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Screening using laboratory parameters for lipid disorders in the pediatrics: Systematic Review and Meta-Analysis

Fahd Ali Al-Thaqafi[1], Ranya Abdullah Hamza Bajuo[1], Ruba Nasser Alkuwaiti[1], Haya Abdullah Alsumail[1], Bandar Abdulmohsen Alshaikh[1], Hassan Ali Alghamdi[1], Abdullah Mohammed Alzahrani Rashed Shukayr Alzahrani[1], Abdulla Grosh Almalki[1], Eman Abdullah Ghaforji[1], Shuruq Mohammed Alghurybi[1], Eman Mohammed Asiri[1], Somaya Essam Salama[1]

1.Al-Azizyah Children Hospital, Laboratory Department

Abstract

Background: Familial hypercholesterolemia (FH) is a prevalent genetic illness that worsens atherosclerotic cardiovascular disease (ASCVD) because of an increased concentration of low-density lipoprotein (LDL) and cholesterol (LDL-C).

Aim: To evaluate the efficiency of screening using laboratory parameters for lipid disorders in pediatric populations, particularly focusing on the sensitivity of family history (FH) of dyslipidemia versus familial hypercholesterolemia of premature cardiovascular disease (CVD) in predicting dyslipidemia in children.

Patients and methods: The search strategy for this systematic review has been designed to ensure a comprehensive identification of relevant investigations. Databases Searched, electronic databases have been searched, including: PubMed, EMBASE, Cochrane Library and google Scholar. A combination of keywords and Medical Subject Headings (MeSH) terms have been used to capture all relevant studies. "Pediatric" OR "Children" OR "Adolescents

Results: The search strategy for this systematic review has been designed to ensure a comprehensive identification of relevant studies. Databases Searched, electronic databases have been searched, including: PubMed, EMBASE, Cochrane Library and google Scholar. A combination of keywords and Medical Subject Headings (MeSH) terms have been used to capture all relevant studies. "Pediatric" OR "Children" OR "Adolescents. Risk of bias of our six investigations has been evaluated by ROB1, most of our studies show high risk as regard detection biases and attrition biases and unclear risk regarding other biases

Conclusion: A family history of dyslipidemia is a stronger predictor of dyslipidemia in children, with a 6.9% higher sensitivity. However, heterogeneity suggests varying factors influencing LDL cholesterol levels.

Key words: FH; ASCVD; LDL; LDL-C.

Introduction

Familial hypercholesterolemia is a prevalent genetic illness that exacerbates atherosclerotic cardiovascular disease due to elevated concentrations of low-density lipoprotein cholesterol. Consequently, it could be regarded as a model illness for hypercholesterolemia and atherosclerotic cardiovascular disease **(1).**

Cases who are homozygous (or compound heterozygous) exhibit significantly elevated cholesterol concentrations and an earlier onset of coronary artery disease in comparison with heterozygous cases **(2).**

Initially, it has been believed that the underlying defect in familial hypercholesterolemia was caused by an elevated synthesis of cholesterol. However, it is now known that the fractional

catabolic rate of low-density lipoprotein is reduced in heterozygous familial hypercholesterolemia individuals in comparison to normal subjects **(2).**

The optimal strategy to screening for familial hypercholesterolemia is presently a contentious matter. In the past, lipid guidelines recommended "targeted screening," which involved administering a fasting lipid profile test to kids with risk factors for familial hypercholesterolemia, including a family history of premature cardiovascular diseases, obesity, or dyslipidemia **(3).**

Nevertheless, this method, regardless of its cost-efficiency, carried the danger of overlooking thirty to sixty percent of the cases who were impacted. Health professionals actively screen for illness among the 1st - and 2nd -degree relatives of cases diagnosed by targeted screening under the term "cascade screening," which is an alternative approach to screening **(3).**

According to the Bogalusa Heart Study, a comprehensive epidemiologic investigation of cardiovascular risk factors in kids and adults, atherosclerotic lesions are associated with cardiovascular risk factors, including smoking, body mass index, systolic and diastolic blood pressure, and serum lipid concentrations. These lesions have been observed to rise with age. Smoking, obesity, and type 2 diabetes mellitus are the primary cardiovascular risk factors among youth (4).

The Familial hypercholesterolemia phenotype and the rise of LDLC are gene-dose dependent. In the rare homozygous or compound heterozygous cases (collectively referred to as Familial hypercholesterolemia homozygotes (HoFH)), who have inherited 2 mutant LDLR genes, plasma cholesterol rises by four to five -fold, and severe coronary artery disease (CAD) happens in the majority of cases within the 1st two decades of life **(5).**

The goal of this investigation was to evaluate the effectiveness of screening using laboratory parameters for lipid disorders in pediatric populations, particularly focusing on the sensitivity of family history (FH) of dyslipidemia versus familial hypercholesterolemia of premature cardiovascular disease in expecting dyslipidemia in kids.

Patients and methods

The search strategy for this systematic review has been designed to ensure a complete identification of relevant investigations. Databases Searched, electronic databases have been searched, including: PubMed, EMBASE, Cochrane Library and google Scholar. A combination of keywords and Medical Subject Headings (MeSH) terms have been used to capture all relevant studies. "Pediatric" OR "Children" OR "Adolescents"

This was six investigations has been involved in the systematic review with a total of 25,012 pediatric patients. Majority of the participants were children and adolescents under 19 years of age. The studies were conducted in diverse regions, including Turkey, Georgia, Iran (Asfahan), West Virginia (USA), Canada, and the Netherlands.

Study Selection Process:

The study began with a comprehensive search of electronic databases to identify relevant studies. A total of 512 studies have been initially recognized, but following removing duplicates, 310 studies were excluded, leaving 200 studies for further review. The titles and abstracts of these 200 studies were carefully examined to determine their relevance to the research question. After this initial screening, the full texts of thirty-five investigation have been reviewed in detail to assess their eligibility for inclusion. Ultimately, 10 investigations have been selected for inclusion in the meta-analysis and systematic review. The PRISMA flowchart (Figure 1) was used to visually

represent the investigations selection process, illustrating the number of studies identified, excluded, and involved at each stage.

Inclusion Criteria: Population: The study must focus on pediatric populations, specifically children aged less than 19 years ,objective: The study must address the screening of lipid disorders or dyslipidemia in children using laboratory parameters ,risk Factors: The study must investigate risk factors like family history (FH) of dyslipidemia, FH of premature cardiovascular disease (CVD), or both and study Design: The study could be of any design, including cross-sectional, retrospective cohort, or other relevant designs.

Exclusion Criteria: Duplicates: Studies that were exact duplicates were excluded ,irrelevant Studies: Studies that did not focus on pediatric populations or did not address lipid disorders or dyslipidemia screening were excluded ,incomplete Data: Studies that did not provide sufficient data for meta-analysis, such as sensitivity, specificity, or LDL cholesterol levels, were excluded and non-English investigations: investigations published in languages other than English have been excluded to ensure consistency in data extraction and analysis.

Characteristics of the Included Studies:

The investigations that have been involved were distinct in terms of their design, location, and population. A combined cohort of 25,012 cases was analyzed in the final analysis, which comprised six separate investigations. The majority of the investigations were cross-sectional in nature, and the participants were minors under the age of nineteen. The baseline and summary characteristics of the investigations that were involved, including the investigation's ID, design, location, risk factors examined, sample size, and age range, are crucial for comprehending the heterogeneity among the investigations that were involved. These details provide an overview of the population and context of each investigation.

Risk of Bias Assessment:

The quality and reliability of the involved investigations have been evaluated using the ROB1 tool, which evaluates potential biases in the research. The assessment focused on several key areas, including detection bias, attrition bias, and other probable sources of bias. The results of the risk of bias evaluation indicated that most of the investigations had an elevated possibility of detection bias and attrition bias, while the risk was unclear for other types of bias. The risk of bias graph (Figure 2) and the risk of bias summary table (Table 2) provide a detailed breakdown of the findings, helping to identify the strengths and limitations of the investigation that have been involved.

Statistical Analysis:

A meta-regression analysis has been carried out to identify the sensitivity of family history (FH) in predicting dyslipidemia in kids. The results showed that FH of dyslipidemia had a 6.9 percent greater sensitivity than FH of premature cardiovascular disease and combined FH of dyslipidemia or premature cardiovascular disease. A pooled meta-analysis has been conducted for LDL cholesterol levels, with a mean difference of 67.8 mg/dL. However, significant heterogeneity was detected across the studies, indicating that factors influencing LDL cholesterol levels may vary widely. A sensitivity analysis has been performed to recognize studies that had a significant impact on the meta-analysis results. The heterogeneity has been evaluated using the I^2 statistic and chi-square test, confirming the statistically significant differences across studies. A forest plot was generated to visually represent the pooled results for LDL cholesterol levels, providing a clear visual summary of the meta-analysis findings.

Results

1.Study selection process:

by searching the electronic databases about 512 studies were identified. We then removed 310 of them as duplicate studies; Afterward, We examined the abstracts and titles of the remaining 200 papers. Following the examination of the complete texts of the thirty-five remaining papers, and finally 10 studies were selected. **Fig. 1:** represents PRISMA flow chart.

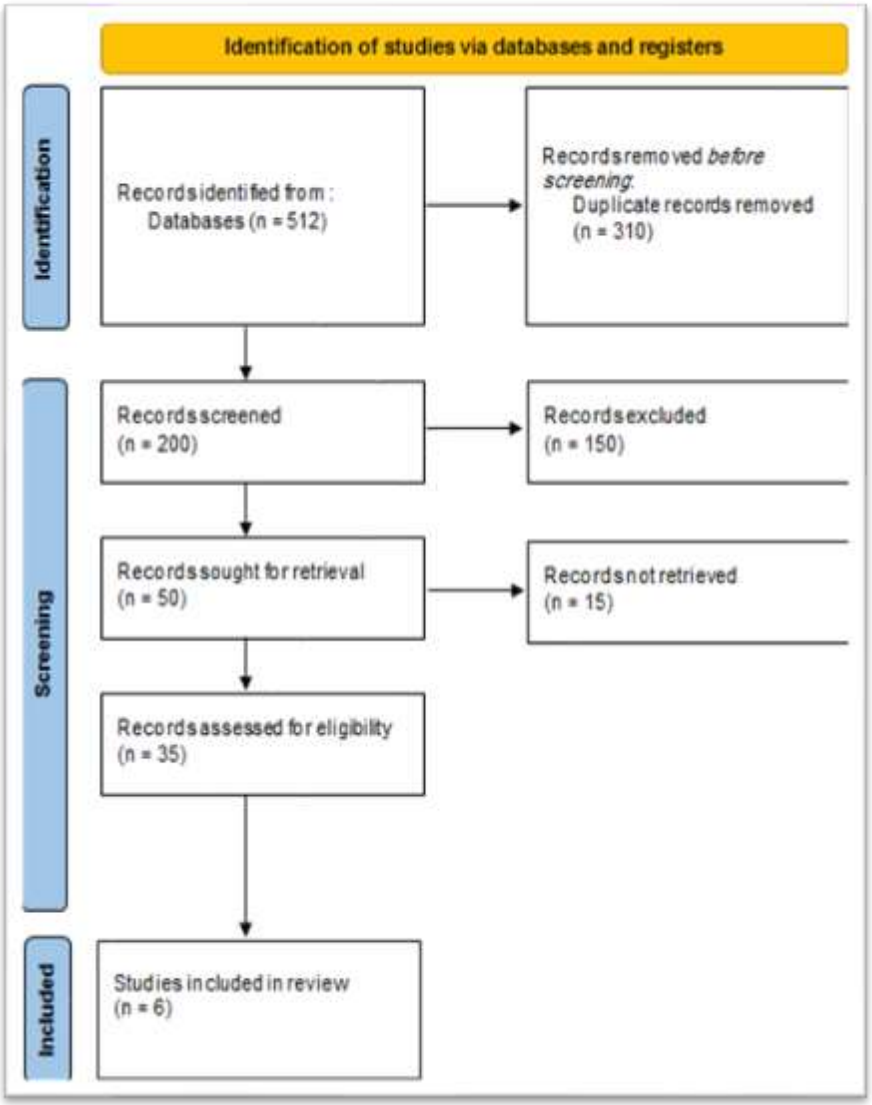

Figure 1: PRISMA flow chart for examine selection process.

2. Baseline and summary characteristics of our included population

We have included six investigations with a total people 25012 patients, Majority of our studies were cross sectional with patients age less than 19 years old. **Demographic data of our involved**

population was represented within table 1.
Table 1: Demographic data of our involved population.

Study NO	Study ID	ıdy design	Site	Type of Risk factor	Sample Size	Age (Years)
1	**Derinoz.(4)**	Cross sectional study	Turkey	Dyslipidemia	2096	5 to 17
2	**Eissa. (6)**	Cross sectional study	Georgia	Dyslipidemia	678	8,11,14
3	**Kelishadi. (7)**	Cross sectional study	Asfahan	Premature CVD	4811	6 to 18
4	**Ritchie.(8)**	Cross sectional study	West vergenia	Dyslipidemia or premature CVD	14468	10.9
5	**O'Loughlin (9)**	Cross sectional study	Canada	Dyslipidemia or premature CVD	2217	9,13,16
6	**Wiegman. (10)**	Retrospect ive cohort	The Netherlands	Dyslipidemia or premature CVD	742	2 to 19

3.Risk of bias assessment:
Risk of bias of our six investigations has been evaluated by ROB1**,** most of our studies show high risk as regard detection biases and attrition biases and unclear risk regarding other biases. For more details regarding risk of bias assessment show Fig.2 for Risk of bias graph, and Table 2 Risk of bias summary.

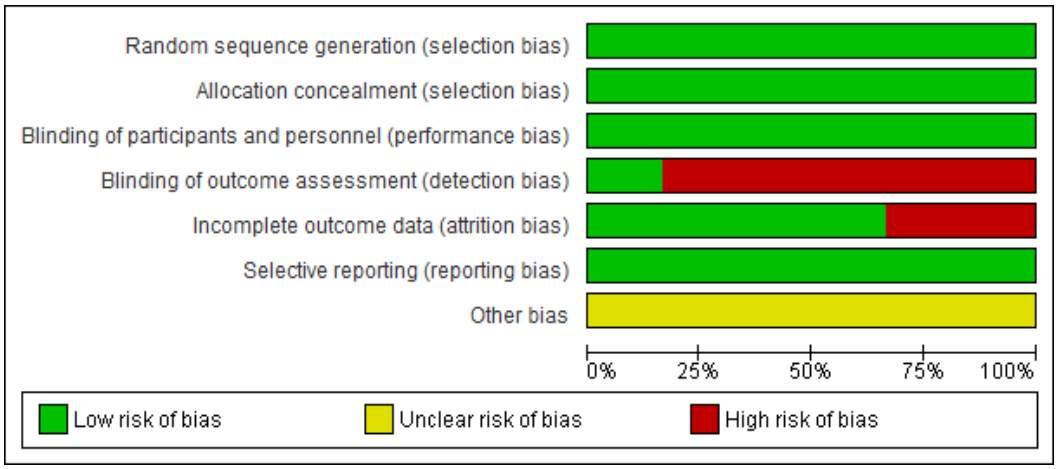

Figure 2: Risk of bias graph.

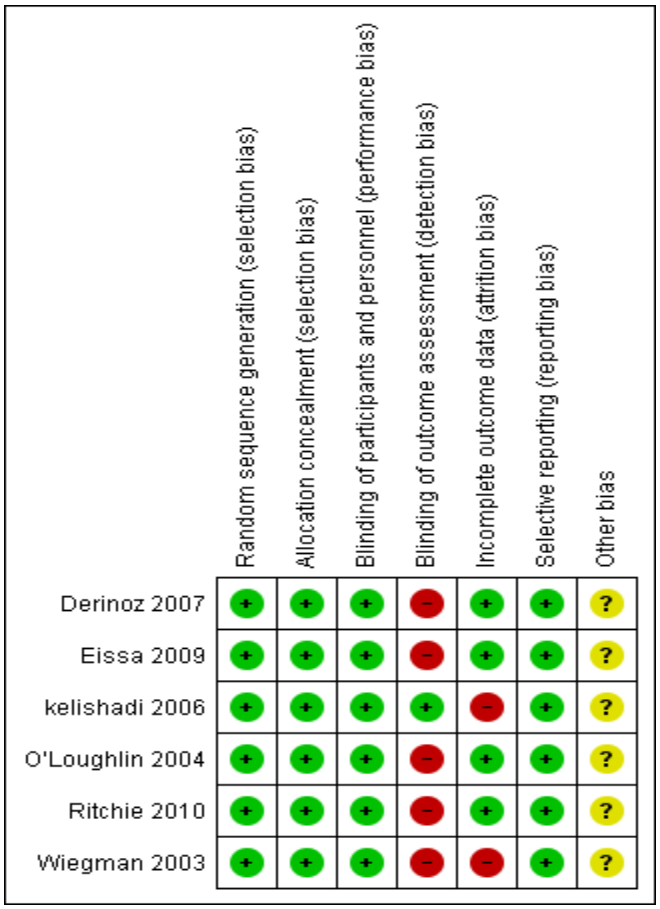

Table 2: Risk of bias summary.

4.Outcomes:

In an effort to identify the potential influencing factors of sensitivity heterogeneity, the selected risk factors to predict dyslipidemia between kids have been examined in 1^{ry} research through meta-regression. This metanalysis demonstrated that the sensitivity of familial hypercholesterolemia of

dyslipidemia was 6.9% greater than that of familial hypercholesterolemia of premature cardiovascular disease, & the familial hypercholesterolemia sensitivity of dyslipidemia or premature cardiovascular disease was 6.9% greater than the sensitivity of familial hypercholesterolemia of dyslipidemia to predict dyslipidemia in kids. Additionally, we performed a sensitivity analysis to detect investigations that were efficient based on the outcomes of the meta-analysis, and the risk factor of the parents was examined as the standards for dyslipidemia screening in kids to identify the factors which are efficient. Our pooled meta-analysis for LDL cholesterol showed pooled MD and 95% CI; 67.8[31.8, 103.8], major heterogeneity was detected among our pooled study with chi-p<0.001 and I^2 100%. **Figure 3:** depicts forest plot for LDL-cholesterol.

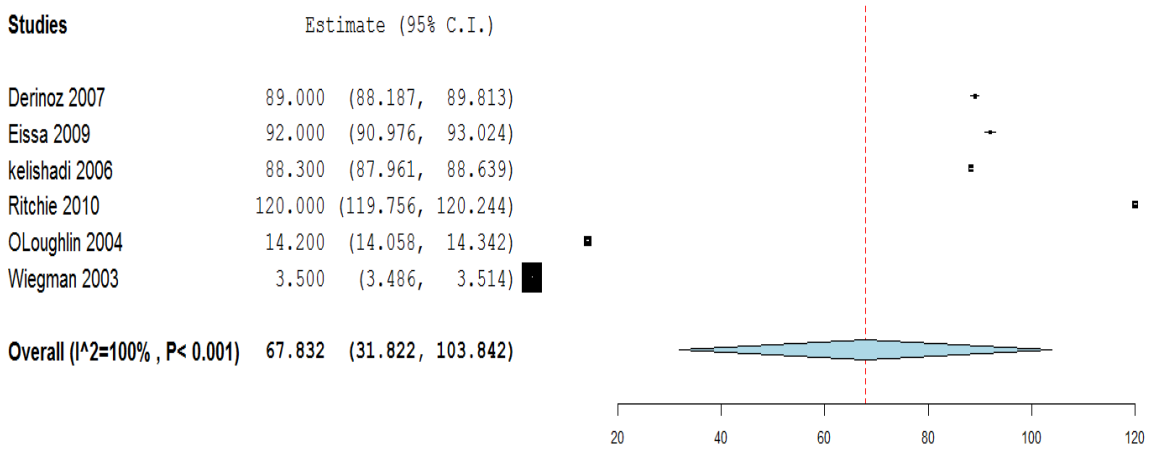

Figure 3: forest plot for LDL-c.

Discussion

In an effort to determine the potential influencing factors of sensitivity heterogeneity, the selected risk factors to predict dyslipidemia between kids have been examined in primary research through meta-regression. The analysis conducted on the current study revealed that the sensitivity of familial hypercholesterolemia for dyslipidemia was 6.9% greater than that of familial hypercholesterolemia for premature cardiovascular disease. Additionally, the sensitivity of familial hypercholesterolemia for dyslipidemia or premature cardiovascular disease was 6.9% greater than that of familial hypercholesterolemia for dyslipidemia to predict dyslipidemia in kids.

Similarly, **Kelishadi R et al., (7)** found a significantly high occurrence of lipid conditions in addition to a low positive and sensitivity and negative predictive value of family history for the detection of dyslipidemia in kids. The familial hypercholesterolemia had a sensitivity of 28.4% in identifying kids with dyslipidemia, and the sensitivity value was 28.4% for a family history of premature cardiovascular disease.

As well, **Eissa MA et al.**, **(6)** who aimed to identify the sensitivity, specificity, and positive predictive value (PPV) of dyslipidemia screening by applying AAP standards with either family history or a body mass index. The AAP guidelines demonstrated a sensitivity of 54% to 66% for FH in dyslipidemia screening.

Additionally, to discover efficient factor for dyslipidemia screening in kids we studied the risk factor of the parents. Additionally, we performed a sensitivity analysis to detect investigations that were efficient based on the outcomes of the meta-analysis. Our pooled meta-analysis for LDL

cholesterol showed pooled MD and 95% CI; 67.8[31.8, 103.8], major heterogeneity was detected among our pooled study with chi-p<0.001 and I^2 100%

Similarly, **Wiegman A, et al., (10)** who aimed to determine the LDL-C concentration that enables the most precise diagnosis of FH in kids from families with known FH and to evaluate if lipoprotein variation in these kids is correlated with premature CVD in relatives, reported that the mean of LDL-C, mmol/L Heterozygous Kids With FH and Nonaffected Siblings, respectively (5.62 ±0.06) and (2.55 ±0.05), as there was no significant difference as regard both groups (p<0.001).

As well, **Kelishadi R et al., (7)** who aimed to detect the mean serum lipid concentrations were insignificantly variant between those with negative or positive family histories of premature cardiovascular disease, with the objective of determining the prevalence of dyslipidemia and the usefulness of self-report family history of premature cardiovascular disease to detect kids with lipid conditions.

Also, **Ritchie SK et al., (8)** who aimed to determine the specificity and sensitivity of family history to determine kids with severe or genetic hyperlipidemias in a rural, predominantly white people, showed a significant correlation between having a positive family history and having hyperlipidemia (also known as having LDL >=130 milligram per deciliter) (P-value =.01).

Furthermore, **Derinoz O et al., (4)** who aimed to determine that kids need to have hypercholesterolemia testing, the definition of a high cholesterol level in kids and the precautions that must be taken to prevent atherosclerosis. They identify a statistically insignificant correlation among elevated cholesterol, HDL, and LDL concentrations and a positive family history.

Conclusion

This study highlighted that a family history (FH) of dyslipidemia is a stronger predictor for dyslipidemia in children compared to a FH of premature cardiovascular disease (CVD), with a 6.9% higher sensitivity for FH of dyslipidemia. Additionally, the combined FH of dyslipidemia or premature cardiovascular disease showed a 6.9percent greater sensitivity than FH of premature CVD alone. However, significant heterogeneity was observed across studies (I^2 = 100%, chi-p < 0.001), suggesting that factors influencing LDL cholesterol levels may vary widely. While the pooled mean difference for LDL cholesterol was significant (67.8 mg/dL), these outcomes highlight the requirement for further research to understand the sources of this variability and improve dyslipidemia screening criteria.

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