

Association of asthma diagnosis with leptin and adiponectin: a systematic review and meta-analysis

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ABSTRACT

There is some evidence which shows that higher levels of serum leptin and lower levels of serum adiponectin are associated with the diagnosis of asthma. This meta-analysis evaluated the association of serum leptin and adiponectin levels with the diagnosis of asthma. We searched the MEDLINE, Cochrane, EMBASE and CINAHL Plus databases up to July 2015. Eligible studies were randomized controlled trials, prospective studies, retrospective studies, case-control studies and cohort studies. 13 studies with 3642 patients were included in the study. The meta-analysis found that in the overall study population, the diagnosis of asthma was associated with higher levels of leptin (pooled standardized difference in means=0.867, 95% CI 0.416 to 1.318, $p<0.001$) and lower levels of adiponectin (pooled standardized difference in means=-0.371, 95% CI -0.728 to -0.014, $p=0.042$) in patients with asthma compared with controls. Subgroup analysis found that higher leptin levels were associated with asthma both in adults (standardized difference in means=1.374, 95% CI 0.621 to 2.126, $p<0.001$) and children (standardized difference in means=0.302, 95% CI 0.010 to 0.594, $p=0.042$). However, borderline association of adiponectin with asthma was seen in adults ($p=0.05$), but not in children ($p=0.509$). Sensitivity analysis indicated that the findings for leptin were robust. Our findings are consistent with higher levels of serum leptin being associated with asthma regardless of age, and low adiponectin levels being associated with asthma in adults only.

INTRODUCTION

Asthma is characterized by reversible airway obstruction and is a prevalent inflammatory airway disease. The incidence of asthma has been rising and has paralleled the increase in the incidence of obesity.¹ Obesity is a known risk factor for asthma.² In adults and children, obesity is associated with about a twofold increase in asthma which is more common in obese than lean adults.²⁻⁴ In addition, a dose-dependent increase in the incidence and severity of asthma is associated with elevated body mass index (BMI), most notably in the children and adolescents.^{2 3 5} Moreover, several studies have found an interaction between obesity and asthma.⁶⁻⁹

Significance of this study

What is already known about this subject?

- Obesity is a known risk factor for the worse asthma outcomes.
- Adipose-derived secreted factor leptin and adiponectin have proinflammatory and anti-inflammatory activities, respectively.
- Higher levels of leptin in obese people may increase lung-associated inflammation thus increasing the risk of asthma.
- Reduction in adiponectin-related anti-inflammatory effects due to obesity may associate with incidence and severity of asthma.

What are the new findings?

- Increased serum levels of leptin and decreased adiponectin are associated with asthma.
- Higher level of serum leptin is associated with asthma regardless of age.
- Adiponectin is weakly associated with asthma in adults, but there is no association in children.

How might these results change the focus of research or clinical practice?

- Adipose tissue microenvironment might play some roles in airway inflammation.

Obesity is concomitant with chronic low-grade systemic inflammation that is thought to cause complications, such as metabolic disease.¹⁰ Systemic inflammation is controlled by the production of a number of energy regulating hormones (adipokines) such as leptin, adiponectin and resistin by the adipose tissue.^{1 11} Recent studies have demonstrated that bone marrow trafficking, survival and function of eosinophil can be regulated by adipokines.¹² Leptin is produced and secreted by the adipose tissue and obese children and adults have elevated leptin serum levels.¹² Leptin receptors are present on human lung cells, including type II pneumocytes, epithelial cells, and macrophages.¹³⁻¹⁵ Leptin has pro-inflammatory activities and population-based studies have found



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an association between the presence of asthma and serum leptin levels in certain populations, such as prepubertal boys and girls, and premenopausal women.^{16–18} However, the association of leptin levels in adults with asthma are less convincing from clinical based studies as the findings have not been consistent.^{19–23}

Adiponectin is predominately an anti-inflammatory adipokine that downregulates proinflammatory cytokines including tumor necrosis factor- α , interleukin 6 (IL-6) and nuclear factor- κ B.¹² Adiponectin also upregulates anti-inflammatory cytokines such as IL-1 receptor antagonists and IL-10.¹² Findings in mice have indicated that adiponectin may directly influence the development of asthma. Studies on mice have found that adiponectin lessens airway changes in individuals suffering with asthma and allergen-induced bronchoprovocation reduces adiponectin levels.^{24–25} However, this relationship has not been well established in humans. Evidence indicate that adiponectin may inhibit the development of asthma in humans.¹ Some, but not all, studies have found a relationship between total serum adiponectin levels and the risk of asthma among women and peripubertal girls.^{17–26–30}

Owing to the inconsistencies in findings from clinical studies for the association of adiponectin or leptin with asthma, we used a meta-analysis to further explore the association of leptin and adiponectin with asthma.

MATERIALS AND METHODS

Search strategy

The methods used in this review comply with the PRISMA guidelines for conducting systematic reviews. We searched the MEDLINE, Cochrane, EMBASE and CINAHL Plus databases up to July 2015. The search terms included 'P: asthma; I+C: leptin or adiponectin level measurement/leptin or adiponectin level ratio (time point); O: risk or incidence of asthma, asthma symptoms/symptom scores, lung function test/FEV₁, QoL questionnaires, Asthma Control Questionnaire (ACQ)'. Included studies were randomized controlled trials, prospective studies, retrospective studies, case-control studies and cohort studies (if OR were provided). Studies had to report quantitatively outcomes of interest and include adiponectin or leptin-level measurement or their ratios. Letters, comments, editorials, case report, proceedings and personal communication were excluded. Two independent reviewers evaluated potential studies for inclusion, and any differences between them were decided by a third reviewer.

Data extraction

The following data was extracted from the studies: age (subgroups: ≤ 2 years, 3–18 years, > 18 years), gender, study design, severity of asthma, follow-up time, timing of intervention, co-treatment, residential area, smoking history, family history, BMI and type of asthma.

Outcome measures

The primary outcome measure was the diagnosis of asthma and the relationship with leptin and adiponectin levels. Subgroup measures were the diagnosis of asthma and the association of leptin and adiponectin stratified by age (≤ 18 and > 18 years).

Statistical analysis

To examine the association between diagnosis of asthma and the mean values of leptin or adiponectin, standardized difference in means of leptin or adiponectin between individuals diagnosed with asthma and control subjects was used as the measure of effect size; a standardized difference in means > 0 indicated higher levels of leptin/adiponectin in asthmatic subjects. If the included studies provided data of median and IQR, the data was transformed to mean and SD according to the method proposed by Hozo *et al.*³¹

Heterogeneity among studies was analyzed using a χ^2 -based Cochran's Q statistic and I^2 . For the Q statistic, p values < 0.10 were regarded as statistically significant for heterogeneity. For the I^2 statistic, heterogeneity was assessed as follows: no heterogeneity ($I^2 = 0$ –25%), moderate heterogeneity ($I^2 = 25$ –50%), large heterogeneity ($I^2 = 50$ –75%) and extreme heterogeneity ($I^2 = 75$ –100%). A DerSimonian–Laird random-effects model was used to calculate the pooled estimates of standardized difference in means.³² A two-sided p value of < 0.05 was considered significant. Subgroup analysis was performed according to age (≤ 18 and > 18 years).

Sensitivity analysis was conducted by excluding studies providing log-transformed values of leptin/adiponectin, and then a leave-one-out approach was used for the remaining studies. The asymmetry of funnel plot was evaluated by Egger's test with one-tailed p value; publication bias existed if one-tailed $p < 0.1$ by Egger's test. Quality in Prognosis Studies (QUIPS) tool was used for quality assessment.³³ Quality assessment was performed by two independent raters, and any uncertainties were decided by a third reviewer. All statistical analyses were conducted using the Comprehensive Meta-Analysis, V.2.0 (Biostat, Englewood, New Jersey, USA) software.

RESULTS

Literature search

Of the 53 articles initially identified, 26 articles were excluded for not being relevant and 14 more were excluded for being duplications, not having a relevant control, not reporting an outcome of interest or having incomplete quantitative data (figure 1). The remaining 13 articles^{16–20–21–23–28–34–40} were included for qualitative and quantitative analysis.

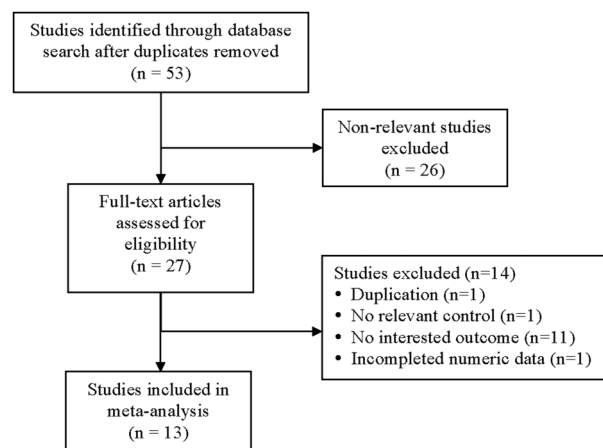


Figure 1 Flow chart for literature search.

Basic characteristics

Of the 13 studies, eight were case-control studies,^{20 21 28 36–38 40 41} four were cross-sectional studies^{16 34 35 39} and one was a cohort study.²³ The total number of patients included were 3742. The sample size ranged from 26 to 240 subjects, with mean or median age ranging from 6 to 57 years. Five of the 13 selected studies recruited children or adolescents. Three studies recruited only female subjects. The mean BMI ranged from 16 to 52 kg/m² (table 1).

Association between asthma and leptin/adiponectin

Twelve studies reported data on the levels of leptin present and 11 on adiponectin. There was extreme heterogeneity among the studies for leptin and adiponectin ($Q=125.3$, $p<0.001$, $I^2=91.2\%$ for leptin, and $Q=67.9$, $p<0.001$, $I^2=85.3\%$ for adiponectin). The pooled results showed that patients with asthma had higher levels of leptin than controls (pooled standardized difference in means=0.867, 95% CI 0.416 to 1.318, $p<0.001$) (figure 2A), and a lower levels of adiponectin than controls (pooled standardized difference in means=−0.371, 95% CI −0.728 to −0.014, $p=0.042$) (figure 2B).

Seven studies provided leptin data for adult subjects (≥ 18 years of age) and younger subjects (≤ 18 years of age).

The analysis found that there was significantly higher level of leptin in adult asthmatic subjects than controls (heterogeneity: $Q=92.3$, $p<0.001$, $I^2=93.5\%$; pooled standardized difference in means=1.374, 95% CI 0.621 to 2.126, $p<0.001$). For younger subjects, the association between asthma and leptin serum levels remained statistically significant but the magnitude of association was not as prominent as that in the case of adult population (heterogeneity: $Q=9.5$, $p=0.050$, $I^2=57.9\%$; pooled standardized difference in means=0.302, 95% CI 0.010 to 0.594, $p=0.042$) (figure 3A).

There was extreme heterogeneity across the studies that provided adiponectin data regardless of age (age >18 -year: $Q=53.2$, $p<0.001$, $I^2=86.8\%$; age ≤ 18 years: $Q=12.1$, $p=0.002$, $I^2=83.5\%$). Pooled results for the adult population showed borderline significance in the association between asthma and low serum adiponectin levels (pooled standardized difference in means=−0.466, 95% CI −0.932 to 0.001, $p=0.050$), while there was no association between adiponectin levels and asthma in the younger population (pooled standardized difference in means=−0.201, 95% CI −0.799 to 0.396, $p=0.509$) (figure 3B).

Sensitivity analysis and publication bias

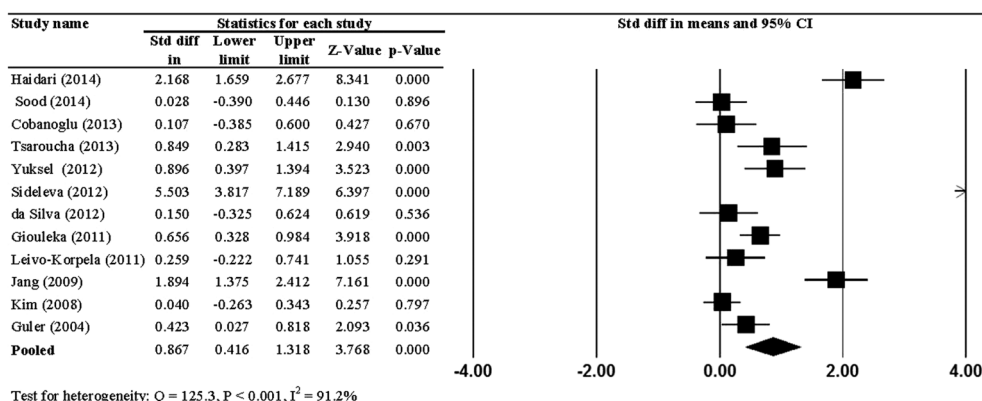
Table 2 summarizes the results of sensitivity analysis. Removal of the study³⁵ that reported leptin levels as log

Table 1 Summary of basic characteristics of selected studies for meta-analysis

Study	Study design	Type of asthma	Number of patients	Mean age (years)	Age ≤ 18 years	Male (%)	Mean BMI
Hayashikawa <i>et al</i> ³⁵	Cross-sectional	Asthma	23	65	N	52	23.1
		No asthma	68	65		53	23.3
Haidari <i>et al</i> ⁴¹	Case-control	Asthma	47	31.28	N	55	24.55
		No asthma	47	35.08		51	24.57
Sood <i>et al</i> ³⁶	Case-control	Asthma	44	34.7	N	32	30.7
		No asthma	44	32		32	30.8
Cobanoglu <i>et al</i> ³⁴	Cross-sectional	Asthma	23	8.2	Y	61	20.3
		No asthma	51	8.8		40	19.1
Tsaroucha <i>et al</i> ²⁰	Case-control	Asthma	32	57.5	N	0	34.4
		No asthma	22	57.6		0	31.2
Yuksel <i>et al</i> ³⁷	Case-control	Obese asthmatic	40	9.3	Y	55	25.1
		Non-obese asthmatic	51	10.4		57	18.6
		No asthma	20	10.7		45	18.1
Sideleva <i>et al</i> ²³	Cohort	Asthma	11	48	N	0	52
		No asthma	15	43		0	43.3
da Silva <i>et al</i> ³⁹	Cross-sectional	Asthma	26	16	Y	25	39
		No asthma	50	17		35	36
Giouleka <i>et al</i> ⁴⁰	Case-control	Asthma	100	52	N	40	28.3
		No asthma	60	50		42	28.8
Leivo-Korpela <i>et al</i> ³⁸	Case-control	Asthma	35	33.9	N	0	23.1
		No asthma	32	33.8		0	22.8
Jang <i>et al</i> ²¹	Case-control	Asthma	60	46.4	N	27	24.08
		No asthma	30	46.4		27	23.8
Kim <i>et al</i> ²⁸	Case-control	Atopic asthma	149	Median: 10.1	Y	66	NR
		Non-atopic asthma	37	Median: 9.0		68	
		No asthma	54	Median: 9.1		46	
Guler <i>et al</i> ¹⁶	Cross-sectional	Asthma	102	5.99	Y	64	17.53
		No asthma	33	6.12		58	16.98

BMI, body mass index; N, no; NR, not reported; Y, yes.

A Leptin



B Adiponectin

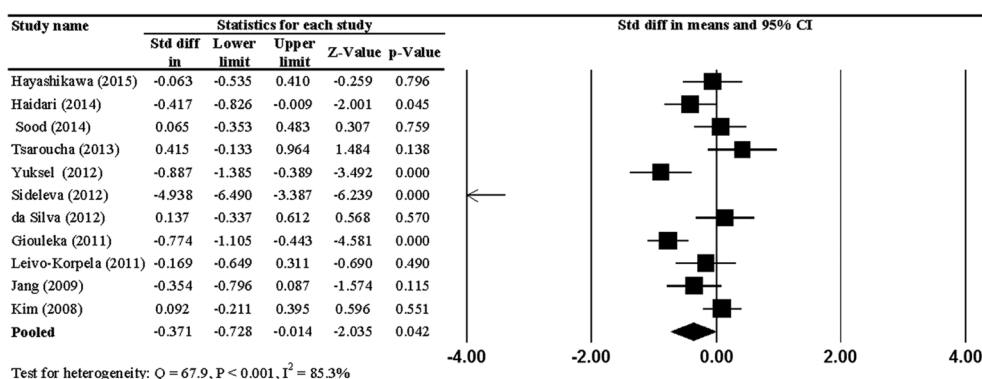


Figure 2 Forest plot for association between asthma versus leptin (A) and asthma versus adiponectin (B).

transformed values did not considerably change the findings. In addition, the pooled estimate effect size was just across the significance threshold when two studies^{21 28} that provided log-transformed values of adiponectin were excluded (pooled standardized difference in means = -0.434 , 95% CI -0.873 to 0.004 , $p=0.052$). Sensitivity analysis using the leave-one-out approach, found that the results for leptin were robust, as the removal of any one study did not dramatically change the direction or the significance of the results. However, for adiponectin, removal of four studies, Sood *et al*,³⁶ Tsaroucha *et al*,²⁰ da Silva *et al*,³⁹ and Kim *et al*,²⁸ impacted the significance of the association of adiponectin with asthma, suggesting that the findings of these studies overly impacted our analysis.

Funnel plots for the leptin and adiponectin results indicated the analysis had publication bias. The study of Sideleva *et al*²³ had larger SE and extreme standardized difference in means in the plots (figure 4). Egger's test showed significant asymmetry in the funnel plots for leptin ($t=2.77$, $df=10$, one-tailed $p=0.010$), but not for adiponectin levels ($t=1.74$, $df=9$, one-tailed $p=0.058$).

Quality assessment

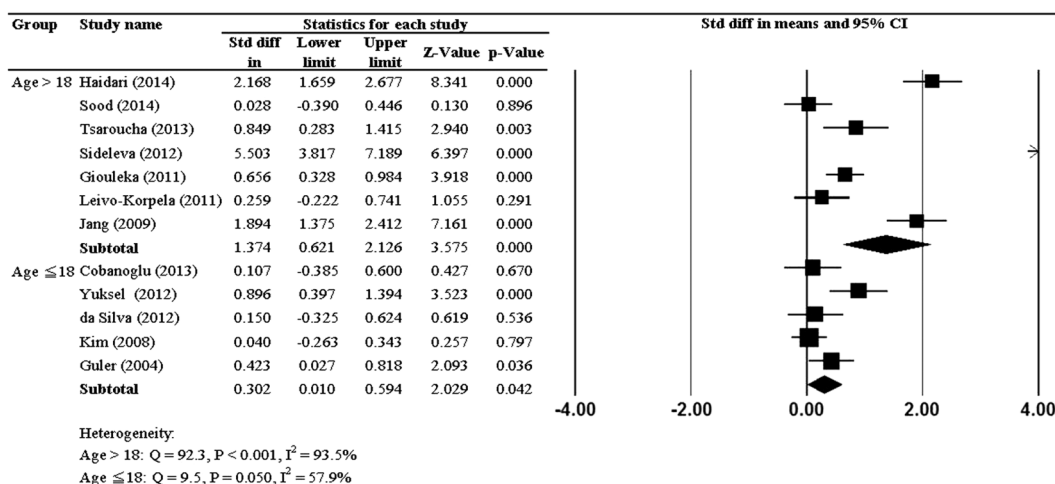
The results of quality assessment found that the scores ranged from six to eight points, indicating that the included studies were of high quality (figure 5). All trials followed the principles of (1) study participation, (2) study attrition,

(3) prognostic factor measurement and (4) outcome measurement. Among the 13 selected trials, 4 of them^{21 34 37 38} had high risk of bias in confounding measurement and accuracy and the Sood *et al* trial had a major concern in analysis.

DISCUSSION

The pathophysiology of asthma and obesity share some characteristics, and a dose increasing BMI is associated with an increased risk of asthma.^{1 12} Adipokines, such as leptin and adiponectin are produced in adipose tissues, and are hypothesized to be involved in a link between asthma and obesity.^{1 12} Our meta-analysis evaluated the association of serum leptin and adiponectin levels with the diagnosis of asthma. We found that in the overall study population, the diagnosis of asthma was associated with lower levels of adiponectin and higher levels of leptin compared with non-asthmatic controls ($p=0.042$). Subgroup analysis found that increased leptin levels were associated with the diagnosis of asthma both in adults and children ($p=0.042$). However, subgroup analysis found a borderline association of adiponectin with the diagnosis of asthma in adults ($p=0.05$), but not in children ($p=0.509$). Sensitivity analysis indicated that the findings for leptin were robust, the findings for adiponectin were overly influenced by the findings of several studies. Publication bias was present for leptin. Quality assessment indicated that, overall, the

A Leptin



B Adiponectin

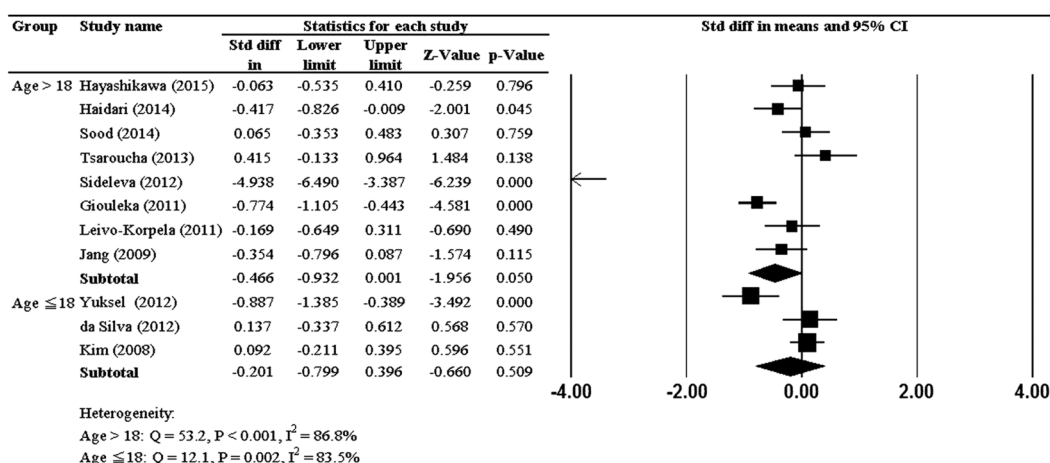


Figure 3 Subgroup analysis for association between asthma versus leptin (A) and asthma versus adiponectin (B) according to age of patients.

studies were of good quality. The findings support the association of leptin with asthma in both adults and children, and possibly an association of adiponectin with asthma in adults. Leptin promotes inflammation and adiponectin reduces inflammation; hence higher leptin levels and lower adiponectin levels may result in increased inflammation in the lung resulting in the development or worsening of asthma.

Our findings are consistent with earlier studies which found leptin that is associated with asthma both in children and adults.^{16–27} In the third national health and nutrition examination survey of subjects (≥ 20 years of age; $N=5876$), leptin was found to be highly associated with asthma, independent of BMI, particularly in premenopausal women.²⁷ Findings from a case-control study in 102 asthmatic and 33 healthy children by Guler *et al*¹⁶ indicated that serum leptin levels were predictive for asthma in boys. This association still remained even after adjusting for obesity.¹⁶ Similarly, Gurkan *et al*⁴² found leptin levels were higher in asthmatic children, independent of BMI. Lessard *et al*¹⁹ also found higher levels of leptin in adult asthmatic subjects than controls. However,

a New Zealand population based birth cohort study of young adults by Sutherland *et al*³⁰ and large sequential cross-sectional study by Jartti *et al*²⁹ did not find leptin to be associated with asthma. In addition, several clinical studies failed to find any differences between asthmatic and controls subjects in leptin levels after controlling BMI.¹ Differences in study design may also have resulted in divergent findings in the clinical and population-based studies.¹ Also, several possibilities exist on why the US-based population study was not repeated in the other two population studies. One was that the severity of obesity was lower in the non-US studies which may have truncated the high end of the range of systemic leptin studied, which is important since the US-based study suggests a non-linear effect for the highest quartile of serum levels with the risk of asthma.^{1–27}

We found that in the overall population asthma was associated with lower levels of adiponectin, but this association was only borderline in adults and was not significant in children. Previous studies have found an association of serum levels of adiponectin in certain populations based on gender and age. A US-based longitudinal cohort study by

Table 2 Sensitivity analysis for association between asthma and leptin/adiponectin

	Standardized difference in means	Lower limit	Upper limit	Z-value	p-value
Leptin					
Excluding studies providing log-transformed values	0.753	0.316	1.190	3.378	0.001
Leave-one-out approach					
Haidari <i>et al</i> ⁴¹	0.543	0.185	0.902	2.970	0.003
Sood <i>et al</i> ³⁶	0.840	0.365	1.315	3.466	0.001
Cobanoglu <i>et al</i> ³⁴	0.829	0.355	1.302	3.428	0.001
Tsaroucha <i>et al</i> ²⁰	0.751	0.280	1.222	3.125	0.002
Yuksel <i>et al</i> ³⁷	0.747	0.273	1.220	3.092	0.002
Sideleva <i>et al</i> ²³	0.545	0.179	0.910	2.920	0.003
da Silva <i>et al</i> ³⁹	0.826	0.350	1.302	3.399	0.001
Giouleka <i>et al</i> ⁴⁰	0.787	0.286	1.288	3.077	0.002
Leivo-Korpela <i>et al</i> ³⁸	0.816	0.337	1.294	3.341	0.001
Kim <i>et al</i> ²⁸	0.845	0.363	1.327	3.437	0.001
Guler <i>et al</i> ¹⁶	0.806	0.316	1.297	3.221	0.001
Adiponectin					
Excluding studies providing log-transformed values	−0.434	−0.873	0.004	−1.941	0.052
Leave-one-out approach					
Haidari <i>et al</i> ⁴¹	−0.458	−0.960	0.044	−1.787	0.074
Sood <i>et al</i> ³⁶	−0.518	−1.012	−0.025	−2.058	0.040
Tsaroucha <i>et al</i> ²⁰	−0.540	−1.005	−0.076	−2.278	0.023
Yuksel <i>et al</i> ³⁷	−0.377	−0.845	0.091	−1.578	0.115
Sideleva <i>et al</i> ²³	−0.201	−0.516	0.115	−1.248	0.212
da Silva <i>et al</i> ³⁹	−0.520	−1.005	−0.036	−2.107	0.035
Giouleka <i>et al</i> ⁴⁰	−0.391	−0.868	0.086	−1.607	0.108
Leivo-Korpela <i>et al</i> ³⁸	−0.486	−0.980	0.008	−1.929	0.054
Kim <i>et al</i> ²⁸	−0.531	−1.035	−0.027	−2.065	0.039

Sood *et al*²⁶ found low serum adiponectin (<7 mg/L) was associated with an increased risk of asthma among women, particularly current smokers. In addition, the study found that in women low serum adiponectin was a better predictor of asthma than BMI.²⁶ They did not find any association of low serum adiponectin with the risk of asthma in men.²⁶ Two cross-sectional studies also found that low serum adiponectin levels were associated with higher risk of asthma among peripubertal girls and premenopausal women.^{17–43} However, three other cross-sectional studies found no association between adiponectin levels and asthma.^{28–30} The difference between these studies may reflect study designs and populations. It may also indicate that more research may be needed regarding the understanding of the adiponectin signaling pathway. Currently, it is unclear whether blood adiponectin level is the appropriate measurement. It is possible that adiponectin levels in some other target tissue, such as lymph nodes or perilymphatic fat tissue, would be more appropriate for evaluating the role of adiponectin and asthma.¹ In addition, it is also possible that adiponectin may be sensitive to diurnal variation which would have confounded the study results.⁴⁴ We did not assess whether gender or gender-related aspects affected our findings.

Similar to other studies, we found that, at least for adiponectin, the association of adipokine with asthma differed between adults and children. It is possible that differences between findings in adults and children in the individual

studies may reflect the possibility that asthma in children may be a more uniform phenotype than in adults and that adiponectin may be associated with only a few of the phenotypes present in adults.¹ The fact we did not see a difference in the relationship of leptin levels between adults and children suggest that leptin levels are less sensitive to variation in the asthma phenotype and possibly may be a better biomarker for the diagnosis of asthma.

Differences in levels of leptin and adiponectin between controls and asthmatics have raised the possibility that these hormones may be biomarkers for asthma control, at least in certain populations. In support of this a few studies have found that treatment of asthmatic children with corticosteroids reduced the levels of leptin in them.⁴⁵ Further studies are required to determine if leptin and/or adiponectin may themselves be potential targets for asthma medications. More information regarding the asthma phenotype in children and adults and their relationship with leptin and adiponectin are necessary to gain greater insight into the role of these adipokines with asthma. Studies that evaluate different asthma endotypes (eg, biomarkers plus clinical function markers plus symptoms) are necessary to better assess the relationship of obesity, adiponectin and leptin with asthma and to give insight into the association of these adipocyte-related markers with specific asthma characteristics.

This study had several limitations. The number of studies included was small and the levels of serum leptin

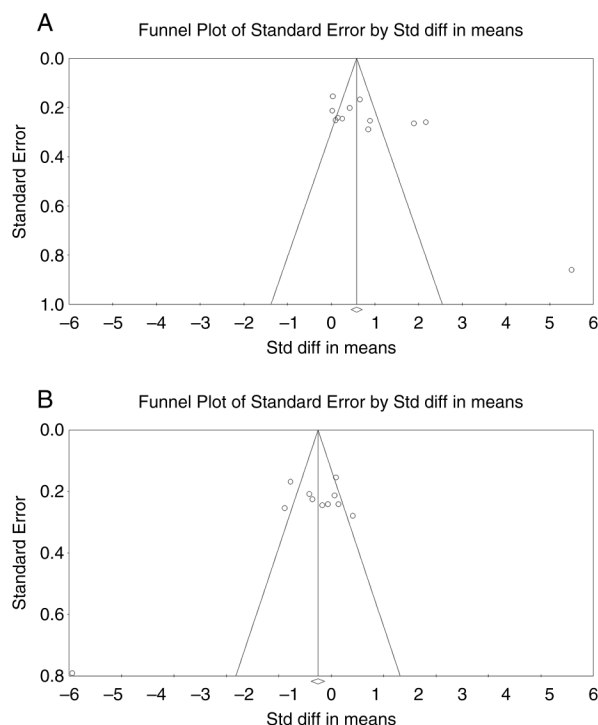
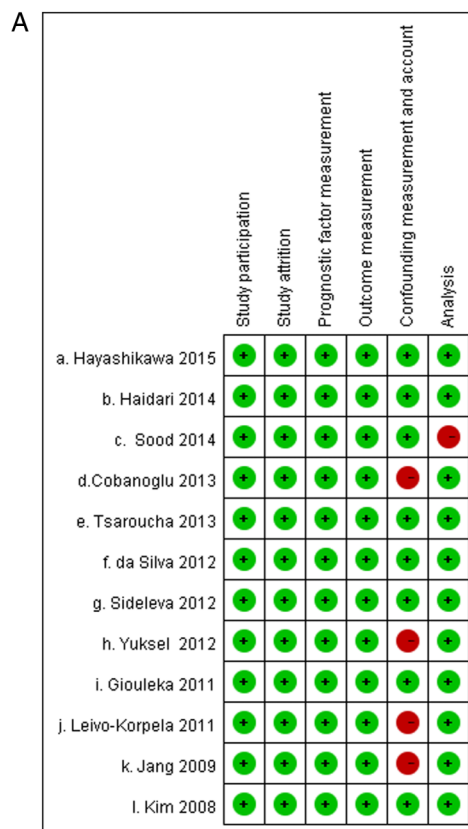


Figure 4 Funnel plot for publication bias. (A) Leptin and (B) adiponectin.

and adiponectin across the studies were measured at only one time point and these points differed with respect to diurnal control, which may have confounded the results. Circulating adiponectin levels exhibited diurnal variation with a reduction in levels during the night and also exhibited ultradian pulsatility.⁴⁶ Oscillating levels of adiponectin may influence the presence or severity of asthma. We also did not evaluate adiponectin or leptin levels in lung lavage samples, which may give additional insight into the role of these molecules in asthma. Sensitivity analysis indicated that the findings of adiponectin were significantly impacted by four studies. In addition, there was publication bias for leptin data. We also did not perform subgroup analysis to stratify the data based on patient characteristics, such as gender, BMI, disease severity, etc. It was not possible to perform these subgroup analyses as the small number of studies would have resulted in a wide range of SDs with would not have had the power to distinguish between groups. The included studies did not consistently define how asthma was diagnosed or the severity of the asthma included. Differences in the severity of asthma may have impacted our results.

CONCLUSION

Our findings are consistent with higher levels of leptin being associated with asthma both in adults and children. In the overall population, low adiponectin levels were associated with asthma. Adiponectin was weakly associated with asthma in adults, but there was no association in children. Further studies are necessary to better understand the role adiponectin and leptin in asthma and what parameters impact this relationship.



B

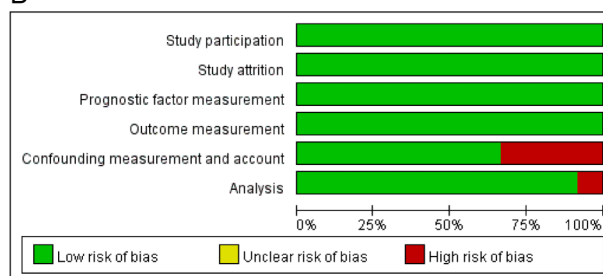


Figure 5 Assessment of the risk of bias. (A) The quality assessment of individual studies and (B) the assessment of each domain in Quality in Prognosis Studies (QUIPS) tool among the pooled studies.

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Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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