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## Review

# Non-high-density lipoprotein cholesterol and risk of cardiovascular disease in the general population and patients with type 2 diabetes: A systematic review and meta-analysis



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### ABSTRACT

**Aims:** To examine the relationship of non-high-density lipoprotein cholesterol (non-HDL-C) level with cardiovascular disease (CVD) risk in type 2 diabetes patients and the general population by conducting a meta-analysis.

**Methods:** We made a comprehensive literature search for relevant observational studies investigating the relationship of non-HDL-C level with CVD risk in the general population and type 2 diabetes patients using the PubMed and Embase databases. Pooled risk ratio (RR) with 95% confidence intervals (CI) was calculated for the highest versus the reference lower non-HDL-C.

**Results:** A total of 13 studies with 156,381 individuals were included. The pooled RR of CVD was 1.59 (95% CI 1.46–1.72) in the general population and 1.99 (95% CI 1.57–2.51) in type 2 diabetes patients. Subgroup analysis showed the similar effect of non-HDL-C on CVD risk between men (RR 1.98; 95% CI 1.70–2.30) and women (RR 1.63; 95% CI 1.35–1.96). However, elevated non-HDL-C was not associated with higher risk of cardiovascular mortality in the general population (RR 1.64; 95% CI 0.96–2.80) and type 2 diabetes patients (RR 1.08; 95% CI 0.57–2.07).

**Conclusions:** Elevated non-HDL-C level is associated with an increased risk of CVD in the general population and type 2 diabetes patients.

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## 1. Introduction

Dyslipidemia is a well known cardiovascular risk factor. Non-high-density lipoprotein cholesterol (non-HDL-C) is believed to reflect low-density lipoprotein cholesterol (LDL-C), intermediate-density lipoprotein, very low density lipoprotein, and lipoprotein particles [1]. The international guidelines recommend non-HDL-C as a secondary target of therapy in individuals with triglyceride over 200 mg/dl [2]. Risk assessment of cardiovascular disease (CVD) should be detected as early as possible. CVD is the main cause of morbidity and mortality in patients with diabetes. Individuals with diabetes were associated with about 2-fold higher risk of CVD than those without diabetes [3]. Non-HDL-C may be superior to LDL-C in CVD risk estimation [4]. Elevated serum non-HDL-C level has been identified as an independent risk factor of stroke [5] and coronary heart disease [6,7]. However, the available epidemiologic studies [8–23] have shown inconsistent results regarding the association between elevated non-HDL-C level and CVD risk. In addition, whether the CVD risk is higher in specific patient population remains inconclusive.

Currently, the association between non-HDL-C level and subsequent risk of CVD has yet been systematically assessed. We therefore performed this meta-analysis to examine the association of elevated non-HDL-C level and subsequent CVD risk in patients with type 2 diabetes and the general population.

## 2. Materials and methods

### 2.1. Data sources and literature search

PubMed and Embase databases were searched up to 20 April 2018 for relevant studies using in combination of the following search keywords: “non-HDL-C” OR “non-high-density lipoprotein cholesterol” AND “cardiovascular disease” OR “CVD” OR “cardiovascular events” AND “follow up”. Addition-

ally, we reviewed reference lists from relevant articles to identify any pertinent studies. No language restrictions were imposed. This meta-analysis was reported according to the reporting checklist of the Meta-analysis of Observational Studies in Epidemiology [24].

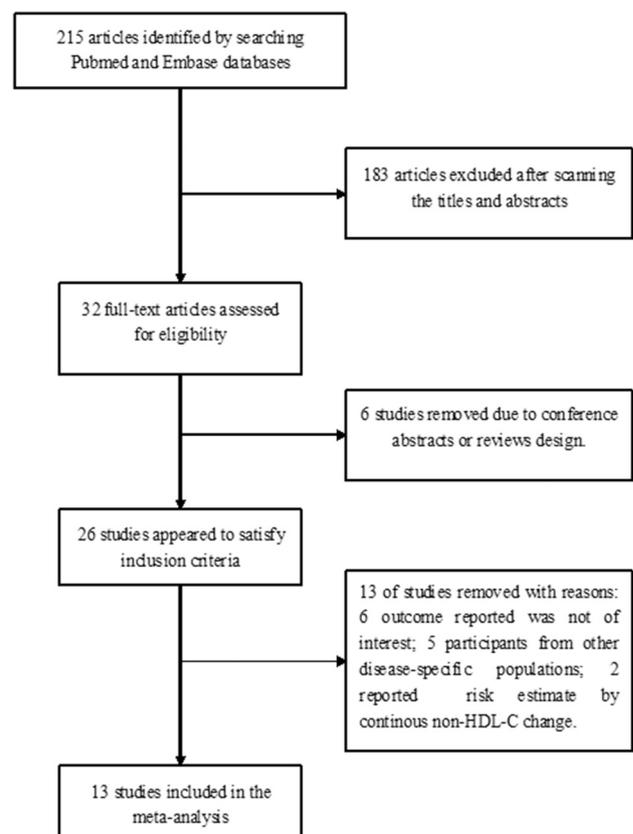


Fig. 1 – Flow diagram showing the study selection process.

**Table 1 – Baseline characteristics of the included studies.**

Author/year	Population	Region	Study design	Subjects (% men)	Age (years)	Cutoff value of non-HDL	Event number HR or OR (95% CI)	Follow-up (years)	Adjusted for variables
Cui 2001 [8]	General population	USA	Prospective study	4462 (53.9)	50.1 ± 6.6	≥220 mg/dL vs. <160 mg/dL	CV death: 347 2.14 (1.50–3.04) M 2.43 (1.47–4.00) W	19	Age
Lu 2003 [9]	Type 2 diabetes	USA	Prospective cohort study	2108 (36.6)	57.3 ± 8.1	>162 mg/dL vs. <127 mg/dL	CVD: 521 2.23 (1.41–3.43) M 1.80 (1.32–2.46) W	9.0	Age, BMI, smoking, study center, SBP, HbA1c, fibrinogen, insulin, and ratio of albumin/creatinine.
Bos 2003 [10]	General population	The Netherlands	Prospective cohort study	1817 (47.8)	50–75	>201 mg/dL (M); >205 mg/dL (W)	CVD: 234 1.54 (1.17–2.03) Normal glucose; 1.20 (0.84–1.71) Abnormal glucose	10	Age, sex, waist-to-hip ratio, hypertension, prevalent cardiovascular disease, smoking and alcohol
Jiang 2004 [11]	Type 2 diabetes	USA	Prospective study	746 (0)	63.1 ± 8.4	Quartiles 4 vs. 1	CVD: 103 2.34 (1.26–4.32)	6.0	Age, BMI, family history of MI, PA, smoking, alcohol, hypertension, fasting status, aspirin use, and HbA1c
Ridker 2005 [12]	General population	USA	Prospective cohort study	15,632 (0)	54.4 ± 7.6	≥180 mg/dL vs. <100 mg/dL;	CVD: 464 2.51 (1.69–3.72)	10.0	Age, blood pressure, BMI, DM, and current smoking status.
Bruno 2006 [13]	Type 2 diabetes	Italy	Prospective cohort study	1565 (43.4)	68.7 ± 10.7	>198 mg/dL vs. <138 mg/dL	CV death: 341 0.79 (0.54–1.15)	11	Age, sex, hypertension, smoking, CHD, AER, fibrinogen, HbA1c and referring physician
Li 2011 [14]	Type 2 diabetes	USA	Prospective cohort study	1122 (46.9)	≥20	≥190 mg/dL vs. <129 mg/dL	CV death: 299 1.53 (0.95–2.45)	12.4	Sex, race/ethnicity, BMI, education, diabetes duration, eGFR, CRP, SBP, HDL, leisure-time PA, smoking, alcohol, and self-reported medication of lower blood cholesterol.
Takeuchi 2014 [15]	General population	Japan	Retrospective cohort study	26,739 (49.0)	47 ± 12	≥190 mg/dL vs. <130 mg/dL	CVD: 285 1.76 (1.17–2.66)	5.0	Age, gender, current smoking, SBP, HbA1c, and BMI
Gu et al 2015 [16]	General population	China	Prospective cohort study	19,268 (47)	48.4 ± 9.1	≥190 mg/dL vs. <130 mg/dL	CVD: 656 1.93 (1.50–2.47) 2.42 (1.74–3.38) M; 1.47 (1.00–2.15) W	7.9	Age, geographic region, urbanization, smoking, alcohol, education, PA, BMI, and hypertension
Ito 2016 [17]	General population	Japan	Prospective cohort study	6701 (41.8)	50.1 ± 12.0	≥189 mg/dL vs. <151 mg/dL;	CV death: 294 0.81 (0.57 – 1.14)	18.2	Age, sex, hypertension, DM, smoking, alcohol and BMI.
Harari 2017 [18]	General population	Israel	Prospective cohort study	4832 (100)	42.1 ± 12.1	≥190 mg/dL vs. <130 mg/dL	CV death: 172 1.80 (1.10–2.96)	22.0	Age, socioeconomic status, education, BMI, hypertension, DM, smoking, coffee intake, alcohol, special diet, doing sport and family history of MI

(continued on next page)

Table 1 – (continued)

Author/year	Population	Region	Study design	Subjects (% men)	Age (years)	Cutoff value of non-HDL	Event number HR or OR (95% CI)	Follow-up (years)	Adjusted for variables
Usui 2017 [19]	General population	Japan	Prospective cohort study	2630 (38.7)	58.9 ± 11.8	≥190 mg/dL vs. <150 mg/dL	CVD: 422 1.33 (0.98–1.81) CKD (-); 1.52 (0.89–2.58) CKD (+)	19.0	Age, gender, SBP, antihypertensive medication, alcohol, DM, BMI, albumin, Hs-CRP, smoking, electrocardiogram abnormality, and regular exercise.
Guan 2018 [20]	General population	China	Prospective cohort study	68,759 (100)	51.1 ± 12.1	≥156.6 mg/dL vs. <109 mg/dL	CVD: 2916 1.55 (1.39–1.72)	8.0	Age, smoking, alcohol consumption, PA, hypertension, DM, and BMI

Abbreviations: M, men; W, women; BMI, body mass index; OR, odds ratio; HR, hazard ratio; CI, confidence interval; BP, blood pressure; SBP, systolic blood pressure; DM, diabetes mellitus; PA, physical activity; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; HbA1c, glycosylated hemoglobin; CHD, coronary heart disease; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; AER, albumin excretion rate; NOS, Newcastle-Ottawa Scale; #Serum non-HDL cholesterol in mmol/L was converted to mg/dL × 38.67.

## 2.2. Study selection

Study inclusion criteria were: (1) prospective or retrospective observational design; (2) participants from the general population or patients with type 2 diabetes; (3) serum non-HDL-C level as exposure of interest; (4) CVD or cardiovascular mortality as outcome of interest; and (5) providing at least age-adjusted odds ratio (OR), hazard ratio (HR) or risk ratio (RR) with corresponding 95% confidence intervals (CI). Studies were excluded if: (1) participants from other disease-specific populations; (2) only reported risk estimate by the continuous level of non-HDL-C changes; and (3) conference abstracts or reviews.

## 2.3. Data extraction and quality assessment

The following data were extracted by two independent authors: first author's last name, year of publication, geographical region, study design, sample sizes, age range or mean age, gender, cutoff value of non-HDL-C comparison, number of CVD or cardiovascular death, maximally adjusted risk estimate, duration of follow-up, and variables adjusted in the multivariable analysis. Disagreements were resolved by consensus or discussed with a third author. We assessed the study quality according to the Newcastle-Ottawa Scale (NOS) of cohort studies [25], which included selection bias, detection bias, and attrition bias. This scale awards a maximum of nine stars to each study. Studies achieving >7 stars were considered good quality.

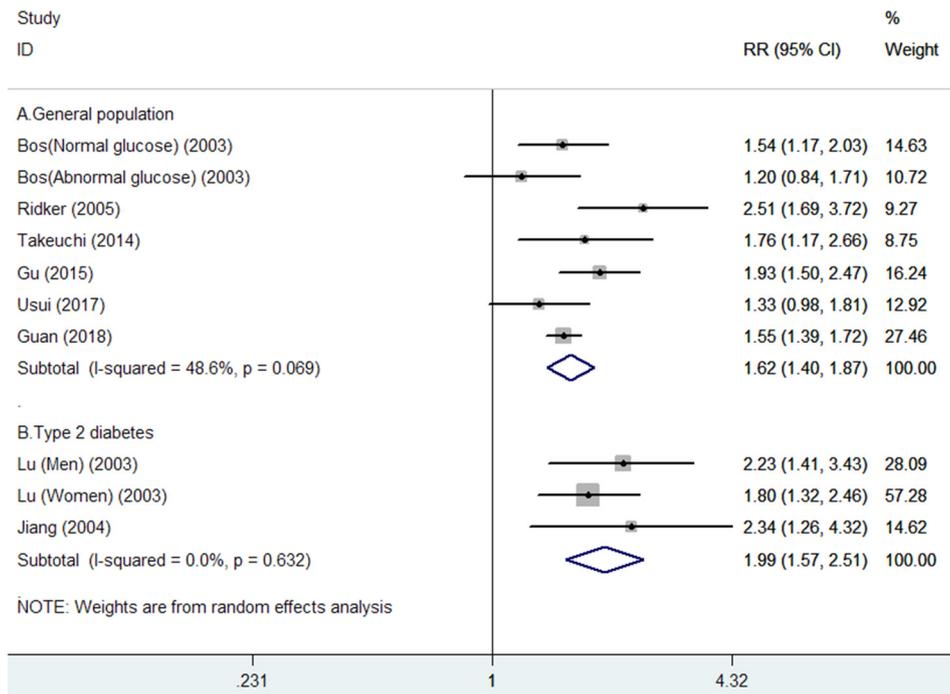
## 2.4. Data synthesis and analysis

The association between elevated non-HDL-C level and CVD events was pooled for the highest versus the reference lowest non-HDL-C level. We determined the between-study heterogeneity using the  $I^2$  statistics and Cochran's Q test. Significant heterogeneity was confirmed with a significance level of  $p < 0.10$  of the Cochran's Q test or  $I^2 > 50\%$ . Due to the anticipated clinical heterogeneity, we applied the random effect model through this meta-analysis. Sensitivity analyses were performed by sequential omission of individual studies to test the robustness of the pooling risk estimates. Begg's rank correlation [26] and Egger's linear regression test [27] were used to detect publication bias. All data were analyzed using STATA software version 12.0 (Stata, College Station, TX, USA).

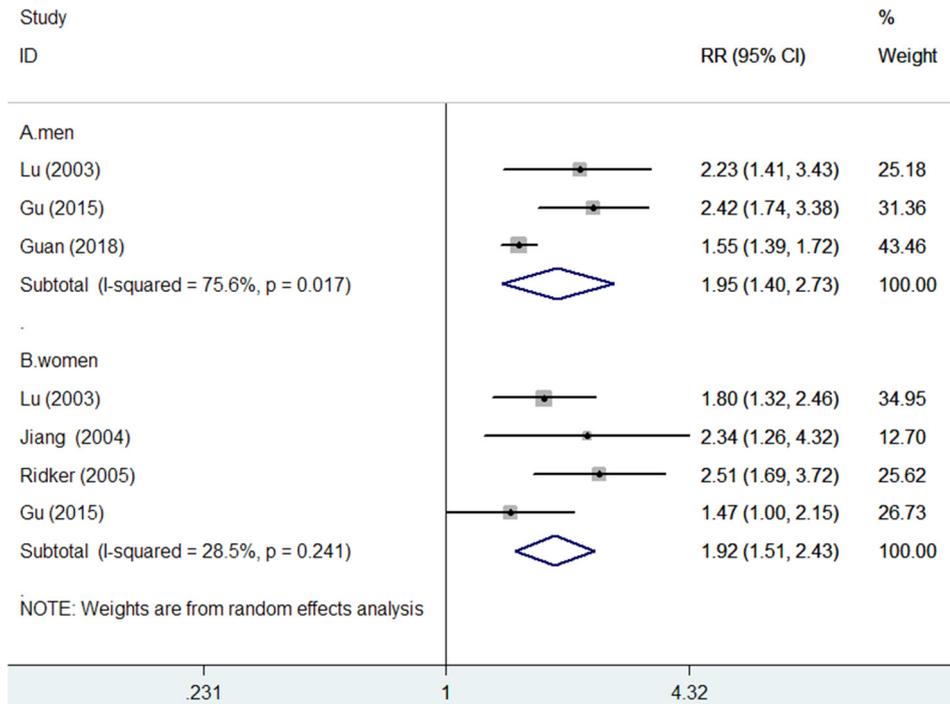
## 3. Results

### 3.1. Search results and study characteristics

A flow chart of the study selection process is shown in Fig. 1. Briefly, our literature search yielded 215 potentially relevant articles. After exclusion of 183 articles by reviewing titles and abstracts, 32 articles were retrieved for detailed assessment. Subsequently, 19 full-text articles were further removed mainly because they were conference abstracts or reviews, irrelevant outcomes or participants from other disease-specific populations. Finally, 13 studies [8–20] were included in the meta-analysis.



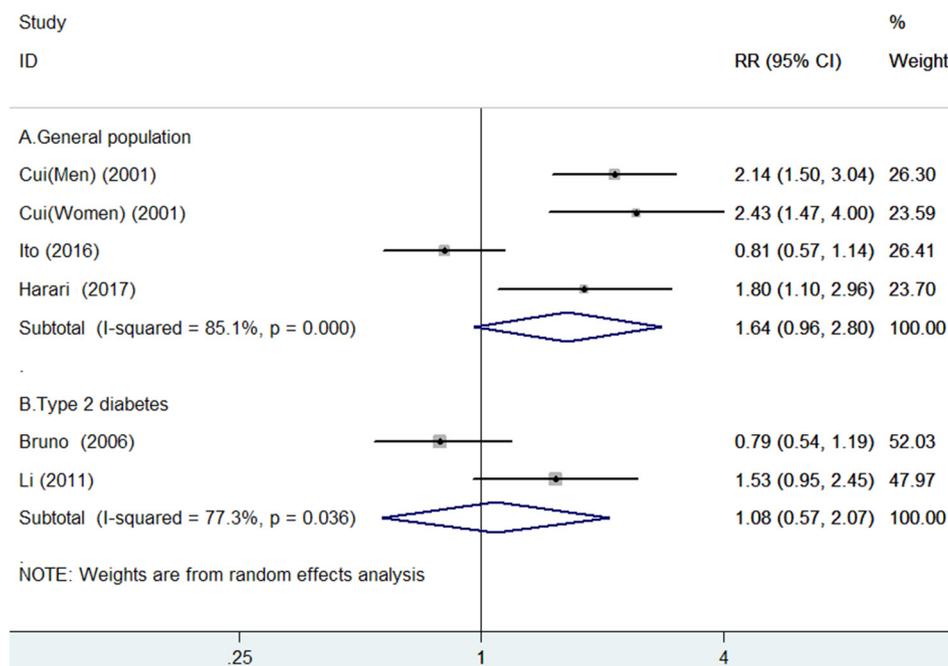
**Fig. 2 – Forest plots showing pooled RR with 95% CI of cardiovascular disease comparing the highest with reference lower category of non-high-density lipoprotein cholesterol.**



**Fig. 3 – Forest plots showing pooled RR with 95% CI of cardiovascular disease by gender.**

The main characteristics of the 13 included studies are summarized in Table 1. A total of 156,381 individuals were identified and analyzed. These studies were conducted in

USA [8,9,11,12,14,28,29], Japan [15,17,19], China [16,20], Israel [18], Italy [13], and The Netherlands [10]. All of these studies were published between 2001 and 2018. Sample size of these



**Fig. 4 – Forest plots showing pooled RR with 95% CI of cardiovascular mortality comparing the highest with reference lower category of non-high-density lipoprotein cholesterol.**

studies varied from 746 to 68,759. Follow-up duration ranged from 7.9 to 22 years. NOS score of included studies ranged from 6 to 8 (Supplemental Table S1).

### 3.2. Non-HDL-C and CVD risk

Six studies [10,12,15,16,19,20] reported the risk estimate of CVD in the general population and two studies [9,11] provided risk estimate of CVD in type 2 diabetes patients. As shown in Fig. 2, the pooled RR of CVD for the highest versus the reference lower non-HDL-C level was 1.62 (95%CI 1.40–1.87) in the general population and 1.99 (95%CI 1.57–2.51) in patients with type 2 diabetes, respectively. Begg's test ( $P = 1.000$ ) and Egger's test ( $P = 0.649$ ) did not show evidence of publication bias for the association of non-HDL-C with CVD risk in the general population. Moreover, the pooled risk estimate of CVD only slightly changed when we changed to a fixed-effect model. Sensitivity analysis revealed that no significant changes of the pooled risk estimate when any of the studies was omitted from the meta-analysis (data not shown).

### 3.3. Gender-specific association between non-HDL-C and CVD risk

Two studies [9,16] provided risk estimate by gender, another two studies [11,12] reported risk estimate among women, and one study [20] reported risk estimate in men. When the highest non-HDL-C level was compared with the reference lower category, the pooled RR of CVD was 1.95 (95% CI: 1.40–2.73) for men and 1.92 (95% CI 1.51–2.43) for women (Fig. 3).

### 3.4. Non-HDL-C and cardiovascular mortality risk

Three studies [8,17,18] provided the risk estimate of cardiovascular mortality in the general population and two studies [13,14] reported risk estimate of cardiovascular mortality in patients with type 2 diabetes. As shown in Fig. 4, the pooled RR of cardiovascular mortality for the highest versus the reference lower non-HDL-C level was 1.64 (95%CI 0.96–2.80) in the general population and 1.08 (95%CI 0.57–2.07) in patients with type 2 diabetes, respectively. However, sensitivity analysis revealed that the pooled RR of cardiovascular mortality was 2.11 (95%CI 1.65–2.71) in the general population when removal of Ito et al's study [17], which suggested the pooling risk estimate may be unreliable.

## 4. Discussion

The current meta-analyses 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. Analyses stratified by gender suggested that elevated non-HDL-C level conferred the similar CVD risk among men and women. However, this meta-analysis did not find a significant association between elevated non-HDL-C level and cardiovascular mortality risk neither in the general population nor type 2 diabetes patients.

Dyslipidemia plays a key role in the development of CVD. However, a large number of patients with dyslipidemia who

received lipid-lowering agents have not attained the recommended non-HDL-C target [30,31]. Lipid-lowering medication can easily modify the serum non-HDL-C level. This meta-analysis reveals that target on serum non-HDL-C level has potential to reduce CVD risk in the general population and patients with type 2 diabetes. Moreover, elevated non-HDL-C level conferred stronger risk of CVD in type 2 diabetic individuals versus the general population. It is clear that type diabetes patients result in a higher risk of CVD than the general population. In the presence of high non-HDL-C level, early management of non-HDL-C is recommended particularly in diabetic individuals.

There appeared to be no gender difference in non-HDL-C level and non-HDL-C was associated with CVD risk in both genders [8,9]. However, the Rancho Bernardo Study indicated that per SD increase in non-HDL-C level was associated with cardiovascular mortality in men but not in women [32]. Therefore, the gender-specific association between non-HDL-C and CVD risk should be further evaluated in future studies.

Serum non-HDL-C level was superior to the LDL-C in CVD risk estimation [33]. Non-HDL-C contains all apolipoprotein-B-including lipoproteins which are more closely correlates with the atherogenic particles. Therefore, non-HDL-C level could be a marker of atherogenic and pathophysiologic effects of multiple apolipoprotein B-containing lipoproteins and triglyceride-rich lipoproteins, which likely improves the predictive value of non-HDL-C for CVD risk. Moreover, non-HDL-C level was highly correlated with coronary atherosclerosis [34]. Particularly, serum level of non-HDL-C is unlikely influenced by non-fasting state [35]. Serum non-HDL-C is considered as a better predictor than LDL-C when the triglyceride level is over 200 mg/dL [36].

The possible limitations of this meta-analysis should be mentioned. First, determination of non-HDL-C level at baseline may have led to misclassification of studied populations in each category. Multiple measurement of follow-up non-HDL-C level could improve the precision. Second, the reported cutoff value of non-HDL-C level varied between studies and we therefore could not establish an optimal cutoff value of higher non-HDL-C level. Third, gender-specific risk estimate of CVD in the stratified analysis may be unreliable because of the small number of studies analyzed.

In conclusion, our meta-analysis indicates that serum non-HDL-C level is independently associated with a greater risk of CVD in the general population and patients with type 2 diabetes. Determination of serum non-HDL-C level may help identify individuals at high risk of CVD. However, whether elevated non-HDL-C level confers higher risk of cardiovascular mortality should be further evaluated in future studies.

### Disclosure of interest

None.

### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.diabres.2018.11.002>.

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