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Association of low-density lipoprotein cholesterol levels with the risk of mortality and cardiovascular events
A meta-analysis of cohort studies with 1,232,694 participants

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Abstract

Background: Lowering elevated low-density lipoprotein cholesterol (LDL-C) is an important strategy to prevent cardiovascular disease (CVD), while some studies report low LDL-C increases all-cause mortality. Our study aimed to explore the appropriate low LDL-C level with the lower CVD risk but with no excess risk for all-cause mortality.

Methods: PubMed, Embase, Cochrane Library, and Web of Science were searched until April 7, 2021. Twenty cohort studies with 1232,694 adults were obtained. Effect size index was evaluated using pooled relative risk (RR) with 95% confidence interval (CI). Heterogeneity was assessed using the Cochran's Q test and I^2 statistic, and heterogeneity sources was investigated using meta-regression. Publication bias was assessed and sensitivity analysis was performed.

Results: The risks of all-cause mortality (RR: 1.34, 95%CI: 1.00–1.80), CVD death (RR: 1.79, 95%CI: 1.26–2.54), CHD death (RR: 2.03, 95%CI: 1.36–3.03) were higher in LDL-C ≥ 160mg/dL than LDL-C of 70–129mg/dL. Both LDL-C of 130–159mg/dL and ≥ 160mg/dL were associated with higher CVD risk than LDL-C of 70–129mg/dL, with RR of 1.26 (95%CI: 1.08–1.47) and 1.70 (95%CI: 1.35–2.14), respectively. Compared to LDL-C of 70–129mg/dL, no association was found between LDL < 70mg/dL and all-cause mortality and CVD events.

Conclusion: Our results found LDL-C ≥ 130mg/dL was associated with the higher risk of all-cause mortality and CVD risk, indicating that adults with high LDL-C should take interventions to regulate the LDL-C level lower than 130mg/dL.

Abbreviations: CHD = coronary heart disease, CIs = confidence intervals, CVD = cardiovascular disease, I^2 = *I*-squared, LDL-C = low-density lipoprotein cholesterol, MI = myocardial infarction, NCEP = National Cholesterol Education Program, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RR = relative risk.

Keywords: CVD event, LDL-C level, meta-analysis, mortality

1. Introduction

Low-density lipoprotein cholesterol (LDL-C) is converted from very LDL-C in plasma, mainly synthesized in the blood vessels and degraded in the liver.[1] In many populations, elevated LDL-C levels are associated with an increased risk of cardiovascular disease (CVD) development and death.[2,3] Also, several studies report that decreasing LDL-C levels by lipid-lowering treatment reduces the risk of CVD events and death.[4,5] It is well-known that CVD is the leading cause of death worldwide, and accounts for approximately 868,662 deaths in the United States annually; of these, coronary heart disease (CHD) accounts for nearly 365,744 (42%).[6] Therefore, it is important

to focus on the changes of LDL-C levels to improve patients' health and survival outcome.

Many studies have explored the association between LDL-C levels and mortality; however, the opposite result to previous studies on CVD sometimes found that the low level of LDL-C is associated with increased risk of all-cause mortality.[7–9] Ravnskov et al[10] also supported that LDL-C levels showed an inverse association with all-cause mortality. In some studies, both low and high LDL-C level have been strongly associated with all-cause mortality.[11,12] In a Korean study, low and high LDL-C level both resulted in the increased risk of all-cause mortality.[11] Also, a study in Denmark reported an U-shaped correlation between LDL-C level and all-cause mortality.[12]

Although lowering the elevated LDL-C level is an important strategy to prevent CVD risk, it remains unclear in the appropriate low LDL-C level with the lower CVD risk but with no excess risk for all-cause mortality. This suggests that the appropriate LDL-C level for people needs to be further explored.

In this study, we performed a meta-analysis based on the currently available studies to explore the potential association of LDL-C levels with the risk of all-cause mortality. The main object of disease prevention is to extend the survival time, and all-cause mortality is the most important and easily determined outcome, and risk of deviation among all outcome indicators is minimal; therefore, we mainly focused on the association between LDL-C level and all-cause mortality. Also, we revealed the association between LDL-C level and CVD as a secondary analysis result.

2. Methods

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13]

2.1. Literature search strategy

Two investigators (K.P. and X.Y.L.) performed the literature search in 4 databases (PubMed, Embase, Cochrane Library, and Web of Science) up to April 7, 2021. Supplementary Table 1, Supplemental Digital Content, http://links.lww.com/MD/I5 shows the search terms and number of articles from PubMed (n = 7496), Embase (n = 11,018), Cochrane Library (n = 15,740), and Web of Science (n = 2516), respectively. Ethical approval was waived because this meta-analysis was based on the published data. Informed consent was not given since individual patient data were not involved.

2.2. Inclusion and exclusion criteria

Inclusion criteria: participants reported with data on LDL-C level; the experimental group with LDL-C < 70 mg/dL, LDL-C of 130–159 mg/dL, and LDL-C ≥ 160 mg/dL, and the control group with LDL-C of 70 to 129 mg/dL; outcome: mortality and CVD event; studies published in English. The cut-points of LDL-C level were chosen according to the National Cholesterol Education Program's (NCEP's) updated clinical guidelines for cholesterol testing and management (Adult Treatment Panel III)[14] and 2016 Chinese guidelines of dyslipidemia.[15]

Exclusion criteria: Topic not meeting the requirements; reviews, meta-analyses, abstracts, editorial materials, letters, protocols, corrections, retracted publications, and case reports; Animal experiments; studies with incomplete data; Data not available (data cannot be extracted for analysis due to unit discrepancy, outcome discrepancy, and so on).


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Records identified (n=36770)
Pubmed (n=7496)
Embase (n=11018)
Web of science (n=15740)
Cochrane (n=2516)
        │
        ▼
Records after duplicates removed (n=21743) ────► Records excluded (n=21225)
                                                 Topic not meeting the requirements (n=10947)
                                                 Reviews or meta-analyses (n=4413)
                                                 Abstracts, editorial materials, letters, protocols,
                                                 corrections, retracted publications (n=3283)
                                                 Not English articles (n=1309)
                                                 Animal experiments (n=1204)
                                                 Case reports (n=54)
                                                 Studies with incomplete data (n=15)
        │
        ▼
Full-text articles screened for
eligibility (n=518) ────────────────────────────► Full-text articles excluded (n=498)
                                                 Groups not meeting the requirements (n=365)
                                                 Data not available (n=133)
        │
        ▼
Cohort studies included in
qualitative synthesis (n=20)
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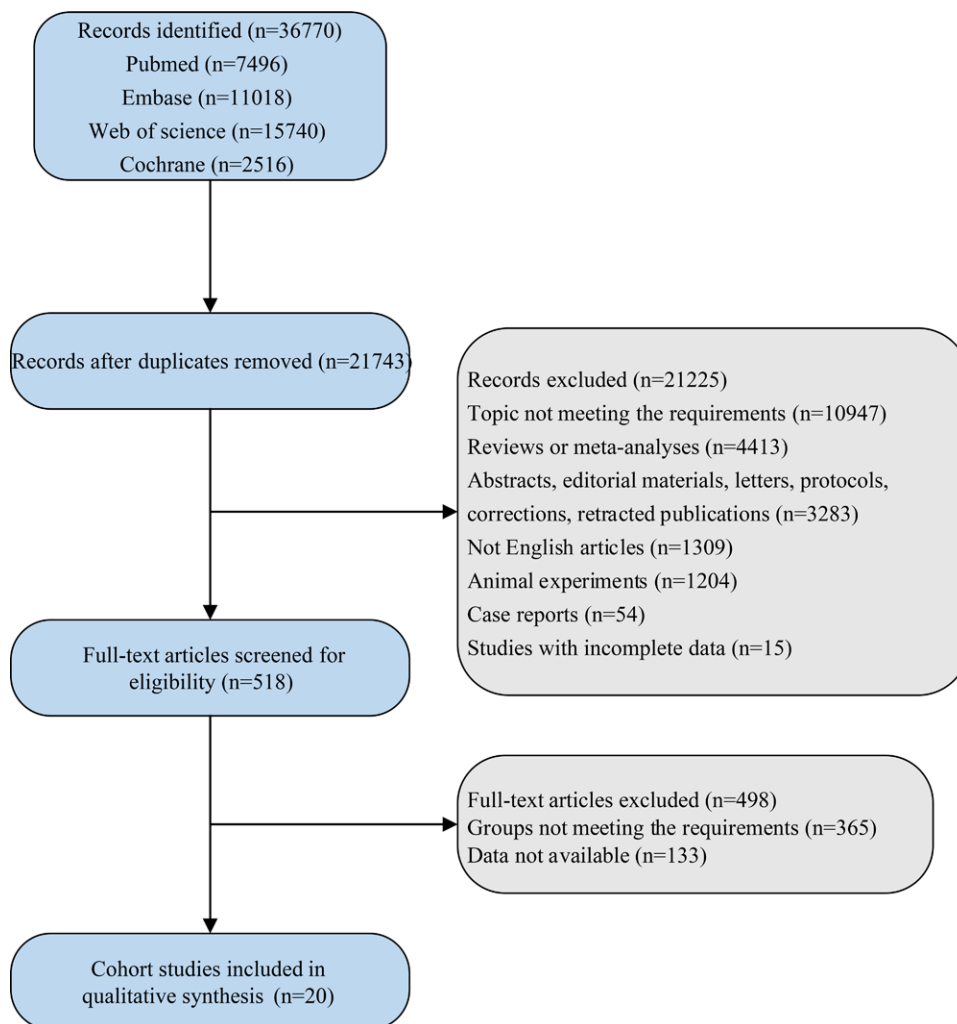
Figure 1. The flow chart of study selection. The figure was created by Visio (v2013, Microsoft, WA).

Table 1

Baseline characteristics of included studies.

Author	Year	Country	Study design	population	Total number	Sex (M/F)	Age (yr)	LDL-C (mg/dL), number	Lipid-lowering medication (number)	Follow-up (yr)	Quality assessment	Outcomes
Curb	2004	USA	Prospective cohort	General	2424	M	77.8	<80 (391), 80–99 (511), 100–119 (623), 120–139 (474), 140–159 (235), ≥160 (134)	0	6	7	d, e
Psaty	2004	USA	Prospective cohort	General	4885	1954/2931	72.3 ± 5.5	≤100 (924), 100–129 (1571), 130–159 (1436), ≥160 (901)	245	7.5	6	a, e, f, g
Kilpatrick	2007	USA	retrospective cohort	Disease	15859	8564/7295	61 ± 16	<40 (167), 40–69 (503), 70–99 (459), 100–129 (205), ≥130 (84)	-	3	4	a, b, d
Cho	2010	Korea	Prospective cohort	Disease	9571	6967/2604	62.6 ± 12.5	<70 (840), 70–99 (2265), 100–129 (3182), 130–159 (2075), ≥160 (1209)	7327	1	5	a, b, d, e, f
Noda	2010	Japan	Prospective cohort	General	91219	30802/60417	40–79	<80 (8788), 80–99 (16776), 100–119 (22840), 120–139 (20357), ≥140 (22458)	2280	10.3*	6	a, b, c, e, d
Wong	2010	USA	Prospective cohort	General	4311	1674/2637	72.5 ± 5.45	<100 (846), 100–130 (1413), 130–160 (1259), ≥160 (793)	190	10.2 ± 4.5	7	d
Farrell	2012	USA	Prospective cohort	General	40718	M	44.8 ± 9.6	<100 (6575), 100–129 (13136), 130–159 (12468), 160–189 (5965), ≥190 (2574)	-	16.7 ± 9.0	7	a, b, c, d, e
Kahn	2013	USA	Retrospective cohort	Disease	2428	1327/1101	Adults	≤70 (1048), 71–100 (801), 101–130 (381), >130 (198)	statins 975, others 136	2.9 ± 2.2	4	d
Tonelli	2013	Canada	Prospective cohort	Disease	836060	418030/418030	49.4 ± 14.8	< 100 (234097), 100–130 (300981), 130–160 (192294), 160–190 (83606), ≥190 (25082)	statin 142130, fibrate or ezetimibe 16721	4	4	d, e, f
Berard	2016	France	Prospective cohort	General	6915	3859/3056	35–44 1822, 45–54 2728, 55–64 2365	<100 (579), 100–129 (1371), 130–159 (2072), ≥160 (2705)	-	10	6	a, b, d
Chinwong	2016	Thailand	Cohort	Disease	405	245/160	64.9 ± 11.5	<70 (110), 70–99 (155), ≥100 (140)	all	1.94(0.92–2.64)*	5	a, e, g
Pletcher	2016	USA	Prospective cohort	General	4860	2331/2529	42.6 ± 4.4	≤100 (846), 101–130 (2281), 131–160 (1421), >160 (312)	34	24.5 ± 8.5	7	d, e
Zhao	2016	USA	Prospective cohort	High CVD risk	3251	1873/1378	73.8	0–69 (109), 70–99 (519), 100–129 (1052), 130–159 (937), ≥160 (634)	176	22.5	4	a, d, e
Harari	2017	Israel	Prospective cohort	General	4832	M	42.1 ± 12.1	<100 (1116), 100–129 (1318), 130–159 (1250), ≥160 (917)	-	22.1 ± 3.2	7	a, b, d
Tsujimoto	2017	Japan	Prospective cohort	High CVD risk	1500	830/670	20–39 116, 40–59 499, 60–79 720, ≥80 165	<70 (269), 70–120 (1013)	808	5.6 ± 3.1	5	a
Abdullah	2018	USA	Prospective cohort	General	36375	26190/10185	42(36–48)*	<100 (6949), 100–129.9 (12426), 130–159.9 (10397), 160–189.9 (4689), ≥190(1914)	-	26.8 (21.2–31.3)*	8	a, b, c, d, e

(Continued)

Table 1
(*Continued*)

Author	Year	Country	Study design	population	Total number	Sex (M/F)	Age (yr)	LDL-C (mg/dL), number	Lipid-lowering medication (number)	Follow-up (yr)	Quality assessment	Outcomes
Zhang	2018	China	Prospective cohort	General	20954	10789/10165	47.4 ± 8.1	<70 (2948), 70–99 (6474), 100–129 (6842), 130–159 (3249), ≥160 (1441)	255	16.4 (8–20)*	6	d, g
Chamberlain	2019	USA	Prospective cohort	Disease	1854	1179/675	66 ± 13.3	<70 (743), 70–100 (644), ≥100 (467)	all	5.9*	5	a, d
Zhang	2019	USA	Prospective cohort	General	36030	16035/19995	52.7 ± 16.6	<100 (5060), 100–129 (16052), 130–159 (12752), ≥160 (2165)	1856	17*	6	e, g
Johannesen	2020	Denmark	Prospective cohort	General	108243	48669/59574	58 (48–67)*	<70 (6412), 70–92 (15681), 93–112 (21289), 113–131 (22207), 132–154 (21892), 155–189 (15999), >189 (4763)	13025	9.4*	6	a

*Medians or medians (interquartile range). a, all-cause mortality; b, CVD death; c, coronary heart disease (CHD) death; d, CVD event; e, CHD event; f, myocardial infarction (MI); g, stroke.
CHD = coronary heart disease; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

2.3. Data extraction

The extraction and appraisal of data were conducted by 2 independent investigators (K.P. and X.Y.L.) who were not involved in the included studies. A third investigator (Z.W.) would resolve the discrepancies based on consensus after discussion. The data were extracted including name of the first author, publication year, country, study design, population, total number, sex, age, LDL-C level, follow-up time and outcomes. The population was classified as general group, high CVD risk group, and original disease group (acute heart failure, chronic kidney disease, acute coronary syndrome, etc.). The stratification of LDL-C level was adapted from the National Cholesterol Education Program guidelines.[16]

2.4. Types of outcome measures

The primary outcome was mortality, including all-cause mortality, CVD death, and CHD death. The secondary outcome was CVD event, including CHD event, myocardial infarction (MI), and stroke.

2.5. Methodological quality appraisal

The quality of cohort studies was assessed by 2 independent investigators (K.P. and X.Y.L.) based on revised Newcastle-Ottawa Scale.[17] The total score of this scale was 9, and the overall study quality was defined as poor (0–3), fair (4–6), and good (7–9).

2.6. Statistical analysis

The STATA 15.1 software (Stata Corporation, College Station, TX) was used for statistical analysis. The effect size index was expressed as relative risk (RR) with 95% confidence intervals (CIs). Heterogeneity was assessed by the Cochran's Q test and quantified with I-squared (I^2), with the greater I^2 value representing the greater heterogeneity. Pooled RR was calculated using a random-effects model ($I^2 \geq 50\%$) or a fixed-effects model ($I^2 < 50\%$). The sources of heterogeneity were searched by meta-regression analyses based on region, population, and accepting lipid-lowering medication. Subgroup analysis was performed to deep explore the association of region, population, and accepting lipid-lowering medication with the outcomes. The power analysis was performed to assess statistical power for results based on less than 5 articles using G*Power 3.1 software (Universität Düsseldorf, Düsseldorf, Germany). The robustness of results for each outcome was evaluated using sensitivity analysis, and Begg's test and Egger's regression test was used to evaluate the publication bias if more than 9 trials were included.[18] $P < .05$ was considered statistically significant.

3. Results

3.1. Study selection and population

After searching the 4 English databases according to retrieval strategy, a total of 36,770 studies were identified. Of these, 21,743 studies were retained after the removal of duplicates. Based on content from titles and abstracts, 21,225 studies were excluded. The eligible 518 full texts were further evaluated; among which, 498 texts were excluded because groups didn't meet the requirements (n = 365) and data were not available (n = 133), and then 20 studies were finally included.[19–38] Figure 1 shows the flow chart of study selection. The included 20 studies were all cohort studies (16 for high quality, 4 for low quality), and a total of 1232,694 adult participants were enrolled. The characteristics and quality assessment score of each included study are shown in Table 1.

3.2. Association of LDL-C levels with mortality

Table 2 summarizes the analysis results on the association between LDL-C and mortality, including all-cause mortality, CVD death, and CHD death. When compared to participants with LDL-C levels of 70 to 129 mg/dL, those with levels < 70 mg/dL and 130 to 159 mg/dL had no greater risk of all-cause mortality, with RR value of 1.33 (95%CI: 0.94–1.89) and 1.05 (95%CI: 0.91–1.22), respectively. The pooled data showed that participants with LDL-C level ≥ 160 mg/dL presented a significant risk of all-cause mortality compared to those with LDL-C level of 70–129 mg/dL (RR: 1.34, 95%CI: 1.00–1.80). In region subgroups, we found no association between LDL-C level ≥ 160 mg/dL and all-cause mortality. In general participants, LDL-C level ≥ 160 mg/dL presented higher risk of all-cause mortality than LDL-C of 70 to 129 mg/dL, with RR value of 1.53 (95%CI: 1.13–2.07). Forest plots of the individual studies used in Table 2 can be found in Fig. 2A–C.

The LDL-C < 70 mg/dL and LDL-C 130 to 159 mg/dL were not associated with the risk of CVD death (RR: 1.72, 95%CI: 0.93 to 3.19; RR: 1.19, 95%CI: 0.86–1.67) compared to LDL-C level of 70 to 129 mg/dL. The RR for CVD death in participants with LDL-C ≥ 160 mg/dL was 1.79 (95%CI: 1.26–2.54) with comparison of LDL-C from 70 to 129 mg/dL. Similarly, LDL-C ≥ 160 mg/dL was associated with an increased risk of CVD death in American participants (RR: 2.15, 95%CI: 1.33–3.47) and in general population (RR: 2.05, 95%CI: 1.46–2.86) compared to 70 to 129 mg/dL LDL-C. Forest plots of the individual studies used in Table 2 can be found in Fig. 3A–C.

For CHD death, compared to participants with LDL-C of 70 to 129 mg/dL, the risk was significantly high in 130–159 mg/dL group (RR: 1.41, 95%CI: 1.21–1.64) and ≥ 160 mg/dL group (RR: 2.03, 95%CI: 1.36–3.03). Forest plots of the individual studies used in Table 2 can be found in Fig. 4A and B. The statistical power was shown in Supplementary Table 2, Supplemental Digital Content, http://links.lww.com/MD/I6.

3.3. Association of LDL-C levels with CVD event

Table 3 displays the analysis results on the association between LDL-C and CVD event, CHD event, MI, and stroke. The control group was LDL-C level of 70 to 129 mg/dL. Compared to the control group, the risk of CVD event was significantly associated with LDL-C level of 130 to 159 mg/dL (RR: 1.26, 95%CI: 1.08–1.47) and LDL-C level ≥ 160 mg/dL (RR: 1.70, 95%CI: 1.35–2.14), but not associated with the LDL-C level < 70 mg/dL (RR: 1.01, 95%CI: 0.81–1.24). Moreover, American participants with LDL-C levels of 130 to 159 mg/dL had a higher risk to suffer CVD event (RR: 1.29, 95%CI: 1.07–1.57). The RR for participants with LDL-C level ≥ 160 mg/dL in America and Asia was 1.80 (95%CI: 1.31–2.47) and 1.50 (95%CI: 1.07–2.11), respectively. In general participants, both LDL-C of 130 to 159 mg/dL and ≥ 160 mg/dL were correlated with the high occurrence of CVD event with comparison of control group, and RR was 1.44 (95%CI: 1.09–1.91) and 1.96 (95%CI: 1.38–2.79), respectively.

For CHD event, the RR was 1.43 (95%CI: 1.12–1.82) and 1.87 (95%CI: 1.44–2.44) in participants with LDL-C level of

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Table 2

Association between LDL-C levels and mortality.

Outcomes	Number of studies	RR (95%CI)	P	I²
All-cause mortality				
< 70 mg/dL (vs 70–129 mg/dL)	7	1.33 (0.94, 1.89)	.109	98.0
Sensitivity analysis		1.33 (0.94, 1.89)		
130–159 mg/dL (vs 70–129 mg/dL)	7	1.05 (0.91, 1.22)	.467	89.5
Sensitivity analysis		1.05 (0.91, 1.22)		
≥ 160 mg/dL (vs 70–129 mg/dL)	8	1.34 (1.00, 1.80)	.050	97.5
Sensitivity analysis		1.34 (1.00, 1.80)		
Region				
America		1.30 (0.88, 1.93)	.194	98.7
Asia		1.34 (0.92, 1.97)	.132	85.7
Europe		1.81 (0.79, 4.18)	.164	NA
Population				
General		1.53 (1.13, 2.07)	.007	93.3
High CVD risk		0.92 (0.88, 0.95)	<.001	NA
Disease		0.97 (0.73, 1.28)	.807	NA
CVD death				
< 70 mg/dL (vs 70–129 mg/dL)	2	1.72 (0.93, 3.19)	.083	88.6
Sensitivity analysis		1.72 (0.93, 3.19)		
130–159 mg/dL (vs 70–129 mg/dL)	5	1.19 (0.86, 1.67)	.297	84.6
Sensitivity analysis		1.19 (0.86, 1.67)		
≥ 160 mg/dL (vs 70–129 mg/dL)	6	1.79 (1.26, 2.54)	.001	89.4
Sensitivity analysis		1.79 (1.26, 2.54)		
Region				
America		2.15 (1.33, 3.47)	.002	92.3
Asia		1.58 (0.86, 2.91)	.144	91.1
Europe		1.81 (0.79, 4.18)	.164	NA
Population				
General		2.05 (1.47, 2.86)	<.001	85.5
Disease		0.97 (0.73, 1.28)	.807	NA
CHD death				
130159 mg/dL (vs 70–129 mg/dL)	2	1.41 (1.21, 1.64)	<.001	44.9
Sensitivity analysis		1.41 (1.21, 1.64)		
≥160 mg/dL (vs 70–129 mg/dL)	3	2.03 (1.36, 3.03)	.001	89.3
Sensitivity analysis		2.03 (1.36, 3.03)		

CI = confidence interval; CVD = cardiovascular disease; CHD = coronary heart disease; I² = I-squared; NA = not available; LDL-C = low-density lipoprotein cholesterol; RR = relative risk.
I² reflected the degree of heterogeneity, with the greater I² value representing the greater heterogeneity.
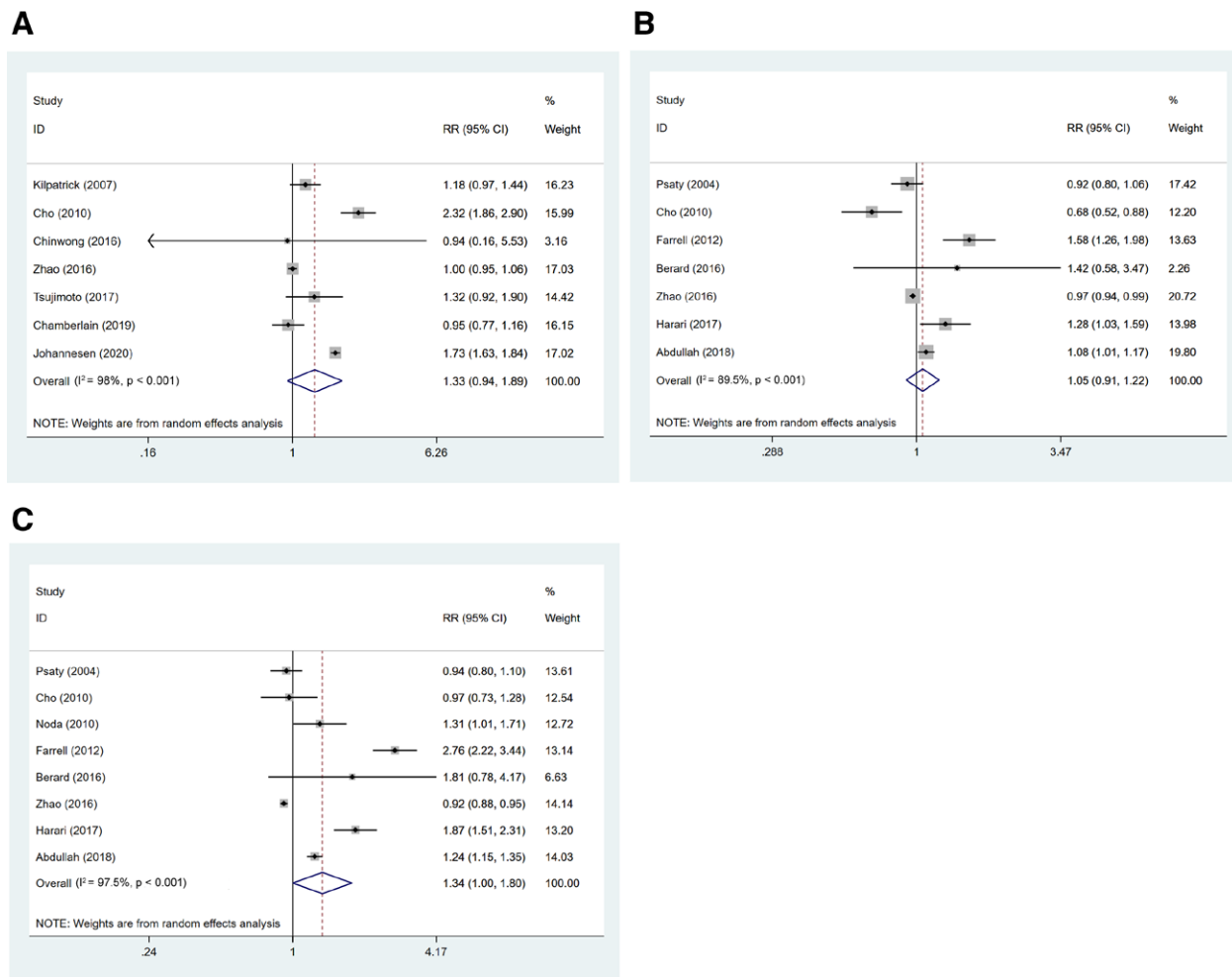
A

B

C

Figure 2. Forest plot for the association of all-cause mortality with LDL-C < 70 mg/dL (A), LDL-C level of 130 to 159 mg/dL (B), and LDL-C ≥ 160 mg/dL (C). The control group was LDL-C level of 70 to 129 mg/dL. I^2 reflected the degree of heterogeneity, with the greater I^2 value representing the greater heterogeneity. Figures are created by STATA software (v15.1, Stata Corporation, College Station, TX). LDL-C = low-density lipoprotein cholesterol.

130 to 159 mg/dL and ≥ 160 mg/dL, respectively. There was no statistical difference between LDL-C < 70 mg/dL and CHD risk. In American participants, general population, and disease population, LDL-C level of 130 to 159 mg/dL was associated with an increased risk of CHD, with RR of 1.44 (95%CI: 1.12–1.85), 1.61 (95%CI: 1.23–2.11), and 1.20 (95%CI: 1.13–1.28), respectively. For participants in America and Asia, LDL-C ≥ 160 mg/dL was associated with a higher CHD risk (RR: 2.01, 95%CI: 1.50–2.70; RR: 1.30, 95%CI: 1.02–1.68). The similar result was shown in general population, disease population, and participants not accepting lipid-lowering medication, with RR of 2.16 (95%CI: 1.61–2.90), 1.63 (95%CI: 1.53–1.74), and 2.05 (95%CI: 1.20–3.50), respectively.

The occurrence of MI was high in LDL-C level of 130 to 159 mg/dL (RR: 1.19, 95%CI: 1.12–1.26) and ≥ 160 mg/dL (RR: 1.39, 95%CI: 1.03–1.87). The similar result was found in disease population, with RR of 1.63 (95%CI: 1.53–1.74). The association of LDL-C with stroke was not significant in < 70 mg/dL group, 130 to 159 mg/dL group, and ≥ 160 mg/dL group. Supplementary Table 2, Supplemental Digital Content, http://links.lww.com/MD/I6 displays the statistical power.

3.4. Sensitivity analysis and publication bias

The sensitivity analysis was performed by sequentially removing the trial to estimate the robustness of the overall results. The results of our study were stable by that no significant change of the results happened after eliminating a trial (Tables 2 and 3). Also, no obvious publication bias was detected using Begg's test and Egger's regression test regarding LDL-C of 130 to 159 mg/dL on CVD event (Z = 1.07, T = 1.52), LDL-C ≥ 160 mg/dL on CVD event (Z = 1.17, T = 1.80), and LDL-C ≥ 160 mg/dL on CHD event (Z = 0.18, T = 0.66) (Table 4).

4. Discussion

Our meta-analysis included 20 cohort studies containing a total of 1232,694 adult participants to explore the association between LDL-C level and mortality and CVD events. According to the overall results, the risk of all-cause mortality, CVD death, and CHD death was higher in participants with LDL-C level ≥ 160 mg/dL compared to those with LDL-C level of 70 to 129 mg/dL. CHD death risk was also higher in LDL-C level of 130 to 159 mg/dL group than in LDL-C level of 70 to 129 mg/dL group. Both LDL-C level of 130 to 159 mg/dL and LDL-C level ≥ 160 mg/dL increased the risk of CVD event, CHD event, and MI compared to LDL-C level of 70 to 129 mg/dL. LDL-C < 70 mg/dL was not found to associate with the all-cause mortality and CVD event.

LDL-C is a main atherogenic lipoprotein and has been identified as the causal risk factor for atherosclerosis and CVD.[4] Since CVD is the main reason for mortality worldwide and accounts for approximately 31% of all deaths,[39] it is logically reasonable that high level of LDL-C may increase
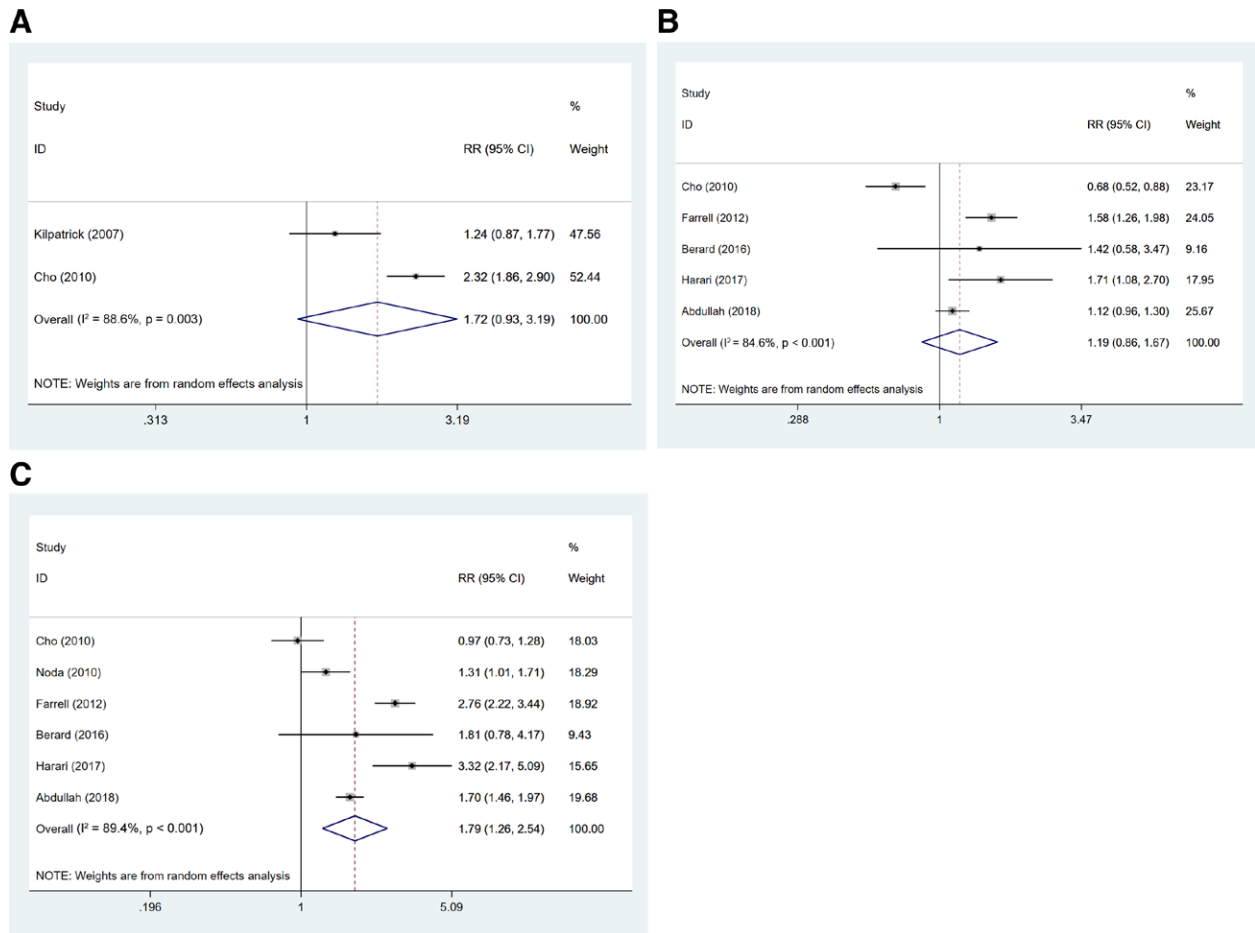
Figure 3. Forest plot for the association of CVD death with LDL-C < 70 mg/dL (A), LDL-C level of 130 to 159 mg/dL (B), and LDL-C ≥ 160 mg/dL (C). The control group was LDL-C level of 70 to 129 mg/dL. I^2 reflected the degree of heterogeneity, with the greater I^2 value representing the greater heterogeneity. Figures are created by STATA software (v15.1, Stata Corporation, College Station, TX). CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

CVD mortality, even all-cause mortality. Consistently, our study found that high LDL-C level (≥ 160 mg/dL) indicated an increased risk of all-cause mortality. In line with our findings, Harari et al[32] found the association of increased LDL-C level with the high risk of all-cause mortality. Also, Schubert et al[40] reported that elevation of LDL-C level increased the hazard of all-cause mortality. Some former epidemiological studies have reported a continuous and graded correlation of LDL-C level to CVD death and CHD death.[6,41] A study from Abdullah et al[34] demonstrated that LDL-C level ≥ 130 mg/dL increased the CHD death by 50%, and LDL-C level ≥ 160 mg/dL presented a significant association with CVD death and CHD death. Similarly, our study showed the high CVD and CHD death when LDL-C level ≥ 160 mg/dL, and CHD death was also high in LDL-C level of 130 to 159 mg/dL. In addition, LDL-C < 70 mg/dL was not found to associate with the risk of all-cause mortality and CVD death when comparing to LDL-C level of 70 to 129 mg/dL. These findings suggested that people should maintain the LDL-C level less than 130 mg/dL. An Israel study has reported that LDL-C < 130 mg/dL was not significantly associated with all-cause mortality and CVD death.[32] The study performed by Yu et al[42] also supported that the target prevention value for all-cause mortality should be 130 mg/dL.

In a defined population, reducing elevated LDL-C level is a crucial strategy in primary and secondary prevention for CVD event.[43,44] Many clinical trials have demonstrated an increased risk of CVD-relevant morbidity correlated with elevation of LDL-C level.[45–47] Additionally, LDL-C has been identified as the primary target to prevent CHD by the NCEP Expert Panel.[16] Previous studies have reported that high LDL-C level increased the risk of an CHD event.[48] A clinical trial of cholesterol lowering in high-risk patients (162 mg/dL) also suggested high LDL-C concentration was associated with the increased risk of CHD.[49] In our meta-analysis, the elevated LDL-C level (130–159 mg/dL or ≥ 160 mg/dL) showed high occurrence of CVD event and CHD event. Navarese et al[5] suggested that LDL-C-lowering therapy was beneficial to patients with higher baseline LDL-C level, with a large reduction in CVD morbidity. They also reported that the overall risk of MI was reduced with the decrease in LDL-C level.[5] A previous cohort study in Japan showed the increased risk of MI in higher concentration of LDL-C.[50] Herein, population with LDL-C level of 130 to 159 mg/dL or ≥ 160 mg/dL had a higher risk of MI. A similar finding was reported in the study of Kim et al[51]

Although our meta-analysis explored the reasonable LDL-C level to prevent both all-cause mortality and CVD event based on a large number of participants, some limitations existed. First, the predictive value of LDL-C level for death risk may be magnified because the included populations were relatively older and some of them may die of increasing age during the long follow-up time. Second, health-related behaviors may be one of the sources of heterogeneity; however, we have no access to the data on this aspect for further analysis. Third, the articles included in our meta-analysis take LDL-C as a classified variable, so that we cannot analyze LDL-C as a continuous variable to explore its linear association with mortality. Fourth, some
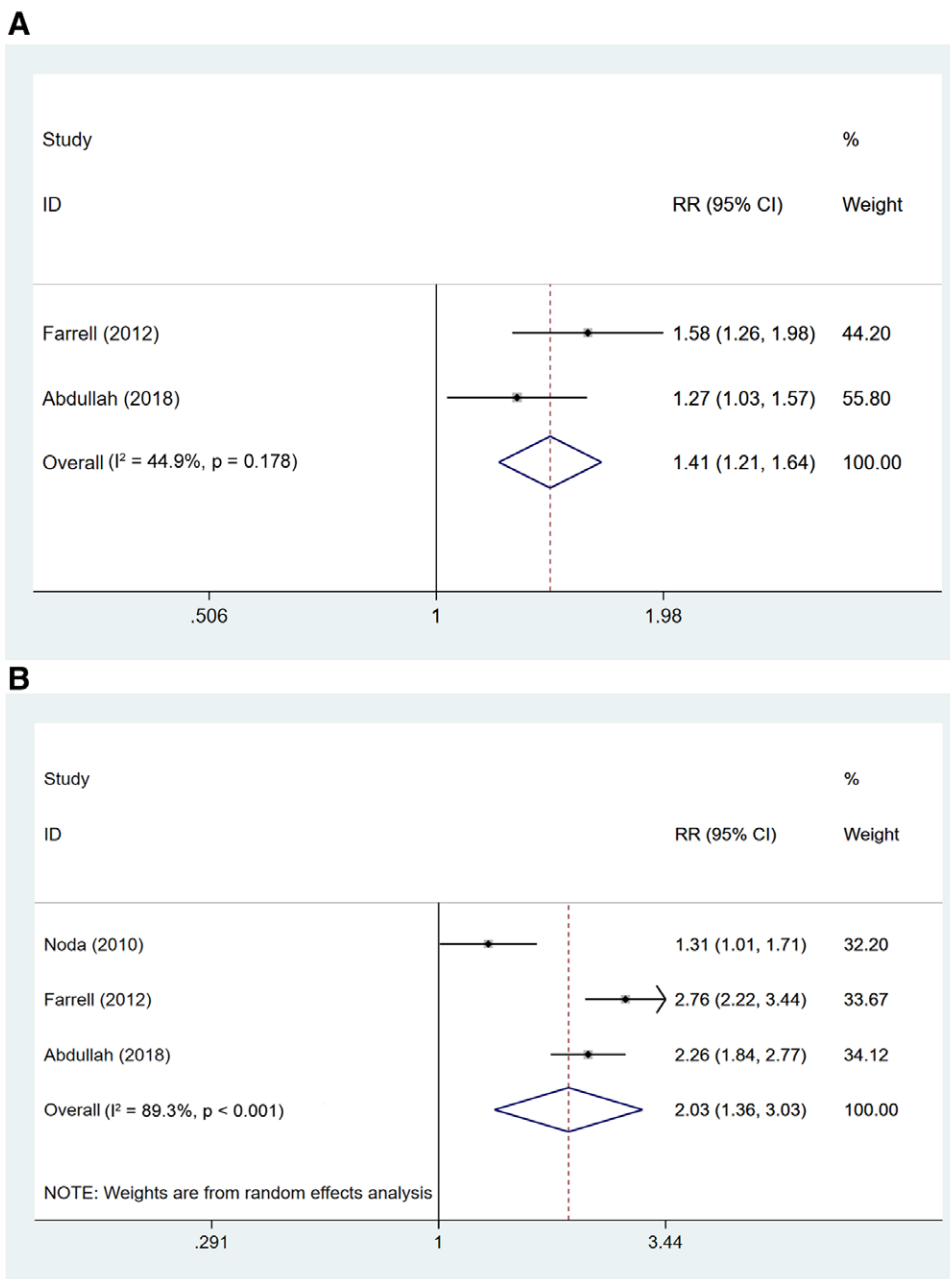
Figure 4. Forest plot for the association of CHD death with LDL-C level of 130 to 159 mg/dL (A) and LDL-C ≥ 160 mg/dL (B). The control group was LDL-C level of 70 to 129 mg/dL. I^2 reflected the degree of heterogeneity, with the greater I^2 value representing the greater heterogeneity. Figures are created by STATA software (v15.1, Stata Corporation, College Station, TX). CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol.

relevant studies that LDL-C level cannot be grouped as we did may be missed.

5. Conclusion

In conclusion, our results showed that high LDL-C level (≥ 130 mg/dL) was associated with the high risk of all-cause mortality and CVD events. This finding may suggest that adults with high LDL-C level should take interventions and lipid-lowering treatment to regulate the LDL-C level less than 130 mg/dL. Our results need to be cautiously interpreted and need to be verified by clinical studies in the future.

Author contributions

KP and YY designed the study. KP wrote the manuscript. XL, ZW, and ML collected, analyzed and interpreted the data. YY critically reviewed, edited and approved the manuscript. All authors read and approved the final manuscript.

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Table 3

Association between LDL-C levels and CVD event.

Outcomes	Number of studies	RR (95%CI)	P	I^2
CVD event				
< 70 mg/dL (vs 70–129 mg/dL)	6	1.01 (0.81, 1.24)	.958	89.1
Sensitivity analysis		1.01 (0.81, 1.24)		
130–159 mg/dL (vs 70–129 mg/dL)	10	1.26 (1.08, 1.47)	.003	93.8
Sensitivity analysis		1.26 (1.08,1.47)		
Region				
America		1.29 (1.07, 1.57)	.009	96.1
Asia		1.21 (0.85, 1.71)	.297	89.6
Europe		1.42 (0.58, 3.47)	.444	NA
Population				
General		1.44 (1.09, 1.91)	.011	94.1
High CVD risk		1.00 (0.95, 1.05)	.951	NA
Disease		1.04 (0.76, 1.40)	.826	93.0
≥160 mg/dL (vs 70–129 mg/dL)	12	1.70 (1.35, 2.14)	<.001	96.9
Sensitivity analysis		1.70 (1.35, 2.14)		
Region				
America		1.80 (1.31, 2.47)	<.001	98.2
Asia		1.50 (1.07, 2.11)	.019	88
Europe		1.81 (0.79, 4.18)	.164	NA
Population				
General		1.96 (1.38, 2.79)	<.001	95.9
High CVD risk		1.01 (0.95, 1.07)	.820	NA
Disease		1.32 (0.85, 2.04)	.221	95.6
Lipid-lowering medication				
No		2.05 (1.20, 3.50)	.009	NA
CHD event				
< 70 mg/dL (vs 70–129 mg/dL)	3	0.80 (0.63, 1.01)	.062	29.8
Sensitivity analysis		0.80 (0.63, 1.01)		
130–159 mg/dL (vs 70–129 mg/dL)	8	1.43 (1.12, 1.82)	.004	97.0
Sensitivity analysis		1.43 (1.12, 1.82)		
Region				
America		1.44 (1.12, 1.85)	.004	97.4
Asia		1.26 (0.67, 2.39)	.470	NA
Population				
General		1.61 (1.23, 2.11)	.001	92.7
High CVD risk		1.05 (0.96, 1.14)	.314	NA
Disease		1.20 (1.13, 1.28)	<.001	0.0
≥160 mg/dL (vs 70–129 mg/dL)	10	1.87 (1.44, 2.44)	<.001	96.6
Sensitivity analysis		1.87 (1.44, 2.44)		
Region				
America		2.01 (1.50, 2.70)	<.001	97.3
Asia		1.30 (1.02, 1.68)	.038	0.0
Population				
General		2.16 (1.61, 2. 90)	<.001	92.7
High CVD risk		1.08 (0.98, 1.18)	.140	NA
Disease		1.63 (1.53, 1.74)	<.001	0.0
Lipid-lowering medication				
No		2.05 (1.20, 3.50)	.009	NA
MI				
130–159 mg/dL (vs 70–129 mg/dL)	3	1.19 (1.12, 1.26)	<.001	0.0
Sensitivity analysis		1.19 (1.12, 1.26)		
≥160 mg/dL (vs 70–129 mg/dL)	3	1.39 (1.03, 1.87)	.031	73.3
Sensitivity analysis		1.39 (1.03,1.87)		
Region				
America		1.40 (0.99,1.98)	.057	85.9
Asia		1.25 (0.57, 2.72)	.576	NA
Population				
General		1.15 (0.89, 1.48)	.293	NA
Disease		1.63 (1.53, 1.74)	<.001	0.0
Stroke				
< 70 mg/dL (vs 70–129 mg/dL)	2	1.15 (0.82, 1.62)	.431	0.0
Sensitivity analysis		1.15 (0.82,1.62)		
130–159 mg/dL (vs 70–129 mg/dL)	4	1.22 (0.93, 1.61)	.150	77.3
Sensitivity analysis		1.22 (0.93,1.61)		
≥160 mg/dL (vs 70–129 mg/dL)	4	1.21 (0.83, 1.75)	.321	79.8
Sensitivity analysis		1.21 (0.83,1.75)		

CI = confidence interval; CVD = cardiovascular disease; CHD = coronary heart disease; I^2 = I-squared; LDL-C = low-density lipoprotein cholesterol; MI = myocardial Infarction; NA = not available; RR = relative risk.

I^2 reflected the degree of heterogeneity, with the greater I^2 value representing the greater heterogeneity.

Table 4

Publication bias of outcomes by Begg's test and Egger's regression test.

Outcomes	Begg's test		Egger's regression test	
	Z	P	T	P
LDL-C of 130–159 mg/dL on CVD event	1.07	.283	1.52	.168
LDL-C ≥ 160 mg/dL on CVD event	1.17	.244	1.80	.102
LDL-C ≥ 160 mg/dL on CHD event	0.18	.858	0.66	.526

CVD = cardiovascular disease; CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol.

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