Childhood obesity in relation to poor asthma control and exacerbations- A meta-analysis

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ABSTRACT: To estimate the association between obesity and poor asthma control or risk of exacerbations in asthmatic children and adolescents, and to assess whether these associations are different by gender.

A meta-analysis was performed on unpublished data from three North-European pediatric asthma cohorts (BREATHE, PACMAN and PAGES) and 11 previously published studies (cross sectional and longitudinal studies). Outcomes were poor asthma control (based on asthma symptoms) and exacerbations rates (asthma-related visits to the emergency department, asthma-related hospitalizations or use of oral corticosteroids). Overall pooled estimates of the odds ratios (ORs) were obtained using fixed or random-effects models.

In a meta-analysis of 46,070 asthmatic children and adolescents, obese children (BMI≥95th percentile) compared with non-obese peers had a small but significant increased risk of asthma exacerbations (OR: 1.17, 95% CI: 1.03-1.34; I^2:54.7%). However, there was no statistically significant association between obesity and poor asthma control (n=4,973, OR: 1.23, 95% CI: 0.99-1.53; I^2: 0.0%). After stratification for gender, the differences in ORs for girls and boys were similar, yet no longer statistically significant.

In asthmatic children, obesity is associated with a minor increased risk of asthma exacerbations but not with poor asthma control. Gender does not appear to modify this risk.

Key words: body mass index, overweight, children, asthma severity.

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INTRODUCTION

Studies have shown that overweight and obesity are associated with an increased risk of asthma in children[1-3]. Mechanisms which might explain how obesity could lead to asthma include increased weight on the chest wall leading to breathing at lower lung volumes[4] and/or pro-inflammatory mediators released by adipocytes[5]. These mechanisms might also lead to children with asthma and who are obese having either more symptoms or worse disease compared with children who are not obese[6]. It has been reported that obese boys have a significantly higher risk of asthma than obese girls[7], although some other studies have found the opposite[8-10]. In addition to the risk of developing asthma, there has been an inconclusive debate about whether obesity is associated with an increased risk of poor asthma control[11-18] and exacerbations[19-24]. Studies reporting on gender differences for the association of obesity and poor asthma control also show conflicting results[14,17]. Luisa et al. reported that obese boys are more at risk of poor asthma control compared to obese girls[14]. In contrast, Kattan and colleagues showed that obese girls had a higher risk of poor asthma control compared to obese boys[17].

Therefore, the purpose of this study was to perform a meta-analysis including unpublished results (from three Northern European asthma cohorts) and all previously published studies on overweight/obesity and the risk of poor asthma control or exacerbations in asthmatic children and adolescents. Additionally, we intended to assess whether this association is different for boys and girls.

METHODS

In this study, we followed the guideline reported by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement[25] for presenting systematic reviews.

Data source:

Studies were identified by conducting a literature search in PubMed and Web of Science with the keywords strategy shown in **Table S1** **(***See supplementary data***)**. Additional articles were retrieved through a manual search of references from articles identified in the initial search. We also included unpublished results of the analysis of three North-European asthma cohorts (BREATHE, PACMAN and PAGES) (**all information regarding methods and the results of these studies are presented as supplementary information**).

Inclusion and exclusion criteria:

Targeted studies were those in which the association of overweight and obesity (body mass index (BMI)≥85th percentile) or obesity (BMI≥95th percentile) with poor asthma control and/or exacerbations rate in children and adolescents was evaluated as, or could be calculated as odds ratios (ORs).

Studies on this association were included in this meta-analysis if they met following criteria:

1) Data on overweight and/or obesity was available (based on BMI percentile).
2) Data on asthma control was available as ACQ[26], ACT[27], NHLBI[28] or GINA guidelines[29] OR
3) Data on severe asthma exacerbations was available either as a) asthma emergency department (ED) visits/ unscheduled health care visits or b) asthma- related hospitalization or c) prescribed courses of oral corticosteroids (OCSs).
4) Only publications in English language available in PubMed and Web of Science before17th of Feb 2015 were considered.

Low-quality studies (criteria for this exclusion are explained later in the quality assessment section) were excluded from this meta-analysis. Studies that evaluated adolescents and adults without showing separate results[30,31] or studies that used other measurements of outcomes (e.g. missing schools due to wheezing and wheezing with exercise)[13,18,32-37] were also excluded. We also excluded studies in which the association of overweight/obesity and uncontrolled asthma was evaluated only in children with an asthma-related ED visit[38-40].

Data extraction:

The following data were extracted: first author, year of publication, study design, patient characteristics (gender, age and number of patients). When available, the crude or adjusted ORs for the association of overweight/obesity and outcomes were extracted from the articles. For the remaining studies, the numbers of exposed/non-exposed subjects were selected to calculate the unadjusted ORs and 95% confidence intervals (CIs). In case the reported association was not obtained from a regression analysis or ORs were not reported, we contacted the authors to provide additional information in order to be included in the meta-analysis.

Quality assessment and publication bias:

Quality assessment of included published studies was assessed independently by three authors (FA, AHM, SJHV) using the checklist of Newcastle-Ottawa Scale (NOS) for cohort-studies or adapted for cross-sectional studies. Using this tool, each study was evaluated on eight items categorized into three groups including the selection of the study group, the comparability of the groups and the assessment of either the exposure or outcome of interest for cross-sectional and cohort studies. When a study met ≥5 NOS criteria, the study was considered to be of high quality. Studies with a NOS score <5 were excluded from the meta-analysis[41]. Publication bias was evaluated by using funnel plots and the Egger test was applied to measure any asymmetry.

Meta-analysis:

Overall pooled ORs, together with 95% CIs of the association between obesity and outcomes were obtained using either a fixed-effects model or a random-effects model. In association BMI and risk of asthma exacerbations, we performed separate meta-analyses in those studies that reported ED visits, hospitalizations due to asthma or OCSs use. Heterogeneity of the studies was tested by the I^2 measure of inconsistency with 25% corresponding to low heterogeneity, 50% to moderate and 75% to high. If significant moderate or high heterogeneities existed, we used a random-effects model instead of a fixed-effects model for the meta-analysis.

In this meta-analysis, for reasons of symmetry, the reported/calculated ORs and lower and upper bounds of the 95% CI were initially log-transformed; the log ORs together with 95% CIs of the log ORs were meta-analyzed using either fixed or random-effects models, then the results were transformed back to the original ORs for reporting.

Sensitivity analyses:

A series of sensitivity analyses was applied to find:

a) The impact of unpublished results on these associations; separate meta-analyses were performed for unpublished and published studies.

b) The effect of different asthma control measurements on the association between obesity and poor asthma control; a separate meta-analysis was performed in those studies that used the ACQ or ACT for asthma control measurement.

c) The effect of different asthma definition on this association; separate meta-analysis for studies with physician-diagnosed asthma and those with self/parental-reported asthma.

d) The effect of severity of asthma on this association; the meta-analysis was stratified based on the source of recruitment, primary versus secondary health care system.

e) The effect of study design on the association between obesity and poor asthma control/exacerbations; separate meta-analyses were performed in cross sectional and longitudinal studies.

P-values of 0.05 were used to assess the statistical significance of main effect associations. We used STATA 12/SE (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

RESULTS

Search results

As shown in **Figure S1**, our literature search yielded 1,060 published articles on overweight/obesity and childhood poor asthma control/exacerbations. After applying the inclusion and exclusion criteria 11 studies remained eligible, and were included in the meta-analysis together with the analyses of the BREATHE, PACMAN and PAGES studies.

Study characteristics:

Features of the included studies are presented in **Table 1**. A total of 52,147 patients from 14 studies were included in this meta-analysis. Sample sizes ranged from 56[12] to 32,321[20] patients. The design of the studies was cross-sectional (8 studies), retrospective or prospective cohort (3 studies) or a randomized clinical trial (3 studies). The studies were performed in the United State (US) (10 studies), the United Kingdom (UK) (2 studies), Japan (1 study) and the Netherlands (1 study). 12 studies evaluated the association of obesity (BMI ≥95th percentile) with the outcomes while in 2 other studies overweight and obesity were combined (BMI ≥85th percentile). Overall, the highest proportion of obese children was observed in the studies conducted in the US (ranging between 23-41%) and the lowest proportion in the study conducted in the Netherlands (10%).

Poor asthma control was studied in 8 studies; three studies used the ACT questionnaire, 4 studies the ACQ questionnaire and one study NHLBI guidelines.

Meta-analysis of combined unpublished and published studies:

The association of obesity with asthma exacerbations was studied in 8 studies by ED visits (4 studies), hospitalization due to asthma (5 studies), OCSs use (6 studies), both ED visits and hospitalization (5 studies) and both ED visits/hospitalization and OCSs use (2 studies). All studies recruited both girls and boys in their studies however the ORs for the association of exposure and poor asthma control were stratified by gender in 7 studies and only in 3 studies for asthma exacerbations.

The quality of the studies was scored according to the three sections of the NOS checklist (selection, comparability and assessment of outcome). The results showed a high quality for all studies included but one scored below the threshold of 5 [22] and was excluded from the meta-analysis (**Table 2**).

The funnel plot and Egger's test showed no evidence of any asymmetry for the association of overweight/obesity with poor asthma control (p-value=0.81) and exacerbations (p-value=0.80), suggesting no publication bias in our meta-analysis (**Fig S2**).

Association BMI and poor asthma control:

The association of obesity and poor asthma control in the total population has been reported by 7 studies [PACMAN, PAGES, 11,12,15-17]. Estimated heterogeneity in these studies was low (p-value: 0.71). The pooled OR for this association of obesity and poor asthma control in the total population was 1.23, 95 % CI: 0.99-1.53; I^2: 0.0%, p-value: 0.06 (**Fig 1**). Gender effect on this association is shown in **Figure 2**; in girls the OR was 0.96 (95% CI: 0.72-1.29; I^2:7.8%, p-value: 0.79) and in boys the OR was: 1.30 (95% CI: 0.92-1.83; I^2:22.9%, p-value: 0.15).

Association BMI and asthma exacerbations:

An estimation of the association between obesity (BMI≥95th percentile) and overweight (BMI> 85th percentile) in asthmatic children and the risk of exacerbations was reported in 8 studies [BREATHE, PACMAN, PAGES, 19-21,23,24]. We performed meta-analysis in those studies that reported ED visits, hospitalizations due to asthma or OCSs use, separately. The results showed that heterogeneity was moderate in the three associations and by applying a random effects model the overall pooled estimate in the association overweight/obesity and OCSs use was shown to be statistically significant, OR: 1.17, 95% CI: 1.03-1.34; I^2:54.7%, p-value: 0.02 when boys and girls combined (**Fig 3**). For the association between overweight/obesity and ED visits (1.04, 95%CI: 0.98-1.11; I^2:0.0%, p-value: 0.21) and between overweight/obesity and asthma-related hospitalizations (1.18, 95%CI: 0.91-1.53; I^2:0.0%, p-value: 0.22), there were no statistically significant associations, however it seemed that there was a trend towards a higher risk of asthma exacerbations in obese compared with non-obese children (**Fig 4 & 5**).

The summarized ORs for the association of obesity (BMI≥95th percentile) with asthma exacerbations showed that obese children were statistically significantly at higher risk of asthma exacerbations measured by OCSs use (1.17, 95%CI: 1.03-1.34; I^2:54.7%, p-value: 0.02). Obese children were also more likely to have ED visits (1.03, 95% CI: 0.65-1.62; I^2:44.3%, p-value: 0.90) and hospitalizations due to asthma (1.23, 95% CI: 0.89-1.69; I^2:0.0%, p-value: 0.21). After stratification by gender, the effect size of the ORs in the association obesity and OCSs use appeared to be similar to the non-stratified ORs although the differences were not statistically significant anymore; OR, 1.30, 95%CI: 0.42-4.07; I^2:76.0%, p-value: 0.65 in girls and OR, 1.19, 95% CI: 0.81-1.74; I^2: 0.0%, p-value: 0.37 in boys. For the association between obesity and ED visits, there were no statistically significant associations for boys (1.27, 95% CI: 0.78-2.09; I^2:0.0%; p-value: 0.34) or girls (0.91, 95% CI: 0.48-1.72; I^2:0.0%, p-value: 0.77).

Sensitivity analyses:

We evaluated the impact of unpublished studies on the association between obesity and poor asthma control and showed that the 95% CIs of the pooled results in this association in published studies **(**OR: 1.26, 95 % CI: 0.99-1.61; I^2: 0.0%) and in unpublished studies (OR: 1.14, 95 % CI: 0.68-1.89; I^2: 11.0%) were the same and overlapping. The associations between obesity and OCSs use in published (OR: 1.20, 95% CI: 1.05-1.38; I^2: 79.4%) and unpublished (OR: 1.03, 95% CI: 0.73-1.46; I^2: 14.1%) studies were similar. The associations of obesity with ED visits and asthma-related hospitalization separately in published versus unpublished studies were also evaluated. The results illustrated that there was no difference between the results of these associations in published (OR: 1.04, 95% CI: 0.98-1.10; I^2: 0.0% and OR: 1.25, 95 % CI: 0.87-1.78; I^2: 0.0%, respectively) and unpublished studies (OR: 1.91, 95% CI: 0.76-4.83; I^2: 0.0% and OR: 1.10, 95% CI: 0.75-1.62; I^2: 0.0%, respectively).

The effect of different measurements of asthma control on the association between BMI and asthma control was evaluated by a sensitivity analysis; the results showed that obesity was significantly associated with poor asthma control measured by ACT (OR: 1.42, 95% CI: 1.08-1.87; I^2:0.0%) but not with ACQ (OR: 0.98, 95% CI: 0.69-1.39; I^2: 0.0%) and the point estimates were in the opposite direction. Obese children were also more likely to have asthma exacerbations measured by ED visits, hospitalizations due to asthma or OCSs use compared with non-obese peers in both combined studies with self/parental reported asthma (OR: 1.24, 95% CI: 0.63-2.44; I^2: 33.2%, OR: 1.23, 95% CI: 0.65-2.30; I^2: 0.0% and OR: 2.04, 95% CI: 0.79-5.25; I^2: 0.0%, respectively) and studies with asthmatic children diagnosed by physician (OR: 1.03, 95% CI: 0.86-1.23; I^2: 10.8%, OR: 1.17, 95% CI: 0.87-1.56; I^2: 0.0%, and OR: 1.16, 95% CI: 1.01-1.32; I^2: 61.3%, respectively). We further stratified the meta-analysis based on recruitment of the patients in the studies. Based on our results obesity was related to increase asthma exacerbations either ED visits or OCSs use in those studies with children recruited from primary care (OR: 1.18, 95% CI: 0.73-1.89; I^2:39.5% and OR: 1.22, 95% CI: 1.06-1.39; I^2:66.1%, respectively) but not in children from secondary care (OR: 0.89, 95% CI: 0.41-1.93; I^2:52.6% and OR: 0.94, 95% CI: 0.68-1.29; I^2:0.0%, respectively).

The effect of study design on these associations was also assessed and the results showed statistically significant association between obesity and poor asthma control in cross sectional studies (OR: 1.32, 95% CI: 1.02-1.72; I^2:0.0%) however obese children in longitudinal studies also were more likely to have poor asthma control compared with non-obese peers (OR: 1.04, 95% CI: 0.70-1.55; I^2:0.0%). The same results were also shown in the associations between obesity and ED visits (OR: 1.06, 95% CI: 0.68-1.63; I^2: 24.8%; OR: 1.04, 95% CI: 0.98-1.11; I^2: 0.0%) and OCSs use (OR: 1.03, 95% CI: 0.73-1.46; I^2: 14.1%; OR: 1.20, 95% CI: 1.05-1.38; I^2: 79.4%) in the cross sectional and cohort studies, respectively.

DISCUSSION

To the best of our knowledge, this systematic review and meta-analysis provides the first quantitative summary estimates of the relation between BMI and poor asthma control/exacerbations. Our analysis in 14 studies included (52,147 asthmatic children and adolescents) shows that obese and overweight children have a slightly higher risk for severe asthma exacerbations, yet not for poor asthma control (based on asthma symptoms).

Furthermore, we showed that gender does not influence these risks.

Childhood obesity has become a global public health issue especially in developed nations. Although data from many countries including US, Netherlands and UK have shown stabilization of obesity levels in children in 1995-2008[42], the results of most recent national estimates of obesity in children aged 2-9 years in US reported that obesity prevalence remains high, almost 17% between 2003 and 2012[43].

Several studies have proposed biological mechanisms, which may underlie the association between obesity and the risk of asthma exacerbations. An increased BMI might cause increased weight on the chest wall leading to breathing at lower lung volumes[4]. A recent meta-analysis suggested that children with higher infant weight gain were associated with asthma outcomes reflecting a direct mechanical effect on lung function[44]. In addition, obesity is associated with a chronic inflammatory state. Adipose tissue macrophages produce pro-inflammatory mediators, and these cells are abundantly present in obese individuals[5]. It is an ongoing debate whether obesity is associated with a distinct inflammatory asthma phenotype[45,46]. It has been suggested that pediatric obesity-associated asthma is characterized by Th1 polarization[47], in contrast to the more common Th2-driven atopic childhood asthma phenotype. Moreover, obesity is associated with a decreased response to bronchodilator medications in children and adolescents with asthma[48,49].

There is increasing evidence that some potential confounders e.g. age, gender, and race do play an important role in the association between obesity and asthma severity. Results of data-analyses in our three pediatric asthma cohorts highlighted the confounding effects of factors including age, eczema, rhinitis, breast feeding, family history of asthma and allergy in the association between obesity and the risk of asthma severity.

Race might also be an important confounder for the relationship between obesity and asthma severity. In PACMAN study, race/ethnicity was an actual confounder in the association obesity and asthma exacerbations. While in previous studies, obesity has been associated with poor asthma control and increased risk for exacerbations independent of race[20] or with a little effect[14,15].

Given the concern that obesity has been implicated in the onset of asthma, it is important to focus on prevention approaches for the individual patient. The positive effects of weight loss on asthma-related health outcomes have been already reported in overweight and obese adults with asthma[50,51]. However, an intervention study aimed at reducing asthma exacerbations by weight reduction strategies would be the only way to answer the question to what extent there is an association between weight reduction and asthma severity in children. Furthermore, it could help in answering the question if “obesity associated asthma” is a distinct asthma phenotype in children.

There are several limitations in the current study that should be addressed. Importantly, heterogeneity in sample size and type of characteristics e.g. geographic regions should be addressed in this study, and that the exposure and outcomes are not uniform across the combined studies. The present study was limited by the use of parental-reported questionnaires based data in some studies, which might be prone to recall bias. Self-reported BMI-data (e.g. in PACMAN) might be less accurate than standardized way using weight and height. Parents may not always be able to give an accurate estimate of their child’s medication use. However, there is a reasonable agreement between parental-reported OCSs use data and pharmacy prescription data within the PACMAN cohort (Cohen’s kappa coefficient is 0.51; results not published). Additionally, definition of asthma control slightly differed between the separate studies; poor asthma control was defined by ACQ, ACT or NHLBI guidelines. Results from our sensitivity analyses showed statistically significant association between obesity and asthma control measured by ACT but not with ACQ. In a meta-analysis of Jia et al. including 21 studies, the ACT and ACQ had also significant differences in the assessment of controlled and not well-controlled asthma[52]. The assessment of asthma control has been limited to 1-week in the ACQ questionnaire but 4 weeks in the ACT questionnaire and NHLBI guidelines, which may have underestimated or overestimated long asthma control for participants[53]. Moreover, seasonal variation has been shown to have a substantial impact on asthma control[53], which might lead to differences in asthma control reported by different studies.

Studies included in our meta-analysis did not all have the same definition of asthma diagnosis however, most studies used physician-diagnosed asthma. Children younger than 5 years can have asthma-like symptoms[54,55] that could be explained by the smaller airways. Therefore, there is a likelihood of misclassified asthmatic children especially in young children. Children in some studies such as PACMAN were recruited through community pharmacies based on regular asthma medication use, while participants of some other studies e.g. BREATHE and PAGES were recruited through primary and secondary asthma clinics, and might, therefore, reflect a more severe population of asthmatics. It is possible that for patients with mild asthma on intermittent bronchodilators alone, being obese might not be associated with severity of asthma, but, while in more severe disease, use of systemic corticosteroids or physical inactivity might lead to a stronger relation of BMI with asthma severity. Another important limitation is about missing values for weight and height in the three cohorts (BREATHE 11%, PACMAN 35% and PAGES 45%) that may have existed in other studies included as well. In most of the other studies included in the meta-analysis there is no information about missing values for BMI. Therefore, our estimates of overweight and obesity should not be interpreted as prevalence rates nor extrapolated to the general pediatric asthma population. Although in the three cohorts we have adjusted for the most important potential confounders such as age, eczema and family history of asthma the possibility remains that some factors which we have not measured still caused confounding, e.g. birth weight, gestational age, puberty, socioeconomic status and genetics. Furthermore, there is a lack of relevant adjustment for the association of BMI and asthma severity in some of the studies included in the present meta-analysis, which might influence this association differentially.

We were unable to check the onset of obesity and the subsequent development of asthma complications in which the time of obesity must be preceded. Therefore, reverse causality might affect these studies for which in subgroup of children especially those with early asthma onset, asthma might precede obesity.

We excluded studies that had different measurement of exposure and outcomes because we intended to reduce heterogeneity as much as possible. A statistically significant higher risk of asthma severity in obese compared with non-obese children was reported by five excluded studies[31,32,34,36,37]. The other four excluded studies[13,33,35,56] showed no significant association between obesity and asthma control. Since the pattern of these results is similar to our main findings we assume that the impact of excluding these studies on the pooled effect estimates of our study probably would be very small.

Multiple sensitivity analyses were used to test the robustness of the findings. Even though the point estimates were a bit different in some of these analyses, the 95% CIs largely overlapped and that these differences were mainly caused by chance findings related to relatively low patient numbers. In our meta-analyses, we have pooled data from primary, secondary and tertiary care. Furthermore, we included studies from different parts of the world (Europe, USA, and Japan). Multiple sensitivity analyses showed the robustness of our findings. Therefore we conclude that our findings are generalizable to most children with asthma.

In summary, we have related asthma severity to BMI in a population of children with asthma and our findings suggest that both overweight and obesity have a small, but statistically significant deleterious effect on the risk of OCSs use (as a marker for asthma exacerbations) but not on poor asthma control. Though a study where an intervention leads to weight reduction in asthmatic children with high BMI is needed to determine the true nature of the relationship between asthma and increasing BMI in children, weight loss is by far the best recommendation.

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Table 1: Baseline characteristics of studies included in the meta-analysis

Source	Study design	Region of study	Study size	Age at follow up time	BMI percentile	Asthma control in 12 months/6 months	Asthma exacerbations in 12 months/6 months	Overweight/ Obesity, %	Well controlled asthma, %	Hospitalization, %	ED visits, %	OCSs use, %
BREATHE	Cross-sectional	UK, Scotland	1,318	4-18	Obesity		OCS use Hospitalization due to asthma	13.4		15.2		25.9
PACMAN	Cross-sectional	Netherlands	648	4-12	Obesity	ACQ	OCS use ED visits	10.3	59.0		6.2	5.1
PAGES	Cross-sectional	UK, Scotland	422	4-17	Obesity	ACT	OCS use Hospitalization due to asthma	15.4	36.2	14.3		39.4
Sasaki M, et al. 2015	Cross-sectional	Japan	3,066	6-11	Obesity	ACT		11.8	85.4			
Lang J, et al. 2015	Cross-sectional	US	56	10-17	Overweight Obesity	ACQ		62.5 41.1	37.5			
Lang J, et al. 2013	Multicenter clinical trial*	US	306		Obesity	ACQ		31	33.7			
Lang J, et al. 2011	Multicenter clinical trial*	US	107	6-17	Obesity	ACQ		23.4	71			
Kattan M, et al. 2010	Randomized clinical trial*	US	368	12-20	Obesity	ACT		35.1	89.1			
Borrell LN, et al. 2013	Cross-sectional	US	2,174	8-19	Overweight Obesity	Asthma control [a]		35.6	17.6			
Sah PK, et al. 2013	Cross-sectional	US	269		Obesity		Hospitalization due to asthma ED visits [b]	24.9		32.7	15.6	
Schatz M, et al. 2013	Cohort	US	10,700	5-17	Obesity		OCSs use [c]	28.1				11.7
Quinto KB, et al.	Cohort	US	32,321	5-17	Overweight		Hospitalization & ED visits due	19.3		NA	NA	NA

2011						to asthma OCS use				
					Obesity	Hospitalization & ED visits due to asthma OCS use	30.0	NA	NA	NA
Luder E, et al. 1998	Cross-sectional	US	209	2-18	Overweight	Hospitalization due to asthma [d] ED visits [e]	39.7	23.9	72.2	
Hom j, et al. 2009	Cohort	US	183	6-18	Overweight	Hospitalization due to asthma ED visits [f]	59.0	36.1	30.1	

[a] Asthma control based on NHLBI guidelines (meeting at least three criteria has been defined as poor asthma control); [b] One time emergency department (ED) visit over the preceding 12 months; [C] Within last 7 days of asthma exacerbations diagnosis; [d] ≥3 times hospitalization per year, [e] ≥10 ED visits during the past year; [f] ≥1 ED visits during the past 30 days

***** Findings in these 3 studies are the results of post hoc analyses of data from randomized clinical trials not specifically designed to assess the effect of obesity on asthma outcomes.

Table 2: Quality assessment of included studies based on NOS checklist

	Selection (Maximum of 4 stars)	Comparability (Maximum of 2 stars)	Outcome assessment (Maximum of 3 stars)
Lang J, et al. 2015	***	**	**
Sasaki M, et al. 2015	***	-	**
Borrell LN, et al. 2013	***	**	**
Lang J, et al. 2013	***	**	**
Schatz M, et al. 2013	***	-	***
Sah PK, et al. 2012	***	-	***
Quinto KB, et al. 2011	****	**	***
Lang J, et al. 2011	****	**	**
Kattan M, et al. 2010	****	**	*
Hom j, et al. 2009	****	-	*
Vargas PA, et al. 2007	***	-	*
Luder E, et al. 1998	***	-	***

In this checklist, the highest quality studies are awarded up to 9 stars.

Fig 1: Pooled odds ratio of the association obesity and poor asthma control in obese compared with non-obese children

Fig 2: Pooled odds ratio of the association obesity and poor asthma control in obese compared with non-obese children, stratified by gender

Fig 3: Pooled odds ratio of the association combined overweight and obesity with oral corticosteroids (OCSs) use

Fig 4: Pooled odds ratio of the association combined overweight and obesity with emergency department (ED) visits

Fig 5: Pooled odds ratio of the association combined overweight and obesity with hospitalization due to asthma

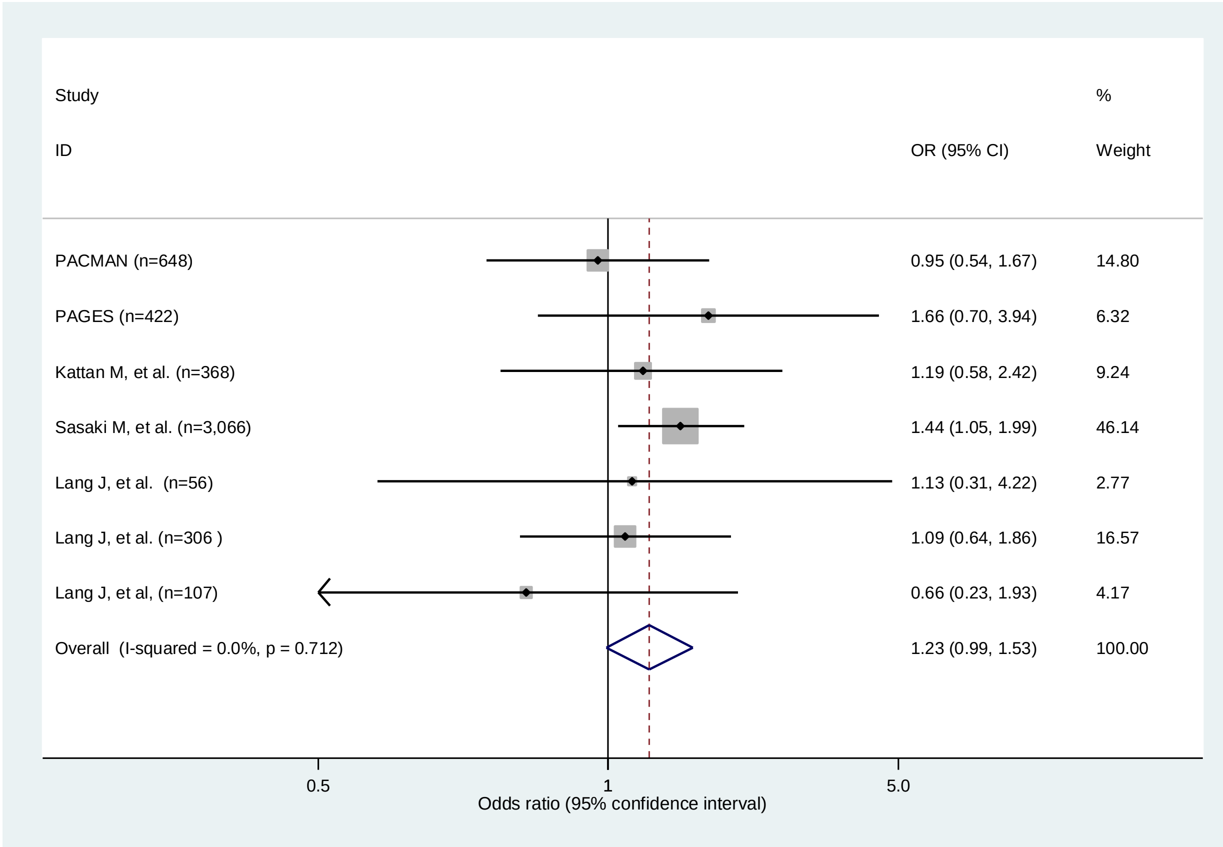
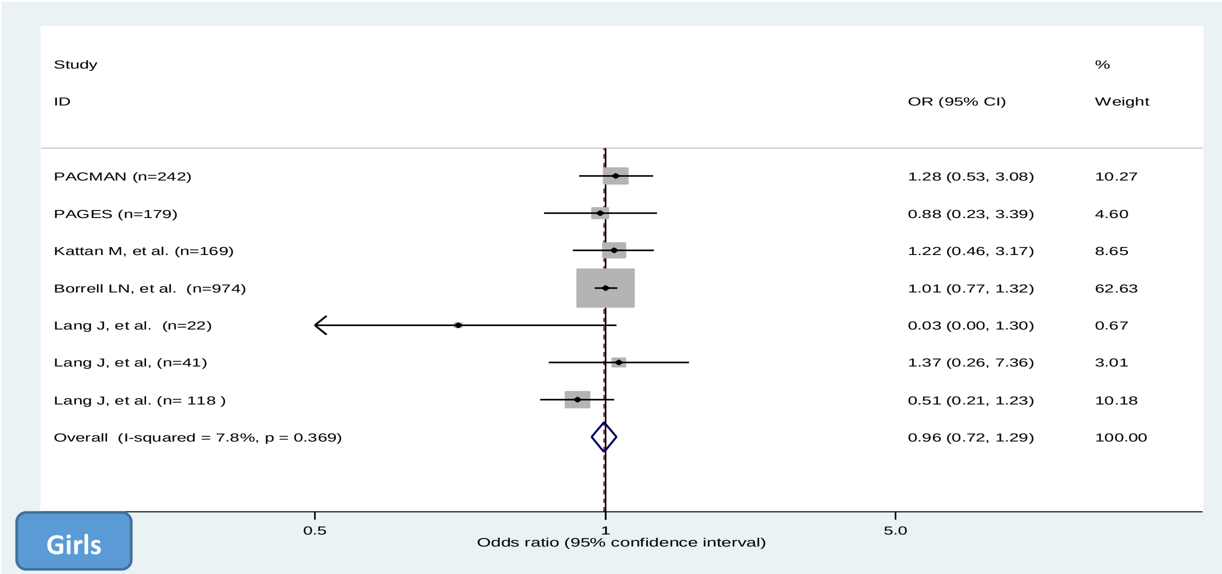


Fig 1: Pooled odds ratio of the association obesity and poor asthma control in obese compared with non-obese children



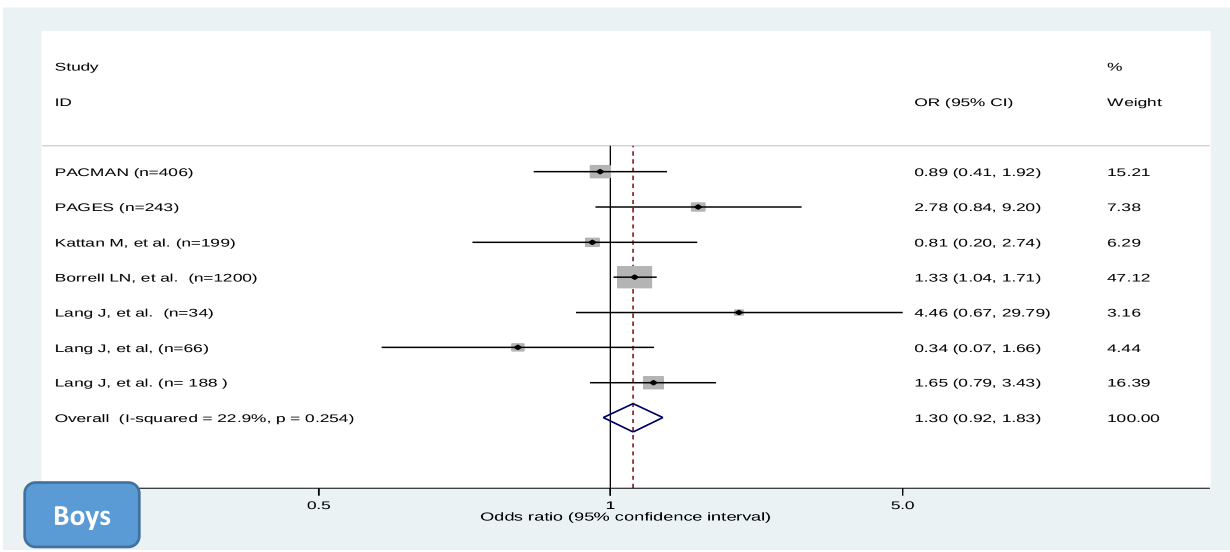


Fig 2: Pooled odds ratio of the association obesity and poor asthma control in obese compared with non-obese children, stratified by gender

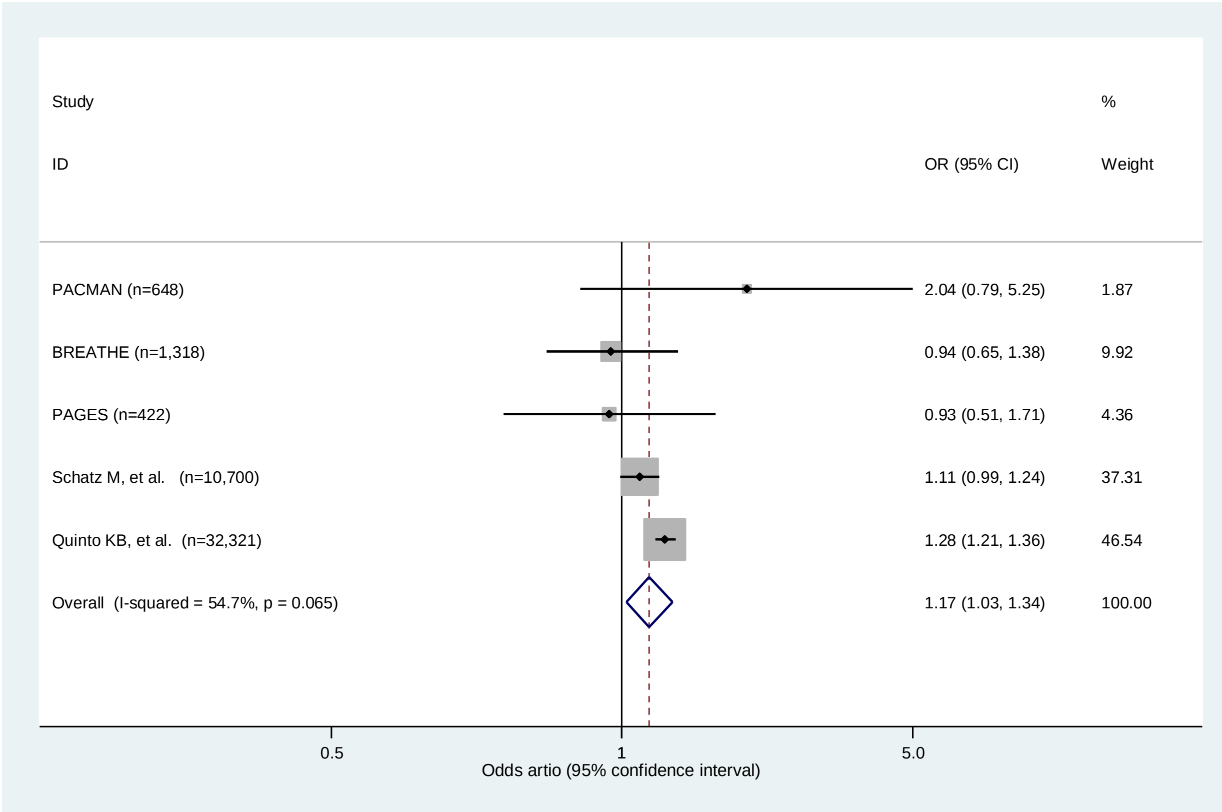


Fig 3: Pooled odds ratio of the association combined overweight and obesity with oral corticosteroids (OCSs) use

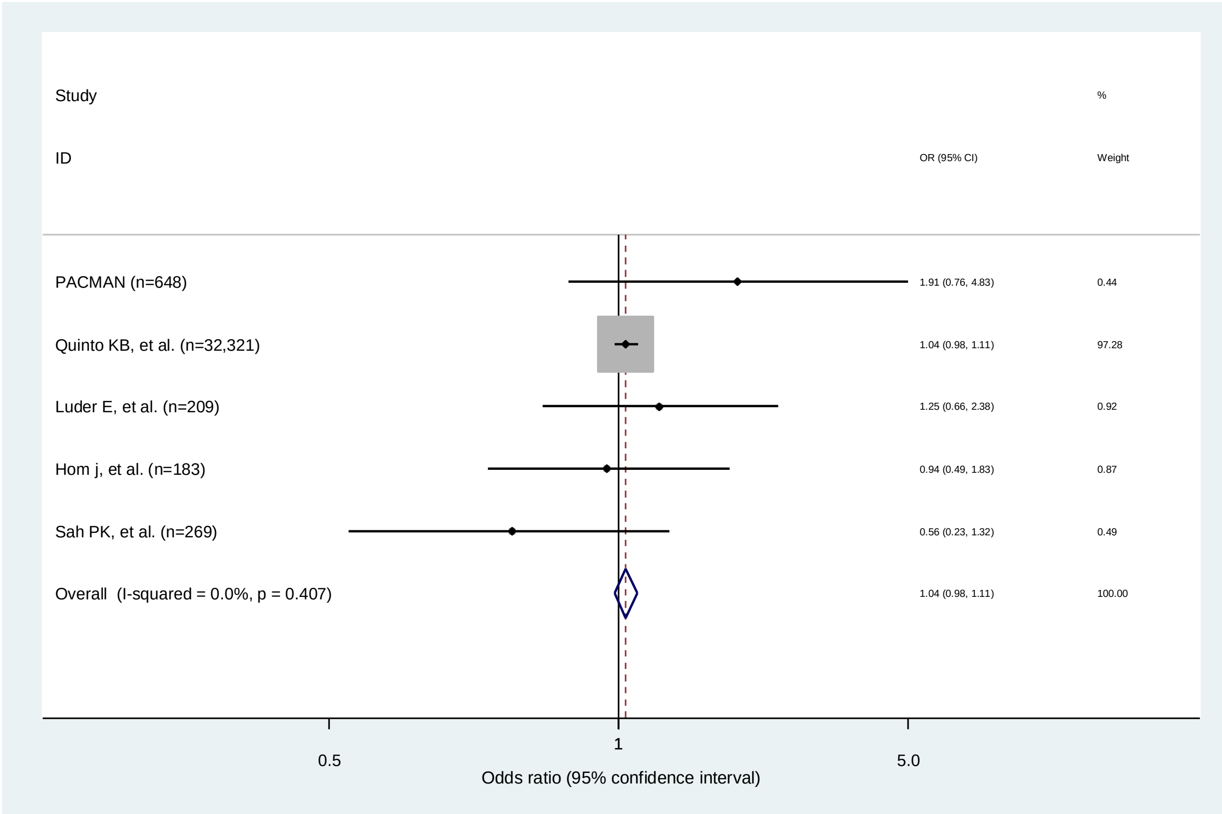


Fig 4: Pooled odds ratio of the association combined overweight and obesity with emergency department (ED) visits

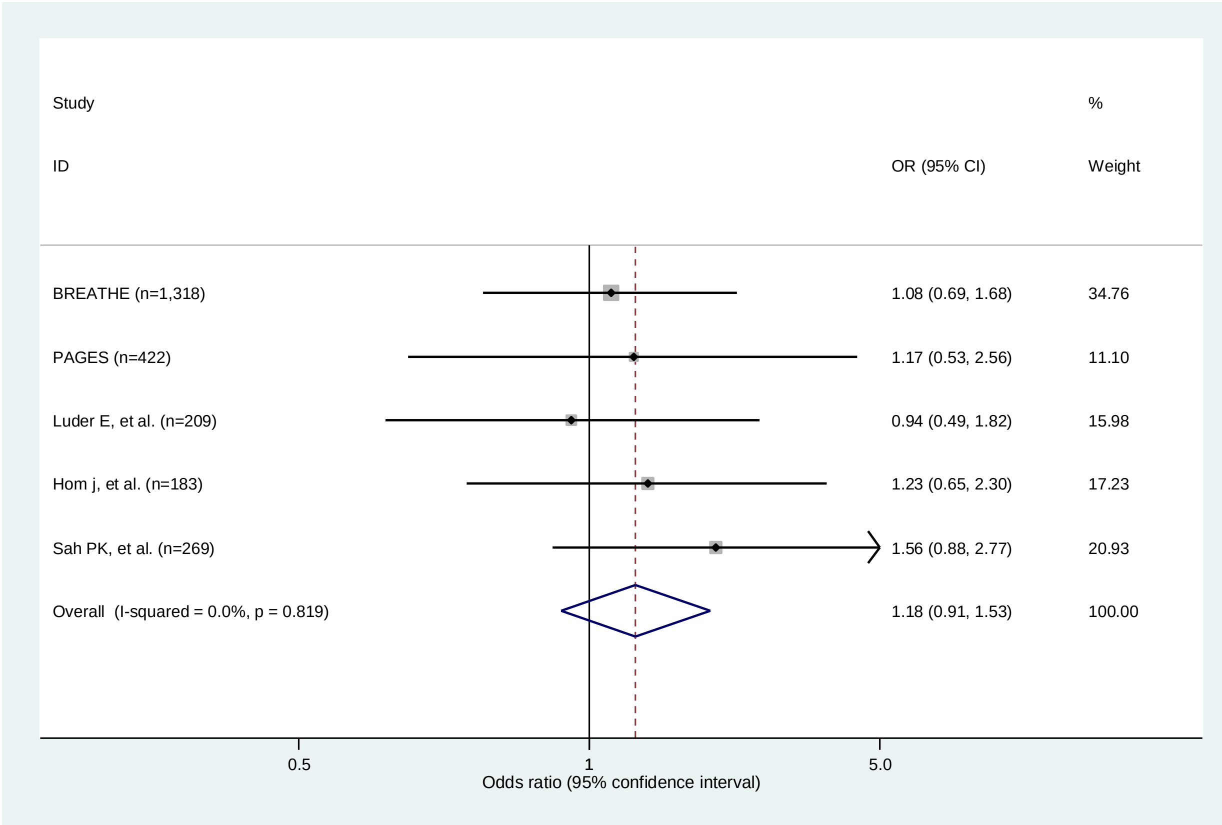


Fig 5: Pooled odds ratio of the association combined overweight and obesity with hospitalization due to asthma