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Impact of low-density lipoprotein cholesterol on cardiovascular outcomes in people with type 2 diabetes: a meta-analysis of prospective cohort studies

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Abstract

Aims—To estimate the prospective association of low-density lipoprotein (LDL) cholesterol on cardiovascular disease (CVD) risk among individuals with type 2 diabetes.

Methods—We used extensive literature searching strategies to locate prospective cohort studies that reported LDL cholesterol levels as a risk factor for incidence of cardiovascular events. We conducted meta-analytic procedures for two outcomes: incident CVD and CVD mortality.

Results—A total of 16 studies were included in this analysis with a mean follow-up range of 4.8–11 years. The pooled relative risk associated with a 1 mmol/L increase in LDL cholesterol among patients with type 2 diabetes was 1.30 (95% confidence interval [CI], 1.19 to 1.43) for incident CVD, and 1.50 (95% CI, 1.25 to 1.80) for CVD mortality, respectively. Subgroup analyses showed that for incident CVD, the pooled relative risk was 1.28 (95% CI, 1.17 to 1.41) for 7 studies adjusted for blood pressure and/or glucose concentration (or insulin concentration, glycated hemoglobin) and 1.40 (95% CI, 1.05 to 1.86) for 3 studies that did not adjust for these variables.

Conclusions—Our study demonstrates that LDL cholesterol was associated with an increased risk for cardiovascular outcomes among patients with type 2 diabetes, independently from other conventional risk factors.

Keywords

type 2 diabetes; meta-analysis; low-density lipoprotein cholesterol; cardiovascular outcomes

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Introduction

Type 2 diabetes, a common and serious condition associated with reduced life expectancy and considerable morbidity, has posed a great burden on patients, their families, and health care systems.[1] The estimated global diabetes prevalence for 2011 is 8.3%, and it is predicted to be increased to 9.9% by the year 2030. [2] It has been estimated that the global health expenditure on diabetes is at least $376 billion in 2010 and will be $490 billion in 2030.[3] Patients with type 2 diabetes have a 2–4 times higher risk of CVD mortality than those without diabetes.[4, 5] Type 2 diabetes is a major risk factor for cardiovascular disease (CVD) accounting for approximately 70% of deaths among these patients.[6, 7]

Although various cardiovascular risk factors are associated with the excessive CVD risk in diabetic patients, elevated blood pressure, hyperglycemia and lipoprotein abnormalities are key contributors.[8, 9]Furthermore, low-density lipoprotein (LDL), the major cholesterol-bearing lipoprotein, is associated with these key contributors.[10–12] LDL cholesterol is widely considered to be the principal atherogenic lipoprotein and a key predictor for CVD risk in patients with diabetes. The positive effects of controlling LDL cholesterol for preventing or slowing CVD development in diabetes has been documented.[13, 14] Therefore, LDL reduction remains the primary target for lipid-lowering therapy, and plasma LDL cholesterol concentration guides intervention strategies for lipid abnormalities in various guidelines.[1, 15–17]

It is hard for single cohort study to adequately quantify the magnitude of the risk due to the limited sample size, while meta-analysis has higher statistical power to detect an effect than individual studies and is a generalization to the population of studies.[18] Two recent meta-analyses evaluating the association of LDL cholesterol level with CVD risk among cohort studies conducted in the general population and both studies reporting an increased risk of CVD events along with increased LDL cholesterol concentrations.[19, 20] To our knowledge, no previous meta-analysis has been reported for estimating the size of LDL cholesterol levels on CVD risk among individuals with type 2 diabetes in prospective studies. To investigate whether long-term LDL cholesterol concentration can reduce the risks for cardiovascular outcomes, we performed a systematic review and meta-analysis on prospective cohort studies to evaluate the association of LDL cholesterol level with the risks of fatal and non-fatal CVD outcomes in individuals with type 2 diabetes.

Methods

Data sources and searches

We searched the MEDLINE database for articles published in English from January 1974 to June 2012 by using Medical Subject Heading (MeSH) terms *cardiovascular diseases; coronary heart disease; heart failure; stroke;* and *diabetes mellitus, type 2*, as well as *hyperlipidemia* and *lipoproteins, LDL* or cholesterol, LDL. We also performed a manual search of references cited by original studies and relevant review articles and queried experts to identify any additional studies. This search provided 581 articles, which were further screened for inclusion from abstracts or full texts.

Study selection

We selected the studies based on the following conditions: 1) study design: prospective cohort studies; 2) study population: patients with type 2 diabetes; 3) studies reported at least one of the outcomes of interest: cardiovascular outcomes (CVD, CVD mortality, coronary heart disease [CHD], fatal CHD, heart failure, and stroke; 4) studies reported a measurement of LDL cholesterol; and 5) studies had follow-up duration ≥ 1 years. We first identified 33 full-text articles and then excluded some if they 1) had no original data (review, editorials, meta-analyses), 2) involved non prospective analysis (e.g., case–control studies), 3) included patients with type 2 diabetes receiving lipid lowering medication at baseline, or 4) were duplicate publications. If separate articles from the same study were published, the article with the most updated data was selected for use in this study. In the case of duplicate publications, only one publication was included.

Data extraction and quality assessment

Data were extracted by two independent reviewers (YW and GH) using standardized data abstraction forms. Disagreements between reviewers were resolved by repeated examination of the original articles and discussion until consensus was achieved. Information on surname of the first author, year of publication, country of origin, mean age, sample size, percentage of male of study participants, number of study participants included in the final analysis, duration of follow-up, outcomes, estimate of the risk of association, variables adjusted in the analyses, and LDL cholesterol measurement method was extracted. For assessment of study quality, we evaluated 6 major items of each study: 1) Was the method for measuring LDL cholesterol validated? 2) Did LDL cholesterol allow quantification as both continuous and categorized variables? 3) Were the outcomes determined by the specified criteria (i.e., medical record) or physician's or patient's judgments such as registry, death certificate, questionnaire, and patients' self-report? 4) Was the total follow-up duration ≥ 5 years? 5) Were major CVD risk factors in the statistical analyses, such as age, sex, blood pressure (hypertension), glucose level (or insulin level, glycated hemoglobin [HbA1c]), smoking, duration of diabetes, treatment, albuminuria, etc.? and 6) Were subjects lost to follow up excluded from the analysis?

During data extraction, we abstracted adjusted relative risk (RR) for the association between LDL cholesterol concentration either as a continuous or a categorical variable and the major outcomes. Standard errors for the estimates were abstracted or derived by using data reported in the original studies. When necessary, the original authors were contacted for additional information.

Reviewers recorded the following as the major outcomes of interest: incident CVD (non-fatal myocardial infarction, non-fatal stroke, and fatal CVD), CVD mortality, incident CHD (non-fatal myocardial infarction and fatal CHD), CHD mortality, heart failure (non-fatal and fatal heart failure), and incident stroke (non-fatal and fatal stroke).

Data synthesis and analysis

Separate meta-analyses of the prospective cohort studies were carried out for two combined outcomes: CVD and CVD mortality due to limited existing studies. All RR estimates included in the pooled analyses were from the most fully adjusted multivariate models.

Most of the studies included in the present analysis reported the RRs of per 1 unit (i.e., 1 mmol/l) change of LDL cholesterol level; therefore, we converted studies that used different units in their original analyses to RRs based on the method previously published.[21] For example, there was 1 study [22] that compared the reported RR of above and below the median value of LDL cholesterol. In order to make these results comparable to the rest of studies, we assumed that there was a normal distribution for LDL cholesterol and used the reported mean and standard deviation to estimate the 25th and 75th percentiles of LDL cholesterol. Then, we divided the log RRs by the difference of these 2 values to estimate the effect of per 1 mmol/L (39 mg/dl) change in LDL cholesterol.[23]

After the RR estimate for each cohort study was converted to reflect per 1 mmol/L increase in LDL cholesterol, the pooled RRs and 95% confidence intervals (CIs) were calculated using the random-effects model. Statistical heterogeneity was assessed using the DerSimonian and Laird's Q statistic and I^2 statistic. The Q test provided information about the presence or absence of between-study heterogeneity, whereas the I^2 statistic quantified the degree of heterogeneity and could be interpretable as the percentage of the total association that may be due to heterogeneity between studies (I^2 >50% was considered a meaningful level of heterogeneity). We also conducted a sensitivity analysis in which each prospective cohort study was excluded in turn to evaluate the influence of that prospective cohort study on the overall estimate. Publication bias was examined using Begg's test.[24] A meta-regression analysis was conducted to explore the sources of statistical heterogeneity in the meta-analyses. Subgroup analyses were conducted by stratifying the analysis according to studies that in different areas. All analyses were conducted using STATA 12.0 (Stata Corporation, College Station, TX).

Results

Of 581 articles that were identified from the literature search, 548 were excluded after an abstract or full-text review (Figure 1). Of the 33 articles for further review, 16 articles [8, 22, 25–38] from 15 independent prospective cohorts were included in the present meta-analysis.

Table 1 summarizes the characteristics of the studies included in the present analysis. The sample size ranged from 133 to 18,673 participants, four studies (25%) had more than 3,000 patients with type 2 diabetes. The mean follow-up time in studies ranged from 4.8 to 11 years. The studies included were geographically heterogeneous: three were conducted in the United States (US), two in the United Kingdom (UK), three in Finland, one in The Netherlands, one in Sweden, one in Iran, one in Italy, two in Japan, and two in China. Most studies had primary care or clinic-based patient populations. Both men and women were included in 15 of the 16 studies, and the remaining study included only women.[31]

Most studies modeled the effect of baseline LDL cholesterol measurements on the risk for CVD outcomes; however, one study[34] used updated mean LDL cholesterol levels and modeled LDL cholesterol as a time-dependent variable in the model.

Quality assessments of the included studies are summarized in Table 2. The overall quality of included studies was good according to our 6-item evaluation criteria. Fourteen of the 16 studies adjusted for major CVD risk factors in the statistical analyses. All had validated methods for measuring LDL cholesterol, and had outcomes determined by specified criteria and excluded participants who were lost during the follow-up. All studies had follow-up time longer than 4 years and only two studies had follow-up of less than 5 years. Nine studies treated LDL cholesterol as continuous variables; two studies treated LDL cholesterol both as continuous and categorized variables; and the remaining five studies treated LDL cholesterol as categorical variables only in the analyses.

Figure 2 presents the individual and pooled RRs for incident CVD and CVD mortality. The pooled RR associated with per 1 mmol/L increase in LDL cholesterol level among patients with type 2 diabetes was 1.30 (95% CI, 1.19 to 1.43) for incident CVD outcomes in 10 independent studies and 1.50 (95% CI, 1.25 to 1.80) for CVD mortality in four independent studies. Begg's test suggested that there was no significant potential publication bias for both incident CVD (P = 0.12) and CVD mortality (P = 0.73). In sensitivity analyses, exclusion of any single prospective cohort study from the analysis did not alter the overall findings of a positive association between LDL cholesterol level and cardiovascular outcomes.

We also analyzed the heterogeneity among the studies of cardiovascular outcomes in persons with type 2 diabetes. The I^2 statistics (P values) for the Q test in the above analyses were 38.3% (0.09) for incident CVD and 0.0% (0.59) for CVD mortality, respectively, pointing to no statistically significant heterogeneity for incident CVD or for CVD mortality.

To further investigate the potential sources of heterogeneity, we conducted subgroup analyses that compared the RR estimates for studies that adjusted for age, sex, blood pressure, and/or glucose concentration (or insulin concentration, HbA1c) with those did not: for CVD, the only outcome that allowed us to conduct subgroup analysis, the pooled RR was 1.28 (95% CI, 1.17 to 1.41) for 7 studies adjusted for blood pressure and/or glucose concentration (or insulin concentration, HbA1c) and 1.40 (95% CI, 1.05 to 1.86) for 3 studies that did not adjust for blood pressure and/or glucose concentration (or insulin concentration, HbA1c). In addition, we also conducted meta-regression and subgroup analyses to compare the RRs for studies that were conducted in different geographic areas. For CVD, area did not contribute to heterogeneity. (P value = 0.15).

Table 3 shows the individual RRs for cardiovascular outcomes according to categories of LDL cholesterol levels. Five studies which reported on ≥3 categories of LDL cholesterol level were included. Among these, only one study[8] reported on both the number of cases and the total number of cases for each category subgroup; thus it was not possible to determine the dose-response relationship between LDL cholesterol level and the risk of cardiovascular outcomes due to the weight calculation. Based on the five studies, three

showed no significant association between LDL cholesterol levels and CVD risk,[8, 30, 32] while a positive association was demonstrated with in the other two studies.[28, 31]

Discussion

The meta-analysis of data for 16 prospective studies provides evidence that increased LDL cholesterol level was associated with increased risks of cardiovascular outcomes among patients with type 2 diabetes. Herein, we report that the risk of incident CVD increased 30% and the risk of CVD mortality increased 50% along with per 1 mmol/L increase in LDL cholesterol.

Our finding that an increased LDL cholesterol level is associated with an increased risk of cardiovascular outcome is consistent with previous studies in general populations.[19, 20] This effect has been shown to be independent of other cardiovascular risk factors. The Merging Risk Factors Collaboration Group evaluated 68 prospective studies and concluded that per 1 SD increase in LDL cholesterol (approximately 0.85 mmol/L) was associated with a 38% increase in CHD risk among a general population after controlling for potential confounders.[20] These reported effect sizes are similar to those estimated in our present study for CVD risk among type 2 diabetic patients, suggesting that the predictive power of LDL cholesterol in non-diabetic subjects is similar to that in individuals with type 2 diabetes. A more recent meta-analysis that included 12 studies of the general population and which aimed to compare the predictive power of LDL cholesterol, non-high-density lipoprotein (HDL) cholesterol and apolipoprotein B, reported a standardized RR ratio of 1.25 (95% CI 1.18–1.33) for cardiovascular risk associated with 1 SD increased LDL cholesterol.[19] As the investigators employed a different parameter to estimate the risk in the meta-analysis,[19] it is not possible to compare the effect size of that study with our finding. Our estimates of risk from prospective studies are also in agreement with the results from the randomized controlled trials (RCTs). [13, 14] A meta-analysis of 14 RCTs showed a one mmol/L reduction in LDL cholesterol resulted in a 12% reduction in CHD mortality, 13% in all-vascular mortality, and 21% reduction in major vascular events in individuals with diabetes.[14] Another meta-analysis of 12 RCTs reported similar results for a 21% reduction for major coronary events in patients with type 2 diabetes.[13] Both studies[13, 14] estimated the number of diabetic patients who could benefit from lipid-lowering treatment: 27 fewer developing major coronary events over 4.5 years [13] and 42 fewer developing major vascular events per 1000 diabetics over 5 years[14], respectively.

Although the mechanisms underlying the association between LDL cholesterol and the risk of CVD outcomes are incompletely understood, several mechanisms have been proposed. [39, 40] It has been shown that exposure to high LDL levels decreased nitric oxide bioavailability. Nitric oxide is one of several molecules by which endothelium maintain the balance between thrombosis and fibrinolysis, regulating the recruitment of inflammatory cells into the vascular wall. Intimal LDL is regarded as the triggering factor of atherosclerosis because of its effect on endothelial dysfunction.[39, 41] Additionally, LDL particles, especially the modified forms, can precipitate atherosclerotic lesions by affecting the vascular endothelium and directly favoring the entry of monocytes into the vascular wall via a process that may be mediated by CD11 and the protein kinase C pathway.[42] In

addition, atherogenic concentrations of LDL contribute to the vulnerability of advanced-staged plaque formation by reducing the migratory capacity of human vascular smooth muscle cells which express a variety of receptors for cholesterol uptake, resulting in the early accumulation of lipids within the plaque.[39, 40, 43, 44] In patients with type 2 diabetes, increased plasma LDL, as a result of reduced turn-over of the LDL particles, would promote cholesterol deposition in the arterial wall.[40, 45] Increased triglyceride-rich lipoprotein level, as observed in type 2 diabetes, promotes the transfer of triglycerides to LDL leading to the formation of small dense triglyceride-rich LDL particles and this is associated with increased cardiovascular risk.[40, 46] Additionally, increased LDL oxidation, as observed in type 2 diabetes, results in rapid uptake of LDL by macrophages and this amplifies the inflammatory atherosclerotic response.[40]

Although extensive evidence from animal studies, clinical trials, and epidemiological studies has confirmed the causal role of LDL cholesterol in atherosclerosis, LDL cholesterol was previously reported to be a predictor of CVD outcomes in patients with diabetes in some, [27, 28, 31] but not all studies. [8, 26, 30, 32] The non-standardized LDL cholesterol measurement may account in part for this discrepancy. In some studies, LDL cholesterol was directly measured,[8, 26, 28–31] while LDL was calculated in others studies.[22, 25, 27, 32–38] The LDL cholesterol direct measurement requires fasting. Previously, LDL cholesterol has been calculated by subtraction HDL cholesterol from the bottom fraction of ultra-centrifuged serum.[25] More recently, LDL cholesterol level is usually calculated using the Friedewald formula based on the measurement of total cholesterol, HDL cholesterol, and triglycerides.[22, 27, 32–38] However, the Friedewald formula requires a fasting triglyceride level <400 mg/dl in order to accurately calculate LDL cholesterol. The calculated LDL cholesterol level is likely to be unreliable because the dyslipidemia in type 2 diabetic patients is characterized by elevated triglyceride and decreased HDL cholesterol. [30, 47] Therefore, other lipid or apolipoprotein measurements or calculated ratios, such as non-HDL cholesterol, apolipoprotein B, total cholesterol/HDL cholesterol, and triglyceride/HDL cholesterol, have been proposed to be used for CVD risk prediction besides LDL cholesterol. Among them, non-HDL cholesterol, which provides the total cholesterol content of LDL cholesterol, intermediate-density lipoprotein, and very-low-density lipoprotein, has been recognized as the secondary target of cholesterol-lowering therapy in individuals with type 2 diabetes.[15] It has been also reported that apolipoprotein B, which reflects the total particle number in LDL cholesterol, intermediate-density lipoprotein, and very-low-density lipoprotein, improves the prediction of CVD outcomes. [32, 48] Besides, the Emerging Risk Factor Collaboration group concluded that the measurements of either total and HDL cholesterol levels or apolipoproteins is enough for lipid assessment in vascular disease.[20] This study was conducted on participants without initial vascular disease, the conclusion of which may not be able to be generalized to people with type 2 diabetes. Although these lipid variables for CVD in the general population have been extensively studied,[19, 20] no meta-analysis so far has compared the predictive power of these variables on CVD outcomes in diabetic patients due to lack of data. This topic certainly deserves further investigations.

The strengths of the meta-analysis presented here include the following: we included large studies with a correspondingly high number of incident cases, which improved the statistical

power to detect significant differences. Our study was based on a comprehensive literature search. We assumed that the inclusion of large studies with follow-ups over 8 years, such as the Strong Heart Study,[8] the Japan Diabetes Complications Study,[38] and the Casale Monferrato Study,[32] and larger cohort study conducted by Eliasson et al.[36] in Sweden, could potentially make our analysis more reliable. There are several limitations to our review. All studies were observational in nature and residual confounding cannot be totally ruled out. The analysis was based on a single measurement of LDL cholesterol. Due to the lacking data, the dose-response relationships between LDL cholesterol and CVD events and mortality could not be estimated in the current analysis. We were also unable to examine cardiovascular outcomes separately; we used two combined outcomes: incident CVD and CVD mortality. Finally, as with any systematic literature review, a limitation is the potential of publication bias; as going against bias is the finding that estimates in our current study are similar to estimates of previous studies.[13, 14, 19, 20]

In conclusion, our results suggest that increased circulating LDL cholesterol is associated with increased risk for cardiovascular outcomes among patients with type 2 diabetes and independent of other conventional risk factors. Our finding supports the notion that patients with diabetes and with elevated LDL cholesterol should be closely followed due to their higher risks for cardiovascular events. Additionally, our data emphasizes the importance of lowering LDL cholesterol to a target goal in patients with diabetes.

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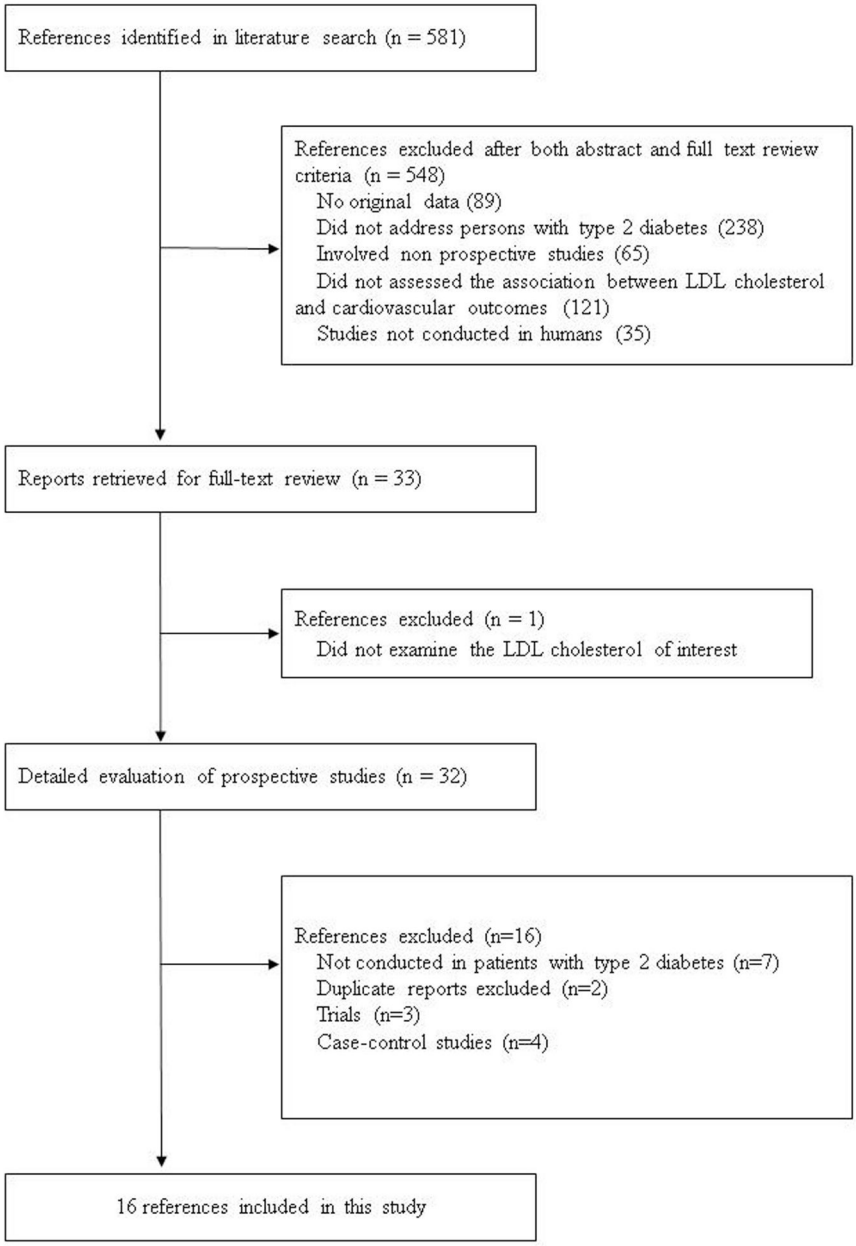

Figure 1.
Flow diagram of studies assessed and included.

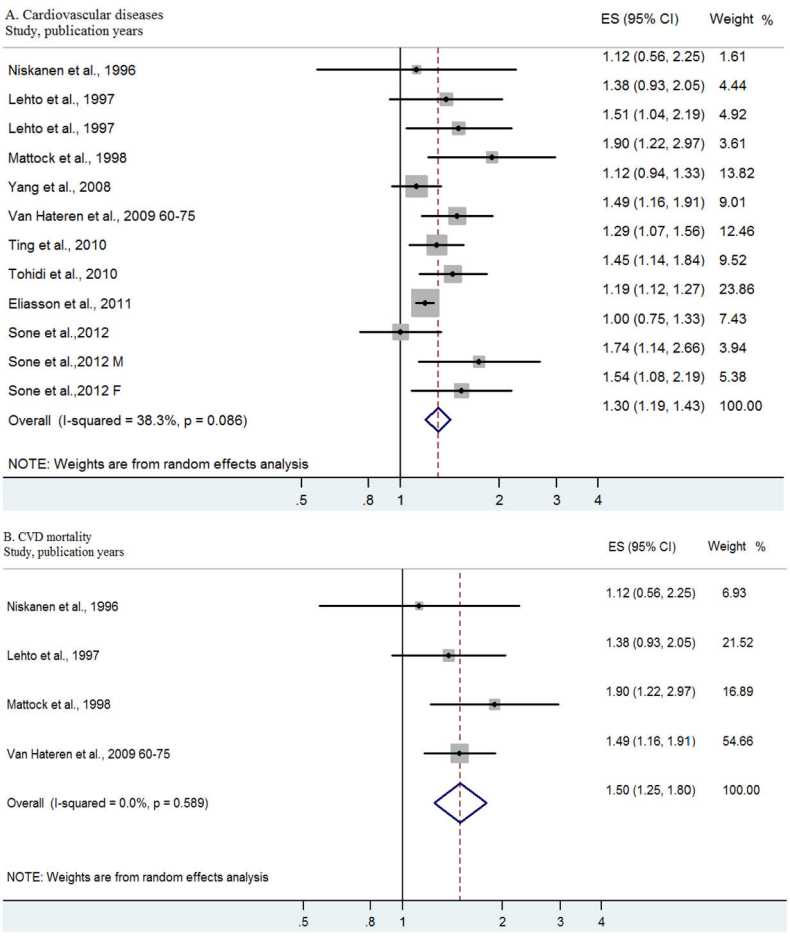

Figure 2.

Forest plot of relative risks (RRs) and 95% confidence intervals (CIs) for the association between per 1mmol/l increase in low-density lipoprotein cholesterol and the main study outcomes risks in type 2 diabetes.

Table 1

Design characteristics of prospective cohort studies on the association between low-density lipoprotein cholesterol and cardiovascular outcomes, 1993–2012.*

Study name	Country	Project	No. of subjects	Age (y)	Men (%)	Outcome	Follow-up time, y	LDL-cholesterol variable		LDL cholesterol measurement	Adjusted covariates
								Continuous	Category		
Laakso et al., 1993 [25]	Finland	Central register, Kuopio University Hospital district	313	56 (men)/58(women)	48.9	CHD mortality, CHD	7.2	√		Calculated by subtraction HDL cholesterol from the bottom fraction of ultra-centrifuged serum	Age
Niskanen et al., 1996 [26]	Finland	Population register, Kuopio	133	45–64	52.6	CVD mortality	5	√		measure	Age, sex, ischemic electrocardiogram, HDL cholesterol, triglycerides, albuminuria, HbA_{1c}, hypertension, smoking history, log fasting insulin, and BMI
Lehto et al., 1997 [27]	Finland	Central register, Kuopio University Hospital district; Turku University Central Hospital district	1059	45–64	54.9	CHD mortality, CHD	7	√		Calculated by Friedewald formula	Age, sex, area, previous MI, total cholesterol, log triglycerides, HDL cholesterol, FPG, and duration of diabetes
Turner et al., 1998 [28]	United Kingdom	UKPDS 23	3,055	25–65	58.1	CHD	7.9		√	measure	Age, sex, HDL cholesterol, HbA_{1c}, SBP, and smoking
Mattock et al., 1998 [29]	United Kingdom	Diabetes clinic at Lewisham Hospital	146	59	56	CHD mortality, all-cause mortality	7	√		measure	Age
Lu et al., 2003 [8]	United States	The Strong Heart Study	2,108	45–74	36.6	CHD, MI, Stroke, CVD	9		√	measure	Age, sex, BMI, smoking status, study center, SBP, HbA_{1c}, fibrinogen, insulin, and albumin to creatinine ratio
Jiang et al., 2004 [30]	United States	The Health Professionals' Follow-up Study	746	46–81	100	CVD	6		√	measure	Age, BMI, family history of myocardial infarction, physical activity, smoking, alcohol consumption, history of hypertension, aspirin use and HbA_{1c}
Schulze et al., 2004 [31]	United States	The Nurses' Health Study	921	30–55	-	CHD	10		√	measure	Age, physical activity, alcohol intake, parental history of CHD, history of high blood pressure, aspirin use, postmenopausal hormone use and BMI
Bruno et al., 2006 [32]	Italy	The Casale Monferrato Study	1,565	68.9	43.4	CVD mortality	11		√	Calculated by Friedewald formula	Age, sex, hypertension, smoking, CHD, AER, fibrinogen, cumulative average individual HbA_{1c} and referring physician
Yang et al., 2008 [33]	China	The Hong Kong Diabetes Registry	3,456	57	45.2	HF	5.52	√		Calculated by Friedewald formula	None
Van Hateren et al., 2009 [34]	Netherlands	The ZODIAC-13 Study (primary care)	881	≥60	39.5	CVD mortality, all-cause mortality	9.8	√		Calculated by Friedewald formula	Unknown selected confounder
Ting et al., 2010 [22]	China	The Hong Kong Diabetes Registry	4,521	54 (non-CVD)/64(CVD)	46.2	CVD	4.9	√		Calculated by Friedewald formula	Age, smoking status, duration of diabetes, $HbA_{1c,}$ ln (ACR +1), use of statins, fibrates, gliclazide and

Study name	Country	Project	No. of subjects	Age (y)	Men (%)	Outcome	Follow-up time, y	LDL-cholesterol variable		LDL cholesterol measurement	Adjusted covariates
								Continuous	Category		
											rosiglitazone during follow-up, and years of enrolment rosiglitazone during follow-up, and years of enrolment
Tohidi et al., 2010 [35]	Iran	The TLGS Study	1,021	54.8	40.5	CVD	8.6	√		Calculated by Friedewald formula	Age, SBP, FPG, lipid lowering use (men) /SBP, FPG, waist to hip ratio, lipid lowering drug use, menopause status and family history of premature CVD (women)
Eliasson et al., 2011 [36]	Sweden	Swedish NDR	18,673	30–70	60.4	CHD	4.8	√	√	Calculated by Friedewald formula	Age, sex, diabetes duration, type of hypoglycemic treatment, $HbA_{1c,}$ SBP, smoking, BMI, albuminuria>20 μg/min, and a history of CVD
Sone et al., 2012 [37]	Japan	The Japan Diabetes Complications Study	1,771	58.2 (mean)	53.1	stroke	7.86	√		Calculated by Friedewald formula	Age, gender, diabetes duration, BMI, SBP, $HbA_{1c,}$ HDL cholesterol, triglycerides, smoking status, and alcohol intake
Sone et al., 2012 [38]	Japan	The Japan Diabetes Complications Study	1,771	40–70	53.1	CHD	8	√	√	Calculated by Friedewald formula	Age, diabetes duration, BMI, SBP, $HbA_{1c,}$ smoking, and alcohol intake

*CHD, coronary heart disease; CVD, cardiovascular disease; HF, heart failure; LDL-cholesterol, low-density lipoprotein cholesterol; BMI, body mass index; SBP, systolic blood pressure; FPG, fasting plasma glucose; HDL cholesterol, high-density lipoprotein cholesterol; AER, albumin excretion rate; ACR, urine albumin-creatinine ratio; HbA_{1C}, glycated hemoglobin

Table 2

Quality assessments on prospective cohort studies on the association between low-density lipoprotein cholesterol and cardiovascular outcomes.*

Reference	1. Is the instrument for measuring LDL cholesterol validated?	2. Does LDL cholesterol allow quantification as both continuous and categorized variables?	3. Are the outcomes determined by the specified criteria (i.e., medical record) or physician's or patient's judgments such as registry, death certificate, questionnaire, and patients' self-report?	4. Is the total follow-up duration ≥5 years?	5. Are major CVD risk factors adjusted for in the statistical analyses?†	6. Are subjects lost-to-follow up excluded from the analysis?	7. Overall quality score
Laakso et al., 1993 [25]	1	0	1	1	1	1	5
Niskanen et al., 1996 [26]	1	0	1	1	1	1	5
Lehto et al., 1997 [27]	1	0	1	1	1	1	5
Turner et al., 1998 [28]	1	0	1	1	1	1	5
Mattock et al., 1998 [29]	1	0	1	1	1	1	5
Lu et al., 2003 [8]	1	0	1	1	1	1	5
Jiang et al., 2004 [30]	1	0	1	1	1	1	5
Schulze et al., 2004 [31]	1	0	1	1	1	1	5
Bruno et al., 2006 [32]	1	0	1	1	1	1	5
Yang et al., 2008 [33]	1	0	1	1	0	1	4
Van Hateren et al., 2009 [34]	1	0	1	1	0	1	4
Ting et al., 2010 [22]	1	0	1	0	1	1	4
Tohidi et al., 2010 [35]	1	0	1	1	1	1	5
Eliasson et al., 2011 [36]	1	1	1	0	1	1	5
Sone et al., 2012 [37]	1	0	1	1	1	1	5
Sone et al., 2012 [38]	1	1	1	1	1	1	6
% Studies scoring "Yes"	100.0%	12.5%	100.0%	87.5%	87.5%	100.0%	5

Low-density lipoprotein, LDL; CVD, cardiovascular disease

*1 = "Yes", 0 = "No", "Unable to determine", or "Not applicable".

†Major CVD risk factors, such as age, sex, blood pressure (hypertension), glucose level (or insulin level, glycated hemoglobin [HbA1c]), smoking, duration of diabetes, treatment, albuminuria, etc., were included in the multivariable analyses.

Table 3

Hazard ratios for cardiovascular outcomes according to low-density lipoprotein cholesterol by different categories*

	Cardiovascular outcomes	Categories	Categories (medians)	Number of events/number of participants	Hazard ratios (95% CI)	P Value for trend
Turner et al., 1998 [28]	CHD	<3.02 mmol/L			1	
		3.02–3.89 mmol/L			1.41 (1.00–2.00)	
		≥3.89 mmol/L			2.11 (1.50–2.95)	
Lu et al., 2003 [8]	CHD	<91 mg/dl		57/728	1	
		91–115 mg/dl		72/683	1.29 (0.90–1.85)	
		>115 mg/dl		103/697	1.90 (1.35–2.67)	
	MI	<91 mg/dl		23/728	1	
		91–115 mg/dl		27/683	1.28 (0.71–2.30)	
		>115 mg/dl		41/697	1.96 (1.14–3.37)	
	Stroke	<91 mg/dl		30/728	1	
		91–115 mg/dl		21/683	0.66 (0.36–1.19)	
		>115 mg/dl		37/697	1.03 (0.61–1.75)	
	CVD	<91 mg/dl		146/728	1	
		91–115 mg/dl		172/683	1.28 (1.02–1.62)	
		>115 mg/dl		203/697	1.61 (1.29–2.02)	
Jiang et al., 2004 [30]	CVD	11.5–102	83.4	21/	1	0.03
		103–126	116	17/	0.84 (0.44–1.59)	
		127–148	138	31/	1.47 (0.85–2.56)	
		149–260	166	34/	1.63 (0.94–2.81)	
Schulze et al., 2004 [31]	CHD		2.54		1	0.016
			3.31		1.34 (0.77–2.35)	
			3.87		1.11 (0.63–1.98)	
			4.65		1.93 (1.15–3.22)	
Bruno et al., 2006 [32]	CVD mortality			82/	1	0.2
				84/	0.90 (0.63–1.28)	
				79/	0.91 (0.63–1.29)	
				70/	0.77 (0.53–1.12)	

*CHD, coronary heart disease; CVD, cardiovascular disease; HF, heart failure; CI, confidence interval.