

Association between Allergies and Hypercholesterolemia: A Systematic Review

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Keywords

Adults · Atopy · Atopic diseases · Atopic predisposition · Immunoglobulin E · Children · Hypercholesterolemia · Lipid metabolism · Allergy · Systematic review

Abstract

Background: There is controversy in the literature regarding the potential relationship between atopic predisposition (AP) and serum cholesterol levels. To this purpose, we reviewed human studies that investigated this possible link.

Methods: Following PRISMA guidelines, a literature search of PubMed and Science Direct for peer-reviewed journal articles in English from January 2003, with updates through to August 2016, was conducted. Relevant publications were reviewed that included pediatric and adult populations. Information on the study design, sample, intervention, comparators, outcome, time frame, and risk of bias were abstracted for each article. **Results:** Of 601 reviewed reports, 18 were included in this systematic review. Fifteen studies assessed the relationship between AP and serum cholesterol levels. Due to the lack both of observational and cross-sectional studies from the literature search at this time (only 8 studies also analyzed confounding factors) there is a high possibility of confounding variables (familial and genetic predisposi-

tion, age, gender, BMI, comorbidity, and medication status) that could not be ruled out. **Conclusion:** Existing studies are heterogeneous, making it difficult to draw broad conclusions. Future studies and more detailed analyses, considering confounding variables and including a larger and homogeneous population, are needed to strengthen the argument for a link between lipid metabolism and atopy.

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Introduction

Atopy is an individual or familial tendency to produce immunoglobulin (Ig)E antibodies in response to low doses of allergens, and to develop allergic diseases including atopic eczema (AE), allergic rhinitis (AR), and asthma, considered the most common chronic diseases in the world [1]. Although extensive experimental and human studies have been performed to identify the immunological cause of atopy, its etiology remains obscure [2–6].

Dyslipidemia, a pathological condition characterized by elevated levels of serum total cholesterol (TC), triglyc-

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eride (TG), low-density lipoprotein cholesterol (LDL), and/or a low level of serum high-density lipoprotein (HDL) [7], has been widely investigated in the context of cardiovascular diseases, but its role in atopic predisposition (AP) as well as in related diseases (AE, AR, and asthma) has only recently been considered.

The evidence for the presence of the links between allergy and cardiovascular/metabolic diseases was described by Potaczek [8], who reported the influence of allergic inflammation on the development of atherosclerosis, through the role of basophils and mast cells in the regulation of lipid metabolism. Therefore, it has been suggested that blood lipid levels could constitute predictors of atopic status and allergic diseases.

Changes in lipid metabolism, impacting on the immune system, may act through several pathways promoting atopic inflammation, allergen predisposition, and, consequently, the onset of atopic diseases [9, 10]. Reports have assessed the reciprocal cross-talk between cholesterol and adaptive immune programming. Both, in fact, share the same immunological pathways including a T helper (Th)1-to-Th2 switch, an increased Th2-type antibody release (IgG1 and IgE) and, the elevated release of proinflammatory Th2-profile cytokines (e.g., interleukin 4, IL-4) [9, 11]. In particular, lipid metabolism has been shown to skew T cell programming, promoting Th2 and Th17 polarization, Th2 and Th17 cytokine profile release (IL-6, IL-1, IL-4, and IL-17) [12, 13] and also the down-regulation of IL-10 synthesis [14]. All these data show how the cytokine dysregulation related to chronic inflammation features both dyslipidemia and AP. In line with these findings, recently, in a pediatric population showing AP, we reported that IgE levels correlated with serum cholesterol levels: positively with TC, LDL, and triglyceride, but negatively with HDL. In addition, we reported that serum IL-10 levels were lower in children affected by dyslipidemia and AP than in children exclusively showing dyslipidemia. Moreover, serum IL-17 and IL-23 levels were significantly higher in children affected both by dyslipidemia and AP than in those with dyslipidemia only. The study demonstrated that severe dyslipidemia, influencing immune response, and sustaining the switch initially from a Th1 to a Th2 response, and successively from cytokine profile Th2 to Th1, could be also responsible for the impaired and exaggerated responses to an exogenous soluble protein antigen [10].

Given the ability of lipoproteins to cross-talk with the immune system [11], higher blood counts of T lymphocyte CD3, CD4, and CD8 subsets have, in fact, been detected in patients showing increased serum levels of LDL

cholesterol (LDL-C) [15], which, oxidized to oxidized (ox)LDL, interacts directly with proinflammatory signal pathways and monocytes/macrophages, which, in turn, “present” the epitopes of oxLDL to T cells, favoring a Th2 skewing [16, 17]. Also, experimental studies reported that granules exocytosed upon the IgE-dependent activation of mast cells bind LDL particles and transport them to macrophages, contributing to the formation of the so-called “foam cells,” a crucial step in the development of atheromatous lesions [18, 19].

Moreover, in order to better investigate the link between lipids and immune cells in the circulation, authors [20], by generating both genomic and whole-blood gene expression profiles, have shown that mediators of inflammation (basophil granulocytes and mast cells) and allergy (IgE) correlate with lipid levels, advancing the hypothesis that the inflammation, allergy and lipid profiles could be functional parts of the same network.

Furthermore, through specific receptors, circulating lipoproteins (LDL and HDL) are taken up by the lung [21] where, granted the synthesis of cholesterol by lung-resident cells [22], they positively influence alveologenesis [23], attenuate airway inflammation and resistance [24], serve as a principal source of the antioxidant vitamin E for alveolar epithelial type II cells [25], promote surfactant synthesis [26], and, finally, support the growth of lung fibroblasts [27]. Nevertheless, an excessive amount of cholesterol impairs alveolar homeostasis, and consequently pulmonary function [28].

Therefore, in the light of these experimental data, the serum cholesterol level and atopy link appears also clinically robust and consistent especially with regard to 2 different atopy outcomes: a biochemical measure of sensitization (serum IgE total levels), and a clinical measure of current atopic disease. However, while several literature findings suggest the role of the lipid profile in the development of atopy [9], other reports differ on the direction of the abovementioned relationship [29–33]. Therefore, in the light of contrasting research strategy findings, through the revision of literature data, this systematic review aims to analyze the latest data and advances on the relationship between the onset of AP and related diseases and serum cholesterol levels.

Methods

Search Strategy and Selection Criteria

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [34] employing 2 databases: PubMed

and Science Direct. On these websites, we searched for articles in the English language, from 1 January 2003 to August 2016, using key terms related to atopic diseases: “atopy,” “allergy,” “atopic sensitization,” “asthma,” “allergic rhinitis,” and “atopic dermatitis,” and 2 key terms related to hypercholesterolemia: “cholesterol” and “hypercholesterolemia.” The electronic search strategy applied for PubMed and Science Direct are reported in Table 1a and b, respectively.

As a rule of thumb, we decided to use the abstracts of articles whose titles indicated they might have examined the association between hypercholesterolemia and atopic diseases. The entire article was read if the abstract indicated that the article potentially met the inclusion criteria. In order to identify additional studies that met the inclusion criteria, we also reviewed the references of the selected articles, and read those whose titles suggested that they could have researched the association between hypercholesterolemia and atopic diseases.

Study Selection

Articles were included in this review according to the following inclusion criteria: English language, publication in peer reviewed journals, and year of publication not before 2003. Articles were excluded by title, abstract, or full text for irrelevance to the investigated issue. Further exclusion criteria were if they were experimental studies, clinical case, clinical series, review articles and, editorial comments.

Data Extraction and Quality Assessment

Data were independently extracted by 2 reviewers (S.M. and G.D.A) according to the Cochrane guidelines [34], and a third reviewer (C.C.) checked the extracted data for accuracy. Another author (L.M.) was available when there was disagreement concerning data extraction and/or quality assessment. Abstracts and potential manuscripts were reviewed and identified for retrieval according to the inclusion criteria. The following information was extracted: study author names; study design (i.e., case-control, cross-sectional, and longitudinal), characteristics of patients (age, weight, and sex), clinical and biological variables, and study outcomes of interest. The principal outcome of interest was the potential link between hypercholesterolemia and atopic diseases. Given the considerable heterogeneity of the study designs and the subjects of the selected studies, the characteristics of the investigated populations and protocols are summarized and study outcome is reported using descriptive statistics without conducting any meta-analyses.

Results

The retrieved articles for the systematic review are reported in Figure 1. Studies evaluating the relationship between hypercholesterolemia and atopic diseases are summarized in Table 2.

As mentioned in Methods, we decided to include only human research studies since 2003, in order to provide a complete and specific perspective of cholesterol in the onset of atopic diseases.

Table 1. List of search terms entered into the PubMed and Science Direct search engines to identify the studies for this systematic review

Search terms	
<i>PubMed</i>	
1	English (language)
2	2003 to date (publication date)
3	atopy
4	allergy
5	atopic sensitization
6	asthma
7	allergic rhinitis
8	atopic dermatitis
9	cholesterol (all fields)
10	hypercholesterolemia
<i>Science Direct</i>	
1	health science (medicine and dentistry) (filter by field)
2	2003 to present (publication date)
3	journal, books, reference works
4	abstract, title, key words
5	atopy
6	allergy
7	atopic sensitization
8	asthma
9	allergic rhinitis
10	atopic dermatitis
11	cholesterol
12	hypercholesterolemia

According to Table 2, Schäfer et al. [30], performing a case-control study within the adult population of the 3rd MONICA survey in Augsburg (Germany), noted a negative linear association between TC and LDL levels and the frequency of atopic sensitization and AR incidence. Conversely, a positive linear association was detected between HDL levels and allergic sensitization, AR, and AE.

Although older research data have been reported [35, 36], we could consider this study as a “milestone” in the investigating research on the atopy/cholesterol relationship, leading to more studies on this possible association [30]. What emerged from the following literature data revision was a great interest regarding the potential link between serum cholesterol levels and atopic sensitization as well as asthma incidence, and a paucity of data and/or not robust scientific evidence on lipid metabolism, AR, and AE. Nagel et al. [37], in a population-based, cross-sectional study on 10-year-old schoolchildren (*n* = 462), measured serum ApoA1 and ApoB levels. They also collected information on atopic disease symptoms and diag-

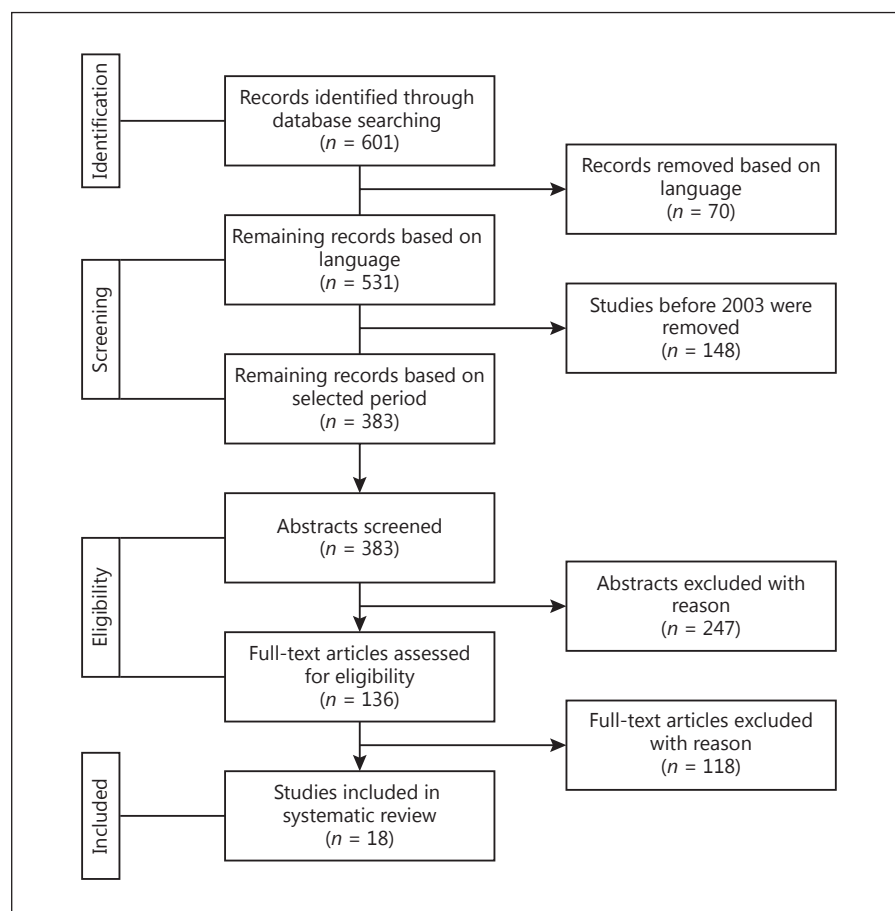


Fig. 1. Flowchart of results of literature search.

noses. Using multivariate logistic regression models, they reported that while plasma ApoB concentrations were not associated with symptoms of either asthma or allergy, serum ApoA1 levels significantly correlated with a high prevalence of atopic or nonatopic wheeze and asthma. In a recent but smaller study, Barochia et al. [38] assessed the abovementioned findings. They enrolled 154 atopic and not atopic adult subjects without asthma, and 159 subjects with atopy and asthma. Serum lipoprotein levels and airflow obstruction were assessed using standard diagnostic assays, and nuclear magnetic resonance and spirometry, respectively. They reported that HDL cholesterol (HDL-C) and ApoA1 were positively correlated with forced expiratory volume in the 1st second (FEV₁%) in subjects with atopy and asthma, but there was a negative correlation between FEV₁% and serum levels of TG, LDL-C, ApoB, and the ApoB/ApoA1 ratio [38]. Previously, in 24 asthmatic patients, Scichilone et al. [39] detected serum LDL subclass levels and a severe degree of airflow obstruction (FEV₁%) and vital capacity (VC%). Although

LDL-1 and LDL-3 levels were similar in the asthmatic and control groups, both were positively associated with predicted VC% and FEV₁%. However, the data coming from their study were affected by the fact that the results were based on a small study sample.

In the same period, Bahreinian et al. [40] performed a prospective evaluation of 352 children recruited at 7–10 years of age in the nested case-control arm of the Study of Asthma, Genes, and Environment, with follow-up until 11–14 years of age. In order to obtain a clearer and more complete elucidation of the possible link between cholesterol levels and atopic disease onset, these authors assumed an allostatic load (AL) value obtained through the measurement of 8 biomarkers (fasting glucose, TC, HDL, dehydroepiandrosterone sulfate, cortisol, systolic and diastolic blood pressure, and waist-to-hip ratio) as a specific marker of the physiologically dysregulated response of the body to stress. They noted that the incidence or onset of asthma increased in adolescents showing higher allostatic load values.

Table 2. Studies evaluating the relationship between atopic predisposition and related diseases and hypercholesterolemia

First author year [ref.]	Number of patients	Children	Adults	Atopic disease and related adopted instrumental parameters	Lipid-related lab and instrumental parameters	Results	Correlation
Schäfer 2003 [30]	1,537		yes	asthma: lung parameters AR AE: SCORAD	TC LDL HDL	1. Negative linear association between TC and LDL-C levels and the frequency of AR and sensitization 2. Positive linear associations between HDL-C levels and AR and AE, and between the intake of PUFA and allergic sensitization 3. Increased risk for atopic diseases with increasing levels of HDL-C and an increasing risk for allergic sensitization with increasing intakes of PUFA	significant
Al-Shawwa 2006 [43]	188	yes		asthma: lung parameters	TC	1. Asthmatic patients reported an increased risk of obesity, higher serum TC levels 2. Hypercholesterolemia was a potential risk factor for asthma independent of obesity	significant
Pesonen 2008 [29]	200	yes		AP: SPT IgE total	TC	1. Allergic subjects had lower TC levels in infancy and childhood than nonatopic subjects 2. The difference was detectable from the age of 2 months	significant
Ouyang 2009 [48]	1,187		yes	AP: SPT	HDL LDL anthropometric dual-energy X-ray absorptiometry-assessed adiposity measures	1. Men reported lower percent body fat but higher rates of allergic sensitization than women 2. In men, the risk of allergic sensitization increased with lower HDL and higher LDL levels 3. In females, lower HDL was associated with an increased risk of allergic sensitization	significant
Nagel 2009 [37]	462	yes		asthma: lung parameters AP: SPT IgE total	ApoA1 ApoB	1. High plasma ApoA1 concentrations were associated with a high prevalence of wheeze and asthma 2. Plasma ApoB concentrations were not associated with symptoms of asthma or allergy	significant
Fessler 2009 [31]	7,005	yes		asthma: lung parameters	TC non-HDL HDL	1. Serum TC and non-HDL-C were lower in patients with current asthma than in subjects without current asthma in the overall population 2. Relationships between cholesterol and asthma/wheeze were independent of BMI and serum C-reactive protein, and similar in atopic and nonatopic participants	not significant
Fessler 2010 [49]	6,854	yes		IgE total	TC non-HDL HDL	1. Marked interracial differences in the relationship between serum cholesterol and atopy in the US population have been reported	significant
Kusunoki 2011 [44]	654	yes		AP: SPT	TC HDL TG	1. A significant positive relationship between the TC and IgE levels 2. A tendency for a positive relationship between the TC and LDL levels in atopic sensitization 3. No association was observed for either the TG or HDL levels and prevalence of allergic diseases	significant
Cottrell 2011 [45]	17,994	yes		asthma: lung parameters	TC LDL HDL TG	1. Asthmatic children were more likely than children without asthma to have higher TG levels	significant
Chen 2013 [47]	237	yes		asthma: lung parameters	TC LDL	1. TC and LDL levels increased progressively in obese asthmatics compared to nonobese asthmatics, obese controls, and nonobese controls 2. In boys, LDL levels were significantly higher in obese asthmatics than in obese nonasthmatics 3. A significant interactive effect of obesity and asthma on hyperlipidemia in boys has been also detected	significant
Scichilone 2013 [39]	24		yes	asthma: FEV ₁ % VC%	LDL	1. Regarding LDL-1 levels, no difference was noted between asthmatics and controls 2. LDL-2 was significantly lower in asthmatics than in controls 3. LDL-3 levels were 2-fold higher in asthmatics, but the difference did not reach statistical significance 4. Smaller subclasses: LDL-4 to LDL-7 were undetectable in controls 5. In asthmatics, LDL-1 was positively associated with VC% and FEV ₁ % predicted 6. LDL-3 was inversely correlated with both VC% and FEV ₁ % predicted	significant

Table 2 (continued)

First author year [ref.]	Number of patients	Children	Adults	Atopic disease and related adopted instrumental parameters	Lipid-related lab and instrumental parameters	Results	Correlation
Bahreinian 2013 [40]	352	yes		asthma: lung parameters	AL	1. Prevalent asthma was four times more likely in boys with high vs. low AL 2. Similar results were observed in the analysis of new-onset asthma in boys. In girls, there were no associations between AL and asthma 3. TC, glucose, and cortisol were associated with a $\geq$ risk of asthma prevalence or onset in boys	significant
Fenger 2013 [46]	85,555		yes	asthma: lung parameters AR	HDL TG	1. Increased BMI and TG as well as low HDL were significantly associated with wheezing 2. The abovementioned associations were stronger in individuals without symptoms of rhinitis than in those with symptoms	significant
Yiallourous 2014 [41]	191	yes		asthma: lung parameters	HDL	1. HDL levels in asthma and wheezing groups were significantly lower than in the controls	significant
Skaaby 2015 [32]	20,048		yes	AP	TC	1. Atopy was not associated with serum TC or BMI, except in women	not significant
Barochia 2015 [38]	154		yes	asthma: FEV ₁ %	ApoA1 ApoB ApoB/ApoA1 ratio LDL HDL TG	1. Serum lipid levels correlated with FEV ₁ % only in the subjects with atopy and asthma 2. Serum HDL and ApoA1 levels were positively correlated with FEV ₁ % in subjects with atopy and asthma 3. A negative correlation existed between FEV ₁ % and serum TG, LDL, TC, ApoB, and ApoB/ApoA1 ratio 4. NMR spectroscopy identified a positive correlation between FEV ₁ % and HDL-NMR particle size as well as the concentrations of large HDL-NMR particles and total IDL-NMR particles in subjects with atopy and asthma 4. LDL-NMR particle size and concentrations of LDL-NMR and VLDL-NMR particles were negatively correlated with FEV ₁ % in subjects with atopy and asthma	significant
Vinding 2016 [42]	411	yes		asthma: FEV ₁ %, FEF-50, FeNO	LDL HDL TG	1. High LDL levels were associated with concurrent asthma, airway obstruction, and specific airway resistance 2. High HDL levels were associated with improved specific airway resistance, decreased bronchial responsiveness, a decreased risk of atopic sensitization, and a trend of reduced FeNO levels 3. High TG levels were associated with atopic sensitization and a trend of increased FeNO levels	significant
Fang 2016 [33]	160	yes		asthma: lung parameters	ApoA1 ApoB TC LDL HDL TG	1. There were no significant correlations between the levels of ApoA1, ApoB, TG, TC and LDL and BMI 2. HDL levels were higher in obese patients	not significant

TC, total cholesterol; LDL/HDL-C, low-density lipoprotein/high-density lipoprotein cholesterol; VLDL, very low-density lipoprotein; TG, triglyceride; AP, atopic predisposition; SPT, skin prick test; AR, allergic rhinitis; AE, atopic eczema; AL, allostatic load; NMR, nuclear magnetic resonance.

Subsequently, in a case-control design, Yiallourous et al. [41], using a logistic regression model, evaluated a possible link between serum HDL levels and asthma in active asthmatic ($n = 68$) and current wheezer ($n = 123$) populations. A significant trend of decreased serum HDL levels was detected in the asthmatic group compared to healthy controls. Although it must be underlined that this study reported a critical bias (asthma diagnosis was based exclusively on a questionnaire), this limitation did not affect the validity of the serum HDL levels at baseline and fol-

low-up. This limit was overcome in the study performed by Vinding et al. [42], who conducted research in the Copenhagen Prospective Studies on Asthma in Childhood 2000 at-risk birth cohort, and noted significant associations between lipid levels and clinical outcomes. In particular, LDL and TG levels were associated with concurrent asthma and airway obstruction, assessed by spirometric parameters and fraction of exhaled nitric oxide (FeNO) levels. On the contrary, HDL correlated with a decreased risk of aeroallergen sensitization, decreased

bronchial responsiveness, and an improvement of specific airway resistance.

From the revision of the literature data, contrasting findings, coming from only 2 research articles, are also provided here. In a cross-sectional study of 7,005 children, Fessler et al. [31] showed that serum TC and non-HDL-C levels were lower in patients with current asthma than in subjects without current asthma in the overall population, but that HDL-C was not different. Thus, although serum cholesterol levels in asthmatic patients were independent of BMI, they were also similar between atopic and non-atopic participants. Moreover, although Skaaby et al. [32] reported that atopy was associated with reversible Westernized lifestyle-related factors, they did not note a positive association between serum TC levels and AP. Recently, Fang et al. [33] enrolled 160 pediatric asthmatic patients, divided into 4 subgroups, according to their BMI. All patients also underwent lipid profile measurements including ApoA1, ApoB, TC, LDL, HDL, and TG. Authors did not report any significant differences in serum lipid profiles in the asthmatic children, and, moreover, these did not represent a risk factor for asthma.

We found that, in the research design, the authors' interest was strongly concentrated on the identification and respective influence of confounding variables (e.g., obesity, gender, and interracial differences) affecting the study outcomes [29, 43–47].

In this regard, Al-Shawwa et al. [43], in a retrospective study performed on 188 subjects 4–20 years of age, confirmed that hypercholesterolemia represented not only a potential risk factor for asthma, but also exercised effects in an independent manner for the presence of obesity. Thus, it has been hypothesized that the association between altered lipoprotein profile and atopy may be due to alterations in dietary fat intake. On the contrary, Pesonen et al. [29], in a cohort of 200 unselected newborns (hypothetically all the babies were on a similar diet, i.e., breast milk only) prospectively followed up from birth to age 20 years, reported that the inverse association between cholesterol levels in infancy and subsequent manifestations of atopy seemed to not be due to atopy-related dietary alterations, because it was already present in early infancy.

These findings were confirmed by Kusunoki et al. [44] in a general population of 11-year-old children. Here, serum TG and LDL levels were significantly positively associated with higher IgE levels and a higher rate of allergic sensitization. Moreover, because gender and BMI were included as confounding factors, the reported associations were independent of sex or obesity. To analyze the

relationship between asthma diagnosis and early derangement in lipids further, independently associated with an increased risk for obesity, Cottrell et al. [45] enrolled a total of 17,994 children, who underwent blood tests in order to identify the lipid profiles in each enrolled patient. A statistically significant association between asthma and abnormal lipid metabolism, beyond BMI association, was detected.

Subsequently, Fenger et al. [46] also tested the hypothesis that metabolic biomarkers associated with adipose tissue dysfunction, the serum TG and HDL values, could be predictive of wheezing and allergic rhinitis, independently of obesity. To explore this possible link, they used data from the Ibermutuamur Cardiovascular Risk Assessment Plan (ICARIA), including 85,555 adults with assessments of self-reported symptoms of allergic diseases. In this population, serum TG and HDL levels were also recorded. Both increased serum TG levels and decreased serum HDL levels were significantly elevated in subjects with wheezing but no rhinitis symptoms. Notably, these associations persisted after the adjustment for parameters for metabolic syndrome and confounding variables.

However, the more recent study by Chen et al. [47] did not confirm these findings. They reported that TC and LDL levels increased progressively in the group order: obese asthmatics versus nonobese asthmatics versus obese controls versus nonobese controls, especially in males.

A study on 1,187 rural Chinese twins reported a significant association between serum cholesterol levels and an AP. In particular, the risk of allergic sensitization increased with lower HDL and higher LDL levels [48], especially in females. Therefore, it has been hypothesized that contrasting reports on the association between serum cholesterol and atopy and confounding factors could be the expression of differences in race and/or other demographic variables. In this regard, Fessler et al. [49], conducted a cross-sectional study of 6,854 pediatric participants from the 2005–2006 National Health and Nutrition Examination Survey, reported in the US population (non-Hispanic Whites [NHWs] and non-Hispanic Blacks [NHBs]). The adjusted HDL-atopy relationship was not significant for NHWs and inverse for NHBs, respectively.

Discussion

Due to the contrasting research findings conducted on the potential relationship between serum cholesterol levels and atopy, this systematic review provides a quan-

titative summary of the world literature on hypercholesterolemia and atopy. Our aim was to expand the understanding of the link between impaired lipid metabolism and atopy, by quantifying the prevalence and exploring the main characteristics of this overlap. The results of the review confirmed this relationship. In particular, through the revision of literature data, a significantly elevated rate of hypercholesterolemia has been reported in subjects with AP compared to those without these high levels. Moreover, patients affected by atopic diseases, such as asthma, AR, or AE, were more likely to show increased serum cholesterol levels than those in the control groups. However, the systematic review showed that patients with hypercholesterolemia and atopy and/or atopic diseases did not share the same demographic features and patterns on a pulmonary function test. Thus, in the absence of specific clinical findings, it is not possible to delineate the traits of a unique phenotype. On the other hand, to date, it is not clear what is causing what, and the question of the chicken-or-egg paradigm remains unanswered.

Specifically, it is important to mention that some of the studies identified were observational, which favor both a major risk of bias in the selection of subjects and the observance of some outcome assessments across studies. In several of the studies included, the most common drawbacks were: a small sample size, the different data collection modalities, and the different outcome measurements used. Data were obtained from population-based, cross-sectional studies or national databases or questionnaires, so, in some cases, it was not possible to identify a neutral and common setting. Another limitation was the different age groups in the study populations. Considering this limit, in fact, it is well known that both atopic sensitization and allergic diseases are not the same in children and adult populations. It appears clear that children, presenting a different physical constitution and breathing pattern from those of adults, are more susceptible to the effects of exposure to allergens, and they also perceive disease and communicate their symptoms in a different manner from adults. On the other hand, in the light of the fact that allergy is a chronic, progressive disorder, with a changing history in the long term, an adult population reports all the effects of a prolonged disease. Moreover, comparing an enrolled population within the same set range of ages, it must also be considered that allergen exposure and the incidence of allergic diseases differ from country to country.

As suggested by the European Panel on LDL Subclasses [50], the composition and size of lipoproteins also af-

fect outcomes. However, in this systematic review, we highlighted that only 2 of the studies investigated the composition and function of subclasses of lipoprotein molecules. Both reported that the size of LDL particles leads to the amplification of the inflammatory cascade in allergic diseases. Barochia et al. [38] reported a positive correlation between FEV₁% predicted and a higher level of HDL or ApoA1 in asthma whereas Scichilone et al. [39] noted that asthma was associated with smaller LDL particles. Conversely, not all studies analyzed this parameter, leading to a lack of data needed to better characterize the precise interaction existing between hypercholesterolemia and atopy.

From the literature search, given the lack both of observational and cross-sectional studies at this time, there is a high possibility of confounding factors (familial and genetic predisposition, age, gender, BMI, comorbidity, and medication status) that could not be ruled out.

All these findings partially explain the reported contrasting data in the included studies. Not all of the studies provided an association between hypercholesterolemia and atopy; however, a nonsignificant result does not demonstrate that the relationship between impaired lipid metabolism and allergy does not exist. Therefore, the reported findings should be interpreted with caution in view of the risk of overestimating the true power of significance from a hypercholesterolemia-atopy association. Future studies and more detailed analyses, considering confounding variables and including a larger and homogeneous population, are needed to strengthen the argument for a link between lipid metabolism and atopy.

Statement of Ethics

This article does not contain any studies on human participants or animals.

Disclosure Statement

The authors declare that they have no conflict of interests.

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