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Non-HDL Cholesterol and LDL Cholesterol as Main Risk Factors for Coronary Heart Disease: Meta-Analysis

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ABSTRACT

Coronary heart disease is a highly frequent illness in both developed and developing countries. Non-HDL cholesterol (non-HDL-c) and LDL cholesterol (LDL-c) levels are biomarkers that doctors frequently utilize to assess the risk of coronary heart disease (CHD). This study was a systematic review and meta-analysis to assess the association between non-HDL-c and LDL-c as major risk factors for coronary heart disease. Cochrane, PubMed, and Science Direct searches were conducted using the keywords "LDL cholesterol," "non-HDL cholesterol," and "coronary heart disease." Any research that describes the analysis of LDL-c and non-HDL-c as key risk factors for CHD and all studies involving patients diagnosed with CHD were included in the literature. A total of seven papers were involved in the qualitative analysis (systematic review), while five studies were included in the quantitative analysis (meta-analysis). The English-language research includes two RCTs, four case-control studies, and one cohort study, with a total of 68,713 individuals. LDL-c parameters were obtained (MD = 8.45; 95 percent CI = 7.03-9.87 p=0.001) and non-HDL-c (p=0.001) (MD = 35.57; 95 percent CI = 33.27-37.88). n-HDL-c may be a more significant parameter of CHD risk because it has a higher MD value.

Keywords: LDL cholesterol, non-HDL cholesterol, coronary heart disease

INTRODUCTION

Coronary Heart Disease (CHD) is a common disease in both developed and developing countries. Previous studies suggested that CHD accounted for 2.2% of the disease burden and 32.7% of cardiac vascular disease worldwide.[1] World Health Organization (WHO) in 2015 reported that cardiac vascular disease kills 17.5 million people, nearly 31% of all diseases worldwide, and causes 7.4 million CHD cases worldwide. This disease is estimated to kill 23.3 million people in 2030. Although CHD mortality has significantly decreased in western countries over the last decade, it still accounts for almost one-third of all fatalities in persons over the age of 35. The fact that deaths from CHD are estimated to increase continuously in developing countries illustrates a need to implement effective primary preventive strategies worldwide and identify risk groups and areas for potential improvement.[2]

Indonesia is the 4th most populated nation worldwide with 250 million people as a population and has experienced a fast economic expansion in recent decades. While the current problem of communicable illnesses and the prospect of developing diseases with epidemic or pandemic potential as crucial public health issues in Indonesia, the burden of disease associated with noncommunicable diseases has emerged as a serious public health issue.[3]

The cardiac vascular disease accounts for almost one-third of all fatalities in Indonesia, and it is the foremost cause of death in the nation. Coronary heart disease and stroke are predicted to kill more than 470,000 people in Indonesia per year.[4] Risk factors that can be altered are high blood pressure, high cholesterol, diabetes, obesity, and smoking, which are the leading causes of cardiac vascular disease in Indonesia. The growing tendency of risk factors over time suggests that the problem of cardiac vascular disease in Indonesia is estimated to rise over time.[5] Some experts presumed that non-HDL cholesterol (non-HDL-c) tests are a better risk marker in primary and secondary prevention studies of cardiac vascular disease.[6]

The Cholesterol Treatment Trialists' (CTT) Collaboration previously published a meta-analysis of 170,000 people in twenty-one studies comparing conventional statin regimens to controls and 5 trials comparing more intensive vs. fewer intensive regimens. The report showed that a 1 mmol per L reduction in LDL cholesterol (LDL-c) with a standard

statin regimen reduced the prevalence of a Major Adverse Cardiac Vascular Event (MACE), which is defined as a non-fatal myocardial infarction or coronary death, stroke, or coronary revascularization procedure by about one-fifth, and a further reduction in LDL-c with more intensive statin regimens resulted in further risk reduction.[7]

As mentioned before, LDL-c is a proven risk factor the presence of non-HDL-c can also indirectly be a risk factor for the incidence of CHD. This happens because non-HDL-c contains all atherogenic cholesterol, not only LDL-c. In addition, non-HDL-c also contains other important components such as apolipoprotein B, which has also been proven to be a risk factor in the incidence of CHD. Therefore, a study needs to be conducted to analyze the effect of non-HDL-c as a risk factor. Both non-HDL-c and LDL-c can be risk factors for CHD, but further analysis is needed regarding the main and more significant risk factors for CHD. Therefore, this study aimed to analyze non-HDL-c and LDL-c as the main risk factors for CHD.

METHODS

This study was carried out using a meta-analysis that aimed to analyze LDL-c and non-HDL-c as the key risk factors for CHD reported as Odd Ratio (OR; IC 95%). The keywords were based on PICO, consisting of P (population): Coronary heart disease patients; I (intervention): LDL cholesterol, non-HDL cholesterol; C (comparison): Control patient; and O (outcome): Determine the main risk factors for CHD. The population used in this analysis was all studies that have analyzed LDL-c and non-HDL-c as the main risk factors for CHD according to the inclusion and exclusion criteria.

The inclusion criteria in this study were as follows: All clinical phase studies that discuss the analysis of LDL-c and non-HDL-c as the main risk factors for CHD; All studies with patients diagnosed with CHD; Studies written in English or Indonesian; Studies published in the last 5 years. The exclusion criteria in this study were as follows: The number of participants less than 10 participants; No data on LDL-c; No data on total cholesterol and HDL-c or; No data on non-HDL-c. The searching protocol was carried out using several databases, such as PubMed, ScienceDirect, and Google Scholar for articles up through the last December 2021. This study was carried out based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline.

The quantitative data from the studies were then collected to calculate the adjusted estimates of the risk using a best-adjusted OR with a 95% Confidence Interval (CI) and p-value below 0.05 ($p<0.05$). The Q-test was used to assess heterogeneity with a p-value below 0.05 ($p<0.05$). Study quality was calculated using Modified Newcastle Ottawa Scale (NOS). Publication bias was also calculated using a funnel plot.

RESULTS AND DISCUSSIONS

After the literature search process, 283 studies were found with 492 from online databases (PubMed, ScienceDirect, and Cochrane) and 1 study from data sources previously identified by the authors. A total of 472 studies were obtained after removing duplicates using computer software (Citation Manager). After the title and abstract screening process, 335 studies were excluded due to the discrepancy between the title of the study and the purpose of the current study and incomplete abstracts, resulting in a total of 137 studies that could be assessed for eligibility. Furthermore, 130 studies wereaexcluded becauseatheyadid not meet the inclusion and exclusion criteria, making 7 studies involved in the qualitative analysis (systematic reviews) and 5 studies involved in the quantitative analysis (meta-analysis). The entire literature search process followed the PRISMA guideline and was summarized through a flowchart (Figure 1).

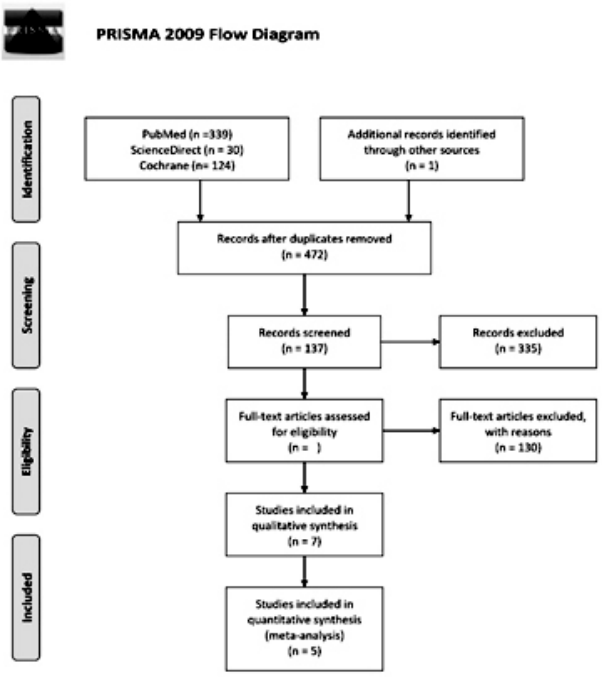

Figure 1. PRISMA flowchart

Table 1. Study characteristics

Author, Year	Population		Total	Age (Mean±SD)		Gender (M vs. F)		Country	Study Design
	Case	Control		Case	Control	Case	Control		
You (2020)[8]	341	250	591	66.67±12.29	60.86±9.69	259 vs. 110	82 vs. 140	China	Case-control
Zeng (2021)[9]	60	385	445	64.5 (55.3-72) *median	65.0 (59-71) *median	280 vs. 41	75 vs. 19	China	Case-control
Koba (2019)[10]	66	49	115	62.2±11.5	61.5±10.1	66 vs. 49	-	Japan	Case-control
Shabana (2020)[11]	500	250	750	59±12.7	55.87±10.37	291 vs. 139	308 vs. 111	Pakistan	Case-control
Ihm (2020)[12]	29	318	347	61.79±9.76	-	221 vs. 126	-	South Korea	Randomized clinical trial
Arca (2018)[13]	36120	30038	66158	67.4±12.8	-	15062 vs. 21058	-	Italy	Cohort
Teramoto (2017)[14]	204	103	307	60.9±9.6	60.5±9.9	142 vs. 66	62 vs. 37	Japan	Randomized clinical trial

Table 2. Comparative analysis of cholesterol levels between CHD patients and control patients

Author, Year	CHD Cholesterol Levels (Mean±SD)		Control Cholesterol Levels (Mean±SD)	
	LDL-c	Non-HDL-c	LDL-c	Non-HDL-c
You (2020)[8]	50.2±16.4	82.4±39.7	46.3±14.4	56.7±16.0
Zeng (2021)[9]	61.2±7.2	75.6±14.4	57.6±9.0	70.2±10.8
Koba (2019)[10]	123.1±34.7	143.8±35.8	123.4±29	148.1±33.8
Shabana (2020)[11]	104.6±37.9	163.1±42.5	78.1±15.4	78±20.4
Ihm (2020)[12]	77.96±1.12	107.94±1.29	-	-
Arca (2018)[13]	2.7±1.0	3.4±1.1	-	-
Teramoto (2017)[14]	80.9±31.5	106.4±30.6	132.8±34	161.0±34.9

All data characteristics of the involved studies are written in Table 1. All studies were written in English, which consist of 2 RCT studies, 4 case-control studies, and 1 cohort study with a total of 68,713 participants. A total of 2 studies were taken from China, another 2 studies were taken from Japan, and each other study was taken from Italy, Pakistan, and South Korea. A total of 37,320 people suffered from CHD and 31,393 people were classified as the control group. A total of 4 studies reported the patient's disease status as Acute Coronary Syndrome (ACS) and 2 other studies reported Chronic Coronary Syndrome (CCS). Most of the studies reported the presence of risk factors such as diabetes and hypertension accompanied by reports of consumption of drugs similar to the statin drug class. All seven studies were analyzed qualitatively; however, because 2 out of 7 studies did not include any of non-HDL-c and LDL-c levels for control patients, only 5 studies were analyzed quantitatively. Non-HDL-c levels and LDL-c levels in CHD patients increased compared to control patients in all five studies.

The quality of the bias assessment using the Cochrane Risk of Bias for Randomized Controlled Trials (RoB) for RCT studies is presented in Table 2. The RoB criteria consist of components of random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), which were calculated automatically in the software into 3 categories of study quality, such as low (low), moderate (fair), and high (high).

Table 3. Comparative data characteristics

Author, Year	Comparative Characteristics				Quality of the Study
	Clinical Diagnosis	Risk Factor	Drug Consumption	Family History	
You (2020)[8]	ACS	Smoking, Hypertension, Hyperlipidemia, Diabetes,	-	-	High (8)
Zeng (2021)[9]	ACS	Diabetes, Hypertension	-	-	High (8)
Koba (2019)[10]	ACS	Beta-blocker	Beta-blocker, Anti-thrombotic drugs, Lipid-lowering drugs, Statin, Ezetimibe, Fibrate, Omega-3 fatty acid	-	High (8)
Shabana (2020)[11]	CCS	Smoking, obesity, hypertension.	-	180 vs 45	High (8)
Ihm (2020)[12]	CHD	Smoking, diabetes mellitus, hypertension, myocardial infarction, angina pectoris, percutaneous coronary intervention	Pitavastatin calcium 2 mg and fenofibrate 160 mg	-	Fair
Arca (2018)[13]	ACS	Hypertension, congestive heart failure, dementia, chronic obstructive pulmonary disease, moderate/severe liver disease	Statin, ezetimibe	-	High (8)
Teramoto (2017)[14]	CHD	Diabetes	Statin, ezetimibe, niacin, fibrate	-	Fair

Meanwhile, based on data analysis, the 2 included RCT studies had a fair risk of bias.

The quality of bias assessment from 4 case-control studies and 1 cohort study using the NOS is presented in Table 3. The NOS criteria have three components, such as patient selection or selection (4 points), group comparability or comparability (2 points), and determination exposure or exposure (3 points). Measurement of domain selection includes proper case definition, representative case, method of selection, and definition of the control group. Measurement of the comparability domain includes a selection of controls for the most and extra factors (additional factors). Measurement of exposure domain includes a method of determining exposure, method of determining cases and controls, and level of nonresponse. The overall score varied from 0 (worst) to 9 (best). Overall quality was rated high (high) (final score >7), moderate (fair) (final score 5 to <7), or poor (low) (final score <4). The results of data analysis showed that the average overall score of the included studies was 8. All studies were known to have high quality (high).

Based on Table 4, There were significant differences in both non-HDL-c levels and LDL-c levels in CHD patients compared to control patients. Based on Table 5, it can be concluded that non-HDL-c and LDL-c levels in CHD patients were close to an ideal category, while both levels were in the ideal category in control patients.

A total of 5 studies were included in the quantitative analysis with a total of 2,208 people

Table 4. Range of non-HDL-c and LDL-c levels of CHD and control patients

CHD Cholesterol Levels (mg/dL)		Control Cholesterol Levels (mg/dL)	
LDL-c	**Non-HDL-c**	**LDL-c**	**Non-HDL-c**
109,54	146,86	67.18	79.62

Table 5. Range of non-HDL-c and LDL-c levels from recent reference[15]

Non-HDL-c	Category	LDL-c
Below 100 mg/dL	Ideal with a very high risk of heart attack	Below 70 mg/dL
Below 130 mg/dL	Ideal for people with heart disease or diabetes	Below 100 mg/dL
From 130 to 159 mg/dL	Close to ideal	From 100 to 129 mg/dL
From 160 to 189 mg/dL	Borderline high	From 130 to 159 mg/dL
From 190 to 219 mg/dL	High	From 160 to 189 mg/dL
≥220 mg/dL	Very high	≥190 mg/dL

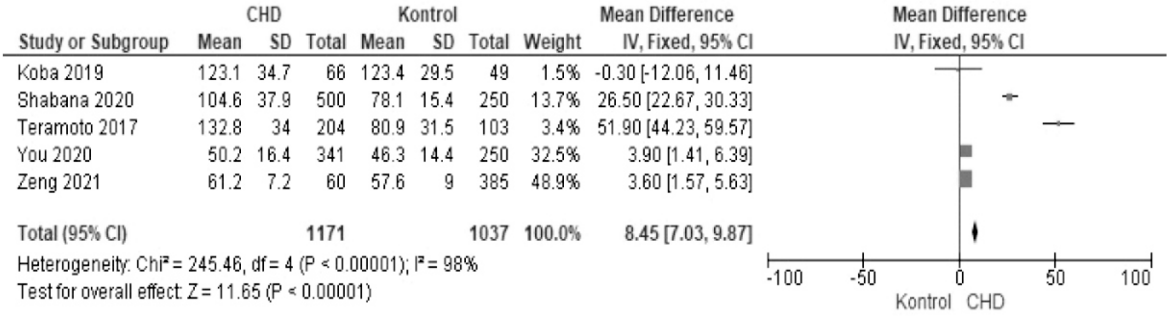

Figure 2. Forest plot for LDL-c

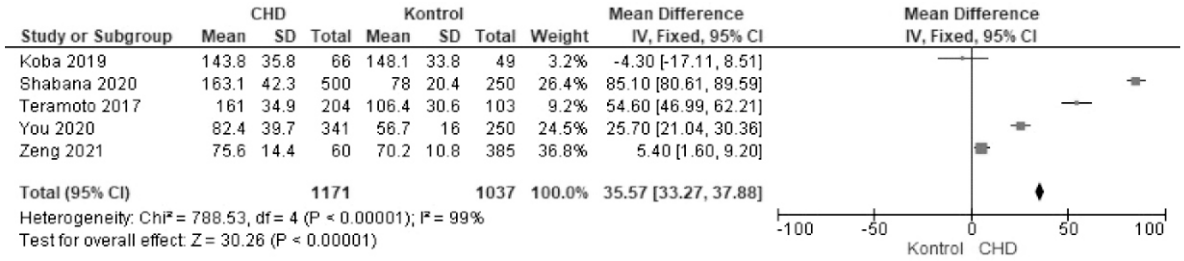

Figure 3. Forest plot for non-HDL-c

including 1171 in the CHD group and 1037 in the control group. Differences in LDL-c and n-HDL-c levels were assessed using the Mean Difference (MD) approach using fixed model analysis. The significance value of the total inclusion study used the p-value in the Z test, a combined estimation test of statistically significant effects with the Z coefficient (Cohen's d) divided by the Standard Error (SE) to determine the p-value. The null hypothesis (Ho) is d=0. A significant Z test suggests that ES is different from zero. In addition, the Z-value can also be represented qualitatively by the location of the diamond shape, which represents the overall effect on the forest plot, whether it is in contact with the midline or not. There was a significant difference based on the analysis of the overall effect on LDL-c and non-HDL-c levels of CHD patients and controls, which indicated that these two values can be used as biomarkers that correlate with the incidence of CHD. Meanwhile, the LDL-c parameter was obtained (MD=8.45; 95% CI=7.03-9.87 p < 0.001) and non-HDL-c (MD=35.57; 95% CI=33.27-c). 37.88 p < 0.001) as described in Figure 2 and 3.

The Q-test was used to evaluate the evidence for heterogeneity (Q). The Q-test uses a weighted calculation of the squared difference between the effects of each study and the combined effects across studies. In addition, the analysis describes the percentage of variation across studies due to heterogeneity with the formula that is 100% x (Q-df)/Q. The analysis showed that the mean difference between LDL-c ($p < 0.001$) and non-HDL-c ($p < 0.001$) levels in both groups was found to have heterogeneity, which was also supported by the I2 test value > 50%. Publication bias was determined by assessing the symmetry of the funnel plot. The graph on the funnel plot was reported symmetrical if the distance between the confidence interval line and the overall effect line (the center line) was the same between the right and left. The graphs in both types of analysis were found to be symmetrical, which indicated a low risk of publication biases described in Figure 4 and Figure 5.

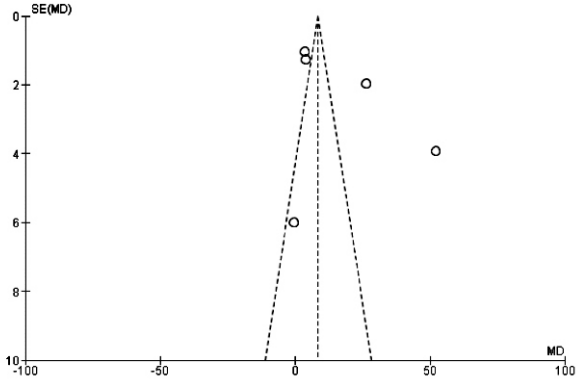

Figure 4. Funnel plot for LDL-c

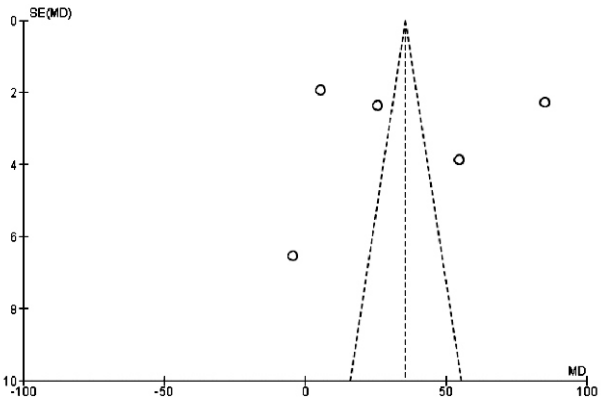

Figure 5. Funnel plot for non-HDL-c

Research consistently showed that the risk of CHD was closely correlated with LDL-c stages. Lowered LDL-c led to a lowered risk of cardiac vascular disease. In addition, a higher decrease in LDL-c led to bigger benefits. A reduction of LDL-c of close to 50% was required to stop the development of atherosclerotic plaques. The European and American Cardiological Associations issued a recent recommendation that emphasized the role opinion-HDL-c levels in assessing the risk of cardiac vascular disease. Non-HDL-c was presumed to be statistically well than LDL-c as a hazard aspect for CHD in this investigation. Abundant clinical research has established the advantages of non-HDL-c in the preclusion of cardiac vascular illness. A 1 mg/dL rise in non-HDL-c levels was shown to rise the hazard of death from the cardiac and vascular disease by 5%. This shows that non-HDL-c levels may be a better prognosticator of lipid hazards than other standard lipid risk variables.[16]

The effect of rising triglyceride levels on LDL-c levels demonstrated that non-HDL-c may be used to estimate the hazard of atherosclerosis and cardiac vascular disease in hypertriglycemic individuals. Another research indicated that the risk of CHD in diabetic samples did not rise with an increase in LDL-c rates, but did increase with an increase in non-HDL-c levels. The study also indicated that non-HDL-c levels in diabetic individuals were a better predictor of CHD death than LDL-c levels. The triglyceride sinking variant in the lipoprotein lipase protein sequence and LDL-c sinking variant in the LDL receptor protein sequence were related to a lesser hazard of CHD in a Mendelian randomization investigation connecting 654,783 applicants (OR 0.771 and 0.773).[17]

The majority of lipid-modifying medications reported as monotherapy showed a correlation between the proportional reduction in non-HDL-c and proportional decrease in CHD risk. Samples with height rates of non-HDL-c were found to be more complex hazard of CHD than those with low rates of LDL-c. Numerous research has looked at the relationship between LDL-c or non-HDL-c and the hazard of CHD. The Hazard Ratio (HR) for CHD in a case-control research sample was 2.76 (95 percent CI, 1.66-4.58) for non-HDL-c levels and 1.81 (95% CI, 1.12-2.93) for LDL-c levels. This indicated that non-HDL-c might be further closely related to CHD hazard than LDL-c. A one-standard-deviation rise in non-HDL-c was related to an amplified hazard of CHD in males (HR 1.22; 95% CI, 1.06-1.40), but not in females (HR 1.28; 95% CI, 1.06-1.56). Patients with increased non-HDL-c (>123 mg/dL) had a substantially larger waist circumference as well as blood total cholesterol, LDL-c, triglycerides, and HDL-c. The concentration of non-HDL-c can also be used to calculate the overall quantity of proatherogenic lipoprotein containing apo-B.

Non-HDL-c levels were linked to more accurate apo-B concentrations than LDL-c values, particularly in samples with higher triglyceride levels.[17]

CONCLUSIONS AND SUGGESTIONS

This study found that there were substantial differences in LDL and non-HDL-c levels between the patients with CHD and controls, indicating that these two parameters can be the risk factors for CHD. Non-HDL-c levels can be a more significant risk factor parameter for CHD because it has a greater mean difference. Other risk factors for CHD reported from the inclusion studies were smoking, diabetes, hypertension, myocardial infarction, dyslipidemia, COPD, and liver disease.

Varying study results remain one of the limitations in this study, making it difficult to determine the definitive conclusion. It is essential to conduct a further investigation regarding the relationship of hyperlipidemia with other risk factors and pay attention to criteria that can cause bias, such as sample size, gender, BMI, dietary pattern, and medication history. Further studies on VLDL, IDL, chylomicrons and apolipoprotein B also need to be carried out considering that they are still at risk for CHD. It was expected that a specific instrument in the future can be developed to calculate non-HDL-c levels and make the determination of non-HDL-c levels much easier.

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