

Associations of adipokines with asthma, rhinoconjunctivitis, and eczema in German schoolchildren

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There is growing evidence for an association between obesity and asthma, but little is known about the underlying mechanisms. We hypothesized that high plasma leptin and low plasma adiponectin concentrations might be related to asthma and allergies in children. Plasma leptin and adiponectin concentrations were measured in a cross-sectional study involving 462 children aged 10 years. Information on disease symptoms and diagnosis was collected by parental questioning. Multivariate linear and logistic regression models were used to assess the association between biomarkers and disease. High leptin levels were associated with increased lifetime prevalence of asthma [odds ratio (OR): 3.76; 95% confidence interval (CI): 1.42–9.92]. The relationship was particularly strong for non-atopic asthma (OR: 5.51; 95% CI: 1.99–17.51). No associations were observed between plasma leptin levels and hay fever, and rhinoconjunctivitis. Low adiponectin levels were associated with increased prevalence of both symptoms of atopic dermatitis (OR: 3.23; 95% CI: 1.28–7.76) and ever-diagnosed eczema (OR: 2.35; 95% CI: 1.13–4.89). In girls and non-atopic children, stronger associations for both leptin and adiponectin levels with asthma than in boys and atopic children were observed. These results suggest that adipokines may contribute to increased asthma and allergy risk in obese subjects. Stronger associations among girls with non-atopic asthma may indicate diverse pathological mechanisms.

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Secular trends of increased obesity and asthma prevalence in both adults and children during the past decades have led to a debate about potential links between both conditions. There is growing evidence of an association between obesity and asthma, which tends to be stronger in women than in men (1, 2). Various mechanisms, i.e. mechanical, immunological, hormonal, and genetic, have been proposed to explain this association (3–5). Adipose tissue secretes bioactive peptides such as leptin and adiponectin, which are collectively named ‘adipokines’.

Leptin is mainly produced by the adipose tissue and corresponds with body mass index (BMI) (6)

by regulating food intake and basal metabolism (7). Because of the expression of leptin receptors in the lung (8), leptin is thought to be associated with inflammation and T-cell function in asthma (9). In animal models, leptin deficiency was associated with increased susceptibility to endotoxin and decreased induction of anti-inflammatory cytokines (10). High leptin levels were associated with higher prevalence of asthma in children (9) and in adults (11). However, no association was found between leptin levels in cord blood and wheeze during the first 2 yr in children (12).

Adiponectin is also synthesized by adipocytes and plays a role in the regulation of insulin

sensitivity (13, 14). In contrast to leptin, adiponectin is inversely associated with obesity in children (15, 16). In mice, high adiponectin concentrations attenuated allergic airway inflammation and hyper-responsiveness (17), suggesting that low levels of adiponectin may be associated with asthma symptoms. Recently, a relationship between adiponectin concentrations in cord blood and wheeze in children during the first 2 yr of life has been reported (12). The aim of this study was to explore the relationship between high plasma leptin concentrations and low adiponectin concentrations in 10-yr-old schoolchildren with respiratory and allergy symptoms.

Materials and methods

Study population

A cross-sectional study was carried out as part of a surveillance program of chronic conditions in children, which included asthma and allergies. The study was coordinated by the Baden-Württemberg State Health Office and approved by the local ethics committee (18). From October 2004 to March 2005, 557 grade 4 schoolchildren (47% boys, 53% girls) were enrolled after written informed consent had been obtained from their parents, in three cities (Kehl, Mannheim, Stuttgart) and rural areas (Aulendorf, Calw, Hohenlohe) in south-west Germany. We investigated the associations of adipokines with asthma, rhinoconjunctivitis, and eczema using the blood samples of 462 children (83%).

Outcome variables

Parental questioning by means of a standardized questionnaire based on the International Study on Allergies and Asthma (ISAAC) was performed (19). Information on asthma, respiratory symptoms, allergy symptoms, and lifestyle variables was collected.

The analyses focused on the prevalence of asthma or allergies during lifetime and the previous year. The relevant questions were: 'Has your child had wheezing or whistling in the chest in the past 12 months?' For rhinoconjunctivitis, the following questions were examined: 'Has your child had a problem with sneezing or running or a blocked nose?' and 'In the past 12 months has this nose problem been accompanied by itchy watery eyes?' For atopic dermatitis the following questions were relevant: 'Has your child ever had an itchy rash, which was coming and going for at least six months?' 'Has the itchy rash at any time affected any of the

following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?' In addition, data on the lifetime prevalence of asthma, eczema, and hay fever were collected. Symptoms of rhinoconjunctivitis were used as a proxy for atopy (20).

Covariates

The children were invited to a physical examination, including the measurement of height and weight in a standardized manner. Body mass index (BMI) was calculated from weight (kg)/height² (m). The question: 'Does a smoker live in your home?' was used to examine environmental tobacco smoke exposure (yes, no). Information on family history of atopy was collected asking, whether one of the family members had/has an atopic disease.

Laboratory methods

Non-fasting ethylenediaminetetraacetic acid (EDTA)-added blood samples were drawn from 462 children. After centrifugation, the samples were aliquoted and stored at -80°C until analysis. All laboratory analyses were performed at the Department of Internal Medicine II-Cardiology, Ulm University Medical Center.

Leptin (pg/ml) was measured by enzyme-linked immunosorbent assay (ELISA) in EDTA-added plasma samples (R&D Systems, Wiesbaden, Germany). The lower detection limit of leptin in this assay was approximately 0.078 ng/ml. The inter-assay coefficient of variation (CV) was 3.86%. Plasma levels of adiponectin (µg/ml) were also determined by a commercial ELISA (R&D Systems). The lower detection limit was 0.246 ng/ml and the inter-assay CV was 5.75%.

For plasma leptin and adiponectin concentrations, no accepted cut-off points were available to define obesity in children. We therefore chose as cut-off points, values above the 90th percentile for leptin and values below the 10th percentile for adiponectin from the distribution of our data.

As plasma leptin concentrations differed significantly by sex, values above the sex-specific 90th percentiles were considered high (cut-off: boys ≥13,918 pg/ml, girls ≥20,292 pg/ml) and compared with lower plasma leptin levels. For adiponectin, the 10th percentile was chosen as the cut-off point (≤ 4.97 µg/ml) and compared with higher plasma adiponectin concentrations.

Statistical analysis

Median and percentile values were calculated using the SAS procedure UNIVARIATE. We used Mann–Whitney U-test for continuous variables (SAS procedure NPAR1WAY) and chi-squared test for proportions. Spearman's correlation coefficients were used to evaluate the association between continuous variables. Logistic regression was used to calculate multivariate odds ratios (OR) and 95% confidence intervals (CI) for the presence of respiratory symptoms and allergies. Models were adjusted for sex, environmental tobacco smoke (yes, no), family history of atopy (yes, no) and also for BMI (kg/m²). Analyses were performed separately by gender. Models with continuous values of the log-transformed exposure variables (leptin, adiponectin) were calculated in order to examine the consistency of the data. Interactions were tested using the Wald test. All provided p-values are two-sided. The statistical software package SAS release 9.1 (SAS Institute, Cary, NC, USA) was used.

Results

Selected characteristics of the study sample according to asthma and atopy are shown in Table 1. Among 462 randomly selected 10-yr-old schoolchildren, 30 (6.7%) suffered from wheeze during the past year and 30 (6.7%) children experienced asthma during their lifetime. Regarding atopy, 41 (9.0%) children experienced rhinoconjunctivitis during the past year, while 52 (11.8%) children ever had hay fever. Compared with the entire group, median age and BMI did not differ statistically significantly in children with wheeze during the past year, rhinoconjunctivitis, and atopic dermatitis. Prevalence of wheeze during the past year was low among girls. Family history of atopy was significantly associated with all outcomes, except wheeze during the past year and hay fever. There was a strong positive correlation for plasma leptin concentrations with BMI ($r = 0.81$, $p < 0.001$), but no correlation was found with plasma adiponectin concentrations ($r = -0.01$, $p = 0.85$). Adiponectin, however, was negatively correlated with BMI ($r = -0.11$, $p = 0.02$) (data not shown).

The associations of plasma leptin levels with asthma and allergies are shown in Table 2. High plasma leptin levels were associated with an increased prevalence of asthma (OR: 3.76; 95% CI: 1.42–9.92). The association of high leptin levels was stronger with non-atopic asthma (OR: 5.51; 95% CI: 1.99–17.51) than with atopic

Table 1. Sample characteristics of 462 schoolchildren by asthma and allergies

Variables	Total	Wheeze past year†	Asthma ever‡	Rhino-conjunctivitis†	Atopic asthma†	Hay fever ever†	Atopic dermatitis†	Eczema ever†
Total (n)	462	447	445	458	394	441	388	444
Continuous, median (range)								
Age (years)	10.0 (8.3–12.6)	9.9 (9.2–11.5)	10.0 (9.2–12.0)	9.8 (9.1–11.9)	9.8 (9.2–10.2)	9.9 (8.7–11.9)	10.0 (9.1–12.0)	9.9 (8.3–12.0)
BMI (kg/m ²)	17.1 (12.9–31.3)	17.0 (12.9–25.7)	18.6 (13.7–27.4)	17.5 (12.9–25.4)	17.6 (13.7–21.8)	17.1 (14.0–24.6)	17.7 (12.9–31.3)	16.5 (12.9–24.1)
Leptin (pg/ml)	3609.0	3454.5	4717.0 (116–59611.0)	3853.0	3464.0	3578.5	5274.5	2373.0
Adiponectin (µg/ml)	(74.1–66596.0)	(116.0–31155.0)		(116.0–27315.0)	(116.0–20662.0)	(299.0–59611.00)	(341.0–37666.0)	(74.1–35044.0)**
Categorical, %								
Girls	53.1	36.7*	36.7	41.5	20.0*	42.3	64.0	55.6
Environmental tobacco smoke (ETS)	47.5	50.0	50.0	41.5	60.0	38.5	46.9	37.0
Family history of atopy	36.9	60.0**	70.0***	59.0**	80.0**	53.0**	68.8***	57.5***
Leptin levels ≥90th percentile	10.2	10.9	14.9*	8.5	2.6	13.6	8.9	17.5
Adiponectin levels ≤ 10th percentile	10.2	6.5	8.7	6.5	0	15.6	28.9	22.0

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

†Numbers in each variable do not add up to total study sample due to missing data.

‡Among 30 children with asthma during lifetime, 11 (37%) children had experienced wheeze during the past year.

Table 2. Associations between plasma leptin (pg/ml) levels and asthma and allergies (OR with 95% CI for logistic and β -coefficient and p-value for linear regression models)

	n/N†	Multivariate‡			Multivariate§ ≥90th percentile		Continuous values§¶ log leptin	
		<90th percentile		95% CI	OR	95% CI	β -coefficient	p-value
		OR	OR					
Wheeze past year	30/429	1	1.97	0.69–5.58	2.40	0.74–7.83	−0.01	0.93
Asthma ever	28/427	1	3.76	1.42–9.92	4.10	1.34–12.51	0.22	0.19
Atopic asthma	10/380	1	1.27	0.15–11.08	1.49	0.14–15.59	−0.03	0.92
Non-atopic asthma	18/388	1	5.51	1.99–17.51	6.42	1.67–24.69	0.40	0.06
Rhinoconjunctivitis	39/438	1	1.12	0.37–3.39	1.18	0.36–3.92	0.06	0.69
Hay fever ever	51/425	1	1.37	0.54–3.49	1.48	0.53–4.17	0.10	0.43
Atopic dermatitis	47/373	1	2.04	0.79–5.27	1.96	0.71–5.45	0.15	0.30
Eczema ever	80/427	1	0.32	0.09–1.07	0.40	0.11–1.43	−0.38	<0.001

†Numbers in each variable do not add up to total study sample due to missing data.

‡Adjusted for sex, family history of atopy, environmental smoking.

§Adjusted for sex, family history of atopy, environmental smoking, BMI in tertiles.

¶log-transformed.

Table 3. Associations between plasma adiponectin (μ g/ml) levels and asthma and allergies (OR with 95% CI for logistic and β -coefficient and p-value for linear regression models)

	n/N†	Multivariate‡			Multivariate§ ≤ 10th percentile		Continuous values§¶ log adiponectin	
		>10th percentile		95% CI	OR	95% CI	β -coefficient	p-value
		OR	OR					
Wheeze past year	30/429	1	0.95	0.27–3.23	0.98	0.28–3.44	0.09	0.84
Asthma ever	28/427	1	1.60	0.51–4.99	1.62	0.52–5.09	0.56	0.20
Atopic asthma	10/380	1	–	–	–	–	−1.27	0.11
Non-atopic asthma	18/388	1	2.70	0.82–8.88	2.74	0.83–9.09	1.35	<0.01
Rhinoconjunctivitis	39/438	1	0.75	0.22–2.59	0.81	0.23–2.80	−0.33	0.41
Hay fever ever	51/425	1	1.52	0.67–3.68	1.60	0.66–3.89	0.36	0.28
Atopic dermatitis	47/373	1	3.23	1.31–7.96	3.15	1.28–7.76	0.51	0.07
Eczema ever	81/428	1	2.35	1.13–4.89	2.59	1.22–5.51	0.84	0.02

†Numbers in each variable do not add up to total study sample because of missing data.

‡Adjusted for sex, family history of atopy, environmental smoking.

§Adjusted for sex, family history of atopy, environmental smoking, BMI in tertiles.

¶log-transformed.

asthma (OR: 1.27; 95% CI: 0.15–11.08). High leptin levels were non-significantly associated with prevalence of wheeze during the past year (OR: 1.97; 95% CI: 0.69–5.58). No statistically significant associations were found between high leptin levels and lifetime prevalence of eczema and symptoms of atopic dermatitis.

Table 3 shows the associations of plasma adiponectin levels with asthma and allergies. The prevalence of asthma was statistically non-significantly increased (OR: 1.60, 95% CI: 0.51–4.99) for low adiponectin levels, whereas no association was found for wheeze during the past year (OR: 0.95, 95% CI: 0.27–3.23). In linear regression analysis, decreasing plasma adiponectin concentrations were associated with non-

atopic asthma (β -coefficient = 1.35, $p < 0.01$) but not with atopic asthma (β -coefficient = −1.27, $p = 0.11$).

Non-significant associations were found for low adiponectin levels with reduced rhinoconjunctivitis (OR: 0.75, 95% CI: 0.22–2.59) and increased hay fever prevalence (OR: 1.52, 95% CI: 0.67–3.68), while low adiponectin levels were associated with increased prevalences of both eczema (OR: 2.35, 95% CI: 1.13–4.89) and symptoms of atopic dermatitis (OR: 3.23, 95% CI: 1.31–7.96).

Mutual adjustment for plasma leptin and adiponectin in the fully adjusted model did not substantially alter the associations (data not shown). The introduction of BMI in the models

Table 4. Associations of serum leptin (pg/ml) and adiponectin (μg/ml) with asthma and allergies by sex (OR with 95% CI for logistic and β-coefficient and p-value for linear regression models)

		Leptin					Adiponectin				
		Multivariate†			Continuous values†‡ log leptin		Multivariate†			Continuous values†‡ log adiponectin	
		<90th percentile	≥90th percentile				<10th percentile	<10th percentile			
	n/N	OR	OR	95% CI	β-coefficient	p-value	OR	OR	95% CI	β-coefficient	p-value
Girls (n = 243)*											
Wheeze past year	11/231	1	2.01	0.40–10.09	−0.06	0.85		na		−0.69	0.36
Asthma ever	10/228	1	13.34	3.18–55.97	0.70	0.04	1	2.87	0.55–14.91	1.75	0.01
Rhinoconjunctivitis	17/234	1	0.51	0.06–4.12	−0.10	0.67		1.48	0.31–7.07	0.09	0.88
Hay fever	22/240	1	0.48	0.06–3.77	−0.24	0.24	1	4.05	1.27–12.86	0.98	0.05
Atopic dermatitis	30/206	1	1.51	0.44–5.19	0.18	0.32	1	3.35	0.98–11.42	0.74	0.11
Eczema ever	44/230	1	0.62	0.17–2.27	−0.12	0.45	1	2.93	1.03–8.31	0.66	0.10
Boys (n = 215)*											
Wheeze past year	19/198	1	2.10	0.53–8.42	0.03	0.90	1	1.70	0.43–6.70	0.52	0.33
Asthma ever	18/199	1	1.30	0.26–6.50	0.02	0.91	1	1.12	0.23–5.48	−0.19	0.74
							1	na			
Rhinoconjunctivitis	22/204	1	1.85	0.48–7.22	0.18	0.36		0.38	0.05–3.00	−0.65	0.22
Hay fever	29/195	1	2.34	0.76–7.22	0.32	0.06	1	0.52	0.11–2.38	−0.15	0.74
Atopic dermatitis	17/184	1	3.55	0.78–16.11	0.10	0.66	1	3.14	0.82–11.97	1.04	0.08
Eczema ever	36/233	1	<0.001		−0.69	<0.01	1	1.81	0.64–5.14	0.35	0.40

†Adjusted for sex, family history of atopy, environmental smoking.

‡log-transformed.

both for leptin and adiponectin levels strengthened the associations for most outcomes. For leptin, in particular, stronger associations were found with asthma ever (OR: 4.10, 95% CI: 1.67–12.51) and non-atopic asthma (OR: 6.42; 95% CI: 1.67–24.69).

In sex-specific analyses (Table 4), stronger associations between high leptin levels and the prevalence of asthma in girls (OR: 13.34, 95% CI: 3.18–55.97) than in boys (OR: 1.30, 95% CI: 0.26–6.50) were found. In contrast to girls, among boys high leptin levels were associated with increased prevalence of hay fever and rhinoconjunctivitis. However, none of these associations for leptin were statistically significant. Low adiponectin levels were associated with increased prevalence of hay fever in girls (OR: 4.05, 95% CI: 1.27–12.86) but not in boys (OR: 0.52, 95% CI: 0.11–2.38).

Discussion

Evidence for an association between plasma leptin levels and asthma

In agreement with previous studies, we found high plasma leptin levels to be associated with increased prevalence of asthma and a trend for wheeze during the past year (9, 21). However, leptin concentrations in cord blood were not

associated with wheeze during the first 2 yr of life (12). The association with asthma was markedly stronger in girls than that in boys. Consistent with results from other studies, we found a more pronounced association between high leptin levels and asthma in girls (2, 11, 22). However, between children with asthma and healthy controls a larger difference of unadjusted mean plasma leptin levels has been reported in boys than in girls (9). Sood et al. found effect modification by menopausal status among women in adjusted analysis, suggesting that sex hormones might be involved in the causal pathway (11). A sex hormone-related pattern is also suggested by the association between BMI and asthma symptoms, which was stronger in girls with onset of puberty before the age of 11 yr (2). Testosterone increases leptin secretion, while estrogens decrease it (23). Thus, it might be speculated that sex hormones affect the relationship with respiratory symptoms by affecting the onset of puberty and inflammatory markers as seen in adults (24). In addition, the body fat pattern *per se* may influence leptin production (25, 26).

Evidence for associations of plasma leptin levels with rhinoconjunctivitis and eczema

Concerning allergies, no clear associations were found for high plasma leptin levels. Prevalence of

hay fever and atopic dermatitis were somewhat increased in children with high leptin levels, while no association was found for rhinoconjunctivitis. Results of experimental studies suggest a protective effect of high leptin levels against allergies (27, 28). Early reports have found positive correlations between serum leptin levels and immunoglobulin (Ig) E levels, particularly among boys (9, 29). Consistent with these reports, we found that plasma leptin concentrations were related to increased prevalences of rhinoconjunctivitis, hay fever and atopic dermatitis in boys, while inverse associations were found in girls. Leptin stimulates T-helper 1 (T_H1) and inhibits T_H2 cytokine production in mice (27), suggesting a protective effect against allergies. In animal studies, leptin deficiency enhanced sensitivity to endotoxin-enhanced reactions (10, 30). These findings are consistent with our observation of a stronger association between leptin levels and non-atopic asthma. Unfortunately, no data on IgE levels or results of skin prick tests are available. Because of the cross-sectional design of our study, the direction of the observed association among non-atopic children remains unclear.

Evidence for associations of plasma adiponectin levels with asthma and rhinoconjunctivitis

The relationship between low adiponectin levels and increased prevalence of asthma is supported by the observation that high adiponectin levels attenuate allergen-induced hyper-responsiveness in mice (17), suggesting a link between adiponectin and asthma. Further evidence came from a study using cord blood, in which high adiponectin levels were associated with increased risk of wheeze during the first 2 yr of life (12). Obesity is accompanied by decreases in adiponectin concentrations, which may lead to a reduction in the favourable effects of adiponectin such as ovalbumin-induced airway inflammation (17). Our findings of a stronger association for non-atopic asthma than for atopic asthma and no clear relationships with rhinoconjunctivitis and hay fever are consistent with these results of experimental studies. Interestingly, low adiponectin levels were associated with an increased prevalence of rhinoconjunctivitis and hay fever in girls but not in boys. We do not have straightforward explanations for these observations. However, testosterone levels seem to correlate with lower serum leptin or adiponectin levels in boys, indicating that other hormonal factors might be involved (23, 31). Further adjustment for BMI had little effect on the estimates in our data, suggesting a different mode of action.

Evidence for an association between plasma adiponectin levels and eczema

A linear relationship between increasing BMI and the presence of atopic dermatitis in women but not in men (32) is consistent with our finding concerning eczema, but not for symptoms of atopic dermatitis. In our data, median adiponectin levels did not differ substantially between girls (median 9.3 µg/ml) and boys (median 9.4 µg/ml), but clearly lower adiponectin levels are seen in men than in women (13), which can be explained by hormonal status in adults (33). As plasma adiponectin levels are sex-specifically associated with lipid profiles (34), it is possible that the sex-specific eczema patterns are also mediated by other metabolic or inflammatory factors.

Study limitations and strengths

Our study has several limitations that need to be considered. Asthma and the occurrence of disease symptoms were reported by parents and may be biased by recall. However, we used a validated ISAAC questionnaire (19). Apart from questions regarding respiratory symptoms, data on diagnosis of asthma and eczema were collected in order to reduce misclassification. Measurement error of the exposure variables seems unlikely, as in our data the leptin and adiponectin levels correlate with BMI (35). However, residual confounding because of the exposure to infections, dietary factors, and physical activity cannot be ruled out. In addition, the nature of the environment (urban–rural) may be a source of residual confounding. In our data, however, further adjustment for study center did not substantially change the estimates in the linear models. Compared with non-obese persons, pulmonary function in obese individuals is characterized by a higher respiratory frequency and smaller tidal volume (36). In our study, however, further adjustment for BMI did not appreciably change the association. The use of non-fasting blood samples may have distorted our results. However, in our data further adjustment for BMI did not substantially affect the associations. The cross-sectional design of our study allows no conclusions regarding causality. Because of the low statistical power of the study and the large number of statistical tests, results have to be interpreted with caution, as some may have occurred by chance alone. The strengths of the present study are its population-based approach, the use of a validated questionnaire, and the measurement of biological markers of exposure.

Conclusion

Our results provide further evidence for an association between plasma leptin concentrations and increased asthma prevalence. For leptin, in particular, this association was markedly stronger in girls than in boys. To our knowledge, this is the first study to explore the relationship between adiponectin levels and symptoms of asthma and allergies. Low adiponectin levels were modestly associated with increased prevalence of non-atopic asthma in a sex-specific manner. In order to clarify the sex-specific disease pattern, additional measurements of sex hormones may be needed. The particularly strong association between low plasma adiponectin levels and increased prevalence of atopic dermatitis suggests differential involvement of adiponectin in various outcomes.

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