high-density lipoprotein cholesterol efflux capacity. Arterioscler Thromb Vasc Biol. 2017;37(10):1956-1962. https://doi.org/10.1161/ATVBAHA.117.309201

45. Cheng W, Rosolowski M, Boettner J, et al. High-density lipoprotein cholesterol efflux capacity and incidence of coronary artery disease and cardiovascular mortality: a systematic review and meta-analysis. Lipids Health Dis. 2022;21(1):47. https://doi.org/10.1186/s12944-022-01657-3

46. Ye H, Xu G, Ren L, Peng J. Cholesterol efflux capacity in coronary artery disease: a meta-analysis. Coron Artery Dis. 2020 Mar 20. https://doi.org/10.1097/MCA.0000000000000886