

Blood lipid levels associate with childhood asthma, airway obstruction, bronchial hyperresponsiveness, and aeroallergen sensitization

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Background: Studies of children's blood lipid profiles in relation to asthma are few, and the results are ambiguous.

Objective: We sought to examine whether the lipid profile is associated with concurrent asthma, altered lung function, and allergic sensitization in children.

Methods: High-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride levels were measured at ages 5 to 7 years in the Copenhagen Prospective Studies on Asthma in Childhood₂₀₀₀ at-risk birth cohort. Asthma and allergic rhinitis were diagnosed based on predefined algorithms at age 7 years along with assessments of lung function, bronchial responsiveness, fraction of exhaled nitric oxide (FENO), and allergic sensitization. Associations between lipid levels and clinical outcomes were adjusted for sex, passive smoking, and body mass index.

Results: High levels of low-density lipoprotein cholesterol were associated with concurrent asthma (adjusted odds ratio [aOR], 1.93; 95% CI, 1.06-3.55; $P = .03$) and airway obstruction: 50% of forced expiratory flow ($\alpha\beta$ coefficient, -0.13 L/s; 95% CI, -0.24 to -0.03 L/s; $P = .01$) and specific airway resistance ($\alpha\beta$ coefficient, 0.06 kPa/s; 95% CI, 0.00 - 0.11 kPa/s; $P = .05$). High levels of high-density lipoprotein cholesterol were associated with improved specific airway resistance ($\alpha\beta$ coefficient, -0.11 kPa/s; 95% CI, -0.21 to -0.02 ; $P = .02$), decreased bronchial responsiveness ($\alpha\beta$ coefficient, 0.53 log- μ mol; 95% CI, 0.00 - 1.60 log- μ mol; $P = .05$), decreased risk of aeroallergen sensitization (aOR, 0.27 ; 95% CI, 0.01 - 0.70 ; $P = .01$), and a trend of reduced FENO levels ($\alpha\beta$ coefficient, -0.22 log-ppb; 95% CI, -0.50 to 0.01

log-ppb; $P = .06$). High triglyceride levels were associated with aeroallergen sensitization (aOR, 2.01 ; 95% CI, 1.14 - 3.56 ; $P = .02$) and a trend of increased FENO levels ($\alpha\beta$ coefficient, 0.14 log-ppb; 95% CI, -0.02 to 0.30 log-ppb; $P = .08$).

Conclusion: The blood lipid profile is associated with asthma, airway obstruction, bronchial responsiveness, and aeroallergen sensitization in 7-year-old children. These findings suggest that asthma and allergy are systemic disorders with commonalities with other chronic inflammatory disorders. (J Allergy Clin Immunol 2015;■■■■:■■■-■■■.)

Key words: Blood lipids, asthma, child, respiratory function tests, inflammation

Hypercholesterolemia initiates a systemic vascular proinflammatory response,^{1,2} which can lead to development of atherosclerotic plaques and increased risk of cardiovascular diseases. Recently, hypercholesterolemia has also been associated with a skewing of the adaptive immune system toward a T_H2 -oriented response,³ which could mediate other diseases, such as asthma and related disorders.⁴⁻⁶ Few studies, mainly those with epidemiologic case-control designs, have examined the relationship between the blood lipid profile and asthma, with very ambiguous results.⁷⁻¹⁰ Importantly, only a few of these studies were performed on children, and no previous prospective studies have investigated the relationship between blood lipid levels and the intermediary end points of lung function, aeroallergen sensitization, fraction of exhaled nitric oxide (FENO), and allergic rhinitis.

We hypothesized that children with asthma and related disorders have skewed blood lipid levels, reflecting a systemic disorder with commonalities with other chronic inflammatory disorders. Therefore the possible relationship between blood lipid levels, asthma, lung function, sensitization, and allergic rhinitis was investigated in the prepubertal children of the Copenhagen Prospective Studies on Asthma in Childhood₂₀₀₀ (COPSAC₂₀₀₀) birth cohort.¹¹

METHODS

COPSAC₂₀₀₀ cohort

COPSAC₂₀₀₀ is a prospective clinical birth cohort study of 411 children born to mothers with a doctor's diagnosis of asthma. The children were enrolled at 1 month of age, excluding children with a gestational age of less than 36 weeks, severe congenital abnormalities, or any lung symptoms before enrollment.¹¹ The children were followed at the COPSAC research unit with 6-month scheduled visits until age 7 years and with acute visits on occurrence of any respiratory, allergy, or skin-related symptoms. The COPSAC pediatricians were solely responsible for diagnosing and treating any such symptoms according to predefined validated algorithms.^{12,13}

Inclusion criteria for the current study were an available blood lipid profile at age 5 to 7 years and a 7-year clinical follow-up visit for

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Abbreviations used

aOR:	Adjusted odds ratio
BMI:	Body mass index
COPSAC ₂₀₀₀ :	Copenhagen Prospective Studies on Asthma in Childhood ₂₀₀₀
FENO:	Fraction of exhaled nitric oxide
HDL-C:	High-density lipoprotein cholesterol
LDL-C:	Low-density lipoprotein cholesterol
PC:	Principal component
PCA:	Principal component analysis
sRaw:	Specific airway resistance

examination of asthma status, lung function, allergic sensitization, and allergic rhinitis.

The study was approved by the Ethics Committee for Copenhagen (KF 01-289/96) and the Danish Data Protection Agency (2008-41-1754). Written and oral informed consent were obtained from both parents at enrollment.

Blood lipid profiles

Venous nonfasting serum samples were obtained at the scheduled visits in the clinic to determine low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride levels. Blood samples were collected in serum separator tubes containing silica and a gel clot (Becton, Dickinson and Company, Franklin Lakes, NJ) and thereafter centrifuged and analyzed within 2 hours. The analyses were performed on a Cobas Integra 400 (Roche, Basel, Switzerland) at the local laboratory.

Children aged 5 to 7 years with at least 1 available blood lipid measurement were included in the study by using the mean of all measured values in the analyses.

Clinical diagnoses at age 7 years

Asthma was diagnosed based on the presence of all of the following criteria: (1) recurrent wheeze, which was defined by troublesome lung symptoms with a burden of 5 or more episodes of 3 or more consecutive days with symptoms captured by daily diary cards filled out from birth by the parents; (2) symptoms judged by the COPSAC pediatricians to be typical of asthma (eg, exercise-induced symptoms, prolonged nocturnal cough, recurrent cough outside the common cold, or symptoms causing waking at night); (3) need for intermittent rescue use of inhaled β_2 -agonist; and (4) improvement of symptoms during a 3-month trial of inhaled corticosteroids and relapse after the end of treatment.^{13,14}

Allergic rhinitis was diagnosed by the COPSAC pediatricians based on relevant aeroallergen sensitization and clinical interviews of the parents (not questionnaires) on history of significant nasal congestion, sneezing, and/or runny nose outside periods with the common cold.¹⁵⁻¹⁷

Objective assessments in the seventh year of life

Spirometry was performed with a pneumotachograph Masterscope Pneumoscreen, system 754,916 spirometer (Erich Jaeger, Wurtzburg, Germany) measuring FEV₁ and 50% of forced expiratory flow values.¹⁸

Whole-body plethysmography measuring specific airway resistance (sRaw) was done with the Master Screen body box (Erich Jaeger, Stuttgart, Germany).^{19,20}

Airway reversibility to bronchodilator was determined as the change in baseline sRaw and FEV₁ 20 minutes after inhalation of 2 doses of 0.25 mg of short-acting β_2 -agonist pressurized metered-dose inhaler (Terbutaline; AstraZeneca, Lund, Sweden) administered through a nonelectrostatic spacer with a facemask.²¹

Airway responsiveness was assessed by using a methacholine challenge test performed with a Wright nebulizer driven by air at 21 psi and a dynamic

flow of 18 L/min starting with an isotonic saline inhalation followed by 0.5 mg/mL methacholine, with subsequent doubling concentrations to a maximum of 64 mg/mL. The provocative dose of methacholine causing a 20% decrease in FEV₁ from baseline (PD₂₀) was the test outcome.²²

Allergen-specific IgE levels were determined by using a screening method (ImmunoCAP, Phadiatop Infant; Pharmacia Diagnostics AB, Uppsala, Sweden) against the most common inhalant allergens in Denmark (cat, dog, horse, birch, timothy grass, mugwort, house dust mites, and molds). Specific IgE values of 0.35 kU/L or greater were considered indicative of aeroallergen sensitization.

Baseline fraction of exhaled nitric oxide (FENO) values were measured at 7 years of age by using an online technique with NIOX Flex (Aerocrine, Solna, Sweden) in accordance with internationally recognized guidelines.^{23,24}

Covariates

Information on race, maternal age at birth, parity, paternal history of asthma, allergy and eczema, household income, older siblings, and passive smoking was obtained through personal interviews during the scheduled visits. Height and weight were measured without clothes at every visit to the nearest 0.1 cm and 0.1 kg. Body mass index (BMI) was calculated and converted to age- and sex-specific *z* scores by using an international World Health Organization reference population.²⁵

Statistical analysis

Log transformation was performed for triglycerides levels and PD₂₀ and FENO values to achieve normality of the residuals before analysis.

Initially, baseline characteristics were compared among included and excluded children by using the χ^2 test, Student *t* test, or Wilcoxon rank sum test. Thereafter, we investigated associations between blood lipid levels and potential confounders using the χ^2 test, Student *t* test, and multiple linear regression, including variables associated with blood lipid levels with a *P* value of less than .1 as covariates in the primary analysis.

Logistic regression models were applied to analyze the association between blood lipid levels and concurrent diagnoses of asthma, allergic rhinitis, and sensitization. The associations between blood lipid levels and lung function indices were analyzed by using multiple linear regression models.

Finally, we applied a data-driven pattern recognition analysis to study lung function assessments in relation to the blood lipid profile. Principal component analysis (PCA) was used to extract underlying latent variables (ie, principal components [PCs]), which describe variation across all 6 different lung function measures in fewer uncorrelated variables.

Results are presented as crude and confounder results adjusted with a .05 significance level cutoff. Missing data were treated as missing observations. Data processing was conducted with SAS version 9.3 for Windows (SAS Institute, Cary, NC).

RESULTS

Baseline

Seventy-three percent (*n* = 301) of the 411 children in the COPSAC₂₀₀₀ cohort had 1 or more blood lipid profile measurements at age 5 to 7 years. Two hundred ninety-six (146 girls) of these children attended the 7-year follow-up visit (see the flowchart in Fig E1 in this article's Online Repository at www.jacionline.org).

Table 1 shows baseline characteristics of the included and excluded children. Maternal age at delivery was higher among included versus excluded children (mean age, 30.35 vs 29.22 years; *P* = .03). The included children had lower post- β_2 -agonist sRaw values (mean, 1.0 vs 1.1 kPa/s; *P* = .04) but in contrast exhibited a trend of lower post- β_2 -agonist FEV₁ (mean, 1.48 vs 1.54 L; *P* = .08). There were no other differences between the groups.

TABLE I. Baseline characteristics of included and excluded children at age 7 years

	No.	Included children (n = 296)	No.	Excluded children (n = 115)	P value
Demographics					
White (% [no.])	296	97.0 (287)	115	95.7 (110)	.50*
Female sex (% [no.])	296	49.3 (146)	115	53.9 (62)	.40*
Household income (% [no.])	282		31		.62*
Low, <€53,000	—	19.5 (55)	—	25.0 (19)	
Average, €53,000–€80,000	—	16.7 (47)	—	19.4 (7)	
High, >€80,000	—	63.8 (180)	—	55.6 (15)	
Mother's age at birth (y), mean (SD)	296	30.35 (4.27)	115	29.22 (5.1)	.03
Older siblings, mean (SD)	291	0.51 (0.67)	94	0.5 (0.76)	.50†
Risk factors					
Paternal atopy (% [no.])	289	49.1 (142)	107	40.2 (43)	.11*
Passive smoking (% [no.])	286	36.7 (105)	39	35.9 (14)	.92*
Anthropometrics					
Birth weight (kg), mean (SD)	296	3.53 (0.54)	115	3.49 (0.47)	.50
BMI (kg/m ²), mean (SD)	290	16.09 (1.67)	38	16.31 (1.44)	.43
Blood lipid measurements					
LDL-C (mmol/L), mean (SD)	296	2.09 (0.55)	—	—	—
HDL-C (mmol/L), mean (SD)	296	1.56 (0.32)	—	—	—
Triglycerides (mmol/L), mean (SD)	296	1.03 (0.52)	—	—	—
Asthma and lung function					
Asthma (% [no.])	296	14.5 (43)	40	10.0 (4)	.44*
FEV ₁ (L), mean (SD)	285	1.44 (0.18)	30	1.48 (0.20)	.25
Post-β ₂ -agonist FEV ₁ (L), mean (SD)	280	1.48 (0.19)	37	1.54 (0.24)	.08
FEF ₅₀ (L/s), mean (SD)	282	1.97 (0.48)	28	2.12 (0.58)	.13
Baseline sRaw (kPa/s), mean (SD)	281	1.22 (0.30)	38	1.26 (0.28)	.45
Post-β ₂ -agonist sRaw (kPa/s), mean (SD)	281	1.0 (0.21)	38	1.1 (0.28)	.04
Methacholine challenge‡ (PD ₂₀ , log-μmol), mean (SD)	232	−0.08 (1.53)	21	0.20 (1.25)	.24
Allergic rhinitis and sensitization					
Sensitization§ (% [no.])	287	35.5 (102)	9	44.4 (4)	.58*
Aeroallergen sensitization (% [no.])	262	29.0 (76)	6	16.7 (1)	.51*
FeNO¶ (log parts per billion), mean (SD)	240	2.03 (0.58)	32	2.00 (0.58)	.80
Allergic rhinitis (% [no.])	283	13.43 (38)	7	0.0 (0)	.30*

FEF₅₀, 50% of forced expiratory flow.*P values calculated by using the χ^2 test.

†P values calculated by using the Wilcoxon rank sum test.

‡Amount of methacholine it takes to produce a 20% decrease in FEV₁.

§IgE >0.35 kU/L.

||Specific IgE >0.35 kU/L for at least 1 of 8 inhaled allergens (cat, dog, horse, birch, timothy grass, mugwort, house dust mites, and mold).

¶FeNO after log transformation.

Blood lipid levels

The mean LDL-C level was 2.09 mmol/L (SD, 0.55 mmol/L), the mean HDL-C level was 1.56 mmol/L (SD, 0.32 mmol/L), and the mean serum triglyceride level was 1.03 mmol/L (SD, 0.52 mmol/L; Table I). Mean age for blood sampling was 6.48 years (SD, 0.53 years), and there was no association between age and lipid levels in this age span. There was a strong inverse association between HDL-C and log-triglyceride levels ($\alpha\beta$ coefficient, -0.25 mmol/L; 95% CI, -0.30 to -0.17 mmol/L; $P < .0001$; $R^2 = 0.14$), whereas there was no correlation between LDL-C and HDL-C levels ($\alpha\beta$ coefficient, 0.02 mmol/L; 95% CI, -0.18 to 0.21 ; $P = .88$; $R^2 < 0.01$) or between LDL-C and log-triglyceride levels ($\alpha\beta$ coefficient, -0.08 mmol/L; 95% CI, -0.20 to 0.04 mmol/L; $P = .20$; $R^2 < 0.01$).

Girls had significantly higher LDL-C levels than boys (mean, 2.17 vs 2.01 mmol/L; $P = .01$). Children exposed to passive smoking in the home had a nonsignificant trend toward lower HDL-C levels (mean, 1.53 mmol/L [SD, 0.32 mmol/L] vs 1.60 mmol/L [SD, 0.32 mmol/L]; $P = .08$) and higher LDL-C levels (mean, 2.16 mmol/L [SD, 0.59 mmol/L] vs 2.05 mmol/L

[SD, 0.53 mmol/L]; $P = .10$). These trends were significant when analyzing number of days exposed to smoking categorized in quantiles (see Table E1 in this article's Online Repository at www.jacionline.org). Furthermore, there was a trend toward association between higher BMI z scores and lower HDL-C levels ($\alpha\beta$ coefficient, -0.041 mmol/L; 95% CI, -0.08 to 0.00 mmol/L; $P = .07$). There were no associations between household income and blood lipid levels (Table II). Therefore all analyses were adjusted for sex, passive smoking, and BMI.

Blood lipid levels and asthma. Of 296 children, 15% ($n = 43$) fulfilled the criteria for an asthma diagnosis. Increasing LDL-C levels were associated with increased risk of asthma at age 7 years, which persisted after confounder adjustment (adjusted odds ratio [aOR], 1.93; 95% CI, 1.06–3.55; $P = .03$; Fig 1), whereas neither HDL-C nor triglycerides levels were associated with asthma (Table III).

Blood lipid levels and lung function. High LDL-C levels were associated with airway obstruction. The association was significant for 50% of forced expiratory flow ($\alpha\beta$ coefficient, -0.13 L/s; 95% CI, -0.24 to -0.03 L/s; $P = .01$) and sRaw

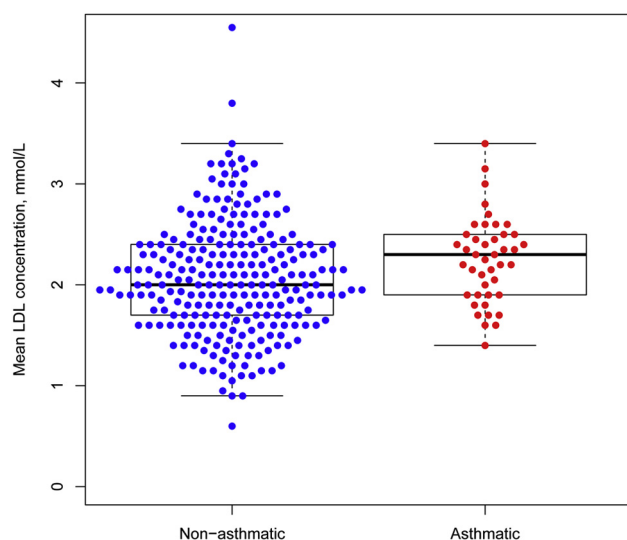
TABLE II. Analysis of potential modifiers of blood lipid levels

	LDL-C		HDL-C		Log-triglycerides	
	a β Coefficient (95% CI)	P value	a β Coefficient (95% CI)	P value	a β Coefficient (95% CI)	P value
z Score BMI	0.02 (−0.05 to 0.09)	.52*	−0.04 (−0.08 to −0.00)	.07*	−0.02 (−0.08 to 0.04)	.54*
Binary and tertiary variables	Mean mmol/L (SD)		Mean mmol/L (SD)		Mean log mmol/L (SD)	
Passive smoking, no vs yes	2.05 (0.53) vs 2.16 (0.59)	.10†	1.60 (0.32) vs 1.53 (0.32)	.08†	−0.06 (0.47) vs −0.12 (0.55)	.71†
Sex, female vs male	2.17 (0.57) vs 2.01 (0.51)	.01†	1.57 (0.31) vs 1.56 (0.33)	.88†	−0.06 (0.47) vs −0.13 (0.52)	.33†
Household income, <€53,000 vs €53,000–€80,000 vs >€80,000	2.13 (0.35) vs 2.08 (0.58) vs 2.10 (0.56)	.92‡	1.57 (0.35) vs 1.62 (0.31) vs 1.54 (0.31)	.35‡	−0.15 (0.50) vs −0.03 (0.46) vs −0.09 (0.50)	.46‡

*P values calculated by using linear regression.

†P values calculated by using the Student *t* test.

‡P values calculated by using ANOVA.

**FIG 1.** Mean LDL level in asthmatic and nonasthmatic children at age 7 years.

(a β coefficient, 0.06 kPa/s; 95% CI, 0.00–0.11 kPa/s; $P = .05$; Table IV).

High HDL-C levels were associated with improved sRaw (a β coefficient, −0.11 kPa/s; 95% CI, −0.21 to −0.02 kPa/s; $P = .02$) and decreased bronchial responsiveness: PD₂₀ (a β coefficient, 0.62 log- μ mol; 95% CI, 0.09–1.15 log- μ mol; $P = .02$).

Triglyceride levels were not significantly associated with any lung function measures.

The general association between blood lipid levels and lung function was further explored in a PCA model including all lung function measurements. Forty-three percent of the variation in lung function data was explained in the first principal component (PC1) and 22% was explained in the second principal component (PC2; see the biplot in Fig E2 in this article's Online Repository at www.jacionline.org). Confirming the findings from conventional statistics, we found a significant inverse association between LDL-C levels and PC1 ($P = .02$) and a positive association between HDL-C levels and PC1 ($P = .02$), which remained significant after confounder adjustment (see Table E2 in this article's Online Repository at www.jacionline.org).

Blood lipid levels and sensitization. High HDL-C levels were associated with a lower risk of sensitization against aeroallergens (aOR, 0.27; 95% CI, 0.01–0.70; $P = .006$). High

triglyceride levels were associated with increased risk of aeroallergen sensitization (aOR, 2.01; 95% CI, 1.14–3.56; $P = .02$), whereas LDL-C levels were not significantly associated with sensitization.

Blood lipid levels and allergic rhinitis. High HDL-C levels showed a nonsignificant reduced risk (aOR, 0.49; 95% CI, 0.16–1.55; $P = .23$), but we found no other significant associations between blood lipid levels and risk of allergic rhinitis (Table IV).

Blood lipid levels and FENO values. There was a trend showing that high HDL-C levels were negatively associated with FENO values (a β coefficient, −0.54 log-ppm; 95% CI, −0.45 to 0.01 log-ppm; $P = .06$), and triglyceride levels were positively associated with FENO values (a β coefficient, 0.14; 95% CI, −0.02 to 0.29; $P = .08$; Table IV).

DISCUSSION

Primary findings

We have demonstrated significant associations between high LDL-C levels and concurrent asthma and airway obstruction in 7-year-old Danish children. Furthermore, high HDL-C levels were significantly associated with better lung function, less bronchial responsiveness, and reduced risk of aeroallergen sensitization. Higher serum triglyceride levels were associated with increased risk of aeroallergen sensitization. Together, these findings suggest that asthma and allergy are systemic disorders with commonalities with other chronic inflammatory disorders.

Strengths and limitations

The primary strength of this study is the 7 years of close clinical surveillance of our birth cohort with longitudinal deep clinical phenotyping and diagnoses solely performed by the COPSAC pediatricians adherent to predefined validated algorithms.^{11,13} The repeated objective clinical assessments at our research clinic, along with day-to-day respiratory symptom diary recordings, provided a highly specific and uniform asthma end point, which is a major advantage compared with studies using cross-sectional and less specific community-based diagnoses.

Another significant strength is the wide range of available objective assessments of lung function, bronchial reversibility, hyperresponsiveness, and FENO measurement performed by skilled research staff according to standard operating procedures. The fact that LDL-C and HDL-C levels were associated with both current asthma and independent assessments of spirometry, whole-body plethysmography, and bronchial responsiveness to

TABLE III. Association between blood lipid levels and asthma status at age 7 years

	Asthma		Crude		Adjusted*	
	Yes, mean (SD)	No, mean (SD)	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
LDL-C (mmol/L)	2.25 (0.42)	2.06 (0.56)	1.86 (1.04-3.30)	.04	1.94 (1.06-3.55)	.03
HDL-C (mmol/L)	1.53 (0.30)	1.57 (0.32)	0.71 (0.25-1.96)	.50	0.81 (0.28-2.37)	.69
Triglycerides (log-mmol/L)	−0.06 (0.48)	−0.10 (0.50)	1.17 (0.61-2.26)	.63	1.193 (0.61-2.34)	.61

*Adjusted for sex, passive smoking, and BMI.

TABLE IV. Relationship between blood lipid levels, lung function measurements, FENO values, and sensitization

Continues variables	LDL-C				HDL-C				Log-triglycerides			
	Crude		Adjusted*		Crude		Adjusted*		Crude		Adjusted*	
	aβ Coefficient (95% CI)	P value	aβ Coefficient (95% CI)	P value	aβ Coefficient (95% CI)	P value	aβ Coefficient (95% CI)	P value	aβ Coefficient (95% CI)	P value	aβ Coefficient (95% CI)	P value
FEV ₁ (L), n = 287	−0.03 (−0.07 to 0.01)	.158	−0.02 (−0.06 to 0.02)	.325	0.02 (−0.05 to 0.09)	.544	0.03 (−0.04 to 0.10)	.360	0.01 (−0.03 to 0.06)	.612	.02 (−0.03 to 0.07)	.362
FEF ₅₀ (L/s), n = 288	−0.14 (−0.24 to −0.04)	.005	−0.13 (−0.24 to −0.03)	.011	0.14 (−0.04 to 0.32)	.122	0.15 (−0.03 to 0.33)	.107	0.06 (−0.05 to 0.17)	.285	0.06 (−0.05 to 0.18)	.280
Post-β ₂ -agonist FEV ₁ (L), n = 283	−0.03 (−0.08 to −0.00)	.081	−0.02 (−0.06 to −0.02)	.292	0.03 (−0.04 to 0.10)	.412	0.05 (−0.02 to 0.12)	.190	−0.02 (−0.07 to −0.02)	.359	−0.01 (−0.06 to −0.03)	.548
Baseline sRaw (kPa/s), n = 283	0.06 (0.00 to −0.11)	.049	0.06 (0.00 to 0.11)	.052	−0.15 (−0.26 to −0.04)	.007	−0.10 (−0.20 to 0.00)	.046	0.01 (−0.07 to 0.08)	.851	0.00 (−0.07 to 0.08)	.953
Post-β ₂ -agonist sRaw (kPa/s), n = 283	0.04 (0.00 to 0.08)	.069	0.04 (−0.01 to 0.09)	.086	−0.04 (−0.12 to 0.03)	.257	−0.04 (−0.12 to 0.04)	.331	−0.01 (−0.06 to 0.04)	.686	−0.02 (−0.07 to 0.04)	.555
Methacholine challenge† (log μmol), n = 233	−0.09 (−0.39 to 0.21)	.555	−0.04 (−0.34 to 0.26)	.801	0.62 (0.09 to 1.15)	.022	0.53 (0.00 to 1.6)	.050	0.03 (−0.30 to 0.37)	.848	0.02 (−0.33 to 0.36)	.921
FENO ₂ ‡ (log-ppb), n = 235	−0.01 (−0.14 to 0.19)	.861	−0.01 (−0.14 to 0.13)	.937	−0.22 (−0.44 to 0.00)	.054	−0.22 (−0.45 to 0.01)	.059	0.14 (−0.01 to 0.29)	.075	0.14 (−0.02 to −0.3)	.079
Binary variables	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95%CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Allergic rhinitis (n = 285)	0.91 (0.48 to 1.70)	.763	0.91 (0.48 to 1.71)	.762	0.50 (0.16 to 1.54)	.228	0.49 (0.16 to 1.55)	.225	0.86 (0.43 to 1.70)	.662	0.86 (0.44 to 1.70)	.672
Sensitization (n = 291)§	0.86 (0.55 to 1.34)	.579	0.95 (0.60 to 1.50)	.824	0.37 (0.17 to 0.80)	.012	0.31 (0.13 to 0.70)	.005	1.66 (1.01 to 2.71)	.043	1.86 (1.11 to 3.12)	.018
Aeroallergen sensitization (n = 264)	0.88 (0.54 to 1.44)	.604	0.92 (0.55 to 1.5)	.752	0.31 (0.13 to 0.75)	.009	0.27 (0.01 to 0.70)	.006	1.95 (1.11 to 3.42)	.020	2.01 (1.14 to 3.56)	.016

Boldface indicates $P < .05$.FEF₅₀, 50% of forced expiratory flow.

*Adjusted for sex, passive smoking, and BMI.

†Amount of methacholine it takes to produce a 20% decrease in FEV₁.

‡FENO after log transformation.

§IgE >0.35 kU/L.

||Specific IgE >0.35 kU/L for at least 1 of 8 inhaled allergens (cat, dog, horse, birch, timothy grass, mugwort, house dust mites, and molds).

methacholine increases confidence in the findings and render the possibility of a chance finding unlikely. Similarly, we found that both HDL-C and triglyceride levels were associated with aeroallergen sensitization and observed trends of association with FENO values, which are increased among children with allergic airway diseases.

It is well known that dyslipidemia relates to sex and lifestyle factors, such as overweight status and tobacco smoking, as confirmed in our data.²⁶ We also demonstrated a strong inverse association between HDL-C and triglyceride levels, serving as a biological validation of the data also observed by others.²⁷ Similar results obtained by both traditional statistics and the data-driven PCA approach are a further advantage of the study.

It might be a limitation that the timing of blood sampling was not fixed and that the children were not fasting before blood collection. Studies show that fasting blood samples predict cardiovascular events better than nonfasting samples.²⁸ Furthermore, the blood lipid profiling was not done at the same age, but we circumvented this issue by using a mean of repeated measurements within a 3-year age frame. Furthermore, we did not find any association between age and lipid levels in this age span, and therefore we do not believe that this lack of standardization mitigates our conclusions.

Another limitation might be exclusion of 115 of 411 children. We found a significant difference for post-β₂-agonist sRaw values between included and excluded children.

Finally, the study is limited from the at-risk nature of the cohort because all mothers have a history of asthma, which might decrease the generalizability because distinct lipid profile, asthma, and sensitization can be genetically associated traits. Therefore our findings need replication in unselected populations.

Interpretation

In support of our findings, 2 previous studies of children/adolescents have reported an association between increased total cholesterol levels and the prevalence of asthma,^{7,8} and 1 study found higher triglyceride levels in asthmatic children compared with control subjects.⁹ In contrast, a study in adults found that asthmatic patients had lower levels of both total cholesterol and triglycerides,¹⁰ and a recent study found that adolescents with asthma and recurrent wheeze had lower HDL-C levels.²⁹ However, the asthma diagnosis in all of these previous studies is based on unspecific questionnaires filled out by the patient or the patient's parents, and none of them include lung function data.

To our knowledge, our study is the first to investigate the association between blood lipid levels, lung function, bronchial responsiveness, and FENO measurements. Our finding of opposite associations of LDL-C and HDL-C levels and lung function supports the hypothesis that an unhealthy blood lipid profile associates with asthma and suggests that such a profile associates with airway inflammation. Furthermore, the associations between HDL-C and triglyceride levels and aeroallergen sensitization propose the presence of a systemic disease process that is not restricted to the airways.^{4,5} The mechanism behind such an association might be that the observed blood lipid profile induces a shift toward an immunologic T_H2-oriented response, which has been demonstrated in mice.³ Additionally, another study found that mice fed with extra cholesterol had signs of airway inflammation evident by higher numbers of eosinophilic cells and increased lymphocyte activation in bronchial lavage fluid.³⁰ These animal studies show that high levels of cholesterol promote inflammation, but this mechanism has not been established in human subjects.

Dyslipidemia has been linked to obesity,³¹ and in recent years, studies have reported an association between obesity and asthma,^{32,33} suggesting dyslipidemia as an intermediary. We found a trend between increased HDL-C levels and decreased BMI, but the significant associations between the observed blood lipid profile and asthma, lung function, and sensitization were independent of BMI.

Dyslipidemia plays a key role in cardiovascular diseases,³⁴ and treatment for such disorders with altered diet, increased physical activity, and statins has shown beneficial effects.³⁵ Studies in adults find that asthmatic patients have a higher degree of arterial inflammation and a higher risk of death from cardiovascular disease.^{36,37} Our study shows that the blood lipid profile known to increase the risk of cardiovascular diseases also confers a risk of asthma and allergy in childhood, suggesting that the same treatment regimen could be relevant for those diseases as well. In fact, 1 case-control study of 16,700 adults showed that prescribing statins to asthmatic patients was associated with decreased risk of asthma-related emergency department visits and less oral corticosteroid use,³⁸ but this has not been confirmed in randomized controlled trials.³⁹ The findings of our study

encourage performance of randomized controlled trials investigating whether children with asthma and traits of dyslipidemia would benefit from dietary changes, increased activity, and for some subgroups, perhaps statin treatment.

Recently, the lipid profile has also been associated with other chronic inflammatory diseases, but the findings draw an ambiguous picture. Inflammatory bowel disease⁴⁰ has been associated with decreased LDL-C levels, systemic lupus⁴¹ and psoriasis⁴² have been associated with high triglyceride levels and low HDL-C levels, and type 1 diabetes⁴³ has been associated with high LDL-C and triglyceride levels and low HDL-C levels. For most of these findings, the lipid profile equals our results, but the differences should be further explored.

Given the cross-sectional study design, it is not possible for us to explore causality, and hence we cannot exclude that the inflammation associated with asthma could lead to this distinct lipid profile instead of the lipid profile promoting asthma. It has previously been shown that asthmatic patients have a decrease in HDL-C levels from childhood to adolescence,²⁹ which could indicate that the distinct lipid profile acts as a biomarker for the degree of inflammation.

Conclusion

The blood lipid profile is associated with asthma, lung function, bronchial responsiveness, and aeroallergen sensitization in 7-year-old children, suggesting that asthma and allergy are systemic disorders sharing dyslipidemia with other chronic inflammatory disorders. Further longitudinal studies are required to evaluate a potential modifiable link between an unhealthy blood lipid profile and asthma and allergic sensitization.⁶

We thank the children and families of the COPSAC₂₀₀₀ cohort study for all their support and dedication. We acknowledge and recognize the unique efforts of the COPSAC research team. We thank the Department of Clinical Biochemistry at Gentofte Hospital for their assistance and cooperation in analyzing the blood samples.

Key messages

- Hypercholesterolemia has been associated with a skewing of the adaptive immune system toward a T_H2-oriented response, which could affect the risk of diseases, such as asthma.
- We discovered that asthmatic children had significantly higher LDL-C levels compared with nonasthmatic subjects, and the lipid profile was further associated with lung function, bronchial responsiveness, and aeroallergen sensitization.
- These findings suggest a link between blood lipid levels, asthma, and allergy and propose that these diseases are systemic disorders with commonalities with other chronic inflammatory disorders.

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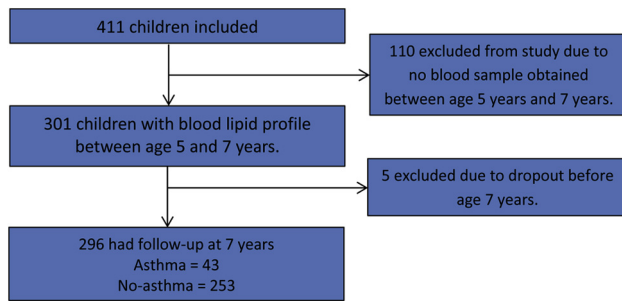


FIG E1. Flowchart showing inclusion of children into this study from the COPSAC₂₀₀₀ study group.

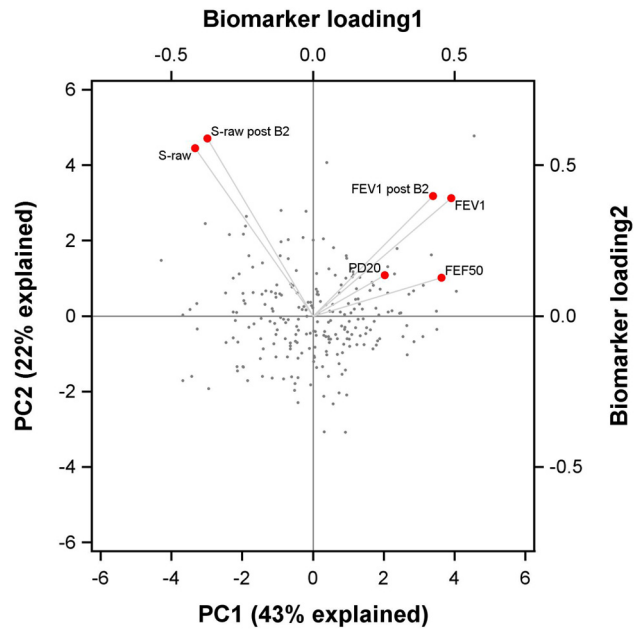


FIG E2. Biplot with loadings of the 2 first PCs generated from the 6 lung functions measurements. *FEF50*, 50% of forced expiratory flow.

TABLE E1. Relationship between passive smoking in quantile variables and blood lipid levels

Passive smoking	LDL-C		HDL-C		Log-triglycerides	
	Mean (SD) mmol/L		Mean (SD) mmol/L		Mean (SD) log-mmol/L	
≤3 d/y vs ≤10 d/y	2.11 (0.53) vs 2.04 (0.45)	.01*	1.51 (0.29) vs 1.49 (0.30)	.02*	−0.01 (0.45) vs −0.09 (0.40)	.46*
vs ≤36 d/y vs > 36 d/y	vs 1.97 (0.54) vs 2.26 (0.62)		vs 1.61 (0.35) vs 1.63 (0.30)		vs −0.11 (0.59) vs −0.14 (0.50)	

**P* values calculated by using ANOVA.

TABLE E2. Relationship between blood lipid levels and PCs generated from lung function measurements

	LDL-C				HDL-C				Log-triglycerides			
	Crude		Adjusted*		Crude		Adjusted*		Crude		Adjusted*	
	a β Coefficient (95% CI)	P value	a β Coefficient (95%CI)	P value	a β Coefficient (95% CI)	P value	a β Coefficient (95% CI)	P value	a β Coefficient (95% CI)	P value	a β Coefficient (95%CI)	P value
PC1	−0.44 (−0.80 to −0.07)	.02	−0.45 (−0.80 to −0.07)	.02	0.84 (0.16 to 1.51)	.01	0.84 (0.16 to 1.51)	.02	−0.13 (−0.55 to 0.29)	.54	−0.09 (−0.53 to 0.34)	.67
PC2	0.05 (−0.20 to 0.30)	.69	0.08 (−0.17 to 0.34)	.50	−0.31 (−0.76 to 0.15)	.19	−0.22 (−0.69 to 0.24)	.34	−0.02 (−0.31 to 0.27)	.90	−0.02 (−0.27 to 0.32)	.89

Boldface indicates $P < .05$.

PC1, First principal component; PC2, second principal component.

*Adjusted for sex, passive smoking, and BMI.