

# Non-HDL-C is associated with the occurrence of acute myocardial infarction in Chinese populations with diabetes

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## Research Article

**Keywords:** non-high density lipoprotein cholesterol, acute myocardial infarction, diabetic population

**Posted Date:** March 28th, 2022

**DOI:** <https://doi.org/10.21203/rs.3.rs-1235925/v2>

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# Abstract

**Background:** Non-HDL-C has been associated with the prognosis and long-term prognosis of acute myocardial infarction, but the association between non-HDL-C and the occurrence of acute myocardial infarction in the Chinese population remains unclear. The purpose of this study is to explore whether non-HDL-C is related to the occurrence of acute myocardial infarction in the Chinese, and to further explore its relationship with the occurrence of acute myocardial infarction in subjects with diabetes.

**Methods and Results:** We reviewed the medical records of patients who visited the Department of Cardiology at the First Affiliated Hospital of the University of South China from May 1, 2012 to September 30, 2020. According to inclusion and exclusion criteria, 6558 subjects were included in the non-AMI group and 3386 subjects were included in the AMI group. In the entire population, non-HDL-C was associated with the incidence of acute myocardial infarction, regardless of adjustment for confounding factors. In non-diabetic patients, non-HDL-C, HDL-C, LDL-C was found to be associated with the occurrence of acute myocardial infarction. In subjects with diabetes, non-HDL-C was associated with AMI without adjusting for confounding factors (Model 1) (OR: 1.268, 95%CI 1.035-1.547, P=0.022), and LDL-C was not associated with AMI (OR: 1.129, 95%CI 0.904 – 1.411, P=0.286), HDL-C was negatively correlated with the incidence of acute myocardial infarction (OR: 0.577, 95%CI 0.418 – 0.796, P < 0.001). After adjusting for age and sex (Model 2), non-HDL-C was positively correlated with the incidence of acute myocardial infarction (OR: 1.371, 95%CI 1.103-1.704, P=0.004), while the correlation between HDL-C and LDL-C and acute myocardial infarction was not observed. After adjusting for age, sex, hypertension/smoking, and BMI (Model 3), non-HDL-C was positively correlated with the incidence of acute myocardial infarction (OR: 1.381, 95%CI 1.103-1.728, P=0.005), and no correlation was observed between HDL-C and LDL-C and acute myocardial infarction.

**Conclusions** In subjects with diabetes, after adjusting for confounders associated with coronary heart disease, non-HDL-C was found to be associated with AMI, whereas HDL-C and LDL-C were not associated with AMI. In addition, non-HDL-C can also be found to be related to the occurrence of acute myocardial infarction in patients without diabetes.

## 1. Introduction

Acute myocardial infarction is the most severe manifestation of coronary heart disease. Nowadays, the relationship between hypercholesterolemia and CHD has been well established, and lipid-lowering therapy is an important strategy in primary and secondary prevention of CHD, and has achieved good clinical prevention and treatment effect<sup>[1-5]</sup>. Non-HDL-C has been included and designated as a secondary intervention target for patients with coronary heart disease in the Guidelines for prevention and treatment of blood lipid in Chinese adults revised in 2016. However, non-HDL-C is more commonly referred to as a common primary therapeutic target associated with LDL-C, or as a secondary target when triglycerides > 200 mg/dl<sup>[6-7]</sup>. Although treatment to control LDL-C successfully reduces the risk of coronary heart disease, there is increasing evidence that there is still a concept called residual cardiovascular risk after

LDL-C reduction with lipid-lowering agents, which makes us have to pay attention to patients at high risk of coronary heart disease who are still at some residual risk after LDL-C reduction<sup>[8-10]</sup>. CETP inhibitors have been used to improve HDL levels, but no significant reduction in cardiovascular events has been observed. This suggests that factors other than HDL concentration may be responsible for the increased risk of CVD<sup>[11]</sup>. There is now more research supporting a relationship between reduction in non-HDL-C and a reduction in cardiovascular risk<sup>[12]</sup>. In addition, individuals with type 2 diabetes with elevated levels of non-HDL-C have a higher risk of cardiovascular disease compared to the general population<sup>[13]</sup>. As early as 2011, the European Society of Cardiology (ESC)/ European Atherosclerotic Society (EAS) Joint Committee issued guidelines<sup>[14]</sup>, which identified non-HDL-C and apolipoprotein B as alternative targets of LDL-C, raising the importance of non-HDL-C in patients with diabetes. Currently, several important guidelines, including the International Atherosclerosis Society (IAS) guideline<sup>[15]</sup>, National Lipid Association (NLA) guideline, and National Institute for Health and Care Excellence (NICE) guideline<sup>[16]</sup>, have flagged non-HDL-C as a primary therapeutic target for patients with CHD. However, blood lipids vary widely among ethnic groups<sup>[17-19]</sup>. As far as is known, more studies have focused on the relationship between non-HDL-C and the prediction of long-term prognosis of cardiovascular disease. Lack of studies on the association between non-HDL-C and the incidence of acute myocardial infarction in diabetic patients in the Chinese population, and lack of more data to support the association between the two. Moreover, in daily clinical practice, most acute myocardial infarction patients admitted to emergency hospitals are non-fasting, and non-HDL-C levels may be less affected by fasting state than serum triglyceride level<sup>[20]</sup>. The present study aimed to investigate the correlation between non-HDL-C cholesterol and the incidence of acute myocardial infarction in a Chinese population that participated in the survey, most of whom were in non-fasting status.

## 2. Subjects And Methods

*2.1 Study Subjects.* We reviewed the medical records of patients who visited the Department of Cardiology at the First Affiliated Hospital of the University of South China from May 1, 2012 to September 30, 2020. According to inclusion and exclusion criteria, 6558 subjects were included in the non-AMI group and 3386 subjects were included in the AMI group. Subjects who had been diagnosed with myocardial infarction, malignancy, mental illness, myocarditis, or regular use of lipid-lowering drugs in the past 1 year were excluded. The subjects were selected in the non-AMI group based on the following inclusion criteria: coronary angiography was completed and no abnormalities were found in the coronary arteries. Patients with AMI were included in the AMI group. AMI was defined based on the universal definition criteria by the joint European Society of Cardiology (ESC)/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force<sup>[21]</sup>. This study was approved by the Ethics Committee of the First Affiliated Hospital of University of South China .

*2.2 Clinical evaluation and laboratory measurements.* The patient's hospitalization information was reviewed in detail, including resident admit notes, present history, history, personal history, progress notes, coronary angiographic surgery record, and blood biochemical results during hospitalization. The data of

the subjects were collected as follows: age, sex, body mass index(BMI= weight (kg)/height (m) <sup>2</sup>), smoking, and blood lipid indexes including TG, TC, LDL-C, HDL-C, and non-HDL-C(TC minus HDL-C). Previous medical history includes medication history, previous hypertension and diabetes, and the diagnosis of hypertension and diabetes at the time of hospitalization. Blood samples were collected within 2 hours of admission from subjects with acute myocardial infarction, rather than on the status of fasting. Measures of lipid profiles (including TC, HDL-C, LDL-C, and TG)were tested by a biochemical autoanalyzer (Cobas 8000, Roche). The results of blood lipid in patients without myocardial infarction were based on the results of the first blood drawing after admission (whether fasting or not).

*2.3 Definition.* Body mass index (BMI) is calculated by dividing weight in kilograms by height in meters squared in kg/m<sup>2</sup>. A trained nurse placed a fist-sized cuff on the participant's right arm, measured baseline blood pressure with a standard mercury sphygmomanometer, and the participant sat and remained rested for more than 15 minutes. Information on smoking habits and medical history, including cardiovascular history, hyperlipidemia, hypertension, and medication for diabetes, was collected by the cardiovascular nurse. Hypertension was defined as systolic blood pressure  $\geq 140$  mm Hg, diastolic blood pressure  $\geq 90$  mm Hg, and/or use of antihypertensive drugs. Diabetes was defined as non-fasting blood glucose level  $\geq 11.1$  mmol/L (200 mg/dL), HbA1c level  $\geq 6.5\%$ , and/or use of antidiabetic drugs. Smoking was defined as smoking at least 400 cigarettes a day for at least a year or in a lifetime, with one cigarette considered equivalent to 1.25 grams of tobacco.

*2.4 Statistical analysis.* Baseline characteristics of participants are described using mean  $\pm$  standard deviation (SD) for continuous variables with a normal distribution or approximate normal distribution, median (interquartile range, IQR) for continuous variables with a skewed distribution, and number (percent) for categorical variables. Binary logistic regression analysis was used to study the relationship between AMI and the risk of LDL-C, HDL-C, and non-HDL-C. Multi-factors logistic regression analyses were performed with no adjustments (model 1), after adjustment for age and gender (model 2), and after adjustment for traditional coronary risk factors (e.g.hypertension, diabetes, smoking, BMI, ) (model 3). Then the patients were divided into the diabetic population and non-diabetic population according to whether they had diabetes or not, and subgroup analysis was also conducted using the above method.

### 3. Results

*Clinical and Laboratory Characteristics of the Subjects.* The clinical and laboratory characteristics of the subjects are shown in Table 1. A total of 9,944 subjects (AMI group 6,558 and non-AMI 3,386) were recruited. The mean age of subjects in the non-AMI group was  $62.21 \pm 9.90$  years, and that in the AMI group was  $66.55 \pm 11.92$  years. The clinical and laboratory characteristics and univariate analysis results of diabetic subjects are shown in Table 2, and non-diabetic subjects are shown in Table 3. In diabetic subjects, the average levels of non-HDL-C, HDL-C and LDL-C in the AMI group were  $3.34 \pm 1.16$  mmol/ L,  $1.15 \pm 0.33$  mmol/ L and  $2.60 \pm 1.06$  mmol/ L, respectively. The mean levels of non-HDL-C, HDL-C and LDL-C in the non-AMI group were  $3.00 \pm 0.96$  mmol/ L,  $1.20 \pm 0.34$  mmol/ L and  $2.32 \pm 0.86$  mmol/ L, respectively. In

univariate analysis, the differences of non-HDL-C, HDL-C and LDL-C between the two groups were statistically significant.

*Multifactor analysis of the correlation between lipid parameters and acute myocardial infarction.* Binary logistic regression was used to analyze the correlation between lipid parameters and acute myocardial infarction. First, the correlation between non-HDL-C, HDL-C and LDL-C was analyzed in the whole sample population (figure 1). In model 1, non-HDL-C, HDL-C and LDL-C were mutually adjusted, and all three were correlated with acute myocardial infarction. Non-HDL-C ( $p < 0.001$ ) and LDL-C ( $p=0.002$ ) were positively correlated, while HDL-C ( $p < 0.001$ ) was negatively correlated. In model 2, after adjusting for confounders of age and sex, only non-HDL-C ( $p < 0.001$ ) was positively associated with AMI, while no association was observed between LDL-C and AMI ( $p=0.150$ ). There was still a negative correlation between HDL-C ( $p < 0.001$ ) and AMI. After adjusting for age, sex, smoking, hypertension, diabetes, and BMI, non-HDL-C ( $p < 0.001$ ) and LDL-C ( $p = 0.005$ ) were positively correlated with AMI, while HDL-C ( $p < 0.001$ ) was negatively correlated with AMI in model 3.

Next, multivariate analysis was performed in diabetic and non-diabetic subjects. It was found that in diabetic subjects when non-HDL-C, HDL-C and LDL-C were adjusted mutually (figure 2), no correlation between LDL-C and acute myocardial infarction was observed ( $p=0.286$ ), and only non-HDL-C and HDL-C were associated with acute myocardial infarction. In model 2, after adjusting for age and sex, the association between HDL-C and AMI was not observed ( $p=0.285$ ), as was LDL-C (0.304). In contrast, the association between non-HDL-C and AMI was stable ( $p = 0.004$ ). After adjusting for age, sex, hypertension, smoking, and BMI, only non-HDL-C showed a stable correlation with acute myocardial infarction ( $p = 0.005$ ). In contrast, there was no significant association between HDL-C, LDL-C and acute myocardial infarction. In non-diabetic subjects (figure 3), the association between non-HDL-C, HDL-C, LDL-C and AMI was observed no matter how the confounders were adjusted.

## 4. Discussion

A total of 9,944 subjects were included in this study, and the cross-sectional study was conducted data from a full population. It was found that HDL-C and non-HDL-C were correlated with the incidence of acute myocardial infarction in the whole sample population. This association remained significant even after adjusting for age, sex, hypertension, diabetes, smoking and BMI. Many observational studies in western populations have shown a significant association between non-HDL-C and coronary heart disease<sup>[22–24]</sup>. Similarly, a Prospective study involving 27,020 participants in China found that higher levels of non-HDL-C were associated with an increased incidence of cardiovascular disease, and the extent to which LDL-C predicted the risk of CVD in Chinese people was similar<sup>[25]</sup>. In addition, most of the lipid results of the patients included in this study were in the non-fasting status, indicating that the non-HDL-C level was associated with the occurrence of acute myocardial infarction even in the non-fasting status. Additionally, A study from Japan followed for up to 20 years reported that non-HDL-C levels were clearly associated with future mortality by coronary heart disease, but not by stroke (The subjects were mostly in the non-fasting status)<sup>[26]</sup>.

The total sample population was subdivided according to whether or not they had diabetes. It was found that LDL-C, HDL-C, and non-HDL-C were associated with the occurrence of acute myocardial infarction in the non-diabetic population after adjustment for age, sex, smoking and other factors, similar to the results in the whole sample population. However, in diabetic patients, non-HDL-C was still associated with the occurrence of AMI after adjustment for gender, age, smoking, hypertension, and body mass index. Conversely, there were no significant associations between HDL-C and LDL-C and the occurrence of AMI. In a meta-analysis of 156,381 patients with non-HDL-C, the combined RR of coronary heart disease in the general population and patients with type 2 diabetes was 1.59(95%CI, 1.46 to 1.72) and 1.99(95%CI, 1.57 to 2.51), and indicated that elevated serum non-HDL-C level was independently associated with an increased risk of CVD in the general population and individuals with type 2 diabetes. When comparing the highest with the reference lower non-HDL-C level, CVD risk increased by 62% and 99% in the general population and type 2 diabetes patients, respectively<sup>[13]</sup>.

In terms of the results of this study, low levels of HDL-C did not differ statistically between the AMI group and non-AMI group in diabetic subjects. Several studies have shown that an inverse relationship between the antiatherosclerotic effects of HDL and the incidence of cardiovascular events, particularly concerning reverse cholesterol transport (RCT), is increasingly being established. In addition to this protective effect, HDL is also associated with other important functions, such as antioxidant protection, regulation of cholesterol efflux, inhibition of cell adhesion molecule expression and leukocyte activation, and induction of nitric oxide production<sup>[27]</sup>. Therefore, low HDL concentrations in patients with diabetes are considered to be one of the major causes of increased cardiovascular risk. However, there have been studies that increased patients' HDL-C levels by using CETP inhibitors, and no significant reduction in cardiovascular events was observed<sup>[11]</sup>. This suggests that there may be other factors besides HDL concentration that contribute to the increased risk of cardiovascular disease in diabetic patients.

In the last few decades, low-density lipoprotein cholesterol (LDL-C) was recommended as the primary treatment target on lipid management in CHD patients<sup>[28-30]</sup>. Selected worldwide dyslipidemia guidelines and expert recommendations, including the American Diabetes Association/American College of Cardiology (ADA/ACC) guidelines<sup>[31]</sup>, Canadian Cardiovascular Society (CCS) guidelines<sup>[32]</sup> and European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines<sup>[33]</sup>, have all identified LDL-C targets of < 70 and < 100 mg/dl for patients at very high- and high-risk for CHD, respectively, and recommended that first-line therapy should target LDL-C reduction. However, trials on the effectiveness of lipid-lowering treatments suggest that the cardiovascular benefits of statins may outweigh their effect on LDL-C levels. Studies have shown that lowering LDL-C in patients with diabetes is insufficient to reduce cardiovascular events to the level of those without diabetes, and intravascular ultrasound studies have shown less plaque regression in patients with diabetes after cholesterol reduction<sup>[34]</sup>. Residual cardiovascular disease risk appears to be partially related to elevated plasma triglycerides and abnormal metabolism of triglyceride-rich lipoproteins (TRLs). These lipoproteins are generally thought to be composed of chylous, VLDLs, and their respective residual lipoproteins (residual lipoprotein particles), many of which are present in intermediate-density lipoproteins<sup>[35-36]</sup>. In 2011, the Joint Committee of the

European Society of Cardiology (ESC)/ European Atherosclerosis Society (EAS) issued guidelines similar to the updated US 2004 guidelines (i.e., diabetes is a high-risk state with an LDL-C target < 70 mg/dl). However, it included non-HDL-C and apolipoprotein B as alternative targets to LDL-C, mainly in patients with T2DM<sup>[14]</sup>. Several studies in Chinese populations have shown that the association between non-HDL-C and cardiovascular disease remains a stronger predictor of LDL-C for coronary heart disease and ischemic stroke in urban populations and in the occupational cohorts<sup>[37]</sup>. In this study, it was found that among diabetic participants, HDL-C, LDL-C and non-HDL-C were included in the model, and LDL-C was not associated with the occurrence of acute myocardial infarction after adjusting for age, sex, hypertension, BMI, smoking and other factors. Even if only HDL-C, LDL-C and non-HDL-C were mutually adjusted, the correlation between LDL-C and the occurrence of acute myocardial infarction was not observed.

Compared with HDL-C, non-HDL-C is associated with the occurrence of acute myocardial infarction in the diabetic population, so more attention should be paid to non-HDL-C in diabetic patients.

Several potential limitations of this study should be considered. First, this study is a single-center study, and the sample population is mainly Han people in the Hengyang region of China, so the generality of other regions and races is limited. Second, data on blood pressure control at admission and history of ACEI/ARB and  $\beta$ -blocker use were missing. Therefore, we cannot rule out the possible influence of the drug on the results of the study. Third, participants in the non-AMI group were excluded from myocardial infarction only by coronary angiography, and the presence of other diseases that may affect the outcome was not excluded. Finally, due to the cross-sectional nature of the study, the current results only show an association between non-HDL-C and acute myocardial infarction. Prospective basic and clinical studies are needed to further confirm causality.

## 5. Conclusion

In diabetic patients, non-HDL-C was associated with the occurrence of AMI after adjustment for confounders associated with coronary heart disease, whereas no association was observed between HDL-C, LDL-C and AMI.

## Abbreviations

AMI, acute myocardial infarction; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; TG, triglycerides.

## Declarations

### Competing interests

There is no conflict of interest.

## Funding

The present study was supported by the Natural Sciences Foundation of Hunan Province (grant no. 2019JJ50538, 2019JJ40268), Scientific Research Fund Project of Hunan Provincial Health Commission B2019123, The Key Guiding Project of Hunan Provincial Health Commission (No. 20201920).

## Ethics approval and consent to participate

The study was approved by the local ethics committee and is in accordance with the declaration of Helsinki on ethical principles for medical research involving human subjects. Written informed consent was obtained from all patients before participation in this study.

## Consent for publication

All authors have read and approved the final version of the manuscript before submission. If the manuscript is accepted, we approve it for publication in Cardiovascular Diabetology.

## Availability of data and material

All datasets used in the current investigation are available from the corresponding author upon reasonable request.

## Authors' contribution

Chen Chen and Su Hua wrote the manuscript. Xiaotian Luo, Jianbo Yue and Chen Chen participated in the collection of original data. Chen Chen and Zhenwang Tang jointly analyzed the data. Chen Chen completed all the figures and tables. Changhui Liu, Yixin Tang and Chen Chen contributed in the conception, design and planning of the study. All authors reviewed the manuscript.

## Acknowledgements

There are no acknowledgements to this manuscript to be declared.

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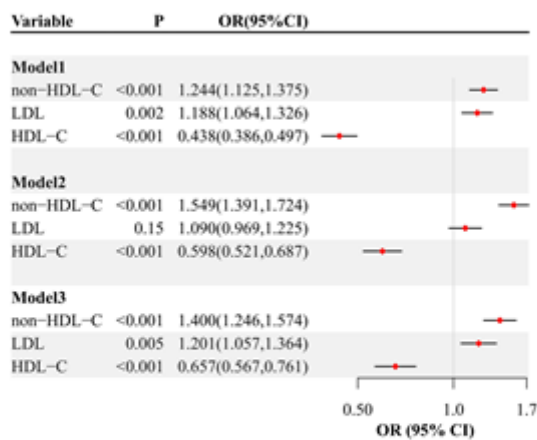
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## Tables

Tables 1 to 3 are available in the Supplementary Files section

## Figures



Model1 Unadjusted;  
 Model2 Adjusted sex and age;  
 Model3 Adjusted sex, age, smoking, hypertension and BMI

Figure 1

LDL-C, HDL-C and NON-HDL-C OR values and 95%CI forest plot in the whole sample population

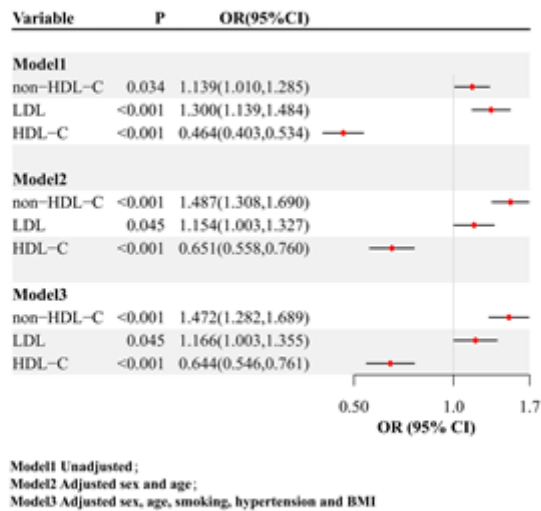


Figure 2

LDL-C, HDL-C and NON-HDL-C OR values and 95%CI forest plot in the diabetic patients

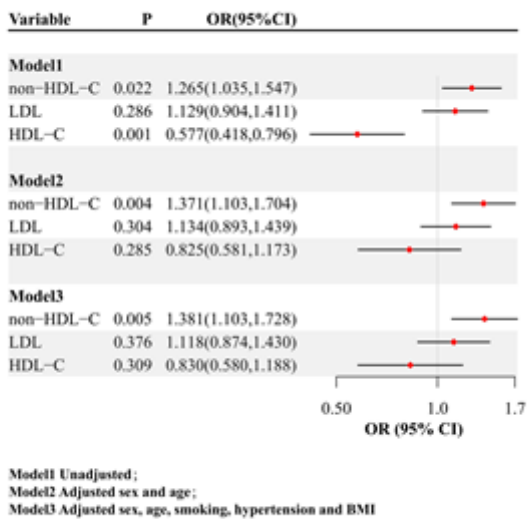


Figure 3

LDL-C, HDL-C and NON-HDL-C OR values and 95%CI forest plot in the non-diabetic patients

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table.pptx](#)