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Birthweight and childhood wheezing disorders: a systematic review and meta-analysis

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Abstract:

BACKGROUND: Previous observational studies have claimed that birthweight and childhood wheezing disorders are associated although the results remained inconsistent. One systematic review and two systematic reviews that included meta-analyses reported inconsistent results. We aimed to conduct a systematic review and meta-analysis to investigate this.

METHODS: An online search of published papers linking childhood asthma and wheezing disorders with birthweight up to February 2014 was carried out using EMBASE and Medline medical research databases. 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 37 studies comprising 1,712,737 participants were included in our meta-analysis. The unadjusted summary ORs for risk of childhood wheezing disorders associated with low birthweight (<2.5kg) were 1.60 (95% CI: 1.39 to 1.85, P<0.001) and 1.37 (95% CI: 1.05 to 1.79, P=0.02) when compared with ≥2.5kg and 2.5-4.0kg birthweight groups respectively. The overall summary OR for high birthweight (>4.0kg) as compared to the 2.5-4.0kg birthweight group was 1.02 (95% CI: 0.99 to 1.04, P=0.13). There was substantial heterogeneity in the unadjusted low birthweight risk estimates which was not accounted for by predefined

study characteristics. There was no significant heterogeneity in the high birthweight risk estimates. There was some evidence of funnel plot asymmetry and small study effects in the low birthweight (2.5kg versus ≥2.5kg and <2.5kg versus 2.5-4.0kg) odds ratio estimates.

CONCLUSION: Our results suggest that low birth (<2.5kg) is an independent risk factor for wheezing disorders during childhood and adolescence although there was substantial heterogeneity among the risk estimates. However, we found no significant association of high birthweight with wheezing disorders.

Key words: birthweight, asthma, wheezing, meta-analysis

What is known on this topic?

- Low birthweight has moderate risk of association with childhood asthma.
- Previous meta-analyses reported inconsistent risk of association of high birthweight with childhood asthma.

What this study adds:

- There is strong risk of association of low birthweight with wheezing disorders.
- There is no significant risk of association between high birthweight and childhood asthma and wheezing disorders.
- There is significant between-study heterogeneity and small study effect among studies that compared the risk of low birthweight (<2.5kg) with the normal (≥2.5kg or 2.5-4.0kg) birthweight group.

Introduction

Asthma is described as the most common chronic disease in children.[1] According to self reported symptoms, the prevalence of childhood wheezing disorders have increased markedly in the past and are projected to rise in the current decade worldwide.[2] There have also been increases in childhood atopic diseases (eczema and rhinoconjuctivitis) and obesity in recent decades.[3 4] This may indicate that the increases were mainly due to environmental and life-style changes. Observational epidemiological studies also suggest that childhood wheezing disorders have strong links with viral respriratory infections,[5] parental smoking,[6] and childhood overweight.[7 8]

Low birthweight (<2.5kg) is the most important factor affecting neonatal and postnatal mortality.[9-11] Low birthweight infants are also more likely to develop health problems including respiratory disorders, asthma in particular, in their childhood and adulthood life.[9 12] Past epidemiological studies have also reported that there is a link between low birthweight and childhood wheezing disorders, although results remained inconsistent. [13] Syntheses of studies have been carried out in the past[14 15], however, the results were inconsistent and the methodologies applied by the authors were less rigorous.

In a meta-analysis of 9 observational epidemiologic studies, it was reported that there was an increase of 20% in childhood asthma risk for high birthweight children. [14] However, the studies included in this meta-analysis of high birthweight and childhood asthma used a variety of definitions for high birthweight and risk estimations. One of the studies used 3.8kg,[16] three used 4.0kg[17-20] and another used 4.5kg[21] as cut-off points, whilst three others used different birthweight measurements;[22-24] four used relative risk[16 20 21 25] and five used odds ratio [17-19 23 24]which could potentially affect the summary risk estimate.

From a meta-analysis of nine studies, Mu et al [15] have recently reported that low birthweight increases the risk of asthma by 28% and 34% for studies that used two and three birthweight categories respectively. However, the population's age and birthweight categorization were not

consistent across the studies included. For example, one of the studies used data driven quartile birthweight categories,[26] another had a mixture of child and adult populations, [19] and three others were treated as adult studies [25 27 28] although the participants were children. And also, one other included study [29] used "asthma attack" as an outcome measure for asthma while this may underestimate the true number of cases as many asthmatics may not experience any "attack" at all.

Until February 2014, more than forty studies that investigated birthweight and childhood wheezing disorders were published. After the recent published meta-analysis, [15] five studies that comprised greater than one million children have been carried out; [30-34] however, the results remain inconsistent. Therefore, we aimed to provide an up-to-date investigation of the association between birthweight and childhood wheezing disorders through a systematic review and meta-analysis of studies, using consistent exposure (birthweight) and risk estimation definitions, and the standard World Health Organization (WHO) definition of age range for children and adolescents.[35]

Methods

Search strategy

The review was carried out in accordance with the PRISMA guidelines for systematic reviews and meta-analyses [36] whilst a protocol was registered with PROSPERO.[37] An online search was carried out using the EMBASE and MEDLINE databases (Figure S1). Two authors (TFM and RCP) independently carried out title and abstract reading. Eligible papers were those published as an article, in English, until February 2014 and reported original research on birthweight and wheezing disorders in children 0-19 years of age. Papers were excluded if birth weight was modelled as a continuous variable, no comparison group or risk estimates of birthweight were presented, the study included adult population with no separate data available for children and adolescents.

Data extraction

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

Data harmonization

Exposure variable (birthweight)

Authors of the included studies used four types of exposure categorization techniques. For comparability and not to lose data due to variation in categorization methods, standardization was undertaken: **1**) Where authors assumed the CDC[38] and 'recent' WHO method[39] (<2.5kg=Low, 2.5-4.0kg=normal and >4.0kg=high) or the 'old' WHO method (<2.5kg=low and ≥2.5kg=normal),[11] 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 **2**) Where authors adopted two or three birthweight categories with CDC or WHO 'normal' category as a reference and where the number of participants in each categories were 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. **3**) Where authors adopted two or three birthweight categories with the CDC 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 [40] before being combined with the other studies for meta-analysis of adjusted risk estimates. **4**) Where authors adopted data driven multiple categories that could not be converted to either of the standard formats, the risk estimates were compiled in a table for descriptive analysis.

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 was assumed for analysis. However, where authors used multiple outcome terms, a term that was highest in the hierarchy and its risk estimate 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 Newcastle-Ottawa quality assessment scale.[41] Two authors carried out assessment of the studies (Table S3).

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 in different parts of the world.[42] Estimates were pooled using the DerSimonian and Laird method.[43]

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.

To quantify between-study heterogeneity, the Cochrane Q-test [44] and the I^2 measure of the proportion of the total heterogeneity explained by between study variation [45] were used. Sub-group meta-analyses and sensitivity analysis of unadjusted risk estimates were performed on nine 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[46] of unadjusted risk estimates were performed using Restricted Maximum Likelihood (REML).

In investigating evidence of publication bias and small study effects, symmetry funnel plots and bias test models [47] [48] were used. 5% significance levels and 95% confidence intervals were adopted throughout. Meta-analyses were carried out in Stata software version 12.[49]

Results

Literature search

A total of 48 studies that reported either the risk estimates or number of cases and non-cases of wheezing disorders in each exposure group were included in the review. The studies were from Europe (48%), Americas (27%), Asia (17%) and Oceania (8%). 37 of the total 48 studies either used the standard birthweight categories or presented data that were convertible to the standard formats. These studies were included in the quantitative analysis (Table 1).

11 of the 48 studies used data driven birthweight categories which were found to be inconvertible into the standard formats (Table S2). The cut-off point ranges for birthweight categories were: 2.0-3.2kg, 2.1-3.2kg, and 3.5-4.5kg, for the 'Low', 'Normal', and 'High' birthweight categories respectively.[21 22 50-57] One other study used 2.7kg as a cut-off point. [58] The variation in the cut-off points made it difficult to aggregate these studies for meta-analysis; hence they were only described (Table S3).

Quality of studies

With a maximum score of 9 points available for each article, of the 37 included in the meta-analysis: thirteen scored >75%, eighteen scored 50-75%, and six scored <50% and their risks of biases can be interpreted as 'low', 'moderate' and 'high' respectively. Out of the 11 articles included in the descriptive analysis (Table S2), four scored >75%, six scored 50-75%, and one scored <50%.

Table 1: Characteristics of studies included in the meta-analysis

Author , year, region	Study design	Sample size	Participants' characteristics	Outcome terms used	Outcome ascertainment	Exposure ascertainment	Exposure categories
Weitzman et al, 1990, [59]USA	RC	2,927	2-5 years mixed	Asthma	Parent	Parent	<2.5 kg and ≥2.5kg
†Seidman et al, 1991,[60] Israel	RC	19,772	17 years boys	Asthma	e-records	e-records	<2.5 kg, 2.5-4.0kg, and >4.0kg
Arshard et al, 1993, [61] UK	PC	1,215	2 years mixed	Asthma	Physician	No mention	<2.5 kg and ≥2.5kg
Azizi et al, 1995,[62] Malaysia	CC	359	1 month-5 years mixed	Asthma	Physician	No mention	<2.5 kg and ≥2.5kg
†Lewis et al, 1995, [63] UK	RC	12,577	5 years mixed	wheezing	Parent	e-records	<2.5 kg, 2.5-4kg, and >4.0kg
†Lewis et al, 1996, [64]UK	RC	18,835	16 years mixed	Wheezing	Parent	e-records	<2.5 kg and ≥2.5kg
Schaubel et al, 1996,[65] Canada	RC	16,207	1-4 years mixed	Asthma	e-records	e-records	<2.5kg and ≥2.5kg
†Sears et al, 1996,[66] New Zealnd	PC	1,037	18 years mixed	Asthma	Physician	e-records	<2.5 kg, 2.5-4kg, and >4.0kg
† Fergusson et al, 1997,[20] New Zealand	RC	888	16 years mixed	Asthma	e-records	e-records	<2.5 kg, 2.5-4kg, and >4.0kg
† Lilljeqvist et al, 1997, [67] Norway	RC	569	7-10 years mixed	Asthma	parent	e-records	<2.5 kg, 2.5-4kg, and >4.0kg
† Slezak et al, 1998,[68] USA	RC	847	3-5 years mixed	Asthma	Parent	No mention	≤2.5kg and >2.5kg
Wjst et al, 1998, [69] Germany	RC	2,470	5-14 years mixed	Asthma	Parent	Parent	<2.5 kg and ≥2.5kg
† Leadbitter et al, 1999, [18] New Zealand	PC	735	13 years mixed	Asthma	Physician	e-records	<2.5 kg, 2.5-4kg, and >4.0kg
† Rasanen et al,2000, [24] Finland	RC	4,502	16 years mixed	Asthma	Parent	Parent	<2.5kg and ≥2.5kg
† Steffensen et al, 2000,[27] Denmark	PC	4,795	18 years boys	Asthma	Physician	e-records	<2.5 kg, 2.5-4kg, and >4.0kg
Annesi-Maesano et al, 2001, UK	RC	4065	0-18 years mixed	Asthma	Parent	Parent	<2.5 kg and ≥2.5kg
† Brooks et al, 2001, [70] USA	RC	8,071	3 years mixed	Asthma	Parent	e-records	<2.5 kg and ≥2.5kg
Ronmark et al, 2002, [71] Sweden	RC	3,247	7-8 years mixed	Asthma	Parent	e-records	<2.5 kg and ≥2.5kg

PC=prospective cohort; RC=retrospective cohort; CC=case-control

† = regrouped birthweight categories

Author , year, region	Study design	Sample size	Participants' characteristics	Outcome terms used	Outcome ascertainment	Exposure ascertainment	Exposure categories
Anand et al, 2003, [72] UK	RC	256	15 years mixed	Asthma	e-records	e-records	<2.5 kg and ≥2.5kg
Benicio et al,2004, [73] Brazil	RC	1,085	6-59 months mixed	Wheezing	Parent	No mention	<2.5 kg and ≥2.5kg
† Bolte et al, 2004, [17] Germany	RC	715	5-7 years mixed	Asthma	Parent	e-records	<2.5 kg, 2.5-4kg, and >4.0kg
Al-kubaisy et al,2005, [74] Iraq.	CC	2,262	6-12 years mixed	Asthma	Parent	Parent	<2.5 kg and ≥2.5kg
† Bernsen et al, 2005, [75] Netherlands	RC	1,710	6 years mixed	Asthma	e-records	e-records	<2.5kg and ≥2.5kg
Nepomnyaschy et al, [76]2006, USA	RC	1,803	3 years mixed	Asthma	Parent	e-records	<2.5 kg and ≥2.5kg
Kiechl-Kohlendorfer et al,2007,[77] Austria	RC	33,808	6-10 years mixed	Asthma admissions	e-records	parent	<2.5 kg and ≥2.5kg
† Remes et al, 2008, [28] Finland	RC	4,660	16 years mixed	Asthma	Parent	No mention	<2.5kg and ≥2.5kg
† Ortqvist et al, 2009, [78] Sweden	RC	10,570	9-12 years mixed	Asthma	Parent	e-records	<2.5kg and ≥2.5kg
Xu et al, 2009, [79] USA	RC	2,409	1-5 years mixed	Asthma	Parent	No mention	<2.5kg, 2.5–4.0kg, and >4.0 kg
Midodzi et al,2010, [80] Canada	PC	8,397	4-5 years mixed	Asthma	Physician	e-records	<2.5 kg and ≥2.5kg
Bjerg et al, 2011,[81] Sweden	RC	2,996	11-12 years mixed	Asthma	Parent	No mention	<2.5 kg and ≥2.5kg
†Mogensen et al, 2011, [82] Sweden	PC	1784	13-14 years mixed	Asthma	Parent	e-records	<2.5kg and ≥2.5kg
Suglia et al, 2011,[83] USA	RC	1,815	3 years mixed	Asthma	Parent	Parent	<2.5kg and ≥2.5kg
†To et al, 2012, [30] Canada	RC	687,194	6 years mixed	Asthma	e-records	e-records	<2.5kg and ≥2.5kg
Wang et al ,2012, [31] Taiwan	RC	78,011	13-16 years mixed	Asthma	parent	e-records	<2.5 kg and ≥2.5kg
† Kallen et al, 2013, [32] Sweden	RC	764,207	2-11 years mixed	Asthma	e-records	e-records	<2.5 kg, 2.5-4kg, and >4.0kg
Miyake et al, 2013, [33] Japan	RC	2004	3 years mixed	Asthma	parent	e-records	<2.5 kg and ≥2.5kg
Yang et al,2013,[34] USA	RC	3,933	7 years mixed	Asthma	e-records	e-records	<2.5 kg and ≥2.5kg

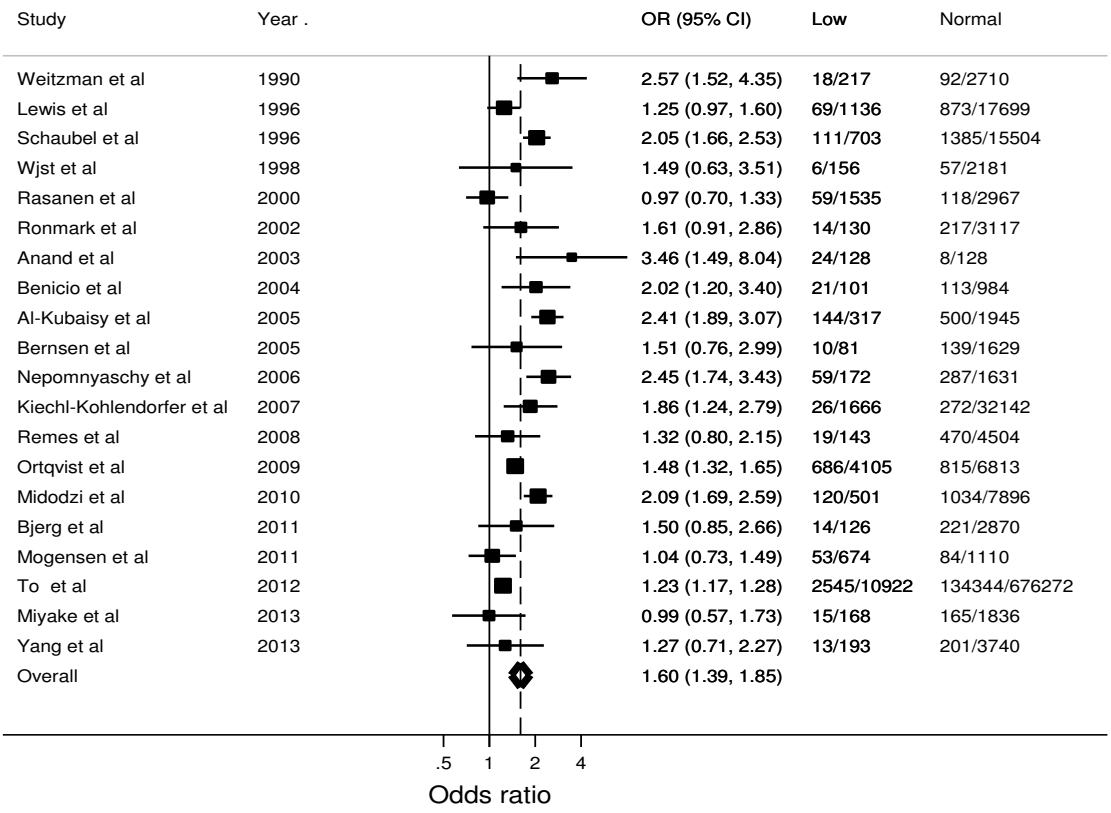
PC=prospective cohort; RC=retrospective cohort; CC=case-control

† = regrouped birthweight categories

Low birth weight and childhood asthma and wheezing disorders

A total of 30 studies contributed data on the number of cases and non-cases of childhood wheezing disorders that included a total of 1,453,042 children. An overall risk estimate of the studies that compared <2.5kg and ≥2.5kg of birthweight showed that there was a significant increased odds of wheezing disorders (OR: 1.60; 95% CI: 1.39 to 1.85, P<0.001) for <2.5kg of birthweight (Figure 1). There was substantial heterogeneity among the studies (I^2 = 82% (95% CI: 74% to 88%). A meta-analysis of 11 studies that comprised 105,071 children and provided adjusted odds ratios for the same birthweight comparison groups also showed an increase of risk by 63% (OR=1.63, 95% CI: 1.32 to 2.01, P<0.001) for the <2.5kg birthweight children (Figure S2).

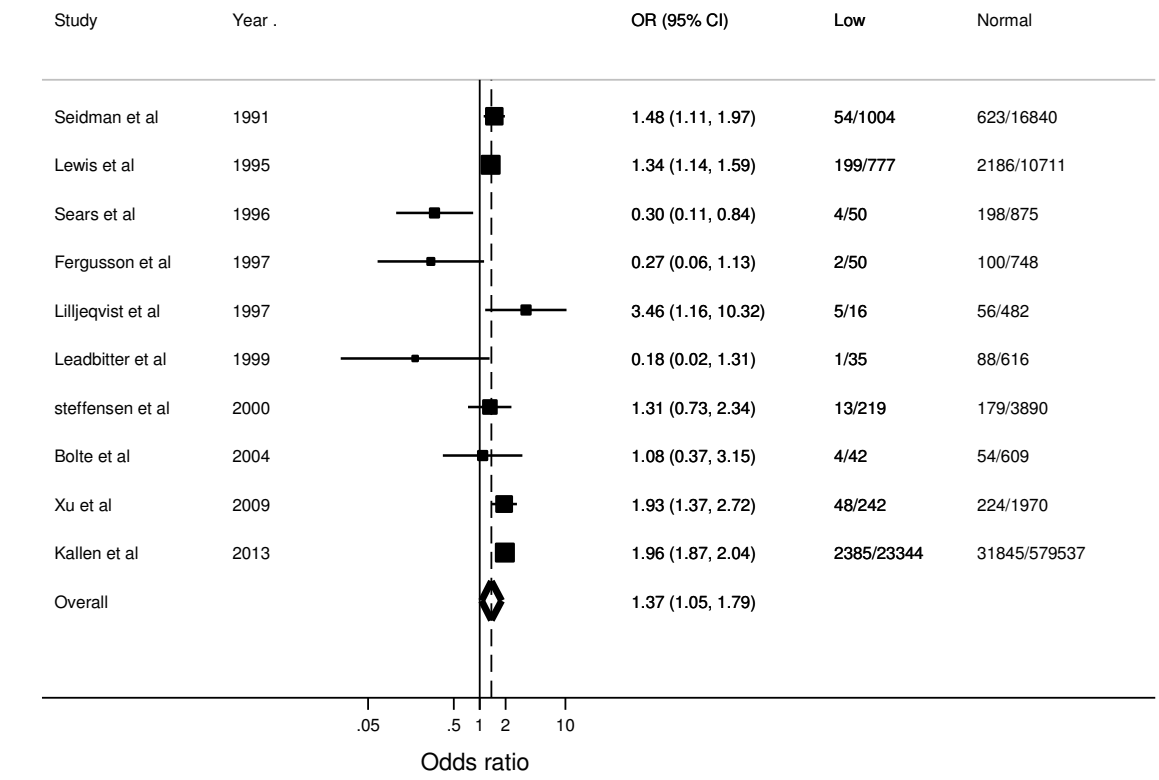
Figure 1: Meta-analysis of unadjusted ORs of 20 studies that presented data on the number of cases and non-cases of wheezing disorders in the normal (≥2.5kg) and low (<2.5kg) birthweight categories.



Heterogeneity chi-squared = 108 (d.f. = 19) p < 0.001, I^2 = 82% (95% CI: 74% to 88%), and the estimate of between-study variance Tau-squared = 0.06.

The summary risk estimate of 10 studies that provided data on 2.5-4.0kg and <2.5kg birthweight comparison groups showed that there is 37% associated risk for the <2.5kg birthweight children (OR=1.37, 95% CI: 1.05 to 1.79, P=0.02), and the between-study variation was very high (I^2=83%, 95% CI: 68 % to 89%) (Figure 2). There was not enough data to carry out meta-analysis of adjusted risk estimates for these birthweight comparison groups—only one study contributed (OR=1.28, 95% CI: 0.81 to 2.03, P=0.3).[79]

Figure 2: Meta-analysis of unadjusted ORs of 10 studies that presented data on the number of cases and non-cases of wheezing disorders in the normal (2.5-4.0kg) and low (<2.5kg) birthweight categories.



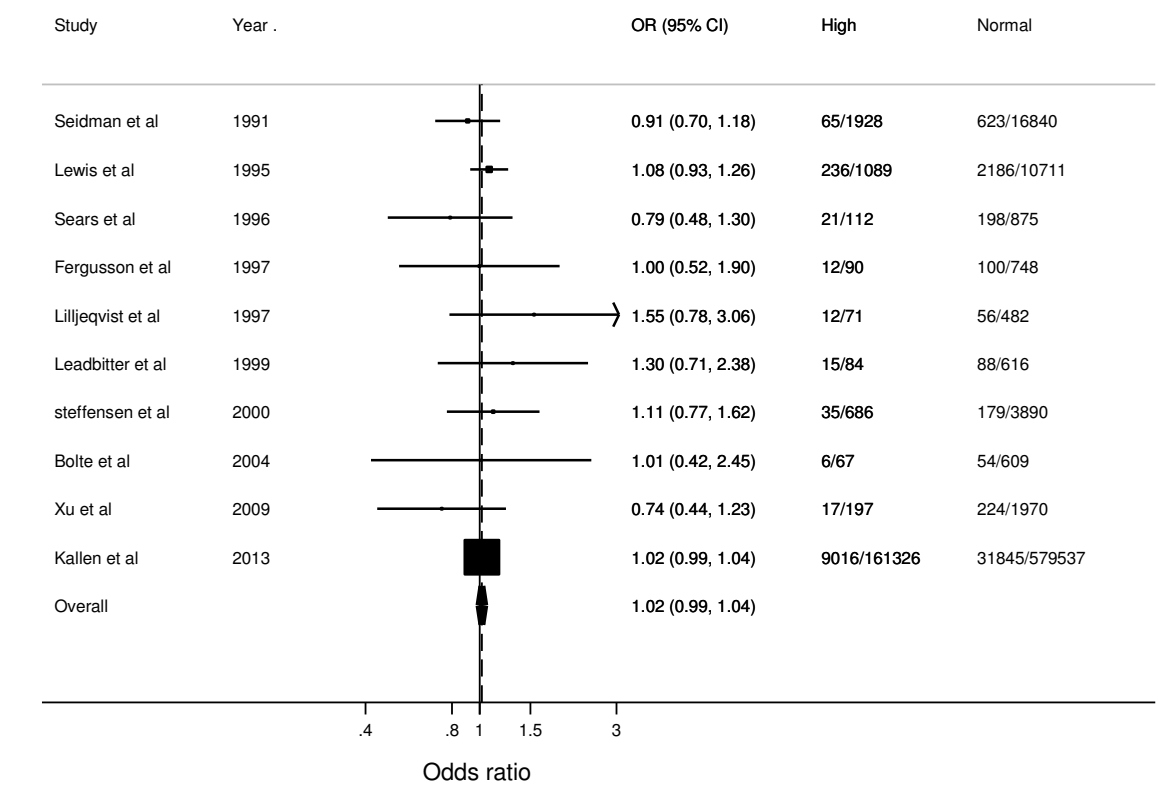
Heterogeneity chi-squared = 50 (d.f. = 9) p < 0.001, I^2 = 83% (95% CI: 68 % to 89%), and the estimate of between-study variance Tau-squared = 0.09.

High Birth weight and childhood asthma and wheezing disorders

A total of 10 studies provided data on the number of cases and non-cases of wheezing disorders on 2.5-4.0kg and >4.0kg birthweight comparison groups that comprised a total of 781,928 children (Figure 3). The overall OR for >4.0kg birthweight on childhood wheezing disorders was 1.02 (95% CI: 0.99 to 1.04, P=0.13), which was not significantly different from 1. There was no

significant heterogeneity among the studies' OR estimates (I^2 = 0%; 95% CI: 0 to 45%). When further investigated if the non-significant heterogeneity was due to the presence of Kallen et al study [32] that has dominated the pooled risk estimate, both the summary risk estimate and the level of heterogeneity remained stable (OR=1.03, 95% CI:0,92 to 1.15 ; Q=6 (d.f. = 8), P = 0.63, I^2= 0%). There was not enough data to carry out meta-analysis of adjusted risk estimates for these birthweight comparison groups—only one study contributed (OR=0.72, 95% CI: 0.42 to 1.23, P=0.23)[79]

Figure 3: Meta-analysis of unadjusted ORs of 10 studies that presented data on the number of cases and non-cases of wheezing disorders in the normal (2.5-4.0kg) and high (>4.0kg) birthweight categories.



Heterogeneity chi-squared = 6 (d.f. = 9) p = 0.73, I^2 = 0% (95% CI: 0% to 45%) and the estimate of between-study variance Tau-squared = 0.00.

Sub-group meta-analyses

A sub-group meta-analyses of 20 studies that contributed data on wheezing disorder cases and non-cases in the low (<2.5kg) and normal (≥2.5kg) birthweight categories showed that the

summary risk estimates remained significant in all subgroups of the *a priori* defined covariates, except if wheezing was used as an outcome term or diagnosis was reported by a parent or the studies were low quality (Table 2). When the same analysis was carried out on the studies that reported adjusted odds ratios for the same birthweight comparison groups, there was no statistically significant risk of association between low birthweight and wheezing disorders if birthweight was extracted from e-records or the study age group were 'five years & above' or the studies were high quality (Table S5).

Table 2: subgroup analysis of 20 studies that presented data on the number of cases and non-cases of wheezing disorders in the normal (≥2.5kg) and low (<2.5kg) birthweight categories.

		OR (95% CI)	n	I^2	P_{het}[a]	P_{het}[b]
Outcome terms used	Asthma	1.60 (1.36, 1.89)	17	84%	<0.001	
	Wheezing	1.50 (0.95, 2.39)	2	63%	0.1	0.27
	Asthma admissions	1.86 (1.24, 2.79)	1			
Outcome ascertainment	E-records	1.68 (1.22, 2.30)	6	84%	<0.001	
	Parent	1.54 (1.28, 1.85)	13	73%	<0.001	<0.001
	Physician	2.09 (1.69,2.59)	1			
Exposure ascertainment	E-records	1.55 (1.31, 1.84)	12	84%	<0.001	
	Parent	1.61 (0.98, 2.65)	4	85%	<0.001	0.001
	No mention	1.79 (1.32, 2.42)	4	24%	0.28	
Age during diagnosis	Five years & above	1.44 (1.24, 1.66)	14	74%	<0.001	
	Under five years	1.83 (1.24, 2.70)	3	74%	0.02	<0.001
	Mixed (0-19 years)	2.14 (1.71, 2.54)	3	0.0%	0.75	
Gender	Mixed	1.60 (1.39, 1.85)	20	83%	<0.001	
	Boys		0			
Sample size	1000+	1.58 (1.37, 1.82)	19	83%	<0.001	
	<1000	3.46 (1.49, 8.04)	1	0		0.03
Study period	<2000	1.76 (1.23, 2.51)	4	74%	<0.001	
	2000+	1.57 (1.34, 1.84)	16	83%	<0.001	0.001
Study type	cohort	1.55 (1.35, 1.79)	19	79%	<0.001	
	Case-control	2.41 (1.89, 3.07)	1			<0.001
Study Quality [c]	High	1.73 (1.26, 2.39)	6	91%	<0.001	
	Medium	1.45 (1.26, 1.67)	11	30%	0.15	0.001
	Low	1.90 (0.90, 3.98)	3	91%	<0.001	

[a] P for heterogeneity within subgroups.

[b] P for heterogeneity between subgroups.

[c] Sensitivity analysis according study quality scores (High: >75%, Medium: 50-75%, and Low: <50%).

When sub-group analyses of 10 studies that contributed data on the wheezing disorder cases and non-cases in the low (<2.5kg) and normal (2.5kg-4.0kg) birthweight groups were performed, the results showed inconsistent risk of association across all the predefined study characteristics. For example, there was no significant association between low birthweight and wheezing disorders if studies used asthma as an outcome term or sample size of less than 1000 was used or studies were published before 2000 (Table 3).

Table 3: subgroup analysis of 10 studies that presented data on the number of cases and non-cases of wheezing disorders in the normal (2.5-4.0kg) and low (<2.5kg) birthweight categories.

		OR (95% CI)	n	I^2	P_{het}[a]	P_{het}[b]
Outcome terms used	Asthma	1.33 (0.95, 1.85)	9	75%	<0.001	
	Wheezing	1.34 (1.14, 1.59)	1			<0.001
Outcome ascertainment	E-records	1.50 (0.98, 2.30)	3	81%	<0.01	
	Parent	1.61 (1.16, 2.24)	4	51%	0.1	<0.001
	Physician	0.49 (0.13,1.89)	3	78%	0.01	
Exposure ascertainment	E-records	1.27 (0.93, 1.72)	9	84%	<0.001	
	No mention	1.93 (1.37, 2.72)	1			0.9
Age during diagnosis	Five years & above	1.10 (0.76, 1.59)	8	66%	<0.01	
	Mixed (0-19 years)	1.96 (1.87, 2. 04)	2	0%	0.9	<0.001
Gender	Mixed	1.32 (0.94, 1.85)	8	84%	<0.001	
	Boys	1.44(1.12, 1.87)	2	0%	0.71	0.04
Sample size	1000+	1.62 (1.29, 2.02)	5	82%	<0.001	
	<1000	0.61 (0.20, 1.91)	5	75%	0.03	0.001
Study period	<2000	1.00 (0.62, 1.63)	6	76%	<0.01	
	2000+	1.95(1.85, 2.05)	4	0.6%	0.39	<0.001
Study type	cohort	1.37 (1.05, 1.79)	10	82%	<0.001	
	Case-control		0			
Study Quality [c]	High	1.14 (0.75, 1.74)	6	81%	<0.001	
	Medium	1.56 (1.10, 2.21)	2	70%	0.06	0.001
	Low	0.86 (0.03, 23.90)	2	88%	<0.01	

[a] P for heterogeneity within subgroups.

[b] P for heterogeneity between subgroups.

[c] Sensitivity analysis according study quality scores (High: >75%, Medium: 50-75%, and Low: <50%).

Subgroup meta-analyses of 10 studies that contributed data on the cases and non-cases of wheezing disorders in the high (>4.0kg) and normal (2.5-4.0kg) birthweight categories showed that the risk of association was not significant across all categories of the predefined study characteristics and the study quality levels (Table 4).

Table 4: subgroup analysis of 10 studies that presented data on the number of cases and non-cases of wheezing disorders in the normal (2.5-4.0kg) and high (>4.0kg) birthweight categories.

		OR (95% CI)	n	I^2	P_{het}[a]	P_{het}[b]
Outcome terms used	Asthma	1.02 (0.99,1.04)	9	0%	0.69	0.45
	Wheezing	1.08 (0.93,1.26)	1	0%	0.73	
Outcome ascertainment	E-records	1.02 (0.99,1.04)	3	0%	0.69	
	Parent	1.06 (0.89,1.25)	4	5%	0.36	0.82
	Physician	1.04 (0.80,1.36)	3	0%	0.40	
Exposure ascertainment	E-records	1.02 (1.00,1.04)	9	0%	0.80	0.22
	No mention	0.74 (0.44,1.23)	1			
Age during diagnosis	Five years & above	1.04 (0.93,1.17)	8	0%	0.73	0.66
	Mixed (0-19 years)	0.96 (0.76,1.22)	2	34%	0.22	
Gender	Boys	0.97(0.79,1.20)	2	0%	0.38	
	Mixed	1.02 (1.00,1.04)	8	0%	0.64	0.66
Sample size	1000+	1.02 (0.99,1.04)	5	0%	0.55	
	<1000	1.02(1.00,1.04)	5	0%	0.55	0.78
Study period	<2000	1.04 (0.92,1.17)	6	0%	0.51	
	2000+	1.02 (0.99,1.04)	4	0%	0.63	0.75
Study type	cohort	1.02 (0.99,1.04)	10	0%	0.73	
	Case-control		0			
Study quality [c]	High	1.02 (0.99, 1.04)	3	0	0.54	
	Medium	1.01 (0.89, 1.15)	4	0	0.42	0.54
	Low	1.26 (0.87, 1.82)	3	0	0.65	

[a] P for heterogeneity within subgroups.

[b] P for heterogeneity between subgroups.

[c] Sensitivity analysis according study quality scores (High: >75%, Medium: 50-75%, and Low: <50%).

When investigating the sources of between-study heterogeneities of the unadjusted low birthweight odds ratios, results showed that 59% (P=0.06) of the variance was explained by the *a priori* selected covariates in the <2.5kg and ≥2.5kg birthweight comparisons (Table S6). However, none of the variance was explained by the *a priori* selected covariates in the <2.5kg and 2.5-4.0kg birthweight comparisons (Table S7).

Investigating biases (small study effects)

The funnel plots showed no evidence of asymmetry for the high (>4.0kg versus 2.5-4.0kg) birthweight unadjusted odds ratios (Figure S3c). However there was some evidence of funnel plot asymmetry for the low birthweight (2.5kg versus ≥2.5kg and <2.5kg versus 2.5-4.0kg) unadjusted odds ratio estimates (Figures S3a & S3b) and low birthweight (2.5kg versus ≥2.5kg)

adjusted odds ratio estimates (Figure S3d). This was also reflected in Egger's tests, with no evidence of small-study effects for figure S3c (p=0.99), but some evidence of asymmetry in effects for figure S3a (p=0.02), figure S3b (p=0.02) and figure S3d (p=0.02).

Discussion

In this meta-analysis, we have found that low birthweight was associated with increased risk of childhood wheezing disorders. The risk of association of high birthweight was not statistically significant in contrast to a previous meta-analysis that reported high birthweight was associated with asthma risk (RR 1.2, 95% CI 1.1 to 1.3).[14] However, it must be noted that the studies included in the previous meta-analysis had used different cut-off points and measurement types for high birthweight, and risk estimation methods (relative risk and odds ratio).

Our pooled risk estimates for low birthweight are moderately higher than those of a recent meta-analysis by Mu et al [15] that reported ORs of 1.28 (95% CI: 1.09 to 1.50) and 1.34 (95% CI: 1.13 to 1.60) for studies that used two and three birthweight categories respectively. However, the birthweight categorization and the age of study population used by the studies in their meta-analysis were not consistent, and the fact that we have included more studies than theirs may have possibly influenced the difference in robustness of the summary risk estimates.

The studies that were not included in our meta-analysis reported inconsistent risk of association for the low birthweight categories (Table S3), although we noted that a recent ISAAC Phase III study that used similar birthweight categories has reported an odds ratio of 1.20 (95%: 1.12 to 1.30).[84] However, all the studies reported that there was no risk of association for the high birthweight group which agreed with our findings.

Based on our pooled odds ratio results, we noted that the adjusted and unadjusted summary odds ratios for two birthweight categories were almost identical. This may strongly suggest that low birthweight is an independent risk factor for childhood wheezing disorders although one has to bear in mind that our analyses also showed some evidence of bias in our funnel plots and Egger's test of bias [47 48] which may indicate that there was potential publication bias towards studies that showed no significant risk of association. [85]

Based on the subgroup analyses of the adjusted and unadjusted subgroup analyses of two birthweight categories, we observed that the summary odds ratios were lower for the studies that were published after 2000 than for those published before. It is also known that the prevalence of low birthweight has been falling[86] while wheezing disorders have been increasing for the last decades in the developed countries.[3] This may imply that the risk of association of low birthweight with wheezing disorders is genuine although there could be an overestimation as 'wheezing', which is the key symptom for asthma and wheezing disorders, can also be caused by other illnesses such as pneumonia, bronchiolitis and other viral infections in children under five.[87]

Based on the heterogeneity measures (Q-test and I^2), we observed that there was a considerable level of between-study variation in the low birthweight unadjusted risk estimates although this could be due to high precision or high sample size studies in our analyses, [88] as noted in the forest plot (Figure 1). The studies were mostly precise and had narrow confidence intervals. However, there was no significant heterogeneity among the unadjusted risk estimates of high birthweight and asthma and this could be due to having less precise risk estimates with wider confidence intervals, demonstrate by the forest plot (Figure 2).

Our work has limitations and results should be interpreted cautiously. Firstly, in our low birthweight and wheezing disorders summary risk estimates, we have found that there was a significant and substantial level of between-study variation that was not explained by our *a priori* selected covariates. We also had a significant funnel plot asymmetry and small-study effect bias estimate in our results for the studies that compared normal (≥2.5kg or 2.5-4.0kg) and low (<2.5kg) birthweight categories. Secondly, as in any systematic review and meta-analysis, we cannot rule out the possibility of potentially relevant studies being missed by our search strategy. Thirdly, our results are based on epidemiologic observational studies and are solely dependent on the quality of the primary studies included. More importantly, we did not

identify any studies conducted in developing countries to include in our meta-analysis so our results may not be relevant in regions not represented in this review.

The strength of our work is that we were able to produce consistent risk estimates due to our use of harmonised data. Combining adjusted risk estimates was a primary choice among previous authors. This technique may, however, under or over estimate the association between exposure and outcome variables due to exclusion of studies that used non-standard birthweight categories 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 low (<2.5kg) and high (>4.0kg) birthweight on asthma and wheezing disorders than if we were to combine multiple cut-off points as used by previous authors. The other strength of this work is also 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 low birth (<2.5kg) is an independent risk factor for wheezing disorders during childhood and adolescence. However, we found no significant effect of high birth weight on asthma or wheezing disorders.

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RCP revised and commented on the manuscript. All authors approved the final version of the manuscript.

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