REVIEW ARTICLE

A systematic review and meta-analysis on screening lipid disorders in the pediatric age group

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Background: Different viewpoints exist about lipid screening in all children or only in children with positive family history (FH) of premature cardiovascular diseases (CVDs) or hypercholesterolemia. This systematic review and meta-analysis aim to assess the effectiveness of lipid screening in children and adolescents according to the existence of positive FH of CVD risk factors. **Materials and Methods:** PubMed, Scopus, and Google scholar were searched to identify relevant papers that were published from November 1980 until 30 November 2013. Irrelevant studies were set aside after studying their title, abstract, and full text. Then, the relevant studies were assessed by using a quality appraisal checklist. We used random effect model for meta-analysis and calculating the total estimation of sensitivity, specificity, and the positive predictive value (PPV) of FH in predicting dyslipidemia among children and adolescents. **Results:** Overall, 17,214 studies were identified in the primary search, out of which 19 primary studies were qualified for study entry. The sensitivity of positive FH of premature CVD or dyslipidemia for predicting dyslipidemia among children varied between 15 and 93. Moreover, the effectiveness of screening children for dyslipidemia according to premature CVD or dyslipidemia in their relatives was low in 86.9% of the primary studies. The total estimation of sensitivity, specificity, and predictive value was 42.6, 59, and 20.7, respectively, according to the meta-analysis results. **Conclusion:** The present meta-analysis indicated that selecting target population for screening children and adolescents for dyslipidemia according to their FH has low sensitivity.

Key words: Children, family history (FH), lipid, meta-analysis, screening

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INTRODUCTION

Cardiovascular diseases (CVDs) are the main cause of mortality and morbidity worldwide. They have multifactorial etiologies, mainly related to genetic and environmental factors.[1,2] A growing body of evidence exists about the early life origins of chronic diseases, and the tracking of CVD risk factors from childhood into adulthood.[2] It is well-documented that high concentration of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) as well as low concentration of high-density lipoprotein cholesterol (HDL-C) are important risk factors of CVD in adults.[1-4] The accumulating number of studies confirmed the tracking of CVD risk factors including dyslipidemia from childhood to adulthood.[3,4] They showed that about 50% of children and adolescents with dyslipidemia will continue to have this disorder as adult.[3-5]

TC levels increase from birth, stabilize at about 2 years of age, reach a peak before puberty, and then turn down slightly during adolescence. Normal values for lipids in

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the pediatric age group are actually defined according to the population distributions of lipid levels from the Lipid Research Clinics (LRC) Prevalence Study, which was conducted in the 1970s. Dyslipidemia is commonly defined as TC higher than 200 mg/dL and LDL-C higher than 130 mg/dL; these values correspond to the 95th percentile of the LRC study.[3,6-8]

Timely identification of children with dyslipidemia is important for considering early interventions to prevent or postpone the development of atherosclerosis.[9] To reduce the burden of CVD, there are two approaches for screening dyslipidemia in children and adolescents. One of these approaches is presented by the American Academy of Pediatrics (AAP), and recommends that individuals aged 2 years and older should be screened for high cholesterol if they have a family history (FH) of premature CVD (≤55 years of age) or a parent with history of hypercholesterolemia (240 mg/dL [6.2 mmol/L] or higher) or existence of other CVD risk factors in a child or adolescent. The other approach proposes universal screening of children and adolescents for dyslipidemia.[2,4,10-12]

Controversial results have been reported in this respect. In the study of Eissa *et al*., using the AAP criteria for screening dyslipidemia had a sensitivity of 54 to 66 and a specificity of 50 to 53, with the positive predictive value (PPV) ranging from 16 to 32. This study indicated that using FH criteria had a low yield for identifying children and adolescents with abnormal lipids and lipoproteins.[9] Bistritzer *et al*. found that screening the offspring of patients with premature CVD was highly productive in identifying young people who were at excessive risk for future coronary artery disease. They proposed that early identification of this young and at-risk population was an opportunity for the early initiation of preventive measures.[4] Allium *et al*. have shown that the prevalence of dyslipidemia was 6.75 times higher in children with parents of hyperlipidemia than in their counterparts.[8] In the study of Lin *et al*. in Taiwan, 16-18% of the children had a positive FH of CVD or hyperlipidemia; also, children with FH of hyperlipidemia were significantly more likely to have elevated TC [odds ratio (OR):1.4, $P < 0.05$] and LDL-C (OR:1.4, $P < 0.05$) than those without such a history but the PPV of hyperlipidemia were less than 13 according to FH.[13] In the study of Promise *et al*., 63 children of the 190 patients had hypercholesterolemia; the sensitivity and specificity of FH for screening the children were 33.2 and 71.5, respectively.[14]

The abovementioned points indicate that the effectiveness of the strategies of screening children for dyslipidemia according to their FH of premature CVD or universal screening remains controversial. Systematic review and meta-analysis may serve in resolving the conflicts and provides credible evidence.[15] The current study is a systematic review and meta-analysis on the results of primary studies that investigated screening dyslipidemia in children and adolescents according to the existence of positive FH of CVD risk factors.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[16]

Search strategy

The search was conducted in December 2013. To find primary studies published electronically from November 1980 until 30 November 2013, we searched the databases of PubMed, Scopus, and Google scholar. The search was conducted in the English language. The main keywords and probable combination of important words were searched. We used the following keywords: Hypercholesterolemia, cardiovascular disease family history, CVD family history, coronary heart disease family history, atherosclerosis family history, CHD family history, Familial hypercholesterolemia, lipid, lipoprotein, LDL, low density lipoprotein, HDL, high-density lipoprotein, HDL-C, high-density lipoprotein cholesterol, LDL-C, low-density lipoprotein cholesterol, cholesterol, TC, triglycerides, TG, dyslipidemia screening, pediatrics, children, childhood, universal screening dyslipidemia, and we used and/or conjunctions. Moreover, reference lists of published studies were also investigated to increase the search sensitivity and to select a higher number of studies. Search evaluation was conducted randomly by two independent researchers, and it was confirmed that all relevant studies were considered.

Studies selection

The titles and abstracts of papers were studied and relevant papers were selected. Then, the full texts of pertinent papers were studied and their findings were rescreened. Two independent researchers (MM and MA) screened the titles and abstracts of the papers identified by the literature searches for their potential relevance or assessed the full text for including them in the review. In the case of disagreement, the discrepancy was determined in consultation with a third arbitrating reviewer (RK). The full texts or summaries of all the searched articles, documents, and reports were extracted. After reviewing and studying the titles, author(s), journal name, and publication year, the repetitive items were excluded. It is noteworthy to mention that for avoiding cross-publication bias, we reviewed findings to identify and to eliminate duplicates. Then, researchers carefully studied the full texts of the articles; the relevant articles were selected and the irrelevant ones were excluded.

Study inclusion eligibility

In this systematic review and meta-analysis, we included all relevant studies that evaluated the program of lipid

screening in a child and obtained at least the minimum score of 8 in the abovementioned checklist.

Study exclusion eligibility

After reviewing and examining the full text or abstract of the articles and after recognizing the disagreements, the studies with the following criteria were excluded:

1. The results of the papers, documents, or reports that were not clear;
2. Review articles; and
3. Evidences that showed the article was not a primary study.

Quality assessment

After determining the related studies in terms of titles and contents, the quality of documents was evaluated by using a checklist [Figure 1]. This checklist considered the study objective, study method, sample size, sampling method, data collection tool, variables evaluation status, and studied target group, and then the analysis status was examined by using 12 questions (one score for each question). The maximum score of this checklist was 12.[17] At the final stage, we selected those articles that obtained at least the minimum acceptable score, and then the related information was extracted and analyzed.

Data extraction

Data were extracted by researchers in terms of article title, first author, publication year, total sample size, sample size according to gender, study setting, data source, mean TC, mean HDL-C, mean LDL-C, TG as well as the percentage of sensitivity, specificity, PPV, and negative predictive value (NPV) for FH of dyslipidemia or premature CVD.

Meta-analysis

In each study, the standard error of sensitivity, specificity, and PPV were calculated based on binomial distribution formula. Finally, the heterogeneity index was determined by using Q- and I-squared test. For determining the existence of heterogeneity among primary studies according to Q test, the significance level was considered as less than 0.05. Furthermore, I_2 test presented a range of 0% (no heterogeneity) to 100% (significant heterogeneity); values of 25%, 50%, and 75% were considered as representing low, medium, and high heterogeneity, respectively.[18] For this study, we considered that I_2 values above 25% or P value <0.05 to be indicative of significant heterogeneity.

No	Questions	Score	
		yes=1	No=0
1	Are the research questions or objectives clearly stated?		
2	Is the study context clearly described?		
3	Is the sample size stated?		
4	Is the calculation of sample size clearly described (is the sample size appropriate according to the research question and variables?)		
5	Is the sampling method clearly described?		
6	Is the sampling strategy appropriate for the research question?		
7	Is the method of data collection clearly described?		
8	Is the data collection method appropriate to the research question?		
9	Is the method of analysis clearly described?		
10	Are the research results clearly stated?		
11	Is the analysis appropriate for the research question?		
12	Are the claims made supported by sufficient evidence?		

Figure 1: Checklist for assessment of the articles' quality

According to the heterogeneity results with meta command in meta-analysis, the random effect model was used to estimate the sensitivity, specificity, and PPV percent of FH of dyslipidemia or CVD for predicting dyslipidemia in children. In order to minimize the random variation of the estimations of studies, we used Bayesian-adjusted estimation in the forest plots. At the final step, the effects of variables, which were determined as probable sources of heterogeneity in the study, were examined by using the meta-regression method. The point estimation for the sensitivity, specificity, and PPV with confidence interval of 95% was calculated in forest plots in which the square size represents the weight of each study and lines in its both sides represent the confidence interval of 95%. Moreover, the sensitivity analysis was conducted to estimate the effect of each primary study in the pooled rate estimation. Analysis was performed by using the Stata software version 11 (Stata Corporation, College Station, TX, USA).

RESULTS

Overall, 17,214 documents were retrieved by searching the electronic databases with maximum sensitivity. We then removed 15,864 of them by applying an operator to have maximum specificity; another 234 remaining documents were also removed because of being repetitive. Thereafter, we studied the titles and abstracts of 1,116 remaining papers out of which 998 were irrelevant and were removed. After studying the full texts of 118 remaining papers, 99 were removed. It is worth mentioning that three further studies were identified and finally 22 studies were selected. Three of them were set aside because they did not meet the inclusion criteria; as a result, 19 primary studies [2,4,9,12-14,19-31] were entered to this study [Figure 2 and Table 1].

In the primary studies entered into this systematic review and meta-analysis, 37,304 children and adolescents were assessed for dyslipidemia. The age group considered in these studies was between 2 years and 20 years. As presented in Table 1, the bases for predicting dyslipidemia in children were the history of premature CVD in parents (in six articles), history of dyslipidemia in parents (in eight articles), and history of premature CVD or dyslipidemia in parents (in nine articles).

In six out of seven studies that reported elevated LDL-C among children with FH of premature CVD or dyslipidemia,

Table 1: Results of primary studies on screening dyslipidemia in the pediatric age group and included in the meta-analysis

First author, publication year	Type of risk factor**	Sample size	Age group	High LDL-C†	Low HDL-C‡	High TC	High TG	Sensitivity (%)	Specificity (%)	PPV□ (%)	Efficacy of screening***
Dennison, 1989[19]	Premature CVD	3313	4-17	FH§>without FH, *P*<0.05	No difference	–	–	25	56	–	Low
Bistritzer, 1995[4]	Premature CVD	107	2-20	25.2*	16.8*	24.3*	14.1*	–	–	–	High
Chen, 1997[12]	Dyslipidemia	711	5-17	FH>without FH, *P*<0.05	FH<without FH, *P*<0.05	–	FH>without FH, *P*<0.05	50	80.4	10.5	Low
Derinoz, 2007[20]	Dyslipidemia	2096	5-17	No difference	No difference	No difference	No difference	–	–	–	Low
Eissa, 2009[9]	Dyslipidemia	678	8,11,14 (years)	13.6*	13.4*	17.9*	25.8	41.3	65.1	15.7	Low
Gagliano, 1993[21]	Premature CVD# or dyslipidemia	224	11-20	–	–	No difference	–	63	46	19	Low
Kelishadi, 2006[22]	Premature CVD	4811	6-18	6.3*	24.8*	6.4*	24.5*	28.4	70.3	44.7	Low
Muratova, 2001[23]	Dyslipidemia	709	10.8****	–	–	No difference	–	21.6	73	53	Low
Ritchie, 2010[24]	Dyslipidemia or premature CVD	14468	10.9****	FH>without FH, *P*<0.05	–	–	–	29	63	–	Low
Griffin, 1989[25]	Dyslipidemia	1005	2-13	FH>without FH, *P*<0.05	–	–	–	15	22	–	Low
	Dyslipidemia or premature CVD							51	13	–	Low
O'Loughlin, 2004[2]	Dyslipidemia or premature CVD	2217	9,13,16 (years)	4.8*	–	–	–	50.6	69.1	7.7	Low
Primrose, 1994[14]	Premature CVD	1012	12-15	–	–	18.8*		33.2	71.5	–	Low
Diller, 1995[26]	Dyslipidemia	232	2-19	9.9*	–	–	–	60.9	74.2	20.6	Low
	Premature CVD							17.4	74.6	7	Low
Liu, 1999[13]	Dyslipidemia or premature CVD	2786	10.1****	FH>without FH, *P*<0.05	No difference	FH>without FH, *P*<0.05	No difference	23.5	82.2	12.4	Low
Bell, 1990[17]	Premature CVD	1140	Fifth–grade students	–	–	13*	–	36	72	16	Low
	Dyslipidemia							53	62	17	Low
	Dyslipidemia or premature CVD							64	47	16	Low
Wiegman, 2003[28]	Dyslipidemia or premature CVD	742	2–19	FH>without FH, *P*<0.05	–	–	–	–	–	–	High
Benuck, 1992[29]	Dyslipidemia or premature CVD	263	3–10	–	–	FH>without FH, *P*<0.05	–	93	21	17	High
Shea, 1990[30]	Dyslipidemia	108	4-5	–	–	–	–	57	59	41	Low
Troxler,1991[31]	Dyslipidemia or premature CVD	110	senior high school students	–	–	–	–	–	–	38	Low

†LDL-C: Low-density lipoprotein cholesterol; ‡HDL-C: High-density lipoprotein cholesterol; □PPV: Positive predictive value; §FH: Family history; #CVD: Cardiovascular disease; *Frequency in children (%); **Type of Risk factor in parent for screening in children; ***Efficacy of CVD or hyperlipidemia family history for prediction dyslipidemia disorder in children according to statements mentioned in each primary study; ****Mean

the frequency of high LDL-C was significantly higher among children with FH of premature CVD or dyslipidemia than in children without this history. In five primary studies that reported the levels of LDL-C among children and adolescents, the frequency of elevated LDL-C varied from 4.8% to 25.2% [Table 1].

One out of four primary studies that reported low HDL-C level among children with FH of dyslipidemia or premature CVD indicated that the frequency of low HDL-C was significantly lower in children with FH of dyslipidemia or premature CVD than in their other counterparts. In these primary studies, the frequency of low HDL-C varied from 13.4% to 24.8% [Table 1].

Two out of five studies that reported high levels of TC among children with FH of dyslipidemia or premature CVD indicated that high cholesterol was significantly more frequent among children with FH of dyslipidemia or premature CVD than in those without this history. The frequency of hypercholesterolemia varied from 6.4% to 24.3% in the five primary studies that reported it [Table 1].

One out of three primary studies that reported high TG levels among children with FH of dyslipidemia or premature CVD indicated that the frequency of hypertriglyceridemia was higher among children with FH of dyslipidemia or CVD than in other children. The frequency of elevated TG varied from 14.1% to 25.8% in primary studies that reported this measure [Table 1]. It is worth mentioning that according to Rithchi *et al*., LDL-C level increased in 9.5% of the 5,798 studied children without FH of dyslipidemia or premature CVD.

The sensitivity of FH of premature CVD or dyslipidemia for predicting dyslipidemia among children varied from 15[25] to 93.[29] In total, 78.9% of primary studies reported sensitivity levels lower than 60%. The specificity of FH of premature CVD or dyslipidemia for predicting dyslipidemia among children varied from 13[25] to 82.2.[13] The PPV varied from 7[26] to 53.[23] In 86.9% of primary studies, the effectiveness of screening children for dyslipidemia on the basis of their FH of premature CVD or dyslipidemia was low [Table 1].

The meta-analysis showed that the sensitivity of FH of dyslipidemia, premature CVD, and dyslipidemia or FH of premature CVD in predicting dyslipidemia among children was 42.5 (28.2-56.8), 28.3 (24-32.5), and 53.4 (37.8-68.9), respectively. The overall sensitivity was 42.6 (35.7-49.6). Furthermore, the specificity of FH of dyslipidemia, premature CVD, and dyslipidemia or premature CVD in predicting dyslipidemia among children was 62.2 (44.2-80.2), 68.7 (61.5-76), and 48.8 (32.1-65.5), respectively. The overall specificity was 59 (50.9-67.1). The PPV of FH of dyslipidemia, premature CVD, and dyslipidemia or premature CVD in predicting dyslipidemia among children was 23.7 (14-33.5), 22.7 (−1.3-46.6), and 13 (9.2-16.8), respectively. After including all primary studies, the overall PPV was 20.7 (12.3-29.1). The significance level of chi-square (<0.001) and I-square indicated that the heterogeneity was very high among primary studies [Table 2 and Figures 3-5].

The selected risk factors for predicting dyslipidemia among children were investigated in primary studies by meta regression to determine the possible influential factors of sensitivity heterogeneity. This analysis indicated that the sensitivity of FH of dyslipidemia was 6.9% higher than the

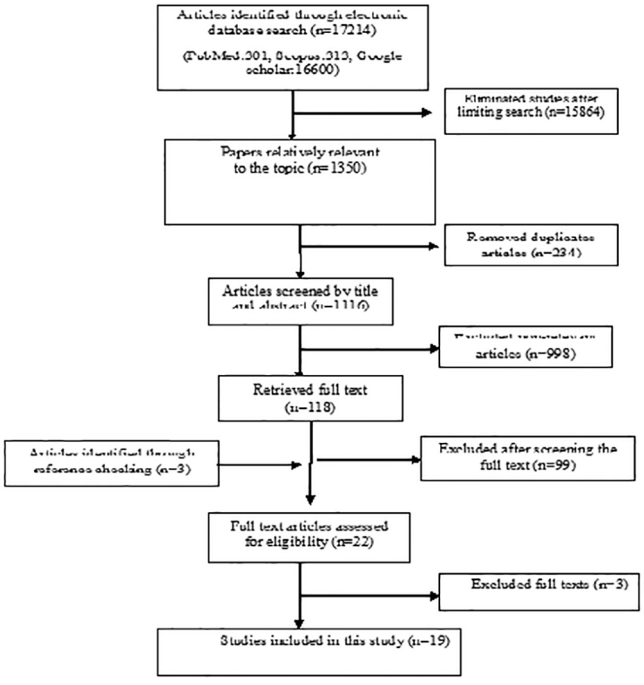

Figure 2: Literature search and review flowchart for selection of primary studies

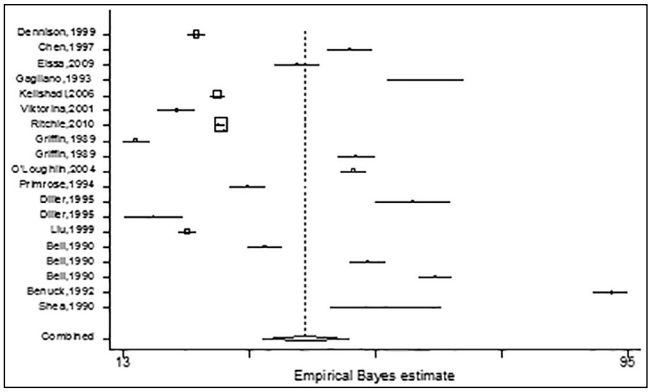

Figure 3: The adjusted sensitivity percentage of predicting dyslipidemia in children in each study and overall by the family history of CVD or dyslipidemia. This chart shows that the minimum and maximum of adjusted sensitivity percent among primary studies is 15.1% and 92.5%, respectively; pooled estimate: 42.6 (35.7-49.6), I2 = 99.5%

Table 2: Pooled estimation of sensitivity, specificity, and positive predictive value of family history of dyslipidemia or cardiovascular disease to predict dyslipidemia in children

Type of risk factor			Sensitivity (%)	Specificity (%)	PPV□ (%)
Dyslipidemia	Pooled estimate (random effect)		42.5 (28.2-56.8)	62.2 (44.2-80.2)	23.7 (14-33.5)
	Heterogeneity test	Chi-square (Q)	695, *P*<001	1120.9, *P*<0.001	130.4, *P*<0.001
		I-square (%)	99.1	99.5	96.2
Premature CVD	Pooled estimate (random effect)		28.3 (24-32.5)	68.7 (61.5-76)	22.7 (-1.3-46.6)
	Heterogeneity test	Chi-square (Q)	78.4, *P*<001	218.8, *P*<001	633.5, *P*<001
		I-square (%)	94.9	98.2	99.7
Dyslipidemia or premature CVD	Pooled estimate (random effect)		53.4 (37.8-68.9)	48.8 (32.1-65.5)	13 (9.2-16.8)
	Heterogeneity test	Chi-square (Q)	2627, *P*<001	3357.8, *P*<001	120.2, *P*<001
		I-square (%)	99.8	99.8	95.8
All primary studies entered to the meta-analysis	Pooled estimate (random effect)		42.6 (35.7-49.6)	59 (50.9-67.1)	20.7 (12.3-29.1)
	Heterogeneity test	Chi-square (Q)	3575.8, *P*<001	4840.8, *P*<001	4017.2, *P*<0.001
		I-square (%)	99.5	99.6	99.7

□PPV: Positive predictive value

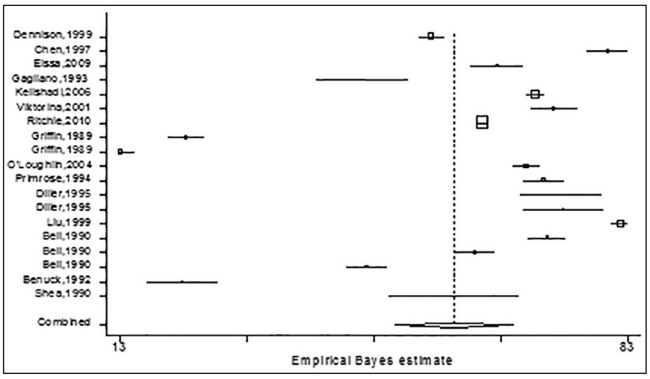

Figure 4: The adjusted specificity percentage of prediction of dyslipidemia in children in each study and overall by the family history of CVD or dyslipidemia. This chart shows that the minimum and maximum of adjusted specificity percent among primary studies is 13.2% and 80.7%, respectively; pooled estimate: 59 (50.9-67.1), I2 = 99.6%

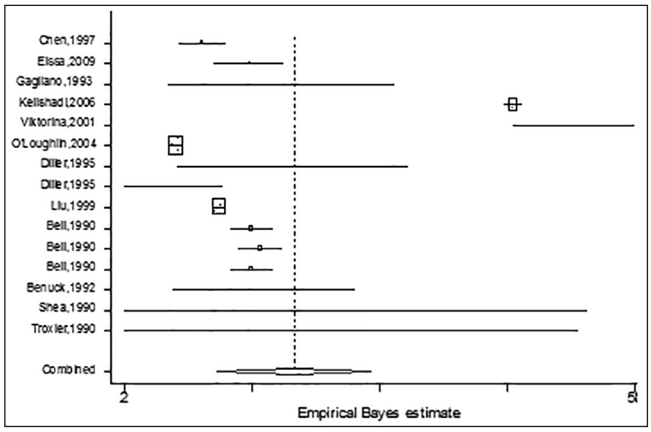

Figure 5: The adjusted PPV percentage of prediction of dyslipidemia in children in each study and overall by the family history of CVD or dyslipidemia. This chart shows that the minimum and maximum of adjusted sensitivity percent among primary studies is 7.4% and 51.4%, respectively; pooled estimate: 20.7 (12.3-29.1), I2 = 99.7%

sensitivity of the FH of premature CVD, and the sensitivity of FH of dyslipidemia or premature CVD was 6.9% higher than the sensitivity of the FH of dyslipidemia in predicting dyslipidemia in children; however, these differences were not statistically significant (β = 6.9, *P* = 0.2). Moreover, the parents' risk factor was investigated as the criteria for dyslipidemia screening in children to determine factors that are effective on specificity (β = −7.2. *P* = 0.2) and PPV heterogeneity (β = −3.8, *P* = 0.3). The meta-regression showed that this factor was not a source of heterogeneity. We also conducted a sensitivity analysis to identify studies that were effective on the results of the meta-analysis. After removing the effective studies, we repeated the meta-analysis in which the Q indicator and I_2 indicator decreased from 35775.8 to 266.2 and from 99.5% to 97.4%, respectively; however, the heterogeneity remained notable and significant.

DISCUSSION

The present systematic review and meta-analysis were conducted in order to appraise screening dyslipidemia in the pediatric age group. It indicated that the frequency of dyslipidemia was higher in children of parents with CVD or dyslipidemia than in other children. However, it is worth mentioning that the prevalence of dyslipidemia among children of parents without CVD or dyslipidemia was notable and a considerable part of dyslipidemia in the populations studied was related to these children. In most primary studies, the effectiveness of parental history of CVD or dyslipidemia was low for predicting dyslipidemia in their children. The results of meta-analysis on sensitivity, specificity, and PPV indicators confirmed that the efficacy of the history of CVD or dyslipidemia was low for predicting dyslipidemia in children.

A study in the US examined the efficacy of FH as the screening criteria for children's hypercholesterolemia. They demonstrated that maternal [odds ratio (OR):7.3] and paternal (OR:2.9) histories of hypercholesterolemia were significantly linked to elevated LDL-C in their children but the sensitivities of maternal and paternal history for

predicting hypercholesterolemia in children were 9 and 15, respectively.[25] A case-control study in Iran showed that the mean TC, LDL-C, and TG were significantly higher, and the mean HDL-C was lower in children with FH of premature CVD than in those without it.[32]

A study in Canada examined the usefulness of parental history of hypercholesterolemia and premature CVD as the screening criteria for hypercholesterolemia in youths. They found that the frequency of a positive parental history was 25.6% and 18.3% among children who had borderline or high LDL-C, and 4.8% had high LDL-C. They also documented that the sensitivity, specificity, PPV, and NPV of parental history were 33.1, 76.0, 23.7, and 83.5, respectively.[2]

Another study in the US found that only 8 out of 37 children with dyslipidemia had a positive FH of premature CVD and 29 did not. The sensitivity of FH was low (21.6) in predicting children with high blood cholesterol concentrations.[23]

The universal lipid screening versus selective screening was compared in a general population of 20,266 American students of the 5th grade. A total of 14,470 (71.4%) children met the criteria of National Cholesterol Education Program (NCEP) guidelines for lipid screening according to positive FH. Out of them, 1,204 (8.3%) had elevated LDL-C, and 170 (1.2%) of the total number of children studied warranted possible pharmacologic treatment (LDL-C ≥160 mg/dL). Of the 5,798 (28.6%) students who did not have a positive FH for premature CVD, 548 (9.5%) had elevated LDL-C. Universal lipid screening could identify children with either modest or more marked elevations in LDL-C who were undetected by the high-risk approach.[24]

Another study among American students indicated that 135 of 2,096 participants had elevated levels of TC (i.e., ≥200 mg/dL) and 83 students had elevated serum LDL-C levels (i.e., ≥130 mg/dL). Of the participants, 64.4% had FH of hyperlipidemia but no relation existed between FH and serum lipid levels. This study suggested that regardless of FH, all children who were above 5 years of age should be screened for hyperlipidemia.[27]

A review article on pediatric screening for hypercholesterolemia in Europe concluded that selective screening strategies mainly based on FH were imperfect. It suggested that the universal screening of 1-9-year-old children was a strategy that was likely to be most effective with respect to sensitivity and specificity for identifying children with elevated cholesterol levels.[33]

Donker *et al*. proposed that although an elevated cholesterol level wasa risk factor for succeeding adult hypercholesterolemia, the predictive value of an increased cholesterol level in childhood was inadequate to rationalize universal screening.[34]

Likewise, Porkka *et al*. suggested that the selection of children for screening serum lipids should be done on the basis of high-risk approach. They reported that universal screening approach was not appropriate because of its limited predictive power for serum lipid levels at the individual level, the incomplete data on the safety of intervention measures on the growing child, and the limited knowledge on the ethical aspect of such a type of screening.[35] Similarly, Elizabeth *et al*. proposed that the general screening of children for hypercholesterolemia was not warranted.[6]

On the other hand, some studies supported the universal screening for dyslipidemia in children. Promise *et al*. suggested that the high-risk approach was not sufficient for screening hypercholesterolemia in children.[14]

Kwiterovich *et al*. showed that the high-risk approach could not identify 17% to 90% of children who had abnormal lipid levels.[36] Likewise, a Finnish study proposed universal screening for dyslipidemia in children.[37] A meta-analysis in 2007 concluded that population screening could be highly effective.[38]

The current systematic review and meta-analysis demonstrated that the sensitivity and PPV of the high-risk approach by selecting screening target population based on the FH of premature CVD or dyslipidemia was low. Given that lipid disorders track from childhood to adulthood and accelerate the process of atherosclerosis,[39,40] it is important to use strategies that would have a higher sensitivity for detecting dyslipidemia in the pediatric age group.

It should be acknowledged that most of the abovementioned studies have determined the serum lipids in the Western populations, and most have focused on TC and LDL-C levels. The ethnic differences in the types of dyslipidemia in children are well-documented;[22,41,42] therefore, it is necessary to conduct more studies on elevated TG and low HDL-C, which are more prevalent than hypercholesterolemia in some populations.

This study has some limitations, which originate from the differences in the methodologies of various studies and in the studied populations. The criteria of defining dyslipidemia are different and the prevalence of dyslipidemia varies in different races and ethnicities; so combining the results of different studies may limit the drawing of a definite conclusion. Moreover, the studied age groups of primary studies were diverse and given that the prevalence of dyslipidemia varies in different age groups, combining the results of different studies

would account for some limitations; however, all studies were in the pediatric age group, and a general assumption can be drawn. The high heterogeneity observed among primary studies of their source not being identified could be regarded as another limitation of the present study. Probably the small sample size of a few of the primary studies included in the current review could be regarded as the reason of heterogeneity not being significant. It should be underscored that this systematic review was performed to overcome the mentioned limitations.

One of the strengths of the present study, which enabled us to reach an explicit and reliable conclusion, is the fact that the reported upper limit of confidence interval of meta-analysis for sensitivity, specificity, and PPV was low and also the efficacy of the high-risk approach for screening children for dyslipidemia was reported in the primary studies.

CONCLUSION

This meta-analysis indicated that selecting the target population for screening children for dyslipidemia based on their parents' risk factors is not accurate, and it might lead to missing many children with dyslipidemia. This meta-analysis proposes universal screening for detecting dyslipidemia in the pediatric age group; however, for implementing this strategy, some issues including the needlestick risk, ethical considerations, and available resources should be also taken into account.

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Conflicts of interest
There are no conflicts of interest.

AUTHOR'S CONTRIBUTIONS

MM contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work AAH contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. RK contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work MH contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MK contributed in the conception and design of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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