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The relationship of serum triglycerides, serum HDL, and obesity to the risk of wheezing in 85,555 adults

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Abstract
Background: Asthma has been linked to obesity and the presence of the metabolic syndrome.
Objective: To explore which components of the metabolic syndrome that were associated with wheezing, a main symptom of asthma. Further, to explore whether these associations were different in individuals with and without rhinitis symptoms.
Methods: We used data from the Ibermutuamur Cardiovascular Risk Assessment Plan (ICARIA) including 85,555 Spanish workers (median age = 34, range = 16–75 years) with assessments of self reported wheezing and rhinitis symptoms. Fasting blood samples were analysed for serum triglyceride (s-TG), HDL (s-HDL) and glucose; blood pressure, waist circumference (WC) and body mass index (BMI) were measured.
Results: In mutually adjusted analyses including all components of the metabolic syndrome and possible confounders, elevated WC (or BMI), elevated s-TG and low s-HDL were significantly associated with wheezing. Odds ratio (OR) with confidence interval (CI) were: elevated WC = 1.54 (1.46–1.62), elevated s-TG = 1.24 (1.18–1.30), low s-HDL = 1.17 (1.12–1.22). These associations were stronger in individuals without than in those with rhinitis symptoms, OR's (CI's) were WC = without rhinitis 1.70 (1.57–1.85) vs. with rhinitis 1.47 (1.37–1.58). Elevated s-TG = without rhinitis 1.36 (1.26–1.46) vs. with rhinitis 1.21 (1.13–1.29). Low s-HDL = without rhinitis 1.24 (1.15–1.34) vs. with rhinitis 1.11 (1.04–1.18).

Abbreviations: WC, waist circumference; s-TG, serum triglyceride; s-HDL, serum HDL cholesterol.

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Conclusions: High s-TG and low s-HDL were associated with wheezing after adjustment for adiposity. This may substantiate elevated s-TG and lowered s-HDL as markers or inducers of inflammation associated disease. The study supports the notion that these biochemical markers have differential effects on different types of wheezing.

Introduction

Epidemiological studies[1] and studies of the effects of weight-loss[2] have clearly shown a link between obesity and asthma, as a well as an association between the metabolic syndrome itself and asthma.[3] However, the type of asthma associated with obesity differs from other types of asthma.[4,5] Cluster analyses indicate that the obesity-associated asthma is characterised by late-onset, is driven by other than eosinophilic cells, and is mainly found among non-atopics.[6] Accordingly, this obesity-associated non-atopic asthma is less responsive to corticosteroid treatment.[7,8]

The mechanisms underlying the link between obesity and asthma are not fully understood. Obesity can lead to adipose tissue dysfunction and a chronic state of low-grade inflammation.[9,10] Dysfunctional adipose tissue is characterised by endoplasmatic reticulum stress[9] and reduced uptake of dietary fatty acids in the adipocytes, leading to dyslipidemia, which may be manifested by hypertriglyceridemia and reduced HDL cholesterol levels.[11] Factor analyses have shown hypertriglyceridemia and serum HDL (s-HDL) to be independent predictors of lung function impairment.[12] Thus, we reasoned that dyslipidemia might also confer a risk of asthma, independently of the level of adiposity. This would lend support to that obesity-associated asthma in non-atopics could be part of the cluster of diseases, such as cardiovascular diseases[13–15] and non-alcoholic fatty liver disease,[16] as suggested earlier.[10] In these diseases, hypertriglyceridemia seems to be an independent risk factor and not simply a marker of the level of obesity or of other serum lipid levels.[17,18] Thus, among the factors of the metabolic syndrome, hypertriglyceridemia and reduced s-HDL could also be involved in asthma pathogenesis independently of the level of adiposity.

The present study tested the hypothesis that factors associated with adipose tissue dysfunction, namely elevated serum triglyceride (s-TG) and lowered s-HDL, are predictive of wheezing, a symptom of asthma, independently of obesity. We also investigated whether associations of these biomarkers with wheezing would differ in persons with and without rhinitis symptoms since rhinitis is associated with atopy.

Methods

Study design

We analysed data from the Ibermutuamur Cardiovascular Risk Assessment Plan (ICARIA) study, which is an on-going study of workers covered by Ibermutuamur, a nationwide Social Security mutual insurance company for accidents at work and occupational diseases that covers a population of approximately one million workers corresponding to 8% of the Spanish working population. Ibermutuamur has a department for prevention and health of workers, who are given routine annual medical check-ups, and the ICARIA study, described elsewhere,[19] examines data taken at the time of the annual check-up, based on the physical examination, laboratory determinations, and a physician-administered structured questionnaire. Local Ethics Committees have reviewed and approved the ICARIA study, and all subjects provided written, informed consent to participate in the study.

The current study is cross-sectional and based on an extra self-administered, structured questionnaire of health-related items including questions of bronchial and nasal symptoms, that was completed (March 2005 to March 2007) by a random sample of 102,961 workers, who were stratified by region of origin in order to ensure nationwide representation.[20] From among all workers who answered the extra questionnaire, we selected those with we selected those with complete data on age, gender, and wheezing, $n = 85{,}555$. There was no difference in any of the covariates used for the analyses between those with complete data on age, gender, and wheezing and those without complete data on one, two, or all three of these variables. We analysed data from medical records and questionnaire responses.

Bronchial and nasal symptoms

The presence of (a) bronchial and (b) nasal symptoms was explored by means of questions on the self-administered questionnaire that were adopted from previously validated questionnaires,[21] as follows:

a) Have you ever had wheezing or whistling in the chest at any time in the last 12 months?
b) Have you ever had a problem with sneezing, or a runny, or a blocked nose when you did not have a cold or the flu in the last 12 months?

Adiposity measures

Anthropometric measurements were made with the subjects wearing light clothing and without shoes. Height was measured to the nearest cm, and weight to the nearest 0.1 kg. Waist circumference was measured to the nearest cm using a tape measure with no pressure on the body surface.

Metabolic abnormalities

Biochemical determinations were performed using serum samples obtained under fasting conditions. The

Table 1 Wheezing according to characteristics of the study population.

	Prevalence, wheezing		Risk of wheezing
	%	(*n*/all)	[a]OR (CI)
Age			
<45 years	17.8	(12021/67390)	Reference
≥45 years	18.8	(3408/18165)	1.04 (1.00–1.08)
Gender			
Females	15.2	(3686/24315)	Reference
Males	19.2	(11743/61240)	1.32 (1.27–1.38)
Rhinitis symptoms			
Absent	9.3	(4561/48791)	Reference
Present	29.9	(10243/34295)	4.20 (4.04–4.36)
BMI			
<18.5 kg/m^2	18.1	(257/1421)	1.20 (1.04–1.37)
18.5–25 kg/m^2	16.0	(6239/38918)	Reference
25–30 kg/m^2	18.1	(5816/32120)	1.11 (1.06–1.16)
≥30 kg/m^2	24.1	(2999/12463)	1.59 (1.51–1.68)
WC			
Normal[b]	17.0	(11074/65329)	Reference
High[b]	24.5	(2701/11025)	1.58 (1.51–1.66)
S-Triglycerides			
<150 mg/dl	16.7	(11448/68472)	Reference
150–400 mg/dl	23.9	(3200/13416)	1.50 (1.44–1.57)
≥400 mg/dl	28.6	(269/942)	1.90 (1.64–2.19)
S-HDL			
Normal[b]	17.2	(11308/65728)	Reference
Low[b]	22.2	(3361/15167)	1.38 (1.32–1.44)
S-LDL			
Normal[b]	18.0	(13600/75564)	Reference
High[b]	18.3	(1829/9991)	0.98 (0.93–1.03)
S-glucose			
Normal[b]	17.8	(13456/75510)	Reference
High[b]	19.6	(1973/10045)	1.07 (1.01–1.13)
Blood pressure			
Normal[b]	17.5	(9098/52097)	Reference
High[b]	18.9	(6331/33458)	1.05 (1.01–1.09)
Metabolic syndrome			
Absent[b]	17.2	(10892/63149)	Reference
Present[b]	25.4	(2113/8334)	1.58 (1.49–1.67)
Occupation			
High level (non-manual)[c]	20.0	(10104/50414)	Reference
Low level (manual)[c]	15.2	(5325/35141)	1.33 (1.28–1.38)
Alcohol consumption			
0–<70 g/week	16.8	(11367/67475)	Reference
70–<280 g/week	21.8	(3609/16519)	1.31 (1.25–1.37)
>280 g/week	29.0	(453/1561)	1.91 (1.71–2.14)
Tobacco use			
Never smoker	9.2	(3055/33215)	Reference
Former smoker	12.1	(1843/15241)	1.29 (1.22/1.38)
Current smoker	28.4	(10495/36914)	3.90 (3.73/4.07)
Physical activity at work			
Sedentary	15.7	(5279/33627)	Reference
Standing	17.3	(3090/17883)	1.09 (1.04–1.15)
Walking	19.6	(3686/18786)	1.26 (1.20–1.32)
Physically demanding	24.5	(2084/8517)	1.64 (1.55–1.75)

%, percentage of individuals with wheezing in the specific group; (*n*/all), number of individuals with wheezing/number of all individuals in the specific group.

[a] Odds ratio (OR) estimates with 95% confidence intervals (CI) were obtained in logistic regression models adjusted for age and gender only; BMI, body mass index; WC, waist circumference; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol.

[b] Defined according to ATP III criteria[23]: abdominal adiposity (waist circumference >102 cm in male subjects or >88 cm in female subjects); high blood pressure (>130/85 mmHg or previous diagnosis of or therapy for hypertension); hypertriglyceridemia (fasting serum triglycerides >150 mg/dl); low HDL cholesterol (<40 mg/dl in male subjects or <50 mg/dl in female subjects); and high serum glucose (>110 mg/dl or previous diagnosis of or therapy for diabetes). Metabolic syndrome was considered when at least three of these criteria were present.

[c] Defined according to the Spanish National Classification of Occupations.[24]

Friedewald equation was used to calculate LDL-cholesterol.[22] All measurements were performed in automatic analysers at reference laboratories following uniform standard procedures and quality controls, as detailed elsewhere.[19]

Metabolic abnormalities were defined according to the Adult Treatment Panel III (ATP III) (2001) criteria for metabolic syndrome.[23] Metabolic syndrome was considered when at least three of the following criteria were present: 1) abdominal adiposity (waist circumference >102 cm in male subjects or >88 cm in female subjects); 2) high blood pressure (pressure >130/85 mmHg or previous diagnosis of or therapy for hypertension); 3) hypertriglyceridemia (fasting serum triglycerides >150 mg/dl); 4) low s-HDL (<40 mg/dl in male subjects or <50 mg/dl in female subjects); and 5)

Table 2 Association of self reported wheezing with selected risk factors. Analyses with either waist circumference (upper panel) or with body mass index (lower panel).

Analyses with WC	Not mutually adjusted	Categorical obesity measures	Continuous obesity measures
	Model 1*	Model 2**	Model 3**
	[a]OR (CI)	[a]OR (CI)	[a]OR (CI)
Waist circumference categorical			
Normal[b]	Reference	Reference	
High[b]	1.63 (1.55–1.72)	1.54 (1.46–1.62)	
Waist circumference continuous			
One standard deviation	1.28 (1.25–1.31)		1.24 (1.22–1.27)
S-Triglycerides			
Normal[b]	Reference	Reference	Reference
High[b]	1.36 (1.30–1.42)	1.24 (1.18–1.30)	1.20 (1.14–1.26)
S-HDL			
Normal[b]	Reference	Reference	Reference
Low[b]	1.28 (1.22–1.34)	1.17 (1.12–1.22)	1.14 (1.08–1.19)
Analyses with body mass index	Model 1*	Model 2**	Model 3***
	[a]OR (CI)	[a]OR (CI)	[a]OR (CI)
Body mass index categorical			
<18.5 kg/m^2	1.10 (0.95–1.27)	1.11 (0.96–1.28)	
18.5–<25 kg/m^2	Reference	Reference	
25–<30 kg/m^2	1.19 (1.14–1.25)	1.15 (1.11–1.21)	
>30 kg/m^2	1.73 (1.64–1.82)	1.61 (1.52–1.70)	
Body mass index continuous			
One standard deviation	1.23 (1.20–1.25)		1.20 (1.17–1.22)
S-Triglycerides			
Normal[b]	Reference	Reference	Reference
High[b]	1.36 (1.30–1.42)	1.20 (1.14–1.26)	1.20 (1.14–1.26)
S-HDL			
Normal[b]	Reference	Reference	Reference
Low[b]	1.28 (1.22–1.34)	1.16 (1.11–1.21)	1.15 (1.09–1.20)

*Model 1, models in the left column were adjusted for potential confounders[a] but there was not a mutual adjustment of obesity measures and serum lipids.

**Model 2 and Model 3 were adjusted for potential confounders and for one obesity measure (WC upper panel, BMI lower panel), S-TG and S-HDL. Model 2 included categorical obesity measures, Model 3 included continuous obesity measures. [a]Potential confounders: age, sex, education, alcohol, tobacco and physical activity during working hours.

[a] Odds ratio (OR) estimates with 95% confidence intervals (CI) were obtained in logistic regression models. WC, waist circumference; HDL, high density lipoprotein; BMI, body mass index.

[b] Defined according to ATP III criteria[23]: abdominal adiposity (waist circumference >102 cm in male subjects or >88 cm in female subjects); hypertriglyceridemia (fasting serum triglycerides >150 mg/dl); low HDL cholesterol (<40 mg/dl in male subjects or <50 mg/dl in female subjects).

hyperglycemia (fasting serum glucose >110 mg/dl or previous diagnosis of or therapy for diabetes).[23]

Occupational data

Specific occupations were classified into nine major categories according to the 1994 Spanish National Classification of Occupations.[24] Non-manual (white-collar) workers were defined as those in the first four categories[1]: general managers and government administrators[2]; scientific professionals, technicians and intellectuals[3]; support technicians and professionals[4]; clerks and related office personnel. Manual (blue-collar) workers were defined as those in the remaining five categories[5]: catering and hospitality, personal and security service workers, and salesmen/women and shop assistants[6]; skilled workers in agricultural and fishing industries[7]; craftsmen/women and skilled workers in manufacturing, construction, and mining[8]; machine installers, operators, and assemblers; and[9] unskilled workers. Physical activity during working hours was classified as sedentary, standing, walking, or physically demanding.

Lifestyle factors

Alcohol consumption was evaluated as the number of standard drinking units (glasses of wine [~10 g], bottles of beer [~10 g], and spirits [~10 g]) regularly consumed per week. Individuals were classified as current smokers, ex-smokers, and never smokers.

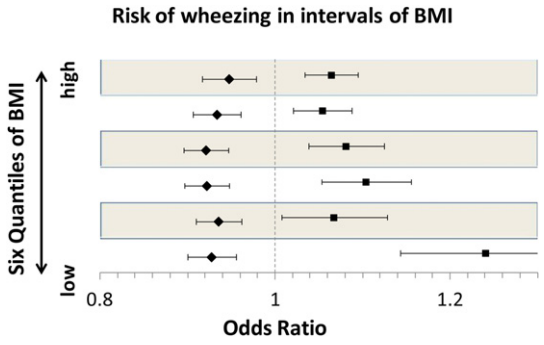

Figure 1 Risk of wheezing per standard deviation of s-HDL and s-TG by level of BMI. Diamonds: s-HDL; squares: s-TG. Odds ratio estimates with 95% confidence intervals indicated by error bars were obtained in one single logistic regression model adjusted for age, sex, adiposity, occupation, alcohol, and physical activity during working hours. S-TG, serum triglyceride; s-HDL, serum high density lipoprotein.

Data analysis

Statistics were performed using the R-statistical package, version 2.13.0 (http://www.r-project.org/). All *p*-values were two-tailed and statistical significance was defined as $p < 0.05$. *P*-values of likelihood ratio tests were used to test for significance of all multivariate analyses. We used logistic regression to model wheezing and rhinitis symptoms. We checked for nonlinear associations between all explanatory variables and logit of the dichotomous outcomes using P-splines within the generalised additive model (R "mgcv" package). For variables with non-linear associations with logit of the dichotomous outcomes, splines were used in the regression models. We tested possible interactions between adiposity measures (BMI or WC) and serum lipids (s-TG of s-HDL) in the regression models. We also tested possible interactions of adiposity measures and serum lipids with both gender and rhinitis symptoms. All multivariate analyses were made with the adiposity measures, the serum lipids, serum glucose and blood pressure as both categorised according to the definitions of the metabolic syndrome and as continuous. We standardised the continuous variables by dividing each variable by its own standard error to facilitate comparison of the magnitude of effects between the different variables. All analyses were checked for the possible influence of outliers. The consistency of the results was also checked by performing all regression analyses both with and without the highest and lowest percentages of observations of the explanatory variables. Further, we made several subgroup analyses: First, we repeated all analyses in the three categories of smoking, namely in never smokers, former smokers and current smokers. Second, we repeated all analyses in individuals younger than 45 years and in individuals 45 years or more. The age-divided analyses were made to compensate for the likely inclusion of COPD-related wheezing in individuals of 45 years or more.

Results

The study population consisted of 85,555 individuals (39.7% female), with a median age of 34 years (range: 16–75 years). The prevalence of wheezing was 18.0% (95% CI 17.8–18.3%). Table 1 presents the initial analyses of the risk of wheezing adjusted only for sex and age. Wheezing was positively associated with BMI, waist circumference, and the presence of high s-TG level, high blood pressure, and metabolic syndrome. Wheezing was inversely associated with s-HDL level. In multiple regression analyses (Table 2), obesity (assessed as either BMI or waist circumference), elevated s-TG level, and low s-HDL level remained significantly associated with wheezing after mutual adjustment of serum lipid level and adiposity (both as categorical and continuous variables). Fig. 1 displays data for the lipids by six levels of BMI. Results are given per standard deviation of each variable (standardized effects), allowing a direct comparison of the strength of the association of s-TG vs. s-HDL with wheezing. The level of s-TG and s-HDL seemed associated with wheezing with fairly the same strength and these associations were fairly similar in normal weight individuals and in overweight/obese individuals. Further, we found no statistically significant interactions between lipid levels and BMI in relation to risk of wheezing (for all interactions, $p > 0.23$).

Smoking status was significantly associated with serum lipids, adiposity and wheezing. Yet, in subgroups of never, former, and current smokers, results were essentially similar to those obtained in the total population. Consistent

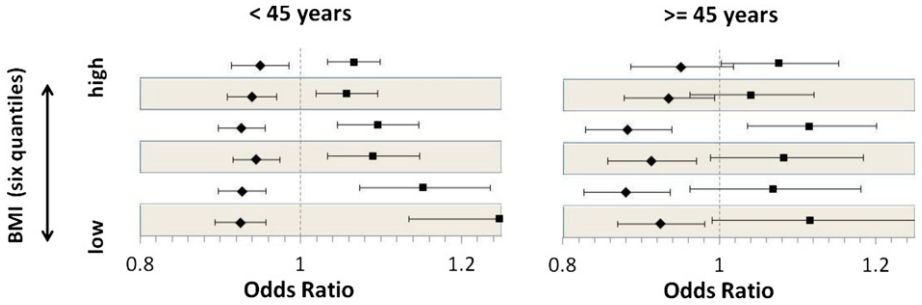

Figure 2 Risk of wheezing per standard deviation of s-HDL and s-TG by level of BMI (six quantiles) in individuals younger than 45 years and 45 years or older. Diamonds: s-HDL; squares: s-TG. Odds ratio estimates with 95% confidence intervals indicated by error bars were obtained in logistic regression models adjusted for age, sex, adiposity, occupation, alcohol, and physical activity during working hours. S-TG, serum triglyceride; s-HDL, serum high density lipoprotein.

with this, test for interaction between smoking status in three categories (never, former, and current smokers) and the lipids and/or adiposity measures were insignificant, *p*-values > 0.30, tobacco*BMI $p = 0.11$.

The associations presented above seemed stronger in the population younger than 45 years than in the population older than 45 years (Fig. 2), even though there was no significant interaction of age or age-splines with serum lipids.

The associations of adiposity, s-TG and s-HDL with wheezing were stronger in persons without rhinitis symptoms than in persons with rhinitis symptoms (Table 3). For the metabolic syndrome as a whole, the risk estimates of wheezing were OR (CI) = 1.37 (1.16–1.62) with rhinitis, but OR (CI) = 2.76 (2.21–3.43) without concurrent rhinitis ($p < 0.001$).

The other two serum measures we examined (s-LDL and s-total cholesterol) showed no significant associations with wheezing in any of the analyses. Alcohol consumption and lower educational level were positively associated with wheezing, and physical activity during working hours was inversely associated with wheezing (unadjusted data shown in Table 1). However, none of these variables or gender changed the adiposity-wheezing association or the associations of s-TG and s-HDL with wheezing (data not shown) when included in the regression models.

Analysing rhinitis separately, there were no associations of rhinitis symptoms with s-TG or measures of adiposity (Table 4, data shown only for BMI), although low s-HDL was positively associated with rhinitis symptoms.

Discussion

We found that high s-TG and low s-HDL, two of the components of the metabolic syndrome, were significantly associated with wheezing, particularly in persons without rhinitis symptoms. Notably, these associations persisted after adjustment for adiposity).

Table 3 Association of adiposity (body mass index, upper panel, and waist circumference, lower panel), s-triglycerides and s-HDL with self reported wheezing in the rhinitis and non-rhinitis population.

Analyses with WC	Risk of wheeze		
	Rhinitis population	Non-rhinitis population	Interaction[b]
	OR[a] (CI)	OR[a] (CI)	*p*-value
Waist circumference			
Normal[d]	Reference	Reference	
High[d]	1.47 (1.37–1.58)	1.70 (1.57–1.85)	0.01
S-Triglycerides			
Normal[d]	Reference	Reference	
High[d]	1.21 (1.13–1.29)	1.36 (1.26–1.46)	0.02
S-HDL			
Normal[d]	Reference	Reference	
Low[d]	1.11 (1.04–1.18)	1.24 (1.15–1.34)	0.02
Analyses with body mass index	**Risk of wheeze**		
	Rhinitis population	Non-rhinitis population	Interaction[b]
	OR[a] (CI)	OR[a] (CI)	*p*-value
Body mass index			
<18.5 kg/m^2	1.20 (1.00–1.44)	0.89 (0.66–1.18)	
18.5–<25 kg/m^2	Reference	Reference	
25–<30 kg/m^2	1.16 (1.10–1.23)	1.22 (1.13–1.31)	
>30 kg/m^2	1.58 (1.47–1.71)	1.87 (1.72–2.05)	0.02[c]
S-Triglycerides			
Normal[d]	Reference	Reference	
High[d]	1.18 (1.10–1.26)	1.30 (1.20–1.41)	0.03
S-HDL			
Normal[d]	Reference	Reference	
Low[d]	1.09 (1.03–1.17)	1.23 (1.13–1.32)	0.02

The rhinitis population was defined as those with self-reported rhinitis symptoms.

[a] Odds ratio (OR) estimates with 95% confidence intervals (CI) were obtained in logistic regression models adjusted for age, sex, education, alcohol, tobacco, and physical activity during working hours as well as for the variables in the upper or lower panel respectively.

[b] Interaction *p*-value, log likelihood test of significance of the interaction terms (rhinitis*covariate); WC, waist circumference; BMI, body mass index; f, females; m, males.

[c] Indicate the *p*-value for the interaction between BMI in four groups and rhinitis.

[d] Defined according to ATP III criteria[23]: abdominal adiposity (waist circumference >102 cm in male subjects or >88 cm in female subjects); hypertriglyceridemia (fasting serum triglycerides >150 mg/dl); low HDL cholesterol (<40 mg/dl in male subjects or <50 mg/dl in female subjects).

The results presented in this paper seemed to be stronger in individuals younger than 45 years. We speculate that wheezing in this group is more likely to be a symptom of asthma than in individuals older than 45 years, and thus high s-TG and low s-HDL may be associated with asthma. However, these results come from subgroup analyses and must be interpreted with caution.

Our results add to earlier findings that insulin resistance and the metabolic syndrome are associated with asthma-like symptoms[25] and with asthma,[3] and corroborate findings from a study that found that elevated s-TG and lowered s-HDL were associated with impaired lung function independently of waist circumference.[12] Our results are also consistent with the fact that improved lung function and reduced asthma severity was noted after duodenal bypass surgery,[26] which significantly improves glycemic control[27] and results in major reductions of hepatic triglyceride content[16]). By contrast, a cross sectional study from Korea with 9942 participants[28] found no association of s-TG and s-HDL with asthma-like symptoms although it is unclear whether possible confounders such as smoking, age, and sex were accounted for in this study. In line with this, a NHANES-study showed that increasing levels of s-TG and decreasing levels of s-HDL were associated with a lower risk of asthma in a study with 7005 individuals[29]; further there was a positive association between increasing levels of s-LDL and risk of asthma.

Table 4 Association of self reported rhinitis symptoms and selected risk factors.

	Risk of rhinitis symptoms
	OR[a] (CI)
Age (years)	0.99 (0.99–0.99)
Gender	
Female	Reference
Male	0.80 (0.76–0.83)
Body mass index	
Continuous, 1SD[b]	0.94 (0.92–0.97)
S-Triglycerides	
Normal[c]	Reference
High[c]	0.99 (0.95–1.03)
S-HDL	
Normal[c]	Reference
Low[c]	1.04 (1.01–1.09)
Blood pressure	
Normal[c]	Reference
High[c]	0.95 (0.91–0.98)
S-glucose	
Normal[c]	Reference
High[c]	0.95 (0.91–1.00)
Physical activity	
(Four categories)	1.02 (0.99–1.06)
Occupation	
High level (non-manual)[d]	Reference
Low level (manual)[d]	1.00 (0.95–1.05)
Tobacco	
Never smokers	Reference
Former smokers	1.07 (1.02–1.11)
Current smokers	1.14 (1.10–1.18)
Alcohol (single units)	1.00 (1.00–1.00)

[a] Odds ratio (OR) estimates with 95% confidence intervals (CI) were obtained in logistic regression model adjusted for all variables in the table.
[b] SD, standard deviation; HDL, high density lipoprotein cholesterol.
[c] Defined according to ATP III criteria.[23]
[d] Defined according to the Spanish National Classification of Occupations.[24]

The observed associations between serum lipids and wheezing (asthma) raise several possibilities. Firstly, increasing s-TG and decreasing s-HDL levels could simply be markers of dysfunctional adipose tissue. This implies that dysfunctional adipose tissue is different from the total amount of adipose tissue in the body, as Franssen and colleagues[30] speculated earlier. This notion is supported by a recent study of hypertriglyceridemia in mice that suggested that elevated s-TG indicates the presence of metabolically-induced inflammation.[31] Another possibility is that increasing s-TG and decreasing s-HDL could either initiate or accelerate ongoing systemic inflammation that would later lead to airway disease, via mechanisms that are not yet understood. However, both the results of our cross-sectional study and the subsequent speculations about the perspectives of the study need to be investigated further in studies designed for this purpose.

Asthma likely consists of different entities, with early onset and predominantly atopic asthma contrasting with late onset and predominantly non-atopic asthma.[5] Earlier studies have found an increased risk of obesity-related asthma among non-atopics.[32,33] We found that adiposity, s-TG and s-HDL were all more strongly associated with wheezing in individuals without rhinitis symptoms than in individuals with symptoms. These associations suggest the presence of a type of asthma that is associated with low grade inflammation/metabolic dysfunction. This notion is supported by another study showing that s-TG was not associated with atopic sensitization per se[34] as well as by our finding that s-TG was not associated with rhinitis symptoms.

One of the strengths of our study was the high number of individuals ($n = 85{,}555$) collected from the ICARIA study of workers from all regions of Spain. Although the young age of the study population meant that the exposure measures of interest, the serum lipids, in general were not markedly elevated/lowered, we nevertheless found consistent associations of s-TGs and s-HDL with wheezing.

Limitations of the study include a cross-sectional design that leaves the direction of the association between serum lipids and wheezing unknown. A better definition of asthma would have been preferable as there certainly is a difference between "wheeze" and "asthma". Unfortunately the study was not originally designed for studying asthma. In this case, several known risk factors for asthma could have been included, e.g. a better definition of atopy, such as one based on skin prick test reactivity or elevated IgE-levels to specific common allergens. Further, we could have differentiated between individuals with early or late onset wheezing, this could have strengthened the associations between serum lipids and late-onset wheezing. We used a rather crude measure of tobacco exposure categorizing participants in 'never', 'former', and 'current' smokers that may have led to

residual confounding. However, we found associations of serum lipids with wheezing in all three categories of tobacco use. We did not examine the effect of diet, although diet could influence the level of serum lipids, e.g. through the amount of fructose, and affect airway inflammation, e.g. through antioxidants.[35,36] Also, genetic pleiotropy could be another possible confounder of our results as some studies have indicated a common background for asthma and endocrine disorders such as diabetes, and for asthma and metabolic syndrome.[37,38] Despite the limitations, most of which would lead the estimates of the analyses closer to null, we did observe consistent associations of serum lipids with wheezing.

In conclusion, we found that high s-TG and low s-HDL were significantly associated with the risk of wheezing in 85,555 Spanish workers and these associations persisted after adjusting in several ways for adiposity. The finding that these associations were mainly seen in individuals without rhinitis symptoms may support the notion that only specific types of asthma are associated with low-grade systemic inflammation.

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Conflict of interest

None.

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