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 Childhood$_{2000}$ 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 (aβ coefficient, −0.13 L/s; 95% CI, −0.24 to −0.03 L/s; $P = .01$) and specific airway resistance (aβ 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 (aβ coefficient, −0.11 kPa/s; 95% CI, −0.21 to −0.02; $P = .02$), decreased bronchial responsiveness (aβ coefficient, 0.53 log-μmol; 95% CI, 0.00-1.60 log-μmol; $P = .05$), decreased risk of aeroallergen sensitization (aOR, 0.27; 95% CI, 0.01-0.70; $P = .01$), and a trend of reduced FENO levels (aβ 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 (aβ 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 Childhood$_{2000}$ (COPSAC$_{2000}$) birth cohort.[11]

METHODS

COPSAC$_{2000}$ cohort

COPSAC$_{2000}$ 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 wakening 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 FEV_1 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 FEV_1 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 ab 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 FEV_1 from baseline (PD_{20}) 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 PD_{20} 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 $COPSAC_{2000}$ 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 I 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 FEV_1 (mean, 1.48 vs 1.54 L; P = .08). There were no other differences between the groups.