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Association between lipid profile and the prevalence of asthma: a meta-analysis and systemic review

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Transparency

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Author contributions

Guarantor of integrity of the entire study: XS, LK, JK; study concepts: XS, LK; study design: XS; definition of intellectual content: LK; literature research: ML, XZ; data acquisition: YR; statistical analysis: YR; manuscript preparation: XS; manuscript editing: XS, YR; manuscript review: XS.

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ABSTRACT

Objective: To explore the association of asthma with serum levels of high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, and triglyceride.

Methods: PubMed, Cochrane, and Embase databases were systematically searched through November 2015 using the following search terms: dyslipidemia, HDL, LDL, triglyceride, cholesterol, and asthma. Eligible studies included randomized controlled trials (RCTs), retrospective, cohort, and cross-sectional studies. Sensitivity analysis and publication bias were performed.

Results: Twenty studies were included in the analysis with a total 32,604 patients (3,458 in the asthma group and 29,146 in the control group). The pooled analysis found that the mean difference between groups was significantly higher in the asthma group for levels of LDL (6.026 mg/dL, 95%CI=2.696 to 9.356, $P<.001$) and total cholesterol (8.161 mg/dL, 95%CI=3.006 to 13.316, $P=0.002$) compared with the control group. No association was observed between asthma and control groups for levels of HDL (mean difference, -0.728, 95%CI=-3.146 to 1.691, $P=0.555$) or triglycerides (mean difference, 1.436, 95%CI=-2.768 to 5.640, $P=0.503$).

Conclusions: Levels of LDL and total cholesterol were higher in patients with asthma than non-asthmatic patients.

Keywords: asthma, high-density lipoproteins, low-density lipoproteins, triglycerides, total cholesterol

Sub-Title: Lipid profile and risk of asthma

INTRODUCTION

A number of studies have demonstrated an association between asthma and metabolic syndrome [1]. Metabolic syndrome is a cluster of biochemical and physiological risk factors that include abdominal obesity, dyslipidemia, raised blood pressure, insulin resistance with or without glucose intolerance, proinflammatory state, and prothrombotic state [2]. Metabolic syndrome has also been shown to increase asthma severity [3, 4]. It is currently unclear if metabolic syndrome is a risk factor for asthma, or if one or more of its components is the risk factor for the airway disease [5]. The underlying mechanisms of the link between asthma and metabolic syndrome is unclear [6]. It is thought that the relationship may be bidirectional between the two diseases [6].

Epidemiology studies have found a potential association of obesity and asthma, and obesity appears to be a predisposition factor for the onset of asthma in both children and adults [6, 7, 8]. In addition, higher BMI has been found to increase the risk of asthma in non-atopic and atopic children [9]. Obesity is thought to increase the risk of Th2 inflammation and atopy; however, the findings have been inconsistent [6, 10, 11]. In support of the role for obesity in asthma, weight loss has been found to substantially improve clinical status, lung function, symptoms, and overall asthma control in overweight severe asthmatic patients [12, 13, 14]. Some clinical studies suggest that asthma in obese subjects may differ from the classical phenotype of the disease [10]. The current guidelines indicate obesity as a factor that impairs control of asthma symptoms and the lack of response to treatment [15, 16].

Asthma is also associated with other markers of metabolic syndrome such as dyslipidemia, hyperglycemia, and insulin resistance [5, 6]. Low levels of serum high density lipoproteins (HDLs) have been found to be associated with an increased risk of asthma in adolescence [17] and high levels of low-density lipoproteins (LDLs) and triglycerides have been implicated to be associated with wheezing in adults [18].

A number of studies have evaluated the relationship of asthma and blood lipid profiles with inconsistent results. The objective of the present study was to investigate the association between asthma and the serum levels of HDL, LDL, total cholesterol, and triglycerides.

METHODS

Search strategy

The study followed the recommendations of the PRISMA guidelines. The following databases were searched through November 2015: PubMed, Cochrane Library, and Embase. The search was performed using the search terms of lipid profile, dyslipidemia, HDL, LDL, triglyceride, cholesterol, and asthma. Eligible studies included randomized controlled trials (RCTs), retrospective, cohort, and cross-sectional studies. Patient population of included studies could have any type of asthma and a control group with no asthma. Studies had to have evaluated lipid profiles of the patients (i.e., [HDL, LDL, triglyceride, and/or total cholesterol. Eligible studies had to be published in English. Ineligible studies included letters, editorials, reviews, commentaries, case reports, personal communications, and proceedings. Studies that did not report quantitatively outcomes of interest were also excluded. Potential studies were screened using a two-step process. First, the title and abstract of each article was examined and citations not meeting the inclusion criteria were discarded. Second, the full-text of the remaining articles were reviewed with respect to the inclusion/exclusion criteria. The reference lists of the relevant studies were hand searched to identify other studies that met the inclusion criteria. Two independent reviewers

identified the eligible studies. If any uncertainties existed regarding eligibility, a third reviewer was consulted.

Data extraction

The following data was extracted from the included papers: name of first author, study design, comparison groups, number of patients, age, body mass index (BMI), smoking history, treatment protocol, and mean forced expiratory volume in one second/ forced vital capacity (FEV₁/FVC). Outcomes extracted included HDL, LDL, total cholesterol, and triglyceride levels. Two reviewers extracted the data and a third reviewer was consulted to adjudicate any disagreements.

Quality assessment

The method of Hayden et al. was used to evaluate the quality of the included studies[19]. This method evaluates six potential sources of bias which are related to study participation, study attrition, prognostic factor measurement, confounding measurement and account, outcome measurement, and analysis. The quality of the studies was appraised by two reviewers. Any disagreements were resolved by a third reviewer.

Statistical analysis

The main outcomes of the study were the association of asthma with lipid profile (i.e., HDL, LDL, total cholesterol, and triglyceride levels). Data were summarized as mean±standard deviations (SD) or mean with P value by group for each study. For studies reporting multiple asthma groups and/or control, asthma data were combined into two comparison groups. Prior to the pooled analysis, all data regarding lipid profiles were transformed to mean ± SD and where necessary converted to the same units (mg/dL). The measure of effect size was defined as difference in means with 95% confidence interval (95% CI) and P value between asthma and control groups.

Study heterogeneity was evaluated using a χ^2 -based Cochran's Q statistic and I^2 . For the Q statistic, P values <.10 were considered statistically significant for heterogeneity. For the I^2 statistic, heterogeneity was assessed as follows: no heterogeneity (I^2 = 0 - 25%), moderate heterogeneity (I^2 =25 - 50%), large heterogeneity (I^2 = 50 - 75%), and extreme heterogeneity (I^2 = 75 - 100%). DerSimonian–Laird random-effects model[20]was performed to calculate pooled estimates of difference in means among the studies. A two-sided P value of <.05 was considered significant. Moreover, to identify whether any covariates affected the effect size, a meta-regression analysis was applied for continuous covariates (mean age, mean BMI, and percent males) and subgroup meta-analysis for categorical covariates (regions and adults vs. non-adults). Sensitivity analysis was conducted using a leave-one-out approach. Publication bias was assessed by funnel plots, and the asymmetry of funnel plots was evaluated by Egger's test with one-tailed P-value. All statistical analyses were performed using the statistical software Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ).

RESULTS

Search results

The literature search identified 397 potential studies of which 369 were excluded after the initial screen for not being relevant (Figure 1). Thirty studies underwent full-text review, and 10 were eliminated for not presenting outcomes of interest, not having relevant objectives, being non-English, not presenting outcomes quantitatively, being a review, did not recruit patients with asthma, or asthma patients had other comorbid diseases.

Twenty studies were included in the analysis [17, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39], of which three were prospective, nine were case-control, seven were cross-sectional, and one retrospective in design (Table 1). A total of 32,604 patients were included; 3,458 in the asthma group (range, 24 to 1,123) and 29,146 in the control group (range, 20 to 15,418). The mean age ranged from 6.5 to 50.5 years old, overall about half the patients were male (range, 36.9% to 84.0%), and the mean BMI ranged from 16.1 to 28.2 kg/m². The percent of patients who smoked ranged from 0% to 63.8% and those exposed to passive smoking ranged from 0% to 58.1%. Mean FEV₁/FVC across the studies ranged from 71 to 84.7.

The lipid profiles for the asthma and control groups are summarized in Table 2. Eighteen studies reported data for HDL, 16 studies presented data for LDL, 17 studies reported results for total cholesterol, and 15 reported data for triglycerides.

Meta-analysis

Heterogeneity of the data was observed for all the lipid profile outcomes (HDL: Q-value= 146.13, df=17, $P<.001$, $I^2=88.37\%$; LDL: Q-value=114.29, df=15, $P<.001$, $I^2=86.88\%$; total cholesterol: Q-value=104.37, df=16, $P<.001$, $I^2=84.67\%$; triglyceride: Q-value=41.88, df=14, $P<.001$, $I^2=66.57\%$) (Figure 2). The pooled analysis found a significant difference between asthma and control groups for LDL and total cholesterol. The pooled analysis found that the mean difference between groups was significantly higher in the asthma group for the levels of LDL (6.026 mg/dL, 95%CI=2.696 to 9.356, $P<.001$) and total cholesterol (8.161 mg/dL, 95%CI=3.006 to 13.316, $P=0.002$) compared with control group (Figure 2B and 2C). No association was observed between asthma and control groups for levels of HDL (mean difference, -0.728, 95%CI=-3.146 to 1.691, $P=0.555$) or triglycerides mean difference, 1.436, 95%CI=-2.768 to 5.640, $P=0.503$) (Figure 2A and 2D).

Meta-regression analysis found the effect size of HDL and LDL were affected by age; levels decreased increasing mean age (P values $\leq .0003$, respectively). In contrast, the effect size of TG rose with greater mean age and mean BMI (P values ≤ 0.0398). The effect size of HDL, LDL, and TC increased with increase percentage of males (P values $< .0001$) (Supplemental Material, Table S1).

The subgroup analysis found that the effect size of TG significantly differed by geographical regions and between adults versus non-adults (P value ≤ 0.0399) (Supplemental Material, Table S2). Subgroup meta-analysis for regions and adults was also performed separately (Supplemental Material, Tables S3 and S4). The combined effect for geographic regions significantly differed between the control and asthma groups with in HDL for India (diff in means=-6.20, $P=0.002$), LDL for Asia, Europe, and India (diff in means=11.58, 11.98, 10.24; P values ≤ 0.032), TC for Asia and India (diff in means=7.72, 21.68; P -values ≤ 0.012), and TG for India and US (diff in means=13.16 and -2.016; P values $< .001$). For adults, the combined effect significantly differed between control and asthma in LDL, TC, and TG for adults (diff in means=8.177, 10.897, and 7.092, respectively; P values ≤ 0.036). The combined effect in LDL also significantly differed for non-adults (diff in means=5.067, $P=0.003$). (Table S4)

Sensitivity analysis

Sensitivity analyses were performed for all the outcomes using a leave-one-out approach (Figure 3). The direction and magnitude of the combined estimates for the four outcomes did not markedly differ with the removal of any one study, indicating that the meta-analysis had good reliability and that the data was not overly influenced by any given study.

Publication bias analysis

Publication bias was assessed by funnel plots with Egger's test (Figure 4). Results of testing asymmetry of funnel plots revealed that publication bias might exist LDL findings ($t = 3.06$, $df = 15$, $P = .004$), but not the other outcomes.

Quality assessment

Overall, little bias was observed across the studies (Figure 5). High risk of bias for outcome measurement and confounding measurement and account were present in three [25, 28, 35] and six [22, 24, 26, 27, 31, 38], respectively. Overall the studies were moderate to high in quality.

Discussion

Several studies have indicated an association of asthma with metabolic syndrome. It is currently unclear if all or only a subset of risk factors for metabolic syndrome may impact asthma. The purpose of this study was to evaluate if blood lipid levels were associated with the presence of asthma. The pooled analysis found that higher levels of LDL and total cholesterol were associated with asthma, but no apparent association was observed for HDL and triglycerides.

A recent meta-analysis also assessed the association between asthma and serum levels of LDL and HDL [40]. Ten studies were included in the analysis. The analysis was subdivided by age and separately evaluated children (<18 years of age) and adults (≥ 18 years of age). They found that children with asthma had lower HDL levels (weighted mean difference, -3.44 ; $P = .005$) compared with non-asthma controls. They saw no difference between children with and without asthma with respect to LDL levels (weighted mean difference, 0.71 ; $P = .82$). However, the study found that in adults, higher LDL levels were associated with asthma (weight mean difference, 8.95 ; $P = .001$) and there was no difference between the asthma and non-asthma groups with respect to HDL levels (-2.01 ; $P = .15$). Our findings are consistent with those observed in adults, but not children. The difference between our study and the prior meta-analysis may reflect differences in the studies included and that our population consisted of both children and adults; we did not perform subgroup analysis by age group.

A number of other factors may impact levels of the blood lipids and hence, their association with asthma, including gender, race, lifestyle, diet, BMI, smoking, and disease severity [5, 6]. However, several studies have indicated that the association of blood lipid profile with asthma is independent of BMI, age, sex, socioeconomic status, and serum high-sensitivity C-reactive protein [33, 39, 41]. The different blood lipids may also be associated with specific characteristics of asthma. Vinding et al. (2016) investigated whether lipid profile was associated with concurrent asthma, altered lung function, and allergic sensitization in children [41]. They found that high levels of LDL were associated with concurrent asthma ($P = .03$) and airway obstruction ($P = .01$) and specific airway resistance ($P = .05$). In the study of Vinding et al., high levels of HDL were associated with improved specific airway resistance, reduced bronchial hyperresponsiveness, and lower risk of aeroallergen sensitization (P values $\leq .05$). They also found that high triglyceride levels were associated with aeroallergen sensitization ($P = .02$) and a trend of increase exhaled nitric oxide (FeNO) ($P = .08$).

The type of LDL present may also impact the relationship with asthma. Scichilone et al. (2013) evaluated whether LDL subclasses were associated with the occurrence and severity of asthma [36]. Low

density lipoproteins can be divided into seven subclasses based on density of size as determined by ultracentrifugation, and each class's influence on inflammation differ [17, 42]. Scichilone et al. found that in mild asthmatics, LDLs with low inflammatory activity (LDL-1 and LDL-2) are lower in persons with asthma than in healthy subjects [36]. In contrast, LDLs with the most proinflammatory activity (LDL-3 and LDL-4) are higher in asthmatic subjects compared with non-asthmatic subjects. LDL-3 was also found to be negatively associated with lung function, suggesting a contribution of LDL-3 to inflammatory changes in the airways [6, 36].

The relationship of LDL and triglycerides with asthma has led to the idea of the use of statins in reducing asthma symptoms [6]. This idea is supported by a systematic review that evaluated whether statins showed benefit in treating asthma [43]. The systematic review did not find evidence that statins would improve lung function in subjects with asthma, but did find they may reduce airway inflammation. The systematic review did not evaluate different types of statins which are known to have different therapeutic effects [43].

The current study has several limitations. The analysis did not stratify by disease severity. In addition, the methods for assessing serum lipids varied across the studies, which may have confounded the results. Moreover, the findings for LDL may be confounded by the presence of publication bias.

In conclusion, this meta-analysis found a significant association between asthma and the serum levels of LDL and total cholesterol. Additional well-designed studies are required to further evaluate the roles of blood lipids, including subclasses of LDLs, in asthma and to understand the potential underlying mechanism on the impact of blood lipids on the development and progression of asthma.

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Del-Rio-Navarro (2010)	Cross-sectional	Mexico (Latin)	Asthma	174	Adolescence	12.6	25.3			
			Control	269		12.8	27.4			
Fessler (2009)	Cross-sectional	United states (US)	Asthma	623	Adult	40.0	49.0%	27.2	21.3%	21.4%
			Control	6382						
Cakmak (2009)	Prospective	Turkey (Middle east)	Asthma	42	Children	9.0	47.6%	0.8		
			Control	32		9.4	31.3%	0.6		
Gulcan (2009)	Case-control	Turkey (Middle east)	Asthma	51	Adult	40.3	37.3%	26.7	25.5%	
			Control	40		39.5	37.5%	26.0	22.5%	
Al-Shawwa (2006)	Retrospective	Midwestern United States (US)	Asthma	50	Children and adolescents	10.8	64.0%	22.6	30.0%	
			Control	138		9.9	54.3%	20.3	8.7%	
Ekmekci (2006)	Case-control	Turkey (Middle east)	Asthma	30	Adult	36.0	25.0		72	
			Control	28		36.0	24.0		84	
Ford (2004)	Cross-sectional	United states (US)	Asthma	1123	Adult	44.6	45.5%	27.4	33.5%	
			Control	15418		44.7	47.8%	26.4	27.9%	
Schäfer(2003)	Nested case-control	Germany (Europe)	Asthma	120	Adult	50.5				
			Control	1417						
Picado (1999)	Case-control	Spain (Europe)	Asthma	118	Adult	41.6	40.7%	24.2	Corticosteroids	
			Control	121		38.8	37.2%	24.3		
Mishra (1996)	Cohort	India (India)	Asthma	30	Adult	41.6	76.6%			
			Control	30		38.4	73.3%			
Yagupsky (1992)	Cross-sectional	Israel (Middle east)	Asthma	48	Children	7.3	54.2%			
			Control	20		7.0	70.0%			

Table 2. Summary of outcomes of selected studies for meta-analysis.

Study name 1 st AU (year)	Methods used to assess serum lipids	Whether the studies utilized fasting or non-fasting serum lipid levels.	Asthma group				Control group			
			HDL (mg/dL)	LDL (mg/dL)	Total cholesterol (mg/dL)	Triglyceride (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	Total cholesterol (mg/dL)	Triglyceride (mg/dL)
Rastogi (2015)	HDL, TC and TG were carried out in fasting serum by enzymatic immunoassay. TG and TC were measured by direct enzymatic measurements, while HDL was separately measured using two reagent homogenous systems with selective detergents to homogenize the lipoprotein of interest	Fasting	47.3 ± 10.98	83.4 ± 20.83	NA	78.95 ± 44.31	51 ± 10.41	79.94 ± 25.98	NA	74.56 ± 38.82
Barochia (2015)	NA	NA	53.8 ± 17.1	112.3 ± 32	191.4 ± 35.7	108 ± 14.167	48.64 ± 16.81	101.09 ± 30.3	175.02 ± 35.05	101.66 ± 13.77
Vinding (2015)	Cobas Integra 400	nonfasting	59.07 ± 11.58	86.87 ± 16.22	NA	83.34 (p=0.630)	60.62 ± 12.36	79.54 ± 21.62	NA	80.07
Yiallourous (2014)	ILab 600 analyzer using ILab chemistry systems	12 hours of fasting	58.32 ± 12.09	95.51 ± 27.47	167.38 ± 30.32	68.45 ± 27.82	59.7 ± 12.5	92.2 ± 25.3	165.7 ± 28.7	69.3 ± 37
Acay (2013)	NA	12-14 hours of fasting	52.09 ± 10.15	122.16 ± 36.28	189.9 ± 41.26	116.59 ± 50.38	42.84 ± 9.48	137.84 ± 40.07	210 ± 53.44	146.74 ± 89.33
Chen (2013)	TG, LDL, and HDL were measured by a biochemistry analyzer.	8 hours of fasting	54.05 ± 11.58	92.66 ± 27.03	162.16 ± 27.03	79.65 ± 44.25	54.05 ± 11.58	81.08 ± 23.17	154.44 ± 27.03	79.65 ± 44.25
Ramaraju (2013)	TC was estimated by enzymatic method.	8-10 hours of fasting	NA	NA	176.45 ± 30.77	NA	NA	NA	163.33 ± 26.38	NA
Scichilone (2013)	LipoPrint [®] System	fasting	50 ± 13	108 ± 25	184 ± 31	119 ± 62	53 ± 13	79 ± 22	151 ± 28	95 ± 38
Yiallourous (2011)	TC and TG were estimated by enzymatic method and HDL was measured with a non-immunological enzymatic reaction.	12 hours of fasting	57.5 ± 12.6	93.1 ± 22.4	164.6 ± 26.6	71.3 ± 33.6	59.9 ± 12.4	91.9 ± 25.5	165.6 ± 29.6	69.3 ± 36.7
Del-Rio-Navarro (2010)	TC, TG, and HDL was determined by the photocolometric method. For TC, coupled enzymatic reactions were used. HDL measurement was by the Roche/Boehringer-Mannheim Diagnostics direct HDL method.	12 hours of fasting	45.65 ± 15.93	NA	169.25 ± 34.68	123.96 ± 71.27	46.61 ± 15.55	NA	167.07 ± 47.41	137.9 ± 87.01
Fessler (2009)	Automated chemistry analyser using commercial kits.	TC and HDL: fasting and nonfasting	54.5 ± 22.46	NA	188.5 ± 34.94	NA	54.5 ± 23.97	NA	192.2 ± 55.92	NA
Cakmak (2009)	NA	Fasting overnight	40.1 ± 9.2	85.2 ± 26.4	150.7 ± 27	114.3 ± 59.3	54.5 ± 15.9	90.2 ± 17.2	153.8 ± 24.7	117.9 ± 31.9
Gulcan (2009)	NA	12 hours of fasting	43 ± 8	121 ± 36	191 ± 43	130 ± 69	48 ± 10	104 ± 30	177 ± 37	130 ± 72
Al-Shawwa (2006)	NA	NA	NA	NA	176.7 ± 39.8	NA	NA	NA	162.9 ± 12.8	NA
Ekmekci (2006)	TC and TG were measured by an enzymatic, colorimetric, end-point assay. HDL was measured by the phosphotungstic acid-magnesium chloride precipitation method.	Fasting overnight	50 ± 82.16	120 ± 147.89	194 ± 216	108 ± 251.952	49 ± 42.33	116 ± 158.75	188 ± 216.95	109 ± 328.073
Ford (2004)	TC and HDL were measured enzymatically with a Hitachi 704 analyzer.	Fasting overnight	50.07 ± 23.17	153.62 ± 2.87	NA	NA	50.58 ± 47.01	153.28 ± 0.77	NA	NA
Schafer (2003)	TC and HDL were measured		55.7	142.2	230.1	NA	55	137.8	227.3	NA

by CHODPAP method.

(p=0.270) (p=0.290) (p=0.540)

Picado (1999)	NA	12 hours of fasting	60 ± 76.37	137 ± 173.95	214 ± 510.55	80 ± 195.53	59 ± 165	132 ± 418	208 ± 473	77 ± 165
Mishra (1996)	NA		46.68 ± 7.7	128.84 ± 14.68	224.6 ± 26.42	119.3 ± 16.6	52.88 ± 7.8	118.6 ± 18.22	194.2 ± 24.8	106.14 ± 12.1
Yagupsky (1992)	TG was determined by the enzymatic- colorimetric method. TC and lipoprotein cholesterol contents were determined by the enzymatic-colorimetric method.	12 hours of fasting	44.95 ± 2.6	78.09 ± 4.56	153.48 ± 9.67	70.03 ± 5.38	36.29 ± 2.32	70.27 ± 3.86	135.52 ± 5.79	74.34 ± 8.85

Data were represented as mean ± SD except for mean with p-value for TG of Vinding (2015) study, and lipid profiles of Schafer (2003) study.

HDL, high-density lipoprotein, LDL, low-density lipoprotein, TC, total cholesterol, TG, triglyceride.

NA, not assessed.

Figure legends

Figure 1. Flow diagram of study selection

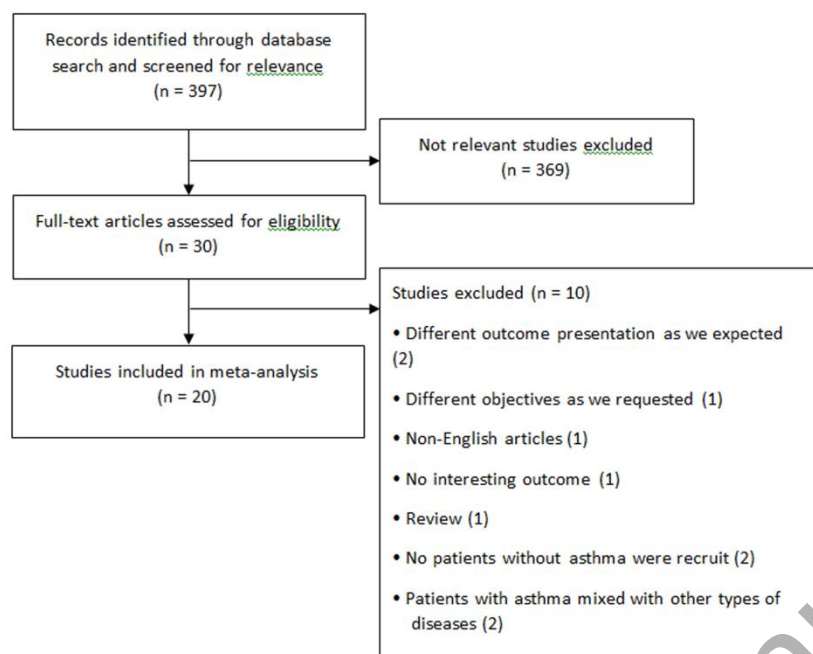
Figure 2. Meta-analysis for association between asthma and (A) high-density lipoproteins (HDL), (B) low-density lipoproteins (LDL), (C) total cholesterol, and (D) triglycerides. Abbreviations: Diff, difference; 95%CI, 95% confidence intervals.

Figure 3. Leave-one-out sensitivity-analysis for association between asthma and (A) high-density lipoproteins (HDL), (B) low-density lipoproteins (LDL), (C) total cholesterol, and (D) triglycerides. Abbreviations: Diff, difference; 95% CI, 95% confidence intervals.

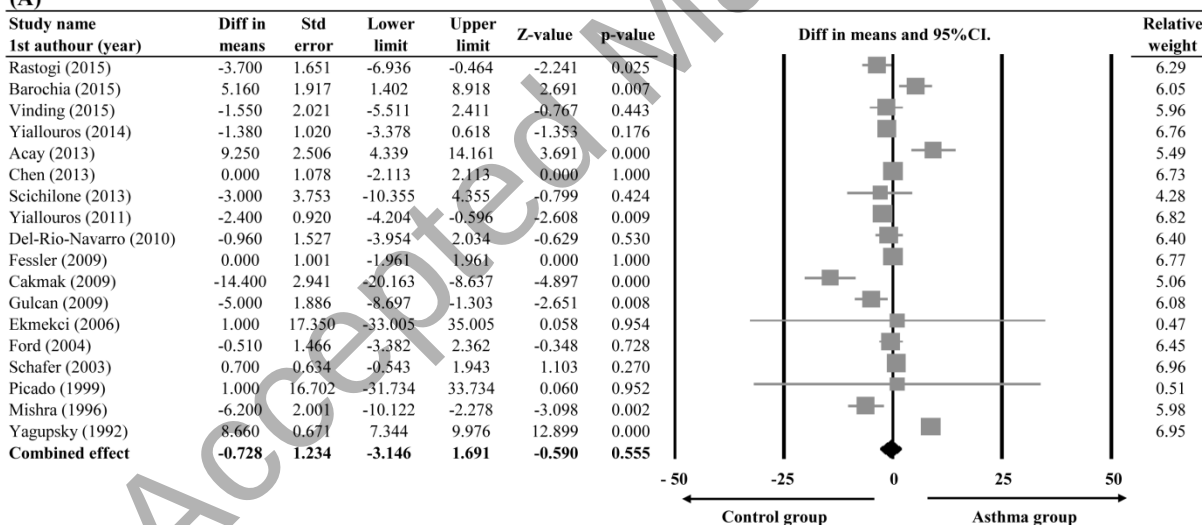
Figure 4. Funnel plot for publication bias of (A) high-density lipoproteins (HDL), (B) low-density lipoproteins (LDL), (C) total cholesterol, and (D) triglycerides. The Egger's test was shown as (A) $t=1.55$, 1-tailed $P=0.070$; (B) $t=3.06$, 1-tailed $P=0.004$; (C) $t=0.85$, 1-tailed $P=0.205$, and (D) $t=0.31$, 1-tailed $P=0.380$.

Figure 5. Quality Assessment

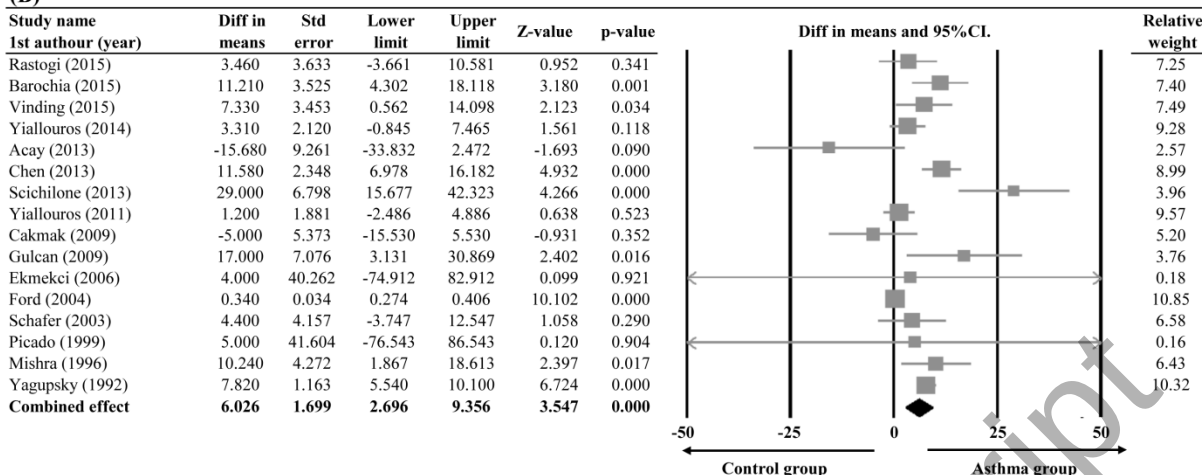
Figure 1



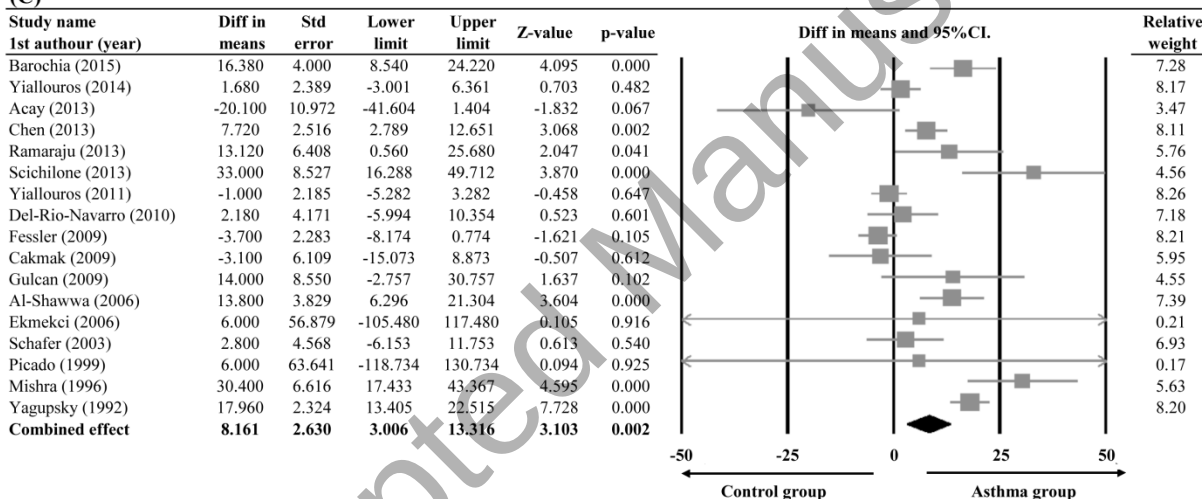
(A)



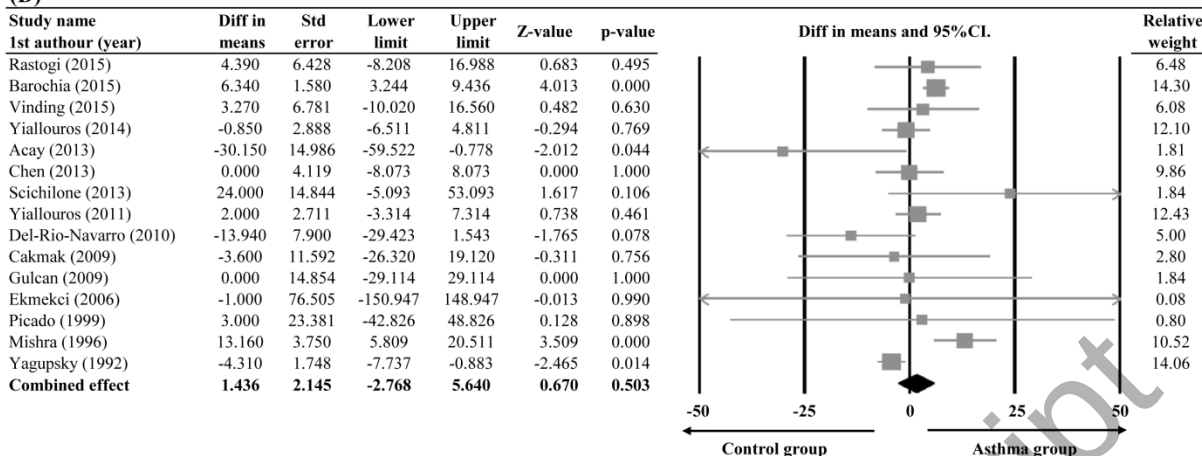
(B)



(C)

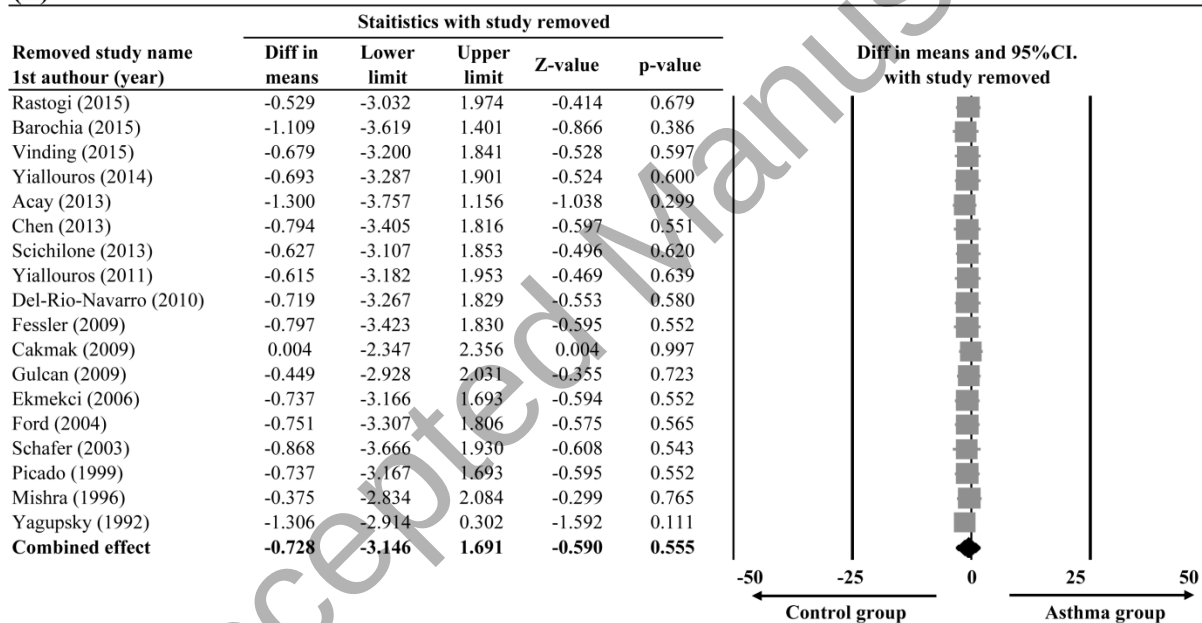


(D)

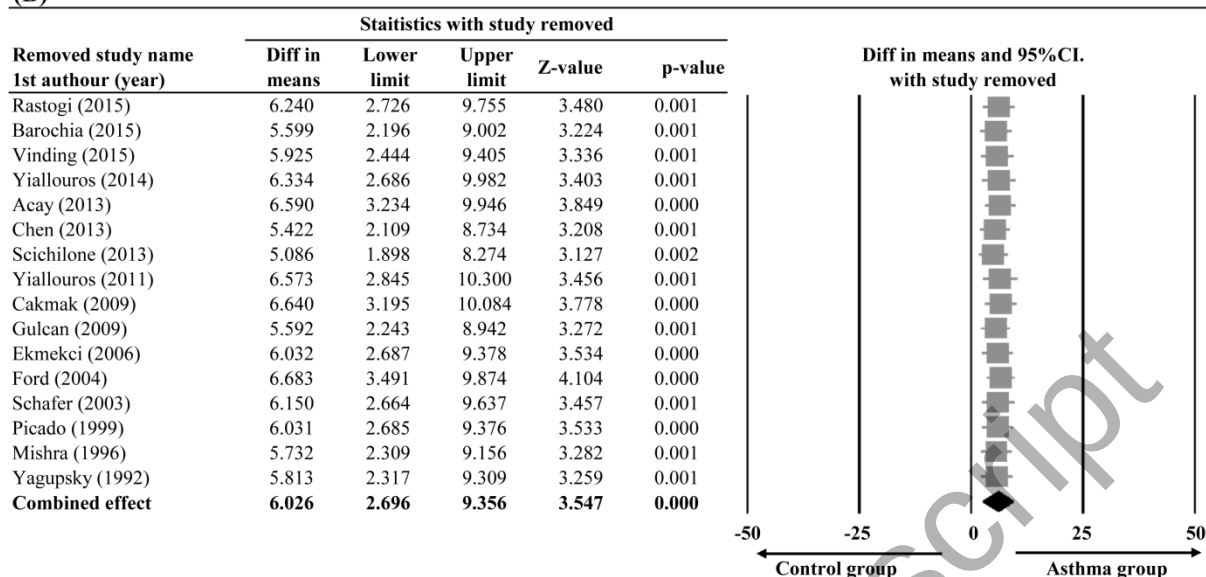


Heterogeneity test: Q-value=41.88, df=14 p-value<.001, I-squared value=66.57%

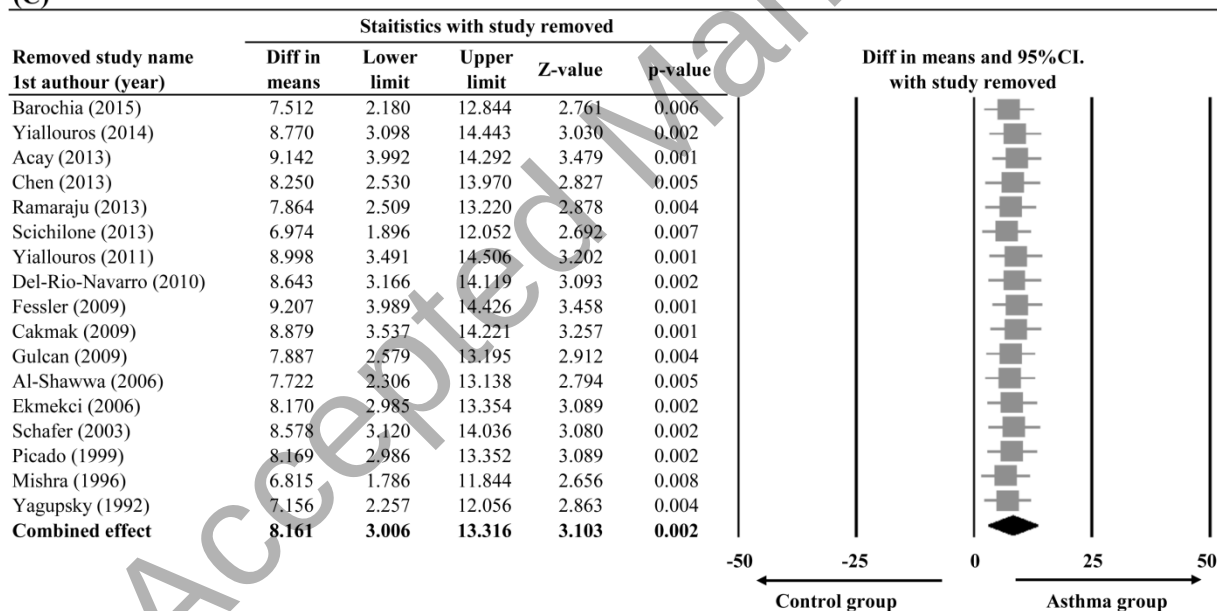
(A)



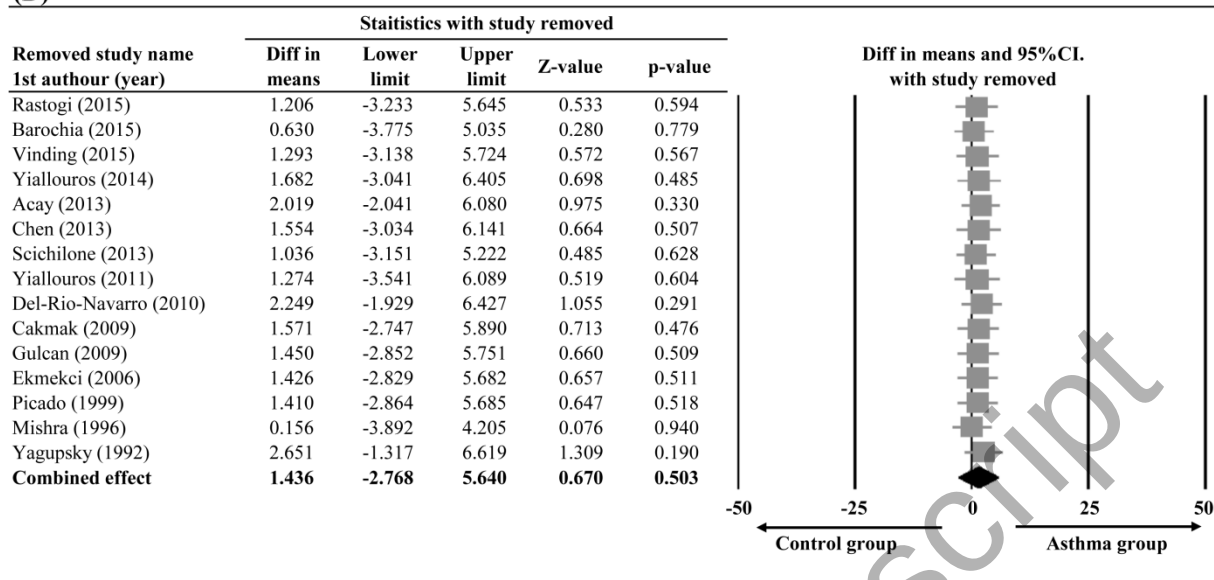
(B)



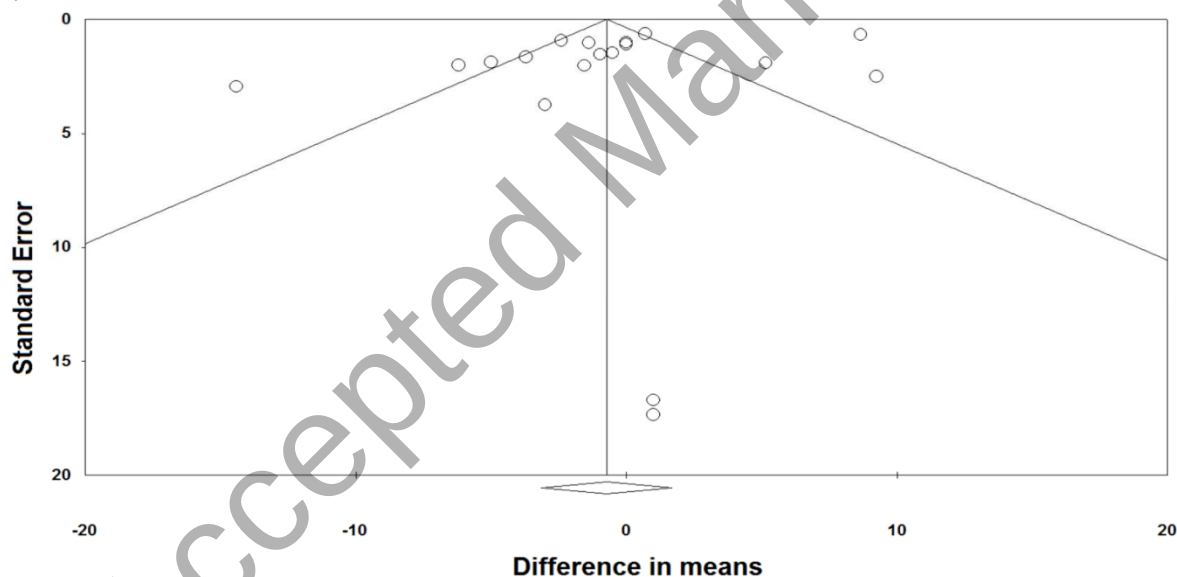
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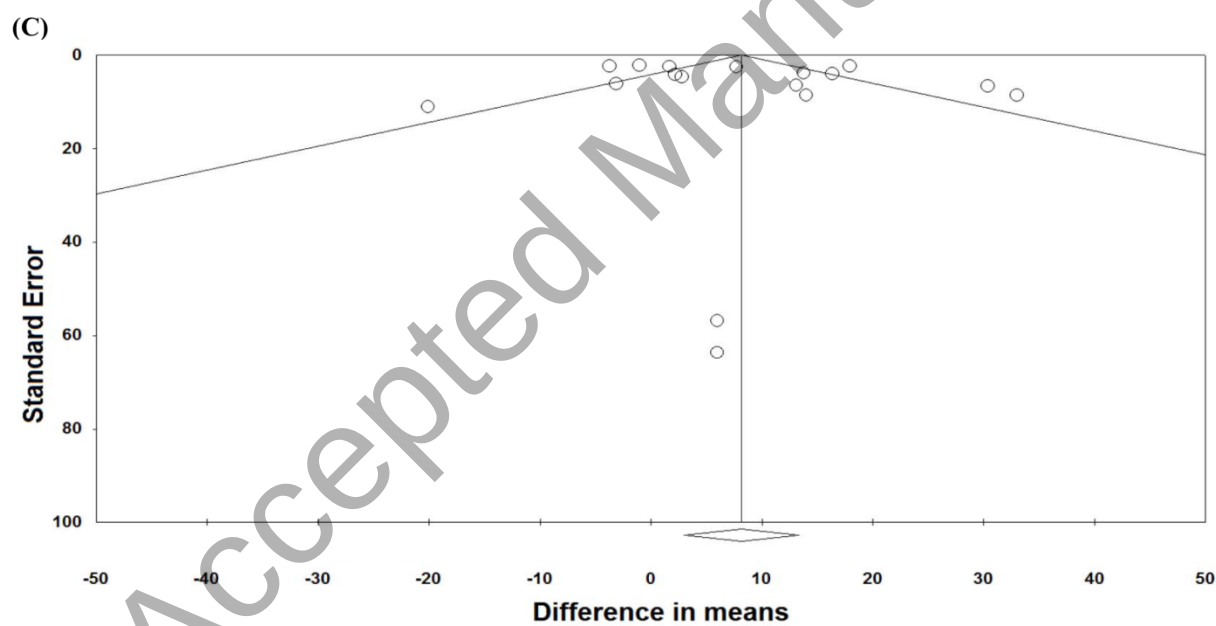
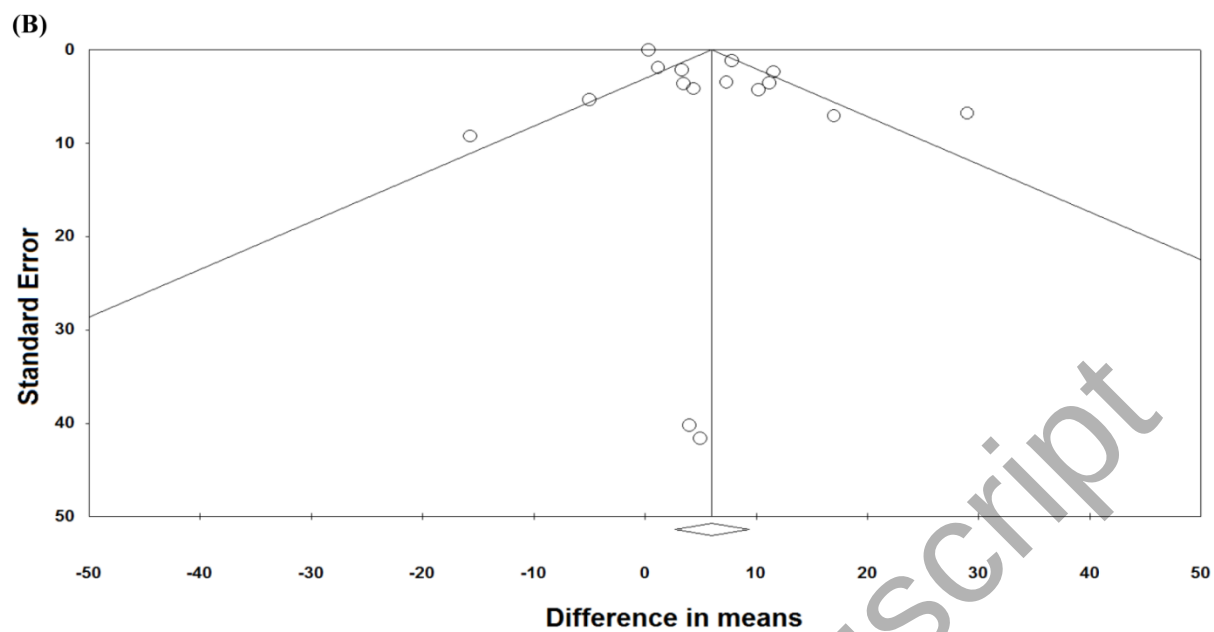


(D)



(A)





(D)

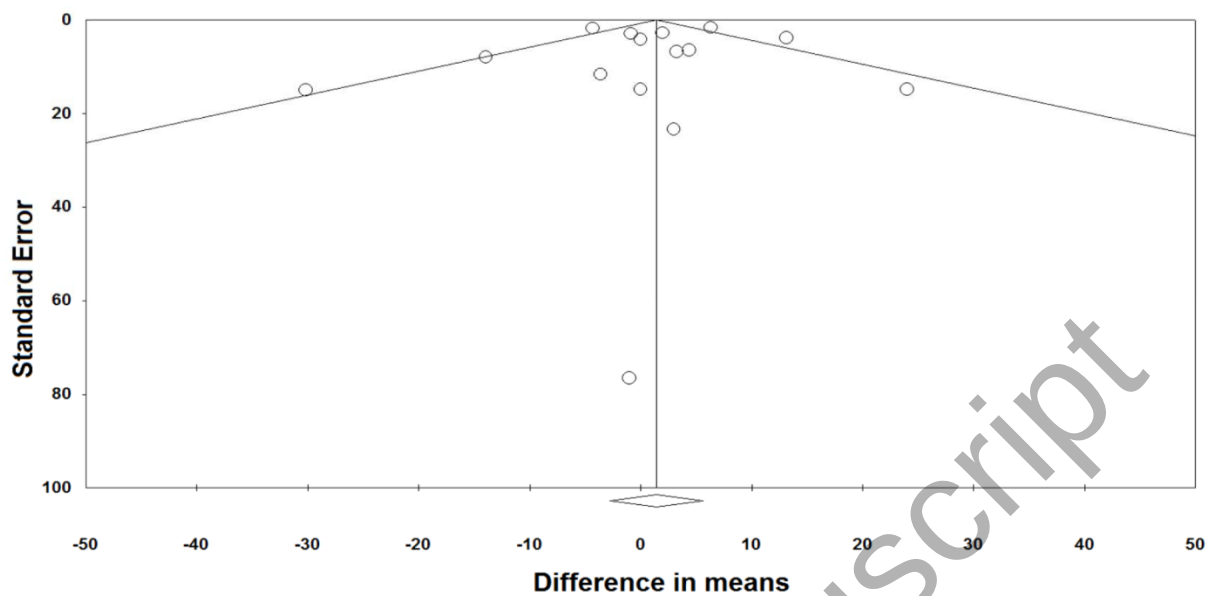


Figure 5

