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A meta-analysis of the effect of high weight on asthma

V Flaherman, G W Rutherford

Background: Prevalence rates for both overweight and asthma have been increasing among children in developed countries over the past two decades. Some recent studies have postulated a causal relation between these but have lacked power to form a definitive conclusion.

Aim: To estimate the effect of high body weight in childhood on the future risk of asthma.

Methods: Medline search (1966 to October 2004), supplemented by manual search of reference lists and grey literature. Cohort studies that examined high body weight at birth or during childhood and future outcome of asthma were included. Data from each study were extracted on exposure status, clinical outcome, and study characteristics.

Results: A total of 402 studies were initially identified, of which 12 met the inclusion criteria. The combined results from four studies that examined the effect of high body weight during middle childhood on the outcome of subsequent asthma showed a 50% increase in relative risk (RR 1.5, 95% CI 1.2 to 1.8). The combined results from nine studies that examined the effect of high birth weight on subsequent asthma had a pooled RR of 1.2 (95% CI 1.1 to 1.3). There was consistency among the results in sensitivity analyses examining studies containing only estimates of odds ratios, studies containing only the outcome of physician diagnosis of asthma, and studies including all definitions of high body weight.

Conclusions: Children with high body weight, either at birth or later in childhood, are at increased risk for future asthma. Potential biological mechanisms include diet, gastro-oesophageal reflux, mechanical effects of obesity, atopy, and hormonal influences. Further research might elucidate the causal pathway, which could improve our understanding of the pathophysiology of asthma and perhaps lead to knowledge of potential preventive interventions.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Primary exposure measure</th>
<th>Place of study, n</th>
<th>Effect size (95% CI)</th>
<th>Primary outcome measure</th>
<th>Age at follow up</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolte, 2004</td>
<td>Birth weight &gt;4 kg</td>
<td>Munich, n = 534</td>
<td>OR 1.52 (0.51 to 4.51)</td>
<td>Physician diagnosed asthma</td>
<td>5-7 y</td>
<td></td>
</tr>
<tr>
<td>Sin, 2004</td>
<td>Birth weight &gt;4.5 kg</td>
<td>Alberta, n = 83595</td>
<td>RR 1.16 (1.04 to 1.29)</td>
<td>Asthma Emergency Department visit</td>
<td>10 y</td>
<td></td>
</tr>
<tr>
<td>Yuan, 2002</td>
<td>Ponderal index &gt; 2.5 g/cm³</td>
<td>Denmark, n = 10440</td>
<td>RR 1.53 (1.11 to 2.13)</td>
<td>Asthma hospitalisation</td>
<td>12 y</td>
<td></td>
</tr>
<tr>
<td>Gilliland, 2003</td>
<td>BMI in 4th, 7th, and 10th grades</td>
<td>Southern California, n = 3792</td>
<td>RR 1.52 (1.14 to 2.03)</td>
<td>Physician diagnosed asthma</td>
<td>11-22 y (4 y after enrolled)</td>
<td></td>
</tr>
<tr>
<td>Xu, 2002</td>
<td>Ponderal index &gt; 2.83 g/cm³</td>
<td>Finland, n = 4719</td>
<td>Effect of birth weight: OR 1.26 (0.88 to 1.82)</td>
<td>Physician diagnosed asthma</td>
<td>31 y</td>
<td></td>
</tr>
<tr>
<td>Chinn, 2001</td>
<td>BMI age 5-6</td>
<td>UK, n = 6744</td>
<td>OR 1.24 (0.82 to 1.88)</td>
<td>Physician diagnosed asthma</td>
<td>9-10 y</td>
<td></td>
</tr>
<tr>
<td>Castro-Rodriguez, 2001</td>
<td>BMI age 11</td>
<td>Tucson, n = 448 (222 boys and 226 girls)</td>
<td>OR 2.7 (0.9 to 8.2) for boys; OR 3.2 (1.1 to 8.8) for girls</td>
<td>Frequent wheeze at age 13</td>
<td>13 y</td>
<td></td>
</tr>
<tr>
<td>Rasanen, 2000</td>
<td>Ponderal index &gt; 27 g/m³²</td>
<td>Finland, n = 4578</td>
<td>OR 1.86 (1.13 to 3.07)</td>
<td>Physician diagnosed asthma</td>
<td>16 y</td>
<td></td>
</tr>
<tr>
<td>Leadbetter, 1999</td>
<td>Birth weight &gt;4 kg</td>
<td>Dunedin, New Zealand, n = 745</td>
<td>RR 1.0 (0.4 to 2.4)</td>
<td>Physician diagnosed asthma</td>
<td>13 y</td>
<td></td>
</tr>
<tr>
<td>Gregory, 1999</td>
<td>Birth weight &gt;4 kg</td>
<td>Southampton, UK, n = 249</td>
<td>OR 1.3 (0.4 to 4.4)</td>
<td>Current wheeze or current use of asthma medication</td>
<td>11-14 y</td>
<td></td>
</tr>
<tr>
<td>Ferguson, 1997</td>
<td>Birth weight &gt;4 kg</td>
<td>Christchurch, New Zealand, n = 891</td>
<td>RR 0.89 (0.51 to 1.6)</td>
<td>Physician diagnosed asthma</td>
<td>16 y</td>
<td></td>
</tr>
<tr>
<td>Schwartz, 1992</td>
<td>Birth weight &gt;3.8 kg</td>
<td>USA, n = 4661</td>
<td>RR 0.92 (0.62 to 1.37)</td>
<td>Physician diagnosed asthma</td>
<td>6 m-11 y</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio; RR, relative risk.
various studies into estimates of the variance of the log(RR), we transformed the interval to a log scale and then calculated standard error. To combine data we used the meta-analysis routine in Stata 8.2 (Stata Corp., College Station, TX). We calculated a pooled summary relative risk according to both a fixed effects model, which used the inverse of the variance as the weight, and a random effects model, which uses the sum of the inverse of the variance and the moment estimator of the variance as the weight. We evaluated the possibility of publication bias with a Begg's funnel plot and with Egger's test.

We analysed the effect of high birth weight and high body weight during middle childhood on the risk of future outcome of asthma. We conducted three sensitivity analyses to examine some of the assumptions of our models. In one, we analysed the estimated effect of any measure of high childhood weight combined on the outcome of asthma. In the second, in order to examine the effect of using odds ratios as estimates of the relative risk, we looked separately at those studies reporting odds ratios. In the third, in order to examine the effect of differences in outcome measures, we looked separately at those studies with an outcome of physician diagnosis of asthma. We used the cumulative meta-analytic technique proposed by Lau and colleagues to check homogeneity of results.

**RESULTS**

Of the 402 papers found by the search, we identified 16 articles that presented original research with unique populations showing the effect of high body weight either at birth or during childhood on the future outcome of asthma. From these, 12 articles expressed future risk of asthma as a dichotomous outcome compared with children of average or normal body weight (table 1). One study was excluded because the effect of body weight was expressed as a continuous outcome, and no method is available to combine continuous results with the results of dichotomous studies. Two studies were excluded because the only available baseline was low body weight, and low body weight in newborns and children may be associated with other risk factors for respiratory disease. One study was excluded because birth weight as an exposure was adjusted for subsequent BMI (table 2). All 12 included studies had medium-to-high quality scores (median score 7; range 6–8 (of 9 possible points)). All 12 were cohort studies, either prospective (n = 8) or retrospective (n = 4). Seven studies reported their results as odds ratios, and five reported relative risks. Of the four studies reporting estimates of effect of high body weight in school aged children on future outcome of asthma, the studies all used BMI >85th centile for age and gender as the predictor variable. In one of the studies eligible for inclusion, data were presented separately for boys and girls without pooling, and we used incidence information from the study to recalculate a pooled summary statistic and a pooled variance. In another eligible study, data were presented separately for boys and girls without sufficient incidence information to allow pooling. For this study we entered results for boys and girls separately into the meta-analysis. RR in these four studies ranged from 1.24 to 3.2. The studies had good homogeneity (p = 0.392). The Der Simonian and Laird estimate of between studies variance was 0.002. The pooled summary RR was 1.5, with both fixed and random effects models giving a 95% CI of 1.2 to 1.8. Thus, studies with an estimate of effect of high body weight in school aged children estimated that those with high body weight have a future risk of asthma equal to 1.5 times the future risk of children without high body weight (fig 1). Analysis for metabis by Begg’s test showed general symmetry around the median line, and Egger’s test revealed no evidence of publication bias.

**High birth weight**

Nine studies reported estimates of the effect of high body weight at birth on risk of future asthma. In these studies, high body weight was identified using either elevated Ponderal index or elevated birth weight. RR for high body weight at birth ranged from 0.89 to 1.86. These nine studies had a low level of heterogeneity (p = 0.440). The Der Simonian and Laird estimate of between studies variance was <0.001. Fixed effects and random effects models gave the same pooled summary RR and CI (RR 1.2, 95% CI 1.1 to 1.3) (fig 2). Analysis for metabis by Begg’s test showed general symmetry around the median line, and Egger’s test revealed no evidence for publication bias.

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**Table 2 Excluded studies**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Reason for exclusion</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laerum, 2004</td>
<td>No dichotomous analysis of effect of high weight on asthma</td>
<td>Continuous outcome reported by 500 g from lowest baseline: OR 0.92 (0.62 to 1.35)</td>
</tr>
<tr>
<td>Gold, 2003</td>
<td>Baseline was lowest quintile</td>
<td>Overweight boys 1.04 (0.60 to 1.82) compared with lowest quintile; middle quintile was 1.01 compared with lowest quintile. Overweight girls 2.24 (1.14 to 4.40) compared with lowest quintile; middle quintile was 2.18 (1.07 to 4.44) compared with lowest quintile</td>
</tr>
<tr>
<td>Katz, 2003</td>
<td>Baseline was lowest quintile</td>
<td>OR 0.92 (0.62 to 1.35) compared with lowest quintile of birth weight</td>
</tr>
<tr>
<td>Shaheen, 1999</td>
<td>Birth weight as exposure was adjusted for adult BMI</td>
<td>OR for effect of birth weight adjusted by BMI was 0.81 (0.55 to 1.18)</td>
</tr>
</tbody>
</table>
We also created a model in which studies of both high birth weight and high BMI during childhood were combined to determine an estimate of the summary effect of increased body weight. All 12 studies were used in this model. Of note, one of the included studies contained information for both high birth weight and childhood BMI >85%, and in the combined model the estimate for the effect of birth weight was used. The range of RR in this combined model was 0.89 to 3.2, with borderline evidence of heterogeneity (p = 0.206). The der Simonian and Laird estimate of between studies variance was 0.012. This level of heterogeneity suggests that the two different exposures of high birth weight and high weight during childhood might be related but distinct. The combined model had a summary relative risk of 1.2 (95% CI 1.1 to 1.3) for the fixed effects estimate and 1.3 (1.1 to 1.5) for the random effects estimate, consistent with the observed borderline heterogeneity.

Odds ratios only

Seven studies reported data for the effect of high weight on risk of future asthma as odds ratios (OR). All of these studies used multivariate logistic regression to obtain results. The effect of high weight on asthma in studies reporting OR was analysed in a subgroup analysis. The range of OR varied from 1.00 to 3.2, with a low level of heterogeneity (p = 0.529). The fixed effects and random effects models gave the same results, with a summary odds ratio of 1.4 (95% CI 1.2 to 1.7).

DISCUSSION

By conducting a systematic review and meta-analysis of the effect of high weight on future risk of asthma, we have obtained an estimate that suggests that high body weight among school aged children increases the risk of future asthma by approximately 50%. The effect of high birth weight appears to be less pronounced but still quite significant, with an RR of 1.2 compared to babies without high birth weight. The association between high weight and asthma remains significant when combining estimates of all age groups for

<table>
<thead>
<tr>
<th>Study</th>
<th>Summary estimate</th>
<th>(95% CI)</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Schwartz (1990)</td>
<td>0.92</td>
<td>(0.62 to 1.37)</td>
<td>0.682</td>
</tr>
<tr>
<td>Ferguson (1997)</td>
<td>0.91</td>
<td>(0.66 to 1.27)</td>
<td>0.577</td>
</tr>
<tr>
<td>Leadbitter (1999)</td>
<td>0.92</td>
<td>(0.68 to 1.26)</td>
<td>0.600</td>
</tr>
<tr>
<td>Gregory (1999)</td>
<td>0.941</td>
<td>(0.70 to 1.27)</td>
<td>0.692</td>
</tr>
<tr>
<td>Rasanen (2000)</td>
<td>1.128</td>
<td>(0.87 to 1.46)</td>
<td>0.358</td>
</tr>
<tr>
<td>Chinn (2001)</td>
<td>1.158</td>
<td>(0.93 to 1.44)</td>
<td>0.188</td>
</tr>
<tr>
<td>Castro-Rodriguez (2001)</td>
<td>1.242</td>
<td>(1.01 to 1.53)</td>
<td>0.043</td>
</tr>
<tr>
<td>Yuan (2002)</td>
<td>1.304</td>
<td>(1.08 to 1.57)</td>
<td>0.005</td>
</tr>
<tr>
<td>Xu (2002)</td>
<td>1.295</td>
<td>(1.10 to 1.53)</td>
<td>0.002</td>
</tr>
<tr>
<td>Gilliland (2003)</td>
<td>1.347</td>
<td>(1.17 to 1.55)</td>
<td>0.000</td>
</tr>
<tr>
<td>Bolte (2004)</td>
<td>1.349</td>
<td>(1.17 to 1.55)</td>
<td>0.000</td>
</tr>
<tr>
<td>Sin (2004)</td>
<td>1.227</td>
<td>(1.13 to 1.34)</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Some studies have found that high birth weight and high BMI in childhood are predictive of future asthma, while others have shown no association.

The purpose of this study was to evaluate the effect of high body weight on the development of asthma. This goal is complicated by the fact that weight is not one of the largest contributors to the development of asthma, and the effect of weight on asthma is likely to be relatively weak compared to other risk factors such as atopy, air pollution, and family history of asthma. It is further complicated by the facts that currently available cohort studies are diverse in both exposure measures and in outcome measures.

Several sources of bias should be considered in the interpretation of these results. First, misclassification of exposure is a potential source of bias in this systematic review, especially due to the acceptance of three different definitions of high body weight, the acceptance of high body weight at a variety of ages, and the possibility that BMI centile standards varied for different cohorts. However, significant misclassification of exposure would be expected to either bias findings towards the null result of no association between exposure and outcome or cause significant heterogeneity in the meta-analysis model. Also, there is no indication that there is a threshold level for weight that sharply demarcates those at increased risk from those with average risk. The levels of homogeneity found in the significant results in the meta-analysis suggest that the association found between high body weight and asthma is not due to misclassification of exposure.

Another potential source of bias is misclassification of outcome. This is a concern both for the meta-analysis as a whole, which includes several different definitions of outcome and includes several different ages for the assessment of outcome, and within the individual studies, especially due to diagnostic bias. Regarding potential misclassification of outcome due to the acceptance of several different criteria for outcome in this meta-analysis, it is important to note that the subset analysis examining the outcome of physician diagnosis of asthma shows results very similar to the other models. This argues against significant bias from the use of several different criteria for outcome. Misclassification of outcome from varying age at time of outcome remains a possible source of bias in this paper, although the relatively good homogeneity in the models would argue against a strong bias from this source.

This paper provides a systematic review and meta-analysis of the studies on this topic and shows that both high birth weight and high BMI during childhood are predictive of future asthma.

What is already known on this topic

- High birth weight and high BMI during childhood are predictive of future asthma
- High birth weight is associated with a RR of 1.2 (95% CI 1.1 to 1.3) for future asthma, while high BMI during childhood is associated with a RR of 1.5 (95% CI 1.2 to 1.8) for future asthma. Over 100,000 children in the United States may suffer from asthma due to childhood overweight.

What this study adds

- This paper provides a systematic review and meta-analysis of the studies on this topic and shows that both high birth weight and high BMI during childhood are predictive of future asthma.

In order to examine the effect of other predictor variables on the relation between body weight and risk of subsequent asthma, the ideal future study would follow a very large cohort of children from birth through adolescence. Simple information such as weight and height would need to be collected at regular intervals, and asthma status would be assessed annually. Such a study could also collect data on types of dietary intake, age of pubertal changes, and gastric and atopic symptoms, and might even be able to perform forced expiratory volume (FEV1) testing to reduce diagnostic bias. This type of research could examine the effects of additional predictor variables both singly and in combination on the relation between high body weight and risk of asthma, and might result in new knowledge about the causes of the disease. Improved knowledge about the causal pathways leading to an association between high body weight and asthma could result in improved understanding of the pathophysiology involved in the dramatic increase in...
prevalence of asthma, which could potentially lead to important knowledge about methods for prevention of this common childhood disease.

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