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Lung function and overweight in school aged children after early childhood wheezing

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3 **Lung function and overweight in school aged children after early childhood**
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45 **Abbreviated title:** Lung function and overweight in wheezy children
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Summary

Background and purpose. Recently, obesity has been connected with wheezing, asthma and reduced lung function. Most previous studies have been cross-sectional. The aim of the present follow-up study was to evaluate the association of preceding or current overweight or obesity with lung function at early and late school age after early childhood wheezing.

Material and methods. From the 100 children hospitalized for **infection associated wheezing** at <24 months of age, 83 attended the control visit at 4.0 years, **82** at 7.2 years and 81 at 12.3 years of age. Flow-volume spirometry was performed in 79 children at 7.2 years and in 80 children at 12.3 years of age. The weight status was assessed by calculating body mass index (BMI) at all visits. Age- and gender-specific BMI standard deviation scores (BMI-SDS) of >1.3 SD and > 2.0 SD were defined to mean overweight and obesity, respectively.

Results. Overweight at both 7.2 and 12.3 years of age was associated with decreased **FEV₁/FVC** (forced expiratory volume in one second/ forced vital capacity). Overweight and obesity at 7.2 years of age were associated with decreased **FEV₁/FVC** and MEF₅₀ (**maximal** expiratory flow at 50 % of FVC) at 12.3 years of age. The results were similar by continuous and categorized analyses, being robust to adjustments for viral findings during early childhood wheezing and asthma maintenance medication at school age.

Conclusion. Overweight and obesity are significant risk factors for **reduced** lung function at school age after early childhood wheezing. Thus, early-life wheezers should avoid excessive weight gain during childhood.

Keywords: child, spirometry, obstruction, overweight, obesity, lung function, wheezing

Abbreviations:

BMI body mass index

BMI-SDS body mass index standard deviation score

TLC total lung capacity

FRC functional residual capacity

FVC forced vital capacity

FEV₁ forced expiratory volume in one second

FEV₁/FVC forced expiratory volume in one second/forced vital capacity

MEF₅₀ maximal expiratory flow at 50% of FVC

MEF₂₅ maximal expiratory flow at 25% of FVC

aOR adjusted odds ratios

CI confidence intervals

RSV respiratory syncytial virus

Introduction

Asthma and overweight or obesity have increased concomitantly among both children and adults during the last three decades in western countries¹⁻³. The studies have suggested an association between wheezing symptoms and obesity⁴⁻⁹, and also between asthma diagnoses and obesity¹⁰⁻¹³. When pulmonary function and bronchial reactivity have been studied objectively, the results have been mainly negative^{5, 14-18}.

In adults, obesity decreases both lung volume, as documented by reduced total lung capacity (TLC), forced vital capacity (FVC) and functional residual capacity (FRC), and airway flows, as documented by decreased forced expiratory volume in one second (FEV₁) and increased airway resistance^{19,20}. In addition, obesity leads to obstruction in peripheral airway²¹, as documented **by decreased** flows at 50% (MEF₅₀) or at 25% (MEF₂₅) of FVC. However, the largest **impact seems to target** at expiratory reserve volume, which means that restriction is the characteristic lung function disorder in obesity^{22,23}. **In addition**, weight reduction in obese **adults elicited** an improvement of lung function²⁴.

In children with asthma suggestive symptoms, high body mass index (BMI) was associated with subnormal lung function in one study¹⁸, but not in two others^{4,5}. **In healthy children**, lung function was either impaired²⁵, improved in boys and girls²⁶ or improved only in girls²⁷ by excessive weight gain

We have prospectively followed-up a cohort of children hospitalized for **infection associated** wheezing at <24 months of age in 1992-1993. **The weights and heights of the children were measured at follow-up visits at the median ages of 4.0, 7.2 and 12.3 years, and spirometry was performed at both visits at school age**²⁸⁻³⁰.

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The aim of the present study was to evaluate the association between overweight or obesity and lung function at school age in former early-life wheezers, with a special focus on the influence of an emerging overweight.

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Material and methods

Study design

One-hundred consecutive children, hospitalized for wheezing associated respiratory infection at age 1-23 months, were recruited into this follow-up study in 1992 -1993³¹.

Maintenance therapy for asthma was one of the exclusion criteria, and the wheezing episode was the first one in 87% of the included children³². The basic data were collected by interviewing the parents during hospitalization using a structured questionnaire. Seven respiratory viruses, including respiratory syncytial virus (RSV), were studied by antigen and antibody assays³². Later, viral studies were supplemented by polymerase chain reaction to RSV and rhinoviruses in frozen samples^{33,34}. In all, RSV was identified in 29/100 and rhinovirus in 27/81 cases^{33,35}.

Three follow-up visits were prospectively organized at the median ages of 4.0 years, 7.2 years and 12.3 years²⁸⁻³⁰. Asthma was present in 33/82 (40.2%) children at the 7.2-year visit²⁹ and in 32/81 (39.5%) children at the 12.3-year visit³⁰. Data on medical history, including the use of asthma medication during the preceding 12 months, were collected by interviewing the parents.

Assessment of weight status

The weights and heights of the children, measured by an experienced nurse using standard methods, were registered in all attending children at all controls visits. Body mass index (BMI) was calculated by using the equation: weight (kg) / [height (m)]². Due to the lack of Finnish references, we applied British gender- and age-specific population-based references. BMI standard deviation score (BMI-SDS), also called Z-score, was

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3 assessed by an obesity calculator (NIBHI 2007)³⁶. This calculator applies British growth
4 references from 1990, produced by the LMS method in 1995^{37,38}, and revised in 1996³⁹.
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6 The LMS method summarizes the distribution of BMI at each age by its median (M),
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8 coefficient of variation (S), and skewness expressed as a Box-Cox power (L) required to
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10 transform the data to normal⁴⁰.
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16 In the present study, we used the same cut-off points for overweight and obesity as
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18 proposed by the British study evaluating the limits of obesity and overweight in different
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20 populations⁴¹. The cut-off point for overweight was BMI >91 percentile (approximating
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22 BMI-SDS >1.3) and for obesity BMI >98 percentile (approximating BMI-SDS >2.0)^{19,41}.
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24 In the British population, these cut-off points corresponds BMI 25 kg/m² and BMI 30
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26 kg/m² levels, respectively, in the 18 years old young adults⁴¹.
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32 *Measurement of lung function*

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34 Lung function was studied by flow-volume spirometer (FVS) (Medikro, Kuopio, Finland)
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36 at the 7.2-year and 12.3-year study visits. The parameters were expressed as percentages
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38 of the gender-specific height-related reference values (% of predicted) for Finnish
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40 children^{42,44}. The parameters registered were FVC (forced vital capacity), FEV₁ (forced
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42 expiratory volume in one second), FEV₁/FVC, MEF₅₀ (maximal expiratory flow at 50 %
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44 of FVC) and MEF₂₅ (maximal expiratory flow at 25 % of FVC). Either the measurement
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46 with the highest FEV₁ (at the 7.2-year study)²⁹ or the composite maximal curve (at the
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48 12.3-year study)³⁰ was in each child recorded for further analyses. The cut-off limits for
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50 abnormal values were 80 % for FEV₁, 88 % for FEV₁/FVC, 62 % for MEF₅₀ and 48 %
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52 for MEF₂₅^{17,30,43}.
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3 Lung function data were available from 79 children at the 7.2-year and from 81 children
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5 at the 12.3-year study visits. The numbers of children with anti-inflammatory
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7 maintenance medication for asthma during the 12 preceding months were 29/79 (36.77%)
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9 at age of 7.2 years and 18/80 (22.5%) at age of 12.3 years. At the 4.0-year visit, weight
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11 status was assessed for 74 children with lung function data available at the 7.2-year visit.
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15 *Statistics*

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18 The data were analysed using SPSS 17.0 software (SPSS Inc. Chicago, IL, USA). Mann-
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20 Whitney U-test was used in univariate analyses and analysis of variance (ANOVA) in
21
22 multivariate analyses for continuous FVS parameters. In the previous studies in this
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24 cohort, RSV etiology of wheezing in early childhood was associated with a non-
25
26 reversible restrictive pattern of lung function and non-RSV etiology (mostly rhinovirus)
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28 with an increased asthma risk and a reversible obstructive pattern of lung function at
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30 school age^{43,44}. Therefore, analyses by ANOVA were adjusted also for RSV etiology of
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32 wheezing in early childhood, in addition to adjustment with anti-inflammatory asthma
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34 medication during the preceding 12 months before the study visit at school age. Logistic
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36 regression analysis, adjusted for RSV etiology of early childhood wheezing and anti-
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38 inflammatory asthma medication during the 12 preceding months before the study visit,
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40 was applied for categorized (by the limits of abnormal values in % predicted) FVS
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42 parameters, and the results were expressed as adjusted odds ratios (aOR) and their 95 %
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44 confidence intervals (95% CI).
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51 *Ethics*

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The study was approved by the joint Research Ethics Committee of Kuopio University and Kuopio University Hospital. Informed written consent was obtained from the parents of the children.

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Results

Overweight was present in 6.0% of children at 4.0 years, in 22.2% at 7.3 years and in 33.3% at 12.3 years of age. Less than 4% of children were obese at 4.0 years of age. The proportion of obese children was 8.6 % at 7.3 years and 19.8% at 12.3 years of age. Three of 5 overweight children at age 4.0 years were overweight at age 7.2 years, and all 3 obese children were obese, respectively. Fifteen of the 16 overweight children at age 7.2 years were overweight at age 12.3 years, and 4 of the 6 obese children were obese, respectively.

In univariate analyses at 7.2 years of age, the only significant association was between current overweight and lower FEV₁/FVC (Table 1). There were no significant associations between previous (4.0 years of age) overweight or obesity and any FVS parameter at age 7.2 years (Data not shown). In multivariate analyses, the association between obesity and lower FEV₁/FVC changed to significant (Table 1). All other associations between previous or current overweight or obesity and FVS remained as unchanged.

In univariate analyses at 12.3 years of age, previous (7.2 years of age) overweight was associated with lower FEV₁/FVC, and current (12.3 years of age) overweight was associated with lower FEV₁/FVC, MEF₅₀ and MEF₂₅ (Tables 2). Similarly, previous obesity was associated with lower FEV₁/FVC, and current obesity was associated with lower FEV₁/FVC, MEF₅₀ and MEF₂₅ (Table 3). In multivariate analyses, the association between current overweight and MEF₅₀ changed to non-significant (Table 2). All other associations between previous or current overweight or obesity and FVS remained as unchanged.

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6 In the logistic regression analyses, both previous and current overweight were significant
7 risk factors for $FEV_1/FVC < 88\%$ at both 7.2 years (Table 4) and at 12.3 years of age
8 (Table 5). Since overweight was highly permanent from 4.0 to 7.3 years of age and from
9 7.2 to 12.3 years of age, respectively, previous and current overweight could not be
10 incorporated as variables in the same model. Therefore, the design of the study did not
11 allow to assess their influences separately. Current obesity was a significant risk factor for
12 $FEV_1/FVC < 88\%$ (aOR 8.07, 95% CI 2.10-31.05) and for $MEF_{25} < 48\%$ (aOR 4.34, 95%
13 CI 1.06-17.79) at 12.3 years of age.
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Discussion

There are three main results in the present study. First, the number of overweight and obese children increased constantly by age during the follow-up after early childhood wheezing until the median age of 12.3 years. Finally, a third was overweight, and about 20% were obese. The figures are higher than those calculated from self-reported weights and heights in 12-18 years old Finnish children in 1999, when 16.7% of the boys and 9.8% of the girls were overweight, and 1.4% and 0.4% were obese, assessed by using age- and gender-related international reference values⁴⁵. Second, current overweight was associated with decreased FEV₁/FVC at both 7.2 and 12.3 years of age. Overweight children had also reduced flows in small airways by MEF₂₅ and obese children by MEF₂₅ and MEF₅₀ at age 12.3 years. FEV₁/FVC is considered as the most sensitive and reliable measure of obstruction, but the reliability of MEF₂₅ has been questioned. Third, overweight and obesity at early school age preceded reduced FEV₁/FVC at age 12.3 years. But, since overweight was highly permanent from early to late school age, the influences of previous and current overweight could not be assessed separately.

The association between excessive weight gain and reduced lung function has been well documented in adults^{14-16,20,22}. In a Finnish study, weight reduction in obese adults even elicited an improvement of lung function²⁴. The effect of excessive weight gain to lung function seems to depend on the degree of obesity and on the presence and severity of asthma. When lung function was studied in 52 non-asthmatic non-obese, in 53 asthmatic non-obese, in 52 obese non-asthmatic and in 53 asthmatic obese adults, lung function was reduced in patients with asthma and obesity, and in addition, FVC and FRC were reduced

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3 in obese adults also with no asthma¹⁶. In a birth cohort from New Zealand, an association
4 was found between increasing BMI and decreasing FEV₁/FVC in 9-26 years old females,
5 but not in males¹⁵. In a study on difficult-to-treat asthma, FEV₁ was increased and FRC
6 and total lung capacity were decreased in obese patients⁴⁶. Thus, controlled studies in
7 adults with asthma^{16,46}, as well as population-based studies in healthy adults^{15,22,23},
8 highlight the connection between obesity and decreased expiratory reserve volumes,
9 which means that restriction is the characteristic lung function disorder in obesity.
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21 In a population study from China, overweight had a beneficial effect on lung function in
22 7 to 20 years old healthy girls²⁷. In a population study from Mexico, lung function
23 improved when weight increased in 8-11 years old healthy children, but after that age,
24 lung function first reached a plateau and then decreased among the obese youths⁴⁷. Lung
25 function by spirometry was compared between 657 overweight and 196 normal weight
26 Greek children, and FVC, FEV₁, MEF_{25-75%} and FEV₁/FVC were reduced in overweight
27 children¹⁸. In a population study from Australia, spirometry was performed in 2464
28 school children⁴⁸. Height-related FVC and FEV₁ increased by growth, but both FVC and
29 FEV₁ decreased in relation to increasing overweight. The result was opposite in an other
30 Australian population study in 5993 children; all variables in the FVS were, irrespective
31 of BMI, within normal limits, but FEV₁ and FVC in the lowest BMI quintile were
32 significantly lower than in other quintiles⁴. All these studies are cross-sectional with no
33 follow-up available. The results seem confusing, but there may be following consistency;
34 mild overweight may be beneficial but when substantial overweight or obesity develops,
35 the effect turns to non-beneficial.
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3 The results of the present follow-up study after early childhood wheezing showed that
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The results of the present follow-up study after early childhood wheezing showed that overweight was associated with reduced FEV_1/FVC at 7.2 and 12.3 years of age and reduced MEF_{50} and MEF_{25} at 12.3 years of age, in disagreement with most population studies in healthy children^{4,5,27,46,47}. However, the associations may be different in children with asthma; about 40% of our patients had asthma and all had wheezed in early childhood. Lung function and weight status were studied as a part of the childhood asthma management program (CAMP) in 1041 American children aged 5-12 years⁴⁹, and increasing BMI was associated with increasing FEV_1 and FVC, but decreasing FEV_1/FVC . The increase in FVC and decrease in FEV_1/FVC are in accordance with the results of our present study. In the CAMP study, weight status and lung function were studied by a cross-sectional design at enrolment of the patients, and no follow-up data have been, at least thus far, published. We found no evidence for a restrictive pattern of lung function disorder in overweight or obese children, though suggested to be present in obese asthmatic adults^{15,16,22,23,46}, and though was demonstrable after early childhood wheezing caused by RSV in 12.3 years old children of the present study^{43,44}.

The mechanisms leading to lung function disorders in association with overweight or obesity may be narrowing of the small peripheral airways²¹, in line with decreased MEF_{50} and MEF_{25} values in the overweight and obese children at the 12.3-year visit of the present study. In addition, decreased compliance of either the lungs due to narrow peripheral airways or the chest wall due to body adiposity may lead to subnormal lung function, including both decreased airway flows which mean an obstructive lung function disorder and decreased lung volumes which means a restrictive lung function disorder⁴⁸. The effect of excessive weight gain on lung function may be age-dependent, which

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3 means that different mechanisms may influence in children and in adults and in children
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5 at different ages. In a case-control study from Denmark, FEV₁ and FVC were reduced in
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7 193 obese men, compared with normal weight 215 controls, at 27 years of age, but after
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9 adjustments with current BMI, childhood BMI at 7 years of age was positively associated
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11 with both FEV₁ and FVC ⁵⁰.
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16 The strengths of the present study are the long, over 10 years prospective follow-up time
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18 and the fact that weights and heights of the children were measured at all control visits by
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20 experienced nurses using calibrated scales, thus allowing a reliable follow-up of the
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22 weight status of the children. Prospectively collected data on potential confounding
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24 factors, like data on viral etiology of early childhood wheezing and use of anti-
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26 inflammatory medication at school age, were available for adjusted analyses. The small
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28 number of the patients is a remarkable limitation, and with no doubt, the study was
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30 underpowered to reveal all presenting associations. Our selected material, children
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32 hospitalized for wheezing at <24 months of age, can be considered as a weakness of the
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34 study lessening the generalizability of the results. On the other hand, early childhood
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36 wheezers are at a high risk for later pulmonary disorders, and knowing the risk factors
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38 relevant in this specific group of children, like overweight and obesity according to the
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40 present results, opens new ways for preventive measures.
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47 In conclusion, overweight and obesity increased constantly by age during follow-up after
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49 wheezing in early childhood until the median age of 12.3 years. Overweight at school age
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51 was associated with bronchial obstruction, as manifested by decreased FEV₁/FVC at 7.2
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53 years and 12.3 years of age, and also with decreased flows in small airways at 12.3 years
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3 of age. Our results stress the importance of the prevention of excessive weight gain at
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5 pre-school and school age in children with early childhood wheezing.
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16 interest in the subjects of this manuscript.
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3 **Lung function and overweight in school aged children after early childhood**
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45 **Abbreviated title:** Lung function and overweight in wheezy children
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Summary

Background and purpose. Recently, obesity has been connected with wheezing, asthma and reduced lung function. Most previous studies have been cross-sectional. The aim of the present follow-up study was to evaluate the association of preceding or current overweight or obesity with lung function at early and late school age after early childhood wheezing.

Material and methods. From the 100 children hospitalized for infection associated wheezing at <24 months of age, 83 attended the control visit at 4.0 years, 82 at 7.2 years and 81 at 12.3 years of age. Flow-volume spirometry was performed in 79 children at 7.2 years and in 80 children at 12.3 years of age. The weight status was assessed by calculating body mass index (BMI) at all visits. Age- and gender-specific BMI standard deviation scores (BMI-SDS) of >1.3 SD and > 2.0 SD were defined to mean overweight and obesity, respectively.

Results. Overweight at both 7.2 and 12.3 years of age was associated with decreased FEV₁/FVC (forced expiratory volume in one second/ forced vital capacity). Overweight and obesity at 7.2 years of age were associated with decreased FEV₁/FVC and MEF₅₀ (maximal expiratory flow at 50 % of FVC) at 12.3 years of age. The results were similar by continuous and categorized analyses, being robust to adjustments for viral findings during early childhood wheezing and asthma maintenance medication at school age.

Conclusion. Overweight and obesity are significant risk factors for reduced lung function at school age after early childhood wheezing. Thus, early-life wheezers should avoid excessive weight gain during childhood.

Keywords: child, spirometry, obstruction, overweight, obesity, lung function, wheezing

Abbreviations:

BMI body mass index

BMI-SDS body mass index standard deviation score

TLC total lung capacity

FRC functional residual capacity

FVC forced vital capacity

FEV₁ forced expiratory volume in one second

FEV₁/FVC forced expiratory volume in one second/forced vital capacity

MEF₅₀ maximal expiratory flow at 50% of FVC

MEF₂₅ maximal expiratory flow at 25% of FVC

aOR adjusted odds ratios

CI confidence intervals

RSV respiratory syncytial virus

Introduction

Asthma and overweight or obesity have increased concomitantly among both children and adults during the last three decades in western countries¹⁻³. The studies have suggested an association between wheezing symptoms and obesity⁴⁻⁹, and also between asthma diagnoses and obesity¹⁰⁻¹³. When pulmonary function and bronchial reactivity have been studied objectively, the results have been mainly negative^{5, 14-18}.

In adults, obesity decreases both lung volume, as documented by reduced total lung capacity (TLC), forced vital capacity (FVC) and functional residual capacity (FRC), and airway flows, as documented by decreased forced expiratory volume in one second (FEV₁) and increased airway resistance^{19,20}. In addition, obesity leads to obstruction in peripheral airway²¹, as documented by decreased flows at 50% (MEF₅₀) or at 25% (MEF₂₅) of FVC. However, the largest impact seems to target at expiratory reserve volume, which means that restriction is the characteristic lung function disorder in obesity^{22,23}. In addition, weight reduction in obese adults elicited an improvement of lung function²⁴.

In children with asthma suggestive symptoms, high body mass index (BMI) was associated with subnormal lung function in one study¹⁸, but not in two others^{4,5}. In healthy children, lung function was either impaired²⁵, improved in boys and girls²⁶ or improved only in girls²⁷ by excessive weight gain

We have prospectively followed-up a cohort of children hospitalized for infection associated wheezing at <24 months of age in 1992-1993. The weights and heights of the children were measured at follow-up visits at the median ages of 4.0, 7.2 and 12.3 years, and spirometry was performed at both visits at school age²⁸⁻³⁰.

The aim of the present study was to evaluate the association between overweight or obesity and lung function at school age in former early-life wheezers, with a special focus on the influence of an emerging overweight.

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Material and methods

Study design

One-hundred consecutive children, hospitalized for wheezing associated respiratory infection at age 1-23 months, were recruited into this follow-up study in 1992 -1993³¹. Maintenance therapy for asthma was one of the exclusion criteria, and the wheezing episode was the first one in 87% of the included children³². The basic data were collected by interviewing the parents during hospitalization using a structured questionnaire. Seven respiratory viruses, including respiratory syncytial virus (RSV), were studied by antigen and antibody assays³². Later, viral studies were supplemented by polymerase chain reaction to RSV and rhinoviruses in frozen samples^{33,34}. In all, RSV was identified in 29/100 and rhinovirus in 27/81 cases^{33,35}.

Three follow-up visits were prospectively organized at the median ages of 4.0 years, 7.2 years and 12.3 years²⁸⁻³⁰. Asthma was present in 33/82 (40.2%) children at the 7.2-year visit²⁹ and in 32/81 (39.5%) children at the 12.3-year visit³⁰. Data on medical history, including the use of asthma medication during the preceding 12 months, were collected by interviewing the parents.

Assessment of weight status

The weights and heights of the children, measured by an experienced nurse using standard methods, were registered in all attending children at all controls visits. Body mass index (BMI) was calculated by using the equation: weight (kg) / [height (m)]². Due to the lack of Finnish references, we applied British gender- and age-specific population-based references. BMI standard deviation score (BMI-SDS), also called Z-score, was

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3 assessed by an obesity calculator (NIBHI 2007)³⁶. This calculator applies British growth
4 references from 1990, produced by the LMS method in 1995^{37,38}, and revised in 1996³⁹.
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6 The LMS method summarizes the distribution of BMI at each age by its median (M),
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8 coefficient of variation (S), and skewness expressed as a Box-Cox power (L) required to
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10 transform the data to normal⁴⁰.
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16 In the present study, we used the same cut-off points for overweight and obesity as
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18 proposed by the British study evaluating the limits of obesity and overweight in different
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20 populations⁴¹. The cut-off point for overweight was BMI >91 percentile (approximating
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22 BMI-SDS >1.3) and for obesity BMI >98 percentile (approximating BMI-SDS >2.0)^{19,41}.
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24 In the British population, these cut-off points corresponds BMI 25 kg/m² and BMI 30
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26 kg/m² levels, respectively, in the 18 years old young adults⁴¹.
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31 *Measurement of lung function*

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33 Lung function was studied by flow-volume spirometer (FVS) (Medikro, Kuopio, Finland)
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35 at the 7.2-year and 12.3-year study visits. The parameters were expressed as percentages
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37 of the gender-specific height-related reference values (% of predicted) for Finnish
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39 children^{42,44}. The parameters registered were FVC (forced vital capacity), FEV₁ (forced
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41 expiratory volume in one second), FEV₁/FVC, MEF₅₀ (maximal expiratory flow at 50 %
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43 of FVC) and MEF₂₅ (maximal expiratory flow at 25 % of FVC). Either the measurement
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45 with the highest FEV₁ (at the 7.2-year study)²⁹ or the composite maximal curve (at the
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47 12.3-year study)³⁰ was in each child recorded for further analyses. The cut-off limits for
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49 abnormal values were 80 % for FEV₁, 88 % for FEV₁/FVC, 62 % for MEF₅₀ and 48 %
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51 for MEF₂₅^{17,30,43}.
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3 Lung function data were available from 79 children at the 7.2-year and from 81 children
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5 at the 12.3-year study visits. The numbers of children with anti-inflammatory
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7 maintenance medication for asthma during the 12 preceding months were 29/79 (36.77%)
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9 at age of 7.2 years and 18/80 (22.5%) at age of 12.3 years. At the 4.0-year visit, weight
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11 status was assessed for 74 children with lung function data available at the 7.2-year visit.
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15 *Statistics*

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18 The data were analysed using SPSS 17.0 software (SPSS Inc. Chicago, IL, USA). Mann-
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20 Whitney U-test was used in univariate analyses and analysis of variance (ANOVA) in
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22 multivariate analyses for continuous FVS parameters. In the previous studies in this
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24 cohort, RSV etiology of wheezing in early childhood was associated with a non-
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26 reversible restrictive pattern of lung function and non-RSV etiology (mostly rhinovirus)
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28 with an increased asthma risk and a reversible obstructive pattern of lung function at
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30 school age^{43, 44}. Therefore, analyses by ANOVA were adjusted also for RSV etiology of
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32 wheezing in early childhood, in addition to adjustment with anti-inflammatory asthma
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34 medication during the preceding 12 months before the study visit at school age. Logistic
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36 regression analysis, adjusted for RSV etiology of early childhood wheezing and anti-
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38 inflammatory asthma medication during the 12 preceding months before the study visit,
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40 was applied for categorized (by the limits of abnormal values in % predicted) FVS
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42 parameters, and the results were expressed as adjusted odds ratios (aOR) and their 95 %
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44 confidence intervals (95% CI).
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51 *Ethics*

The study was approved by the joint Research Ethics Committee of Kuopio University and Kuopio University Hospital. Informed written consent was obtained from the parents of the children.

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Results

Overweight was present in 6.0% of children at 4.0 years, in 22.2% at 7.3 years and in 33.3% at 12.3 years of age. Less than 4% of children were obese at 4.0 years of age. The proportion of obese children was 8.6 % at 7.3 years and 19.8% at 12.3 years of age. Three of 5 overweight children at age 4.0 years were overweight at age 7.2 years, and all 3 obese children were obese, respectively. Fifteen of the 16 overweight children at age 7.2 years were overweight at age 12.3 years, and 4 of the 6 obese children were obese, respectively.

In univariate analyses at 7.2 years of age, the only significant association was between current overweight and lower FEV₁/FVC (Table 1). There were no significant associations between previous (4.0 years of age) overweight or obesity and any FVS parameter at age 7.2 years (Data not shown). In multivariate analyses, the association between obesity and lower FEV₁/FVC changed to significant (Table 1). All other associations between previous or current overweight or obesity and FVS remained as unchanged.

In univariate analyses at 12.3 years of age, previous (7.2 years of age) overweight was associated with lower FEV₁/FVC, and current (12.3 years of age) overweight was associated with lower FEV₁/FVC, MEF₅₀ and MEF₂₅ (Tables 2). Similarly, previous obesity was associated with lower FEV₁/FVC, and current obesity was associated with lower FEV₁/FVC, MEF₅₀ and MEF₂₅ (Table 3). In multivariate analyses, the association between current overweight and MEF₅₀ changed to non-significant (Table 2). All other associations between previous or current overweight or obesity and FVS remained as unchanged.

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6 In the logistic regression analyses, both previous and current overweight were significant
7 risk factors for FEV₁/FVC <88% at both 7.2 years (Table 4) and at 12.3 years of age
8 (Table 5). Since overweight was highly permanent from 4.0 to 7.3 years of age and from
9 7.2 to 12.3 years of age, respectively, previous and current overweight could not be
10 incorporated as variables in the same model. Therefore, the design of the study did not
11 allow to assess their influences separately. Current obesity was a significant risk factor for
12 FEV₁/FVC <88% (aOR 8.07, 95% CI 2.10-31.05) and for MEF₂₅ <48% (aOR 4.34, 95%
13 CI 1.06-17.79) at 12.3 years of age.
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Discussion

There are three main results in the present study. First, the number of overweight and obese children increased constantly by age during the follow-up after early childhood wheezing until the median age of 12.3 years. Finally, a third was overweight, and about 20% were obese. The figures are higher than those calculated from self-reported weights and heights in 12-18 years old Finnish children in 1999, when 16.7% of the boys and 9.8% of the girls were overweight, and 1.4% and 0.4% were obese, assessed by using age- and gender-related international reference values⁴⁵. Second, current overweight was associated with decreased FEV₁/FVC at both 7.2 and 12.3 years of age. Overweight children had also reduced flows in small airways by MEF₂₅ and obese children by MEF₂₅ and MEF₅₀ at age 12.3 years. FEV₁/FVC is considered as the most sensitive and reliable measure of obstruction, but the reliability of MEF₂₅ has been questioned. Third, overweight and obesity at early school age preceded reduced FEV₁/FVC at age 12.3 years. But, since overweight was highly permanent from early to late school age, the influences of previous and current overweight could not be assessed separately.

The association between excessive weight gain and reduced lung function has been well documented in adults^{14-16,20,22}. In a Finnish study, weight reduction in obese adults even elicited an improvement of lung function²⁴. The effect of excessive weight gain to lung function seems to depend on the degree of obesity and on the presence and severity of asthma. When lung function was studied in 52 non-asthmatic non-obese, in 53 asthmatic non-obese, in 52 obese non-asthmatic and in 53 asthmatic obese adults, lung function was reduced in patients with asthma and obesity, and in addition, FVC and FRC were reduced

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3 in obese adults also with no asthma¹⁶. In a birth cohort from New Zealand, an association
4 was found between increasing BMI and decreasing FEV₁/FVC in 9-26 years old females,
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6 but not in males¹⁵. In a study on difficult-to-treat asthma, FEV₁ was increased and FRC
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8 and total lung capacity were decreased in obese patients⁴⁶. Thus, controlled studies in
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10 adults with asthma^{16,46}, as well as population-based studies in healthy adults^{15,22,23},
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12 highlight the connection between obesity and decreased expiratory reserve volumes,
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14 which means that restriction is the characteristic lung function disorder in obesity.
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21 In a population study from China, overweight had a beneficial effect on lung function in
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23 7 to 20 years old healthy girls²⁷. In a population study from Mexico, lung function
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25 improved when weight increased in 8-11 years old healthy children, but after that age,
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27 lung function first reached a plateau and then decreased among the obese youths⁴⁷. Lung
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29 function by spirometry was compared between 657 overweight and 196 normal weight
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31 Greek children, and FVC, FEV₁, MEF_{25-75%} and FEV₁/FVC were reduced in overweight
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33 children¹⁸. In a population study from Australia, spirometry was performed in 2464
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35 school children⁴⁸. Height-related FVC and FEV₁ increased by growth, but both FVC and
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37 FEV₁ decreased in relation to increasing overweight. The result was opposite in an other
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39 Australian population study in 5993 children; all variables in the FVS were, irrespective
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41 of BMI, within normal limits, but FEV₁ and FVC in the lowest BMI quintile were
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43 significantly lower than in other quintiles⁴. All these studies are cross-sectional with no
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45 follow-up available. The results seem confusing, but there may be following consistency;
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47 mild overweight may be beneficial but when substantial overweight or obesity develops,
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49 the effect turns to non-beneficial.
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3 The results of the present follow-up study after early childhood wheezing showed that
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6 overweight was associated with reduced FEV₁/FVC at 7.2 and 12.3 years of age and
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9 reduced MEF₅₀ and MEF₂₅ at 12.3 years of age, in disagreement with most population
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11 studies in healthy children^{4,5,27,46,47}. However, the associations may be different in
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13 children with asthma; about 40% of our patients had asthma and all had wheezed in early
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15
16 childhood. Lung function and weight status were studied as a part of the childhood
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18 asthma management program (CAMP) in 1041 American children aged 5-12 years⁴⁹, and
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20 increasing BMI was associated with increasing FEV₁ and FVC, but decreasing
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22 FEV₁/FVC. The increase in FVC and decrease in FEV₁/FVC are in accordance with the
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24 results of our present study. In the CAMP study, weight status and lung function were
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26 studied by a cross-sectional design at enrolment of the patients, and no follow-up data
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28 have been, at least thus far, published. We found no evidence for a restrictive pattern of
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30 lung function disorder in overweight or obese children, though suggested to be present in
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32 obese asthmatic adults^{15,16,22,23,46}, and though was demonstrable after early childhood
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34 wheezing caused by RSV in 12.3 years old children of the present study^{43,44}.

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40 The mechanisms leading to lung function disorders in association with overweight or
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42 obesity may be narrowing of the small peripheral airways²¹, in line with decreased
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44 MEF₅₀ and MEF₂₅ values in the overweight and obese children at the 12.3-year visit of
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46 the present study. In addition, decreased compliance of either the lungs due to narrow
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48 peripheral airways or the chest wall due to body adiposity may lead to subnormal lung
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50 function, including both decreased airway flows which mean an obstructive lung function
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52 disorder and decreased lung volumes which means a restrictive lung function disorder⁴⁸.

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56 The effect of excessive weight gain on lung function may be age-dependent, which
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3 means that different mechanisms may influence in children and in adults and in children
4 at different ages. In a case-control study from Denmark, FEV₁ and FVC were reduced in
5 193 obese men, compared with normal weight 215 controls, at 27 years of age, but after
6 adjustments with current BMI, childhood BMI at 7 years of age was positively associated
7 with both FEV₁ and FVC⁵⁰.
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16 The strengths of the present study are the long, over 10 years prospective follow-up time
17 and the fact that weights and heights of the children were measured at all control visits by
18 experienced nurses using calibrated scales, thus allowing a reliable follow-up of the
19 weight status of the children. Prospectively collected data on potential confounding
20 factors, like data on viral etiology of early childhood wheezing and use of anti-
21 inflammatory medication at school age, were available for adjusted analyses. The small
22 number of the patients is a remarkable limitation, and with no doubt, the study was
23 underpowered to reveal all presenting associations. Our selected material, children
24 hospitalized for wheezing at <24 months of age, can be considered as a weakness of the
25 study lessening the generalizability of the results. On the other hand, early childhood
26 wheezers are at a high risk for later pulmonary disorders, and knowing the risk factors
27 relevant in this specific group of children, like overweight and obesity according to the
28 present results, opens new ways for preventive measures.
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47 In conclusion, overweight and obesity increased constantly by age during follow-up after
48 wheezing in early childhood until the median age of 12.3 years. Overweight at school age
49 was associated with bronchial obstruction, as manifested by decreased FEV₁/FVC at 7.2
50 years and 12.3 years of age, and also with decreased flows in small airways at 12.3 years
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3 of age. Our results stress the importance of the prevention of excessive weight gain at
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6 pre-school and school age in children with early childhood wheezing.
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For Peer Review

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Table 1. Flow-volume spirometry (FVS, % of predicted, mean, SD) in 74 study subjects at 7.2 years of age, in relation to current overweight or obesity (at 7.2 years of age).

Parameters in FVS ^b	Current overweight ^a		Current obesity ^a					
	Yes (N=16) Mean, (SD)	No (N=58) Mean, (SD)	Univariate p	Multivariate p ^d	Yes (N=7) Mean, (SD)	No (N=72) Mean, (SD)	Univariate p ^c	Multivariate p ^d
FVC	108.71 (19.75)	102.06 (16.48)	0.252	0.219	106.73 (8.78)	103.27 (18.00)	0.448	0.467
FEV₁	100.16 (14.16)	99.95 (13.94)	0.977	0.890	96.58 (4.78)	100.33 (14.46)	0.523	0.574
FEV₁/FVC	92.63 (8.95)	98.47 (8.93)	0.017	0.025	90.81 (7.62)	97.76 (9.17)	0.076	0.034
MEF₅₀	84.00 (17.73)	85.10 (20.39)	0.700	0.814	81.30 (19.03)	85.19 (19.87)	0.546	0.615
MEF₂₅	66.00 (19.85)	71.27 (22.76)	0.394	0.454	62.77 (17.30)	70.78 (22.50)	0.398	0.305

^a Overweight BMI-SDS >1.3 (obese children included); obesity BMI-SDS > 2,0

^b FVC (forced vital capacity), FEV₁ (forced expiratory volume in one second), FEV₁/FCV, MEF₅₀ (maximal expiratory flow at 50% of FVC) and MEF₂₅ (maximal expiratory flow at 25% of FVC), expressed as % of predicted.

^c Mann-Whitney U -test

^d Analysis of variance, adjusted for RSV etiology of early wheezing and current anti-inflammatory asthma medication (during the preceding 12 months).

Table 2. Flow-volume spirometry (FVS, % of predicted, mean, SD) in 80 study subjects at 12.3 years of age, in relation to previous (at 7.2 years of age) and current (at 12.3 years of age) overweight.

Parameters in FVS ^b	Previous overweight ^a		Univariate p ^c	Multivariate p ^d	Current overweight ^a		Univariate p ^c	Multivariate p ^d
	Yes (N=16) Mean, (SD)	No (N=58) Mean, (SD)			Yes (N=27) Mean, (SD)	No (N=53) Mean, (SD)		
FVC	101.03 (8.40)	97.21 (13.20)	0.131	0.306	100.56 (11.50)	96.38 (12.68)	0.162	0.164
FEV₁	90.21 (12.96)	93.03 (12.96)	0.684	0.420	90.68 (13.60)	93.02 (21.50)	0.439	0.500
FEV₁/FVC	89.15 (10.06)	96.01 (7.63)	0.013	0.003	90.09 (8.81)	96.81 (7.36)	0.001	0.001
MEF₅₀	74.88 (20.68)	83.91 (18.82)	0.121	0.095	75.63 (20.47)	84.39 (17.70)	0.037	0.076
MEF₂₅	64.49 (23.75)	73.18 (19.25)	0.138	0.139	62.96 (19.58)	76.13 (19.85)	0.006	0.009

^a BMI-SDS >1.3

^b FVC (forced vital capacity), FEV₁ (forced expiratory volume in one second), FEV₁/FVC, MEF₅₀ (maximal expiratory flow at 50% of FVC) and MEF₂₅ (maximal expiratory flow at 25% of FVC), expressed as % of predicted.

^c Mann-Whitney U -test

^d Analysis of variance, adjusted for RSV etiology of early wheezing and current anti-inflammatory asthma medication (during the preceding 12 months).

Table 3. Flow-volume spirometry (FVS, % of predicted, mean, SD) in 80 study subjects at 12.3 years of age, in relation to previous (at 7.2 years of age) and current (at 12.3 years of age) obesity.

Parameters in FVS ^b	Previous obesity ^a		Univariate p ^c	Multivariate p ^d	Current obesity ^a		Univariate p ^c	Multivariate p ^d
	Yes (N=6) Mean, (SD)	No (N=68) Mean, (SD)			Yes (N=16) Mean, (SD)	No (N=64) Mean, (SD)		
FVC	99.05 (9.47)	97.95 (12.65)	0.797	0.769	98.39 (9.12)	97.64 (13.12)	0.674	0.837
FEV₁	87.28 (13.30)	92.87 (12.89)	0.434	0.318	87.44 (12.69)	93.43 (12.86)	0.136	0.116
FEV₁/FVC	87.76 (6.99)	95.12 (8.57)	0.022	0.026	88.85 (9.78)	95.97 (7.51)	0.010	0.002
MEF₅₀	70.46 (15.72)	82.97 (19.52)	0.132	0.107	71.68 (18.81)	83.87 (18.41)	0.025	0.028
MEF₂₅	60.03 (10.59)	72.34 (20.84)	0.113	0.130	61.02 (21.40)	74.35 (19.68)	0.021	0.024

^a BMI-SDS >2

^b FVC (forced vital capacity), FEV₁ (forced expiratory volume in one second), FEV₁/FVC, MEF₅₀ (maximal expiratory flow at 50% of FVC) and MEF₂₅ (maximal expiratory flow at 25% of FVC), expressed as % of predicted.

^c Mann-Whitney U -test

^d Analysis of variance, adjusted for RSV etiology of early wheezing and current anti-inflammatory asthma medication (during the preceding 12 months).

Table 4. Logistic regression: abnormal lung function in flow-volume spirometry (FVS) at 7.2 years of age, in relation to previous (at 4.0 years of age) and current (at 7.2 years of age) overweight.

Abnormal FVS ^b	Previous overweight ^a		aOR ^c (95% CI)	Current overweight ^a		aOR ^c (95% CI)
	Yes (N=5)	No (N=69)		Yes (N=17)	No (N=57)	
FEV₁<80%	0	4	-	1	3	1.01 (0.10-10.58)
FEV₁/FVC<88%	3	10	15.46 (1.65-145.26)	6	7	3.71 (1.01-13.60)
MEF₅₀<62%	2	11	6.46 (0.772-33.95)	3	11	0.89 (0.21-3.80)
MEF₂₅<48%	2	12	4.74 (0.61-36.76)	3	11	0.89 (0.22-3.70)
At least one abnormal parameter	3	16	6.63 (0.89-49.46)	6	14	1.63 (0.51-5.22)

^a BMI-SDS >1.3

^b FVC (forced vital capacity), FEV₁ (forced expiratory volume in one second), FEV₁/FVC, MEF₅₀ (maximal expiratory flow at 50% of FVC) and MEF₂₅ (maximal expiratory flow at 25% of FVC), expressed as % of predicted.

^c Odds ratio (95% confidence interval) adjusted for RSV etiology of early wheezing and current anti-inflammatory asthma medication (during the preceding 12 months)

Table 5. Logistic regression: abnormal lung function in flow-volume spirometry (FVS) at 12.3 years of age, in relation to previous (at 7.2 years of age) and current (at 12.3 years of age) overweight.

Abnormal FVS ^b	Previous overweight ^a		aOR ^c (95% CI)	Current overweight ^a		aOR ^c (95% CI)
	Yes (N=16)	No (N=58)		Yes (N=24)	No (N=50)	
FEV₁<80%	2	10	0.70 (0.13-3.60)	5	9	1.00 (0.29-3.46)
FEV₁/FVC<88%	6	6	5.64 (1.43-22.20)	8	5	4.02 (1.14-14.22)
MEF₅₀<62%	3	9	1.29 (0.30-5.54)	7	6	2.64 (0.78-8.97)
MEF₂₅<48%	4	6	3.51 (0.76-16.13)	6	5	2.47 (0.65-9.38)
At least one abnormal parameter	6	17	1.45 (0.45-4.67)	11	15	1.70 (0.63-4.55)

^a BMI-SDS >1.3

^b FVC (forced vital capacity), FEV₁ (forced expiratory volume in one second), FEV₁/FVC, MEF₅₀ (maximal expiratory flow at 50% of FVC) and MEF₂₅ (maximal expiratory flow at 25% of FVC), expressed as % of predicted.

^c Odds ratio (95% confidence interval) adjusted for RSV etiology of early wheezing and current anti-inflammatory asthma medication (during the preceding 12 months)

Table 1. Flow-volume spirometry (FVS, % of predicted, mean, SD) in 74 study subjects at 7.2 years of age, in relation to current overweight or obesity (at 7.2 years of age).

Parameters in FVS ^b	Current overweight ^a				Current obesity ^a			
	Yes (N=16) Mean, (SD)	No (N=58) Mean, (SD)	Univariate p	Multivariate p ^d	Yes (N=7) Mean, (SD)	No (N=72) Mean, (SD)	Univariate p ^c	Multivariate p ^d
FVC	108.71 (19.75)	102.06 (16.48)	0.252	0.219	106.73 (8.78)	103.27 (18.00)	0.448	0.467
FEV₁	100.16 (14.16)	99.95 (13.94)	0.977	0.890	96.58 (4.78)	100.33 (14.46)	0.523	0.574
FEV₁/FVC	92.63 (8.95)	98.47 (8.93)	0.017	0.025	90.81 (7.62)	97.76 (9.17)	0.076	0.034
MEF₅₀	84.00 (17.73)	85.10 (20.39)	0.700	0.814	81.30 (19.03)	85.19 (19.87)	0.546	0.615
MEF₂₅	66.00 (19.85)	71.27 (22.76)	0.394	0.454	62.77 (17.30)	70.78 (22.50)	0.398	0.305

^a Overweight BMI-SDS >1.3 (obese children included); obesity BMI-SDS > 2,0

^b FVC (forced vital capacity), FEV₁ (forced expiratory volume in one second), FEV₁/FVC, MEF₅₀ (maximal expiratory flow at 50% of FVC) and MEF₂₅ (maximal expiratory flow at 25% of FVC), expressed as % of predicted.

^c Mann-Whitney U -test

^d Analysis of variance, adjusted for RSV etiology of early wheezing and current anti-inflammatory asthma medication (during the preceding 12 months).

Table 2. Flow-volume spirometry (FVS, % of predicted, mean, SD) in 80 study subjects at 12.3 years of age, in relation to previous (at 7.2 years of age) and current (at 12.3 years of age) overweight.

Parameters in FVS ^b	Previous overweight ^a		Univariate p ^c	Multivariate p ^d	Current overweight ^a		Univariate p ^c	Multivariate p ^d
	Yes (N=16) Mean, (SD)	No (N=58) Mean, (SD)			Yes (N=27) Mean, (SD)	No (N=53) Mean, (SD)		
FVC	101.03 (8.40)	97.21 (13.20)	0.131	0.306	100.56 (11.50)	96.38 (12.68)	0.162	0.164
FEV₁	90.21 (12.96)	93.03 (12.96)	0.684	0.420	90.68 (13.60)	93.02 (21.50)	0.439	0.500
FEV₁/FVC	89.15 (10.06)	96.01 (7.63)	0.013	0.003	90.09 (8.81)	96.81 (7.36)	0.001	0.001
MEF₅₀	74.88 (20.68)	83.91 (18.82)	0.121	0.095	75.63 (20.47)	84.39 (17.70)	0.037	0.076
MEF₂₅	64.49 (23.75)	73.18 (19.25)	0.138	0.139	62.96 (19.58)	76.13 (19.85)	0.006	0.009

^a BMI-SDS >1.3

^b FVC (forced vital capacity), FEV₁ (forced expiratory volume in one second), FEV₁/FVC, MEF₅₀ (maximal expiratory flow at 50% of FVC) and MEF₂₅ (maximal expiratory flow at 25% of FVC), expressed as % of predicted.

^c Mann-Whitney U -test

^d Analysis of variance, adjusted for RSV etiology of early wheezing and current anti-inflammatory asthma medication (during the preceding 12 months).

Table 3. Flow-volume spirometry (FVS, % of predicted, mean, SD) in 80 study subjects at 12.3 years of age, in relation to previous (at 7.2 years of age) and current (at 12.3 years of age) obesity.

Parameters in FVS ^b	Previous obesity ^a		Univariate p ^c	Multivariate p ^d	Current obesity ^a		Univariate p ^c	Multivariate p ^d
	Yes (N=6) Mean, (SD)	No (N=68) Mean, (SD)			Yes (N=16) Mean, (SD)	No (N=64) Mean, (SD)		
FVC	99.05 (9.47)	97.95 (12.65)	0.797	0.769	98.39 (9.12)	97.64 (13.12)	0.674	0.837
FEV₁	87.28 (13.30)	92.87 (12.89)	0.434	0.318	87.44 (12.69)	93.43 (12.86)	0.136	0.116
FEV₁/FVC	87.76 (6.99)	95.12 (8.57)	0.022	0.026	88.85 (9.78)	95.97 (7.51)	0.010	0.002
MEF₅₀	70.46 (15.72)	82.97 (19.52)	0.132	0.107	71.68 (18.81)	83.87 (18.41)	0.025	0.028
MEF₂₅	60.03 (10.59)	72.34 (20.84)	0.113	0.130	61.02 (21.40)	74.35 (19.68)	0.021	0.024

^a BMI-SDS >2

^b FVC (forced vital capacity), FEV₁ (forced expiratory volume in one second), FEV₁/FCV, MEF₅₀ (maximal expiratory flow at 50% of FVC) and MEF₂₅ (maximal expiratory flow at 25% of FVC), expressed as % of predicted.

^c Mann-Whitney U -test

^d Analysis of variance, adjusted for RSV etiology of early wheezing and current anti-inflammatory asthma medication (during the preceding 12 months).

Table 4. Logistic regression: abnormal lung function in flow-volume spirometry (FVS) at 7.2 years of age, in relation to previous (at 4.0 years of age) and current (at 7.2 years of age) overweight.

Abnormal FVS ^b	Previous overweight ^a		aOR ^c (95% CI)	Current overweight ^a		aOR ^c (95% CI)
	Yes (N=5)	No (N=69)		Yes (N=17)	No (N=57)	
FEV₁<80%	0	4	-	1	3	1.01 (0.10-10.58)
FEV₁/FVC<88%	3	10	15.46 (1.65-145.26)	6	7	3.71 (1.01-13.60)
MEF₅₀<62%	2	11	6.46 (0.772-33.95)	3	11	0.89 (0.21-3.80)
MEF₂₅<48%	2	12	4.74 (0.61-36.76)	3	11	0.89 (0.22-3.70)
At least one abnormal parameter	3	16	6.63 (0.89-49.46)	6	14	1.63 (0.51-5.22)

^a BMI-SDS >1.3

^b FVC (forced vital capacity), FEV₁ (forced expiratory volume in one second), FEV₁/FVC, MEF₅₀ (maximal expiratory flow at 50% of FVC) and MEF₂₅ (maximal expiratory flow at 25% of FVC), expressed as % of predicted.

^c Odds ratio (95% confidence interval) adjusted for RSV etiology of early wheezing and current anti-inflammatory asthma medication (during the preceding 12 months)

Table 5. Logistic regression: abnormal lung function in flow-volume spirometry (FVS) at 12.3 years of age, in relation to previous (at 7.2 years of age) and current (at 12.3 years of age) overweight.

Abnormal FVS ^b	Previous overweight ^a		aOR ^c (95% CI)	Current overweight ^a		aOR ^c (95% CI)
	Yes (N=16)	No (N=58)		Yes (N=24)	No (N=50)	
FEV₁<80%	2	10	0.70 (0.13-3.60)	5	9	1.00 (0.29-3.46)
FEV₁/FVC<88%	6	6	5.64 (1.43-22.20)	8	5	4.02 (1.14-14.22)
MEF₅₀<62%	3	9	1.29 (0.30-5.54)	7	6	2.64 (0.78-8.97)
MEF₂₅<48%	4	6	3.51 (0.76-16.13)	6	5	2.47 (0.65-9.38)
At least one abnormal parameter	6	17	1.45 (0.45-4.67)	11	15	1.70 (0.63-4.55)

^a BMI-SDS >1.3

^b FVC (forced vital capacity), FEV₁ (forced expiratory volume in one second), FEV₁/FVC, MEF₅₀ (maximal expiratory flow at 50% of FVC) and MEF₂₅ (maximal expiratory flow at 25% of FVC), expressed as % of predicted.

^c Odds ratio (95% confidence interval) adjusted for RSV etiology of early wheezing and current anti-inflammatory asthma medication (during the preceding 12 months)