Asthma is a common disease in childhood. Obesity is increasing health problem related to asthma. The use of inhaled corticosteroids (ICS) for childhood asthma has steadily increased. This long term follow-up study contains 100 children hospitalized for wheezing in infancy and followed until 12.3 years of age. In the present study, we evaluated the association between overweight and asthma, allergies and lung function and ICS’ effect on bone mineral density at early teenage in this asthma risk group.
Weight, Asthma, and Bone Mineral Density

A Prospective Follow-Up Study after Early Childhood Wheezing
VIRPI SIDOROFF

Weight, Asthma, and Bone Mineral Density

A Prospective Follow-Up Study after Early Childhood Wheezing

To be presented by permission of the Faculty of Health Sciences, University of Eastern Finland for public examination in AT100, at Joensuu Campus, Joensuu on Saturday, December 14th 2013, at 13 noon

Publications of the University of Eastern Finland
Dissertations in Health Sciences
Number 203

Department of Paediatrics, Institute of Clinical Medicine, School of Medicine
Faculty of Health Sciences
University of Eastern Finland
Joensuu
2013
Author’s address: Department of Paediatrics
North Karelia Central Hospital
JOENSUU
FINLAND

Department of Paediatrics
Institute of Clinical Medicine, School of Medicine
University of Eastern Finland
Kuopio University Hospital
KUOPIO
FINLAND

Supervisors: Professor Matti Korppi, M.D., Ph.D.
Paediatric Research Centre
University of Tampere
TAMPERE
FINLAND

Mari Hyvärinen, M.D., Ph.D.
Department of Paediatrics
Kuopio University Hospital
KUOPIO
FINLAND

Reviewers: Docent Outi Mäkitie, M.D., Ph.D.
Children’s Hospital
Helsinki University Central Hospital
HELSINKI
FINLAND

Docent Mikael Kuitunen, M.D., Ph.D.
Children’s Hospital
Helsinki University Central Hospital
HELSINKI
FINLAND

Opponent: Docent Merja Kajosaari, M.D., Ph.D.
Children’s Hospital
Helsinki University Central Hospital
HELSINKI
FINLAND
ABSTRACT:
Growing evidence shows that overweight children face increased asthma risk. The link between asthma, allergy, lung function, and obesity in children is unclear. Paediatric use of inhaled corticosteroids (ICS) for asthma has steadily increased. However, knowledge of long-term safety to bone health is insufficient. Between 1991 and 1992, 100 children, aged 1–23 months, hospitalised for wheezing were recruited to an early-intervention bronchiolitis study. An additional 14 children were recruited and later included in the study group. Follow-up visits organised at median ages of 4.0, 7.2, and 12.3 years consisted of medical examinations, weight and height measurements, and skin prick tests for common indoor and outdoor allergens. Exercise challenge tests were performed to show bronchial hyperreactivity (BHR). At the median age of 12.3 years, bone mineral density (BMD) was measured by dual-energy x-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT). The history of ICS consumption was collected from medical records. Cumulative doses and the duration of ICS therapy were calculated. The participation rate was 82/100 at age 7.2 and 81/100 at age 12.3 years, and 89/114 children attended the BMD study. At 12.3 years of age, 38% of participants were asthmatic, 33% were overweight, and 20% were obese. There was no association between previous or current overweight or obesity and asthma or BHR at 7.2 or 12.3 years of age. The current overweight was associated with decreased FEV1/FVC (forced expiratory volume in 1 sec/forced vital capacity) at both 7.2 and 12.3 years of age and reduced flows in small airways at 12.3 years of age. The results were similar in continuous and categorised analyses, being robust to adjustments for viral findings at study entry and asthma medication at school age.

During follow-up, 73 children received ICS medication, and 16 did not. The mean cumulative ICS dose was 517 mg (in the range of 31 –1,813 mg). The cumulative ICS dose was associated with reduced BMD measured by DXA in the femoral neck (\( r = -0.320, r^2 = 0.10, \text{adj.} p < 0.05 \)), and with a lower total bone (\( r = -0.177, r^2 = 0.031; \text{adj.} p = 0.016 \)), cortical (\( r = -0.136, r^2 = 0.019, \text{adj.} p = 0.019 \)), and trabecular (\( r = -0.160, r^2 = 0.026; \text{adj.} p = 0.036 \)) BMD documented by pQCT in the radius. The lumbar spine BMD and the apparent volumetric BMD of femoral neck were reduced when ICS were used regularly before 6 years of age (\text{adj.} p < 0.05). Similar age-specific changes were not found in the radius or the tibia. No significance was found for distal tibia. The results remain similar after adjusting with known confounding factors.

In conclusion, overweight and obesity were significant risk factors for reduced lung function at school age in this asthma-risk group. The present study did not reveal a connection between asthma and overweight. The use of ICS during childhood may reduce BMD measured during early teenage years. Children suffering from early-life wheezing should avoid excessive weight gain during childhood and use the lowest sufficient ICS dose to maintaining adequate asthma control.

National Library of Medicine Classification: WD 210, WD 300, WE 270, WS 288
Medical Subject Headings: Hypersensitivity; Asthma/Therapy; Bone Density; Bronchial Hyperreactivity; Bronchiolitis; Child; Absorptiometry, Photon; Follow-Up Studies; Tomography, x-ray; Obesity; Airway Obstruction; Overweight; Spirometry; Respiratory Sounds
Sidoroff, Virpi.
Weight, Asthma and Bone Mineral Density: A Prospective Follow-Up Study after Early Childhood Wheezing
University of Eastern Finland, Faculty of Health Sciences

ISBN (print): 978-952-61-1312-8
ISSN (print): 1798-5706
ISSN (pdf): 1798-5714
ISSN-L: 1798-5706

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TIIVISTELMÄ:
Ylipainoisten lasten astmariski on lisääntyyn, mutta yhdistävät tekijät astman, allergioiden, keuhkojen toiminnan ja ylipainon välillä ovat epäselviä. Lasten astman hoidossa hengitettävien kortikosteroidien (ICS) käyttö on yleistä. Tiedot ICS-lääkityksen pitkäaikaishaitta luustolle ovat puutteelliset. Vuosina 1991-1992 aloitettiin seurantatutkimus astman riskitekijöistä varhaisen hengenahdistuksen jälkeen. Tutkimukseen rekrytoitiin 100, 1-23 kuukauden ikäistä, sairaalahoitoon hengenahdistuksen takia joutunutta lasta. Tutkimuskäyntit totetutuvit 4.0, 7.2 ja 12.3 vuoden keskimääräisessä iässä sisältäen lääkärin tutkimuksen, pituuden ja painon mittaukset ja allergiatutkimukset ihopistokokeina. Kouluiässä tutkittiin keuhkojen toimintaa ja hyperreaktivisuutta spirometrialla ja juoksurasituskokeella. 12.3 vuoden iässä luustontiheys tutkittiin kahdella eri radiologisella menetelmällä: Dual energy x-ray absorptiometryllä (DXA) ja perifeerisellä kvantitatiivisella tietokonetomografialla (pQCT). ICS-kokonaisannokset ja käyttöaika laskettiin haastatelujen ja sairaskertomusten perusteella. Luustontiheys tutkimukseen kutsuttiin mukaan 14 lasta, jotka oli rekrytoitu tutkimukseen, mutta jotka eivät osallistuneet alun hoitotutkimukseen. Seurantakäynneille osallistu i 82/100 lasta 7.2 vuoden iässä, 81/100 lasta 12.3 vuoden iässä ja 89/114 lasta osallistui luustotutkimukseen 12.3 vuoden iässä. Lapsista 38% oli astmaatikkoja, 33% ylipainoisia ja 20% lihavia. Astmalla tai keuhkojen hyperreaktiivisuudella ja tutkimushetken ylipainolla 12.3 tai 7.2 vuoden iässä ei todettu keskinäistä yhteyttä. Tutkimushetken ylipainolla todettiin yhteys alentuneeseen (nopean uloshengityksen vitaalikapasiteetin ja uloshengityksen sekuntikapasiteetin suhteeseen (FEV1/FVC) spirometriassa 7.3 ja 12.3 vuoden keskimääräisessä iässä. Pienten ilmateide n virtaus todettiin matalammaksi ylipainoisilla lapsilla 12.3 vuoden iässä. Todetut yhteydet säilyivät merkittävinä myös vakioita analyysi varhaisen hengenahdistuksen virusetiologialla ja astmalääkityksellä kouluiässä. Seurannan aikana 73 lasta sai jaksoittain ICS-lääkitystä, 16 lasta ei saanut tutkimusaikana ICS-lääkitystä. Keskimääräinen kokonaislääkeannos oli 517mg (vaihteluväli 21-1813mg). ICS-annoksen ja reisiluunkaulan matalamman luuntiheyden (DXA) välillä todettiin yhteys (r = −0.320, r² = 0.10, vakioitu. p < 0.05). Myös ICS-annoksen ja matalamman radiuksen (pQCT) kokonaisluuntiheyden (r = −0.177, r² = 0.031; vakioitu. p = 0.016), kortikaalisen (r = −0.136, r² = 0.019, vakioitu. p = 0.019) ja trabekulaarisen (r = −0.160, r² = 0.026; vakioitu. p = 0.036) välillä todettiin yhteys. Lannerangan luuntiheys (DXA) oli matalampi niillä lapsilla, joilla ICS-lääkitys oli toestutunut säännöllisesti vain alle 6-vuotiaana (vakioitu. p < 0.05). Käyttöikään sidonnaisia muutoksia ei todettu radiuksessa tai tibiassa. TIBI-analyyssissä merkittäviä yhteyksiä luustontiheyden ja ICS-lääkityksen osalta ei löydetty. Tulokset säilyivät samanlaisina tunnetuilla sekoittavilla tekijöillä vakioimisen jälkeen. Yhteenvetona voidaan todeta ylipainon ja lihavuuden ole van merkittävä riskitekijä alentuneelle keuhkojen toiminnalle kouluiässä niillä lapsilla jo suurentunut astmariski. Tämä tutkimus ei osoittanut yhteyttä astman ja ylipainon välillä. Varhaisen hengenahdistuksen jälkeen normaalipainoon pyrkiminen edistää keuhkojen toimintaa. Lapsuudessa käytetty ICS-lääkitys voi vaikuttaa luustontiheyteen myöhemmässä kouluiässä ja nuoruudessa. Astmalääkitystä tarvitsevilla lapsilla tulee pyrkiä aktiivisesti pienimpään ICS-annokseen, millä hoitotasapaino säilyy hyvänä.
TYTÖSTÄMÄ:


To my family
To my family
Acknowledgements

This follow-up study was carried out in Kuopio University Hospital, Department of Pediatrics in 1992-2004. I want to thank former heads of the department of Pediatrics who have enabled the primary study and long follow-up time. Researchers, Tiina Reijonen, MD, PhD, Anne Kotaniemi-Syrjänen, MD, PhD collecting the previous follow up data I used in my study, they are warmly acknowledged.

I am honored I got Professor Matti Korppi, MD, PhD as my primary supervisor. He is the heart and soul of this long follow up study. His guidance to the fascinating world of research has been dedicated, warm and always encouraging. The research skills he has taught me helped me until the end of the project and reach forward. I would like to thank him also for companionship when travelling to congresses and our friendship that grew during those days. It has been a pleasure to work under his guidance.

I own my deepest thanks to my second supervisor Mari Ylinen, MD, PhD for introducing me to the data she carefully collected. I learned from her the practical skills of research work and the conventions of presenting research to academic audiences. She has been an excellent help and support during this project and I revere her skill to notice all incoherence in manuscripts. She is also a dear friend of mine, which I found especially precious.

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I express my sincere thanks to my co-writers: Eija Piippo-Savolainen, MD, PhD for participating in the study design when I started this project, Liisa Kröger MD, PhD for her large knowledge of children's bone density and friendly discussions and support, Professor Heikki Kröger, MD, PhD for encouragement with bone study and his knowledge on this large area and Toni Rikkonen, PhD for doing bone mineral density measurements and introducing the methods to me.

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My warm thanks belong also to personnel at the Department of Clinical Physiology and Nuclear Medicine for organising the bone mineral density measurements I analysed in these theses and all the other clinics I could trust when handling this follow up data.

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My special thanks belong to my colleagues in the North Karelia Central Hospital for their interest in my research; their simple question: “How are things going with the study?” mean a lot to me. I would also like to thank them for guidance in the clinical world of paediatrics. My special thanks belongs to Marketta Dalla Valle, MD my tutor, for long conversations we have had and friendship during these years, Tiina Reijonen, MD, PhD for warm support and encouraging my self-confidence as researcher and head of department Risto Lantto, MD for his reassuring comments.

I send my thanks also to Cambridge NHS University Hospital Addenbrookes to Dr. Richard Iles under whose supervision I spend magnificent three months at the summer 2012 and learned many new things about lung development and lung function of children and to Dr. Theodore Dassios for his companionship during research exchange.

I gratefully thank all my friends for their friendship and the wonderful moments I have shared with you. I express my deepest thanks to my mother in law Hilkka Sidoroff, for all the help she has offered me in household work and for taking care of our children. Without her practical help I would not be able to complete this work.

I express my loving thanks to my parents Leena and Esko Pietikäinen, from whom I have learned the most valuable things in life. I thank them for the love and encouragement they give me throughout my life. Alongside them I give my loving thanks to my sisters Soile Pietikäinen and Anu zu Dohna, for all the joys and worries you have shared with me and all the support and unofficial English language editing you have done. I also thank their husbands Paolo Deluca and Constantin zu Dohna and my niece Venla and nephews Lari, Mikael and Samuel for the relaxing time I have spent with you all.

Finally, the most special thanks belong to my dear husband Mikko, who has shared life with me and whose love and never-ending trust in my ability has carried me through these hectic years. Mikko and our beloved children Jeremia, Katariina and Irene bring sunshine to my life every day.

Financially this study was supported by the National Paediatric Research Foundation, Tampere Tuberculosis Foundation, and National Graduate School for Clinical Investigations, North Karelia Central Hospital and University of Eastern Finland, which are sincerely acknowledged.

Joensuu, November 2013

Virpi Sidoroff
List of the original publications

This dissertation is based on the following original publications:


IV  Sidoroff V, Rikkonen T, Hyvärinen MK, Kröger L, Kröger H, Korppi M. Inhaled corticosteroids and bone mineral density by quantitative computed tomography: 11-year follow-up after early-life wheezing. *Submitted*

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<tr>
<td>AD</td>
<td>Atopic dermatitis</td>
<td>FEV1</td>
<td>Forced expiratory volume in 1 sec</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
<td>FEV1/FVC</td>
<td>Forced expiratory volume in 1 sec/forced vital capacity</td>
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<tr>
<td>aOD</td>
<td>Adjusted odds ratio</td>
<td>FRC</td>
<td>Functional residual capacity</td>
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<tr>
<td>AR</td>
<td>Allergic rhinitis and allergic rhinoconjunctivitis</td>
<td>FVS</td>
<td>Flow-volume spirometry</td>
</tr>
<tr>
<td>aBMD&lt;sub&gt;vol&lt;/sub&gt;</td>
<td>Apparent volumetric bone mineral density</td>
<td>FVC</td>
<td>Forced vital capacityICS</td>
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<tr>
<td>BHR</td>
<td>Bronchial hyperreactivity</td>
<td>MEF50</td>
<td>Maximal expiratory flow at 50% of FVC</td>
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<td>BMI</td>
<td>Body mass index</td>
<td>MEF25</td>
<td>Maximal expiratory flow at 25% of FVC</td>
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<tr>
<td>BMI-SDS</td>
<td>BMI standard deviation score (z-score)</td>
<td>NPA</td>
<td>Nasopharyngeal aspiration</td>
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<tr>
<td>BMD</td>
<td>Bone mineral density</td>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>BMD&lt;sub&gt;areal&lt;/sub&gt;</td>
<td>Areal bone mineral density</td>
<td>PBM</td>
<td>Peak bone mass</td>
</tr>
<tr>
<td>BMD&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>Bone mineral density of total bone</td>
<td>PFT</td>
<td>Pulmonary function test</td>
</tr>
<tr>
<td>BMD&lt;sub&gt;trab&lt;/sub&gt;</td>
<td>Bone mineral density of trabecular bone</td>
<td>pQCT</td>
<td>Peripheral quantitative computed tomography</td>
</tr>
<tr>
<td>BMD&lt;sub&gt;cort&lt;/sub&gt;</td>
<td>Bone mineral density of cortical bone</td>
<td>RSV</td>
<td>Respiratory syncytial virus</td>
</tr>
<tr>
<td>BMC</td>
<td>Bone mineral content</td>
<td>SPT</td>
<td>Skin prick test</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
<td>TBMC</td>
<td>Total bone mineral content</td>
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<td>cOD</td>
<td>Crude odds ratio</td>
<td>TLC</td>
<td>Total lung capacity</td>
</tr>
<tr>
<td>DXA</td>
<td>Dual-energy X-ray absorptiometry</td>
<td>TV</td>
<td>Tidal volume</td>
</tr>
<tr>
<td>ECT</td>
<td>Exercise challenge test</td>
<td>WC</td>
<td>Waist circumference</td>
</tr>
<tr>
<td>ERV</td>
<td>Expiratory reserve volume</td>
<td>WHR</td>
<td>Waist–hip ratio</td>
</tr>
<tr>
<td>FE&lt;sub&gt;No&lt;/sub&gt;</td>
<td>Exhaled nitric oxide</td>
<td>BMD&lt;sub&gt;vol&lt;/sub&gt;</td>
<td>Volumetric bone mineral density</td>
</tr>
</tbody>
</table>

**Additional Terms:**
- BHR: Bronchial hyperreactivity
- BM: Bone mineral density
- BMD<sub>areal</sub>: Areal bone mineral density
- BMD<sub>tot</sub>: Bone mineral density of total bone
- BMD<sub>trab</sub>: Bone mineral density of trabecular bone
- BMD<sub>cort</sub>: Bone mineral density of cortical bone
- BMC: Bone mineral content
- CI: Confidence interval
- cOD: Crude odds ratio
- DXA: Dual-energy X-ray absorptiometry
- ERV: Expiratory reserve volume
- FE<sub>No</sub>: Exhaled nitric oxide
- ECT: Exercise challenge test
- ERV: Expiratory reserve volume
- FRC: Functional residual capacity
- FVS: Flow-volume spirometry
- FVC: Forced vital capacity
- FRC: Functional residual capacity
- MEF50: Maximal expiratory flow at 50% of FVC
- MEF25: Maximal expiratory flow at 25% of FVC
- NPA: Nasopharyngeal aspiration
- OR: Odds ratio
- PBM: Peak bone mass
- PFT: Pulmonary function test
- pQCT: Peripheral quantitative computed tomography
- RSV: Respiratory syncytial virus
- SPT: Skin prick test
- TBMC: Total bone mineral content
- TLC: Total lung capacity
- TV: Tidal volume
- WC: Waist circumference
- WHR: Waist–hip ratio
Wheezing illnesses during childhood are common and well-known risk factors for the later onset of asthma (1-3). There are several phenotypes of wheezing (3). The increasing prevalence of obesity has introduced new phenotype, obesity-induced wheezing, and later obesity-related asthma (4). The connection between overweight and asthma has been confirmed in epidemiological studies and meta-analyses (5,6). Overweight has an independent mechanical effect on lung function (5), and it may decrease lung compliance (7). In children, studies have shown that there are also benefits to lung function from weight gain (8), depending on the age during admission (9). Allergic diseases, like atopic dermatitis, have been associated with overweight (10), however with conflicting results (11). The mechanism may be different from the eosinophilic inflammation seen in allergic asthma, because obesity increases more the risk for non-atopic asthma (12). Asthma, lung function, and allergy are all related to overweight, but the interactions and causalities are still unknown.

Inhaled corticosteroids (ICS) are recommended widely as the first line of therapy for asthma (13,14), and the benefits of ICS treatment are undeniable (15). Growth retardation is the most monitored side effect of ICS medication, lately shown to cause only minor effects on adult height (16). Although safer than systemic corticosteroids, ICS can potentially cause detrimental effects on bone health (17). In clinical trials and follow-up studies, ICS have been safe for bone mineral density (BMD) (18-20). In childhood asthma, ICS medication could be long lasting and continue throughout rapid growth periods in early childhood and teenage years when BMD accretion is also rapid (21). The long-term consequences of decreased BMD accretion in childhood and adolescence are not known. Dual-energy x-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT), both low in radiation, are accepted methods of measuring BMD in children (22). There are references for paediatric BMD measured with DXA but not with pQCT, but the threshold describing significantly low BMD is not known for either method (23,24).

The purpose of the present study was to evaluate the effect of overweight on asthma, allergies, and lung function in children known to have a higher asthma risk after severe early childhood wheezing and to assess the impact of ICS on BMD at the median age of 12.3 years.
1 Introduction

Wheezing illnesses during childhood are common and well-known risk factors for the later onset of asthma (1-3). There are several phenotypes of wheezing (3). The increasing prevalence of obesity has introduced new phenotype, obesity-induced wheezing, and later obesity-related asthma (4). The connection between overweight and asthma has been confirmed in epidemiological studies and meta-analyses (5,6). Overweight has an independent mechanical effect on lung function (5), and it may decrease lung compliance (7). In children, studies have shown that there are also benefits to lung function from weight gain (8), depending on the age during admission (9). Allergic diseases, like atopic dermatitis, have been associated with overweight (10), however with conflicting results (11). The mechanism may be different from the eosinophilic inflammation seen in allergic asthma, because obesity increases more the risk for non-atopic asthma (12). Asthma, lung function, and allergy are all related to overweight, but the interactions and causalities are still unknown.

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2 Review of the Literature

2.1 WHEEZING ILLNESSES IN CHILDHOOD

The aetiology of wheezing in early childhood is multifactorial, including virus infections, allergies, and environmental factors (2,25). Bronchiolitis is the most common acute illness and cause of hospitalisation in infancy (26). According to American and British guidelines, bronchiolitis is the first respiratory viral infection with symptoms and signs of respiratory effort and wheezing in children less than 2 years of age (27,28).

The prevalence of bronchiolitis during the first year of life is 18%–32% and 9%–17% during the second year (3,27,29). The hospitalisation rate is 1%–3%; hospitalisation is highest among babies less than 6 months of age (30). A respiratory syncytial virus (RSV) is the most common virus resulting in hospitalisation (31,32), and another common aetiology of bronchiolitis in older children is a human rhinovirus, a known risk factor for later asthma (33).

Some of the children diagnosed with bronchiolitis in infancy suffer episodic wheezing during childhood, and some of them are diagnosed with asthma later (34). Because of the heterogeneity in the aetiology of wheezing, the diagnosis of bronchiolitis is used only for children less than 12 months of age in some studies (25,35) and clinical guidelines (36,37). Actually, the first classification of acute respiratory infections in children defined bronchiolitis as being diagnosed to children under 6 months of age (38).

2.2 ASTHMA IN CHILDHOOD

2.2.1 Worldwide prevalence

Asthma is a chronic inflammatory disease with variable airflow obstruction and bronchial hyper responsiveness. Symptoms include recurrent episodes of wheezing, shortness of breath, and cough (13). Asthma prevalence has increased since the 1970s (39).

According to the International Study of Asthma and Allergies in Childhood (ISAAC), the prevalence of asthma in children 6–7 years of age varies from 4% in Northern and Eastern Europe up to 29% in Oceania and in teenagers 13–14 years of age from 5% to 22% in the respective regions (40). Further, asthma prevalence in English-speaking centres was 28% in childhood and 20% in teenage years (40). During the last 10 years, the prevalence of asthma symptoms has slightly decreased or reached a plateau in Western countries (41,42).

Asthma prevalence figures from Finland are old. The prevalence has been between 4%–8% in 13- to 14-year-old adolescents (43). In the Kuopio region, the lifetime prevalence of asthma in a population-based study has been estimated to be 4% in 7- to 12-year-old children (44).
2.2.2 Asthma phenotypes and epidemiological risk factors for asthma
Childhood asthma is a multi-origin disease. Several phenotypes have been illustrated with different origins, severities, treatments and outcomes, as summarised in recent reviews (13,45). The common phenotypes described for wheezing and asthma during childhood are early-onset transient, early-onset persistent and late-onset wheezing (45). Classifications into virus-induced, allergy-induced, multi trigger, exercise-induced, and obesity-related have also been used (13).

In the longitudinal birth cohort studies, the major risk factors for asthma and wheezing include the parents’ history of asthma, the child’s atopy or atopic dermatitis in the first year of life, other allergic diseases, and maternal smoking during pregnancy (2,29,45-48). In cross-sectional paediatric studies, risk factors have been similar (3,46), and they have emphasised the role of early immunoglobulin E (IgE) sensitisation in later wheezing symptoms (3).

The late onset of wheezing, at over 3 years of age, has been associated with increased asthma risk (47). Persistent wheezing has been associated with abnormalities in lung function in children 6 years of age, which could lead to asthma in adulthood (49). The virus infections in the first years of life, especially RSV and rhinovirus infections are risk factors for asthma (33,50-52). Rhinovirus infections are also associated with asthma exacerbations at all ages (53).

Recently, genetic, nutritional and environmental factors have been new focuses of asthma studies (54,55).

2.3 GUIDELINES TO THE DIAGNOSIS AND MANAGEMENT OF BRONCHIOLITIS AND CHILDHOOD ASTHMA

2.3.1 Diagnosis and management of bronchiolitis
There is neither an explicit diagnostic tool for bronchiolitis (26) nor consensus about treatment; therefore, the care of patients varies between hospitals (56). The national and international guidelines recommend that diagnosis of bronchiolitis should be based on current epidemiologic data and clinical examination; laboratory tests and a chest x-ray should not routinely be taken (27,57).

Management of bronchiolitis should include monitoring whether oxygen supply and proper hydration are needed (27,57). Bronchodilators should not be used routinely and should be continued only if there is a positive response. The routine use of corticosteroids should also be avoided (27). Although there is evidence showing that oral dexamethasone together with inhaled adrenaline could shorten the length of hospitalisation (36). A meta-analysis demonstrated the effectiveness of inhaled adrenaline alone for bronchiolitis (58), but a recently published large double blind study showed a uniform effect between racemic adrenalin and NaCl inhalations, and an on-demand medication was more beneficial compared to the fixed schedule (59). Inhaled hypertonic saline is a promising new therapy (36). For severe bronchiolitis, nasal continuous positive airway pressure (NCPAP) has been used successfully, and it might decrease the need of intubation and ventilation in small babies (60).
2.3.2 Diagnosis and management of childhood asthma
There are national and international recommendations for the diagnosis and management of childhood asthma (13,14,61). In the Finnish guidelines, asthma can be clinically diagnosed in small children if they have had three wheezing episodes in a 1-year period, and there are one or more risk factors for asthma (i.e., atopic disease or parental asthma exists) (14). From 3 years of age, in both national and international guidelines, tests showing abnormal lung function are recommended, and for school-aged children, it is compulsory to perform spirometry and/or an exercise challenge test (ECT) for asthma diagnosis (14,61,62).

ICS are the recommended first line of therapy for asthma in children and adults (13,14,15). The use of ICS has improved symptom control in asthma and decreased hospitalisation for asthma in children (15,34,63,64). Aside from and combined with ICS, montelukast and short- and long-acting β-agonists are used for asthma medication in children (13,14,34). ICS potentially cause side effects, and on the other hand, the common reason for treatment failure is compliance; therefore, it is important to optimise ICS treatment in children (65). There is evidence that the early treatment with anti-inflammatory therapy could prevent irreversible airway injury and improve lung function (65,66).

2.4 ASSOCIATION BETWEEN ASTHMA, LUNG FUNCTION, ALLERGY AND OVERWEIGHT IN CHILDHOOD

2.4.1 Definitions of overweight and obesity
The established definitions of overweight and obesity in adults are BMI > 25 for overweight and BMI > 30 for obesity. The definition is more complex for growing children. Age- and sex-specific BMI cut-offs based on national references are advisable to use. If such national references are not available, international references can be used, but that approach is less reliable (7,67). Based on international surveys, BMI > 91st percentile has been used to define overweight and BMI > 98th percentile to define obesity, corresponding with BMI > 25 and BMI > 30 in young adults (7,67). Definitions vary in different studies. For example, BMI > 95th percentile has been used as a cut-off point for overweight (68,69). In the United States, the recommended cut-off points (70) are BMI > 85th percentile for overweight and BMI > 95th percentile for obesity, which have been used in some studies (69,71). The BMI percentiles can be expressed as age- and gender-specific BMI standard deviation scores (BMI-SDS), also called z-scores.

Waist circumference (WC), waist–hip ratio (WHR), or skinfold thickness can be used to estimate overweight and body fat content (72,73). WC has been correlated nearly completely with age- and sex-specific BMI in children (74). Scanning methods and bioelectrical impedance are used to measure body fat in studies (73), but not in clinical practice.

2.4.2 Epidemiology of overweight and obesity in childhood
The prevalence of overweight and obesity is increasing in Europe (75) and worldwide (68,69). In Europe, the prevalence of overweight varies from 10% to 36% in 7- to 11-year-
old children and from 8% to 23% in 14- to 17-year-old children (75). In the United States, a plateau in the increase of overweight and obesity was reached in the 20th century (76), and the prevalence of overweight among adolescents has stayed between 16% and 17% (69). There is strong tracking with increased BMI from childhood and adolescence to adulthood (77,78).

The latest prevalence figures from Finland are from 2006. At that time, 9.8% of 5-year-old boys were overweight, and 2.5% were obese. The figures were 17.7% and 2.5%, respectively, for girls at the same age (79). At 12 years of age, the prevalence of overweight was 23.6% and obesity 4.7% in boys, and 19.1% and 3.2% in girls, respectively (79). In the Finnish birth cohort studies, combined information shows a trend of increased BMI in 12-to15-year-old boys and in 12-year-old girls (80).

2.4.3 Obesity-related illnesses in childhood
Overweight is a growing public health issue in childhood and adolescence (72,81). Obesity and overweight have been associated with poorer overall health, psychosocial health, as well as health-related quality of life (81-83). Further, overweight increases health care utilisation (84).

Overweight has been associated with low-grade inflammation, which was thought to be the link between obesity and metabolic syndrome (85). Type 2 diabetes is associated with obesity in adults and in children (72,86). The prevalence of non-alcoholic fatty liver disease is increased among overweight adolescents (87). Asthma and other respiratory illnesses and their symptoms are commonly associated with overweight (81,84). Childhood obesity is a risk factor for cardiorespiratory diseases and is associated with high blood pressure (88-91).

2.4.4 Lung function and overweight
Obesity causes mechanical changes in the airways, where the elasticity of the chest wall decreases, and the airway resistance increases (7). Obesity could lead to airway smooth muscle contraction, which induces restriction and impairment of lung function (5). In adults, obesity decreases total lung capacity (TLC), tidal volume (TV), expiratory reserve volume (ERV), functional residual capacity (FRC), and forced expiratory volume in 1 sec (FEV1) (5,7,92,93). Peripheral airway obstruction due to obesity has been documented by decreased flows at 50% of forced vital capacity (FVC) (MEF50) (93). Overall, it can be said that the restrictive pattern of lung function disorder has been more characteristic in obesity than the obstructive pattern.

In healthy obese children, the influence of obesity has been complex. In a Chinese survey, lung function was studied in 2,179 schoolchildren at the median age of 10 years. Among them, asthma-presumptive symptoms were more common in obese children, but in spirometry, FEV1 actually increased (94). In line with this, overweight had a beneficial effect on lung function in healthy 7- to 20-year-old girls in another study (8). In a Taiwanese study, lung function and bronchial hyperreactivity (BHR) were measured in 1,459 teenagers, and there was a decreased risk for BHR in the lowest BMI groups (95). In a population study of 5,993 children aged 7–12 years, all variables in the spirometry were, irrespective of BMI, within normal limits. But FEV1 and FVC in the lowest BMI quintile
were significantly lower than in other quintiles (96). No associations between BHR and BMI were found, but asthma and atopy were associated with high BMI in girls (96). In the other population study, lung function improved when weight increased in healthy 8- to 11-year-old children, but beyond that age, lung function first reached a plateau and then decreased among the obese youths (9).

Childhood weight can affect lung function in adulthood. In a Danish longitudinal population-based study, 193 obese and 205 non-obese men were studied, and their age-adjusted FVC and FEV1 were compared against birth weight, weight at 7 and 13 years of age, and current weight (97). Weight at 7 years of age was positively correlated with FEV1 and FVC in an analysis adjusted for current weight, smoking, and education. Current overweight was strongly associated with decreased lung function in an adjusted linear regression (97).

The exercise capacity of obese children is impaired; they have increasing breathing effort and more dyspnoea (5). In healthy pre-teenagers, body fat has predicted airways narrowing after exercise (98). In addition, overweight children have more behavioural problems, and they are physically less active (99).

2.4.5 Asthma and overweight; mechanism
The epidemics of asthma and obesity have proceeded concomitantly, and plenty of studies have evaluated the association between them. There is a consensus on the link between obesity and asthma or respiratory symptoms (5). A meta-analysis from cohort studies concluded that children with higher body weight are at greater risk for future asthma (6).

Obesity has been associated with more severe asthma symptoms (100-102) and reduced responses to asthma medication (103), leading to an increased use of medication (104). Birth weight has been associated with increased asthma risk at teenage years (105,106), but this is not so in all studies (107). In adults, weight loss has lessened asthma symptoms (108) and improved lung function in asthmatic patients (109).

Former studies have discussed whether obesity-related asthma is an own asthma phenotype—asthma with non-eosinophilic inflammation and decreased response to conventional asthma treatment (4,110).

The mechanism between obesity and asthma or lung function disorder in children is multifactorial (Figure 1). There is some evidence that asthma and obesity might share the same origins in early childhood (111). Common genes have been found for both conditions (100). Early-life factors like nutrition during pregnancy, an early childhood sedentary lifestyle, and exercise habits later might have an influence on both obesity and asthma (5,111). The other proposed mechanisms between overweight and asthma are reduced chest wall compliance, systemic inflammation, insulin resistance, and co-morbidities like gastro-oesophageal reflux or common genetic aetiology (5).
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Obesity leads to low-grade inflammation and the increase of adipokines and other obesity-related inflammatory mediators (5). Leptin, one of the adipokines, has been assumed to modulate the connection between obesity and asthma (113), being associated with both non-atopic (114) and atopic asthma (115). Results on other inflammatory mediators vary: resistin had a negative association with asthma in one study (116), and low adiponectin levels have been associated with an increased risk of allergic diseases and asthma (114), but another study found no association (117).

The asthma symptoms related to obesity have not been associated with BHR (100,118,119), or the results have been conflicting (119,120). Also, in studies where the association between asthma and obesity has been evaluated together with atopic sensitisation, the results for atopic sensitisation have been mostly negative (121,122). In adults, obese asthmatics have had lower exhaled nitric oxide (FE_{NO}) and sputum eosinophil levels (123). It is unlikely that allergic inflammation is the basis of the asthma-obesity relation (12,121).

Figure 1. Mechanisms between obesity, asthma and lung function in children, according to Jensen 2012 (112). Common factors can lead obesity and asthma; in obese children increased lean mass improves lung development and increased fat mass causes negative effects on lungs via complex pathways.
Obesity affects lung function itself and modifies the asthma-obesity connection. This topic is discussed further in detail in section 3.4. Other lung-related diseases like sleep-disordered breathing might also have an effect on obesity-related asthma (124).

Age could be one modifying component in the asthma-obesity relation in children, and it seems that the influence of obesity is more notable in younger children (125,126). Sex and race might modify the relation between asthma and obesity, but the results are too conflicting to confirm the association (104,119,127-131).

2.4.6 Asthma and overweight studies

Birth cohort studies
There are six large birth cohort studies evaluating the asthma-obesity relation in children. The most recent prospective birth cohort study from Brazil followed 4,439 children aged 10–11 and 14–15 years (132). They assessed asthma symptoms with an ISAAC questionnaire in both follow-up times. The prevalence of wheezing at 15 years of age and persistent wheezing at both 11 and 15 years of age was higher in obese children in adjusted analysis. The results were similar when obesity was measured with skinfold thickness (132). An Australian study found a significant association between the BMI z-score at 14 years of age and a change in the z-score from 5 to 14 years of age and parent-reported asthma, but the weight at 5 years of age did not predict asthma at 14 years of age (133). The National Longitudinal Survey of Youth (NLSY), with a 14-years of follow-up time, found an increased risk for asthma in boys—but not in girls—who were overweight (BMI > 85th percentile) at 2–3 years of age or during the whole follow-up time (134). In another cohort, BHR was measured, and they reported an association between persistent or current high BMI and dyspnoea or BHR at 8 years of age (120). An earlier high BMI, if it has become normal, was not a risk factor for either dyspnoea or BHR (120). Wheeze, asthma, and atopy were associated with BMI in females in one birth cohort study (127).

Under school age, the risk of getting asthma diagnosis was increased in overweight (> 85th percentile) and obese (> 95th percentile) children, especially in boys, and in non-atopic children (135). In the birth cohort study of children with a high genetic asthma risk, obesity at 1 year of age decreased asthma risk at 6 and 8 years of age, but being overweight at 5 years of age increased asthma risk (136).

Population-based cohort studies
A large population-based study from the United States used medical records to collect weight and height details and asthma diagnoses from 681,122 children at 6 to 19 years of age, and 10.9% of children currently had asthma (104). Overweight and obese children had higher asthma risk, and increasing weight was associated with increased corticosteroid use and emergency department visits (104). Greek schoolchildren, 6–11 years of age were studied in a cohort of 2,715 children; BMI > 85th percentile was an independent risk factor for asthma, but only in girls (131). A low birth weight was associated with asthma risk and overweight or obesity later in life amplified the risk of asthma in both girls and boys in a large study among junior high school students in Taiwan (106).
In a longitudinal study, high BMI and weight gain were reported to be risk factors for newly onset asthma in school-aged girls (137). Girls with the highest annual increase in BMI, compared with the lowest quintile, had a 1.5-fold risk to asthma, and boys in both the smallest and largest annual weight-change groups had an increased asthma risk (137).

The relation of asthma and obesity is consolidated in studies where asthma symptoms have been more severe in obese patients, like in a retrospective cohort study of 33,321 asthmatic children aged 5 to 17 years, recruited from Californian clinics and followed for 1 year, overweight and obesity increased the β-agonist use and increased the risk for oral corticosteroid prescriptions after adjusting the results with multiple confounding factors, (101).

In a population-based cohort study from Australia, females were at risk for adult-onset asthma if they were overweight or obese at 7 years of age, but lung function at 7 years of age did not correlate to later asthma (138). The Finnish prospective population-based cohort study did not find an association between asthma and increased BMI in childhood or adolescence, but in adulthood, there was an association between asthma and BMI and female gender (117).

Cross-sectional studies
Cross-sectional questionnaire-based studies have also connected asthma symptoms and reported asthma with obesity in children. Obesity associated with exercise induced respiratory symptoms in a questionnaire-based study in Belgium (139). Overweight was related to emergency department visits and also with hospitalisation and missing school days for asthma in boys in a study from United States (140). In a Spanish study, obesity was a risk factor for current severe non-allergic asthma in children (122). An older study from the United Kingdom found an association between asthma symptoms with obesity assessed by BMI, but not with skinfold measurement, and the association was stronger in girls, but only in multi-ethnic inner-city populations (141).

There are also studies with negative results, such as the National Longitudinal Survey of Children and Youth (NLSCY), which did not find any association between asthma and obesity in 11,199 children aged 4 to 11 years (142). In an Italian study, 554 asthmatics and 625 age-matched controls were studied, and BMI and asthma characteristics were registered, but with no connection between obesity and asthma. However, the children receiving ICS were more obese (143). In New Zealand, data from two surveys 10 years apart were compared; 900–1,300 children at 11 to 12 years of age attended the studies in 1989 and 2000. There was an increase in asthma symptoms and diagnoses between the years, but the difference was not explainable with an increase in BMI (118). In a later survey, BMI-SDS was associated with current wheeze, ICS use, and other drug use (118).

In summary, the asthma-to-obesity connection is obvious at an epidemiological level despite of some negative studies (Table 1), but the direction of the effect and the causality have thus far remained as open.
<table>
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<tr>
<th>Study population</th>
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<th>Method</th>
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<th>Obesity-associated findings</th>
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<td>Medical records</td>
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¹ The International Study of Asthma and Allergies in Childhood ISAAC
² Inhaled Corticosteroids ICS
³ Bronchial hyperreactivity BHR
⁴ The National Longitudinal Survey of Youth NLSY
⁵ National Longitudinal Survey of Children and Youth NLSCY
2.4.7 Lung function and overweight studies

Epidemiologic, birth cohort, cross-sectional, and case-control studies have been done to find out how obesity modifies lung function in asthmatic children and adults. There is a relation between asthma and obesity, but when pulmonary function and bronchial reactivity were studied objectively, the results were mainly negative.

Birth cohort studies

In the Tucson Children’s Respiratory Study (a birth cohort of 1,246 children), lung function, bronchodilator response, and peak expiratory flow variation were studied at 11 years of age, and respiratory symptoms and weight status were measured at 6 and 11 years of age (119). An association was revealed between weight gain before puberty and an increased risk of new asthma diagnoses and BHR at 11 years of age (119). In another birth cohort study from New Zealand, high BMI was associated with asthma and atopy, but inversely associated with FEV1/FVC in 9- to 26-year-old females, and no association between weight and BHR was found (127).

Clinical trials and case-control studies

A large clinical trial, Childhood Asthma Management study (CAMP), found an association between higher BMI and increased FVC and FEV1, but decreased FEV1/FVC ratio (144). In a later analysis from the CAMP study, lung function reduction was also associated with a decreased response to inhaled budesonide in overweight and obese children compared with normal-weight asthmatic children (103).

A case-control study from Italy compared lung functions of 118 pre-pubertal children; the groups were obese asthmatic, normal-weight asthmatic, obese non-asthmatic, and normal-weight non-asthmatic children (145). Asthma had an independently significant association with lung function and airway inflammation. Obesity was related to PEF and MEF75 in a multivariate analysis, but obesity and BHR were not related. FEV0.60 was significantly higher in asthmatic children, but was also increased in obese non-asthmatic children compared with normal-weight non-asthmatic children, suggesting the presence of obesity-induced pro-inflammatory changes (145). Another study with similar groups of 7- to 11-year-old children performed the pulmonary function test in 120 children, and obese asthmatic patients had the lowest FEV1/FVC ratio when compared with other groups (110). In an adult study, lung function was reduced in patients with asthma and obesity, and in addition, FVC and FRC were also reduced in obese non-asthmatic adults (146).

Cross-sectional and cohort studies

Recently, a cross-sectional French study explored the relation of weight status and asthma characteristics in 491 asthmatic children aged 6–15 years (147) and found a positive association between weight and FVC or FEV1 in females, but overweight and obese children had reduced TLC and residual volume/TLC (147).

In a large population-based study from Israel, obese children wheezed more frequently, and asthma diagnoses were more common among them, but no association between overweight or obesity and lung function was found (148). In fact, BHR was more
common among non-obese asthmatic children compared with obese asthmatic children (148). In another study, peak expiratory flow rates (PEFR) from 1,322 asthmatic children aged 4–9 years were similar in obese (> 95th percentile) and normal-weight children, but obese children had more symptoms, emergency hospital visits, and oral corticosteroids intake (149). In a Greek schoolchildren cohort, a high BMI was an independent risk factor for asthma and atopy. In addition, FVC, FEV1, MEF25–75%, and FEV1/FVC were reduced in overweight (> 85th percentile) children, but no difference was found between asthmatic and non-asthmatic children (131). In an asthma referral population, no differences were found in lung function between obese and normal-weight 4- to 18-year-old children (150).

In adults, obese (BMI > 30) patients with difficult-to-treat asthma had higher FEV1% and lower FRC/TLC% than non-obese patients, with no correlation between obesity and FEV1 (123). Also, an epidemiological study failed to show any association between obesity and obstruction or BHR in a population where weight and asthma and airway symptoms were associated with one another (151).
In summary, overweight might have an independent effect on lung function, but studies are too controversial to make any final conclusions. Obesity seems not to provoke BHR in children.

### 2.4.8 Allergic diseases and overweight; mechanism

Allergy and overweight have increased concomitantly like asthma and overweight, but the connection is less studied. Allergic diseases were surveyed in the ISAAC study (152). The trends in prevalence of allergic diseases varied and allergic rhinitis/rhinoconjunctivitis (AR) and atopic dermatitis (AD) have increased more than asthma in the last decade (152). AR prevalence in Europe varies between 2.9%–10% in younger children and between 4.5%–20% in teenagers, and AD prevalence varies between 2.5%–22% and 2%–15.6%, respectively (152).

There are studies where atopy or allergic diseases are associated with overweight (95,96,127,131,153), but several studies have not been able to confirm the association (120,139,154,155). High BMI has not been an independent risk factor for allergy when adjusted with asthma (121,122). The connection between allergic diseases and obesity is complex and dependent on age (10) and sex (11,139). The increased eosinophilic inflammation due to overweight is probably not the main mechanism between atopy and overweight (12).

Fat tissue produces inflammatory mediators; these changes in inflammatory mechanism have been assumed to explain the relation between overweight and allergic diseases like overweight and asthma association. In a large German study, low adiponectin levels and symptoms of AD and diagnosed AD correlated, whereas high leptin was associated with higher incidence of non-allergic asthma, but no associations were found between adipokines and hay fever or AR (114).
2.4.9 Allergy and overweight studies

Population-based studies
In the large National Health and Nutritional Examination Survey (NHANES) 2005–2006 from a cohort of over 4,000 children, overweight and obesity were associated with higher IgE levels, and atopy and food allergies increased among obese children (153). A Japanese questionnaire study found conflicting results; in 50,868 non-selected schoolchildren, obesity was related to higher atopic sensitization and AD prevalence, but lower BMI was related to higher AR and atopic conjunctivitis prevalence and the association was stronger in boys (11). A third large population study was done in Belgium in 1,576 non-selected schoolchildren, where atopic sensitization was increased among underweight girls, but no association was found between obesity and allergic respiratory symptoms, AD, or AR (139). When clinical data of 5,999 children from seven epidemiological studies were combined, a significant association was found between allergy and overweight, but only in girls (96).

Case-control and longitudinal birth cohort studies
In a practice-based case-control study, 414 children and adolescents with AD were compared with 828 healthy controls aged 1–21 years during a 7-year follow-up time (10). Early childhood obesity, starting before 5 years of age, and prolonged obesity in childhood was risk factors for AD, and obesity was associated with more severe AD (10).

The longitudinal birth cohort follow-up study also found an association between weight gain and AD at 5 and 8 years of age, but no association between BMI and sensitisation in prick test was found (154). In a birth cohort study from New Zealand, 1,000 individuals were followed until 9–26 years of age, and an association was found between higher BMI and allergy in females, but not in males (127).

Cross-sectional studies
In a multi-centre cross-sectional study of 15,454 young adults from Europe, Australia, New Zealand, and the United States, obesity was not associated with AR or with atopic sensitization (155). In a cross-sectional Taiwanese study of 1,459 high school children, highest BMI quintiles had an increased risk for atopy (positive skin prick tests) and AR in adjusted analysis, but only for females (95). The more recent Taiwanese study of unselected schoolchildren reported a high prevalence of AR (47.8%) and eczema (10.8%) and atopic sensitization (57.3%) measured by IgE levels (156). Allergic diseases were more common among boys, and eczema incidence was slightly increased in obese children (156).

In Summary, the connection between obesity and AD has been documented, but for other atopic diseases, the results have varied.

2.5 BONE MINERAL DENSITY IN CHILDHOOD

2.5.1 Bone development during childhood and adolescence
Infancy and puberty are times of rapid bone accretion during childhood (21). Bones grow in size in parallel with BMD accrual (157). Bone mineralisation with the modelling and
remodelling process is essential for normal bone growth (158). The peak bone mass (PBM) is gained mostly during teenage years (159). The most rapid increase of BMD is at Tanner stages 4 and 5, and bone mass accretion continues over puberty (21,160). It has been estimated that 40%–62% of BMD is genetically determined (161). Normal skeletal development and bone growth are dependent on multiple factors, such as balanced nutrition, hormonal influences, and physical activity (24,158).

2.5.2 Risk factors for low bone mineral density
Race, sex, and ethnicity affect BMD. Individuals of Caucasian origin have lower BMD than blacks, already seen in childhood and adolescence (158,162,163). Females have lower BMD than males since adolescence, when adjusted with pubertal state (162). Late onset of puberty is an independent risk factor for low BMD (164).

The main nutritional variables affecting BMD are calcium and vitamin D. The American Academy of Pediatrics (AAP) guidelines recommended a daily dose of 10 µg vitamin D (165), and the Finnish national guidelines recommend 10 µg supplementation for children less than 2 years of age and 7.5 µg for children more than 2 years of age (166). New studies have shown that a low vitamin D level is more detrimental to Caucasians than blacks (163). The recommended daily calcium intake is 800–1,500 mg. An increase in the intake of milk and other dairy products is beneficial to bone mineralisation during childhood (167).

BMD is dependent also on physical activity (158,159,168). It has been estimated that an active lifestyle can be responsible for up to 17% of the BMD variation (159). How physical activity affects BMD is dependent on age and sex (161).

The impact of overweight on BMD has been controversial in previous studies. A recent study found an overweight-related decrease of cortical BMD in adult males, and an increase of trabecular BMD in adult females, who had overweight in adolescence (169). In another study, a reduced bone size was associated with high fat mass in 8-18 years old children (170). Two previous studies have reported negative results between overweight and BMD in children and adolescents when adjusted with fat mass, lean mass, and/or body weight (171,172). In a Finnish study, normal body fat content was beneficial to bone health during growth, whereas both obese and low-weight children and adolescents had lower BMD (173). Obese and overweight children and adolescents are prone to have fractures compared with normal-weight controls, though the mechanism is unknown and likely multifactorial (173,174). There is a remarkable tracking in BMD; children who have low BMD are also more likely to have low BMD in adulthood if effective interventions are not performed (175).

Chronic underlying illnesses including different neuromuscular disorders, endocrine diseases, gastrointestinal diseases, cystic fibrosis, juvenile arthritis and iatrogenic factors like corticosteroids and cancer treatments as well as a history of earlier fractures are significant risk factors for decreased BMD (24,176).
2.5.3 Bone mineral density measurements and low bone mineral density in childhood and adolescence

Bone is a composite tissue; it includes organic collagen and inorganic minerals forming a bone matrix and non-bone tissue (176). Trabecular and cortical bone are arranged differently depending on both the composition and geometrical structure. When measuring BMD, it is important to consider the bone’s tissue type, mass, and volume (176). During growth, the proportions of trabecular and cortical bone vary, and therefore, the total BMD is usually used to measure BMD changes during childhood (176). The difference between bone growth and actual BMD accretion needs attention when measuring BMD in children. In areal BMD (BMD_{areal}), BMD increases when the bone size grows, though volumetric BMD (BMD_{vol}) remains the same (176). BMD_{areal} is highly dependent on the bone size and height of the child, and thus, BMD is underestimated in children of short stature (177,178). Therefore, mathematical models have been developed to estimate apparent volumetric BMD (aBMD_{vol}) (179,180).

DXA is the most common method for measuring BMD in children and adults. The common sites are whole body, lumbar spine and femoral neck. DXA measures two-dimensional BMD_{areal} (g/cm²). Quantitative ultrasound (QUS) is easy to use for peripheral bone sites like calcaneus or tibia, and no radiation is needed for measuring. However, both bone size and cortical thickness affect the results; this is the limitation of the method (176). pQCT allows the measurement of BMD_{vol} (g/cm³) in radius or tibia and the evaluation of cortical and trabecular bone separately, and, in addition, the approximation of bone strength (176,181). The radiation dose in both DXA and pQCT is low, and it is acceptable to use these methods for evaluating growth and development of bone in growing children (22). In pQCT examinations, the radiation is < 3 µSv per scanning (182). The natural background radiation in Finland is 0.04–0.30 µSv/h (183).

The International Society for Clinical Densitometry (ISCD) has published recommendations for paediatric bone density measured by DXA (184). Age-, gender-, and height-specific reference values should be used and presented as z-scores. Instead of osteopenia or osteoporosis, the term “low bone mass for chronologic age” is recommended to be used when the BMD z-score is less than −2.0 SD (184). The osteoporosis diagnosis should be based on a clinically significant fracture history and a low BMD in DXA measurement (177,184). The threshold for an increased fracture risk in children is not known (24,177).

### 2.6 INHALED CORTICOSTEROIDS, SIDE EFFECTS AND BONE HEALTH IN CHILDREN

ICS are the drug of choice for an anti-inflammatory therapy of asthma. Beclomethasone dipropionate, budesonide, fluticasone propionate, and triamcinolone are in clinical use in Finland. ICS have different efficacy and safety profiles (185). Altogether, absorption from the lungs, absorption of swallowed ICS, and first-pass inactivation influence the level of corticosteroids in systemic circulation and systemic side effects (185).

Systemic corticosteroids have severe side effects on bone metabolism, mineralisation, and growth (185). Direct effects on bone tissue consist of the suppression of...
osteoblast activity and the promotion of osteoclast activity, and indirect effects are due to secondary hypogonadism, secondary hyperparathyroidism, and decreased secretion of adrenal androgens (185). Corticosteroids cause a decrease in both cortical and trabecular BMD (186). ICS have less side effects than systemic corticosteroids, and the benefits of ICS in the treatment of asthma are undeniable (15,17). The main concerns when ICS have been used for a long time are the potential harmful effects on children’s growth and BMD.

2.6.1 Inhaled corticosteroids and bone mineral density studies

**Short-term observational studies**
Most of the studies evaluating the association between ICS therapy and BMD in children and adolescents have been cross-sectional or short-term longitudinal studies. The studies have not been able to reveal any association between ICS use and BMD or bone biomarkers (187-195). In these studies, BMD\_areal has been measured by DXA in the lumbar spine region.

The most recent study examined 230 asthmatic pre-pubertal children and 170 controls at the median age of 8.9 years (196). Participants had used fluticasone propionate for at least 5 years with a 200 µg mean daily dose, and controls were newly diagnosed asthma patients with no history of ICS medication. BMD was measured from the lumbar spine with DXA, and z-scores were compared between cases and controls. There were no significant differences between the groups in BMD or in cortisol and osteocalcin levels measured at the same time (196).

Density-related ultrasound was applied in one study (187). Some tendency to reduced BMD was observed in 173 asthmatic children, among whom 56% used ICS. The medium daily dose as fluticasone equivalents was 286 µg for 6 months, and in this group, there were significantly more children with reduced BMD. As expected, consumed ICS doses were dependent on asthma severity, and higher physical activity was associated with better asthma control (187).

**High-dose observational studies**
The use of ICS with high doses was evaluated in two studies (197,198). In a cross-sectional study, 49 asthmatic children aged 5–19 years who were treated with a daily dose of > 1,000 µg inhaled fluticasone propionate were compared with 32 healthy controls. There were no significant differences in biochemical markers or in sex-specific, age-related, bone age-corrected BMD, measured from the total body and from the lumbar spine (197). In contrast, a study of 76 pre-pubertal asthmatic children receiving budesonide propionate > 800 µg and, in addition, periodical oral corticosteroids had lower weight-adjusted BMD in the lumbar spine compared with children receiving 400–800 µg of budesonide propionate or no ICS at all (198). Weight was an independent predictor of BMD in multivariate analysis (198).

**Long-term observational studies**
Long-term studies have not revealed significant changes in BMD in children treated with ICS (18,19,63).
In the longest follow-up of children with asthma thus far, the CAMP study, the cumulative ICS dose was associated with decreased bone mineral accretion, seen only in boys, in 7 years’ follow-up time (18). Oral corticosteroids were allowed when necessary, and their use produced a dose-dependent reduction in bone mineral accretion, again seen only in boys (18).

In a Danish study, 157 asthmatic children receiving inhaled budesonide and 111 without ICS medication were followed up for 3–6 years. The total body BMD was measured by DXA, and no significant differences were observed in BMD, bone mineral content, total body calcium, or body composition between the groups (19).

The dependence between height and BMD needs special attention in long-term follow-up studies, in which the measured BMDarea could increase when the bone grows without any increase in BMDvol (24).

**Randomised and controlled trials**

Three randomised and controlled studies were done to test the ICS effect on BMD (20,63,199,200). In the French study, 174 children aged 6 to 14 years with persistent asthma were randomised to receive 200 µg of inhaled fluticasone propionate or 8 mg of nedocromil sodium daily. BMD was measured by DXA in the lumbar spine and the femoral neck at baseline, and 12 and 24 months later, and no significant differences were found between the groups (63).

The Finnish randomised, controlled, double-blind study included 136 children aged 5–10 years with recently diagnosed asthma (20). Two study groups received 200 µg of budesonide daily for 18 months or 200 µg of periodical budesonide daily when needed based on symptoms, and the control group received disodium cromoglycate daily for 18 months. BMD in the lumbar spine was measured by DXA before and after intervention. Daily treatment, but not periodical treatment, with budesonide diminished both BMD and height velocity compared with the group treated with daily disodium cromoglycate. However, the findings change to insignificant when adjusted with height. Authors concluded that changes in BMD interacting with changes in height suggest that a follow-up of children’s height might give an approximation of ICS effects on bone (20).

In a 15 years old randomised, controlled, double-blind trial, 23 children diagnosed with asthma, but without history of recurrent ICS medication, were allocated to receive 200 µg of fluticasone propionate and 400 µg of beclomethasone per day and were followed up for 20 months (199). DXA was performed at the baseline, and at the end of the study, and no significant difference in BMD between groups was found (199). The clear shortcoming of the study was the lack of control group with no ICS therapy; in addition, confounding factors were not included in the analysis (199).

**2.6.2 Inhaled corticosteroids and fractures**

ICS consumption can impair on BMD, but BMD is not parallel to fracture risk in childhood (201). Asthma is associated with an increased risk for injuries (202,203), and ICS use and bronchodilator therapies both have been associated with an increased fracture risk in children (201). Maybe, asthma itself, not inhaled medication to asthma, is the main factor for
increased fracture risk. The asthmatic children may have alterations in cortical bone geometry, not related to therapy, but seem to be related to an increased fracture risk (204).

2.6.3 Inhaled corticosteroids’ effect on growth
Glucocorticoids inhibit growth due to the decrease in growth hormone secretion, insulin-like growth hormone secretion, and direct inhibition of collagen synthesis (205). The use of ICS has been associated with temporary growth retardation in childhood, however with no significant effect on height in adulthood (17,206,207). This was confirmed in a recent review (208). Although the CAMP study reported a 1.2 cm decrease in adult height in children who used ISC during childhood, the decrease was seen after 2 years’ treatment, and it was not progressive or cumulative (16). There is preliminary evidence of the benefits of a new ICS, ciclesonide, which has resulted in less growth reduction than other ICS during the first years of treatment (208).

2.6.4 Other side effects of inhaled corticosteroids
The potential side effects of corticosteroids include adrenal insufficiency and hypothalamus-pituitary axis insufficiency, but the risk of hypoglycaemia is small if ICS are used with conventional doses (209,210). The risk increases if a high dose of ICS, especially fluticasone propionate, is used for a long time aside with topical and intranasal steroids (209). Patients using ICS have a dose-dependent risk of skin thinning and bruises as well as a risk of a cataract in adults (17). Available data does not show an increased risk to these less common side effects in children if low or moderate doses are used (210).
3 Aims of the Study

The principal aims of the present post-early-life wheezing study were to evaluate the association between weight status and asthma, allergy, and lung function at school age and to explore the association between the use of ICS during childhood and BMD assessed at later school age in children who suffered from severe wheezing in infancy.

The specific aims of the study were as follows:

1. to evaluate the association between weight status and asthma or allergy at preschool and school age after early childhood wheezing, with a special focus on the influence of emerging overweight, including the association between weight status and atopic sensitisation or bronchial reactivity;

2. to explore the association between overweight or obesity and lung function at school age after early childhood wheezing, with a special focus on the influence of an emerging overweight;

3. to study the association between the use of ICS during childhood and the $\text{BMD}_{\text{areal}}$ during adolescence by DXA in the lumbar spine and femoral neck and to compare $\text{BMD}_{\text{areal}}$ measurements and $\text{aBMD}_{\text{vol}}$ results;

4. to evaluate the association between the use of ICS during childhood and $\text{BMD}_{\text{vol}}$ during adolescence by pQCT in the distal tibia and radius.
4 Subjects and Methods

4.1 ORIGINAL STUDY DESIGN, ENROLMENT OF THE PATIENTS, AND BACKGROUND DATA

One hundred consecutive children hospitalised for respiratory-infection-associated wheezing at the age of 1–23 months were recruited into this follow-up study in 1992–1993 (211). Exclusion criteria were maintenance therapy for asthma, presence of a chronic cardiopulmonary disease or respiratory failure in admission. The wheezing episode was the first one in 87% of the included children (211).

Background data were collected by interviewing the parents during hospitalisation using a structured questionnaire, which included history of wheezing and AD, family history of asthma and other atopic diseases, information on maternal smoking during pregnancy, later exposure to tobacco smoke, and pets at home and day care attendance (212). Seven respiratory viruses, including RSV, were studied using antigen and antibody assays (213).

The aims of the primary study were to evaluate the acute-phase treatment of bronchiolitis and to start the prospective follow-up study to explore the impact of an early-life intervention with anti-inflammatory medicines, including ICS (212), and to reveal risk factors for asthma after early-life wheezing (213).

4.1.1 The early childhood intervention protocol

After hospitalisation, children were randomised into three intervention groups; 34 were treated with inhaled budesonide 1,000 µg per day for 8 weeks and then 500 µg per day for a further 8 weeks, and 34 were treated for 8 weeks with 80 mg of sodium cromoglycate per day and then 60 mg per day for a further 8 weeks (212). The control group consisted of 32 children who had no anti-inflammatory medication. The follow-up protocol included visits at 6 and at 16 weeks and at 8 and 12 months after the beginning of the study (213).

4.1.2 Virus determination

Seven viral pathogens were studied in nasopharyngeal aspirates (NPA) and paired sera, including both antigen and antibody tests for RSV (213). Later, frozen NPA samples were studied by polymerase chain reaction for RSV and rhinoviruses (214,215). In all, RSV was identified in 29 of 100 cases and rhinovirus in 27 of 81 cases (216).

4.2 FOLLOW-UP VISITS DURING CHILDHOOD

Three follow-up visits were prospectively organised after the intervention (Figure 2). Three years after the index wheezing, 83 children attended the preschool-age visit at 4.0 years of median age (217). Six years after the index wheezing, 82 children attended the early school-age visit at 6.3 years of median age (218). The third follow-up visit was arranged 11 years after the index wheezing, and 81 of 100 children attended the later school-age visit at 12.3 years of median age (50).
4.2.1 Medical examination and anthropometric measurements
A research doctor performed the medical examination at all follow-up visits (50,213,216,218). During each visit, an experienced nurse measured weight and height using a stadiometer and a calibrated weight scale. At the late school-age visit, a pubertal stage was examined and recorded (50,219,220). Parents and children were interviewed using a structured questionnaire and asthma and allergic symptoms during the preceding 12 months were recorded. Ongoing asthma medication was registered, and the use of ICS between follow-up visits was noted (50).

4.2.2 Definition of asthma and asthma prevalence at follow-up visits
At the preschool-age follow-up visit at 4.0 years of median age, 45 (51%) of 89 children were considered having asthma. The criteria for asthma were as follows: the child had continuous anti-inflammatory medication for asthma, or the child had suffered from two or more doctor-diagnosed wheezing episodes after the index wheezing (217). In the early school-age follow-up visit, asthma was present in 33 (40%) of 82 children. The criteria for asthma were as follows: the child had continuous inhaled anti-inflammatory medication for asthma, or the child had two or more parent-reported, doctor-diagnosed wheezing episodes or parent-reported prolonged (> 4 weeks) cough without infection during the preceding 12 months and the exercise challenge test (ECT) was pathological (218). At late
school-age visit, 32 (40%) of 81 children had asthma with the following criteria: the child had continuous or intermittent inhaled anti-inflammatory medication for asthma during the preceding 12 months, or the child had two or more parent-reported, doctor-diagnosed wheezing episodes or prolonged (> 4 weeks) cough apart from infection during the preceding 12 months and the ECT was pathological (50).

4.2.3 Allergy tests and atopic diseases
Allergen-specific IgE antibodies were measured at 2000, from frozen samples collected during index wheezing (50). At the control visits, doctor-diagnosed AD and AR during the preceding 12 months were recorded (50,217,218). Skin prick tests (SPTs) were performed at school-age control visits against common indoor and outdoor allergens like pollens and animal dander (50,218). The reactions with a mean diameter of at least 3 mm were defined to be positive, and no reactions were allowed for negative controls (saline). Atopic sensitisation was defined as the presence of at least one positive result in SPTs to indoor or outdoor allergens (50,218).

4.2.4 Risk factors for asthma in this cohort
In the previous studies from this cohort, predictive factors for asthma at 12.3 years of median age were AD and specific IgE sensitisation to inhalant, but not to food allergens as group, registered during index wheezing (50). Asthma was more common in children who were > 12 months old when hospitalised for wheezing (50). Parental asthma or atopic diseases, or exposure to pets or maternal smoking during pregnancy, were not risk factors for asthma during adolescence in the adjusted analysis (50). The non-RSV aetiology for bronchiolitis was a significant risk factor for later asthma at 7.2 years of median age (214,216).

4.2.5 Lung function measurements and bronchial reactivity
Lung function was studied using flow-volume spirometry (FVS) (Medikro, Kuopio, Finland) at 7.2 and 12.3 years of median age (221,222). The parameters were expressed as percentages of the gender-specific height-related reference values (% predicted) for Finnish children (222,223). FVC, FEV1/FVC, MEF50, and MEF25 were registered. The measurement with the highest FEV1 was recorded for analysis in the early school-age study (221). In the later school-age visit, the composite maximal curve for each child was recorded (222). The used cut-off limits for abnormal values were 80% for FEV1, 88% for FEV1/FVC, 62% for MEF50, and 48% for MEF25 (221,222,224). Lung function data were available from 79 children at 7.2 years of median age and from 81 children at 12.3 years of median age (221,222).

BHR was studied at both school-age control visits (221,222). The ECT was performed as an 8-minute free outdoor running test, including heart rate monitoring (Polar Sport Testes; Polar Electro, Kempele, Finland), and done after baseline FVS. At the early school-age visit, FVS was repeated 10 minutes after exercise, and the two FEV1 falls of > 12% and > 15% were used as cut-off points for increased bronchial reactivity (221). At the late school-age visit, the FVS was repeated 5, 10, and 15 minutes after exercise, and >
10% fall in FEV1 was regarded as positive BHR (222). In addition, metacholine challenge test was performed at 12.3 years of age (222).

4.3 CURRENT STUDY DESIGN AND DATA

The data concerning lung function, bronchial reactivity, allergic sensitisation, and asthma were collected during the study visits. Data were analysed together with the weight and height data from the same study visits to explore the effect of overweight and obesity on these parameters. The BMD was measured at the follow-up visit at 12.3 years of age. Fourteen children, hospitalised for wheezing during enrolment to the primary study in the Kuopio University Hospital, but not willing to attend the intervention trial, were invited to the follow-up study visit at 12.3 years of median age. Their background information was collected with a questionnaire and by interviewing the parents. Their data were used in the BMD study only. The ICS consumption history for all participants was collected, with the parents' written consent, from the hospital and primary health care medical records.

4.3.1 Definition of obesity

For the evaluation of the weight status, the body mass index (BMI) was calculated by using the following equation: weight (kg) / [height (m²)]. BMI standard deviation scores (BMI-SDS), also called z-scores, were calculated by using the freely available obesity calculator (225). This calculator applies British age- and sex-specific growth references from 1990, produced by the LMS method in 1995 (226,227) and revised in 1996 (228). The LMS method summarises the distribution of BMI at each age by its median (M), coefficient of variation (S), and skewness expressed as a Box-Cox power (L) required to transform the data to normal (229).

The International Obesity Task Force workshop for childhood obesity evaluation recommends the use of BMD > 91st percentile as a cut-off point for overweight and > 98th percentile for obesity, corresponding to BMIs > 25 and > 30 kg/m², respectively, in 18-year-old young adults (67). In this study, we used the corresponding BMI-SDS cut-off points: BMI-SDS > 1.3 for overweight and BMI-SDS > 2.0 for obesity (7,67).

The Finnish national growth charts, presenting weight for height, are used to evaluate the weight in clinical practice (230). In weight for height, the cut-off point for overweight and obesity varies depending age, and the method is not in international use. Finnish sex-specific and age-related BMI references were published in 2011 (231), and thus were not available for the present study.

4.3.2 Data on inhaled corticosteroid medication

None of the children had asthma or had used ICS before recruitment in the study (213). As a part of the early-life intervention, 23 of 84 children had received budesonide for 16 weeks immediately after hospitalisation (213). Later in childhood, 40%–50% of the children had been diagnosed with asthma and 15%–37% were on ICS medication for asthma during the follow-up period (50).
There was no scheduled protocol for maintenance medication with ICS after the 16-week early childhood intervention. Asthma medication was prescribed when required, based on the presence of asthma diagnosis, symptoms, and individual clinicians’ decisions. The data on ICS consumption during childhood were collected at the later school-age visit by charting the hospital and primary health care records and by interviewing the parents using structured questionnaires. The durations and daily doses of ICS therapy were collected. The dose of fluticasone propionate was multiplied by 2 to be equivalent with the doses of budesonide and beclomethasone dipropionate in the calculations; with the awareness of the fact the ICS are not equal to each other (185). The cumulative doses and the total time of ICS therapy were calculated and also noted separately for the two age periods: 0–6 years and 6–12.3 years (median). A continuous or intermittent use of ICS for 6 months or longer during the 6-year age period was considered as a regular use.

Oral and parenteral corticosteroid courses were collected and presented as cumulative doses and classified with the cut-off points at the 10th, 50th, and 90th percentiles. Children who never received ICS formed the control group of the study.

**4.3.3 Bone mineral density measurements**

The BMD was measured at the late school-age visit in the Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital. BMD was measured by two separate methods, DXA and pQCT. BMD was measured in children followed from the index wheezing episode onwards, and from those additional 14 children invited to the BMD study at the late school-age visit.

**4.3.4 Dual-energy x-ray absorptiometry**

DXA measurements were performed by trained nurses, using the same scanner (Lunar Radiation Corp., Madison, WI) for all 89 children. Measurements were obtained from the lumbar spine at the L2–L4 level and from the femoral neck region. Quality assurance tests using the Lunar DPX scanner have shown an inter-assay variation ranging between 0.08% (for lumbar spine) and 2.3% (for femoral neck) in children (232).

DXA measures the $BMD_{\text{areal}}$ (g/cm$^2$), which is dependent on bone size (179,233,234). The $aBMD_{\text{vol}}$ (g/cm$^3$) was calculated to minimise the effect of bone size on the results (179). Femoral neck $aBMD_{\text{vol}}$ was calculated according to the following equation: $aBMD_{\text{vol}} = BMD \times (4/\pi) \times (\text{height for measurement area} / \text{measurement area for femoral neck})$; and lumbar spine $aBMD_{\text{vol}}$ was calculated according to the following equation: $aBMD_{\text{vol}} = BMD \times (4 / (\pi \times \text{width of measurement area in the lumbar spine}))$ (232). Finnish and international reference values are available for both $BMD_{\text{areal}}$ and $aBMD_{\text{vol}}$, allowing expression of the results in z-scores (232,235). However, there are no specific cut-off points for an increased risk of clinical manifestations such as fractures (23). We used both $BMD_{\text{areal}}$ and $aBMD_{\text{vol}}$ as continuous variables without reference-based classifications.
4.3.5 Peripheral quantitative computed tomography

pQCT was performed to measure volumetric total BMD, trabecular BMD, and cortical BMD (BMD_{tot}, BMD_{trab}, and BMD_{cort}, respectively) (Stratec XCT 2000; Stratec Medizintechnik, Pforzheim, Germany) at the distal radius and distal tibia. Image data were analysed using commercial pQCT analysis software (Bonalyse Geanie 2.1, Jyväskylä, Finland). Volumetric thresholds were adjusted within the software for the automated analysis to match the current adolescence bone density values. After the completion of autoanalysis, results were visually verified by the researcher (Toni Rikkonen, Ph.D.). BMD and cortical thickness were measured at the distal radius (4% site) and distal tibia measurements from the medial malleolus to the medial condyle (33% site). There are no Finnish reference values for pQCT for children available, neither are there specific cut-off points for an increased risk of clinical manifestations (23). Therefore, we analysed the BMD as continuous variables without reference-based classifications.

4.4 ETHICS

The study was approved by the Research Ethics Committee of Kuopio University and Kuopio University Hospital. Informed written consent was obtained from the parents of the children. The methods used in the study, like blood tests, lung function tests, and BMD measurement with DXA, are routinely used in pediatric clinical practice. Only pQCT is a new method not routinely used, but the level of radiation is low, and concerns only peripheral parts of the body, that is radius and tibia in the present study. Both DXA and pQCT are internationally accepted methods to the measurement of BMD in children for research purposes.

4.5 STATISTICS

In the analysis between asthma, allergy, and weight status, logistic regression was used for both univariate and multivariate analyses. The results were expressed as crude odds ratio (cOR) and adjusted odds ratio (aOR) with 95% confidence intervals (95% CI). The analysis for an association between weight status and asthma or BHR was adjusted for AD in the infancy and RSV aetiology of wheezing. The analysis for an association between weight status and allergy or atopic sensitization was adjusted for sex and RSV aetiology of wheezing. The presence of AD in infancy had a strong interaction with later allergy and atopic sensitization; therefore, AD was not included in the analyses. The age on admission, although interacting with the viral aetiology of bronchiolitis, was included in all analyses as a continuous variable.

In the analysis of lung function data, the Mann–Whitney U-test was used in univariate analyses and the analysis of variance (ANOVA) was used in multivariate analyses for continuous FVS parameters. The ANOVA analyses were adjusted for the RSV aetiology of index wheezing, in addition to adjustment with anti-inflammatory asthma medication during the preceding 12 months before the study visit. Logistic regression analysis, adjusted for the RSV aetiology of index wheezing and anti-inflammatory asthma medication during the 12 preceding months before the study visit, was applied for
Peripheral quantitative computed tomography (pQCT) was performed to measure volumetric total BMD, trabecular BMD, and cortical BMD (BMDtot, BMDtrab, and BMDcort, respectively) (Stratec XCT 2000; Stratec Medizintechnik, Pforzheim, Germany) at the distal radius and distal tibia. Image data were analysed using commercial pQCT analysis software (Bonalyse Geanie 2.1, Jyväskylä, Finland). Volumetric thresholds were adjusted within the software for the automated analysis to match the current adolescent bone density values. After the completion of autoanalysis, results were visually verified by the researcher (Toni Rikkonen, Ph.D.). BMD and cortical thickness were measured at the distal radius (4% site) and distal tibia measurements from the medial malleolus to the medial condyle (33% site). There are no Finnish reference values for pQCT for children available, neither are there specific cut-off points for an increased risk of clinical manifestations. Therefore, we analysed the BMD as continuous variables without reference-based classifications.

In the BMD study, Student’s t-test was used for continuous variables in univariate analyses and ANOVA in multivariate analyses for the BMD measured by DXA. The analysis was adjusted for age, sex, weight as BMI-SDS (normal, overweight, and obesity), and the pubertal stage (pre-puberty and early puberty vs. puberty), and use of systemic corticosteroids (10th, 50th, and 90th percentiles). Height was also included in the model when BMDareal was the outcome. The results are expressed as means with 95% CI. Pearson’s correlation coefficients (r, r²) were used for estimating correlations.

Data were analysed using SPSS version 17 for weight study data and DXA data and SPSS version 19 for pQCT data (SPSS Inc., Chicago, IL).
5 Results

5.1 CHARACTERISTICS OF THE STUDY POPULATION

At the late school age, 81 children, 60 boys and 21 girls, attended the follow-up visit. Figures for asthma, regular ICS medication, overweight (BMI-SDS > 1.3) and obesity (BMI-SDS > 2.0) at the follow up visits are shown in Figure 3.

Weight and height data at both follow-up visits at school age were available from 74 children. Overweight was highly persistent; nearly all (15/16) children who were overweight or obese at 7.2 years of age were overweight or obese also at 12.3 years of age. In addition, 16% of normal-weight children at the early school-age visit were overweight or obese at the teenage visit.

![Bar chart showing prevalence of asthma, regular ICS therapy, overweight, and obesity during the three follow-up visits.](image)

Figure 3. Prevalence of asthma, regular ICS therapy, overweight, and obesity during the three follow-up visits.

5.2 RELATION BETWEEN ASTHMA, ALLERGY, AND OVERWEIGHT

There were no significant associations between asthma, BHR, AD, AR, or atopic sensitisation and overweight (Table 2) or obesity in adjusted analyses at the early school-age visit (I/Table 1). Similarly, there were no significant associations between overweight and asthma or allergic parameters at the early teenage visit (Table 2), except the association between obesity and lower prevalence of AD (aOR = 0.09, 95% CI = 0.01–0.76).
Table 2. Asthma and allergic diseases at early and late school age in children after early childhood wheezing: an association with overweight

<table>
<thead>
<tr>
<th>Asthma or allergic diseases at the school-age control visits</th>
<th>Overweight at 7.2 years of age(^1)</th>
<th>aOR (95% CI)(^2)</th>
<th>Overweight at 12.3 years of age(^1)</th>
<th>aOR (95% CI)(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>/n = 33/31</td>
<td>Yes n = 19</td>
<td>1.14 (0.35–3.65)</td>
<td>Yes n = 27</td>
<td>2.05 (0.70–6.00)</td>
</tr>
<tr>
<td>Asthma</td>
<td>No n = 63</td>
<td></td>
<td>No n = 54</td>
<td></td>
</tr>
<tr>
<td>/n = 13/17</td>
<td>Bronchial hyperreactivity(^3)</td>
<td>1.41 (0.36–5.51)</td>
<td>1.76 (0.51–6.07)</td>
<td></td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>Yes n = 26</td>
<td>0.83 (0.29–2.37)</td>
<td>0.87 (0.30–2.50)</td>
<td></td>
</tr>
<tr>
<td>/n = 26</td>
<td>No n = 33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>Yes n = 33/27</td>
<td>0.46 (0.15–1.47)</td>
<td>1.18 (0.43–3.25)</td>
<td></td>
</tr>
<tr>
<td>/n = 33/27</td>
<td>No n = 27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopic sensitisation(^4)</td>
<td>Yes n = 38/50</td>
<td>1.32 (0.42–4.18)</td>
<td>0.53 (0.20–1.45)</td>
<td></td>
</tr>
<tr>
<td>/n = 38/50</td>
<td>No n = 27</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) BMI-SDS > 1.3.
\(^2\) Odds ratio (aOR), and 95% confidence interval (95%CI) by logistic regression: Asthma and BHR were adjusted for age, atopic dermatitis in infancy, and RSV aetiology of bronchiolitis; AD, AR and AS were adjusted for age, sex, and RSV aetiology of bronchiolitis.

3 FEV1 decrease > 12% in the exercise challenge.

4 At least one positive reaction in SPTs.

Sensitisations to indoor and outdoor allergens were analysed separately at the late school-age visit, and previous sensitisation at 7.3 years of age was added to the adjusted model. Current overweight and obesity at the late school-age visit were associated with a decreased risk for sensitisation to outdoor allergens; aOR = 0.10, 95% CI = 0.02–0.52 for overweight and aOR = 0.03, 95% CI = 0.00–0.27 for obesity.

The previous overweight at 7.2 years of median age was not associated with asthma, BHR, AD, AR, or atopic sensitisation at 12.3 years of median age (Table 3), corresponding association were non-significant also for obesity (I/Table 3).
Table 3. Asthma and allergic diseases at late school age and overweight at early school age in children after early childhood wheezing: an association with overweight

<table>
<thead>
<tr>
<th>Asthma or allergic diseases at the late school-age control visit</th>
<th>Overweight at 7.2 years of age(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes n=16</td>
</tr>
<tr>
<td>Asthma n=28</td>
<td>7</td>
</tr>
<tr>
<td>Bronchial hyperreactivity(^2) n=17</td>
<td>3</td>
</tr>
<tr>
<td>Atopic dermatitis n=24</td>
<td>3</td>
</tr>
<tr>
<td>Allergic rhinitis n=24</td>
<td>4</td>
</tr>
<tr>
<td>Atopic sensitisation(^3) n=45</td>
<td>8</td>
</tr>
</tbody>
</table>

\(^1\) Overweight BMI-SDS >1.3; \(^b\) Obesity BMI-SDS >2 (Body mass index standard deviation score = Z-score)

\(^2\) FEV1 decrease >12% in the exercise challenge

\(^3\) At least one positive reaction: 36 to indoor and 38 to outdoor allergens.

\(^4\) Odds ratio (aOR), and 95% confidence interval (95% CI) by logistic regression: asthma and BHR adjusted for age, atopic dermatitis in infancy and RSV aetiology of bronchiolitis; AD, AR and AS adjusted for age, gender and RSV aetiology of bronchiolitis.

5.3 INFLUENCE OF OVERWEIGHT ON LUNG FUNCTION AT SCHOOL AGE

5.3.1 Univariate analyses

At the early school-age visit, current overweight was associated significantly with lower FEV1/FVC (Table 4). There were no significant associations between other FVS parameters and overweight (Table 4) or obesity (II/Table 1). Previous overweight (Table 5) at the preschool-age control visit had no significant association with any FVS parameters at 7.2 years of median age. There was not possibility to evaluate effect of previous obesity because low incidence of obesity.

Table 4. Flow-volume spirometry at 7.2 years of median age in relation to current overweight

<table>
<thead>
<tr>
<th>Parameters in FVS(^2)</th>
<th>Current overweight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (N=16)</td>
</tr>
<tr>
<td>FVC</td>
<td>108.71 (19.75)</td>
</tr>
<tr>
<td>FEV1</td>
<td>100.16 (14.16)</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>92.63 (8.95)</td>
</tr>
<tr>
<td>MEF50</td>
<td>84.00 (17.73)</td>
</tr>
<tr>
<td>MEF25</td>
<td>66.00 (19.85)</td>
</tr>
</tbody>
</table>

\(^1\) Overweight BMI-SDS >1.3; \(^b\) Obesity BMI-SDS >2 (Body mass index standard deviation score = Z-score)

\(^2\) 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.

Data are presented as mean (SD). FVC, forced vital capacity; FEV1, forced expiratory volume in 1 sec; FEV1/FCV and MEF50, maximal expiratory flow at 50% of FVC; MEF25, maximal expiratory flow at 25% of FVC, expressed as % predicted.

There was no significant association between FVC or FEV1 and overweight or obesity at school-age visits (Table 4 and II/Tables 2 and 3). Previous overweight and obesity at 7.2 years of median age associated significantly with lower FEV1/FVC at 12.3 years of median age (Table 6). Current overweight and obesity associated significantly with lower FEV1/FVC, MEF50\(^%\) (Table 6) and with MEF25 (p 0.006 and p 0.021 respectively) at late school age (II/Tables 2 and 3).
Table 4. Flow-volume spirometry at 7.2 years of median age in relation to current overweight

<table>
<thead>
<tr>
<th>Parameters in FVS²</th>
<th>Current overweight¹</th>
<th>Univariate p³</th>
<th>Multivariate p⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (N=16)</td>
<td>Mean, (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No (N=58)</td>
<td>Mean, (SD)</td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>108.71 (19.75)</td>
<td>102.06 (16.48)</td>
<td>0.252</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.219</td>
</tr>
<tr>
<td>FEV₁</td>
<td>100.16 (14.16)</td>
<td>99.95 (13.94)</td>
<td>0.977</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.890</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>92.63 (8.95)</td>
<td>98.47 (8.93)</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.025</td>
</tr>
<tr>
<td>MEF₅₀</td>
<td>84.00 (17.73)</td>
<td>85.10 (20.39)</td>
<td>0.700</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.814</td>
</tr>
<tr>
<td>MEF₂₅</td>
<td>66.00 (19.85)</td>
<td>71.27 (22.76)</td>
<td>0.394</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.454</td>
</tr>
</tbody>
</table>

¹ Overweight BMI-SDS >1.3
² 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.
³ Mann-Whitney U-test
⁴ Analysis of variance, adjusted for RSV aetiology of early wheezing and current anti-inflammatory asthma medication (during the preceding 12 months).

Table 5. Flow volume spirometry at 7.2 years of median age and association to weight at the preschool-age

<table>
<thead>
<tr>
<th>FVS at 7.2 years of age</th>
<th>Weight at 4.0 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overweight ¹</td>
</tr>
<tr>
<td></td>
<td>n = 5</td>
</tr>
<tr>
<td></td>
<td>Normal weight n = 67</td>
</tr>
<tr>
<td>FVC</td>
<td>107.95 (8.8)</td>
</tr>
<tr>
<td>FEV₁</td>
<td>98.39 (13.27)</td>
</tr>
<tr>
<td>FEV%</td>
<td>90.99 (9.53)</td>
</tr>
<tr>
<td>MEF₅₀</td>
<td>79.44 (23.23)</td>
</tr>
<tr>
<td>MEF₂₅</td>
<td>59.43 (21.44)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD). FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 sec; FEV₁/FVC and MEF₅₀, maximal expiratory flow at 50% of FVC; MEF₂₅, maximal expiratory flow at 25% of FVC, expressed as % predicted.
¹ Overweight BMI-SDS > 1.3.
² Mann-Whitney U-test and ANOVA, adjusted for the RSV aetiology of early wheezing and current anti-inflammatory asthma medication.

There was no significant association between FVC or FEV₁ and overweight or obesity at school-age visits (Table 4 and II/Tables 2 and 3). Previous overweight and obesity at 7.2 years of median age associated significantly with lower FEV₁/FVC at 12.3 years of median age (Table 6). Current overweight and obesity associated significantly with lower FEV₁/FVC, MEF₅₀% (Table 6) and with MEF₂₅ (p 0.006 and p 0.021 respectively) at late school age (II/Tables 2 and 3).
Table 6. Spirometry in the 80 study subjects at 12.3 years of median age in relation to previous and current overweight and obesity. P-values refer to the difference between patients with and without previous or current overweight or obesity

<table>
<thead>
<tr>
<th></th>
<th>FVC³</th>
<th>FEV1/FVS³</th>
<th>MEF 50%³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Univariate p⁴</td>
<td>Multivariate p⁵</td>
</tr>
<tr>
<td>Previous overweight¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 16)</td>
<td>101.03 (8.40)</td>
<td>0.131</td>
<td>0.306</td>
</tr>
<tr>
<td>No (n = 58)</td>
<td>97.21 (13.20)</td>
<td>96.01 (7.63)</td>
<td>83.91 (18.82)</td>
</tr>
<tr>
<td>Previous obesity²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 6)</td>
<td>99.05 (9.47)</td>
<td>0.797</td>
<td>0.769</td>
</tr>
<tr>
<td>No (n = 68)</td>
<td>97.95 (12.65)</td>
<td>95.12 (8.57)</td>
<td>82.97 (19.52)</td>
</tr>
<tr>
<td>Current overweight¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 27)</td>
<td>100.56 (11.50)</td>
<td>0.162</td>
<td>0.164</td>
</tr>
<tr>
<td>No (n = 53)</td>
<td>96.38 (12.68)</td>
<td>96.81 (7.36)</td>
<td>84.39 (17.70)</td>
</tr>
<tr>
<td>Current obesity²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 16)</td>
<td>98.39 (9.12)</td>
<td>0.674</td>
<td>0.837</td>
</tr>
<tr>
<td>No (n = 64)</td>
<td>97.64 (13.12)</td>
<td>95.97 (7.51)</td>
<td>83.87 (18.41)</td>
</tr>
</tbody>
</table>

¹ BMI-SDS > 1.3, at 7.2 and 12.3 years of age.
² BMI-SDS > 2.0, at 7.2 and 12.3 years of age.
³ FVC, forced vital capacity; FEV1/FCV and MEF50, maximal expiratory flow at 50% of FVC, expressed as % predicted.
⁴ Mann-Whitney U-test.
⁵ ANOVA, adjusted for RSV aetiology of early wheezing and current anti-inflammatory asthma medication (during the preceding 12 months)
5.3.2 Multivariate analyses

In the multivariate analysis at the early school-age visit, both overweight and obesity associated significantly with decreased FEV1/FVC (Table 4 and II/Table 1). At the later school-age visit, the association of current overweight with FEV1/FVC and MEF25% remained as significant after adjusting with RSV aetiology of index wheezing and current anti-inflammatory asthma medication, but the association with MEF50 became non-significant (Table 6 and II/Tables 2 and 3).

5.3.3 Logistic regression

Previous and current overweight were significant risk factors for decreased FEV1/FVC (< 88% of predicted) at the early school-age (Table 7) and late school-age visits (Table 8). At late school age, current obesity was also a significant risk factor for abnormal FEV1/FVC (< 88%) (aOR = 8.07, 95% CI = 2.10–31.05) and MEF25 (< 48%) (aOR = 4.34, 95% CI = 1.06–17.79). The weight did not associate to decreased FEV1 (Table 7 and 8).

Because overweight was highly persistent between the study visits, previous and current overweight could not be incorporated in the same multivariate model. Therefore, it was not reliable to evaluate causality and influences separately.

Table 7. Logistic regression: abnormal lung function in FVS at the early school-age visit, in relation to previous and current overweight

<table>
<thead>
<tr>
<th>Abnormal FVS²</th>
<th>Previous overweight¹,⁴</th>
<th>aOR (95% CI)³</th>
<th>Current overweight¹,⁵</th>
<th>aOR (95% CI)³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 5)</td>
<td>No (n = 69)</td>
<td>Yes (n = 17)</td>
<td>No (n = 57)</td>
</tr>
<tr>
<td>FEV &lt;80%</td>
<td>-</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>FEV1/FVC &lt; 88%</td>
<td>3</td>
<td>10</td>
<td>15.46 (1.65–145.26)</td>
<td>6</td>
</tr>
<tr>
<td>MEF50 &lt; 62%</td>
<td>2</td>
<td>11</td>
<td>6.46 (0.77–33.95)</td>
<td>3</td>
</tr>
</tbody>
</table>

¹ BMI-SDS > 1.3.
² FEV1/FCV and MEF50, maximal expiratory flow at 50% of FVC, expressed as % predicted.
³ Odds ratio (95% CI) adjusted for RSV aetiology of early wheezing and current anti-inflammatory asthma medication (during the preceding 12 months).
⁴ Overweight at 4.0 years of median age.
⁵ Overweight at 7.2 years of median age.
### Table 8. Logistic regression: abnormal lung function in FVS at the late school-age visit, in relation to previous and current overweight

**12.3 years of median age**

<table>
<thead>
<tr>
<th>Abnormal FVS²</th>
<th>Previous overweight¹ ⁴</th>
<th>aOR (95% CI)³</th>
<th>Current overweight¹ ⁵</th>
<th>aOR (95% CI)³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 16)</td>
<td>No (n = 58)</td>
<td>Yes (n = 24)</td>
<td>No (n = 50)</td>
</tr>
<tr>
<td>FEV1 &lt;80%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>10</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>0.70</td>
<td>(0.13–3.60)</td>
<td>1.00</td>
<td>(0.29–3.46)</td>
</tr>
<tr>
<td>FEV1/FVC &lt;88%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>6</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>5.64</td>
<td>(1.43–22.20)</td>
<td>4.02</td>
<td>(1.14–14.22)</td>
</tr>
<tr>
<td>MEF50 &lt;62%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>9</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>1.29</td>
<td>(0.30–5.54)</td>
<td>2.64</td>
<td>(0.78–8.97)</td>
</tr>
</tbody>
</table>

¹ BMI-SDS > 1.3.
² FEV1/FCV and MEF50, maximal expiratory flow at 50% of FVC, expressed as % predicted.
³ Odds ratio (95% CI) adjusted for RSV aetiology of early wheezing and current anti-inflammatory asthma medication (during the preceding 12 months).
⁴ Overweight at 7.2 years of median age.
⁵ Overweight at 12.3 years of median age.
5.4 BONE MINERAL DENSITY BY DUAL-ENERGY X-RAY ABSORPTIOMETRY

BMD$_{\text{areal}}$ was measured and aBMD$_{\text{vol}}$ was calculated for 65 boys and 24 girls by DXA. Among these 89 children, 37% were overweight and 24% were obese, and 28% of boys and 38% of girls were at puberty (M/G3-5). Pubertal children had higher BMD$_{\text{areal}}$ and aBMD$_{\text{vol}}$ in the lumbar spine and higher BMD$_{\text{areal}}$ in the femoral neck compared with prepubertal children (Table 9). In the lumbar spine, BMD$_{\text{areal}}$ and aBMD$_{\text{vol}}$ were lower in boys than in girls (Table 9). Overweight or obesity had no significant association with BMD$_{\text{areal}}$ or aBMD$_{\text{vol}}$ in the lumbar spine or femoral neck (Table 9).

Table 9. The association between BMDs measured by DXA and gender, pubertal stage, and weight at 12.3 years of age in 89 children hospitalised for wheezing in early childhood

<table>
<thead>
<tr>
<th></th>
<th>BMD$_{\text{areal}}$ mean (95% CI)$^1$</th>
<th>aBMD$_{\text{vol}}$ mean (95% CI)$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lumbar spine L2–L4</td>
<td>Femoral neck</td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
<td>0.95 (0.88–1.02)*</td>
</tr>
<tr>
<td>Male</td>
<td>65</td>
<td>0.83 (0.80–0.85)</td>
</tr>
<tr>
<td>Pre- and early puberty$^3$</td>
<td>64</td>
<td>0.82 (0.80–0.85)*</td>
</tr>
<tr>
<td>Pubertal$^3$</td>
<td>24</td>
<td>0.97 (0.91–1.03)</td>
</tr>
<tr>
<td>Normal weight$^4$</td>
<td>56</td>
<td>0.85 (0.81–0.88)</td>
</tr>
<tr>
<td>Overweight$^4$</td>
<td>33</td>
<td>0.89 (0.82–0.96)</td>
</tr>
</tbody>
</table>

$^1$ Areal BMD (g/cm$^2$) measured by DXA.
$^2$ Apparent volumetric BMD (g/cm$^3$) calculated from DXA measurements.
$^3$ Tanner stages M1-2 and G1-2 as pre-puberty and early puberty, M3-5 and G3-5 as puberty.
$^4$ Normal weight BMI-SDS < 1.3 SD, overweight BMI-SDS > 1.3 SD.

The mean cumulative dose of systemic corticosteroids during the follow-up period was 161 mg (range = 10–1,784 mg, SD = 346, n = 34), showing no correlation with lumbar spine BMD$_{\text{areal}}$ ($r = 0.058$, $r^2 = 0.00$) or aBMD$_{\text{vol}}$ ($r = -0.137$, $r^2 = 0.02$), nor with femoral neck BMD$_{\text{areal}}$ ($r = -0.026$, $r^2 = 0.00$) and aBMD$_{\text{vol}}$ ($r = -0.088$, $r^2 = 0.01$). When analysed as categorised (at the 10th, 50th, and 90th percentiles), there was no significant association between systemic corticosteroids use and BMD in the lumbar spine or femoral neck.
5.4.1 Effect of inhaled corticosteroids on bone mineral density in the lumbar spine and femoral neck

The mean cumulative dose of ICS expressed as budesonide equivalents during the whole follow-up period was 517 mg (range = 31–1,813 mg). There was a significant negative association between the cumulative ICS dose and the BMD\(\text{areal}\) (adj. \(p = 0.000\)) and aBMD\(\text{vol}\) (adj. \(p = 0.006\)) in the femoral neck (Figure 4 and III/Figures 1A and 1B). The analysis of variance was adjusted for use of systemic corticosteroids, age, sex, weight status by BMI-SDS and pubertal stage, and height in the analysis of areal BMD. However, the correlations were weak: for BMD\(\text{areal}\), \(r = -0.32, r^2 = 0.10\); for aBMD\(\text{vol}\), \(r = -0.28, r^2 = 0.08\). There was no significant association between the cumulative ICS dose and the BMD in the lumbar spine (Figure 4 and III/Figures 2A and 2B).

![Figure 4](image)

Figure 4. The distribution of BMD\(\text{areal}\) in lumbar spine and femoral neck at 12.3 years of median age in relation to the cumulative dose of ICS used during follow-up time. The presence of puberty is shown in figures.

In the lumbar spine, both BMD\(\text{areal}\) and aBMD\(\text{vol}\) were significantly lower in those 12 children who were treated with regular ICS medication only at less than 6 years of age compared with those 21 children who never received ICS therapy (Table 10). The findings were similar after adjusting with age, sex, pubertal stage, weight status, and the use of systemic corticosteroids, and in the case of BMD\(\text{areal}\) with the additional adjustment for height. Concerning the femoral neck, such association was found only with aBMD\(\text{vol}\) (\(p = 0.031\)) (III/Table 2). Twelve children had used ICS regularly only between 6 and 12.3 years of age, and there was no significant association with BMD at age 12.3 years (Table 10 and Figure 5 and III/Table 2).
Effect of inhaled corticosteroids on bone mineral density in the lumbar spine and femoral neck

The mean cumulative dose of ICS expressed as budesonide equivalents during the whole follow-up period was 517 mg (range = 31–1,813 mg). There was a significant negative association between the cumulative ICS dose and the BMD areal (adj. $p = 0.000$) and $aBMD_{vol}$ (adj. $p = 0.006$) in the femoral neck (Figure 4 and III /Figures 1A and 1B).

The analysis of variance was adjusted for use of systemic corticosteroids, age, sex, weight status by BMI -SDS and pubertal stage, and height in the analysis of areal BMD. However, the correlations were weak: for $BMD_{areal}$, $r = −0.32$, $r^2 = 0.10$; for $aBMD_{vol}$, $r = −0.28$, $r^2 = 0.08$. There was no significant association between the cumulative ICS dose and the BMD in the lumbar spine (Figure 4 and III /Figures 2A and 2B).

**Figure 4.** The distribution of BMD areal in lumbar spine and femoral neck at 12.3 years of median age in relation to the cumulative dose of ICS used during follow-up time. The presence of puberty is shown in figures.

In the lumbar spine, both $BMD_{areal}$ and $aBMD_{vol}$ were significantly lower in those 12 children who were treated with regular ICS medication only at less than 6 years of age compared with those 21 children who never received ICS therapy (Table 10). The findings were similar after adjusting with age, sex, pubertal stage, weight status, and the use of systemic corticosteroids, and in the case of $BMD_{areal}$ with the additional adjustment for height. Concerning the femoral neck, such association was found only with $aBMD_{vol}$ ($p= 0.031$) (III /Table 2). Twelve children had used ICS regularly only between 6 and 12.3 years of age, and there was no significant association with BMD at age 12.3 years (Table 10 and Figure 5 and III/Table 2).

### Table 10. Bone mineral density at the median age of 12.2 years in children who had regularly used inhaled corticosteroids (ICS) before school age and at school age, compared to children who had never used ICS

<table>
<thead>
<tr>
<th>Regular use of ICS during childhood$^2$</th>
<th>$BMD_{areal}^1$ (mean, 95% CI)$^3$</th>
<th>$aBMD_{vol}^1$ (mean, 95% CI)$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lumbar spine L2-4 p$^4$ Femoral neck p$^4$</td>
<td>Lumbar spine L2-4 p$^4$ Femoral neck p$^4$</td>
</tr>
<tr>
<td>Only at 0-6 years N= 12</td>
<td>0.81 (0.74-0.90) 0.010 (0.83-1.00)</td>
<td>0.27 (0.25-0.30) 0.006 (0.36-0.40)</td>
</tr>
<tr>
<td>Only at 6-12.2 years N= 12</td>
<td>0.88 (0.77-0.99) 0.514 (0.86-1.05)</td>
<td>0.31 (0.28-0.35) 0.454 (0.38-0.46)</td>
</tr>
<tr>
<td>No ICS use during the 12.2 years follow-up N= 21</td>
<td>0.85 (0.82-0.93) 0.94 (0.90-0.98)</td>
<td>0.30 (0.28-0.31) 0.41 (0.39-0.44)</td>
</tr>
</tbody>
</table>

$^1$ BMD measured by dual energy X-ray absorptiometry (DXA), apparent volumetric BMD calculated

$^2$ Regular use; over 6 months use of ICS during the 6-year age period

$^3$ 95% confidence interval

$^4$ The analysis of variance adjusted for the cumulative dose of systemic corticosteroids (mg) classified with cut-off points at the 10th, 50th and 90th percentiles, gender, pubertal stage (Tanner stage M1-2 and G1-2 as pre- and early pubertal, M3-5 and G3-5 pubertal), age and weight as BMI-SDS (normal, overweight, obesity). Height (cm) was included in the model for analysis of areal BMD.
Figure 5. Areal BMD_{areal} and aBMD_{vol} in the lumbar spine and femoral neck of children who never used ICS and in those who regularly used ICS only before school age or only at school age.

* Adjusted p < 0.05 between children never received ICS and children received ICS regularly before school age.
5.5 BONE MINERAL DENSITY BY PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY

BMD$_{\text{vol}}$ was measured for 62 boys and 20 girls by pQCT. Among these 82 children, 38% were overweight and 26% were obese, and 19% of boys and 40% of girls were at puberty (M/G3-5). BMD$_{\text{tot}}$ and BMD$_{\text{cort}}$ were higher in girls than boys in the tibia (Table 11). Pubertal children had higher BMD$_{\text{tot}}$ and BMD$_{\text{cort}}$ in the radius compared with pre-pubertal or early pubertal children (Table 11). Age and weight status, as classified by BMI-SDS (normal weight, overweight, and obesity), had no correlation with BMD in the radius (radius BMD$_{\text{tot}}$, $r = 0.247$, $r^2 = 0.06$) or tibia (BMD$_{\text{tot}}$, $r = 0.073$, $r^2 = 0.01$). Systemic corticosteroid use had no significant associations with BMD in the radius (BMD$_{\text{tot}}$, $r = 0.063$, $r^2 = 0.00$) or tibia (BMD$_{\text{tot}}$, $r = 0.062$, $r^2 = 0.00$).

Table 11. The association between BMD$_{\text{vol}}$ (g/cm$^3$) in distal tibia and radius (mean, 95% CI) and sex and pubertal stage at the median age of 12.3 years in 81/82 children hospitalized for wheezing in infancy

<table>
<thead>
<tr>
<th>Bone Mineral Density in Tibia and Radius$^1$</th>
<th>Mean, (95% CI)$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female N=20</td>
<td>Male N=61/62</td>
</tr>
<tr>
<td>Tibia BMD$_{\text{tot}}$</td>
<td>383.8 (360.7-406.9)</td>
</tr>
<tr>
<td>Tibia BMD$_{\text{cort}}$</td>
<td>585.00 (572.2-597.9)</td>
</tr>
<tr>
<td>Radius BMD$_{\text{tot}}$</td>
<td>118.1 (103.6-132.7)</td>
</tr>
<tr>
<td>Radius BMD$_{\text{trad}}$</td>
<td>84.8 (73.6-96.0)</td>
</tr>
<tr>
<td>Radius BMD$_{\text{cort}}$</td>
<td>203.3 (178.2-228.3)</td>
</tr>
</tbody>
</table>

$^1$ BMD measured by pQCT
$^2$ 95% confidence interval
$^3$ Tanner stage M1-2 and G1-2 as pre- and early pubertal, M3-5 and G3-5 pubertal, two boys refused pubertal examination

* Two independent-samples t-test, $p < 0.05$, between males and females or pre-pubertal/early pubertal and pubertal children
The correlation between BMD\textsubscript{tot} and BMD\textsubscript{cort} in the radius and tibia was as follows: for BMD\textsubscript{tot}, $r = 0.376$, $r^2 = 0.14$; and for BMD\textsubscript{cort}, $r = 0.348$, $r^2 = 0.12$ (Figure 6).

Figure 6. The correlation between BMD\textsubscript{tot} and BMD\textsubscript{cort} in the distal radius and in tibia, $r^2 = 0.14$, $r^2=0.12$ respectively.

5.5.1 The effect of inhaled corticosteroids to the bone mineral density in distal radius and tibia measured by peripheral quantitative computed tomography

The cumulative ICS dose (mean $= 537$ mg, range $= 31$–1,813 mg) as budesonide equivalents had a significant negative correlation with BMD\textsubscript{tot} ($r = -0.175$, $r^2 = 0.031$, adj. $p = 0.016$), BMD\textsubscript{cort} ($r = -0.138$, $r^2 = 0.019$, adj. $p = 0.016$), and BMD\textsubscript{trab} ($r = -0.155$, $r^2 = 0.022$, adj. $p = 0.039$) in the radius. The correlations were weak (figure 7). For associations, the analysis of variance was adjusted for use of systemic corticosteroids, age, sex, weight status by BMI-SDS and pubertal stage (Figure 7). The correlations were weak. The corresponding correlations were weaker and associations non-significant for cortical thickness, or for BMD\textsubscript{tot} and BMD\textsubscript{cort} in the tibia.
The correlation between BMD_{tot} and BMD_{cort} in the radius and tibia was as follows: for BMD_{tot}, $r = 0.376$, $r^2 = 0.14$; and for BMD_{cort}, $r = 0.348$, $r^2 = 0.12$ (Figure 6).

The effect of inhaled corticosteroids to the bone mineral density in distal radius and tibia measured by peripheral quantitative computed tomography (pQCT) was assessed. The cumulative ICS dose (mean = 537 mg, range = 31–1,813 mg) as budesonide equivalents had a significant negative correlation with BMD_{tot} ($r = -0.175$, $r^2 = 0.031$, adj. $p = 0.016$), BMD_{cort} ($r = -0.138$, $r^2 = 0.019$, adj. $p = 0.016$), and BMD_{trab} ($r = -0.155$, $r^2 = 0.022$, adj. $p = 0.039$) in the radius. The correlations were weak (Figure 7). For associations, the analysis of variance was adjusted for use of systemic corticosteroids, age, sex, weight status by BMI -SDS and pubertal stage (Figure 7).

When the regular ICS use was analysed separately for consumption at less than 6 years of age and between 6 and 12.3 years of age, there were no significant differences in BMD_{tot} in the radius or tibia between children who used ICS regularly and children who never used ICS (Table 12). Results were non-significant also for BMD_{cort} and BMD_{trab} in the radius and BMD_{cort} in the tibia (Data not shown).

Figure 7. The distribution of BMD_{tot}, BMD_{cort} and BMD_{trab} in radius at 12.3 years of median age in relation to the cumulative dose of ICS used during follow-up time. Correlations and association in adjusted ANOVA shown in figures.
Table 12. MBD$_{\text{tot}}$ (g/cm$^3$) in radius and tibia at the median age of 12.3 years in children with regular ICS use only before 6 years of age or between 6 to 12.3 years of age, compared to BMD$_{\text{tot}}$ in radius in children who had never used ICS

<table>
<thead>
<tr>
<th>Regular ICS use$^1$</th>
<th>MBD$_{\text{tot}}$ in radius (mean, 95% CI)$^2$</th>
<th>p$^3$</th>
<th>MBD$_{\text{tot}}$ in tibia (mean, 95% CI)$^2$</th>
<th>p$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only at age 0-6 years</td>
<td>N=12</td>
<td>127.50 (113.58-140.49)</td>
<td>ns</td>
<td>334.58 (315.39-353.78)</td>
</tr>
<tr>
<td>Only at age 6-12.3 years</td>
<td>N=10</td>
<td>132.70 (112.83-152.57)</td>
<td>ns</td>
<td>387.60 (458.41-416.79)</td>
</tr>
<tr>
<td>No ICS use during the 12.3 years follow up</td>
<td>N=18</td>
<td>123.11 (116.02-130.21)</td>
<td></td>
<td>357.28 (336.85-377.70)</td>
</tr>
</tbody>
</table>

$^1$ Regular use; over 6 month use of ICS during the 6-year age period

$^2$ 95% confidence interval

$^3$ The analysis of variance adjusted for sex, pubertal stage (Tanner stage M1-2 and G1-2 as pre and early pubertal, M3-5 and G3-5 pubertal), age, height (cm) and weight as BMI-SDS (normal, overweight, obesity) and used systemic corticosteroids (classified by 10th, 50th and 90th percentiles)

Discussion

6.1 RELATION OF OVERWEIGHT AND ASTHMA, LUNG FUNCTION, AND ALLERGY IN CHILDREN

6.1.1 Asthma

This prospective follow up study comprised the children who experienced severe wheezing in early childhood and were followed longitudinally for 11 years and thus enables to inspect the influence of weight developed and ICS consumptions to the outcomes asthma, like lung function and BMD. The present study did not find any association between asthma and earlier or current obesity or overweight. Reasons may be the rather low proportion of overweight (33%) and especially obese (20%) children, although the proportions were higher than on average in Finnish children (19.1% –23.6% and 3.2%–4.7%, respectively) (80) and the cohort being small. In line with the present study, when objectively measured BHR was demanded for the asthma diagnosis, the other studies have been negative also (96,118,151).

In previous studies, most often the asthma symptoms and diagnoses have been asked from parents and have been based on subjective observations (11,132,133,148,149) and the connection between asthma and obesity is known (5,6,236). In the present study, we did not find connections between BHR and earlier weight at 7.2 or current weight at 12.3 years of age, in line with results from another asthma study (237). In longitudinal studies, the results have varied. In a 9-month follow-up, obese (BMI > 95 %) children had more wheezing, more use of medicines, and more emergency room visits, but no association was found with PEF rates monitored at home (149). Another study did not find any associations between asthma, AR, AD, or BHR at 10 years of age and current or previous weight status (237). In a birth cohort, an earlier persistent and current overweight associated with both dyspnoea and BHR at 8 years of age, whereas earlier overweight did not predict BHR if weight had normalised (120).

The asthma severity might be one factor modifying the asthma-obesity relation. In the present study, we did not monitor asthma severity or the sedentary lifestyle, and both might affect the results. Poor asthma control could lower the level of physical activity and further lead to weight gain. Another notable issue, the possible causality between obesity and asthma, was not possible to evaluate in the present study. In a large retrospective cohort study, 5- to 17-year-old obese asthmatic children used more β-agonists and more oral corticosteroids, with a conclusion that obesity is associated with a risk of worse asthma control (101). In the National Longitudinal Survey of Youth (NLSY) with a 14-year follow-up time, boys had an increased risk of asthma if they became overweight (BMI > 85th percentile) at 2–3 years of age or were overweight during the whole follow-up time (134). Also, girls who gained weight at school age had an increased risk of asthma in another study (137).

Age, puberty and sex have a role in the asthma-obesity relation. In the present study, we did not evaluate an association between overweight during the index wheezing episode at less than 2 years of age and later asthma, mainly because of the small numbers of overweight children at that age. In addition, the cohort was too small, not allowing a relevant analysis for boys and girls separately. Therefore, age on admission and sex were
6 Discussion

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6.1.1 Asthma
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In the present study, we did not find connections between BHR and earlier weight at 7.2 or current weight at 12.3 years of age, in line with results from another asthma study (237). In longitudinal studies, the results have varied. In a 9-month follow-up, obese (BMI > 95 %) children had more wheezing, more use of medicines, and more emergency room visits, but no association was found with PEF rates monitored at home (149). Another study did not find any associations between asthma, AR, AD, or BHR at 10 years of age and current or previous weight status (237). In a birth cohort, an earlier persistent and current overweight associated with both dyspnoea and BHR at 8 years of age, whereas earlier overweight did not predict BHR if weight had normalised (120).

The asthma severity might be one factor modifying the asthma-obesity relation. In the present study, we did not monitor asthma severity or the sedentary lifestyle, and both might affect the results. Poor asthma control could lower the level of physical activity and further lead to weight gain. Another notable issue, the possible causality between obesity and asthma, was not possible to evaluate in the present study. In a large retrospective cohort study, 5- to 17-year-old obese asthmatic children used more β-agonists and more oral corticosteroids, with a conclusion that obesity is associated with a risk of worse asthma control (101). In the National Longitudinal Survey of Youth (NLSY) with a 14-year follow-up time, boys had an increased risk of asthma if they became overweight (BMI > 85th percentile) at 2–3 years of age or were overweight during the whole follow-up time (134). Also, girls who gained weight at school age had an increased risk of asthma in another study (137).

Age, puberty and sex have a role in the asthma-obesity relation. In the present study, we did not evaluate an association between overweight during the index wheezing episode at least 2 years of age and later asthma, mainly because of the small numbers of overweight children at that age. In addition, the cohort was too small, not allowing a relevant analysis for boys and girls separately. Therefore, age on admission and sex were
included as the confounding factors in the adjusted analyses. In literature, one longitudinal study, higher weight at 1 year of age was associated with better lung function at 6 and 8 years of age, but later, overweight changed to be a risk factor (136). In another study, obesity reduced lung function without any major symptoms before puberty. During adolescence, FEV1% and FEV1/FVC was reduced in obese girls; and in adults, there were no differences in lung function between obese and non-obese subjects (125). In the Tucson Children’s Respiratory Study, early puberty and obesity were both associated with unremitting asthma after puberty (238). In available studies, the results are rather conflicting due to sex interactions (119,127,128,131).

These inconsistent findings support, that although obesity increases the asthma risk at the population level, it might cause more asthmatic symptoms rather than effect the asthma prevalence per se. Asthma associated with obesity differs from atopic asthma and may even be an own phenotype (4,110,239,240). Obesity decreases responses to asthma medication, and weight reduction improves lung function; both can be seen as a demonstration of causality in the asthma-obesity relation (Shore, Johnston 2006), but more likely, as a sign of obese asthma phenotype characterised by non-atopic airway inflammation (4,110).

To clarify the complex interaction between weight and asthma, longitudinal preferably prospective and stratified studies with multivariate models are needed to answer the following questions: Is excessive weight gain an independent significant risk factor for asthma? Are there certain risk groups that should obtain special attention? Do obese asthmatic children need a different treatment compared with allergic asthmatic children?

6.1.2 Lung function
The results of the present long-term follow-up study after early childhood wheezing showed that overweight was associated significantly with reduced FEV1/FVC at school age and with reduced MEF50 and MEF25 at late school age.

In healthy children, overweight has had a beneficial effect on lung function (8,9), but decreased lung function related to obesity has also been reported (131). However, benefits might change during adolescence; lung function seems first to reach a plateau and then to decrease among the obese youths (9). Normal weight is probably the most beneficial to lung health; also, low weight was associated with significantly lower FEV1 and FVC compared with normal weight children (96).

Overweight might have a different effect on lung function in asthmatic than in non-asthmatic children; approximately 40% of our patients had asthma, and all had wheezed in early childhood. In line with the findings of the present study, in the CAMP study, an increasing BMI was associated with increasing FEV1 and FVC but decreasing FEV1/FVC (144). In the post hoc analysis of the CAMP data, overweight children had decreased responses to ICS when assessed with lung function measurements (103). Obesity-related lower FEV1/FVC has been reported in a birth cohort study (127), lower residual volume/TLC ratios in a case-control study (110) and in a cross-sectional study (147).

The decrease of MEF50 and MEF25 values in the overweight and obese children at the teenage visit indicates that overweight and obesity might narrow the small peripheral airways, as described to occur in obese subjects (93). In addition, the decreased compliance of either the lungs due to the narrow peripheral airways or the chest wall due
to body adiposity may lead to subnormal lung function, including both decreased airway flows, which means an obstructive lung function disorder, and decreased lung volumes, which means a restrictive lung function disorder (241).

In a Danish study on the effect of childhood weight on lung function in adulthood, FEV1 and FVC values were reduced in obese men at 27 years of age, but the childhood BMI at 7 years of age was positively associated with both FEV1 and FVC (97).

The results of the different studies seem confusing, but there might be some consistency; mild overweight may be beneficial, but when substantial overweight or obesity develops, the effect turns to detrimental. The effect of excessive weight gain on lung function may be age dependent, and different multifactorial mechanisms may influence children and adults.

6.1.3 Allergies
In the present study, excessive weight gain at late school age decreased the occurrence of AD and sensitisation to outdoor allergens. There are only a few other follow-up studies concerning the relation between weight status and atopic diseases (127,154). Contrary to the present study, atopy and IgE levels associated with height and weight in the birth cohort study (127), and AD was connected to weight gain (11,154). In the previous studies, AR has been less common in obese children (11), and underweight children even had a higher risk for atopy in one study (123).

The association between allergy and weight may be sex dependent (95,96,114,127). In pooled data from seven epidemiological studies, allergy and overweight associated in girls (96), in line with the birth cohort studies (127). The present data were too small for relevant stratified sex-based analyses on the association between overweight or obesity and atopic diseases.

The link between weight status and asthma is poorly known. The most common presumption is that overweight or obesity reduces the production of inflammatory mediators which further modify the development of allergy. However the mechanism probably differs from the asthma obesity connection, which seems to be stronger in non-atopic individuals (12).

6.2 THE EFFECT OF INHALED CORTICOSTEROIDS’ ON BONE MINERAL DENSITY IN CHILDREN

6.2.1 Dual x-ray absorptiometry
The present follow-up study reveals the association between ICS use and reduced BMD measured by DXA at 12.3 years of age. The impact of ICS was seen in two separate ways: high cumulative ICS doses associated with reduced BMD in the femoral neck, and a significant negative effect on BMD in the lumbar spine and in the femoral neck emerged when ICSs has been used regularly before 6 years of age. Well-known confounding factors such as age, gender, pubertal stage, height, and weight status and the use of systemic corticosteroids were included in adjusted analyses with no substantial changes in results. Unfortunately, we did not have the exact data of physical activity and dietary habits to add in to the model.

Previous long-term follow-up studies have not found similar impacts on BMD, or findings have only been marginal (18,19,63). In the largest CAMP study with 4–7 years of follow-up time, the use of 200 µg of budesonide daily was associated with decreased bone
mineral accretion, and oral corticosteroids produced a dose-dependent reduction in bone mineral accretion in the lumbar spine, but only in boys (18). The Danish study did not find any significant differences in total BMD, bone mineral content, or total body calcium between the ICS and the non-ICS groups during 3–6 years of follow-up time (19). The most recent retrospective cross-sectional study did not find significant differences in lumbar BMD between pre-pubertal children using intermittent fluticasone with a 200 µg mean daily dose for 5 years and newly diagnosed asthmatic children with no history of ICS medication (196).

Studies with intermediate follow-up times have similar results. Fluticasone use for 2 years did not affect BMD accretion in the lumbar spine and femoral neck compared with nedocromil sodium (63). In line with the present study, an Australian study reported that the ICS therapy for 9–20 months reduced total bone mineral content in pre-pubertal children when compared with controls (190), but unfortunately, long-term follow-up results are not available.

The median cumulative ICS dose was higher in the present study than in the three previous studies (20,63,190,196). The high cumulative dose of ICS up to 1,800 mg might be one reason for positive results in this study.

Bone size influences the BMD_{areal} values; this can be minimised by the calculated aBMD_{vol}, which is similar in large and small bones (242). In the present study, aBMD_{vol} and BMD_{areal} gave similar results, and BMD_{areal} results were stable when adjusting with height. In the Helsinki Early Intervention Childhood Asthma study, daily treatment with budesonide reduced BMD compared with daily disodium cromoglycate in the crude analysis, but the results changed to negative when adjusted with height (20). The researchers discussed that monitoring height growth is sufficient for BMD monitoring. The interaction between height and BMD requires special attention in long-term follow-up studies. Bone size growth is not equal with the accretion of bone mineral content during growth (24). Thus, if the baseline BMD is low, it could stay low despite height growth (175). Therefore, the suggested height monitoring alone (20) may not be sensitive enough to estimate all significant changes in BMD in children receiving ICS medication.

Two separate findings of the present study might be explainable by bone physiology. The lumbar spine consists mainly of trabecular bone that has a rapid turnover, and the femoral neck consists mainly of cortical bone that has a slower turnover; therefore, lumbar spine is more susceptible to hormonal and metabolic effects (24). The previous studies in children have focused on the lumbar spine, thus mainly reflecting the effects on trabecular bone (18-20,63), and only one study has also assessed femoral neck (63). In this study, high cumulative doses during childhood were associated with changes in the femoral neck representing less frequently studied cortical bone. On the other hand, there might be a critical period in early childhood for changes in the lumbar spine representing trabecular bone.

BMD is dependent on age, sex, pubertal stage, and race (162,181). Physical activity increases BMD, and overweight could decrease BMD, but the effects seem to be sex and age specific (161,169,170). The number of study subjects in the present study was too small for sex-specific analyses, but the sex, age and pubertal stage were taken into account in the analyses. In addition, we could not evaluate the effects of ICS on growth in height because bone age was not studied by radiology. The Tanner classification is not sufficiently exact for the estimation of pubertal stage in growth studies. Also, the ICS preparation can
affect the results; the swallowed fluticasone propionate has low bioavailability and therefore negative results in studies done with it cannot be generalized to concern other ICS’s (196). In the present study, children used various drugs, and doses were estimated as the budesonide equivalents.

6.2.2 Peripheral quantitative computed tomography

To our knowledge, there are no previous paediatric studies on the effect of ICS on BMD measured with pQCT. In the present study, the use of ICS for asthma during childhood was associated with reduced BMD$_{vol}$ measured by pQCT at the median age of 12.3 years. The pQCT results are in accordance with the findings with DXA. Increasing cumulative ICS doses associated with decreasing BMD$_{vol}$, BMD$_{cort}$ and BMD$_{trab}$ in the distal radius. The results were similar after adjusting with potential confounding factors, such as age, sex, pubertal stage and weight status, and the use of systemic corticosteroids. There were no significant associations with BMD in the tibia. The present study did not find any age-specific differences in the ICS effect on BMD in pQCT measurements, and we could not confirm the finding that pre-schoolers are in the critical age for ICS side effects to BMD, which occurs in the DXA study.

Another new method, the density-related ultrasound, was applied in one study observing a tendency to reduced BMD in the calcaneal bone of children using ICS compared with a non-ICS group (187,187). In that study, asthma severity was associated with decreased BMD and physical activity with higher BMD; both are well-known confounding factors in BMD measurements. However, the ultrasonography is not comparable to DXA in diagnostic accuracy (243).

In the present study, data on physical activity were not systematically collected. Significant findings were in distal radius, whereas BMD in the tibia was not affected. Tibia is under substantial physical loading, which could prevent bones from detrimental effects of ICS. The benefits of physical activity to BMD and bone development are well known (159,161). In the present study, BMD was lower in the radius than that in the tibia, in agreement with earlier studies, but the correlation between the tibia and the radius BMD was lower than that in other studies (244).

6.3 METHODOLOGICAL ASPECT

6.3.1 Study design

This study was originally planned to evaluate the treatment of young wheezy children and to prevent recurrent obstructions, both being common, thus far unresolved issues in paediatrics. One hundred children younger than 2 years of age were recruited, most of them during their first wheezing episode. Background data were collected during the index wheezing episode in hospital, and follow-up data were collected during the prospectively scheduled follow-up visits, at 4.0, 7.2 and 12.3 years of median age. Only doctor-diagnosed asthma and other diseases were accepted. During this long-term follow-up study, the term bronchiolitis was originally used for index wheezing leading to hospitalisation at less than 24 months of age. Currently, early childhood wheezing is the more proper term for virus-induced wheezing in this age group, and it is used in the present thesis.

Increasing evidence has confirmed the relation between asthma and obesity, obtained mostly from epidemiological and birth cohort studies. At least in adults, asthma related to obesity is not equal to atopic asthma. This selected data give new information
about how obesity affects lung function in children who have suffered from wheezing provoked by infection in early childhood and are at risk of developing asthma. However, since obesity was strongly tracked from early school age to later school age, it was not possible to do any conclusions about the causality. The pulmonary function test results, both at early and later school age, gave opportunity to evaluate age differences in the influence of obesity. Atopic sensitisation was also possible to be estimated at both ages.

We used international references to define overweight and obesity, applying a British reference calculator for counting BMI-SDS. When starting the analyses of this thesis, the Finnish BMI-SDS curves based on national data were not available, but weight-for-height definitions of childhood overweight and obesity were used. The weight-for-height definitions vary between preschool-aged and school-aged children and are not internationally used. The new Finnish age- and height-related, sex-specific BMI curves are now available (231). The prevalence of obesity, calculated by new references, has remained nearly the same in boys (4.7% earlier vs. 4.4% currently), but for girls, the new Finnish references give notably lower figures of obesity (3.2% vs. 1.8%) (79,231). Thus, the prevalence of obesity would have been slightly lower in the present data, if the new Finnish BMI-for-age curves would have been used.

The attendance rate at the age of 12.3 years was good, 81% among those participating in the intervention trial, although the follow-up time was long. In addition, 14 children were hospitalised at the same time, and having fulfilled the inclusion criteria but refused to participate in the early intervention study, they attended the study visit at a later school age. This enables statistically relevant combined analyses in the BMD study. The follow-up data and entry to medical cards gave us reliable information about ICS use and other used corticosteroid medication. Nutritional, sport, and other lifestyle habits were not collected during the interview, which may have confounded the BMD results.

In the present study, no control group were recruited. One-third of the children had not been diagnosed as asthmatic, but only 21 children had never used any ICS; they were used as an internal control group in the BMD analyses.

In the BMD analyses, ICS use continuously or intermittent, more than 6 months was considered as a regular use. ICS medication for the prevention of recurrent wheezing in children at risk of asthma seldom continues for a long time; for asthma, it could continue through childhood. The overall ICS duration varied greatly, and therefore, we had difficulties to place the most appropriate time limit for regular use. We decided to use the shortest period used in previous studies to evaluate association between ICS and BMD, which has been 6 months (192-194). One aim of the study was to evaluate if there are age-specific associations between ICS use and BMD. Many children need ICS at preschool age but “grow out” of the wheezing tendency at school age. Because of the limited number of asthma patients and the varying periods of ICS use, the ICS use was analysed only in two groups, under school aged and school-aged use.

The results of this study can be generalised to concern children who have suffered from severe early childhood wheezing. The BMD study results can be assumed also to reflect changes in BMD in other children using ICS medication.

6.3.2 Strengths of the study
The main strength of this prospective, longitudinal post-bronchiolitis study is the long follow-up time, up to the median age of 12.3 years and a high participation rate. The viral
aetiology of wheezing infection was verified and the atopic sensitisation was tested (50,216,218,245). The diagnosis of asthma and AD were based on medical examination and strict criteria (50,212,218). Weights and heights were measured at all control visits with objective standard methods, allowing a reliable longitudinal BMI monitoring. Risk factors were carefully evaluated in the previous studies from the same cohort, allowing a proper use of adjusted analyses. In addition, data on the important confounding factors, such as pubertal stage and systemic corticosteroid use, were available, together with basic demographic information.

Although data on the use of ICS were collected retrospectively, which can be considered as a weakness of the study, ICS use was recorded relatively accurately due to participation in the follow-up study. In Finland, the diagnosis of asthma and the prescription of medication for asthma are performed by a paediatrician; hence, diagnostic accuracy can be considered to be good. The researcher had access to all medical cards, in hospital and primary health care, to collect the ICS data and data on the systemic corticosteroid medications.

6.3.3 Limitations of the study
The small number of the patients is a main limitation of the study. The study was evidently underpowered to reveal all associations between the studied variables. In addition, the material of the study was selected lessening the generalizability of the results. On the other hand, the group consisting of children hospitalised for wheezing in early life is important in health care; their risk for later pulmonary disorders is increased, and therefore, the knowledge of potential risk factors like obesity is important particularly in them.

Another shortcoming in the BMD study was the lack of bone age measurement because the Tanner classification is not sufficiently exact in the estimation of pubertal stage in growth studies. Therefore, we were not able to evaluate the effects of ICS on growth in height. Physical activities and diets, including vitamin D and calcium intake, were not systematically recorded, which is also a clear shortcoming of the study.

The numbers of children in the present study were too small for any relevant sex-specific analyses, which need to be counted as a shortcoming because sex is assumed to be one modifying factor between weight and asthma and atopic diseases. Also, results in previous BMD studies have been sex specific.
7 Conclusions

This prospective follow-up study had two focuses: the associations between weight status and asthma, atopy, and lung function during teenage years after hospitalisation for wheezing in infancy and the effect of ICS use during childhood on BMD in early adolescence. All children had suffered from severe bronchiolitis in infancy, about one-third of the patients had persistent asthma diagnosis later, and about one-fourth did not receive any corticosteroid medication during the follow-up time.

In the present study, there was no association between previous or current overweight or obesity and asthma or BHR at 7.2 or 12.3 years of (median) age. Overweight was associated with bronchial obstruction, as manifested by decreased FEV1/FVC at 7.2 years and 12.3 years of age and decreased flows in small airways at 12.3 years of age. Overweight and obesity at early school age preceded reduced FEV1/FVC at age 12.3 years. Nevertheless, since overweight was highly persistent from early to late school age, the influence of previous and current overweight could not be assessed separately, and the present study could not estimate causality. Preliminary evidence was found that obesity may associate with a reduced risk of allergy at late school age, but the biological mechanism for this association is unknown and we could not estimate if there is any causality in this outcome either.

The BMD study revealed that the use of ICS during childhood may reduce BMD measured at teen age in children hospitalised for wheezing in infancy. High cumulative ICS doses were associated with reduced BMD in the femoral neck. Reduced BMD in the lumbar spine and in the femoral neck when apparent volumetric BMD was calculated was associated to regular ICS use before 6 years of age. Height-adjusted areal BMD and apparent volumetric BMD gave almost similar results. High cumulative doses during childhood were also associated with changes in volumetric BMD in the distal radius, including all its components: total, cortical, and trabecular bone. There were no significant associations between ICS use and BMD in tibia. The results remain similar when adjusted for known potential confounding factors: age, gender, pubertal stage, and weight status and use of systemic corticosteroids.

These results stress the importance of prevention of excessive weight gain in preschool-aged and school-aged children after early childhood wheezing. The prevention of overweight may prevent asthma and at least asthma-like symptoms. Asthma treatment with ICS can have detrimental effects on BMD. However, the clinical manifestations can occur later, in middle-aged adults or even in the elderly. Titrating ICS medication is recommended to the lowest possible dose to maintain asthma control. Also, proper asthma diagnosis with pulmonary function tests is important to target the needed long-term medication for children. Based on these preliminary results, we recommend considering the measurement of BMD in children with a long history of ICS medication, especially if they have other risk factors for low BMD.

Long-term follow-up studies are needed to clarify the complex connections and causality between asthma, allergic diseases, and weight. Further studies on how ICS during childhood affects adult BMD and bone mass are needed.
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Asthma is common disease in childhood. Obesity is increasing health problem related to asthma. The use of inhaled corticosteroids (ICS) for childhood asthma has steadily increased. This long term follow-up study contains 100 children hospitalized for wheezing in infancy and followed until 12.3 years of age. In the present study, we evaluated the association between overweight and asthma, allergies and lung function and ICS' effect on bone mineral density at early teenage in this asthma risk group.