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SYSTEMATIC REVIEWS AND META-ANALYSES

Dyslipidemia in adults with congenital heart disease: A systematic review and meta-analysis

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Dyslipidemia

Abstract *Aims:* Several particular characteristics of patients with congenital heart disease could affect lipid levels. The objectives of this study were: a) to analyze the prevalence of dyslipidemia in congenital heart disease patients; 2) to compare lipid levels between congenital heart disease patients and a control group.
Data synthesis: This systematic review and meta-analysis was performed according to PRISMA guidelines (PROSPERO CRD42023432041). A literature search was performed to detect studies that have reported lipid levels or the prevalence of dyslipidemia in congenital heart disease patients. We performed a qualitative analysis (studies that reported dyslipidemia prevalence) and quantitative analysis (studies that compared lipid values between congenital heart disease patients and controls). In total, 29 observational studies involving 22,914 patients with congenital heart disease and 641,086 controls were eligible for this review. The reported presence of "hyperlipidemia" or "dyslipidemia" ranged from 14.3% to 69.9%. When studies analyzed lipid variables dichotomously between congenital heart disease patients and controls, the results were conflicting. The quantitative analysis showed that patients with congenital heart disease have lower levels of total cholesterol (MD: −18.9 [95% CI: −22.2 to −15.7]; I^2 = 93%), LDL-C (MD: −10.7 [95% CI: −13.1 to −8.3]; I^2 = 90%) and HDL-C (MD: −6.3 [95% CI: −7.7 to −4.9]; I^2 = 95%) compared to controls.
Conclusions: The qualitative analysis showed some concerns, but the quantitative analysis indicates that congenital heart disease patients showed lower levels of total cholesterol, LDL-C, and HDL-C compared to controls. New research should be developed to clarify this relevant topic.

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1. Introduction

Congenital heart disease refers to structural abnormalities in the heart that develop before birth. The incidence of congenital heart disease in adults has been steadily increasing over the past two decades [1]. Furthermore, due to advancements in cardiac surgery and perioperative care for congenital heart disease, approximately 85% of infants born with cardiac defects now have the potential to live into adulthood [2,3]. Currently, there are more adult patients with congenital heart disease than pediatric cases.

Atherosclerosis is the primary pathophysiological substrate of cardiovascular disease and stands as the leading cause of morbidity and mortality in developed nations [4]. Although the progression of the atherosclerotic process occurs gradually, initial alterations in the arterial wall can be detected at an early stage in life [5]. Notably, lipids play a crucial role in all stages of the atherosclerotic process [6].

Several prospective cohorts have conducted research on the association between traditional lipid markers in childhood and the development of cardiovascular events in adulthood [7,8]. However, it is important to note that these studies focused on individuals from the general population rather than specifically on patients with congenital heart disease. This distinction is significant because the pathophysiological processes observed in patients with congenital heart disease are unique and may not be applicable to the general population.

In patients with certain congenital heart disease pathologies, decreased cardiac output and chronically elevated central venous pressure can have a profound impact on various organ systems, particularly the liver [9]. Cholesterol levels are regulated by a delicate balance between absorption and synthesis, with the liver playing a crucial role in the synthesis process. As a result, the altered cardiac conditions in congenital heart disease patients may affect cholesterol metabolism differently compared to individuals without cardiac defects. On the other hand, the physical inactivity observed in many patients with congenital heart disease may contribute to the development of metabolic disorders such as obesity, diabetes, and dyslipidemia [10].

The existing literature includes several observational studies that have examined lipid markers in adult patients with congenital heart disease. These studies vary in their focus, with some reporting only the prevalence of dyslipidemia in congenital heart disease patients, while others have compared lipid values between the congenital heart disease population and a control group [11–39].

By conducting a systematic review and meta-analysis, our objective is to provide a comprehensive understanding of the prevalence of dyslipidemia in congenital heart disease patients and to compare lipid values between congenital heart disease patients and controls.

2. Methods

2.1. Data extraction and quality assessment

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [40]. This systematic review was registered in PROSPERO (CRD42023432041).

A literature search was conducted to identify studies that have evaluated lipid levels in congenital heart disease patients. Two reviewers performed the search using the electronic databases PubMed/MEDLINE, Embase, Science Direct, Scopus, and Cochrane Controlled Trials. The search terms used included “congenital heart disease” in combination with the following terms: “cholesterol”, “low-density lipoprotein cholesterol (LDL-C)", “high-density lipoprotein cholesterol (HDL-C)”, “triglycerides”, “dyslipidemia”, and “lipoproteins”. The final search for articles concluded on May 31, 2023.

This study was based on the following research question: Do adults with congenital heart disease show different lipid levels or different prevalence of dyslipidemia compared to individuals without congenital heart disease? The following inclusion criteria were used to select eligible studies: (1) Observational studies developed in humans; (2) Studies that reported dyslipidemia prevalence in patients with adult congenital heart disease. All types of adult congenital heart disease included in the selected studies were considered by this review; 3) Studies comparing the lipid profile between adult patients with congenital heart disease and controls. Studies that included predominantly adult patients were also considered. There were no idiomatic, geographical or publication restrictions. Excluded studies included expert opinions, reviews and case-series. Study characteristics were extracted by two independent investigators. Discrepancies among investigators were resolved by consensus.

The primary outcome of interest was the measurement of lipid levels or the assessment of the proportion of dyslipidemia in each study. For studies that solely reported the prevalence of dyslipidemia in congenital heart disease patients, we conducted a qualitative analysis. In contrast, for studies that compared lipid values between congenital heart disease patients and controls, we conducted a quantitative analysis (meta-analysis). Values from the overall congenital heart disease population were included in the analysis. Congenital heart disease subgroup data from three studies that did not report lipid values in the total population were also included.

The potential risks of bias were assessed for all the included studies using the Cochrane tool specifically developed for this purpose [41]. The ROBINS-I tool was utilized to evaluate bias across seven different domains, which include confounding bias, selection bias in participants, intervention classification bias, bias due to

deviations from intended intervention, bias due to missing data, outcome measurement bias, and bias in the selection of reported results. Each domain was rated as 'Serious,' 'Moderate,' or 'Low' based on the judgment of the authors.

2.2. Statistical analysis

The summary effect on the primary endpoint was estimated. Measures of effect size were expressed as mean difference (MD), and the I^2 statistic was calculated to quantify between trial heterogeneity and inconsistency. Depending on the value of I^2, a fixed effects model ($I^2 < 40\%$) or a random effects model ($I^2 > 40\%$) was chosen. To compare mean effects between subgroups, a Z test was used. When the summary/dispersion measures were not mean and standard deviation, conversion tools previously suggested by the literature were used [42]. Statistical analyses were performed using the R software for statistical computing version 3.5.1 with additional specific packages [43]. A two-tailed p value < 0.05 was considered statistically significant.

2.3. Reporting bias assessment

A funnel plot using the standard error (SE) for log MD was created. In addition, Egger's regression intercept tests were done. A p-value less than 0.1 was considered significant for the linear regression test.

2.4. Sensitivity analyses

A sensitivity analysis was performed. It consists of replicating the results of the meta-analysis, excluding in each step 1 of the studies included in the review.

3. Results

After a comprehensive screening process of the titles and abstracts, we identified 1433 articles that were potentially relevant to our study. Of these, 1250 studies were excluded due to duplication or lack of alignment with the study's purpose. Upon a thorough reading of the remaining articles, 154 studies were further removed as they did not report the event of interest. A flow diagram illustrating the screening process can be found in Fig. 1.

A total of 29 observational studies, involving 22,914 patients with congenital heart disease and 641,086 controls, were deemed eligible for qualitative synthesis [11–39]. However, it is important to note that the majority of participants were contributed by two studies: Saha et al. included 2006 congenital heart disease patients and

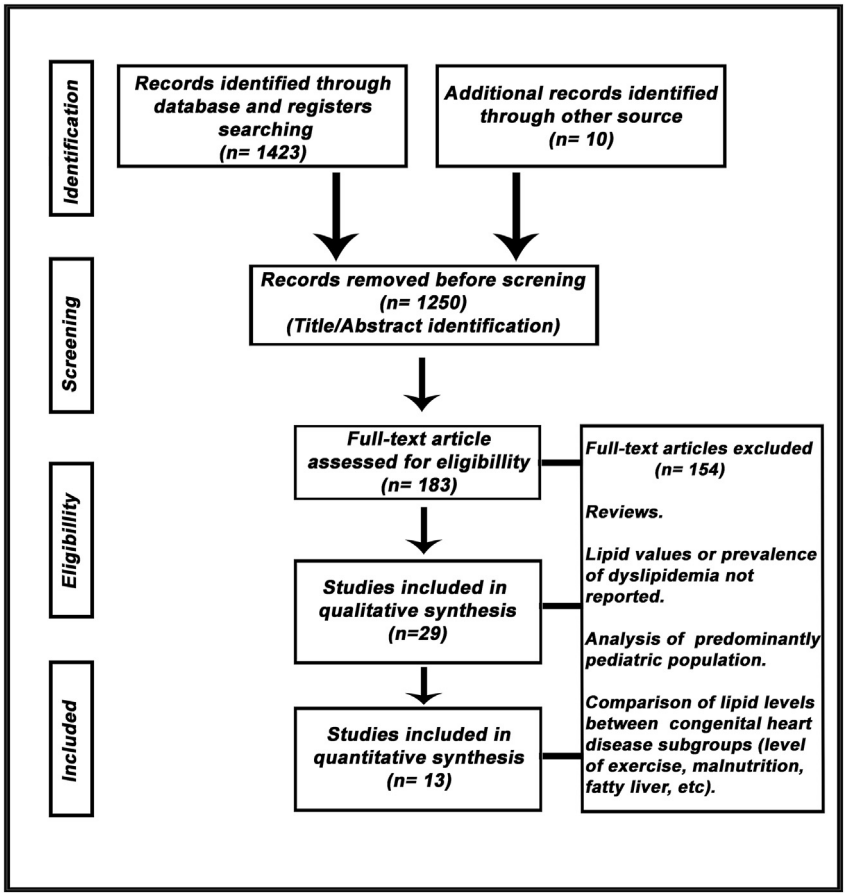

Figure 1 Flow diagram of the study screening process.

497,983 controls [31], while Levene et al. included 13,896 congenital heart disease patients and 138,960 controls [37].

Among the selected studies, thirteen reported the prevalence of dyslipidemias exclusively in the congenital heart disease population, while 16 compared the congenital heart disease population with a control group. Out of these 16 studies, 13 provided lipid values for both groups, allowing for quantitative analysis through meta-analysis. The remaining three studies compared the proportion of different dyslipidemias in both groups.

In total, 22 studies were assessed as having a moderate risk of bias, while 4 studies were assessed as having a serious risk of bias. The studies with a serious risk of bias exhibited methodological issues primarily in the domains related to outcome measurement and the selection of reported results. The quality of the selected studies can be detailed in Fig. 2.

3.1. Studies that evaluated the prevalence of dyslipidemia without a control group

A total of 9 cross-sectional studies [11,13,16,20,29,33,34,38,39] and 4 cohort studies [23,25–27] provided information on the prevalence of dyslipidemia among different groups of congenital heart disease patients. The reported presence of "hyperlipidemia" or "dyslipidemia" varied across studies, ranging from 14.3% to 69.9%. Additionally, one study specifically reported hypocholesterolemia as a lipid disorder [11]. It is worth noting that the definitions of "dyslipidemia" and the specific groups of congenital heart disease patients evaluated varied among the studies. Table 1 presents the characteristics of the studies that reported the prevalence of dyslipidemia without evaluating a control group.

3.2. Studies that compare congenital heart disease patients with a control group

In total, 10 cross-sectional studies [12,14,15,17,18,21,30,35–37], one case-control study [22], and 5 cohort studies [19,24,28,31,32] compared congenital heart disease patients with a control group. The majority of these studies evaluated the levels of total cholesterol, LDL-C, HDL-C, and triglycerides. One study specifically assessed lipoprotein(a) [Lp(a)] levels but did not find significant differences between the congenital heart disease and control groups (Lp(a) > 30 mg/dL: 28.2% vs. 25.6%, non-significant p-value) [17]. The characteristics of the studies that compared congenital heart disease patients with a control group are presented in Table 2.

The results of the 5 studies that analyzed lipid variables in a dichotomous manner showed contradictory findings. Moon et al. [18] reported that the cyanotic congenital heart disease group had a lower proportion of individuals with hypercholesterolemia compared to the corrected congenital heart disease and control groups ($p < 0.001$). Similarly, another study demonstrated that congenital heart disease patients had a significantly lower prevalence of dyslipidemia compared to the control group [30]. In contrast, Deen et al. [19] found that congenital heart disease patients more frequently had hypertriglyceridemia (triglycerides >150 mg/dL: 36.9% vs. 15.9%) and lower HDL-C levels (<40 mg/dL in men and <50 mg/dL in women: 59.5% vs. 14.4%) compared to the controls (all $p < 0.01$). Likewise, studies by Saha et al. [31] and Levene et al. [37] reported that congenital heart disease patients were more frequently diagnosed or treated for dyslipidemia (41.1% vs. 18.7%, $p < 0.001$) or had a higher prevalence of hyperlipidemia (40.6% vs. 28.9%, $p < 0.05$) compared to control groups.

In the analysis of studies that reported lipid values as numerical variables, the quantitative analysis showed that patients with congenital heart disease have lower levels of total cholesterol (MD: −18.9 [95% CI: -22.2 to −15.7]; $I^2 = 93\%$), LDL-C (MD: −10.7 [95% CI: -13.1 to −8.3]; $I^2 = 90\%$) and HDL-C (MD: −6.3 [95% CI: −7.7 to −4.9]; $I^2 = 95\%$) compared to the control group (Figs. 3 and 4A). No differences were found in triglyceride levels between the two groups (MD: −0.2 [95% CI: -7.8 to 7.6]; $I^2 = 98\%$) (Fig. 4B).

The graphical (Fig. 5) and analytical evaluation (total cholesterol: $p = 0.429$, LDL-C: $p = 0.296$, HDL-C: $p = 0.810$, triglycerides: $p = 0.617$) do not suggest publication bias. Sensitivity analysis demonstrated the robustness of the results (Fig. 6).

4. Discussion

Several cardiovascular risk factors are increasingly prevalent in adult patients with congenital heart disease [44]. Previous reports showed that patients with congenital heart disease were more often obese and hypertensive compared with the general population [45]. Similar findings have been reported with the prevalence of diabetes mellitus [46]. However, the exploration of dyslipidemia and lipid levels in congenital heart disease patients has been limited and has yielded conflicting results. This systematic review encompasses the comprehensive body of evidence on the presence of dyslipidemia in congenital heart disease patients.

Historically, children with congenital heart disease have been restricted from exercise, contributing to a sedentary lifestyle as well as increased cardiovascular risk factors [47]. Additionally, there is a substantial social disadvantage (employment problems, lower educational level) in adult patients with congenital heart disease, which could also negatively influence cardiovascular risk factors [46]. These specific circumstances surrounding congenital heart disease patients have been proposed as potential mechanisms related to raised lipid levels. However, other mechanisms associated with congenital heart disease have been linked

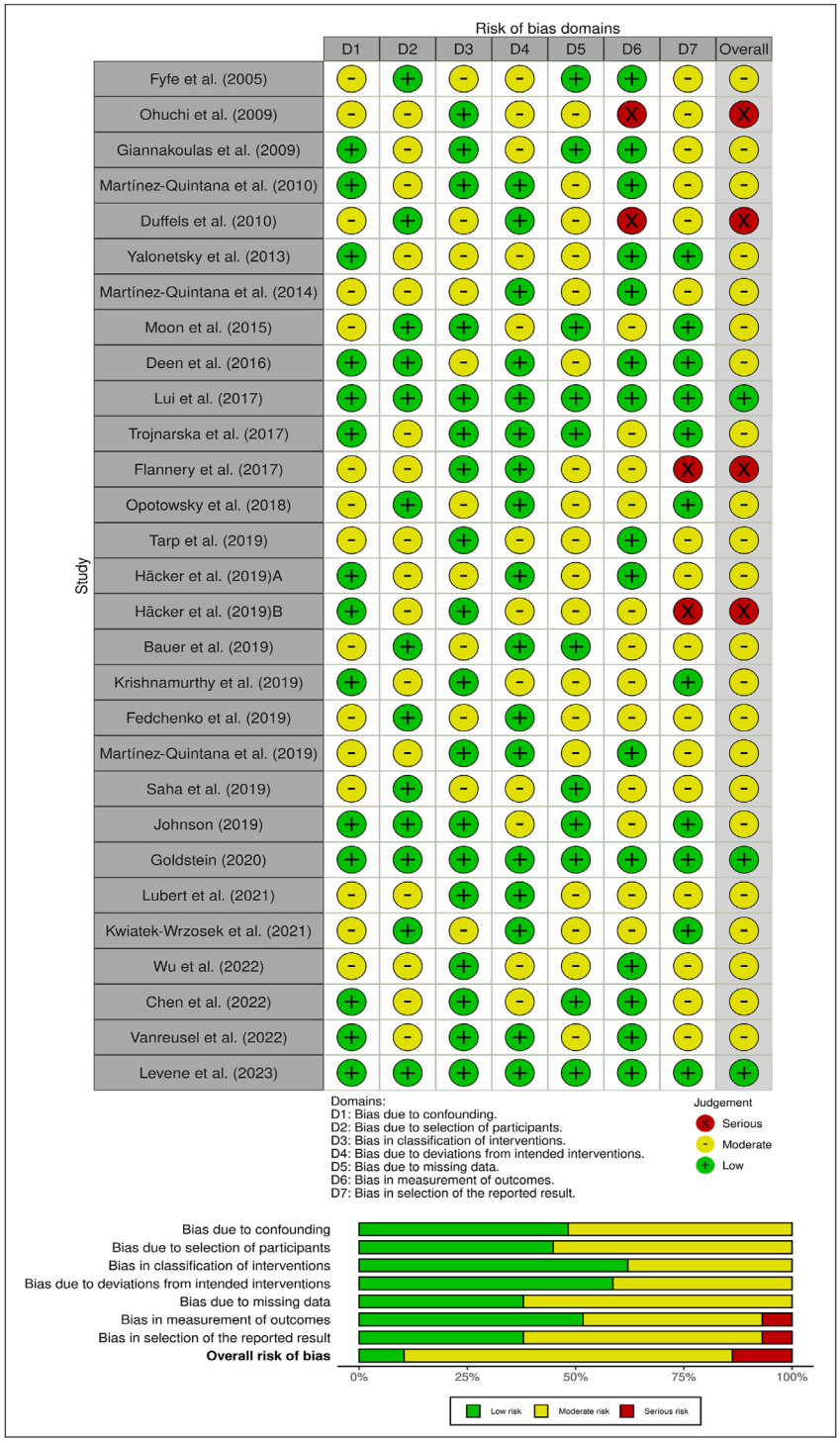

Figure 2 Bias assessment of included studies.

to hypocholesterolemia, including factors such as cyanosis, hypoxemia, erythrocytosis, hemodynamic changes, and genetic determinants [32]. Additionally, chronic inflammation and liver dysfunction have been suggested as alternative pathophysiological mechanisms, particularly in severe forms of congenital heart disease [48,49]. Interestingly, the association between congenital heart disease and lipids could be bidirectional in certain cases. For example, several molecular mechanisms promoting dyslipidemia are activated in bicuspid aortic valve patients, which could be reversely correlated with valvular calcification and progression of the related diseases, from

Table 1 Characteristics of included studies without a control group.

Study (year)	Design	n	Population	Main findings
Fyfe et al. (2005)	Cross-sectional	279	Cyanotic patients not operated (group A); cyanotic patients rendered acyanotic by operation (group B), acyanotic patients not operated (group C), and patients acyanotic before and after operation (group D). Mean age 39.8 years; 45.9% men.	Groups A and B had lower TC levels than groups C and D ($p < 0.05$). TC < 160 mg/dL: 58% (group A), 52% (group B), 10% (group C), and 12% (group D). Groups C and D had higher HDL-C levels than groups A and B ($p < 0.001$).
Giannakoulas et al. (2009)	Cross-sectional	250	Adult patients with congenital heart disease underwent selective coronary angiography for reasons other than suspected CAD. Mean age 51.4 years; 52.8% men.	Hyperlipidemia: 19.1% (all patients), 22.9% (simple), 15.4% (intermediate), 10.0% (complex); p value not significant.
Yalonetsky et al. (2013)	Cross-sectional	141	Adults with congenital heart disease and angiographically confirmed atherosclerotic CAD. Mean or median age not reported; 69% men.	Hyperlipidaemia: 47% (all patients), 54% (secundum atrial septal defect), 30% (bicuspid aortic valve disease), 75% (tetralogy of Fallot), 30% (coarctation of the aorta), and 57% (Eisenmenger syndrome); p value not reported.
Lui et al. (2017)	Cross-sectional	178	Adults with congenital heart disease of moderate or great complexity. Patients with Eisenmenger syndrome were excluded. Mean age 37.1 years, 51% men.	Dyslipidemia: 20%. TC > 200 mg/dL: 17%; LDL-C >190 mg/dL: 3.4%; High LDL-C (according to AHA guidelines): 6%; HDL-C <40 mg/dL: 28%, triglyceride >200 mg/dL: 11%.
Opotowsky et al. (2018)	Prospective cohort	707	Adults with congenital heart disease. Mean age 39 years, 51% men.	Hyperlipidaemia: 14.3%.
Häcker et al. (2019)A	Prospective cohort	551	Adult patients with congenital heart disease aged 30 years or older. Mean age 43.9 years, 51.7% men.	LDL-C >190 mg/dL: 2%; HDL-C <40 mg/dL: 8.3%, triglyceride >150 mg/dL: 26%.
Häcker et al. (2019)B	Prospective cohort	512	Adult patients with congenital heart disease aged 30 years or older. Mean age 43 years, 51.1% men.	HDL-C <40 (men) or <50 mg/dL (women): 13.2%, triglyceride >150 mg/dL: 26.2%.
Bauer et al. (2019)	Prospective cohort	539	Adult patients with congenital heart disease (different complexities) with CV risk factors or documented acquired CV conditions. Mean age 38.4 years, 51.8% men.	Hyperlipidaemia: 15% (men 16.8%, women 13.2%).
Fedchenko et al. (2019)	Cross-sectional	72	Adult patients with coarctation of the aorta. Mean age 43.5 years, 58.3% men.	Hyperlipidaemia [TC ≥ 5 mmol/L (193 mg/dL) or LDL-C ≥3 mmol/l (116 mg/dL)]: 58.3%. LDL-C <2.6 mmol/L (100 mg/dL): 31.9%
Johnson et al. (2019)	Cross-sectional	73	Patients ≥35 years that underwent nonemergent cardiac surgery. Median age 44 years, 53% men.	Dyslipidemia: 18% (Non-CAD patients: 11%; CAD patients: 69%, $p < 0.001$).
Goldstein et al. (2020)	Cross-sectional	629	Adult patients with congenital heart disease who died during the study period. Median age 64.2 years, 54.7% men.	Hyperlipidemia: 48.5%. It was more common among those with shunt and valve lesions (49% and 64.4%, respectively) than in those with severe congenital heart disease (35%).
Kwiatek-Wrzosek et al. (2021)	Cross-sectional	322	Congenital heart disease patients older than 60 years. Median age 66 years, 34% men.	Dyslipidemia (LDL-C above target according to 2016 ESC guidelines, previous diagnosis of dyslipidemia, or current lipid-lowering therapy): 64.9%. Mild complexity: 67.3%; moderate/severe complexity: 55.9% ($p = 0.13$).
Wu et al. (2022)	Cross-sectional	186	Adults with congenital heart disease (different complexities). Median age 30 years, 50% men.	TC > 200 mg/dL: 20%, non-HDL-C >130 mg/dL: 34%, HDL-C <40 mg/dL: 32%. TC was higher among patients with simple congenital heart disease ($p = 0.03$) and HDL-C was lower among patients with complex congenital heart disease ($p = 0.05$).

AHA: American Heart Association; CAD: coronary artery disease; CV: cardiovascular; ESC: European Society of Cardiology; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol.

Table 2 Characteristics of the studies that compare congenital heart disease patients with a control group.

Study (year)	Design	Population	Lipid markers
Ohuchi et al. (2009)	Cross-sectional	Adult patients with congenital heart disease (n = 205). Unrepaired cyanotic (n = 16), Fontan (n = 67) and biventricular physiology (n = 122) patients groups. Mean age 24 years. Control group: healthy individuals (n = 27).	TC, LDL-C, HDL-C, triglycerides.
Martínez-Quintana et al. (2010)	Cross-sectional	Adult patients with congenital heart disease (n = 158) without LLT (cyanosis or acyanosis with or without operation). Median age 28.3 years; 59.5% men. Control group: unaffected age- and sex-matched subjects (n = 152).	TC, LDL-C, HDL-C, triglycerides.
Duffels et al. (2010)	Cross-sectional	Cyanotic patients with congenital heart disease (n = 54). Mean age 38 years, 56% men. Patients with a prior Fontan procedure and patients using LLT were excluded. Control group: unaffected age- and sex-matched subjects (n = 54).	TC, LDL-C, HDL-C, triglycerides
Martínez-Quintana et al. (2014)	Cross-sectional	Patients with congenital heart disease older than 14 years (n = 117) without LLT. Median age 27.2 years; 55.5% men. Control group: unaffected age- and sex-matched subjects (n = 152).	TC, LDL-C, HDL-C, triglycerides, Lp(a).
Moon et al. (2015)	Cross-sectional	Adult patients with congenital heart disease (n = 135). Group I: cyanotic disease (n = 45, mean age 43.1 years); group II: surgically corrected congenital heart disease (n = 90, mean age 48.4 years). Control group: unaffected age-, sex-, and BMI matched subjects (n = 135).	TC, LDL-C, HDL-C, triglycerides.
Deen et al. (2016)	Retrospective cohort	Adults with congenital heart disease (n = 448). Patients were subcategorized as “simple” (simple complexity) or “complex” (moderate or great complexity). Mean age 32.3 years, 52.1% women. Control group: unaffected age- and sex-matched subjects (n = 448).	HDL-C, triglycerides.
Trojnarska et al. (2017)	Cross-sectional	Congenital heart disease cyanotic adults patients (n = 36). Median age 42.3 years, 47.2% men. Control group: healthy individuals (n = 35).	TC, LDL-C, HDL-C.
Flannery (2017)	Case-control	Adults with congenital heart disease (n = 248). Median age 50.6 years. Control group: unaffected age- and sex-matched subjects (n = 744).	TC, LDL-C, HDL-C.
Tarp et al. (2019)	Prospective cohort	Adults with congenital heart disease (n = 74). Median age 49.5 years, 57% women. Control group: unaffected age-, sex-, smoking-, and BMI matched controls (n = 74).	TC, LDL-C, HDL-C, triglycerides.
Krishnamurthy et al. (2019)	Retrospective cohort	Patients with coarctation of the aorta >16 years (n = 131). Mean age 46.1 years, 46% women. Control group: unaffected age- and sex matched controls with low to intermediate risk for ACS at time of their emergency department presentation (n = 259).	TC, HDL-C.
Martínez-Quintana et al. (2019)	Cross-sectional	Congenital heart disease patients >14 years (n = 818), with simple (n = 462), moderate (n = 228) and great (n = 128) complexity. Median age 33 years, 56% men. Control group: unaffected age- and sex-matched subjects (n = 1955).	TC, LDL-C, HDL-C, triglycerides.
Saha et al (2019)	Prospective cohort	Adults patients with mild to moderate congenital heart disease (n = 2006), comprising 1082 participants with isolated aortic valve defects and 924 with non-complex defects. Control group: unaffected age-matched subjects (n = 497,983).	Hyperlipidemia prevalence.
Lubert et al. (2021)	Prospective cohort	Adult patients with a Fontan circulation (n = 164). Median age 30.3 years, 42% women. Control group: healthy subjects (n = 81).	TC, LDL-C, HDL-C, triglycerides, non-HDL-C.

(*continued on next page*)

Table 2 (*continued*)

Study (year)	Design	Population	Lipid markers
Chen et al. (2022)	Cross-sectional	Adult patients with congenital heart disease with (n = 20) or without (n = 101) PAH. NonPAH group: median age 80 years, 80% women. PAH group: median age 38 years, 73.3% women. Control group: unaffected subjects (n = 81).	TC, LDL-C, HDL-C, triglycerides.
Vanreusel et al (2022)	Cross-sectional	Adult patients with congenital heart disease without diabetes or CAD (n = 36), Median age 31.5 years, 50% women. Control group: unaffected age- and sex-matched subjects (n = 36).	TC, LDL-C, HDL-C, triglycerides.
Levene et al. (2023)	Cross-sectional	Adult patients (n = 13,896) with simple (73.8%) and moderate to complex (26.2%) congenital heart disease, 48.9% women. Control group: unaffected age- and sex-matched subjects (n = 138,960).	Hyperlipidemia prevalence.

ACS: Acute Coronary Syndrome; BMI: body mass index; CAD: Coronary artery disease; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; LLT; lipid-lowering therapy; Lp(a): Lipoprotein(a); PAH: pulmonary arterial hypertension; TC: total cholesterol; VLDL-C: Very Low-Density Lipoprotein Cholesterol.

aortic stenosis to aortopathies [50,51]. Therefore, interpreting lipid levels in these patients becomes extremely complex if we do not consider the associated factors and the specific patient groups being studied.

When examining studies that reported the prevalence of dyslipidemia without a control group, a wide range of values was observed. Importantly, the definition of "dyslipidemia" was heterogeneous. However, the prevalence of dyslipidemia reported in the general population seems to be included in the observed range [52,53]. Out of the 13 studies analyzed in this review, 11 included a mix of patients with simple defects, moderate complexity defects, and complex defects, although only 7 of them analyzed lipid values across these different groups [11,13,16,25,33,34,39]. The results were conflicting, with five studies showing a lower frequency of hypercholesterolemia in the most severe patients [11,13,25,34,39], while the other two did not demonstrate the same pattern [16,33]. However, it is important to note that these last two studies included patients with coronary disease [16] and elderly subjects [33], which could introduce bias into the results.

When analyzing studies that compared lipid levels between patients with congenital heart disease and a control group, it is important to consider two scenarios. The results of studies that assessed lipid variables in a dichotomous manner showed contradictory findings. Surprisingly, the two larger studies seemed to demonstrate opposite results compared to the meta-analysis [31,37]. The study by Levene et al. primarily included patients with simple defects (74%), with one-third of them having diabetes. Additionally, the code used to define "hyperlipidemia" encompassed a wide range of lipid disorders. Consequently, it is unclear whether the higher proportion of patients with dyslipidemia was due to elevated total cholesterol or low HDL-C levels. On the other hand, the study by Saha et al. exclusively included low-complexity patients, and the proportion of men was significantly higher in the congenital heart disease group (59.6% vs. 45.5%). Once again, the definition of "dyslipidemia" used in this study does not provide information about which lipid markers were responsible for the reported difference.

Beyond the different congenital heart disease or the different definitions of dyslipidemia analyzed in the included studies, other differences between populations, such as diet, body mass index, level of physical activity, or lipid-lowering medication, could partly explain the heterogeneity of the results.

However, the results of studies that analyzed lipid variables in a continuous form were more consistent. This is particularly evident when analyzing total cholesterol levels, as almost all studies showed lower total cholesterol levels in congenital heart disease patients. The exception was the study by Moon et al. [18], which reported higher lipid levels in the subgroup of patients with surgically corrected defects.

Similar findings were observed for LDL-C levels, with congenital heart disease patients showing 10.7 mg/dL lower LDL-C levels than controls. This finding could be epidemiologically and clinically relevant since LDL-C plays

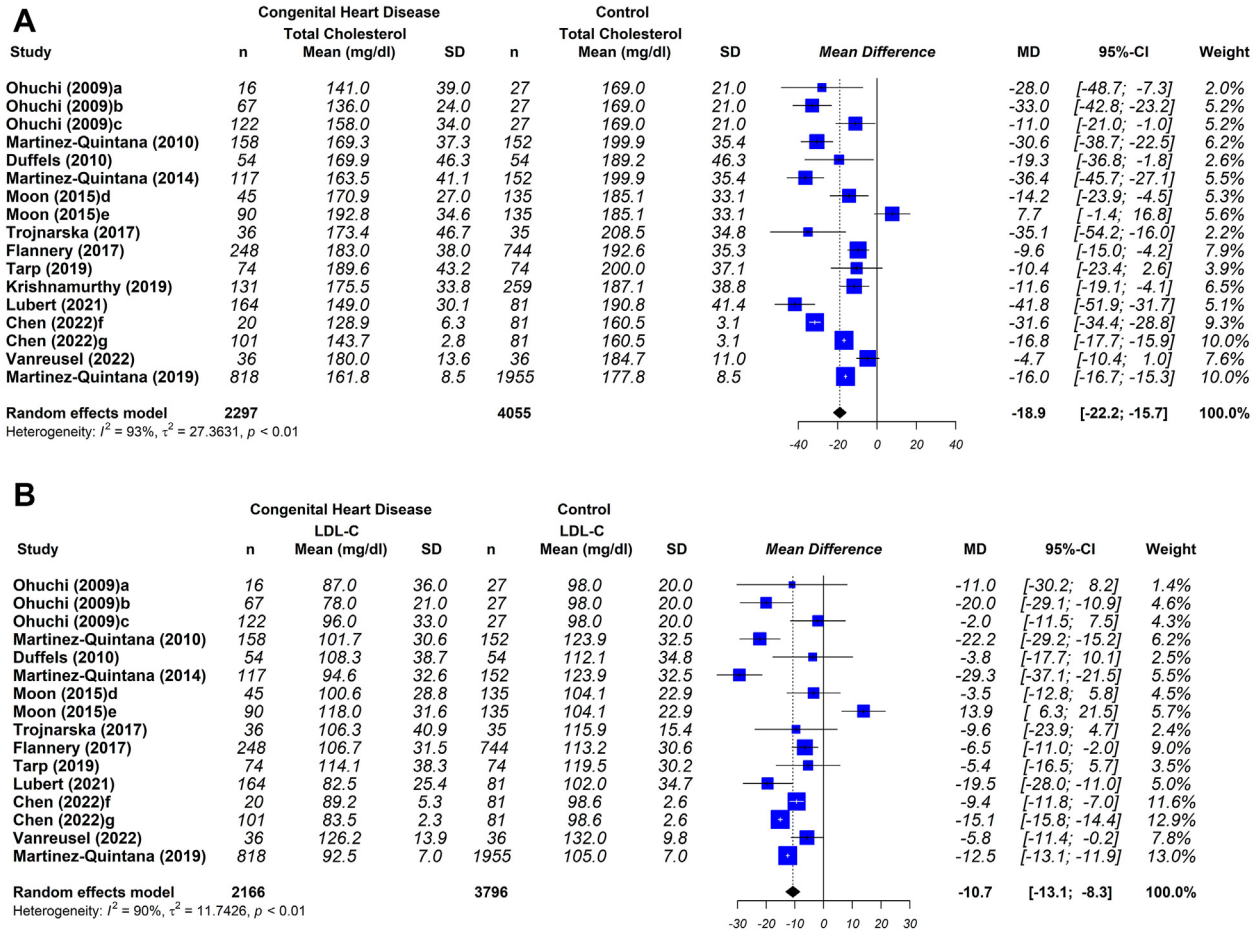

Figure 3 Quantitative analysis. Total cholesterol (A) and LDL-C (B) levels in congenital heart disease and control groups. Random effects model. Mean difference (MD), standard deviation (SD), 95% confidence intervals (CI) and I^2 statistics. a: Unrepaired; b: Fontan; c: Biventricular; d: Cyanotic congenital heart disease; e: Surgically corrected congenital heart disease; f: congenital heart disease-non pulmonary arterial hypertension; g: congenital heart disease-pulmonary arterial hypertension.

a causal role in atherosclerotic cardiovascular disease with a slightly more than 20% risk reduction in major vascular events per 1.0 mmol/L decrease of LDL-C levels [54].

Consistent results were also observed when analyzing HDL-C values, with all studies, except for the study by Krishnamurthy et al. reporting lower HDL-C levels in congenital heart disease patients. However, it is important to note that the study by Krishnamurthy et al. exclusively included patients with coarctation of the aorta, and the controls were individuals with low to intermediate risk for acute coronary disease at the time of their emergency department presentation. Early epidemiological studies have consistently demonstrated a linear inverse association between HDL-C levels and cardiovascular events [55]. However, major clinical trials aimed at increasing HDL-C levels have reported conflicting results [56]. Furthermore, several epidemiological studies have suggested a U-shaped curve for HDL-C levels, whereby very low or very high levels of HDL-C may be associated with increased cardiovascular risk [57]. Therefore, the clinical significance of the lower HDL-C levels observed in congenital heart disease patients remains unresolved. Finally, HDL functionality is superior to HDL-C in the prediction of cardiovascular risk [58]. Additionally, HDL particles are a more sensitive assessment of HDL [59]. Then, it is a limitation that the primary articles do not report

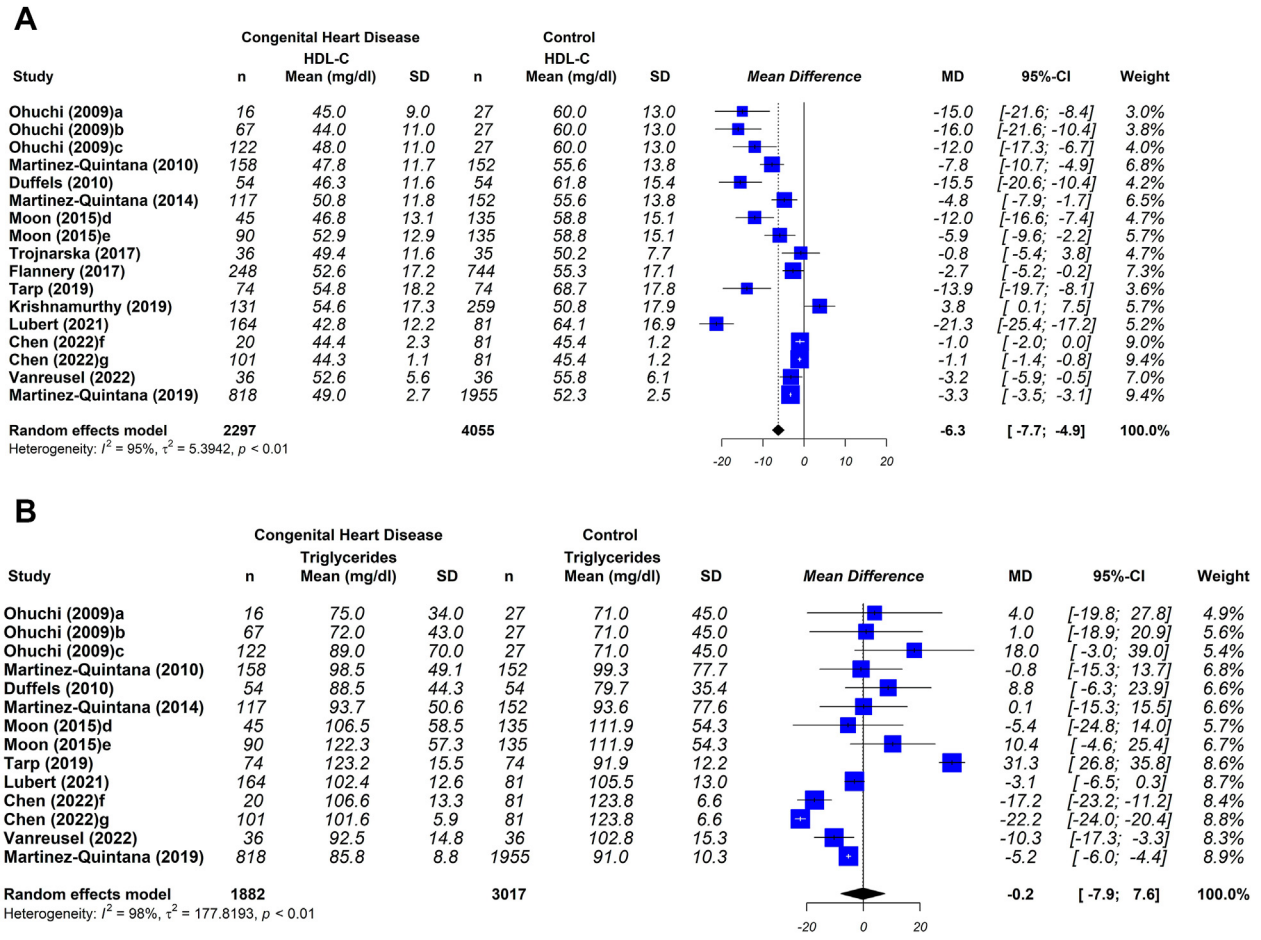

Figure 4 Quantitative analysis. HDL-C (A) and triglyceride (B) levels in congenital heart disease and control groups. Random effects model. Mean difference (MD), standard deviation (SD), 95% confidence intervals (CI) and I^2 statistics. a: Unrepaired; b: Fontan; c: Biventricular; d: Cyanotic congenital heart disease; e: Surgically corrected congenital heart disease; f: congenital heart disease-non pulmonary arterial hypertension; g: congenital heart disease-pulmonary arterial hypertension.

assessment of HDL function or concentrations of the different HDL particles.

We found no differences in triglyceride levels in the quantitative analysis. Importantly, a common concern when analyzing the level of triglycerides is the large number of confounding factors that can affect them. The clinical value of this lipid variation is speculative, since the existence of an independent association between triglyceride levels and atherosclerotic vascular disease has long been controversial in the general population [60].

Finally, since only one study evaluated Lp(a) levels, we cannot establish a definitive conclusion. In the general population, high levels of Lp(a) are an independent risk factor for atherosclerotic cardiovascular diseases and with aortic valve stenosis, through mechanisms associated with increased atherogenesis, inflammation, and thrombosis [61]. Further research on this topic would be valuable.

This systematic review presented several limitations. First, there were clinical heterogeneities, including differences in population characteristics and definitions of dyslipidemia. Because most of the studies evaluated did not report data, it was not possible to perform an analysis of lipid values in the different congenital heart disease subgroups. Additionally, there was high statistical heterogeneity in the quantitative analysis. While I^2 is commonly used to assess heterogeneity, it is not a perfect measure and its value depends on the precision and size of the included studies. In this case, the high heterogeneity may

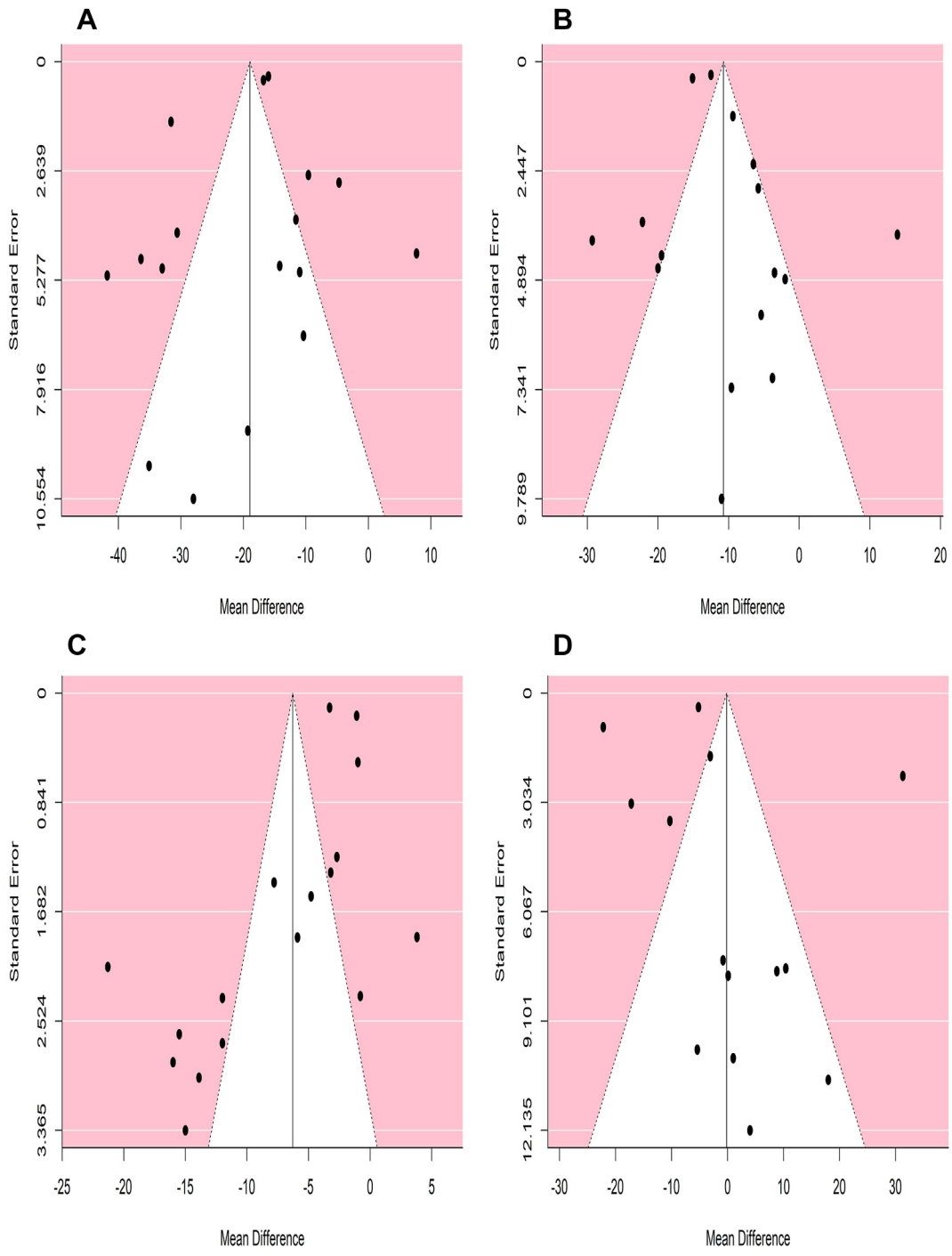

Figure 5 Funnel plot to assess publication bias. Total cholesterol (A), LDL-C (B), HDL-C (C) and triglyceride (D).

be attributed more to the magnitude of the effect rather than the direction of the effect. Nonetheless, the results remained robust in the sensitivity analysis. Second, the meta-analysis relied on study-level data and did not have access to individual participant data. Finally, the qualitative analysis only included observational studies, which inherently carry biases and confounders. For example, some potentially confounding variables such as level of physical activity, body mass index, diet, and lipid-lowering mediation were not considered in this review.

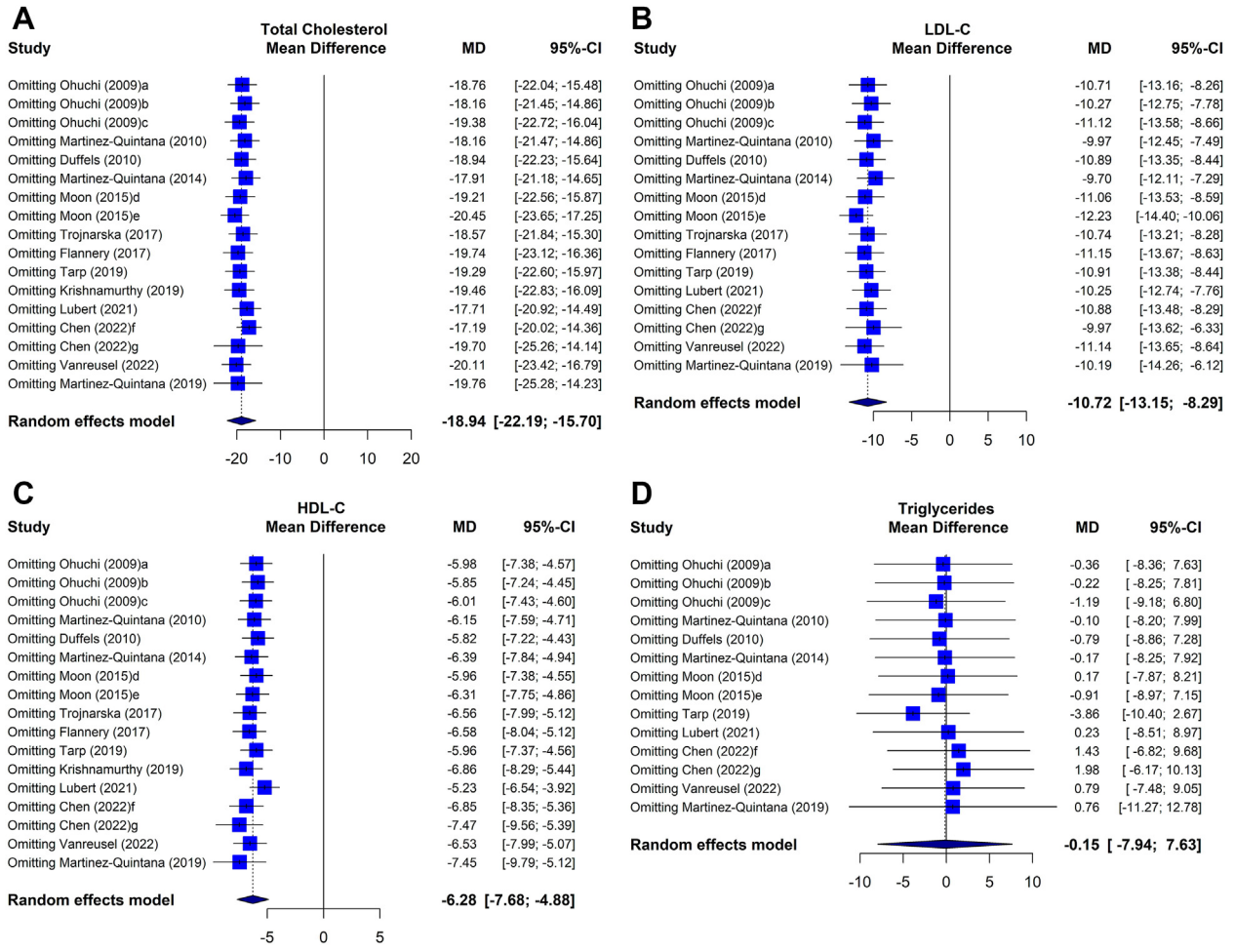

Figure 6 Sensitivity analysis of all the studies evaluated. MD: standardized mean difference; CI: confidence interval. Total cholesterol (A), LDL-C (B), HDL-C (C) and triglycerides (D). a: Unrepaired; b: Fontan; c: Biventricular; d: Cyanotic congenital heart disease; e: Surgically corrected congenital heart disease; f: congenital heart disease-non pulmonary arterial hypertension; g: congenital heart disease-pulmonary arterial hypertension.

5. Conclusion

The analysis of lipid markers in congenital heart disease patients is indeed challenging due to the complex pathophysiological processes associated with congenital heart disease. This systematic review highlights the prevalence of dyslipidemia in congenital heart disease patients, involving various lipid markers. The quantitative analysis indicates that congenital heart disease patients have lower levels of total cholesterol, LDL-C, and HDL-C compared to controls. The qualitative analysis showed some concerns that should be clarified in future research. It is essential to establish standardized definitions of dyslipidemia, to examine the different congenital heart disease groups separately, and to consider the multiple confounding factors when conducting future analyses. By addressing these issues and obtaining more robust evidence, we can enhance our understanding of the lipid profiles in congenital heart disease patients and improve clinical management strategies.

Ethical considerations

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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Author contributions

WM and LB participated in the conception and design of the research. WM, LB and PC participated in the data collection. The interpretation of the data and the statistical analysis was done by WM and ML. WM, LB and LL drafted the manuscript. All authors performed a critical review of

the final document. All authors have read and agreed to the published version of the manuscript.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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