REVIEW

Assessment of estimated low-density lipoprotein-cholesterol (LDL-c) equations: a systematic review and meta-analysis

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Abstract

Background Low-density lipoprotein cholesterol (LDL-c) is the major determinant of cardiovascular disease burden. This study critically reviewed the published literature and performed a meta-analysis to compare and to determine which other equations provide the best means of estimating LDL-c in clinical settings.

Method English articles indexed in PubMed, Science Open, Biomed central and SpringerLink databases were searched with searches being conducted in or after 2001 up to date. According to the predefined inclusion and exclusion criteria, 22 articles out of the 17,970 retrieved were eligible for quantitative analysis. Data were pooled and meta-analysis performed using a random-effects model, and the results are described as event rates (pooled correlation coefficient).

Main body of the abstract All the twelve equations showed positive correlation with the respective direct low-density lipoprotein-cholesterol measurements. The pooled estimates showed a stronger positive correlation between Martin's low-density lipoprotein-cholesterol equation and the direct low-density lipoprotein-cholesterol measurement [0.96 (95% CI 0.94–0.98)] as compared to Friedewald's equation and the direct method [0.94 (95% CI 0.92–0.96)]. At triglycerides levels > 400 mg/dl, Martin's low-density lipoprotein-cholesterol equation established better performance (77.78%) than the Friedewald's equation. In studies where triglycerides levels > 400 mg/dl were excluded Martin's low-density lipoprotein-cholesterol equation still established better performance (83.33%) than the Friedewald's equation.

Short conclusion Our data suggest that Martin's equation showed a better performance than Friedewald equation. Martin's equation can serve as a more accurate method to estimate low-density lipoprotein cholesterol as compared to Friedewald's equation especially in situations of the same racial background.

Keywords Cardiovascular disease, Low-density lipoprotein cholesterol, Friedewald's equation, Martin's equation

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Background

Cardiovascular diseases (CVD) in recent times have been reported by the world health organization (WHO) as the leading cause of death worldwide, with high serum low-density lipoprotein cholesterol (LDL-c) a major risk factor of CVD worldwide (Ephraim et al. 2018). It is estimated by WHO that about 17.9 million lives are lost every year due to CVD. Many studies have consistently reported a strong positive correlation between CDV and high serum LDL-c, hence the need for an accurate estimation of LDL-c in clinical practice to monitor and evaluate patients risk of developing CVD (Martin et al. 2013; Ephraim et al. 2018).

Several novel formulas for calculating serum LDL-c have been reported in many research studies all over the world as an ideal formula better with regard to accuracy (Puavilai and Laoragpongse 2004; Puavilai et al. 2009; Martin et al. 2013; Mehta et al. 2018; Alpdemir and Alpdemir 2021) yet there seems to be no consensus on the best method of estimating serum LDL-c with regard to accuracy of results and convenience. The direct estimation method of measuring serum LDL-c is widely accepted as the most accurate method of estimating LDL-c but this method cannot be routinely employed in many clinical settings due to cost and the fact that it is quite complex to use (Puavilai et al. 2009). So due to cost and complexity of direct estimation of serum LDL-c, the indirect method of estimating serum LDL-c using standardized Friedewald's equation (sFE) is routinely employed in many clinical settings for assessing the coronary risk of patients (Ballantyne et al. 2000). Many other studies compared several other indirect serum LDL-c measurement formulas which were generally referred to as modified Friedewald's equation (mFE) in many of those research studies and reports from those research studies indicate that most of proposed modified formulas are more accurate in estimating serum LDL-c in instances of hypertriglyceridemia (Puavilai and Laoragpongse 2004; Alpdemir and Alpdemir 2021).

Elevated triglycerides often above 300 mg/dl in serum results in a significant accuracy decline in the indirect estimation of serum LDL-c using standardized Friedewald's equation according to many research studies, and this is the practical limitation of the standardized Friedewald's equation (Puavilai and Laoragpongse 2004; Ephraim et al. 2018; Mehta et al. 2018). This leads to a misclassification of patients with high coronary risk index as patients with low or normal coronary risk index (Mehta et al. 2018). Another significant limitation of sFE is that serum LDL-c of a non-fasting sample cannot be accurately measured (Puavilai et al. 2009).

Regardless of the reported limitations of sFE, a research study conducted by Puavilai and Laoragpongse (2004) reported that calculating LDL-c using the sFE produced results that strongly correlates with direct measurement of LDL-c which is used as a reference (gold standard) in many of the research works which seeks to assess the validity or accuracy of sFE results compared to other modified LDL-c calculation method. However, the researchers of this study noticed that the LDL-c level from the direct measurement (reference standard) was higher than calculating one using sFE if the serum triglyceride is higher than 300 mg/dL (Puavilai and Laoragpongse 2004).

Hence, due to the lack of consensus on the best means of calculating an important clinical parameter as serum LDL-c there is a need for a broader or a more holistic approach in determining the best means of estimating LDL-c in serum in terms of accuracy and a systematic review which seeks to deliver a meticulous analysis and summary of all relevant research works about this subject can best achieve that.

Methods

Literature research

This review study systematically identified and critically evaluated and analyzed existing primary literature to make recommendations on the best equation to estimate LDL-c in resource limited areas. In this literature review, the Medline (PubMed), ScienceOpen, Biomedcentral and SpringerLink electronic databases were searched. The search was based on the following keyword terms or their derivatives or synonyms: LDL cholesterol and equation. The search used 'free terms' and 'index terms' funneled using the Boolean operators (OR, AND), into the search string; (LDL cholesterol OR low-density Lipoprotein cholesterol) AND (equation OR formula) as described in Table 1.

Table 1 Search term strategy used

	Searches
1	LDL cholesterol
2	Low-density lipoprotein cholesterol
3	1 OR 2
4	Equation
5	Formula
6	4 OR 5
7	3 AND 6

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting and reporting systematic review were followed.

Criteria for considering studies for this review
Studies whose report did not present enough information to allow full assessment of eligibility or studies reported only in a non-English language were excluded. Published studies which are not original or primary research articles such patents, reviews, reports, newsletters, book, book chapters and conference papers were excluded from this study. Primary studies that employed diagnostic method comparison or method validation of calculated LDL-c were considered eligible for this study. Studies that were published earlier than 2001 were considered ineligible for review (Table 2).

Participants
Studies recruiting or involving populations of healthy and diseased subjects who meet the condition required for testing for serum lipids including being in a fasting state were eligible for inclusion (Table 2).

Index test and reference standards
Studies were required to estimate LDL-c using methods of direct measurement/assay of LDL as reference standard with or without an added test method as reference standard. Studies evaluating, validating or comparing any equation for LDL-c estimation in addition to the Friedewald's LDL-c equation were considered eligible for inclusion. Studies that evaluated only one LDL-c equation were considered ineligible (Table 2).

Data collection
Search results from the various databases were subjected to automated screening for eligibility using electronic filters available in the electronic databases based on pre-determined eligibility criteria as described in Table 2. Using pro-forma, eligibility of potentially relevant articles was assessed based on full text publications excluding non-English language reports. Due to the number of studies identified, hand search and search of bibliography of included studies were not sourced. The outcomes of the selection process are described in Fig. 1.
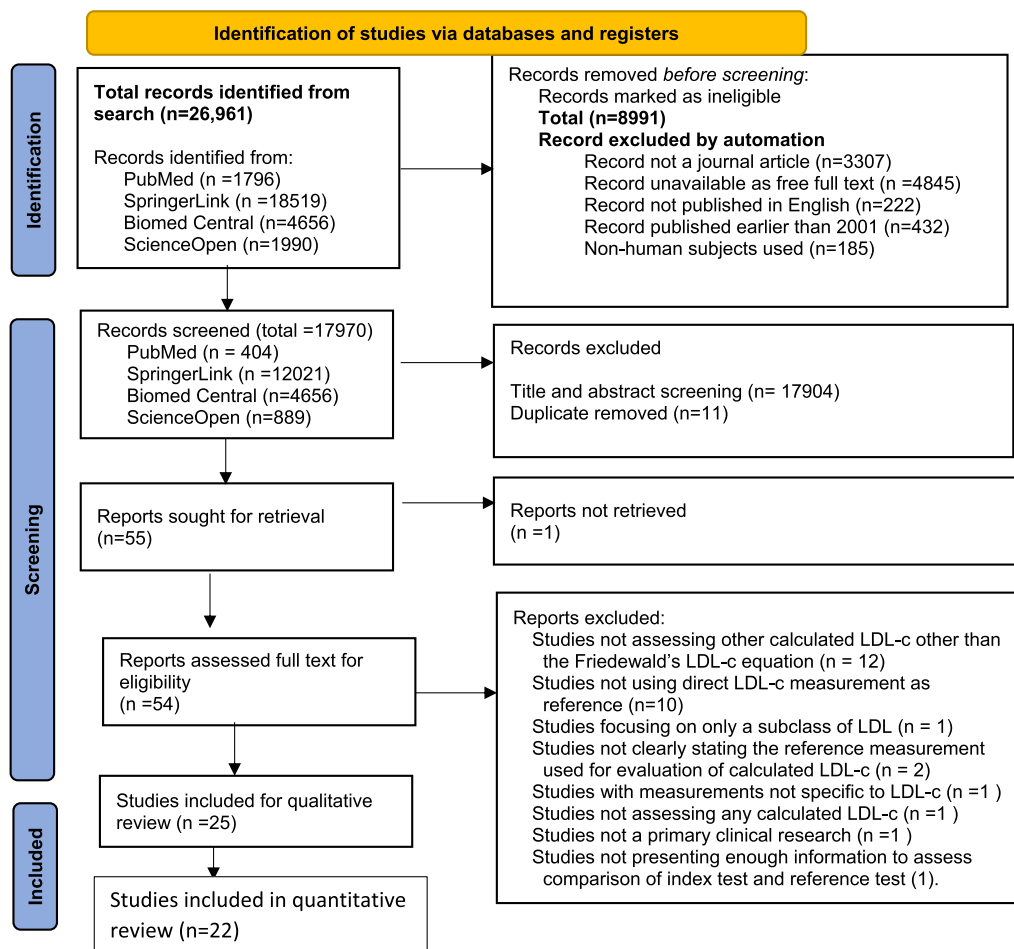
Appraisal of included studies and risk of bias
Two authors independently assessed the risk of bias of included studies, and disagreements were resolved through discussion. The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) was employed to evaluate the methodological quality. Four domains of entries were participant's selection, index test, reference standard and flow and timing. Definitions and judgment criteria for each domain are available in Cochrane Handbook.

Data extraction and management
Data relating to the correlation coefficient 'r' (Pearson correlation coefficient, Spearman rank correlation and intraclass correlation coefficient) estimation of each comparison of index test (calculated LDL-c equation) with reference test (direct LDL-c assays) were extracted and used for the meta-analysis. In three studies where coefficient of determination (r^2) was reported, correlations

Table 2 Inclusion and exclusion criteria for selection of studies

Inclusions criteria	Exclusions criteria
1. Studies on assessing the estimation of LDL-c using equations	1. Studies not reporting on the assessment of LDL-c equations
2. Evaluation studies where direct LDL-c was used as the reference standard	2. Evaluation studies where direct LDL-c was not used as a reference standard
3. Studies published in or after the year 2001	3. Studies published before 2001
4. Articles published in the English language	4. Articles unavailable in the English language
5. Journal articles	5. Non-journal articles
6. Primary research studies (both quantitative and qualitative studies)	6. Non-primary research studies such as literature reviews and systematic reviews
7. Studies related to estimating patient's quality of life	7. Studies not related to patient's quality of life
8. Full-text articles available	8. Full-text articles unavailable
9. Primary studies with abstracts (method comparison and validation studies)	9. Primary studies without Abstract
10. Studies that reported on other LDL-c equations other than only the Friedewald's equation	10. Studies that assessed only the Friedewald's LDL-c equation

Identification of studies via databases and registers

Total records identified from search (n=26,961)

Records identified from:
PubMed (n =1796)
SpringerLink (n =18519)
Biomed Central (n=4656)
ScienceOpen (n=1990)

Records removed *before screening*:
Records marked as ineligible
Total (n=8991)
Record excluded by automation
Record not a journal article (n=3307)
Record unavailable as free full text (n =4845)
Record not published in English (n=222)
Record published earlier than 2001 (n=432)
Non-human subjects used (n=185)

Records screened (total =17970)
PubMed (n = 404)
SpringerLink (n =12021)
Biomed Central (n=4656)
ScienceOpen (n=889)

Records excluded

Title and abstract screening (n= 17904)
Duplicate removed (n=11)

Reports sought for retrieval (n=55)

Reports not retrieved (n =1)

Reports assessed full text for eligibility (n =54)

Reports excluded:
Studies not assessing other calculated LDL-c other than the Friedewald's LDL-c equation (n = 12)
Studies not using direct LDL-c measurement as reference (n=10)
Studies focusing on only a subclass of LDL (n = 1)
Studies not clearly stating the reference measurement used for evaluation of calculated LDL-c (n = 2)
Studies with measurements not specific to LDL-c (n =1)
Studies not assessing any calculated LDL-c (n =1)
Studies not a primary clinical research (n =1)
Studies not presenting enough information to assess comparison of index test and reference test (1).

Studies included for qualitative review (n =25)

Studies included in quantitative review (n=22)

Fig. 1 PRISMA flowchart on selection of studies in this review

coefficient was recalculated using the formulae, and direction of slope ($\sqrt{r^2}$) was reported. In studies where estimates of coefficients were reported in strata or subgroups, the pooled or overall correlation coefficient was estimated by using the Schmidt–Hunter's method for estimating pooled correlation coefficients. Also, characteristics of each study (such as the year of study publication, method of direct LDL-c used, type of study, location and sample size) were extracted from each study (Table 3). The author's surname and year of publication of the study were used as identities for each study (Table 3).

Statistical analysis and data synthesis

For each test type, we plotted estimates of the observed correlation coefficients in forest plots. These plots illustrate the variation in test performance between studies. The Hedges–Olkin method for pooled correlation coefficient was used to calculate overall correlation coefficients. The summary estimates were plotted using forest plots. The random effect model was used as significantly large heterogeneity was observed among the studies. The StatsDirect statistical tool was used for the meta-analysis.
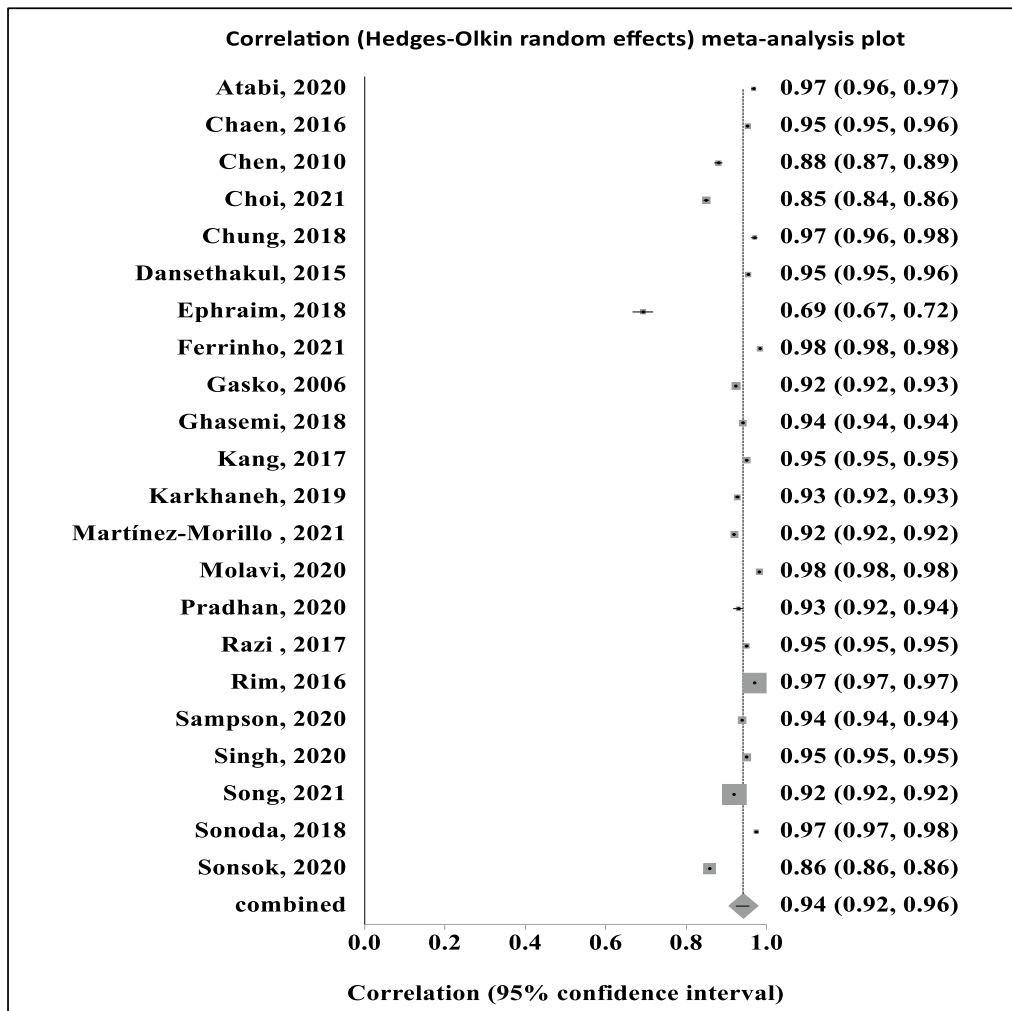
Investigations of heterogeneity

We inspected forest plots to visually assess heterogeneity between study-specific estimates of correlation. A heterogeneity test (I^2 heterogeneity test) was also performed to ascertain the variations in the outcomes of interest among the various studies.

Table 3 Characteristics of selected studies

Author	Year	Type of study	Ref. method	Study participants	Setting	Sample size	Unit used	Excluded TG > 400 mg/dl
Atabi et al.	2020	Comparative study	Direct methods in which blocking agents inhibit lipoproteins other than LDL	General adult workers	Iran	500	mg/dl	Yes
Chaen et al.	2016	Validation study	Selective solubilization method	Type 2 diabetics	Japan	1828	mg/dl	Yes
Chen et al.	2010	New tool	Not specified	Out patients	China	2180	mg/dl	No
Choi et al.	2021	Validation study	Enzymatic method	Korean adults	South Korea	8250	mg/dl	No
Chung et al.	2018	Validation study	Not specified	Patients with coronary artery calcium score (CACS) ≥ 300	South Korea	299	mg/dl	Yes
Dansethakul et al.	2015	New tool	Homogenous enzymatic method	Residents of urban Thailand visiting for annual medical check-ups	Thailand	1786	mg/dl	No
Ephraim et al.	2018	Comparative study	Enzymatic method	Patients with no evidence of metabolic disease visiting laboratory in Ghana	Ghana	1518	mmol/l	Yes
Ferrinho et al.	2021	Comparative study	Direct colorimetric method	General Portuguese population	Portugal	1689	mg/dl	Yes
Gasko et al.	2006	Validation study	Not specified	Brazilian adult population	Brazil	10,000	both	No
Ghasemi et al.	2018	Validation study	Direct enzymatic method	General	Iran	4750	mg/dl	Yes
Kang et al.	2017	Comparative study	Enzymatic method	Koreans	South Korea	4270	mg/dl	yes
Karkhaneh et al.	2019	Comparative study	Enzymatic colorimetric assay	People from Tehran city	Iran	2752	mmol/l	No
Lee et al.*	2016	Validation study	Enzymatic homogeneous assay	Korean adults	South Korea	5790	mg/dl	No
Martínez-Morillo et al.	2021	Comparative study	Enzymatic colorimetric assay		Spain	6113	mmol/l	No
Molavi et al.	2020	Comparative study	Enzymatic method	Iranian children and adolescent	Iran	3844	mg/dl	No
Pradhan et al.	2020	Validation study	Enzymatic method		Nepal	538	mg/dl	No
Razi et al.	2017	Comparative study	Enzymatic photometric method	Type 2 diabetics	Iran	1721	mg/dl	No
Rim et al.	2016	Comparative study	Enzymatic method	General adult patients	South Korea	168,316	mg/dl	Yes
Sajja et al.*	2021	Comparative study	VAP, a rapid ultracentrifugation technique	General	USA	111,939	mg/dl	No, all cases have TG > 400
Sampson et al.	2020	Validation study	B-quantification	Not specified	Not specified	8656	mg/dl	No
Singh et al.	2020	Validation study	Not specified	New York residents	USA	10,936	mg/dl	No
Song et al.	2021	Comparative study	Homogeneous direct assay	Asymptomatic Korean adults	South Korea	177,111	mg/dl	No
Sonoda et al.	2018	Validation study	Selective solubilization method	Japanese cardiovascular disease patients treated with statin	Japan	385	mg/dl	No
Sonsok et al.	2020	Comparative study	Homogenous direct enzymatic assay	Residents of Nadun district	Thailand	32,258	mmol/l	No
Vujovic et al.*	2010	Validation study	Enzymatic colorimetric assay	Patients visiting for routine checkup	Serbia	1043	mmol/L	No

*Studies not included in the meta-correlational analysis due to insufficient information

Pooled correlation coefficients

Correlation (Hedges-Olkin random effects) meta-analysis plot

Study	Correlation (95% CI)
Atabi, 2020	0.97 (0.96, 0.97)
Chaen, 2016	0.95 (0.95, 0.96)
Chen, 2010	0.88 (0.87, 0.89)
Choi, 2021	0.85 (0.84, 0.86)
Chung, 2018	0.97 (0.96, 0.98)
Dansethakul, 2015	0.95 (0.95, 0.96)
Ephraim, 2018	0.69 (0.67, 0.72)
Ferrinho, 2021	0.98 (0.98, 0.98)
Gasko, 2006	0.92 (0.92, 0.93)
Ghasemi, 2018	0.94 (0.94, 0.94)
Kang, 2017	0.95 (0.95, 0.95)
Karkhaneh, 2019	0.93 (0.92, 0.93)
Martínez-Morillo , 2021	0.92 (0.92, 0.92)
Molavi, 2020	0.98 (0.98, 0.98)
Pradhan, 2020	0.93 (0.92, 0.94)
Razi , 2017	0.95 (0.95, 0.95)
Rim, 2016	0.97 (0.97, 0.97)
Sampson, 2020	0.94 (0.94, 0.94)
Singh, 2020	0.95 (0.95, 0.95)
Song, 2021	0.92 (0.92, 0.92)
Sonoda, 2018	0.97 (0.97, 0.98)
Sonsok, 2020	0.86 (0.86, 0.86)
combined	0.94 (0.92, 0.96)

Correlation (95% confidence interval)

Fig. 2 The pooled correlation coefficient of Friedewald's LDL-c equation compared to direct measurement in determining levels of LDL-c from all included studies. There was a positive correlation between Friedewald's LDL-c equation and direct measurement in determining levels of LDL-c [0.94 (95% CI 0.92–0.96)]

Results
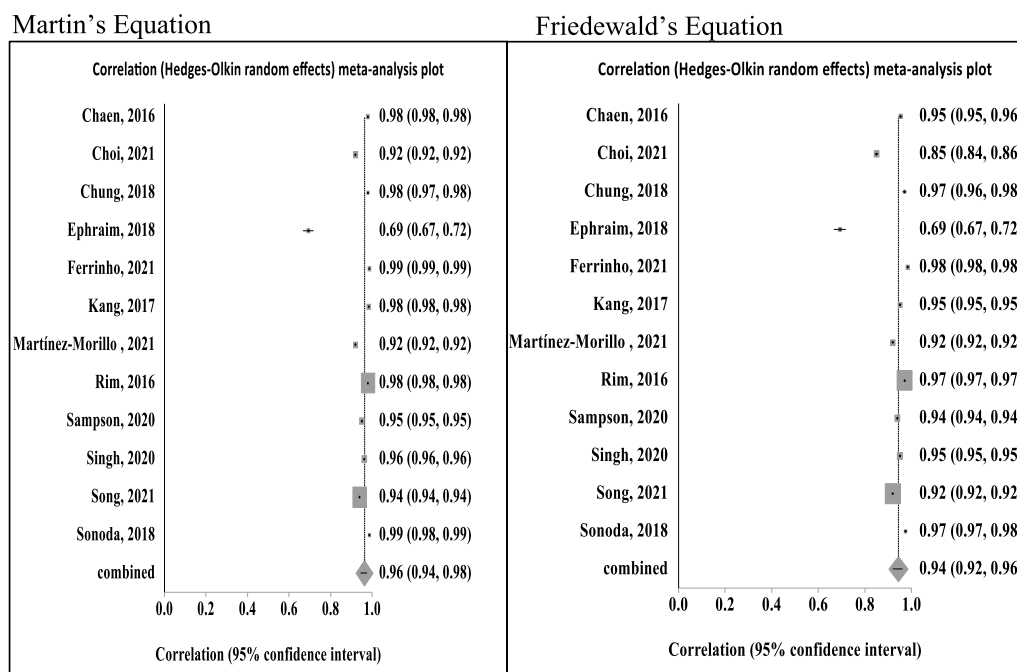
Pooled correlation coefficients

See Figs. 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14.

Discussion

A causal relationship between LDL-c levels and CV outcomes has been demonstrated in countless randomized controlled clinical trials (Steinberg 2005; Baigent et al. 2010; Levinson 2020; Mach et al. 2020; Piani et al. 2021). Direct measurements of LDL-c are still costly, time-consuming, not fully standardized and not universally available (Nauck et al. 2002; Miller et al. 2010; Langlois et al. 2018; Piani et al. 2021). Generally, LDL-c is alternatively estimated using the empirical Friedewald equation in most clinical environments (Bairaktari et al. 2005; Brown 2020). Nevertheless, many groups have consistently evaluated the accuracy of the Friedewald equation in different ethnicities or various disease entities and proposed alternative formulas for more precise LDL-c estimation until today (Table 4). To date, none of the proposed alternative methods have replaced the Friedewald equation in routine clinical practice and the lack of consensus on the best means of calculating LDL-c necessitated this study. Thus, to determine the best means of estimating LDL-c, this study evaluates the accuracy of the different equations known to calculate LDL-c levels.

Indeed, our data showed a positive correlation between Friedewald's LDL-c equation and direct measurement of LDL-c (D-LDL-c) from all the included studies [0.94 (95% CI 0.92–0.96)] (Fig. 2). Overall, all the twelve formulas
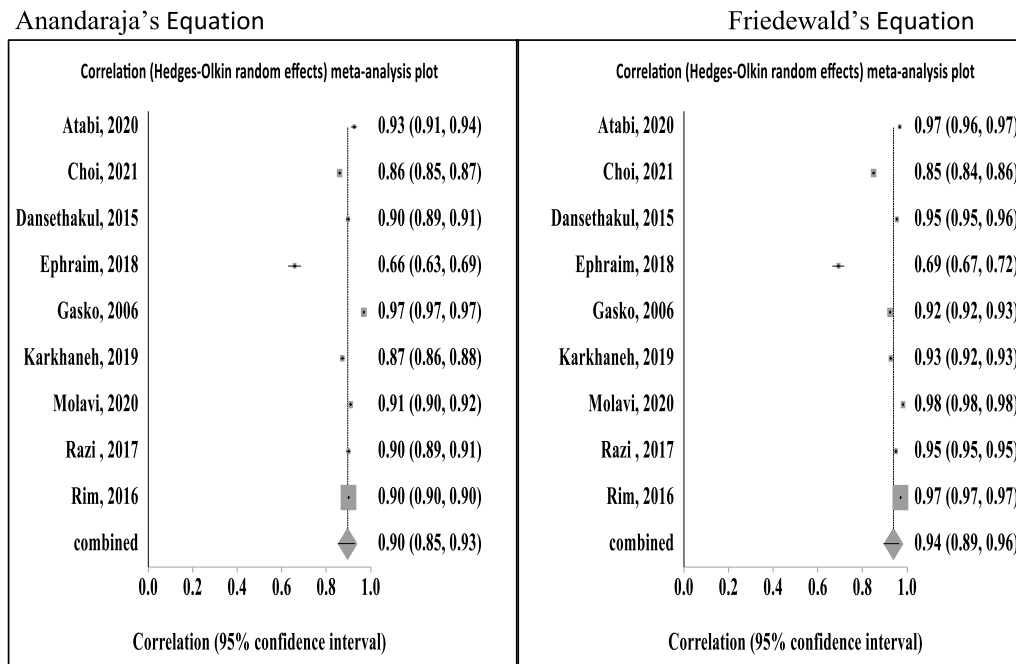
Fig. 3 The pooled correlation coefficient of Friedewald's and Martin's LDL-c equation compared to direct measurement in determining levels of LDL-c from matching studies. The pooled correlation between Martin's LDL-c equation and the direct measurement in determining levels of LDL-c as well as the correlation between the Friedewald's LDL-c equation and the direct measurement in determining levels of LDL-c. This correlation pooled 12 studies in the analysis. There was a positive correlation between Martin's LDL-c equation and the direct measurement in determining levels of LDL-c [0.96 (95% CI 0.94–0.98)]. Similarly, Friedewald's LDL-c equation positively correlated with the direct measurement in determining levels of LDL-c [0.94 (95% CI 0.92–0.96)]. However, there was a stronger positive correlation between Martin's LDL-c equation and the direct measurement in determining levels of LDL-c compared to Friedewald's equation and the direct method
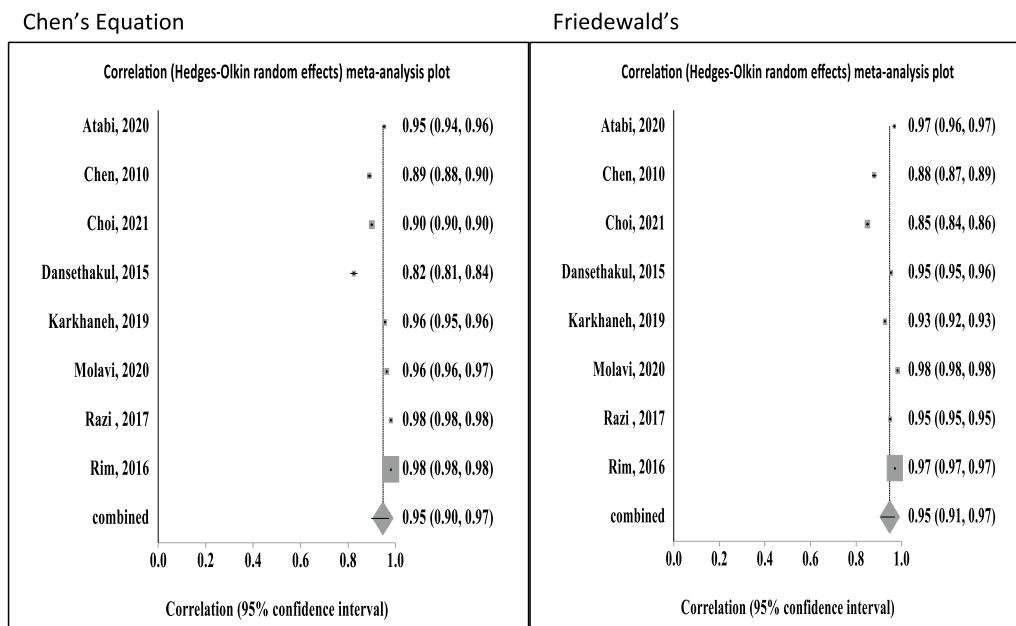
showed a good positive correlation with the respective D-LDL-c (Figs. 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13) and Martin's equation (ME) had the highest correlation with D-LDL-c level measurement compared to all other formulas (Fig. 3). This present result can be validated from a study conducted by Rim et al. (2016) which reported that ME provided best agreement in a large Asian cohort as compared to other equations. Similarly, another study conducted on Korean population also showed that ME provided better results compared to other equations (Kang et al. 2017). However, our finding is not in agreement with the work of Cordova et al. (2020) who revealed that Martin's equation is not accurate for estimating LDL-c in Southern Brazilians unless TG is between 300 and 400 mg/dl as well as Khan et al. (2017) whose work among the Pakistani population showed that the Teerakanchana equation (TE) provided higher correlation with D-LDL-c level followed closely by Martin equation. Also, our present results contradict studies conducted among the Indian population. They validated from their study that TE provided stronger correlation with the D-LDL-c level, followed by Vujovic equation (Dar et al. 2022), while in another study conducted among the Indian population Vujovic equation was preferred over others

for calculating LDL-c level (Wadhwa and Krishnaswamy 2016). The differences in the performance (i.e., correlation with D-LDL-c level) of the equations in measuring D-LDL-c levels could be associated with the racial differences.

Again, a study conducted by Piani et al. (2021) on a large, random and blinded Italian population showed that Sampson equation provided higher correlation to measured D-LDL-c level. This outcome is not in keeping with our present data which revealed that ME is highly correlated with measured LDL-c levels. Here, we strongly believe that the difference in the outcomes could be due to the techniques employed in the estimation of the lipid levels. While Piani et al. (2021) estimated D-LDL-c level by employing the Sampson equation after all lipid samples were analyzed using direct homogeneous assay, Martin's equation estimated D-LDL-c levels after cholesterol concentrations (LDL-c, VLDL-c and HDL-c) and triglycerides were directly measured by density-gradient ultracentrifugation and the ARCHITECT C-8000 system, respectively. These methodologies have different underlying principles and could possibly influence the estimated D-LDL-c level.
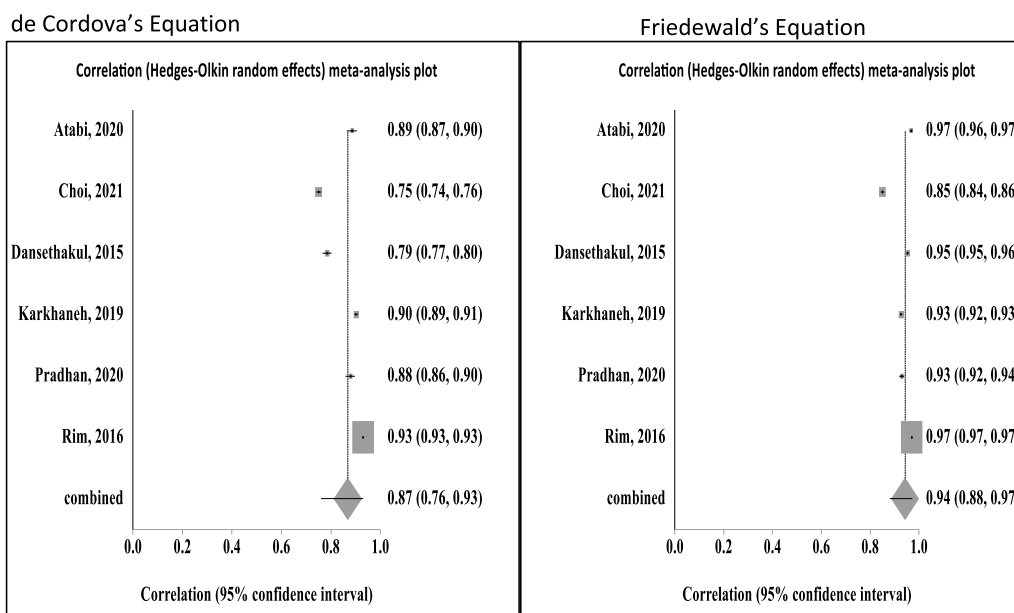
Anandaraja's Equation

Correlation (Hedges-Olkin random effects) meta-analysis plot

Atabi, 2020	0.93 (0.91, 0.94)
Choi, 2021	0.86 (0.85, 0.87)
Dansethakul, 2015	0.90 (0.89, 0.91)
Ephraim, 2018	0.66 (0.63, 0.69)
Gasko, 2006	0.97 (0.97, 0.97)
Karkhaneh, 2019	0.87 (0.86, 0.88)
Molavi, 2020	0.91 (0.90, 0.92)
Razi , 2017	0.90 (0.89, 0.91)
Rim, 2016	0.90 (0.90, 0.90)
combined	0.90 (0.85, 0.93)

0.0   0.2   0.4   0.6   0.8   1.0

Correlation (95% confidence interval)

Friedewald's Equation

Correlation (Hedges-Olkin random effects) meta-analysis plot

Atabi, 2020	0.97 (0.96, 0.97)
Choi, 2021	0.85 (0.84, 0.86)
Dansethakul, 2015	0.95 (0.95, 0.96)
Ephraim, 2018	0.69 (0.67, 0.72)
Gasko, 2006	0.92 (0.92, 0.93)
Karkhaneh, 2019	0.93 (0.92, 0.93)
Molavi, 2020	0.98 (0.98, 0.98)
Razi , 2017	0.95 (0.95, 0.95)
Rim, 2016	0.97 (0.97, 0.97)
combined	0.94 (0.89, 0.96)

0.0   0.2   0.4   0.6   0.8   1.0

Correlation (95% confidence interval)

Fig. 4 The correlation coefficient of Friedewald's and the Anandaraja's LDL-c equations with direct measurement in determining levels of LDL-c from 9 matching studies. The Anandaraja's LDL-c equation and the direct method of determining LDL-c gave a positive correlation [0.90 (0.85–0.93)] as well as positive correlation between the Friedewald's equation and the direct method [0.94 (95%0.89–0.96)]. However, there was a stronger positive correlation between the Friedewald's equation and the direct method compared to the Anandaraja's equation

Chen's Equation

Correlation (Hedges-Olkin random effects) meta-analysis plot

Atabi, 2020	0.95 (0.94, 0.96)
Chen, 2010	0.89 (0.88, 0.90)
Choi, 2021	0.90 (0.90, 0.90)
Dansethakul, 2015	0.82 (0.81, 0.84)
Karkhaneh, 2019	0.96 (0.95, 0.96)
Molavi, 2020	0.96 (0.96, 0.97)
Razi , 2017	0.98 (0.98, 0.98)
Rim, 2016	0.98 (0.98, 0.98)
combined	0.95 (0.90, 0.97)

0.0   0.2   0.4   0.6   0.8   1.0

Correlation (95% confidence interval)

Friedewald's

Correlation (Hedges-Olkin random effects) meta-analysis plot

Atabi, 2020	0.97 (0.96, 0.97)
Chen, 2010	0.88 (0.87, 0.89)
Choi, 2021	0.85 (0.84, 0.86)
Dansethakul, 2015	0.95 (0.95, 0.96)
Karkhaneh, 2019	0.93 (0.92, 0.93)
Molavi, 2020	0.98 (0.98, 0.98)
Razi , 2017	0.95 (0.95, 0.95)
Rim, 2016	0.97 (0.97, 0.97)
combined	0.95 (0.91, 0.97)

0.0   0.2   0.4   0.6   0.8   1.0
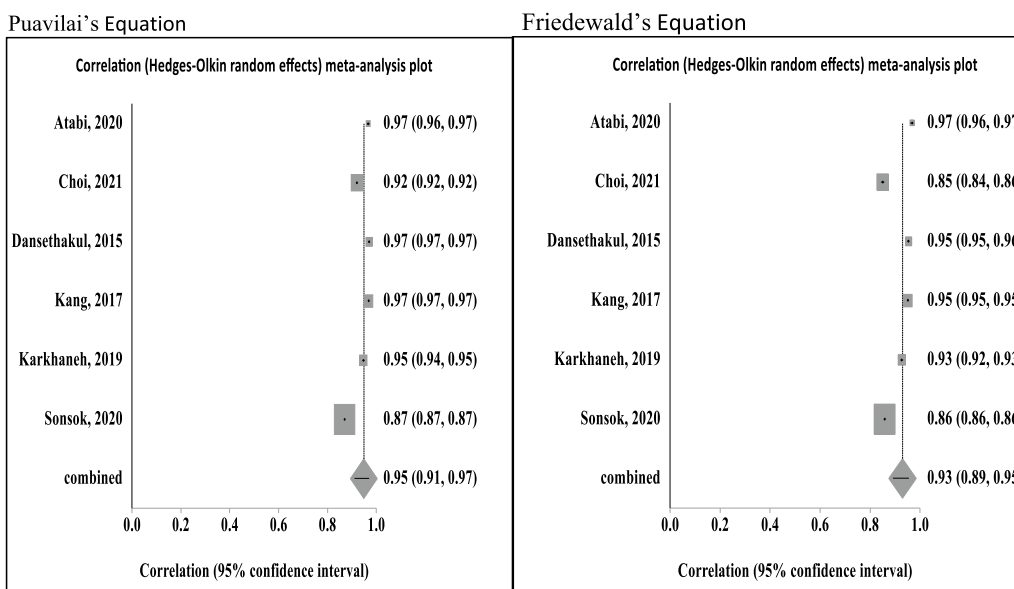
Correlation (95% confidence interval)

Fig. 5 The correlation coefficients of Friedewald's and the Chen's LDL-c equations with direct measurement in determining levels of LDL-c from 8 pooled matching studies. The two equations established a positive correlation between the direct method of determining LDL-c [0.95 (95% CI 0.90–0.97)]. There was no statistical difference between the correlation coefficients of Chen's equation and the direct measurement as well as Friedewald's equation and the direct method

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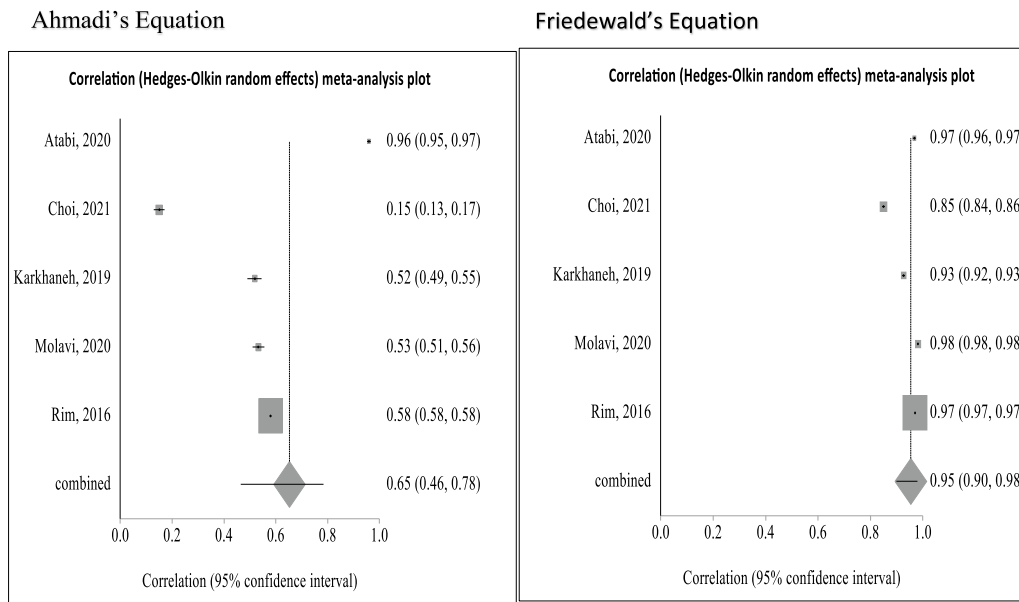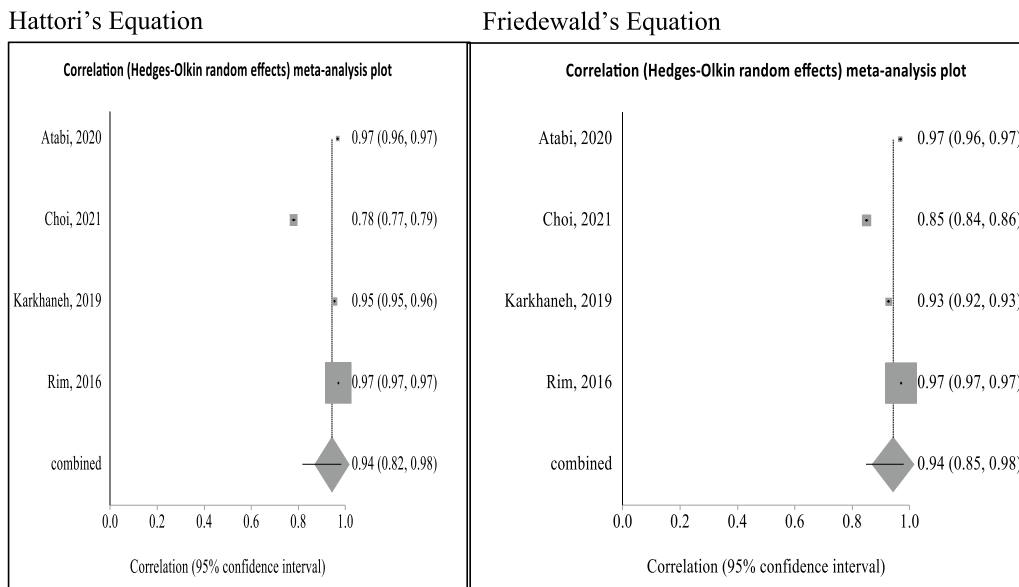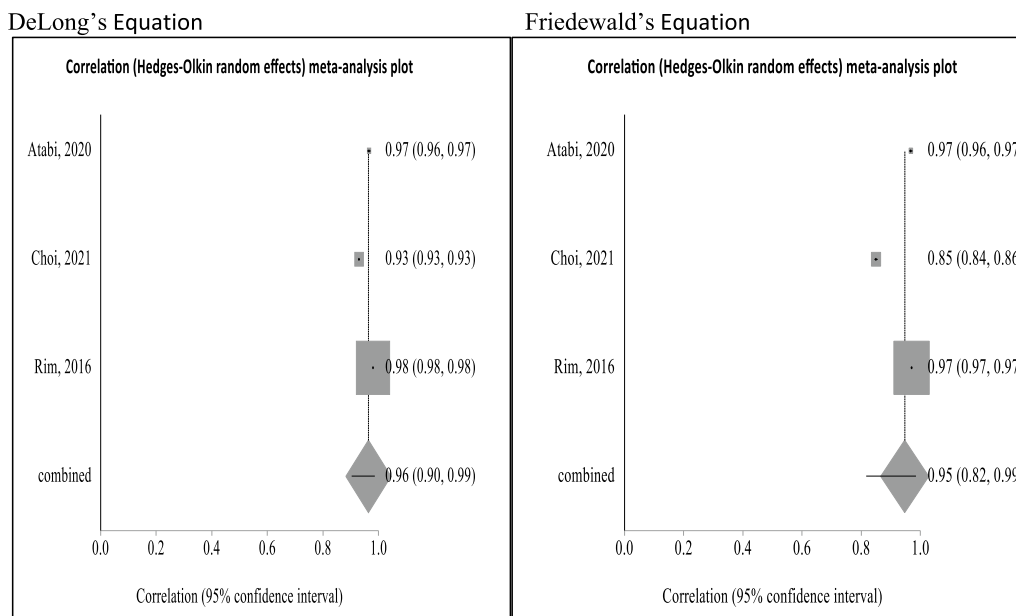Page 9 of 18

de Cordova's Equation

Friedewald's Equation

Fig. 6 The correlation coefficients of the Friedewald's and the de Cordova's LDL-c equations with the direct measurement in determining levels of LDL-c pooled from 6 matching studies. The de Cordova's LDL-c equations and the Friedewald's equation both demonstrated a positive correlation with the direct method of measuring LDL-c [0.87 (95% CI 0.76–0.93) and 0.94 (95% CI 0.88–0.97), respectively]. However, the Friedewald's equation established a stronger positive correlation with the direct method of determining LDL-c compared with the de Cordova's LDL-c equation

Puavilai's Equation

Friedewald's Equation

Fig. 7 The correlation coefficients of Friedewald's and the Puavilai's LDL-c equations with direct measurement in determining levels of LDL-c from 6 matching studies. Both equations demonstrated a positive correlation with the direct method of measuring LDL-c. However, the Puavilai's equation established a stronger correlation with the direct method [0.95 (95% CI 0.91–0.97)] than Friedewald's LDL-c equation [0.93 (95% CI 0.89–0.95)]

Moreover, our study found the lowest correlation between Ahmadi's equation (AE) and the measurement of D-LDL-c level [0.65 (95% CI 0.46–0.78)] (Fig. 8). Interestingly, our findings are consistent with the results of Karkhaneh et al. (2019) and Molavi et al. (2020), where AE provided lowest correlation for Iranian population likewise in the Pakistani population (Khan et al. 2022). The reason why Ahmadi equation does not perform well
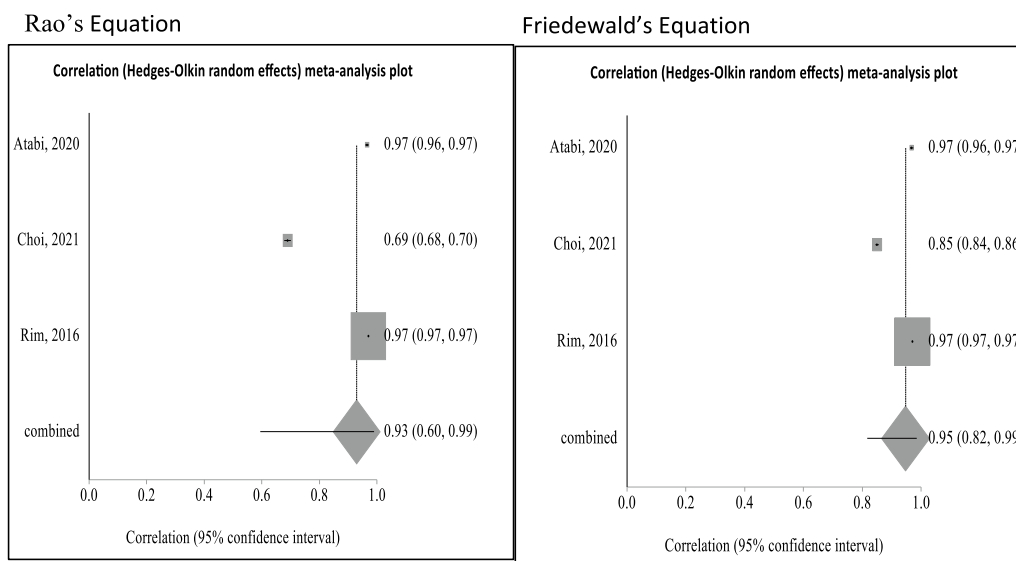
Ahmadi's Equation

Friedewald's Equation

Fig. 8 The correlation coefficients of Friedewald's and Ahmadi's LDL-c equations with direct measurement in determining levels of LDL-c from 5 matching studies. Though both equations established a positive correlation with the direct method of measuring LDL-c, the Friedewald's LDL-c equation presented with a stronger positive correlation with the direct method [0.95 (95% CI 0.90–0.98)] than the Ahmadi's LDL-c equation [0.65 (95% CI 0.46–0.78)]

Hattori's Equation

Friedewald's Equation

Fig. 9 The correlation coefficients of Friedewald's and the Hattori LDL-c equations with direct measurement in determining levels of LDL-c from 4 matching studies. Both the Friedewald's and the Hattori LDL-c equations demonstrated a positive correlation with the direct method of measuring LDL-c. There was no statistical difference in their correlation coefficients

Vujovics's Equation   Friedewald's Equation
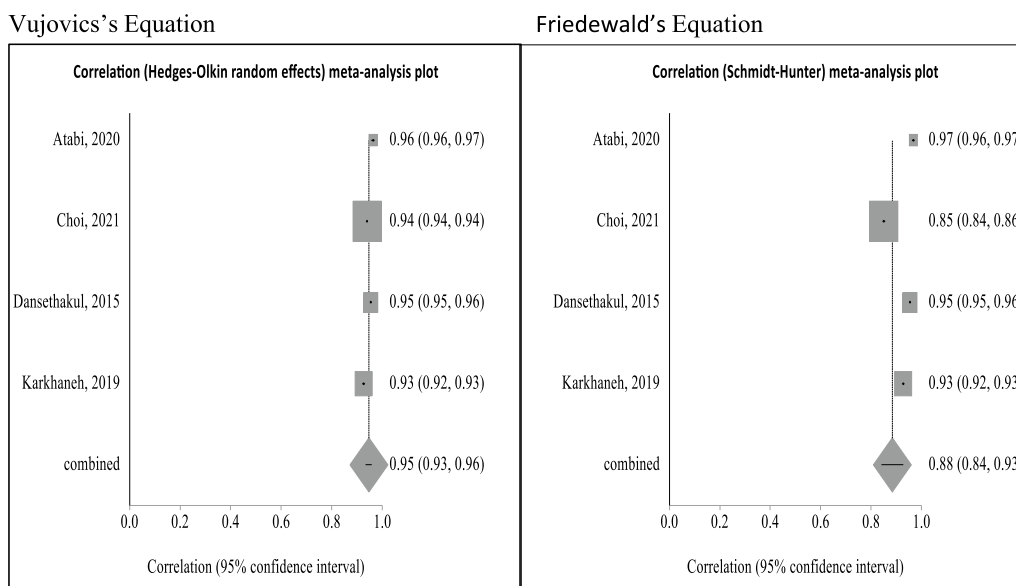
Fig. 10 The correlation coefficients of Friedewald's and the Vujovic's LDL-c equations with direct measurement in determining levels of LDL-c pooled from 4 from matching studies. Both equations established a positive correlation with the direct method. Nevertheless, Vujovic's LDL-c equation demonstrated a stronger positive correlation with the direct method [0.95 (95% CI 0.93–0.96)] than Friedewald's equation [0.88 (95% CI 0.84–0.93)]

DeLong's Equation   Friedewald's Equation

Fig. 11 The correlation coefficients Friedewald's and the DeLong's LDL-c equations with direct measurement in determining levels of LDL-c pooled from 3 matching studies. Both equations had a positive correlation with the direct method, but DeLong's LDL-c equation gave a strong correlation with the direct method [0.96 (95% CI 0.90–0.99)] compared with Friedewald's equation [0.95 (95% CI 0.82–0.99)]

could be due to the fact that this equation was derived only from the patients with high cholesterol (> 250 mg/dL, > 6.45 mmol/L) (Rim et al. 2016).

In addition, one interesting finding in our study is that studies that used LDL-c equations (Choi, DeLong, Puavilai and Molavi) established better performance (100%) than the Friedewald equation (FE) at serum triglycerides (TG) levels > 400 mg/dl (Fig. 14A). This is partly in conformity with the report of Wadhwa and Krishnaswamy (2016) who compared LDL cholesterol
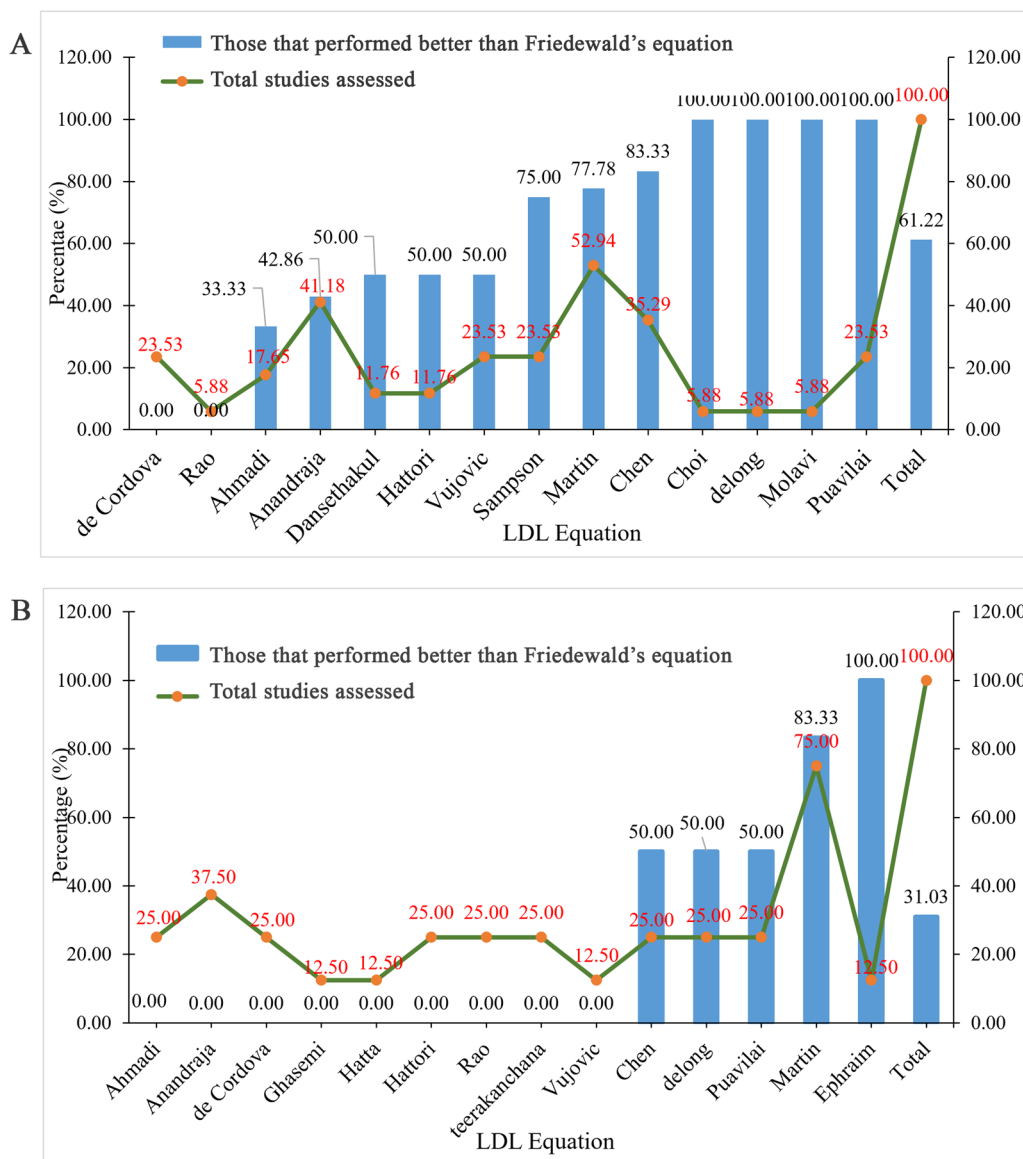
Rao's Equation

Friedewald's Equation

Fig. 12 The correlation coefficients of Friedewald's and the Rao's LDL-c equations with direct measurement in determining levels of LDL-c from 3 matching studies. Both equations established a positive correlation with the direct method of measuring LDL-c; however, Friedewald's equation demonstrated a stronger positive correlation with the direct method [0.95 (95% CI 0.82–0.99)] than the Rao's LDL-c equation [0.93 (95% CI 0.60–0.99)]

Sampson's Equation

Friedewald's Equation
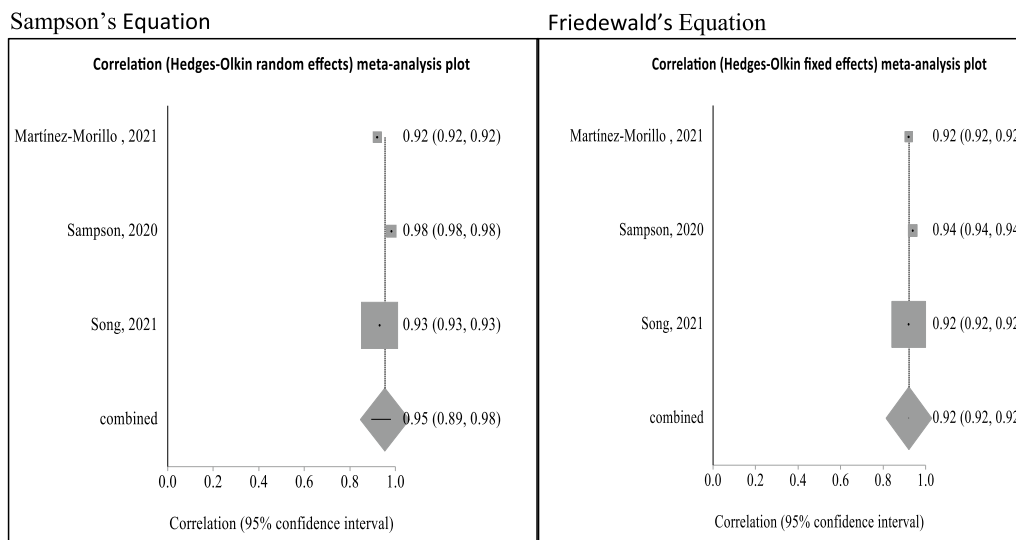
Fig. 13 The correlation coefficients of Friedewald's and the Sampson's LDL-c equations with direct measurement in determining levels of LDL-c from 3 matching studies. Though both equations had a positive correlation with the direct method of measuring LDL-c, the Sampson's LDL-c equation showed a stronger positive correlation with the direct method [0.95 (95% CI 0.89–0.98)] as compared with the Friedewald's equation [0.92 (95% CI 0.92–0.92)]

estimated using various formulae with directly measured LDL cholesterol in Indian population. While our study validates that Choi, DeLong, Puavilai and Molavi LDL-c equations gave better performance (100%) than the Friedewald equation (FE) at TG levels > 400 mg/dl, they reported that for TG range > 400 mg/dL, Vujovic

equation correlated best with direct measurement of LDL-c levels. Nonetheless, this is contradictory to the study conducted by Sha et al., in Bangladeshi population who concluded that FE can be used up to serum TG concentration of 700 mg/dL (Sha et al. 2015). Here, the variance in the performance of the equations in

Fig. 14 The proportions of LDL-c equations performing better than Friedewald's equation in studies where TG > 400 mg/dl were included or excluded. **A** Triglycerides levels > 400 mg/dl included. About 6 matching studies that included serum triglycerides levels > 400 mg/dl, 100% of these studies established better performance of the Choi, DeLong and Molavi LDL-c equations than the Friedewald's equation (Fig. 14A). **B**: Triglycerides levels > 400 mg/dl excluded. However, in about 24 studies, 100% of the studies demonstrated better performance of the Puavilai LDL-c equation compared with Friedewald's equation. In about 13 studies that excluded serum triglycerides levels > 400 mg/dl, 100% recorded better performance of the Ephraim's LDL-c equation than the Friedewald's equation. This was followed by the Martin's LDL-c equation with 83% out of the 75 studies assessed (Fig. 14B)

estimating D-LDL-c levels at serum triglycerides (TG) levels > 400 mg/dl may be associated with sample size, fasting and non-fasting state of study participants, ethnicity and procedures employed in estimating lipid levels.

Furthermore, Cordova and Cordova suggested a new formula that performed better than Friedewald formula in Brazilian population over a wide TG range (de Cordova and de Cordova 2013). The results of this present study show FE performed better than Cordova equation (CE). Hence, we are in support of the findings of Wadhwa and Krishnaswamy (2016) that Cordova formula does not provide any significant advantage over Friedewald formula in Indian population. This study supports the study done by Gupta and Singh (2012), which concluded that Anandaraja formula does not provide any advantage

Table 4 Types of LDL-c Equations

Name of equation	Count	%	Formula	Studies
Ahmadi's equation	5	5.3	$LDL = (TC/1.19) - (HDL/1.1) + (TG/1.9) - 38$	Choi (2021)
				Karkhaneh (2019)
				Molavi (2020)
				Rim (2016)
				Atabi (2020)
Anandaraja's equation	9	9.6	$LDL = (0.9 \times TC) - (0.9 \times TG/5) - 28$	Atabi (2020)
				Choi (2021)
				Dansethakul (2015)
				Ephraim (2018)
				Gasko (2006)
				Karkhaneh (2019)
				Molavi (2020)
				Razi (2017)
				Rim (2016)
Chen's equations	8	8.5	$LDL = (TC - HDL) \times 0.9 - (TG \times 0.1)$	Atabi (2020)
				Choi (2021)
				Dansethakul (2015)
				Karkhaneh (2019)
				Molavi (2020)
				Razi (2017)
				Rim (2016)
Choi's equations	1	1.1	$LDL = TC - 0.87 \times HDL - 0.13 \times TG$	Choi (2021)
Dansethakul's equations	2	2.1	$LDL = 0.9955TC - 0.9853HDL\text{-}C - 0.1998TG + 7.1449$	Dansethakul (2015)
				Sonsok (2020)
de Cordova's equation	6	6.4	$LDL = 0.7516 \times (TC\text{-}HDL)$	Atabi (2020)
				Choi (2021)
				Dansethakul (2015)
				Karkhaneh (2019)
				Pradhan (2020)
				Rim (2016)
DeLong's equation	3	3.2	$LDL = TC - (HDL + 0.16 \times TG$	Atabi (2020)
				Choi (2021)
				Rim (2016)
Ephraim's equation	1	1.1	$LDL\ (mmol/L) = TC\text{-}HDL\text{-}TG/4$	Ephraim (2018)
Friedewald's equation[a]	22	23.4	$LDL = TC\text{-}HDL\text{-}(TG/5)$	All included studies
Ghasemi's equation	1	1.1	$LDL = TC\text{-}HDL\text{-}TG/4$	Ghasemi (2018)
Hatta's equation	1	1.1	$LDL = TC\text{-}HDL\text{-}TG/4$	Kang (2017)
Hattori's equation	4	4.3	$LDL = (0.94 \times TC) - (0.94 \times HDL) - (0.19 \times TG)$	Atabi (2020)
				Choi (2021)
				Karkhaneh (2019)
				Rim (2016)

Table 4 (continued)

Name of equation	Count	%	Formula	Studies
Martin's equation	12	12.8	LDL-C = TC-HDL-C-TG/adjustable factor	Chaen (2016)
				Choi (2021)
				Chung (2018)
				Ephraim (2018)
				Ferrinho (2021)
				Kang (2017)
				Martínez-Morello (2021)
				Rim (2016)
				Sampson (2020)
				Singh (2020)
				Song (2021)
				Sonoda (2018)
Molavi's equation	1	1.1	LDL = (0.97 × TC) − (0.93 × HDL) − (0.19 × TG)	Molavi (2020)
Puavilai's equation	6	6.4	LDL = TC-HDL-(TG/6)	Atabi (2020)
				Choi (2021)
				Dansethakul (2015)
				Kang (2017)
				Karkhaneh (2019)
				Sonsok (2020)
Rao's equation	3	3.2	LDL = [(4.7 × TC) − (4.364 × HDL-C) − TG]/4.487 LDL = TC-HDL − {TG × [0.203 − (0.00011 × TG)]} LDL = [(4.7 × TC) − (4.364 × HDL-C) − TG]/4.487	Atabi (2020) Choi (2021) Rim (2016)
Sampson's equation	3	3.2	LDL-C = TC/0.948 − HDL-C/0.971 − (TG/8.56) + (TG × (Non-HDL-C/2140) − TG^2/16100) − 9.44	Martínez-Morello (2021) Sampson (2020) Song (2021)
Teerakanchana's equation	2	2.1	LDL-C = (0.91 × TC) − (0.634 × HDL-C) − (0.111 × TG) − 6.755	Atabi (2020) Rim (2016)
Vujovic's equation	4	4.3	LDL = TC-HDL-(TG/6.58) LDL = TC-HDL-(TG/6.58) LDL-Cal = TC-HDL-C-TG/3 LDL = TC-HDL-(TG/6.58)	Atabi (2020) Choi (2021) Dansethakul (2015) Karkhaneh (2019)
Total	94	100		

[a] The First formulated LDL-c equation

over Friedewald formula for LDL-c estimation in Indian population (Gupta and Singh 2012). This is contradictory to the study done by Anandaraja et al., which found their formula more accurate than Friedewald formula for TG < 350 mg/dL (Anandaraja et al. 2005). Also, the modified Friedewald equation developed by Puavilai also correlated well with direct measurement and performed better than Friedewald formula at TG range > 200 mg/dL in Thai population (Puavilai and Laoragpongse 2004). It could be observed clearly that changes in TG range have the ability to affect the final value of the D-LDL-c irrespective of the equations that would be used.

Again, Ahmadi equation (AE) has been validated in Iranian subjects at TG < 300 mg/dL (Ahmadi et al. 2008). In our study, it performed better than FE at TG > 400 mg/dL. However, when TG > 400 mg/dL were excluded, it performed poorly than FE (Fig. 14A and B). Hence, it might not be suitable to be used in other populations.

Besides, Hattori equation (HE) developed by Hattori et al. had shown to perform better than FE in Japanese population which does not provide any advantage over FE in Indian population (Hattori et al. 1998). Our study outcome indicates that HE performed better than FE at TG > 400 mg/dL. However, without TG > 400 mg/dl

inclusion, it performed poorly than FE (Fig. 14A and B). Again, this supports the claim that some of the D-LDL-c might not be suitable to be used in other populations because of racial differences.

Strength and limitations

The present study has one major strength and some limitations. We have analyzed all the principal LDL-c estimation formulas used in several studies. Hence, we strongly believe that our study is a representative of various racial origins and gives a generalizability to other populations. However, one major limitation in this study is that some studies were not included in the meta-correlational analysis due to insufficient information. In addition, several studies that we used in our study measured direct LDL-c by different assay methods such as Roche analyzer and Sekisui reagent instead of the recommended gold standard method of beta quantification. This could lead to incorrect comparisons of formulas with direct LDL-c data obtained from different methods.

Even though Martin's equation has proven to be a better assessment tool than the other equations, it is limited by several factors. First, the Martin's equation requires validation in an independent population and using other laboratory techniques. Second, factors such as race/ethnicity, obesity, diabetes and insulin resistance, which may affect variance in the adjustable factor (TG/VLDL-c ratio), were not available for analysis during the formulation of the Martin's equation. Finally, the study that formed the Martin's equation examines 1-time estimation of lipid levels. This is a major limitation because the study did not address the problem of intraindividual variation in lipid levels which has a greater potential to influence the adjustable factor.

Conclusion

Our data suggest that all the twelve formulas showed positive correlation with the respective D-LDL-c measurements. Martin's equation provided the highest correlation with D-LDL-c measurement than the most used Friedewald equation. Again, at high TG ranges (i.e., TG > 400 mg/dl), Martin's equation gave a better performance than Friedewald equation. Therefore, Martin's equation can serve as a more accurate method to estimate LDL-c as compared to Friedewald equation especially is situations of the same ethnicity or race.

Abbreviations

AE	Ahmadi's equation
CI	Confidence interval
CVD	Cardiovascular diseases
CE	Cordova equation
D-LDC	Direct low-density lipoprotein cholesterol
FE	Friedewald's equation
HE	Hattori's equation
ME	Martin's equation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
TE	Teerakanchana's equation
TG	Triglyceride
WHO	World Health Organization

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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