



Meta-analysis of the association between asthma and serum levels of high-density lipoprotein cholesterol and low-density lipoprotein cholesterol

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ABSTRACT

Background: The reported associations of blood lipid profiles with asthma are ambiguous.

Objective: To explore the association between asthma and the serum levels of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C).

Methods: A systematic search was performed in the PubMed, MEDLINE, Cochrane Library, and Chinese Biomedical Literature databases.

Study Selection: Ten studies were identified. We divided these studies into 2 subgroups according to age: children (<18 years old) and adults (≥18 years old).

Results: In children, the asthma group had lower HDL-C levels (weighted mean difference, −3.44; 95% confidence interval [CI], −5.83 to −1.04; $P = .005$) compared with the nonasthma group, whereas the serum levels of LDL-C in these 2 groups were not statistically different. In contrast, in adults, the asthma group had higher LDL-C levels (weighted mean difference, 8.95; 95% confidence interval, 3.55–14.35; $P = .001$) compared with the nonasthma group, whereas the HDL-C levels were not statistically different.

Conclusion: There is a significant association between asthma and the serum levels of HDL-C and LDL-C. Moreover, this association differs in children and adults.

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Introduction

An association between asthma and obesity has been documented in children and adults.^{1,2} An alternate-day calorie restriction diet has been reported to improve asthma symptoms by decreasing levels of serum cholesterol and triglycerides.³ Therefore, to investigate the lipid profile in individuals with asthma may be important for asthma control treatment. However, the reported associations of asthma with blood lipid profiles have been reported as positive, negative, or no association.^{4–15} To explore the association between asthma and the serum levels of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), we undertook this systemic review.

Methods

Search Strategy and Inclusion Criteria

We searched the PubMed, MEDLINE, Cochrane Library, and Chinese Biomedical Literature online databases, using the strategy *HDL-C OR LDL-C OR lipoprotein AND asthma* and all the text words and subject heading keywords. There was no limit for the year of publication. Furthermore, we reviewed the references of the included studies to identify additional resources. Abstracts were screened independently by 2 authors (J.P. and Y.H.) based on the following inclusion criteria: (1) there should be at least 2 groups (asthma group and nonasthma group) and (2) the study should report the mean serum levels of HDL-C or/and LDL-C of these 2 groups.

Data Extraction

The following study characteristics were extracted: authors, study design, location, sample size, age range, asthma definition, and control groups. Our outcomes were the mean difference of the HDL-C and LDL-C levels between the asthma and nonasthma groups. Any disagreement was solved with the help of a third reviewer (Yan Zhao, MD), when necessary.

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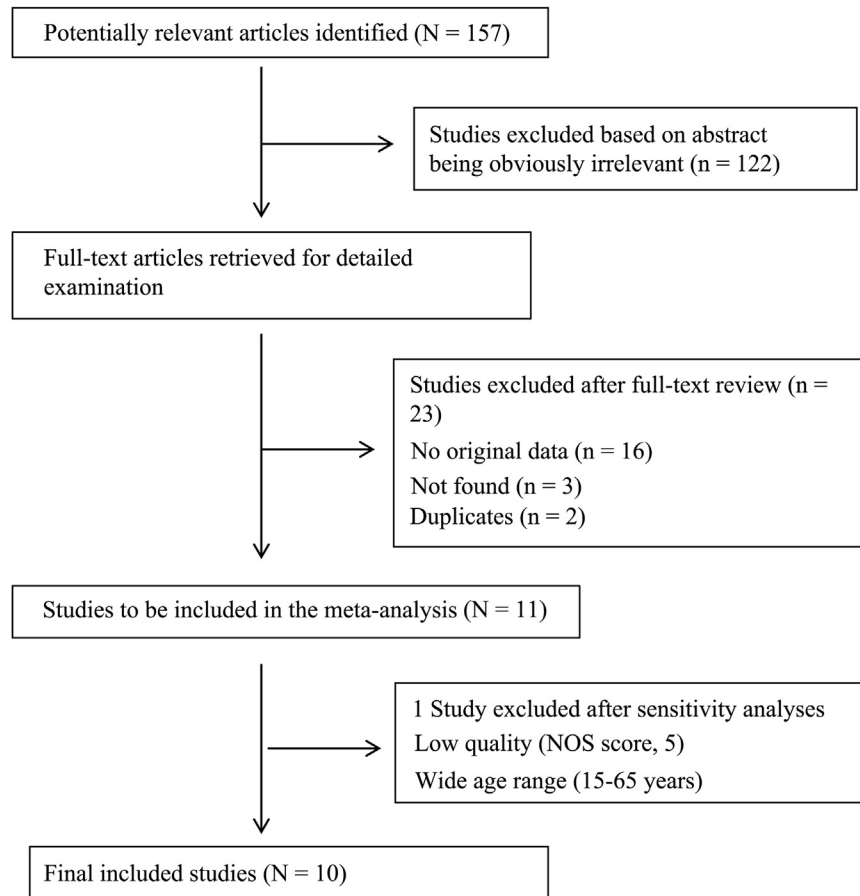


Figure 1. Flowchart of selection of studies included in the meta-analysis. NOS indicates Newcastle-Ottawa Quality Assessment Scale.

Assessment of Study Quality

We use the Newcastle-Ottawa Quality Assessment Scale (NOS) to assess the methodologic quality of the studies. The NOS consisted of 8 questions with a maximum point of nine. A total score of 6 or greater was used to indicate high-quality studies, and a total score of 5 or less indicated low-quality studies.

Statistical Analyses

The statistical analyses were performed with Review Manager version 5.3 (Cochrane Collaboration, Baltimore, Maryland). Heterogeneity among the studies was assessed with the χ^2 test and I^2 and was considered significant when $P < .05$ for the χ^2 test or I^2 was greater than 50%. The weighted mean difference (WMD)

Table 1
Characteristics of the Included Studies

Study	Study design	Population	Sample size (experimental/control)	Age range or mean (SD), y	Experimental group	Control group	NOS score
Vinding et al ⁴	Prospective cohort	Swiss	43/253	5–7	Pure asthma or comorbid allergic rhinitis	Healthy controls or allergic rhinitis	6
Yiallourous et al ⁵	Prospective cohort	Cyprus	61/783	11–1 and 16–17	Active asthma ^a	Healthy controls or current wheezing ^b	9
Chen et al ⁶	Case-control	China	237/225	10–15	Asthma	Healthy controls	6
Yiallourous et al ⁷	Case-control	Cyprus	440/3542	11–12	Asthma	Healthy controls or current wheezing or night time cough	6
Cakmak et al ⁸	Case-control	Turkey	42/32	6–16	Asthma	Healthy controls	8
Acay et al ⁹	Case-control	Turkey	40/40	15–65	Pure asthma or comorbid COPD	Healthy controls or pure COPD	5
Gulcan et al ¹⁰	Case-control	Turkey	51/40	40.3 (7.8)	Asthma	Healthy controls	6
Ekmekci et al ¹¹	Case-control	Turkey	30/28	36 (1)	Pure asthma or comorbid atopy	Healthy controls	6
Ford et al ¹²	Case-control	United States	1047/14532	>20	Asthma	Healthy controls	6
Picado et al ¹³	Case-control	Spain	118/121	28–78	Asthma	Healthy controls	8
Mishra and Pandey ¹⁴	Case-control	Not mentioned	30/30	35–47	Asthma	Healthy controls	8

Abbreviations: COPD, chronic obstructive pulmonary disease; NOS, Newcastle-Ottawa Quality Assessment Scale.

^aWheezing in the past 12 months and with a diagnosis of asthma.

^bWheezing in the past 12 months but without the diagnosis of asthma.

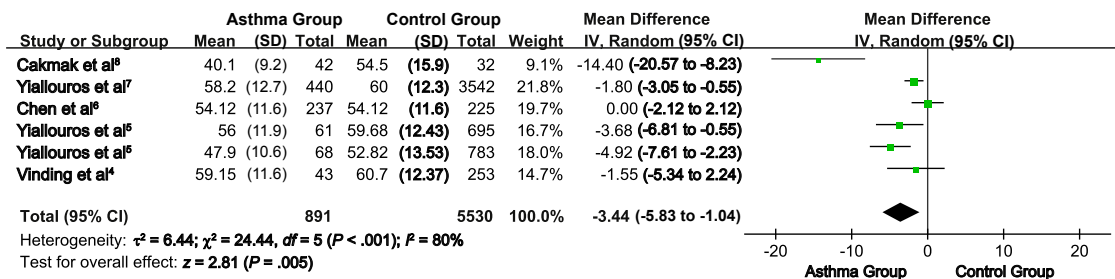


Figure 2. Serum levels of high-density lipoprotein cholesterol in children.

was calculated for continuous variables using the fixed-effect model or the random-effects model, as appropriate.

Subgroup Analyses

Subgroup analyses were performed according to age group (<18 vs ≥ 18 years). If in a study all the participants were younger than 18 years, the study was included in the children subgroup. If all the participants were 18 years or older, the study was included in the adult subgroup. If some participants were younger than 18 years and others were 18 years or older, we excluded the study.

Results

Study Selection

Twelve eligible studies were identified. Study selection is summarized in Figure 1. A total of 35 studies were selected and retrieved for a full review; 1 study was excluded because its control group included the participants who ever had asthma, 2 duplicate studies were excluded, 3 studies were excluded because we could not get the full text, 23 studies were excluded because no original data were available for the serum levels of HDL-C and LDL-C. After sensitivity analysis, we excluded 1 study because of the markedly reduced heterogeneity and the low-quality (NOS score, 5) and wide age range (15–65 years). Finally, we selected 10 studies for the meta-analysis.

Study Characteristics

The characteristics of the included studies are summarized in Table 1. There were 2 cohort studies and 11 case-control studies published between 1996 and 2016 (Table 1). The included studies had been performed in the United States, China, Swiss, Cyprus, Turkey, and Spain. Eleven studies reported the serum levels of HDL-C, whereas only 10 studies reported the serum levels of LDL-C. The NOS quality scores of the studies ranged from 5 to 9, with a median of 6.7.

Serum Levels of HDL-C With Asthma

In children, the asthma group had significantly lower HDL-C levels (WMD, -3.44 ; 95% CI, -5.83 to -1.04 ; $P = .005$) compared

with the nonasthma group (Fig 2). In adults, the serum levels of HDL-C were not different between the 2 groups (WMD, -2.01 ; 95% CI, -4.73 to 0.71 ; $P = .15$) (Fig 3).

Serum Levels of LDL-C With Asthma

In children, no significant differences were found in the LDL-C levels of the 2 groups (WMD, 0.71 ; 95% CI, -5.46 to 6.88 ; $P = .82$) (Fig 4). However, in adults, the asthma group has significantly higher LDL-C levels (WMD, 8.95 ; 95% CI, 3.55 – 14.35 ; $P = .001$) compared with the control group (Fig 5).

Discussion

In this study, we compared the serum levels of HDL-C or LDL-C between the asthma and nonasthma groups. On the basis of 10 cohort studies, this meta-analysis indicates that there is an association between asthma with the serum levels of HDL-C and LDL-C, and this association differs in children and adults. Children with asthma tend to have lower serum levels of HDL-C, whereas adults with asthma tend to have higher serum levels of LDL-C.

To our knowledge, the heterogeneity may come from sex, race, lifestyle, body mass index (BMI), smoking, and the definition bias of the asthma and control groups because the serum cholesterol level may be influenced by sex, lifestyle, BMI, and smoking.¹⁶ However, 3 studies found that the significant associations between blood lipid profile and asthma were independent of BMI.^{4,5,17} In addition, one study reported that this association is independent of age, sex, BMI, socioeconomic status, and serum high-sensitivity C-reactive protein.¹⁷ Through the sensitivity analysis, we found only one study with positive results. Further exclusion of any single study failed to appreciably alter the association. Publication bias was evaluated visually by funnel plots (Fig 6), which is mildly asymmetric. For children, the funnel plot is nearly symmetric, whereas for adults, the funnel plot is still mildly asymmetric, which may suggest that there is a publication bias in the adult subgroup because the funnel plot has low power when testing the publication bias for fewer than 10 studies.

In further investigations, some researchers studied the association among different states or severities of asthma^{11–13} with

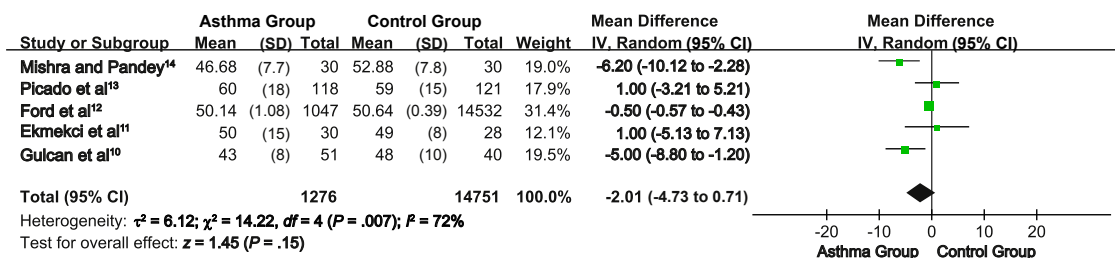


Figure 3. Serum levels of high-density lipoprotein cholesterol in adults.

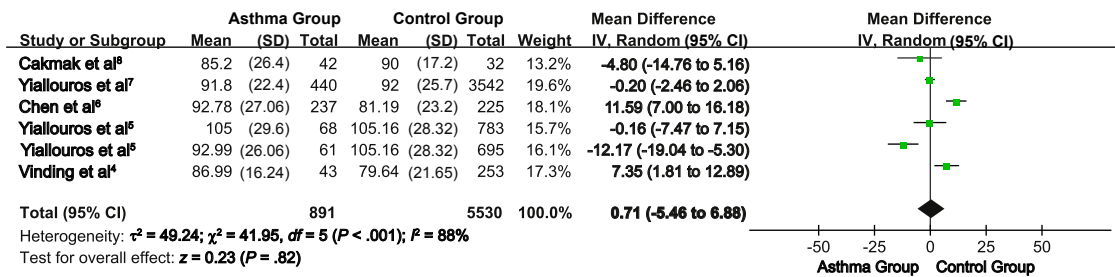


Figure 4. Serum levels of high-density lipoprotein cholesterol in children.

the HDL-C levels and some simultaneously considered different categories of HDL-C (categorized by the numerical levels of HDL) and different states or severities of asthma.^{5,7} They found the risk for asthma appeared particularly pronounced among those with the lowest levels of HDL-C (<40 mg/dL),^{4,5} whereas the serum levels of HDL-C or LDL-C do not differ among different states or severities of asthma.^{5,7,11–13} In the future, more studies are needed to confirm these findings and to investigate whether the different categories of LDL-C (categorized by the numerical levels of LDL) influence the prevalence of asthma. Apart from this, one study investigated the association of blood lipid levels, lung function, bronchial responsiveness, and fraction of exhaled nitric oxide (FeNO) measurements. In addition, this study found that high LDL-C levels were associated with airway obstruction, whereas high HDL-C levels were negatively associated with FeNO values.⁴ This finding helps explain the mechanism of how lipoproteins take part in the pathogenesis of asthma. Interestingly, in a study of 462 Chinese children, investigators found that asthma was associated with higher LDL-C levels other than lower HDL-C levels.⁶ Similar findings were reported in a study of Japanese schoolchildren in which the associations of total cholesterol, LDL-C, and atopy were investigated.¹⁸ Fessler et al¹⁹ also discovered that increases in total cholesterol and non-HDL-C increased the risk of atopy, but this association was race specific. This finding indicates that maybe human race or diet style has an effect on the association of asthma and serum lipid profiles. In addition, a pronounced sex difference in the associations between asthma and lipid profiles and in the joint effect of obesity and asthma on hyperlipidemia was identified in the study of Chen et al.⁶ Different dietary patterns among males and females or the effect of steroid hormones might explain the sex difference.⁶

As for the mechanism of the association of dyslipidemia and asthma, several reports and a recent review suggest that inflammation of the lung is influenced by lipoproteins and/or defects in lipoprotein metabolism.²⁰ Animal studies have found that high levels of cholesterol promote inflammation, but this mechanism has not been established in human subjects.²¹ In

addition, the hypercholesterolemia induces a shift toward an immunologic T_H2 -oriented response and then enhances pulmonary allergic inflammation, which has been found in mice.²² Another possible explanation for the link between asthma and HDL-C is that they share a common genetic influence between low HDL-C and allergic sensitization according to a report in 1,187 Chinese twins. Lower HDL-C and higher LDL-C levels were associated with greater risk of allergic sensitization.²³ In accordance with this, our former study found that obesity can increase the sensitivity to methacholine in children with asthma.²⁴ However, why the factors associated with asthma are different in children and adults is still unclear. Only 2 reports from the Third National Health and Nutrition Examination Survey found high serum HDL-C levels to be associated with higher lung function (forced expiratory volume in 1 second) and reduced risk for allergic sensitization in children but not in adults.^{25,26} In addition, they discovered that the role of low HDL-C in the development of asthma may be important in children but not in adults or elderly people. This finding suggests that age is a factor that could interact with the lipid-asthma association and may explain discrepancies in findings among studies.²⁶

However, this research has some limitations. Because of the limited studies we included, no studies considered the phenotypes of asthma, which is the increasing focus in the literature. We cannot further investigate the association between the lipid profile and the different asthma phenotypes, which require us to performed further studies. In addition, from the funnel plot, we can see that there is a slight publication bias.

In conclusion, through this meta-analysis, we found that the serum levels of HDL-C and LDL-C have an association with asthma, and this association differs between children and adults. This finding suggests a potential role of these lipoproteins in the pathogenesis of asthma and may help to partly explain the positive association between obesity and asthma. As for the possible mechanism, some research indicates that the blood lipid profile can influence the lung function, inflammation of the lung, and the allergic sensitization. Furthermore, our findings can guide us in planning asthma control treatment.

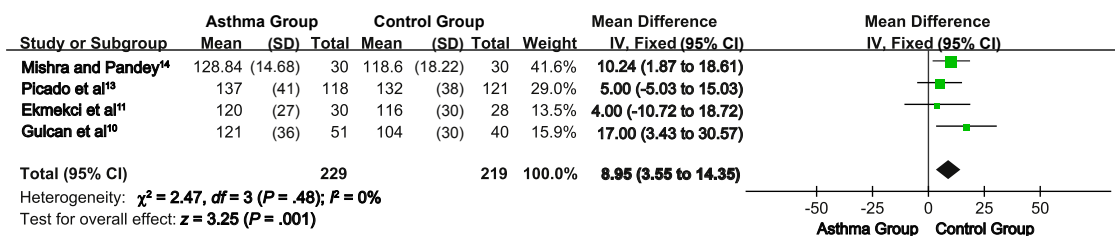


Figure 5. Serum levels of high-density lipoprotein cholesterol in adults.

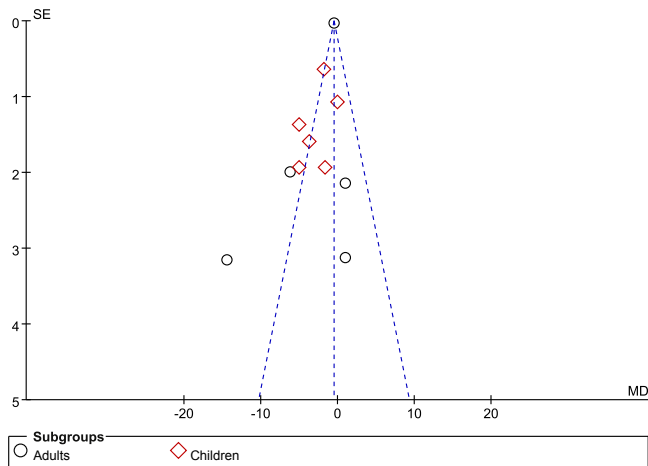


Figure 6. Funnel plot. The vertical line indicates the summary effect estimate from the random-effects model and the corresponding pseudo 95% confidence intervals converging as a function of the SE of the effect estimate. The smaller studies with large SEs were scattered around the summary effect estimates. Overall, the funnel plot is slightly asymmetric. However, for children, the funnel plot is nearly symmetric, whereas for adults, the funnel plot is still mildly asymmetric, which may suggest there is a publication bias in adult because the funnel plot has low power when testing the publication bias for fewer than 10 studies.

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