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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Serum lipid levels are associated with allergic rhinitis, nasal symptoms, peripheral olfactory function, and nasal airway patency in children

To the Editor

Extensive studies support the presence of links between dyslipidemia and allergic diseases, and there has been with particular emphasis on allergen sensitization,¹⁻³ asthma,^{2,4} and atopic dermatitis (AD). Although evidence supporting a link of allergic rhinitis (AR) with dyslipidemia is limited and controversial,^{2,3} many researchers have focused on the relationship of obesity and rhinitis, rather than blood lipids.⁵

This study determined the association of different blood lipids with current rhinitis and rhinitis-related parameters, including nasal symptoms, peripheral olfactory function, and nasal volume. Therefore, we investigated the relationship of different components of the blood lipid profile with AR and rhinitis-related parameters in fifth-

APPENDIX 1

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and sixth-grade students enrolled in the Seongnam Atopy Project 2017 (SAP₂₀₁₇) cohort.

This prospective, general population-based, cross-sectional study examined children from 11 randomly selected elementary schools in Seongnam City (Korea) between January 2017 and October 2017. We investigated 620 fifth- and sixth-grade elementary school students (10-12 years old) who participated in the SAP₂₀₁₇ cohort, sponsored by the Seongnam City Government. The study protocol was approved by the appropriate Institutional Review Board of CHA University (2017-04-049), and written informed consent documents were obtained from all parents or guardians of children who participated.

We reviewed the questionnaires to identify demographic factors and investigate prevalence of allergic diseases. The presence of current allergic disease (asthma and rhinitis) was diagnosed using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, based on symptoms in the previous 12 months.⁶ Children who had rhinitis and allergen sensitization to a serum allergen-

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; B, beta coefficients; BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein; IgE, immunoglobulin E; IL, interleukin; ISAAC, International Study of Asthma and Allergies in Childhood; LDL-C, low-density lipoprotein; NAR, nonallergic rhinitis; OR, odds ratio; SAP₂₀₁₇, Seongnam Atopy Project 2017; T4SS, Total Four Symptom Score; TG, triglycerides.

specific IgE were classified as having AR, and those who had rhinitis were nonsensitized as having nonallergic rhinitis (NAR). The control group consisted of children without current rhinitis.

The severity of AR (mild or moderate-severe) was categorized using the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines. The nasal symptom score was determined using the Total Four Symptom Score (T4SS, range: 0-12) by calculating the sum of scores for sneezing, nasal itching, nasal obstruction, and rhinorrhea for 1 month.⁷ The presence of parental asthma, AD and AR, and asthma was based on diagnoses by physicians. Overweight was defined as a body mass index (BMI) of 85 percentile or greater and obese as a BMI of 95 percentile or greater using age- and sex-specific equations based on the 2007 Korean national growth charts.⁸

We also determined each subject's blood lipid profile, serum total immunoglobulin E (IgE), serum 6 common inhalant allergen-specific IgEs (*Dermatophagoides farina*, cat dander, dog dander, *Alternaria*, birch, and Japanese hop), peripheral olfactory function (using olfactory threshold test), and nasal volume (using acoustic rhinometry). We defined an olfactory threshold score below the 10th percentile as hyposmia, depending on the age and sex of the participant.⁹

All analyses were conducted using SPSS version 23.0 (IBM Co, Armonk, NY, USA). Multiple linear, binary, or multinomial logistic regression models were used to calculate the odds ratio (OR) and 95% confidence interval (CI), or the beta coefficients (B) and standard error (SE), after adjustment for age, sex, height, BMI category (normal weight, overweight, and obese), and parental AD, AR, and asthma. Additionally, a *P* value below .10 in Student's *t* test, one-way ANOVA, or simple regression analysis was used as the criterion for selecting potential confounding factors (asthma, aeroallergen sensitization, log-transformed total IgE, and baseline nasal patency) for multiple regression analysis. A *P* value below .05 was considered statistically significant.

A total of 620 children were enrolled in the SAP₂₀₁₇ study group, and 463 (74.7%) of them met the study criteria by completing the blood sampling, olfactory threshold test, and acoustic rhinometry test. Next, we excluded the 68 children with NAR and used the ARIA guidelines to classify participants as having no rhinitis (control) (*n* = 198, 50.1%), mild AR (*n* = 36, 9.1%), or moderate/severe AR (*n* = 161, 40.8%). Multinomial regression analysis indicated that total cholesterol (*P* for trend = .026) and low-density lipoprotein (LDL-C) (*P* for trend = .049) were associated with the severity of AR (Table 1). However, we found no associations of different blood lipid levels with NAR (data not shown). We examined whether AR and serum lipid profiles interact to affect BMI, but in this case, we did not find a significant interaction effect of total cholesterol (*P* = .135), LDL-C (*P* = .127), high-density lipoprotein (HDL-C) (*P* = .143), or log triglycerides (TG) (*P* = .183). These results suggest no interaction between AR and serum lipid profiles on BMI.

The olfactory threshold, in which a score below the 10th percentile was classified as hyposmia, was 3.4 for boys and 2.7 for girls. Thus, 47 (10.2%) participants had hyposmia. Table 2 shows the aORs and 95% CIs for the relationship of hyposmia with different blood lipids and nasal patency. These results indicate significant associations of hyposmia with total cholesterol (aOR, 0.986; 95% CI, 0.973-0.999; *P* = .037) and HDL-C (aOR, 0.957; 95% CI, 0.929-0.987; *P* = .005). Moreover, baseline nasal airway patency associated negatively with total cholesterol (*B* = −0.010; *SE* = 0.004; *P* = .004) and LDL-C (*B* = −0.012; *SE* = 0.004; *P* = .002) and that decongested nasal airway patency negatively associated with log-TG (*B* = −0.995; *SE* = 0.487; *P* = .041) (Table 2).

The 265 children with rhinitis had a median T4SS of 2.00 (interquartile range: 1.00-4.00). Multiple linear regression analysis indicated statistically significant associations of T4SS with total

TABLE 1 Multinomial regression analysis of the relationship of different blood lipid levels with the severity and nasal symptoms of AR (*n* = 395)

	Severity of AR (control, n = 198; mild AR, n = 36; moderate/severe AR, n = 161)						
	Control vs mild rhinitis		Control vs moderate/severe rhinitis		Mild rhinitis vs moderate/severe rhinitis		P value for overall model
	aOR (95% CI)	P value	aOR (95% CI)	P value	aOR (95% CI)	P value	
Blood lipid profiles							
Total cholesterol	0.993 (0.998-1.008)	.353	1.010 (1.001-1.019)	.037	1.017 (1.002-1.032)	.028	.026
LDL-C	0.994 (0.978-1.011)	.485	1.010 (1.000-1.020)	.046	1.016 (1.000-1.033)	.057	.049
HDL-C	1.005 (0.975-1.035)	.758	1.006 (0.987-1.025)	.535	1.001 (0.972-1.031)	.937	.820
Log-TG	0.582 (0.090-3.746)	.569	1.387 (0.453-4.246)	.567	2.383 (0.377-15.074)	.356	.618

AD, atopic dermatitis; aOR, adjusted odds ratio; AR, allergic rhinitis; BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; IgE, immunoglobulin E; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Risk factors were adjusted by age, sex, height, BMI category (healthy weight, overweight, and obese), asthma, log-transformed total IgE level, and physician-diagnosed AD, AR, and asthma in parents.

Numbers in bold indicate a significant difference (*P* < .05).

TABLE 2 Multivariate logistic and linear regression analysis of the relationship of different blood lipid levels with hyposmia and nasal patency

	Hyposmia		Baseline nasal airway patency ^a			Decongested nasal airway patency ^b			Nasal symptom score (T4SS) ^c		
	aOR (95% CI)	P value	B	SE	P value	B	SE	P value	B	SE	P value
Blood lipid profiles											
Total cholesterol	0.986 (0.973-0.999)	.037 ^d	−0.010	0.004	.004 ^e	−0.006	0.004	.158 ^f	0.016	0.006	.005^g
LDL-C	0.989 (0.974-1.003)	.128 ^d	−0.012	0.004	.002 ^e	−0.006	0.004	.151 ^f	0.018	0.006	.004^g
HDL-C	0.957 (0.929-0.987)	.005^d	−0.003	0.007	.649 ^e	0.011	0.008	.184 ^f	0.007	0.012	.537 ^g
Log-TG	1.125 (0.245-5.169)	.880 ^d	−0.249	0.440	.572 ^e	−0.995	0.487	.041^f	0.297	0.719	.680 ^g

AD, atopic dermatitis; aOR, adjusted odds ratio; AR, allergic rhinitis; B, beta coefficients; BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; SE, standard error; T4SS, total four symptoms score; TG, triglycerides.

Numbers in bold indicate a statistically associated ($P < .05$).

^aThe nasal volume from 0 to 5 cm into the nasal cavity was defined as the baseline nasal airway patency.

^bThe decongested nasal airway patency was defined by measuring the volume 15 min after administration of a topical alpha agonist (one puff of intra-nasal xylometazoline [1 mg/mL]) to each nostril.

^cNasal symptom score (T4SS) in patients with rhinitis ($n = 265$).

^dRisk factors were adjusted by age, sex, height, BMI category (normal weight, overweight, and obese), allergen sensitization, physician-diagnosed AD, AR, and asthma in parents, and baseline nasal airway patency.

^eRisk factors were adjusted by age, sex, height, BMI category (normal weight, overweight, and obese), and physician-diagnosed AD, AR, and asthma in parents.

^fRisk factors were adjusted by age; sex; height; BMI category (normal weight, overweight, and obese); physician-diagnosed AD, AR, and asthma in parents; and aeroallergen sensitization.

^gThe risk factors were adjusted by age, sex, height, BMI category (normal weight, overweight, and obese), aeroallergen sensitization, log-transformed total IgE level, and physician-diagnosed AD, AR, and asthma in parents.

cholesterol ($B = 0.016$; $SE = 0.006$; $P = .005$) and LDL-C ($B = 0.018$; $SE = 0.006$; $P = .004$) (Table 2).

To our knowledge, this is the first large sample study of urban children to comprehensively investigate the association of different blood lipids with AR and rhinitis-related parameters. We demonstrated that the levels of different blood lipids were associated with the severity of AR, nasal symptoms, baseline nasal airway volume (reduced reversible nasal airway congestion), decongested nasal airway volume (reduced irreversible nasal airway obstruction), and hyposmia (peripheral olfactory dysfunction).

Previous researchers have focused on the association of rhinitis with metabolic conditions, such as obesity.⁵ However, we assessed the relationship of rhinitis with different blood lipids after adjusting for confounding by BMI. Dyslipidemia is an indication of the chronic inflammatory response.¹⁰ Elevated TG and LDL-C lead to proinflammatory signaling and increased expression of TNF- α and interleukin (IL)-6.^{10,11} In contrast, HDL-C has an anti-inflammatory effect, in that, it modulates T-cell activation^{10,11} and may improve the olfactory threshold. A recent study of children reported associations of different blood lipids with the anti-inflammatory cytokine IL-10 and the proinflammatory cytokines IL-17 and IL-23.¹¹ Based on the results of this study, we speculate that the presence of a chronic inflammatory state, as indicated by dyslipidemia, affects the lower airway² and the nasal airway.

Our study of a large sample of urban children indicated significant relationships of dyslipidemia with AR severity, nasal symptoms, and several rhinitis-related parameters. Clinicians should be aware of

these associations so they can make timely diagnoses and initiate treatment for children with rhinitis and dyslipidemia.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Having small-for-gestational-age infants was associated with maternal allergic features in the JECS birth cohort

To the Editor,

Being small for gestational age (SGA) is associated with significant perinatal outcomes, such as foetal and neonatal distress, and long-term complications, such as insulin resistance and cardiovascular disease.^{1,2} Maternal history of chronic diseases such as hypertension can be a risk factor for being SGA.³ Asthma is one of the most frequent chronic diseases encountered during pregnancy, and Murphy et al⁴ reported that maternal asthma was associated with an increased risk of SGA in their systematic review. Based on those results, we hypothesized that inflammatory reactions caused by allergic diseases might increase the risk of intrauterine growth retardation (IUGR). To our knowledge, the association of SGA with maternal IgE sensitization and allergic diseases other than asthma has not been reported. The aim of this study was to

investigate the association between SGA and allergic diseases during pregnancy.

The Japan Environment and Children's Study (JECS) is a nationwide, multicentre, prospective birth cohort study described elsewhere.^{5,6} The physician's diagnosis of an allergic disease was verified by a questionnaire, and the lifetime prevalence of these conditions was assessed. The total serum and allergen-specific IgE titres of the mothers during pregnancy, assayed by ImmunoCAP (Thermo Fisher Scientific, Inc., Sweden), were analysed by an independent clinical laboratory. The present study is based on the data set "jecs-ag-20160424", which was released in June 2016. SGA was defined as a birthweight and length below the 10th percentile for gestational age [ICD-10 P05.1] based on the new, age-specific Japanese standards for birth size.⁷