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Childhood body mass index and wheezing disorders: a systematic review and meta-analysis

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Abstract:

BACKGROUND: It has been claimed that overweight/obesity and childhood asthma and wheezing disorders are associated, although the results of observational studies have remained inconsistent. We conducted a systematic review and meta-analysis to investigate this.

METHODS: An online search of published papers linking childhood asthma and wheezing with overweight/obesity up to May 2014 using EMBASE and Medline medical research databases was carried out. Summary odds ratios (OR) were estimated using random-effects models. Sub-group meta-analyses were performed to assess the robustness of risk associations and between-study heterogeneity.

RESULTS: A total of 38 studies comprising 1,411,335 participants were included in our meta-analysis. The summary ORs of underweight (<5th percentile), overweight (>85th to <95th percentile), and obesity (≥95th percentile) were 0.85 (95% CI: 0.75 to 0.97; P=0.02), 1.23 (95% CI: 1.17 to 1.29; p<0.001), and 1.46, (95% CI: 1.36 to 1.57, P<0.001) respectively. Heterogeneity was significant and substantial in all three weight categories, and not accounted for by predefined study characteristics.

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CONCLUSION: Our results suggest that underweight is associated with a reduced risk of childhood asthma, and overweight and obesity are associated with an increased risk of childhood asthma. Although our findings assert that overweight/obesity and childhood asthma are associated, the causal pathway and temporal aspects of this relationship remain unanswered and deserve further epidemiological investigation.

Running title: Childhood Body Mass Index and wheezing disorders

Introduction:

Asthma is a major chronic disease of childhood whose prevalence, based on self reported symptoms has increased in recent times and is projected to rise in the future (1 2). Alongside this trend in asthma, the global prevalence of overweight or obesity in infants and under five has increased from 31 million to 44 million during 1990-2012 with the potential of a further 60% increase in the coming decade (3).

Previous observational epidemiologic studies suggested that overweight/obesity and childhood asthma are associated although the results remain inconsistent. A meta-analysis of four observational epidemiologic studies had reported that there is a 50% (relative risk=1.50; 95% CI: 1.2 to 1.8) increased risk of childhood asthma for overweight (4). However, the included studies used a variety of risk estimate definitions: three used odds ratio,(5-7) and another used relative risk (8).

Results from a recent meta-analysis of 6 cohort studies by Chen et al (9) reported relative risks of 1.19 (95% CI: 1.03 to 1.37) and 2.02 (95% CI: 1.16 to 3.5) of childhood asthma for overweight and obesity respectively. In a meta-analysis of 6 prospective studies, Egan et al (10) also reported that there is a 35% (relative risk= 1.35, 95% CI: 1.15 to 1.58) and 50% (relative

risk=1.50, 95% CI: 1.22 to 1.83) increase in risk of childhood asthma for overweight and obesity respectively (10). However, the age of study populations, Body Mass Index (BMI) categorizations, and risk estimate definitions were not consistent across the studies included in the two meta-analyses. For example, in the meta-analysis by Egan et al,(10) one study used data driven quintile BMI categories (11), whilst the other two studies used only high risk children (12 13), two used relative risk (8 11), one used hazard ratio (14), and the other three used odds ratio(12 13 15) as risk estimate definitions. Likewise, in the meta-analysis by Chen et al (9), one study included adult population (≥ 21 years old) (16), and another used <25th, 25th-84th, and ≥85th percentiles for underweight, normal, and overweight respectively, another one used bronchitis as the outcome variable instead of asthma or wheezing symptoms (17),

Combining studies that included child and adult populations, used non-standard and inconsistent BMI categories and variety of risk estimate definitions in a meta-analysis may bias the summary risk estimates. For example, suppose that two studies used 30th percentile, three used 10th percentile and four other used 5th percentile as cut-off points for underweight. Then, it becomes difficult to combine these 9 studies in a meta-analysis as the cut-off points used are not equivalent. The last group used a standard BMI cut-off point for underweight (5th percentile) and the other two groups used cut-off points of convenience where some individuals grouped as underweight in these studies are normal BMI according to the standard BMI categorization methods. Similarly, although the estimates from odds ratio and relative risk are similar when the disease is rare (<10%), they diverge as the prevalence increases (18), potentially biasing the summary risk estimates derived from combined odds ratios and relative risks.

Up to May 2014, there were more than forty observational studies that reported original data, comprising more than a million people, less than 10% of whom have been included in the previous meta-analyses. We hypothesize that combining studies that vary in exposure (BMI) categorizations, outcome and risk estimate definitions, and have adult populations may potentially under or over estimate the summary risk estimate of BMI on childhood wheezing

disorders. Based on these observations, we aimed to provide an up-to-date and more consistent investigation of the association between overweight/obesity and childhood asthma and wheezing disorders through a systematic review and meta-analysis of studies, using consistent exposure and risk estimation definitions, and the standard World Health Organization (WHO) definition of the age range for children and adolescents (19).

Methods:

Search strategy:

The review was carried out in accordance with the PRISMA guidelines for systematic reviews and meta-analyses (20). An online search of observational studies (cohort, case-control, and cross-sectional), published as an article in English language, was carried out using EMBASE and MEDLINE databases (Figure 1). A literature search was carried out by the first author. Eligible studies were those original reports on childhood wheezing disorders and BMI, covering 0-19 years of age, published until May 2014. Table S1 gives the details of terms and phrases used for the literature search.

To avoid assuming a linear association, papers were excluded if BMI was modelled as a continuous variable. Publications were also excluded if authors used data-driven multiple categories of BMI, and if the number of categories presented were generally too few (<4) to allow combination with studies through estimating nonlinear dose-response curves (21). Papers were also excluded if no risk estimates or comparison groups were presented, or if an adult population was included with no separate risk estimate or data for children available.

Data extraction:

Studies were selected by two independent reviewers. The following study characteristics were extracted: authors, year of publication, country, study design, sample size, study age group, outcome (diagnosis) term used, exposure (BMI) categories used, exposure categorization method, outcome ascertainment, and exposure ascertainment. Data extraction was carried out independently by two reviewers. Differences were resolved by consensus.

Data standardization:

Exposure variable (BMI):

Data on exposure variable presented varied according to the cut-off points of BMI categories adopted by authors. **1)** The CDC: <5th percentile, ≥5th and <85th percentiles, ≥ 85th-<95th percentiles, and ≥95th percentile for underweight, normal, overweight, and obese categories respectively (22). **2)** The International Obesity Task Force: Age and sex specific cut-off points that are extrapolated from the adult BMI cut-offs of 18.5kg/m^2, 25kg/m^2, and 30kg/m^2 for underweight, overweight, and obesity respectively (23 24). **3)** The WHO: 85th-95th percentile and ≥95th percentiles or 1SD+ and 2SD+ for overweight and obese respectively (25). **4**) Data driven multiple BMI categories.

For comparability and not to lose data due to variation in categorization methods, data harmonization was undertaken. **A**) Where authors used one of the standard category methods (CDC, IOTF or WHO), the reported adjusted risk estimates and data on the number of cases and non-cases of each weight comparison group were combined for meta-analysis without any change. **B)** Where authors adopted data driven BMI categories with the CDC, IOTF or WHO normal category as a reference and where the number of participants in each category was available, the stratum based number of cases and non cases were aggregated before being combined with the other studies for meta-analysis of unadjusted risk estimates. **C**) Where authors adopted two or three birthweight categories with CDC, IOTF or WHO normal category

as a reference and provided adjusted risk estimates, the stratum based risk estimates were aggregated using recommendations from Hamling et al (26) before being combined with the other studies for meta-analysis of adjusted risk estimates.

Outcome variable:

Study authors used one or multiple outcome terms in their reporting. Again, for comparability among studies, where authors used a single outcome, e.g. asthma or wheezing, the quoted outcome term by the author and its risk estimate were assumed for analysis. However, where authors used multiple outcome terms, a term that was highest in the hierarchy and its risk estimates were assumed for analysis. For example, if asthma and wheezing were used together, asthma was preferred over wheezing.

Quality assessment:

Papers included in this review were assessed for risks of bias using the Newcastle-Ottawa quality assessment scale (27). Each of the studies was assessed for three quality components: selection of study population, comparability (adjustment for covariates) and outcome or exposure. Table S3 gives the details of studies with respective scores.

Statistical analysis:

In the meta-analyses of all studies, random effects models were preferred as we made an assumption that the studies were not functionally identical and the aim of our meta-analysis was to generalize about other populations (28), Estimates were pooled using the DerSimonian and Laird method (29).

If studies presented stratum-specific estimates (e.g. by gender), then to provide correct measures of heterogeneity, the risk estimates were aggregated using fixed effect models before being combined with the other studies for meta-analyses of adjusted risk estimates in a random-effects model. Likewise, where authors reported the number of cases and non-cases in each stratum, the total number of cases and non-cases were aggregated before being combined

with the other studies for meta-analyses of unadjusted risk estimates of all studies. Odds ratios were the principal summary measures.

To quantify between-study heterogeneity, the Cochrane Q-test (30) and the I^2 measure of the proportion of the total heterogeneity explained by between study variation (31) were used. Sub-group meta-analyses and sensitivity analysis of unadjusted risk estimates were performed on *a priori* selected covariates (study characteristics) in order to assess the robustness of the risk associations and levels of between-study heterogeneities. In order to account for the sources of between-study heterogeneity, meta-regression (32) of unadjusted risk estimates was performed using Restricted Maximum Likelihood (REML).

In investigating evidence of publication bias and small study effects, symmetry funnel plots and bias test models were used (33 34). 5% significance levels and 95% confidence intervals were adopted throughout. Meta-analyses were carried out in Stata software version 12 (Stata Corp, College Station, TX, USA).

Results:

Literature search:

In total, 2887 non-duplicate papers were available and screened; 2800 excluded due to non-relevance and 87 were read in full (Fig 1). Out of the 87 papers, 44 were included in the review. A total of 38 studies reported either the risk estimates or number of cases and non-cases of wheezing disorders in each exposure group were included in the meta-analysis (Table S2). The studies were from Europe =11, Americas =18, Asia =7 and Oceania=2.

Results from six studies were not combined with the other studies for meta-analysis as five of them used slightly different percentile cut-off points (35-39) and another used pooled data from over different continents and presented a summary risk estimate (40).

Quality of studies:

With the maximum of 9 points for each article, of the 38 included in the meta-analysis: twenty-five scored 7-9, thirteen scored 5-6, and their risks of biases can be interpreted as 'low' and 'moderate' respectively(Table S2).

Underweight and childhood wheezing disorders:

A total of 7 studies presented data on the number of cases and non-cases in underweight and normal BMI groups comprising a total of 772,040 children (7 41-46). The summary risk estimate of the studies showed that there was a significant decrease odds of wheezing disorders (OR= 0.85, 95% CI: 0.75 to 0.97; P=0.02) for the underweight children (Figure 2). There was considerable heterogeneity among the studies (Q=29, d.f.=6, P<0.001; I^2=79%, 95% CI: 58% to 89%). When a meta-analysis was performed on four studies (7 47-49) that provided adjusted risk estimates, the overall OR was 0.96 (95% CI: 0.75 to 1.23, P=0.75) with very low heterogeneity among studies (Q=2, d.f=3, P=0.65; I^2=0%) (Figure S1).

Overweight and childhood wheezing disorders:

A total of 29 studies presented data on the number of cases and non-cases in the overweight and normal BMI groups that included a total of 1,075,042 children (7 8 41-46 50-69). The summary of the ORs showed that there was a significant increased risk of wheezing disorders (OR: 1.23, 95% CI: 1.17 to 1.29; p<0.001) (Figure 3). There was a considerable heterogeneity among the studies (Q=78, d.f. = 28; I^2 = 64%; 95% CI: 46% to 76%). When meta-analysis was carried out on 21 studies (7 47-49 55-58 60 61 64-73) that presented adjusted risk estimates of overweight on childhood wheezing disorders, the summary risk estimate was slightly accentuated (OR=1.30, 95% CI: 1.19 to 1.42; P<0.001) whereas the between-study heterogeneity substantially decreased (Q=27, d.f.=20, P=0.12; I^2=27%, 95% CI: 0.0 to 57%) (Figure S2).

Obesity and childhood wheezing disorders:

A total of 20 studies presented data on the number of cases and non-cases of wheezing disorders in the normal and obese group that comprised 1,003,076 children (7 41-43 45 50-52 54 55 57 59-61 64 66 67 69 74). The overall risk estimate showed that there was a significant increase in the risk of wheezing disorders for obesity (OR =1.46, 95% CI: 1.36 to 1.57) (Figure 4). There was substantial heterogeneity among the studies (Q= 111, d.f. = 20; I^2 = 82% (95% CI: 73% to 88%). However, when the analysis was repeated on the adjusted risk estimate of obesity on wheezing disorders available from 16 studies (7 8 47-49 57 60 61 64 66 67 69 72 74 75), the heterogeneity was attenuated (Q=28, d.f=14, P=0.02; I^2=46%, 95% CI: 3% to 70%) whilst the summary risk estimate slightly increased (OR=1.60, 95% CI: 1.42 to 1.81) (Figure S3).

Sub-group meta-analyses:

Subgroup meta-analysis of underweight risk estimates on childhood wheezing disorders from 7 studies showed that the strength of the risk estimates remained stable across each subgroup of the predefined covariates. The heterogeneities across each subgroup of the covariates were significant while except for the covariate 'exposure categorization method', the heterogeneities between each subgroup of the covariates were not significant (Table 1).

When subgroup meta-analysis of the 29 studies by the predefined study characteristics was carried out, except for the IOTF categorization method and papers published before 2000 that were not statistically significant, the strength and direction of the summary risk estimates in each subgroup remained stable (Table 2). The within subgroup heterogeneity was not significant for the wheezing outcome term, e-records outcome ascertainment, parental exposure ascertainment, WHO BMI categorization method, sample size less than 1000, and case-control study design where it was significant for the rest of the subgroups (Table 2). Except for outcome ascertainment, age group during diagnosis, sample size, and study design subgroups, there was no significant heterogeneity between each subgroup of the other covariates.

A subgroup meta-analysis of 21 studies that presented the risk estimate data of obesity on childhood wheezing disorders by the *a priori* selected covariates was performed, except for the case-control study design subgroup, the strength and direction of the summary risk estimates in each subgroup remained stable. There were significant within subgroup heterogeneities except for the outcome ascertainment through a child, exposure ascertainment not mentioned, IOTF BMI categorization method, and sample size less than 1000 subgroups. Also, except for the sample size subgroups, there were significant heterogeneities between each subgroup of the other covariates (Table 3).

When investigating the sources of between-study heterogeneity in the overweight/obesity and wheezing disorders risk estimates, the results showed that none of the heterogeneity was explained by the *a priori* selected covariates (Tables 4 & 5). No meta-regression analysis was carried out for underweight risk estimates on childhood wheezing disorders due to not having enough observations for the model to converge.

When sensitivity analysis of the summary unadjusted risk estimates were carried out according to the number of BMI categories used by authors, the summary OR of overweight on asthma for two, three, and four BMI categories were 1.48 (95% CI: 1.19 to 1.84), 1.24 (1.14 to 1.35), and 1.15 (1.09 to 1.21) respectively (Table 2). When the same analysis was carried out on obesity risk estimates, the summary OR of obesity on wheezing disorders for two, three, and four BMI categories were 2.05 (1.42 to 2.95), 1.48 (1.30 to 1.67) and 1.40 (1.26 to 1.56) respectively (Table 3). Furthermore, the summary odds ratios remained similar when the studies were clustered according to study quality and developmental stage of children (i.e. under-five, school age (5-7 years), puberty (8-14 years), adolescence or beyond puberty (15-19 years), and mixed stages).

Investigating biases (small study effect):

The funnel plots for the unadjusted risk estimates of BMI on childhood wheezing disorders showed some evidence of asymmetry in the overweight (P=0.04), but not in the underweight and obese categories (P=0.92 and P=0.31 respectively) (Figure S4).

Discussion:

In this more comprehensive meta-analysis, we have found that there is a significant increase of childhood wheezing disorders risk by 23% (OR: 1.23, 95% CI: 1.17 to 1.29) and 46% (OR=1.46, 95% CI: 1.36 to 1.57) for overweight and obesity respectively. We have also found that there is a significant 15% reduction of wheezing disorders risk for underweight (OR= 0.85, 95% CI: 0.75 to 0.97). If we were to restrict our meta-analysis only for the cohort studies as Chen et al (9) and Egan et al (10) did, the summary relative risk estimates for overweight and obesity are 1.21 (95% CI: 1.08 to 1.36) and 1.42 (1.31 to 1.54) respectively. However, our summary relative risk estimates for only cohort studies may not be comparable to that of Egan et al(10) as the risk estimate definition was not consistent across the studies included in their meta-analysis. Our overweight summary relative risk estimates for only cohort studies and that reported by Flaherman and Rutherford (4) meta-analysis may also not be comparable for the same reasons.

One notable difference between our study and the three previous meta-analyses results is that our summary risk estimates have narrower confidence intervals and are more robust than those previously reported. This is likely to be due to the larger number of participants in our meta-analysis. It could be also due to our usage of data harmonization, consistent definition of the risk estimates and BMI categorization methods, and the usage of standard WHO child and adolescent age range definition (19).

Based on our sub-group meta-analyses results of the unadjusted risk estimates, we noted that the summary ORs estimates tended to attenuate as the number of BMI categories used by study authors increased. For example, the summary associated risk of overweight on wheezing disorders for authors that used two BMI categories was twice and thrice of those which used

three and four BMI categories respectively (Table 2). A similar pattern was also observed in the obesity risk estimates according to the number of BMI categories used by authors (Table 3).

Our sub-group meta-analyses by study design showed that the summary risk estimates of the cohort and cross-sectional studies are very similar, both for the overweight and obesity risk estimates. This may indicate that cross-sectional studies can be as credible as cohort studies although the findings need to be validated by other meta-analyses in other fields or with more data included. Cross-sectional studies are also easier and cheaper to conduct than case-control and cohort studies, and this can have implication for cost saving and efficiency.

We investigated the effects of age and developmental stage of children on the association between BMI and childhood wheezing disorders by classifying the age of children into 'under-five', 'five years and above' and 'mixed age group'; and developmental stage into 'under-five', 'school age (5-7 years)', puberty (8-14 years)', adolescence (15-19 years)' and 'mixed stages'. However, we found no significant effect on the risk of association.

Based on the heterogeneity measures (Q-test and I^2), we observed that there was a considerable level of between-study variation in the underweight, overweight and obesity unadjusted risk estimates although this could be due higher sample size studies in our analyses (76). As noted in the forest plots, there were a few studies with large samples and high precision of risk estimates that can have dominating effects for the between-study heterogeneities (Figures 3&4). However, the same pattern was not observed in the adjusted risk estimates: the between-study heterogeneities were low in underweight, overweight, and obesity risk estimates (Figures S2& S3).

In our attempt to uncover the effects of study level covariates to the observed significant between-study heterogeneity in the underweight, overweight, and obesity unadjusted risk estimates on childhood wheezing disorders, none of the predefined covariates (study characteristics) explained the between-study variations.

Our analyses have certain limitations. Firstly, in all BMI categories unadjusted summary risk estimates on wheezing disorders, we found that there was a significant and substantial level of between-study variation that was not explained by our *a priori* selected covariates. We may be reassured though that our summary risk estimates were consistently similar with those of the adjusted summary risk estimates (except for underweight) and the between-study variations ranged 0-49%. Secondly, we also had some evidence of funnel plot asymmetry which may indicate a potential small study effect such as potential publication bias (33).

Thirdly, as in any systematic review and meta-analysis, we cannot rule out the possibility of potentially relevant studies being missed by our search strategy. Fourthly, our results are based on epidemiologic observational studies and are solely dependent on the quality of the primary studies included. Particularly, wheezing disorders were ascertained through self administered questionnaires in the majority of the studies included that may cause a potential bias to the risk estimates.

The strength of our work is that we were able to produce consistent risk estimates due to our use of harmonised data. Combining only adjusted risk estimates may under or over estimate the association between exposure and outcome due to either exclusion of studies that used multiple BMI categories convertible to one of the standard formats or combining all irrespective of the type of exposure categorization method used. In order to improve validity of the summary risk estimates, we implemented data harmonization techniques and were able to include more studies than if we were to use previous authors' techniques: most importantly, we were able to produce more consistent summary risk estimates of underweight, overweight, and obesity on wheezing disorders than if we were to combine non-standard multiple cut-off points. The other strength of this work is that we extracted and analysed both adjusted and unadjusted risk estimates, which can be used as an internal validation with each other.

In conclusion, our results suggest that underweight is associated with a reduced odds of childhood wheezing disorders, and overweight and obesity are associated with an increased

odds of wheezing disorders. However, although our findings assert that overweight/obesity and childhood wheezing disorders are associated, the causality or temporal relationship remains unanswered and deserves further scrutiny in epidemiological studies.

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Contributors: TFM, RGF and RCP conceived the idea. TFM performed the literature search. TFM, RGF and RCP contributed to study design, literature search, and data extraction and study selection. TFM performed all the statistical analyses, interpretation of results and drafted the manuscript. DCG provided advice on statistical analyses and interpretation of results. DCG, RGF, RCP revised and commented on the manuscript. All authors approved the final version of the manuscript.

Competing interests: none declared.

List of tables:

Table 1: subgroup analysis for unadjusted risk estimates of underweight on childhood wheezing disorders

		OR (95% CI)	n	I^2	P_{het}[a]	P_{het}[b]
Outcome terms used	Asthma	1.74 (1.50, 2.02)	7	79%	<0.001	
	wheezing		0			
Outcome ascertainment	E-records/trained	1.08(0.64, 1.8)	2	88%	<0.01	
	child	0.87 (0.83, 0.91)	1			0.06
	parent	0.81 (0.50,1.31)	4	81%	<0.01	
Exposure ascertainment	E-records/trained	0.84 (0.62, 1.15)	5	85%	<0.001	
	child	0.87 (0.83, 0.91)	1	0%		
	Parent		0			0.27
	No mention	1.42 (0.69, 2.89)	1	0.0%		
Exposure categorization method	CDC	0.90 (0.82, 0.97)	5	62%	0.03	
	IOTF	0.45 (0.33, 0.61)	1	0%		<0.001
	WHO	0.82 (0.57, 1.18)	1	0%		
Age during diagnosis	Five years & above	0.84 (74.15, 0.96)	6	82%	<0.001	
	Mixed (0-19 years)	1.42 (0.69, 2.90)	1	0%		0.17
	Under five years		0			
Gender	Boys		0			
	Girls		0			
	Mixed	0.85 (0.75,097)	7	79%	<0.001	
Sample size	<1000	1.42 (0.69, 2.89)	1			
	1000+	0.84 (0.74, 0.96)	6	82%	<0.001	0.17
Study period	<2000		0			
	2000+	0.85 (0.75, 0.97)	7	79%	<0.001	
Study Design	cohort	0.62 (0.34, 1.17)	2	94%	<0.001	
	Case-control		0			0.12
	Cross-sectional	0.85 (0.75, 0.97)	5	59%	0.05	
Number of BMI categories [c]	Two		0			
	Three	1.09 (0.62, 1.91)	2	79%	0.03	0.07
	Four	0.81 (0.71, 0.93)	5	81%	<0.001	

[a] P for heterogeneity within each subgroup.
[b] P for heterogeneity between each subgroup.
[c] Sensitivity analysis

Table 2: subgroup analysis for unadjusted risk estimates of overweight on childhood wheezing disorders

		OR (95% CI)	n	I^2	P_{het}[a]	P_{het}[b]
Outcome terms used	Asthma	1.23 (1.17, 1.29)	27	66%	<0.001	0.44
	wheezing	1.23 (1.05, 1.42)	2	0%	0.5	
Outcome ascertainment	E-records/trained	1.19 (1.05, 1.36)	5	40%	0.16	
	child	1.30 (1.05, 1.60)	4	64%	0.04	<0.01
	parent	1.27 (1.15, 1.40)	20	64%	<0.001	
Exposure ascertainment	E-records/trained	1.22 (1.14, 1.32)	24	59%	<0.001	
	child	1.13 (1.11, 1.15)	1			
	Parent	1.54 (1.32, 1.80)	2	0%	0.77	<0.001
	No mention	1.38 (1.01, 1.88)	2	42%	0.18	
Exposure categorization method	CDC	1.24 (1.17, 1.30)	18	65%	<0.001	
	IOTF	1.07 (0.86, 1.33)	8	75%	<0.001	0.74
	WHO	1.21 (1.06, 1.39)	3	0%	0.98	
Age during diagnosis	Five years & above	1.21 (1.15, 1.28)	17	67%	<0.001	
	Mixed (0-19 years)	1.21 (1.07, 1.37)	12	55%	0.01	0.03
	Under five years		0			
Gender	Boys		0			
	Girls		0			
	Mixed	1.23 (1.17, 1.29)	29	64%	<0.001	
Sample size	<1000	1.57 (1.10, 2.23)	4	38%	0.17	
	1000+	1.21 (1.16, 1.27)	25	64%	<0.001	0.01
Study period	<2000	1.06 (0.46, 2.42)	1	0%		
	2000+	1.23 (1.17, 1.29)	28	65%	<0.001	0.84
Study design	cohort	1.26 (1.09, 1.47)	8	67%	<0.01	
	Case-control	1.45 (1.03, 2.05)	2	0%	0.41	0.16
	Cross-sectional	1.24 (1.15, 1.34)	19	66%	<0.001	
Number of BMI categories [c]	Two	1.48 (1.19, 1.84)	7	78%	0.08	
	Three	1.24 (1.14, 1.35)	17	35%	<0.001	0.01
	Four	1.15 (1.09, 1.35)	5	74%	<0.001	

[a] P for heterogeneity within each subgroup.
[b] P for heterogeneity between each subgroup.
[c] Sensitivity analysis

Table 3: subgroup analysis for unadjusted risk estimates of obesity on childhood wheezing disorders

		OR (95% CI)	n	I^2	P_{het}[a]	P_{het}[b]
Outcome terms used	Asthma	1.43 (1.33, 1.54)	20	81%	<0.001	0.001
	wheezing	1.94 (1.60, 2.36)	1			
Outcome ascertainment	E-records/trained	1.81 (1.39, 2.36)	4	75%	0.01	
	child	1.28 (1.25, 1.31)	3	0%	0.86	<0.001
	parent	1.49 (1.31, 1.69)	14	57%	<0.001	
Exposure ascertainment	E-records/trained	1.50 (1.37, 1.65)	17	60%	0.001	
	child	1.28 (1.25, 1.31)	1			
	Parent		0			<0.001
	No mention	1.60 (1.11, 2.31)	3	53%	0.12	
Exposure categorization method	CDC	1.41 (1.30, 1.53)	13	86%	<0.001	
	IOTF	1.57 (1.24, 1.98)	7	45%	0.10	0.002
	WHO	1.94 (1.60, 2.36)	1	0%		
Age during diagnosis	Five years & above	1.42 (1.29, 1.55)	10	69%	<0.001	
	Mixed (0-19 years)	1.53 (1.30, 1.80)	11	88%	<0.001	0.05
	Under five years		0			
Gender	Boys		0			
	Girls		0			
	Mixed	1.46 (1.36, 1.57)	29	82%	<0.001	
Sample size	<1000	1.75 (1.15, 2.65)	4	50%	0.12	
	1000+	1.45 (1.34, 1.55)	17	84%	<0.001	0.07
Study period	<2000	3.39 (1.49, 7.73)	1	0%		
	2000+	1.45 (1.35, 156)	20	82%	<0.001	0.03
Study design	cohort	1.58 (1.29, 1.94)	5	67%	0.02	
	Case-control	1.65 (0.45, 6.1)	2	88%	0.01	<0.001
	Cross-sectional	1.46 (1.36, 1.57)	14	62%	<0.001	
Number of BMI categories [c]	Two	2.05 (1.42, 2.95)	1			
	Three	1.47 (1.30, 1.67)	15	57%	<0.01	0.02
	Four	1.40 (1.26, 1.56)	5	94%	<0.01	

[a] P for heterogeneity within each subgroup.
[b] P for heterogeneity between each subgroup.
[c] Sensitivity analysis

Table 4: Meta-regression results of overweight on wheezing disorders

	OR (95% CI)	P-value
Outcome terms used (ref=Asthma)	1.14 (0.74, 1.74)	0.54
Outcome ascertainment (ref= e-records/trained)	1.04 (0.89, 1.21)	0.60
Exposure ascertainment (ref=e-records/trained)	1.04 (0.92, 1.17)	0.51
Exposure categorization method (ref=CDC)	0.90 (0.76, 1.07)	0.22
Age during diagnosis (ref=Five-and-above)	0.93 (0.73, 1.19)	0.56
Sample size (ref=less than 1000)	0.76 (0.49, 1.19)	0.22
Study period (ref=before 2000)	0.70 (0.22, 2.20)	0.52
Study type (ref=cohort)	0.98 (0.87, 1.10)	0.66
Overall		0.64

Table 5: Meta-regression results of obese on wheezing disorders

	OR (95% CI)	P-value
Outcome terms used (ref=Asthma)	1.18 (052, 2.71)	0.67
Outcome ascertainment (ref= e-records/trained)	0.90 (0.73, 1.11)	0.29
Exposure ascertainment (ref=e-records/trained)	0.98 (0.82, 1.19)	0.83
Exposure categorization method (ref=CDC)	1.20 (0.85, 1.70)	0.28
Age during diagnosis (ref=Five-and-above)	0.97 (0.66, 1.43)	0.87
Sample size (ref=less than 1000)	0.77 (0.42, 1.42)	0.37
Study period (ref=before 2000)	1.73 (0.52, 5.84)	0.34
Study type (ref=cohort)	1.06 (0.88, 1.28)	0.51
Overall		0.52

List of captions:

Figure 1: Literature search flow-chart

Figure 2: Summary unadjusted odds ratio of 7 studies that presented the number of cases and non-cases of asthma in the underweight and normal weight group. Heterogeneity chi-squared = 29 (d.f. = 6) $p < 0.001$, I^2 =79% (95% CI: 58% to 89%), and the estimate of between-study variance Tau-squared = 0.01.

Figure 3: Summary unadjusted odds ratio of 29 studies that presented the number of asthmatic and non-asthmatic children in normal and overweight groups. Heterogeneity chi-squared = 77 (d.f. = 28) $p < 0.001$, I^2 = 64% (95% CI: 46% to 76%), and the estimate of between-study variance Tau-squared = 0.004.

Figure 4: Summary unadjusted odds ratio of 21 studies that presented the number of asthmatic and non-asthmatic children in normal and obese groups. Heterogeneity chi-squared = 111 (d.f. = 20) $p < 0.001$, I^2 = 82% (95% CI: 73% to 88%), and the estimate of between-study variance Tau-squared = 0.008.

Fig S1: Summary of adjusted risk estimates of underweight on childhood wheezing disorders**.** Heterogeneity chi-squared=1.64 (d.f=3, P=0.65), I^2=0% (95% CI:0 to72%), and the estimate of between study variance Tau-squared=0.0.

Figure S2: Summary of adjusted risk estimates of overweight on childhood wheezing disorders. Heterogeneity chi-squared = 27 (d.f. = 20) p = 0.13, I^2 = 27% (95% CI: 0% to 57%), and the estimate of between-study variance Tau-squared = 0.01.

Figure S3: Summary of adjusted risk estimates of obesity on childhood wheezing disorders. Heterogeneity chi-squared = 28 (d.f. = 14) p = 0.02, I^2 = 49% (95% CI: 8% to 72%), and the estimate of between-study variance Tau-squared = 0.02.

Fig S4: Egger's funnel plots of BMI and childhood asthma and wheezing disorder studies**.** a) Underweight b) Overweight c) Obesity risk estimate funnel plots. In all funnel plots, the middle solid line is the summary OR estimate and the two diagonal dotted lines are the 95% confidence limits around the summary OR, and the slant solid line is fitted regression line for Egger's small-study effect test.

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