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A systematic review of the association between obesity and asthma in children

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Abstract

Aims—To provide a comprehensive integration of contemporary studies focusing on the relationship between obesity and asthma in paediatric populations.

Background—The simultaneous increase in asthma and obesity prevalence has been widely discussed over the past twenty years. Although studies have discovered a positive correlation between the two, evidence-based findings are needed to develop nursing interventions.

Data Sources—An electronic database search was conducted for studies published between January 1966 - May 2011. Additional articles were identified through the reference lists of reviewed papers.

Review Methods—A quantitative systematic review was undertaken to aggregate evidence regarding the association between obesity and asthma in children. Inclusion/exclusion criteria and quality appraisal were applied to ensure research primarily designed to study the relationship between obesity and asthma in children was included.

Results—The majority of studies support a positive association between obesity and asthma in children. Among correlates recognized as important effect modifiers, gender was the most prominent, with obese girls more likely to have asthma diagnoses than obese boys. Scrutinization of covariates in selected studies revealed that most related to children's demographic characteristics and were inconsistent across the studies.

Conclusions—This review was designed to integrate contemporary scientific findings on the association between obesity and asthma by including a large number of studies with variant research designs. To identify high-risk groups and develop nursing interventions to help children affected by both epidemics, more interdisciplinary and well-designed investigations focusing on an expanded spectrum of correlates including demographic and behavioural factors are warranted.

Keywords

body mass index (BMI); asthma; obesity; overweight; children; systematic review; nursing

Introduction

A concurrent increase in both obesity and asthma among children has been identified worldwide over the past two decades (Chinn & Rona 2001, Wickens *et al*. 2005), especially in developed countries. In the US, the prevalence of childhood asthma has increased from

3.5% in 1980 - 9.6% in 2009 (Moorman *et al.* 2007, Zahran *et al.* 2011). Also, the number of overweight and obese children has also risen significantly over the past twenty years (Ogden *et al.*2006). According to a recent nationwide survey targeting 0-17 year olds in the USA, nearly 25% and 13% were obese and diagnosed with asthma, respectively. Obesity was significantly associated with asthma especially among children aged 13-17 (Ahmad *et al.* 2009).

Due to the simultaneous increasing prevalence of both asthma and being overweight or obese, their association has been widely discussed as an area where further inquiry is needed (Beuther 2009). Several studies have reported an association between asthma and being overweight or obese, in both adult and paediatric populations (Chinn 2003). Both cross-sectional (von Kries *et al.* 2001) and longitudinal (Castro-Rodriguez *et al.* 2001, Gilliland *et al.* 2003) studies have revealed positive correlations between asthma and obesity. Some prospective studies support the hypothesis that obesity leads to an increased risk of asthma among children and adults (Burgess *et al.* 2007, Gilliland *et al.* 2003). Furthermore, scientists have found that loss of body weight significantly reduced asthma-related symptoms (Eneli *et al.* 2008).

Although scientists have reviewed studies synthesizing evidence regarding the relationship between asthma and obesity (Beuther *et al.* 2009), the results from studies conducted with paediatric populations yielded more inconsistent results than those from adult populations (Ford 2005). One meta-analysis focusing on children with asthma concluded that children with high body weight in their early lives (birth weight, high BMI in 10^{th} grade) were more likely to have future asthma even in adulthood. This meta-analysis searched studies from Medline from 1966 until 2004, but excluded all cross-sectional or case-control research and only included 12 longitudinal studies (Flaherman & Rutherford 2006). Synthesizing results from longitudinal studies only provides evidence-based insight regarding causal pathways or mechanisms; however, retrieving and expanding the synthesis to include all relevant studies could extend our insight into important potential confounding factors. A review was conducted recently but only included studies published up to January 2009 and the target population was limited to adolescents (Eneli *et al.* 2008). With the rapidly accumulating evidences of studies in this area, a more updated systemic review is needed to explore our knowledge and develop theory-based nursing interventions.

The Review

Aim

This review was designed to explore the relationship between asthma and obesity in children by searching studies from January 1966 up to May 2011 and incorporating research findings from publications with a variety of designs. To generate findings comparable to other published reviews (Beuther 2009, Noal *et al.* 2011), this review includes studies that examined the correlation between asthma prevalence and overweight/obesity as defined by BMI index in children by aggregating evidence from an in-depth analysis of included studies, summarizing shared characteristics and identifying the common confounding or influential factors reported in each investigation. By conducting this review, a comprehensive integration of contemporary studies focusing on the relationship between obesity and asthma in paediatric populations is provided.

Design

The main purpose of this report is to explore the relationship between asthma and obesity in children. The clinical nature of this issue is best resolved by collecting relevant evidence from primary studies in a systematic review (Counsell 1997). Therefore, a quantitative

systematic review of the literature was performed following the guidelines published by Centre for Reviews and Dissemination (2009).

Search methods

Before the online literature search process began, two authors met to set up the inclusion and exclusion criteria. Then a two-step selection process was conducted. First, the primary author independently implemented the search strategy across four online databases. Second, after reviewing all the titles and select abstracts, chosen articles were listed and printed for further evaluation by the primary author. Consultation with other two authors determined final eligibility of retrieved articles.

The inclusion criteria for target studies were: (a) research stated that it was primarily designed to examine the relationship between obesity as defined by body mass index (BMI) and asthma diagnosis confirmed by parent/self-reports or/and objective measurements; (b) the target population of the research was children aged 0-18; (c) research was published in English. Exclusion criteria were: (a) case reports, meta-analyses, or systemic review articles that did not adopt a research design; (b) research had no clear definition of childhood overweight or obesity using body mass index (BMI); (c) neither asthma diagnosis nor overweight/obese status was the primary research exposure or outcome. Eligible articles were retrieved from four electronic databases: Pubmed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), The Cochrane Library and Medline. Each of the following keywords: ‘overweight’, ‘obesity’, ‘body mass index’, ‘body weight’ and ‘anthropometry’ were searched concurrent with ‘asthma’. The earliest year surveyed in Medline was 1966 with the final literature checked May, 2011. Additional eligible articles were identified by manually checking the reference lists of included studies.

Search outcome

The initial search strategy identified 2550 articles across the four databases. After title review, 2074 reports were excluded as irrelevant or duplicates. Abstract review further ruled out 408 papers that did not meet the inclusion criteria. Most studies were deleted because they were not designed ‘primarily’ to explore the relationship between asthma and obesity. For example, asthma and body mass index (BMI) were co-factors in two studies focusing on the effect of breastfeeding on both asthma and obesity (Mai *et al.* 2007, Oddy *et al.* 2004) while the focus of another report was the response to an asthma-specific disease management program of 174 children some of whom were obese (Kwong *et al.*2006). Other studies were excluded because the majority of study subjects were not children (Chen *et al.* 2005), or the child subjects had other health concerns (Mai *et al.* 2004). The full-texts of the remaining 68 articles were accessed online or through the printed publications in the National Taiwan University library or by online transmission from the interlibrary system at the University of Washington. After careful content reading, nine studies were further excluded as asthma or obesity was not the primary outcome or exposure measure including those studies only adopting asthma-related symptoms such as wheezing (Saldiva *et al.* 2007) or airway hyperresponsiveness (Jang *et al.* 2006) to validate the asthma diagnose. Twenty-five more studies were ruled out because they failed to clearly define being overweight or obese with BMI cutoff points. After manually checking the references of all the selected papers, one more article was retrieved and included (Rodriguez *et al.* 2002). Thus, finally a total of 35 studies were included in this review. The detailed process for selection of eligible publications is outlined in Figure 1.

Quality appraisal

A quality appraisal and validity assessment tool was adapted from previously published review articles (Cummings *et al.* 2008, Estabrooks *et al.* 2001, Wulff *et al.* 2011). Twelve

items representing the four major characteristics (research design, samples, measurement and statistical analysis) of each selected study were evaluated. This tool was originally a numeric scale and a total score assigned to each study representing its quality level. However, distinguishing high or low quality studies by using the summary scores is not recommended by Centre for Reviews and Dissemination (2009) and the Cochrane Handbook for Systematic Reviews (Higgins *et al.* 2011). Therefore, each item was coded as 'Y' (yes), 'N' (no) or 'P' (partial) instead of a total score. The content of the quality appraisal tool and the description of the appraisal results were listed in Table S1 and S2 (see supplementary files in the online version of this article). Two primary authors independently evaluated the quality of selected studies and 80% agreement was achieved.

Data extraction and synthesis

A predefined review matrix was applied to retrieve and organize relevant data from selected reports (Garrard 2007). The primary author then independently extracted and listed each the design/objective, sample size, target population, exposure and outcome indicators, confounding factors, statistical methods and conclusion of each piece of research. After consulting with the other two authors to resolve difficulties in synthesizing or interpreting data, the most common items in selected studies such as study population, asthma and obesity definitions, confounding factors and main study results were listed in separate tables for further analysis and comparison.

Results

Study characteristics

Publication years and recruited sample—More than half of the reviewed articles were published within 7 years (2005-2011). Most of the studies were conducted in the United States (almost 40% of the selected publications). Only a small proportion of studies were from non-western developed countries; three were from Asia (He *et al.*2009, Leung *et al.*2009, Yoo *et al.* 2011) and one was from Israel (Bibi *et al.*2004). Due to the broad inclusion criteria for study design, 31 were cross-sectional studies and 5 were longitudinal studies.

The developmental stage of the populations recruited in selected studies covered all paediatric age groups from infants (Rodriguez*et al.* 2002), preschoolers (Vargas *et al.* 2007) to adolescents (Gennuso *et al.* 1998, Hasan *et al.* 2006). A combined school-age and adolescence population was most frequent, but five studies mainly recruited adolescents (Bertolace *et al.* 2008, Bidad *et al.* 2007, Cassol *et al.* 2006, Hasan *et al.* 2006, Leung, *et al.* 2009). The numbers of subjects analyzed in each study varied greatly. The smallest number of subjects was 94 children in a case-control designed study led by Henkin *et al.* (2008). The study with the largest sample (N=102,273) was conducted by Ahmad *et al.* (2009) in the US.

Several studies used data originally collected for other large-scale surveys (Epstein *et al.* 2000, Sithole *et al.*2008, Vahlkvist & Pedersen 2009). Although, a large number of subjects and data can be withdrawn through those national-wide databanks, none of them were designed primarily for examination of the relationship between children asthma and obesity. And many of them completed subject recruiting procedures more than 10 years ago (Belamarich *et al.* 2000, Figueroa-Munoz *et al.* 2001, von Mutius *et al.* 2001).

Definitions of childhood asthma and obesity—The heterogeneity regarding the asthma definitions was noticed in different studies. The majority adopted a parent/self - report of physician-diagnosed asthma as a confirmative indicator of asthma diagnosis. About one third of included research provided objective measurement(s) to confirm asthma such as

FEV1 (Forced Expiratory Volume in 1 sec), FVC (Forced Vital Capacity), $FEF_{25-75\%}$ (Forced expiratory $flow_{25-75\%}$) and peak expiratory flow rate (PEFR) (Gilliland *et al.* 2003, Luder *et al.*1998). Others looked for allergic manifestations by collecting results from bronchial or airway hyper-responsiveness testing (BHR or AHR) (Bibi *et al.* 2004) or serum lipid profile and IgE level (Leung *et al.* 2009). In addition, some studies gathered indicators representing asthma severity such as emergency room visits; school days missed, or rescue medication usage to capture a more thorough picture of the children's asthma severity (Belamarich *et al.* 2000, Bibi *et al.* 2004, Jacobson *et al.* 2008, Vargas *et al.* 2007).

Though there was heterogeneity regarding the definition of childhood obesity across reviewed studies, half of them agreed that the 85th and 95th BMI percentiles were applicable cutoff points to identify overweight/obese children. Children were labeled as 'overweight' or 'risk for overweight' while their BMI were between 85th and 95th percentiles and 'obese' or 'overweight' while their BMI were beyond the 95th percentile (Gilliland *et al.* 2003, Luder *et al.* 1998).

Relationship between asthma and obesity

Positive association between asthma and obesity—Among the 35 studies included, 27 reports found a positive association between overweight/obesity with asthmatic symptoms. The positive association was confirmed across the whole paediatric age spectrum. Overweight or obese children were found 1.16-6.8 times more likely to have or develop new asthmatic symptoms compared with normal weight children (Castro-Rodriguez *et al.* 2001, Gilliland *et al.*2003). The majority of the studies adopted a cross-sectional design (N = 31). Among these, 24 confirmed the positive relationship between childhood obesity and asthma (Table 1). Three of four longitudinal studies also concluded that higher BMI during early childhood predicted future incidence of newly-diagnosed asthma or asthma-like symptoms (Table 2).

In addition to identification of a positive relationship between BMI and asthma in the majority of studies included, some were able to elucidate the pattern of the relationship. Both Kwon *et al.* (2006) and Sithole *et al.* (2008) found a linear relationship between BMI and asthma prevalence in 2-11 year old girls and in both boys and girls age 10-11 years old. A U-shaped relationship between BMI and asthma prevalence in boys age 2-11 years was identified by Kwon *et al.* (2006). Two cross-sectional studies (Sithole *et al.* 2008, von Kries *et al.* 2001) reported a dose-response relationship among BMI and asthma prevalence. Sithole *et al.* (2008) estimated that a unit increase of body mass index was associated with a 6% increase in asthma prevalence.

Among those studies that tried to correlate obesity with both atopy and asthma, the relationship between high BMI and asthmatic symptoms is conflicting. However, half of the above mentioned studies that identified a positive association between obesity and asthma all failed to recognize a coexistence of any allergic disease (Bibi *et al.* 2004, Mai *et al.* 2003, von Kries *et al.* 2001). Interestingly, the other half that discovered a negative finding in the association between obesity and atopic diseases could also not verify a positive correlation between asthma and obesity (Leung *et al.* 2009, Schachter *et al.* 2003, Vignolo *et al.* 2005). This result may justify the implication that the obesity-asthma linkage is more noticeable in nonatopic children.

Effect modifiers of the association between asthma/asthmatic symptoms and obesity—Rather than being controlled as confounders, some factors were identified in reviewed studies as effect modifiers of the interaction between asthma and obesity (Kwon et al. 2006). Gender, appeared to be the most discussed effect modifier. More than one fourth of reviewed studies (N = 12) reported a gender effect on the relationship between obesity

and asthma or asthmatic symptoms; nine of these studies used cross-sectional (Figueroa-Munoz et al.2001, Jacobson et al. 2008, Kwon et al. 2006, Kuschnir &da Cunha 2009, Schachter et al. 2003, Shamssain 2006, Tsai et al. 2007, von Kries et al. 2001, Yoo et al. 2011) and three longitudinal designs (Castro-Rodriguez et al. 2001, Gilliland et al. 2003, Mannino et al. 2006). More than half of the studies concluded that the association between BMI and asthma was stronger in girls than boys (Castro-Rodriguez et al. 2001, Figueroa-Munoz et al. 2001, Jacobson et al. 2008, Kuschnir &da Cunha 2009, Schachter et al. 2003, von Kries et al. 2001). Complicating a parsimonious explanation, Kwon et al. (2006) found a U-shape BMI-asthma relationship among boys but a linear BMI-asthma correlation among girls.

Other than gender, some researchers also discovered that ethnicity may mediate the association between obesity and asthma. Kwon *et al.* (2006) revealed that Hispanic children accounted for a larger portion of children who were both overweight/obese and had asthma than Black and non-Hispanic children. Ahmad *et al.* (2009) also concluded that the asthma-obesity association was more prominent among black children than white children.

Factors scrutinized in studies on the asthma and obesity association—Factors other than obesity and asthma indicators that were incorporated in the reviewed studies are inconsistent. The number of related factors included in studies ranged widely from only two (Cassol *et al.* 2006) to more than ten (Gilliland *et al.* 2003). Most were treated as confounders and controlled when examining the relationship between asthma and obesity. This inconsistency may result from the various interests and objectives emphasized by different researchers and be associated with the variant purposes of original surveys.

Those scrutinized factors in reviewed papers can be categorized into two major different types. First and the most gathered was the type of factors conveying mostly the demographic information such as household income, social class, ethnicity, parents' education level, allergic disease history of children/families and active or passive environmental tobacco smoke (ETS) exposure. The other less scrutinized type consisted of modifiable factors concerning the children's risk behaviour such as children's dietary habits or patterns (Luder *et al.* 1998, Vázquez-Nava *et al.* 2010, von Kries *et al.* 2001, Wickens *et al.* 2005), exercise (Wickens *et al.* 2005), physical activity (Yoo *et al.* 2011), TV-watching time (Epstein *et al.* 2000) and sedentary life style (Kuschnir & da Cunha 2009).

Discussion

The findings from this review support a positive relationship between obesity and asthma in all paediatric populations from infants to young adults. Among the 35 studies included, the majority of them found a positive association between being overweight/obese and asthmatic symptoms. In addition, three of four studies conducted with a longitudinal or prospective design concluded that higher BMI during early childhood predicted future increased incidence of newly-diagnosed asthma or asthma-like symptoms. The prospective studies included in this review help clarify the causal relationship between obesity and asthma as did the meta-analysis of longitudinal studies conducted earlier (Flaherman & Rutherford 2006).

Several of the reviewed articles did not identify an association between obesity and asthma (Chinn &Rona 2001, Henkin *et al.* 2008, Leung *et al.* 2009, Schachter *et al.* 2003, To *et al.* 2004, Vázquez-Nava *et al.* 2010, Vignolo *et al.* 2005). However, some of those negative results need further careful consideration. All these studies, except one longitudinal survey conducted by Chinn and Rona (2001), were cross-sectional. Henkin et al. (2008) only drew their results from a small population (N=94). Vázquez-Nava *et al.* (2010) drew conclusions

out of non-significant statistical results ($P > 0.05$); and none of these studies used USA samples and other non-USA samples did show positive relationships between obesity and asthma.

This review reveals that the obesity-asthma link appears to be more prominent in girls, which is consistent with several study findings in adult populations where obese women are more likely to have asthma or worse asthma control (Beckett *et al.* 2001, Guerra *et al.* 2002, Varraso *et al.* 2005). Both Castro-Rodriguez *et al.* (2001) and Herrera-Trujillo *et al.* (2005) identified a stronger correlation between asthma and obesity in girls with early onset of puberty. There is still no satisfactory explanation of the underlying mechanism; however, hormones or changing body composition have been implicated since early onset of puberty in children is positively related to persistent asthma after puberty (Guerra *et al.* 2004).

Compared with sex modification in the relationship between obesity and asthma, the evidence of other correlated factors interacting both with obesity and asthma seems to be less consistent. Only Kwon *et al.* (2006) and Ahmad *et al.* (2009) reported ethnicity as a mediating factor in asthma and obesity. They concluded that children with different ethnic backgrounds may be differentially affected singularly by both obesity and asthma. The paucity of constant findings regarding the effect of ethnicity may result from the inconsistency of incorporating diverse populations into studies and analyzing ethnic data as an important effecter. Ethnic disparity has been identified in obesity and asthma prevalence respectively in paediatric populations (Eaton *et al.* 2010, Zahran *et al.* 2011). More cross ethnic group or cross nation studies are needed to clarify the role of ethnicity in the obesity-asthma linkage.

The discord regarding the number and type of confounders controlled or examined in the articles included in this review prevented the generation or integration of a more comprehensive result. However, as the health conditions related to both obesity and asthma are complex and related to a tangled set of host and environmental risk factors, the lack of a ‘standard’ list of correlates in obesity-asthma studies is not unexpected (Bateman *et al.* 2008, Davison & Birch 2001). Two tentative explanations may be proposed for this absence. First, as previously noted, scientists of several reviewed studies picked up associated variables from a set of correlates selected for a pre-existing databank's original research objectives. Although researchers can readily benefit from retrieving information from the large amount of samples contained in each databank, using this approach, some important variables modifying or confounding the obesity-asthma correlation may be omitted or neglected. Second, there does not seem to be a precedent protocol which can be adopted to guide the variable selection process. This can be illustrated by the observation that even though both Epstein *et al.* (2000) and von Mutius *et al.* (2001) analyzed data from the same databank (NHANES III), they ended up controlling for a different set of covariates when evaluating the asthma-obesity relationship.

Although scientists incorporated variant correlates in evaluation of the obesity-asthma linkage, most covariates controlled or reviewed in selected studies were indices conveying demographic information. Fewer studies elucidated behavioural contributors mediating or moderating these two epidemics. However, both obesity- or asthma-focused studies have already recognized many important behavioural variables affecting obese or asthmatic status such as diet or physical activity, respectively (Berntsen 2011, Devereux & Seaton 2005, Ludwig *et al.*2001, Trost *et al.* 2001). Although several investigations included in this review have already explored the role of behavioural variables in the obesity-asthma association, more well-constructed studies may achieve more conclusive findings (Vázquez-Nava *et al.* 2010, Wickens *et al.* 2005). The exploratory nature of the studies included in this review may explain why the demographic features were more discussed. However, by

accumulating more solid evidence confirming the positive relationship between asthma and obesity, scientists can take the next step to further explore the impact from other 'mutable' behavioural correlates contributing to both health problems. The identified 'modifiable' or 'mutable' behavioural risk factors may guide investigators to develop practical preventive strategies for clinicians and help children stay away from adopting detrimental behaviours or lifestyles that threaten their health (Beckett *et al.* 2001).

Accumulating evidence from recent research points to the advent of a distinct 'obesity asthma' phenotype and suggests that obesity may contribute to asthma through a non-allergic pathway (Jensen *et al.* 2011, Lugogo *et al.* 2010). Reports with positive findings have concluded that the obesity-asthma association is somehow independent from allergic sensitization, which is in accordance with the findings found in an adult population (van Veen *et al.* 2008). The speculation about a new phenotype called 'obesity asthma' not only recognizes the importance of obesity with respect to its impact on the development and severity of asthma, but may also persuade researchers to adopt innovative rather than conventional strategies to explore the underlying mechanism. Based on this preliminary finding generated by this review, the next step for upcoming systematic reviews or meta-analyses may mainly focus on those studies with objective measurements of childhood asthma so that the linkage of obesity to a specific asthma phenotype may be found. In addition, larger scale collaboration with scientists from various specialties and fields contributing their ideas to formulate an integrated mechanism delineating the interplay between asthma and obesity is also warranted.

Although scientists are still looking for a satisfactory explanation delineating the interplay between obesity and asthma, we nurses and other clinical health providers are already challenged by the deviated response to regular asthmatic treatment in children with these two epidemics. In parallel with effort to identify the demographic attributes related to both epidemics, identifying the behavioural factors correlated with both diseases is also important. Conducting more prospective research incorporating a broader spectrum of correlates will help to identify high-risk groups with specific demographic attributes and also help develop effective interventions focusing on eliminating risk behaviours contributing to both obesity and asthma. Given the evidence that weight reduction has been found significantly related to improvement in asthma outcome in an adult population (Eneli *et al.* 2008), the role of behavioural factors or lifestyles should be one of the leading areas of study in the future obesity-asthma research (Jensen *et al.* 2011, Lang 2010). Only by identifying and targeting modifiable behaviours detrimental to both obesity and asthma can scientists further conceive practical interventions to alleviate the double health burden among children suffering from both epidemics (Lang 2010).

Limitations

To formulate a concrete result from this review, preset criteria for including or excluding related reports was adopted; however, applying those criteria to article selection may have resulted in limitations. First, including studies mainly concentrating on the relationship between obesity and asthma may have omitted some investigations with positive outcomes relating obesity to asthma. In one excluded report, obesity was only treated as one risk factor leading to the development of asthma (Rodriguez *et al.* 2002); in another report BMI index was only controlled as one confounder to explain the other exposure's effect on the asthma incidence (Oddy & Sherriff 2003). Although these studies generated results confirming a significant association between obesity and asthma, they jeopardize the integrated process of this review increasing heterogeneity and ambiguity.

Second, the selection of studies using BMI as a primary index to define obesity filtered out some reports, particularly those targeting younger paediatric populations such as infants

(Guerra *et al.* 2004, Taveras *et al.* 2008). It is possible to argue that BMI is not a favorable standard by which to identify childhood obesity (Musaad *et al.* 2009); however, it remains a popular and reasonable indicator for large epidemiologic surveys worldwide (Barlow 2007, Lazarus *et al.*1996).

Third, only incorporating published papers with a clear BMI cutoff point to confirm obese or overweight status also ruled out some studies which may have positive findings. Reports excluded in this category mostly manipulated BMI as a continuous variable. Most of them concluded that higher BMI was accompanied by higher asthma prevalence and many of them were longitudinally designed and thus would have provided further evidence for the obesity-asthma link making our interpretations more conservative in nature (Davis *et al.* 2007, Guerra, *et al.* 2004, Hancox *et al.* 2005, Michelson *et al.* 2009). Using BMI cutoff points to define obesity may yield acceptable specificity and sensitivity to identify subgroups with greater risk for potential comorbidity (Lazarus *et al.* 1996).

Another limitation relates to the definition of childhood asthma. In the absence of a 'gold standard' to measure or diagnose childhood asthma (Remes *et al.* 2002), the heterogeneity of asthma definitions from included studies seems to be inevitable. Though adopting objective measurements can ensure scientists with more confidence to confirm childhood asthma, data gaining from pulmonary tests is somehow unreliable and not recommended as a standard diagnostic procedure especially in children aged 5 or younger (Pedersen *et al.* 2011, Werk *et al.* 2000). To aggregate evidence from contemporary research with a wide spectrum of age groups, the inclusion of studies containing this young population may limit the interpretation of this review. However, after excluding a significant amount of studies failing to provide any subjective or objective evidence to confirm asthma diagnosis, this concern should be eliminated to certain extent. Although most studies confirmed the asthma status by subjective reports of a physician-diagnosed asthma, it is a widely accepted strategy to identify childhood asthma in many epidemiologic surveys (van Wonderen *et al.* 2010) and found relatively accurate in children (Joesch *et al.* 2006). Though there was no study excluded during the quality appraisal process, the description listed in Table S2 presenting how each study scored on each appraised item can fully report the quality of reviewed studies (Higgins et al. 2011). Also, common biases especially for the performance and detection biases were also taken into account by exaniminig and presenting the appraisal results of the measurements (BMI measurement and asthma indicators) adopted by each study (Table S1 and S2).

Conclusions

This review includes a large number of studies on the relationship between obesity and asthma with various research designs. Although the inclusion of investigations with variant research methods may compromise the validity of the evidence, by conducting this review we provide a comprehensive integration of contemporary studies focusing on the relationship between obesity and asthma in paediatric populations. Data from this review provide ongoing evidence that there is a positive relationship between high BMI and asthma in children. The nature of the association appears to be complex; however, with studies identifying linear, U-shape and dose-dependent relationships between BMI and asthma (Kwon *et al.* 2006, Sithole *et al.* 2008, von Kries *et al.* 2001). Similar to previous meta-analyses in adult and child populations, most longitudinal studies reviewed agreed that children who were overweight or obese in early life have an increased risk of newly diagnosed asthma in the future.

Female gender and ethnicity were recognized as important effect modifiers that alter the relationship between asthma and obesity. In accordance with research results found in

adults, the obesity-asthma linkage seems to be more prominent in girls though more well-constructed studies are needed to achieve a more conclusive result. The lack of a standard set of confounders controlled in the included studies and a lack of studies looking at the impact of behavioural factors on the relationship between obesity and asthma were revealed by this review. Conducting more prospective or cohort studies with a collection of meaningful factors based on previous obesity-asthma focused studies, rather than solely relying on pre-existing databanks, may generate further knowledge of the underlying mechanisms of the association.

While scientists are still looking for a satisfactory explanation of the interplay between obesity and asthma, we nurses and other clinicians are already challenged by the deviated responses from obese and asthmatic children treated with the regular regimen. Given the evidence found in adults that weight reduction is significantly associated with improvement in asthma outcome, the role of behavioural factors or lifestyles should be one of the major areas of study in future obesity-asthma research. Nurses as the primary healthcare providers should help children and their families by developing effective nursing interventions to avoid unhealthy life-styles or behaviours leading to the comorbidity of both health burdens. However, a larger scale of interdisciplinary collaboration for conducting more well-designed research by scrutinizing an expanded spectrum of correlates (demographic to behavioural risk factors) related to both epidemics is needed to identify high-risk groups with specific demographic attributes and develop effective nursing interventions applicable to the primary and clinical settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary Statements

What is already known about this topic

- The concurrent increase in asthma and obesity prevalence has been noticed and discussed in many research papers.
- Studies conducted in different populations have confirmed a positive association between asthma and obesity, but the research conclusions pertaining to children are more inconsistent than those from adults.

What this paper adds

- Although some studies did not recognize the relationship between asthma and obesity in children, the majority of studies reviewed supported a correlation between childhood asthma and obesity.
- Using retrieval of data from pre-existing databanks may not only preclude further exploration of influential correlates or effect modifiers that interact with both epidemics but also relate to insufficient consideration of the impact of behavioural factors on the relationship between obesity and asthma.
- Among several important effect modifiers, gender was the most consistent and prominent in the relationship between asthma and obesity; the obesity-asthma linkage seems to be more obvious in girls.

Implications for practice and/or policy

- More well-structured studies primarily designed to investigate the relationship between asthma and obesity in children are needed to elucidate the complex interplay between asthma, obesity and most influential covariates.
- Prospective investigations should incorporate an expanded spectrum of correlates representing children's demographic and behavioural attributes so that scientists can develop effective intervention targeting not only of high-risk subgroups but also children with detrimental life-styles or behaviours.
- Larger scale of interdisciplinary collaboration for conducting well-designed research by scrutinizing demographic and behavioural risk factors related to both epidemics is needed to identify high-risk groups and develop effective nursing interventions to help high-risk children and family to adopt healthier life-styles and behaviours.

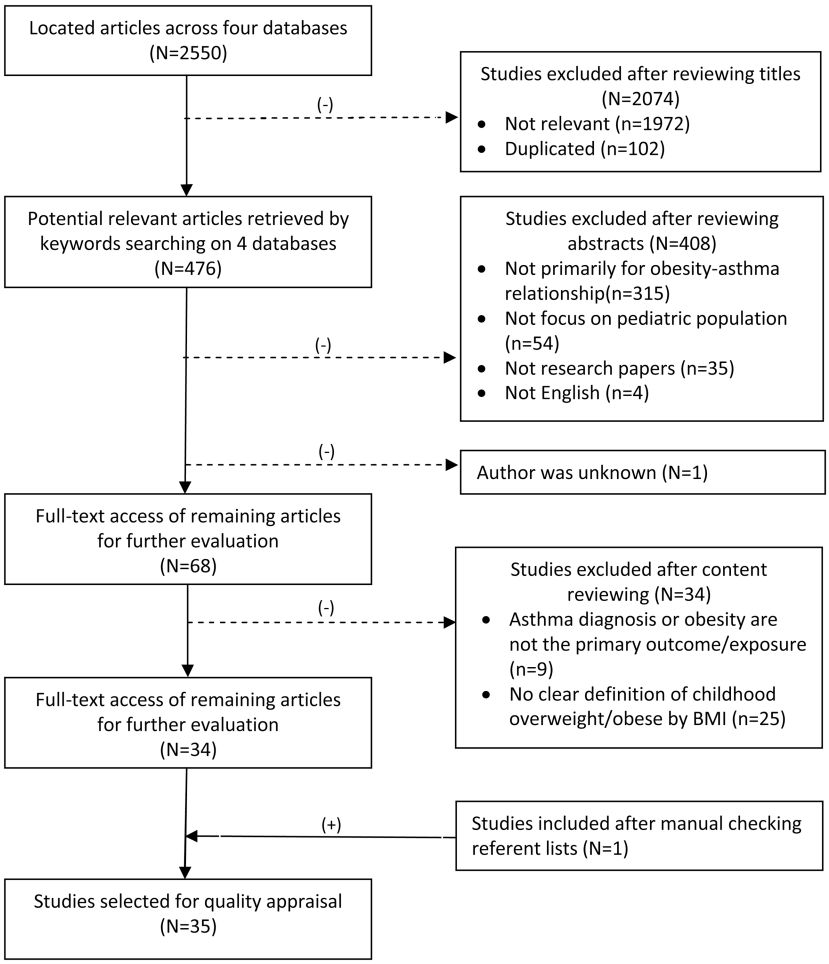

Figure 1. Selection process of included studies

Table 1

Cross-sectional studies (N=31)

Author/population	Definition of		Confounding factors	Main result	
	Obesity	Asthma			
Ahmad, 2009/N=102,273; 0-17yr; USA	Overweight: BMI ≥85th<95th Obese: BMI≥95th	Subjective: Parental-report of children ever diagnosed asthma by physician Objective: None	Age, gender, ethnicity, educational level of family, family structure, poverty level, health insurance, ETS	**1**	A significant association between obesity and asthma (OR=1.33, 95% CI: 1.22-1.44).
				2	Gender (male) and race (black children) were significantly associated with asthma (OR=1.910, 95% CI: 1.587-2.298; 1.714, 95% CI: 1.275-2.305).
Belamarich, 2000/N=1322; 4-9yr; USA	Nonobese: BMI>5th <95th Obese: BMI≥95th	Subjective: Parental-report of asthma dx by doctor, wheezing episodes, PEFR, emergency visits(EDs) Objective: PEFR	Age, gender, family income, caretaker's mental health, environmental tobacco smoke (ETS)	**1**	Obese and non-obese children did not differ in terms of age, gender, family income, passive smoke exposure, caretaker's mental health, or SPTs reactivity to indoor allergens.
				2	Obese group had higher mean number of days of wheeze per 2-week period (4.0 vs 3.4, p<.02), unscheduled EDs (39% vs 31%, p<.04).
Bertolace, 2008/N=421;15-16yr; Brazil	Overweight: BMI≥85th<95th Obese: BMI≥95th	Subjective: Self-report of asthma diagnosis or asthmatic symptoms (ISSAC questionnaire) Objective: None	Age, gender, race, social position, location of residency	No significant positive association between increased BMI and the prevalence of asthma (p=.076).	
Bibi, 2004/N=5984; around 8yr; Israel	Overweight: None Obese: BMI≥95th	Subjective: Parental-report of children ever diagnosed asthmatic by a physician Objective: FEV1, FVC, AHR test	Age, gender, parental education and smoking habits, family crowdedness	**1**	Asthma, wheezing and inhaler use more common in obese children (p<.038).
				2	Asthma was diagnosed more among obese children (p<.008).

Author/population	Definition of		Confounding factors	Main result	
	Obesity	Asthma			
Bidad, 2007/N=2900;11-17yr; Iran	Overweight: BMI≥85th<95th Obese: BMI≥95th	Subjective: Self-report of asthma diagnose while interviewed by trained physician Objective: None	Age, gender, physical scores, waist/hip circumstances, waist-to-hip ratio, gastroesophageal reflux disease hx	**1**	More frequent asthma among obese students (p=.041).
				2	Waist circumference, hip circumference and the waist-to-hip ratio greater in asthmatic students (p<.05).
Cassol, 2006/N=4010; 13-14yr; Brazil	Nonobese: BMI<85th and triceps skinfold thickness<85th) Obese: BMI≥85th and triceps skinfold thickness ≥85th	Subjective: Self-report of wheezing or asthma attacks in the previous year (ISAAC questionnaire)questionnaire Objective: None	Age, gender	**1**	Significant relationship between obesity and 'wheeze ever' (OR=1.28, 95% CI: 1.08-1.52), 'wheeze with exercise' (OR=1.36, 95% CI: 1.11-1.66), 'asthma ever'(OR=1.29, 95% CI: 1.03-1.62) and severe asthma (OR=1.55, 95% CI: 1.08-1.51).
				2	In boys, a significant association between obese and 'wheeze ever' (OR=1.38, 95% CI: 1.01-1.88).In girls, a significant positive relationship between obesity and 'asthma ever' (OR=1.36, 95% CI: 1.11-1.66).
Epstein, 2000/N=5154;6-16yr; USA	Obese: BMI≥85th	Subjective: Parental-report of children ever diagnosed asthma by a physician Objective: None	Age, gender, race/ ethnicity, TV watching time, family income	**1**	Controlling for gender, age and race/ethnicity, asthma children 1.53 (95% CI: 1.25-2.46) times more likely to be obese than children without asthma.
				2	Asthma, TV watching and maternal BMI as independent predictors of youth obesity.
Figueroa-Munoz, 2001/N=14908;4-11y; England/Scotland	Obese: BMI≥90th	Subjective: Parental-report of asthma and asthmatic symptoms	Age, gender, ethnicity, family size, father's	BMI and sum of skinfolds were strongly and significantly associated with each of the asthma	

Author/population	Definition of		Confounding factors	Main result
	Obesity	Asthma		
		Objective: None	social class, living region, ETS	outcomes in girls only among inner city samples (OR=1.28, 95% CI: 1.11-1.48)
Gennuso, 1998/N=171;4-16yr; USA	Obese: BMI≥85th <95th Very obese: BMI≥95th	Subjective: None Objective: Medical record review for asthma dx	Age, gender, ethnicity	Significantly more children with asthma were obese (30.06%) compared with controls (11.6%) (p=.004).
Hasan, 2006/N=109; 13-18yr; USA	Overweight: BMI≥85th Obese: None	Subjective: Self-report of asthma symptoms Objective: Asthma dx confirmed by FEV_1, FVC	Age, gender, ethnicity	Children with asthma almost 1.5 (RR=1.49, 95% CI: 1.015-2.17) times more likely to be overweight compared with children without asthma.
He, 2009/N=2179; 8-13yr; China	Overweight: BMI≥85th<95th Obese: BMI≥95th	Subjective: Parental-report of children ever been diagnosed w/asthma by physicians Objective: FEV_1, FVC, FEF_{25}, FEF_{75}, FEF_{25-75}	Age, gender, allergy hx, physical activity, parental smoking and allergy	Overweight or obese was positively associated with asthma with significant statistical level (obese boy: OR=1.35, 95% CI: 0.24-7.45; obese girls: OR=2.44, 95% CI: 0.62-9.59).
Henkin, 2008/N=94; 4-18yr; England	Risk for overweight: BMI≥85th<95th Overweight: BMI≥95th	Subjective: None Objective: Medical record review for asthma dx	Age, gender, atopic dermatitis and allergic rhinitis hx,food allergy or other allergies	**1** The odds ratio in this analysis using BMI greater than 85th for asthmatic children vs. nonasthmatic children was 0.92 (95% CI: 0.40-2.20). **2** No significant association between various measures of BMI and asthma in this population.
Jacobson, 2008/N=517; 3.4-4.6yr; USA;	Risk for overweight: BMI≥85th<95th Overweight: BMI≥95th	Subjective: Parental-report of children's asthma dx/ symptoms, meds use, EDs Objective: None	Age, gender, parental hx of asthma, birth place, parental birth place, parental education and employment, sibling's allergies, ETS	Body mass was associated with asthma among girls (OR=2.0, 95% CI: 1.1-3.7), but not boys (OR=1.4, 95% CI: 0.8-2.6).
Kuschnir, 2009/N=2858; 13-14yr; Brazil	Only one category—BMI≥85th	Subjective: Self-report of asthma and asthmatic symptoms Objective: None	Age, gender, household pet, sedentary life, ETS	**1** Asthma prevalence increased with higher BMI (p=.02). **2** Positive association between asthma and overweight in adolescent girl only, regardless of sedentary lifestyle and environmental factors

Author/population	Definition of		Confounding factors	Main result
	Obesity	Asthma		
				(OR=1.51, 95% CI: 1.07-2.13).
Kwon, 2006/N=853; 2-11yr; USA	Risk for Overweight: BMI≥85th<95th Overweight: BMI≥95th	Subjective: Parental-report of asthma dx, asthma-like symptoms, asthma related EDs Objective: None	Age, gender, race/ ethnicity, nativity, insurance status, ETS	**1** Strong associations that differ by gender between BMI percentiles **2** Among boys, asthma associated both with overweight (OR=2.4, 95% CI: 2.4-4.3) and underweight (OR=2.9, 95% CI: 1.1-7.7) compared with normal weight. **3** Among girls, asthma associated with at risk for overweight (OR=2.6, 95% CI: 1.4-5.0) and overweight (OR=2.1, 95% CI: 1.2-3.8) compared with normal weight.
Leung, 2009/N=486; 14-18yr; Hong Kong	Overweight: BMI≥85th<95th Obese: BMI≥95th	Subjective: Self-report of asthma dx Objective: lipid profile and inflammatory biomarkers	Age, gender, allergic rhinitis and eczema hx; serum	Obesity not associated with asthma or atopy in Chinese children (p=. 257).
Luder, 1998/N=209; 2-18yr;USA	Risk for Overweight: BMI≥85th<95th Overweight: BMI≥95th	Subjective: Parental report of asthmatic symptoms and meds use Objective: Asthma dx by a doctor PEFR measurement	Age, gender, race, prematurity, breast feeding, avoidance of foods for asthma, ethnomedical-folk remedies, insurance status, ETS	Prevalence of overweight significantly higher in children with moderate to severe asthma than in their peers (OR=1.34, 95% CI: 0.99-1.82).
Mai, 2003/N=457; 11-13yr; Sweden	High BMI: BMI≥75th Overweight: BMI≥95th	Subjective: Parental-report of ISAAC, asthma dx, current wheezing and asthma severity Objective: AHR test	Age, gender, SPTs for allergens, episodes of hay fever	**1** Current wheeze associated with high BMI (OR=1.7, 95% CI: 1.0-3.6). **2** Overweight had an even more pronounced effect (OR=1.9, 95% CI: 1.0-3.6). **3** Asthma severity associated with high

Author/population	Definition of		Confounding factors		Main result
	Obesity	Asthma			
					BMI (OR=2.0, 95% CI: 1.0-4.0).
Rodriguez, 2002/N=12388; 2months-16yr;USA	Only one category—BMI≥85th	Subjective: Parental- report of current diagnosed asthma Objective: None	Age, gender, race/ ethnicity, household head's education, family income/size, insurance status, urban status, ETS	**1**	Children with BMI≥85th have greater risk in having current asthma (OR=1.94, 95% CI: 1.09-3.46).
				2	A strong independent association between obesity and current asthma in children and adolescents.
Schachter, 2003/N=5993; 7-12yr; Australia	Overweight: BMI≥85th<95th Obese: BMI≥95th	Subjective: Recent wheeze hx, recent asthma hx/dx Objective: FEV_1, FVC, PEFR	Age, gender, SPTs for allergens, AHR hx, ETS	**1**	BMI was a risk factor for wheeze ever (OR=1.06, p=.007) and cough (OR=1.08, p=. 001), but not for recent asthma (OR=1.02, p=. 43) or AHR (OR=0.97, p=.17)
				2	Higher BMI associated with higher prevalence of atopy (p=.005), wheeze ever (p=.001) and cough (p<.001) in girls.
Shamssain, 2006/N=7000; 5-16yr; England	Overweight: BMI≥85th<95th Obese: BMI≥95th	Subjective: Self-report of asthma diagnose and asthmatic symptoms Objective: None	Age, gender, ETS	**1**	Boys and girls in the highest BMI percentile had higher prevalence of asthma and asthma symptoms than those in the middle and lowest percentile (OR=1.26, 95% CI: 1.02-1.51; OR=1.16, 95% CI: 0.91-1.50).
				2	Association between overweight and exercise-induced wheezing stronger in boys than girls (OR: 2.66 vs 1.69).

Author/population	Definition of		Confounding factors	Main result
	Obesity	Asthma		
Sithole, 2008/N=3804; 10-11yr; Canada	Overweight: BMI≥20.4(boys) BMI≥20.5(girls) Obese: BMI≥24.8 (boys) BMI≥25.1 (girls)	Subjective: Parental-report of children diagnosed with asthma Objective: None	Age, gender, parental education, household income, neighborhood income	A unit increase of BMI associated with 6% increase of prevalence for asthma both in boys and girls.
To,2004/N= 11199; 4-11yr; Canada;	Obese: BMI≥85th	Subjective: Parental- report of asthma dx, prescribed inhalants, asthma attacks, limited activities by asthma Objective: None	Age, gender, single child status; parental smoking, maternal asthma hx and depression, SES	No statistical association between obesity and asthma among Canadian children age 4 to 11 years.
Tsai, 2007/N=2290; 5th-graders; Taiwan	Risk for Overweight: BMI≥85th<95th Overweight: BMI≥95th	Subjective: Self-report physician diagnosed asthma and respiratory symptoms Objective: None	Age, gender, TV-watching time, Physical activity	Obesity was positively associated with an increased risk of suspected asthma in boys (aOR=1.56, 95% CI: 1.07-2.29), but not in girls.
Vargas, 2007/N=1029; 3-5yr; USA	Risk for Overweight: BMI≥85th<95th Overweight: BMI≥95th	Subjective: Parental-report of asthma morbidity, symptoms, health care/meds use, school days missed, quality of life Objective: Physician diagnosed or algorithm identified asthma	Age, gender, ETS, SPTs	Prevalence of overweight significantly higher in children with asthma compared with the two control groups (Arkansas prekindergarten group: p=.05 and National Health and Nutrition Examination Survey [NHANES]: p<.001, respectively).
Vázquez-Nava, 2010/N=1160; 4-6yr; Mexico	Overweight: BMI≥85th<95th Obese: BMI≥95th	Subjective: Parental-report of children diagnosed with asthma Objective: None	Age, gender, related symptoms (dry cough, wheezing, sleep disturbance), ETS, physical activity, intake of high sugar/oil food	**1** Overweight (OR=1.02, 95% CI: 0.66-1.58, p>.05) and obesity (OR= 0.94, 95% CI: 0.68-1.30, p>.05) were not associated with asthma and wheezing. **2** No association found between overweight, obesity and asthma-associated hospitalization (overweight: OR=0.41, 95% CI: 0.09-1.80, p>.05; obesity: OR=0.35, 95% CI: 0.11-1.04, p>.05).
Vignolo, 2005/N=1179; 2.2-16.1yr; Italy	Only one category—BMI-SDS(BMI standard deviation score units) ≥2	Subjective: None Objective: Medical record review for asthma dx, FEV1, FVC, $FEF_{25-75\%}$	Age, gender, allergic symptoms, IgE, SPTs for allergens	**1** The proportion of the overweight/obesity subjects was similar in two groups (p=.08). **2** BMI-SDS significantly higher in controls than in asthmatics (p=.04).

Author/population	Definition of		Confounding factors		Main result
	Obesity	Asthma			
				3	No correlation between BMI-SDS and pulmonary function tests (r= -.03; p=.51).
von Kries, 2001/N=9357; 5-6yr; German	Overweight: BMI>90th≤97th Obese: BMI>97th	Subjective: Parental-report of asthma diagnosed by physician and asthma severity. Objective: None	Age, gender, prematurity, breast-feeding, febrile episodes in 0-1 yr, full-fat milk consumption; parental education and atopic diseases hx, living environment, ETS	**1**	A clear dose effect between the asthma prevalence and the proportional of overweight/obesity incidence (5.7% asthma in BMI<90th; 6.5% asthma in overweight; and 9.9% in obesity).
				2	The adjusted odds ratio for asthma in girls was 2.12 (95% CI: 1.22-3.68) for overweight and 2.33 (95% CI: 1.13-4.82) for obesity.
von Mutius, 2001/N=7505; 4-17yr; USA;	Obese: BMI≥75th	Subjective: Parental-report of diagnosed or treated for asthma, or still had asthma Objective: None	Age, gender, ethnicity, ETS, birth weight, breast fed, household size; SPTs for allergens	**1**	Significant positive relationship between BMI and asthma (OR=1.77, 95% CI: 1.44-2.19)
				2	No effect modification by gender or ethnic group seen in obesity-asthma relationship.
Wickens, 2005/N=305;10.1-12.6yr;New Zealand	Overweight: *Boys*:BMI$_{at10y}$≥19.8BMI$_{at12.5y}$≥21.6 *Girls*:BMI$_{at10y}$≥19.9 BMI$_{at12.5y}$≥22.1 Obese: *Boys*:BMI$_{at10y}$≥24.0BMI$_{at12.5y}$≥26.4 *Girls*:BMI$_{at10y}$≥24.1 BMI$_{at12.5y}$≥27.2	Subjective: Parental-report of wheezing and asthma dx, meds use and hospital admissions for asthma Objective: PEFR variability before and after exercise, AHR to exercise test	Age, gender, ethnicity, birth weight; family allergic hx, family size, ETS, father's education, frequency of exercise and hamburger consumption;SPTs for allergens	**1**	Increasing BMI standard deviation score was significantly associated with current wheeze (p=0.002), inhaled steroid use (p=.004) and the use of any medication (p=.001).
				2	Some evidence for an association of obesity with asthma symptoms and treatment but not explain increasing prevalence of asthma.

Author/population	Definition of		Confounding factors		Main result
	Obesity	Asthma			
Yoo, 2011/N=717; 15-17yr; Korean	Overweight: BMI≥85th	Subjective: Self-report of Self-report of asthma and asthmatic symptoms (ISAAC questionnaire) Objective: AHR test	Age, gender, recent physical activity, current smoking, parental smoking/education, family hx of allergic dx	**1**	Overweight male adolescents more frequently reported asthmatic symptoms compared with normal weight subjects (11.5 vs. 6.3%, p=.02).
				2	The presence of AHR was more common only among overweight adolescent girls (32.8 vs. 18.0%, p=.028).

*ATS: American Thoracic Society

Table 2

Longitudinal studies (N=4)

Author/population	Definition of		Confounding factors	Main result	
	Obesity	Asthma			
Castro-Rodriguez, 2001/N=1246; 6,8,11,13yr; USA	Overweight: BMI≥85th<95th Obese: BMI≥95th	Subjective: Parental-report of wheezing episodes,classified into frequent/ infrequent or incident/persistent wheezing Objective: PEF variability, broncho-dilator response test	Age, gender, start of puberty, exercise, SPTs for allergens, esinophil counts and methacholine challenge; parental allergic hx, maternal smoking and education, number of siblings	Females who became overweight or obese between 6yr and 11yr were between 5.5 (95% CI: 1.3-23.3)and 6.8(95% CI: 2.4-19.4) times more likely to develop new asthma at 11 or 13yr compared with females who did not become overweight or obese during the same time period.	
Chinn, 2001/N=8983;8-9yr; England	Overweight: ≥25th BMI<30th Obese: BMI≥30th	Subjective: Parental-report of asthma or wheezing Objective: None	Age, gender, ethnicity, birth weight, length of gestation, parental smoking, number of siblings	**1**	Increasing BMI cannot explain increasing of asthma.
				2	Obesity as a marker of recent lifestyle differences now associated with both asthma and overweight.
Gilliland, 2003/N=3792;7-18y; USA	Overweight: BMI≥85th<95th Obese: BMI≥95th	Subjective: Parental-report of a new physician diagnose of asthma Objective:FEV_1, FVC, $FEF_{25-75\%}$	Age, gender, ethnicity, birth weight, puberty onset age, team sports, smoking hx, parental allergic hx, insurance status, ETS, household characteristics	**1**	Risk of new-onset asthma was higher in overweight/obese children (RR=1.52, 95% CI: 1.14-2.03) and in boys.
				2	Association of overweight with new-onset asthma was significantly greater in nonallergic children (RR=1.77, 95% CI: 1.26-2.49) than in allergic children (RR=1.16, 95% CI: 0.63-2.15).
Mannino, 2006/N=4393; Enrolled from birth and 14yr at follow up; USA	High BMI: BMI≥85th	Subjective: Parental-report of asthma dx, meds use and doctors' visits Objective: None	Age, gender, ethnicity, birth weight, prenatal maternal smoking, poverty status	**1**	BMI≥85th at age 2-3 yr was a risk factor for subsequent asthma in boys only (HR=1.6, 95% CI: 1.1-2.4).
				2	Higher rate of incident asthma among children whose BMI≥85th compared with those BMI<25th (10.4 vs 6.4 cases per 1000 person-years).