

From DEPARTMENT OF WOMEN'S AND CHILDREN'S HEALTH  
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**ASTHMA IN ADOLESCENTS,  
DURING THE TRANSITION FROM CHILD TO  
ADULT, EFFECTS ON PHYSIOLOGICAL  
PARAMETERS AND HEALTH RELATED  
QUALITY OF LIFE**

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## ABSTRACT

The aims of this thesis were to evaluate physiological and allergic aspects and consequences of asthma and possible correlation between Health Related Quality of Life (HRQOL) and atopy, lung function, bronchial hyper-responsiveness and regular physical exercise. Possible risk factors for deterioration among patients in their late teenage years prior to and following transfer to adult healthcare were examined. The study was designed to investigate possible differences between boys and girls, changes over time in these respects and additionally the impact of randomized referral to either a specialized asthma clinic or primary care on the same factors.

In this prospective study, conducted at the asthma/allergy clinic of the Childrens Hospital at Huddinge University 155 teenagers (69 females) with asthma were followed over a five year period. The patients were recruited consecutively and were screened employing spirometry, histamine challenge (to investigate bronchial hyper-responsiveness), skin prick test for allergy, and filled out "The Living With Asthma Questionnaire" both at the time of entry into the study and after 2 and 5 years of follow-up. An exercise test and questions about regular performed exercise were carried out at baseline and 5 years later. Adolescents with mild-to-moderate asthma were assigned randomly to care at the adult asthma clinic or primary care.

When entering the study 89% were atopic. Lung-function increased from 94.0% of predicted ( $FEV_1$  mean value for the whole group (SD 12.9%) to 97.7% over the study period. Their Bronchial hyper-responsiveness decreased ( $PD_{20}$  for histamine chloride was median 440 $\mu$ g at entrance and increased five years later to 790 $\mu$ g) and working capacity decreased. At all three time points HRQOL for the men was generally better than that of the women. After five years HRQOL increased for both men and women but still the men had better HRQOL at the total score (of the scale) compared to the women. Young women who exercised regularly exhibited significant better HRQOL than those who did not whereas regular exercise had no impact on the HRQOL of the young men. Women with severe asthma demonstrated a poorer HRQOL than those suffering from mild-to-moderate asthma. Lung function, atopy, bronchial hyper-responsiveness did not exert any impact on HRQOL. Poor adherence to asthma treatment was associated with lower HRQOL as well as bronchial hyper-responsiveness. Adolescents with mild-to-moderate asthma showed no difference in HRQOL regardless of whether they received specialized treatment or primary care, lung function, atopy or bronchial hyper-responsiveness.

Suffering from asthma during late adolescence was associated with lower HRQOL for women than for men and this negative impact on adolescent women was enhanced when asthmatic symptoms were more severe. The HRQOL of both male and females improved as they grew older and entered adulthood. Lung function improved but hyper-responsiveness persisted. Female gender and poor adherence to asthma treatment exerted negative impact on bronchial-hyper responsiveness and HRQOL which emphasizes the importance of health care programs that include patient education and support for adolescents with asthma as they are transferred from pediatric to adult health care. Mild-to-moderate asthma care can be equally handled in the primary care system.

**Key words:** Adherence, adolescents, asthma, females, physical exercise, Quality of Life, transition, young adults.



## LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to into the text by their roman numerals (I-II).

- I. **Sundell K**, Bergström S-E, Hedlin G, Ygge B-M, Tunsäter A.  
Quality of Life in adolescents with asthma, during the transition from child to adult. *The Clinical Respiratory Medicine*, accepted June 2010
  
- II. **Bergström S-E**, Sundell K, Hedlin G  
Adolescents with asthma: Consequences of transition from pediatric to adult healthcare. *Respiratory Medicine* (2010) 104, 180-187

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## LIST OF ABBREVIATIONS

ATS	American Thoracic Society
BHR	Bronchial hyper responsiveness
BMI	Body Mass Index
FEV <sub>1</sub>	Forced expiratory volume in one second
FVC	Forced vital capacity
HRQOL	Health Related Quality Of Life
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroids
kP	Kilo pond
OR	Odds ratio
PD <sub>20</sub>	Provocation dose with a decrease in FEV <sub>1</sub> with 20%
QoL	Quality of Life
rpm	Rates per minute
SF-36	Short form 36 Health Survey
WHO	World Health Organization
WHOQOL	World Health Organization Quality Of Life



# 1 INTRODUCTION

Asthma, a multi-factorial disease and one of the most common chronic diseases among adolescents, affects approximately 10% of teenagers in Sweden and most other Western countries [1, 2]. Worldwide asthma is estimated to affect 300 million individuals [3]. Probably the prevalence of asthma increases with age. Recently a Swedish report states that 7% of four- years-old children and 5% of twelve-years-old children and approximately 10% of the adult population have asthma [4]. Adolescent asthma is almost as common as this disease is in young children and more frequent than in adults [5]. There is some concern that asthma during adolescence may predispose an individual for chronic obstructive lung disease later on. Previous studies indicate that FEV<sub>1</sub>/FVC ratio at 35 years of age is significantly lower among individuals who suffer from childhood asthma that persists beyond the age of 16. Strachan as well as Sears have demonstrated that in males the severity of asthma decreases significantly during the progression from childhood to adulthood, whereas females exhibit a tendency to develop more serious asthma during adult life [6-8]. Chronic asthma affects daily activities in many patients with influence on quality of life and the need of medical treatment [9, 10].

## 1.1 ASTHMA, BRONCHIAL HYPER RESPONSIVENESS AND ATOPY, A SYSTEMIC DISEASE

Asthma is characterized by variable airflow obstruction, chronic inflammation (in which eosinophils are considered to play a major role [11]) and bronchial hyper-responsiveness (BHR). This hyper responsiveness indicates an increased sensitivity to irritants, which may be classified either as specific (allergen induced) or as non-specific (induced by physical stimuli such as cold air and exercise, pharmacological agonists such as histamine and metacholine, respiratory infections, etc [12, 13].) Asthma can be intermittent, or persistently mild, moderate or severe. Severity varies among individuals and can change in one individual over time [14]. As a systemic disease, allergic asthma is often associated with other allergic manifestations as rhinitis, eczema and food allergy which are common in children and adolescents [15, 16]. Respiratory inflammation commonly affects both the upper and lower respiratory tracts concurrently. Attention to the presence of asthma in patients with rhinitis or inversely is of importance while this condition often affect HRQOL more negatively as asthma alone [17-20]. While the physiological factors that influence one's risk for developing asthma have been examined extensively, the psychological aspects of this condition have been less well characterized [21]. There is also a lack of studies among adolescents between the ages 17-20 years old. Most studies are carried out in older or younger populations.

## 1.2 ASTHMA TREATMENT

In accordance to the "Global Initiative for Asthma management and prevention" (GINA), asthma treatment decisions are made based on the severity of the disease [10]. The goal of modern asthma treatment is to achieve and maintain asthma control in a long term perspective. Prevention and avoidance of exacerbating and amplifying factors are of the highest importance together with pharmacological therapy. The

medical treatment consists of multiple medications of which corticosteroids,  $\beta_2$ -agonists mostly delivered by inhalation and antileukotriens are the most common for the asthma patient. To understand and follow the medical treatment regimens the patient needs good knowledge about the asthma disease, how to use the different inhalers and how to avoid factors that can result in exacerbations. Often lifestyle changes as eg. the need of daily medication, giving up smoking, getting rid of a pet and starting with regular physical exercise, are necessary to achieve asthma control. Therefore patient education and support to necessary changes in daily life are important parts of the total treatment of asthma [22].

### **1.3 ADHERENCE TO ASTHMA TREATMENT**

Adherence is defined by the World Health Organisation (WHO) as the extent to which a person's behaviour in terms of taking medication, following a diet, and or executing lifestyle changes, corresponds with the agreed recommendations from a health care provider [23]. Research across a range of chronic illnesses indicates rates of non-adherence of approximately 30% in children with chronic illness with a trend towards even higher rates (about 50%) among adolescents with asthma [24, 25]. Several earlier studies indicate that the major reason for poor asthma control is that patients fail to adhere to their treatment [26-28].

There are many reasons why adolescents are reluctant to take their asthma medication. They may be self-conscious about using inhalers because they do not want to appear different from their peers. Denying the severity of their symptoms and the need for regular treatment is also common. Worries about side effects and concerns about becoming dependent on their medication are not unusual [28].

### **1.4 TEENAGE PERIOD AND PSYCHOSOCIAL DEVELOPMENT**

The period of normal adolescent development can be divided in to three stages as characterized by Towns [29]:

- 1 Early adolescence: 12-14 years. Preoccupation with the physical changes of puberty.
- 2 Middle adolescence: 15-16 years. Separating from parents and establishing a sense of self peers among peers as a worthwhile individual is the primary task.
- 3 Late adolescence: 17-19 years. At this time, with the development of abstract reasoning skills and more future-oriented thinking, defining functional roles in terms of work, lifestyle and forming long-term relationships becomes more common.

In the age period between 17-19 years important psychological changes occur at the same time as the teenager strives for emancipation and must make decisions of importance for his/her future [30].

### **1.5 RISK FACTORS**

Having asthma may be associated by the adolescent with being different to his or her peers and can be resented, denied, hidden or ignored. This can result in varying degrees of non-adherence to treatment plans and as a consequence predispose adolescents with

asthma to poor asthma control with increased morbidity and mortality[31]. For that reason good and specific developed treatment plans for this age group are of great importance [32]. Asthma can affect teenagers in different ways according to their developmental stage. During late adolescence it could have a negative impact on “vocational options” and “concerns about relationships and children” [29].

## **1.6 TRANSITION FROM CHILD TO ADULT HEALTH CARE**

During the adolescence, patients with chronic diseases experience at least two kinds of transition: (i) transition from parental management to self management and (ii) transition from child centered to adult centered health care. This transition period could be an additional challenge to achieve adherence. There is considerable evidence that adolescent asthma patients are the most non-adherent and that asthma outcome is closely related to medication adherence [24, 33]. When leaving child health care adolescents with asthma are at risk of dropping out of regular medical care if the transition is not prepared carefully [34, 35].

## **1.7 SPORTS-PHYSICAL ACTIVITY**

In late adolescent period, teenagers are generally not offered organized participation in sporting activities and initiative for physical exercise must be taken on an individual basis [36]. It has previously been shown that older children and adolescents do not have the same intrinsic requirement of physical activities as young children. Physical activity promotion in schools is therefore recommended at this time [37]. Welsh et al demonstrate that training programs significantly improve aerobic fitness in children and adolescents with asthma, reducing the frequency of hospitalizations and wheezing, absenteeism from school, the number of consultations with physicians and use of medication, as well as improving HRQOL[38].

## **1.8 HEALTH RELATED QUALITY OF LIFE (HRQOL)**

Many attempts have been made to define the term “Quality of Life” (QOL), however most researchers agree that QOL is a multidimensional construct [39]. The definitions of quality of life are often linked to health and emphasize such components as happiness, personal well-being, life satisfaction, and impact of illness on social, emotional, occupational, and family domains. The “World Health Organization Quality of Life Group” (WHOQOL) defines QOL as the individual’s perception of his/her position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns [40]. The overall QOL can be described as the dynamic interaction between the external conditions of the individual’s life and the internal perception of those conditions. The term “Health Related Quality Of Life” (HRQOL) emphasize that we are focusing on the effects of disease and its treatment. HRQOL has now become a standard end point in many randomized clinical trials and other studies to identify those aspects of HRQOL that may be affected by the therapy or trials that are expected to improve HRQOL [39].

Chronic asthma has consequences on an individual’s lifestyle. This requires continuous adaption to daily medication, avoid triggers, regular visits to healthcare centers and coping with occasional exacerbations. These demands impose on most aspects of the

adolescent's life, including school, meals, sports, travel and dating (HRQOL). It is not surprising that low self-esteem and social dependence, which may in them self render effective asthma management more difficult, are more common among adolescents with a chronic disease than among their healthy peers [30, 41, 42].

In order to measure HRQOL a number of instruments have been constructed. There are accepted methods of developing instruments that measure HRQOL [43]. There are two kinds of instruments measuring HRQOL: generic instruments and disease-specific instruments. The construction of generic instruments is based on large population surveys. This type of instruments gives an opportunity to compare scores between asthma and other chronic diseases while disease –specific instrument measures the impact of a specific disease on HRQOL [44]. The instruments used today are tested for reliability, responsiveness, validity and interpretability. At the time when this study was designed (1993) we only used the disease- specific “Living with Asthma Questionnaire” [45], because using both generic and disease-specific instruments was not common at that time. The nowadays often used generic instrument SF-36 was adapted for Swedish conditions in 1995 [46].

## 2 AIM

The overall aim of this thesis was to study adolescents with asthma during the transition period from childhood to adulthood and especially the impact of asthma on Quality of Life. The specific aims were:

- To prospectively analyze HRQOL in adolescents with asthma over a five year period and to study if there were any differences between boys and girls in the development of the disease.
- To investigate correlations between HRQOL and atopy, bronchial hyper responsiveness, lung function and regular exercise.
- To compare HRQOL, atopy, bronchial hyper responsiveness, lung function and regular physical exercise in patients receiving care at a hospital-based asthma/allergy clinic with those followed-up in the primary care organization.
- To identify possible risk factors for deterioration among patients with asthma in late adolescence prior to and following transfer to adult health care.

### **3 MATERIAL AND METHODS**

The papers in this thesis present results from a prospective five- year follow up study concerning adolescents with asthma. The main objective was to study factors affecting asthma prognoses in the age period when transition from child to adult health care take place

#### **3.1 STUDY POPULATION**

Initially 156 young people; including 69 women and 87 men with asthma were recruited consecutively from the asthma/allergy clinic at the Children´s Hospital, Huddinge. All subjects fulfilled the ATS criteria for asthma [47]. They had visited our clinic regularly for at least three years for treatment of their asthma and in several cases, other allergies such as allergic rhinitis and eczema. Their mean age at the time of entry into the study was 17.7 years (range 15.9-21.9, median 17.1) with six being older than 20 years of age. Of our subjects 77% reported receiving regular treatment with inhaled corticosteroids.

Information concerning medication was supplied by the patients themselves and not based on drug prescriptions. Patients inhaling  $\geq 600$  ug corticosteroids (budesonide or equivalent) as daily dosage or demonstrating a FEV<sub>1</sub> that was <80% of the expected despite such inhalation of corticosteroids were designated as suffering from severe asthma, while in the other cases the asthma was considered to be mild-to-moderate [48]. The former group was followed up at the adult asthma clinic (n=53), while those with mild-to-moderate asthma were randomly assigned to the adult asthma clinic (n=51) or to primary care (n=46).

Two of our original patients could not continue to participate due to mental retardation, one was found to have a disease of the chest wall in addition to his asthma; and three declined to continue, so that the final study group included a total of 150 subjects. Patients who admitted that they often did not take their prescribed drugs and/or who missed more than two consecutive clinical visits (without a reasonable explanation) were considered to demonstrate “poor adherence to asthma management”. Exposure to tobacco smoke at home was reported by 42 patients, of whom 13 where themselves active smokers at the time of entry.

#### **3.2 STUDY DESIGN**

All subjects in paper I and paper II were evaluated with respect to a skin prick test, spirometry, a bronchial challenge with histamine and Health-Related-Quality-of Life (HRQOL) at the time of their entry into the study and in connection with follow-up two and five years later. An exercise test and questions about regularly performed exercise were also carried out at the time of entry and five years later (Table I). The examinations took place at the adult outpatient clinic for Asthma and allergy at Huddinge University Hospital and were performed by the author at all three occasions. At the time of entry into the study the exercise tests were performed by a physiotherapist and the author together.



**Table I. Performed examinations during the study period**

	<b>At entry into the study</b>	<b>After 2 years</b>	<b>After 5 years</b>
<b>HRQOL</b>	<b>X</b>	<b>X</b>	<b>X</b>
<b>Skin pricktest</b>	<b>X</b>	<b>X</b>	<b>X</b>
<b>Lung function test with Spirometry</b>	<b>X</b>	<b>X</b>	<b>X</b>
<b>Histamine challenge</b>	<b>X</b>	<b>X</b>	<b>X</b>
<b>Exercise test and BMI</b>	<b>X</b>		<b>X</b>
<b>Questions about regular performed exercise</b>	<b>X</b>		<b>X</b>

### **3.3 THE CLINICAL INVESTIGATIONS**

We used a Vitalograph spirometer (Vitalograph, Buckingham, UK) and forced expiration in the standing position without noseclips were employed in accordance with the criteria of ATS [47].

#### **Test for allergy**

The skin prick test was performed with standard dilutions (100,000 BMU/ml) of 12 different allergens (*birch, timothy, grass, mugwort*, cat, horse, dog, dermatophagoides pteronyssinus, cladosporium, alternaria, aspergillus fumigates, fish and peanut) in 50% glycerol (Soluprick, ALK, Denmark). The reaction was regarded as positive if the diameter of the wheal was  $\geq 3$ mm.

#### **Bronchial challenge with histamine**

At the time of entry into and in connection with the follow-ups two and five years later, each subject inhaled histamine phosphate through an automatic inhalation-synchronised jet nebulizer (Spira Elektro 2) equipped to provide an adjustable aerosol delivery time, as described previously [49]. Three concentrations of histamine diphosphate were applied (1, 8 and 64mg/ml); at each concentration 2, 4, 8 breaths were taken and FEV<sub>1</sub> was determined 3 min after each dose. The dose of histamine inducing a reduction in FEV<sub>1</sub> of  $\geq 20\%$  (PD<sub>20</sub>FEV<sub>1</sub>) was calculated by linear interpolation employing a logarithmic scale.

#### **Exercise test and BMI**

A sub maximal exercise test on an ergometer cycle (Ergomed 824E, Monark, Sweden) was performed and evaluated as described previously [50, 51] upon entry into the study and in connection with the five-year follow up. Since submaximal working capacity was being assessed, each subject inhaled a  $\beta_2$  agonist and warmed up by cycling gently for 10 min prior the actual test, in order to prevent an asthmatic reaction. Heart rate was measured continuously with a Polar sport tester. The initial workload was set at 0.5 or 1.0 kP on bases of weight, gender and exercise habits. A constant pedal speed of 50

rpm was maintained throughout the test and heart rate was recorded every minute until steady state was reached. The body-mass index (BMI) was calculated as weight in kg/ (height in m)<sup>2</sup>. Regular performed exercise was defined as participating in regular sport activities more than 2 h each week.

### **Health-Related-Quality-Of-Life (HRQOL)**

HRQOL was assessed with the “Living with Asthma Questionnaire”, translated with validation into Swedish and adapted to Swedish circumstances [45, 52]. This questionnaire encompasses 11 domains including a total of (68 items), i.e. (1) *Social and leisure activities*; (2) *Sports*; (3) *Holidays*; (4) *Sleep*; (5) *Work and other activities*; (6) *Colds*; (7) *Mobility*; (8) *Effects on others*; (9) *Medication usage*; (10) *Sex*; (11) *dysphoric states and attitudes*. This instrument also evaluates two cognitive (activities and avoidance) and two emotional factors (distress and preoccupation), as well as compensating for bias (i.e., the tendency to agree with items irrespective of their content).

The subject responded to each statement as “untrue”, “slightly true” or “very true” or chose the alternative “not applicable”. The quality-of-life in each domain was calculated, according to Hyland, as the sum of the scores for all individual items divided by the number of items, i.e., the mean scores which were subsequently analyzed as continuous variables.

### **3.4 STATISTICAL ANALYSES**

Since some of the values for FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, PD<sub>20</sub>, (log transformed), working capacity and BMI for the three different time-points (i.e. entry and the two- and five-year follow ups) were not obtained for all subjects, these data were analyzed statistically employing a mixed model. The variables FEV<sub>1</sub>, FEV<sub>1</sub>/FVC and log PD<sub>20</sub> were analyzed utilizing a linear model for repeated measures, with estimation by the REML procedure and the covariance structure set to compound symmetry. The associations between each of these outcome variables and set of prognostic parameters (i.e. sex, adherence to asthma treatment, exposure to tobacco smoke and furry animals, BMI, exercise habits and the presence and trend over time of rhino-conjunctivitis, eczema or significant skin prick test to either pollen allergens or furry animals) were analyzed, as were two- and three-way interactions.

A robust model was estimated for each outcome variable and the slope parameters and confidence intervals associated with each prognostic variable estimated. Patient impairment with respect to FEV<sub>1</sub>, FEV<sub>1</sub>/FVC and the histamine challenge (PD<sub>20</sub>FEV<sub>1</sub>) was recorded as “yes” or “no” and these binary outcomes analyzed by logistic regression. In order to evaluate the association between each outcome variables, a linear model for the log odds was established and the odds ratio (OR) and confidence interval associated with each prognostic variable estimated. Where indicated, Student’s *t*-test or Pearson Chi-square test were used to compare subgroups of study population. The differences in HRQOL between men and women were analyzed (for each subject) in connection with the two and five-year follow-ups utilizing the non parametric Wilcoxon Signed Rank Test. Comparison of the various factors (gender, atopy, physical activity, asthma severity and follow-up in primary care or at the specialized outpatient clinic) was carried out with the non parametric Mann-Whitney test. Possible

correlations between HRQOL and lung-function and degree of hyper-responsiveness were examined with the Spearman's rho procedure. In connection with all these comparisons, a p-value of  $<0.05$  was considered to be statistically significant. Finally in paper **II** adjustment for atopy, physical activity, gender, severity of asthma, treatment with inhaled steroids, smoking habits (active, passive) and adherence to asthma treatment was obtained with logistic regression.

All analyses were performed using the SPSS statistical package version 14.0 (SPSS Inc, Chicago, IL, USA) or Statistica version 7.1 (StatSoft Tulsa, OK) software.

### **3.5 ETHICAL CONSIDERATIONS**

These two studies were approved by the Ethics Committee at the Huddinge University Hospital and informed consent, based on oral and written information was received from both the patients involved and their parents.

## 4 RESULTS

Paper I and paper II show, that asthma can affect HRQOL negatively in females and that regular physical activity in young females increase HRQOL. Furthermore our investigation demonstrates that the HRQOL improves with age during the transition period from child to adult for both males and females. Pulmonary function rarely deteriorated over the five-year study period, but for the great majority of the study population bronchial hyper responsiveness persisted. Female gender and poor adherence to asthma treatment exerted a negative impact on HRQOL and bronchial hyper responsiveness. Adolescents with mild-to-moderate asthma regardless of whether they received specialized treatment or primary care showed no difference in HRQOL, lung function, atopy, bronchial hyper-responsiveness and working capacity.

Additional data from our subjects at the time of their entry into the study are shown in table 2.

**Table 2. The basic data of the subjects in paper I and II at the time of their entry into the study**

Parameter	The entire study population		Mild to moderate asthma	
	( <i>n</i> = 150)	( <i>n</i> = 53)	Randomized to specialized clinic ( <i>n</i> = 51)	Randomized to primary care ( <i>n</i> = 46)
Females (%)	43	35	68	64
Mean ages in years	18	18	17	17
Positive skin prick test (%)	89	87	86	96
Regular treatment with inhaled steroids (%)	77	84	17	17
Demonstrating with BHR	72	75	76	65
Working Capacity				
- High	58	47	65	60
- Medium	24	29	23	28
- Low	16	24	14	12
Exercised regularly	57	45	67	63
BMI >25 %	19	24	17	18

**Paper I** shows the *Health-Related-Quality-of-Life (HRQOL)* in the study group in connection to gender, asthma severity, atopy, lung function, BHR and regular performed exercise over a five year period.

At all three time points HRQOL for the men was generally better than that of the women both in terms of the overall scores of the scale ( $p < 0.001$ ) and in 6 of the 11 domain of the scale. After five years HRQOL increased for both men and women but still the men had better HRQOL at the total score of the scale compared to the women. Regular physical exercise (i.e., running, ball sports, aerobics etc.  $\geq$  two hours each week) at the time of entry into the study exerted a significant positive effect on the overall mean HRQOL score for the female subjects, as well as on their scores for 6 of the individual domains and the sub domains reflecting cognitive factors (i.e., activity and avoidance) and the emotional factor disability. However, after five years of follow-up these differences were no longer observed (shown in paper I). In contrast regular exercise had no impact on the HRQOL of the young men.

Young women suffering from severe asthma at the time of entry into our study had a lower overall mean score ( $p < 0.05$ ) than did the women with mild-to-moderate asthma at this same time-point. However after 5 years of follow-up, all of these differences had disappeared. In the cases of the young men the severity of asthma exerted no significant impact on the overall mean score. However, after five years of follow-up these differences were no longer observed.

**Table 3. Quality of Life outcomes at the time of entry into the study among females and males assessed with the “Living with Asthma Questionnaire”**

	Males	Females	P-value*
Overall score	2.6 (0.03)	2.5(0.04)	<b>&lt; 0.005</b>
Social and leisure activities	2.6 (0.04)	2.3 (0.05)	<b>&lt; 0.005</b>
Sports	2.8 (0.05)	2.6 (0.06)	< 0.01
Holidays	2.5 (0.05)	2.4 (0.07)	0.38
Sleep	2.8 (0.04)	2.7 (0.05)	<b>&lt; 0.01</b>
Work	2.5 (0.04)	2.4 (0.06)	0.10
Colds	2.5 (0.06)	2.2 (0.06)	<b>&lt; 0.005</b>
Mobility	2.8 (0.03)	2.5 (0.05)	<b>&lt; 0.005</b>
Effects on others	2.5 (0.04)	2.4 (0.05)	0.15
Medication usage	2.5 (0.05)	2.3 (0.06)	0.18
Sex	2.9 (0.04)	3.0 (0.02)	0.13
Dysphoric states and attitudes	2.7 (0.03)	2.5 (0.04)	<b>&lt; 0.01</b>
Activity	2.7 (0.03)	2.5 (0.05)	<b>&lt;0.01</b>
Avoidance	2.6 (0.03)	2.5 (0.05)	<b>&lt;0.005</b>
Disability	2.7 (0.04)	2.2 (0.04)	<b>&lt;0.05</b>
Apprehension	2.5 (0.04)	2.2 (0.05)	<b>&lt;0.01</b>

Standard error within brackets

\*Mann-Whitney Test

P-value = the difference between males and females

At the time of entry into the study the major differences described above were not altered by adjusting for atopy, regular exercise, gender, treatment with inhaled steroids, smoking habits (active, passive) and severity of asthma employing a logistic regression model. However, this model did reveal that poor adherence to the recommended asthma treatment was associated with lower HRQOL (OR= 0,29; 95% CI= 0.11-0.73;  $p<0.01$ ).

There was no correlation between the FEV<sub>1</sub> value (as a percentage of the predicted value) and overall HRQOL throughout the study. Neither atopy nor bronchial hyper-responsiveness appeared to exert any impact on HRQOL. The HRQOL's of subjects receiving primary care or care at the specialized asthma clinic were similar and the HRQOL, lung function, bronchial responsiveness, working capacity and atopy of the drop-outs were the same as for those who completed this study.

**Paper II** shows the clinical results concerning asthma severity, atopy, lung function, BHR, working capacity, BMI and regular performed exercise and gender differences over the five year study period.

### **Skin Prick tests**

When entering the study 89% were atopic and sensitization towards all three animal dander was more frequent among females (47.8%) than males (26.2%,  $p= 0.005$ , Student's t-test). No significant changes in responses to the skin prick tests were observed during the five-year study period.

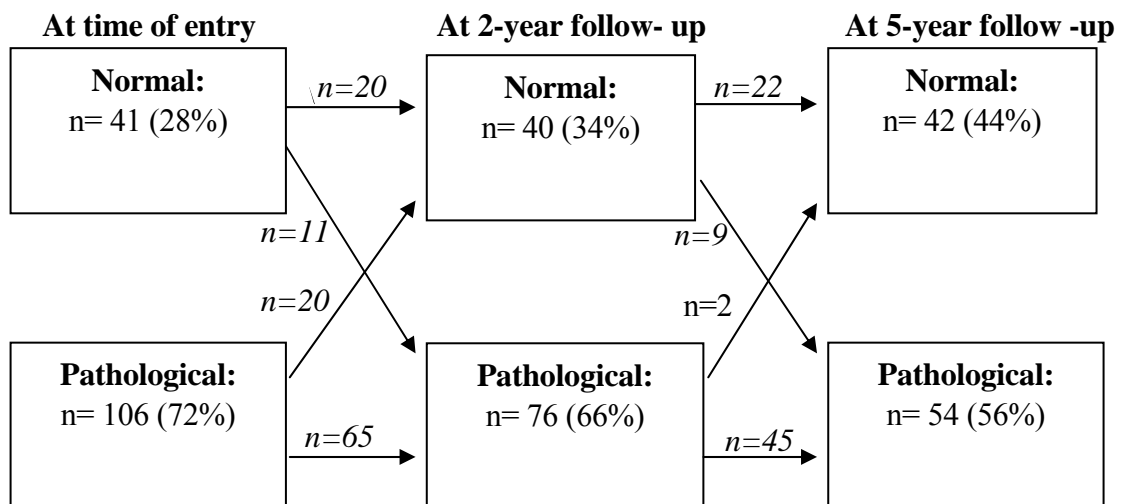
### **Lung function**

Lung-function for the whole group increased from 94.0% of predicted (FEV<sub>1</sub> mean value for the whole group to 97.7%,  $p<0.01$ ) over the five year study period. A multiple regression model demonstrated no correlation between FEV<sub>1</sub> (% pred) and any of the independent factors examined (gender, poor adherence, exposure to tobacco smoke, pets at home, BMI, regular exercise a positive skin prick test to either pollen allergens or furry animals, treatment with ICS or transfer to primary care).

### **Bronchial challenge test**

The proportion of our patients classified as having (BHR) to histamine decreased during the five-year study period ( $p=0.01$ ). However, the PD<sub>20</sub> for a considerable number of our subjects also deteriorated to  $\leq 880 \mu\text{g}$  indicating an ongoing variation during this late teenage period (Figure 1). The only risk factor for PD<sub>20</sub>  $\leq 880 \mu\text{g}$  in connection with the five-year follow-up was "poor adherence" to treatment, whereas regular exercise was associated with reduced BHR.

## Variability in the PD<sub>20</sub> FEV<sub>1</sub> histamine during the 5-year study period



**Figure 1** Schematic illustration of the numbers (%) of subjects with normal (>880 ug) and pathological ( $\leq 880\mu\text{g}$ ) PD<sub>20</sub> FEV<sub>1</sub> histamine at the time of entry and at two- and five- years of follow up. The numbers in italic illustrate the carry-over of patients between the follow-up periods.

When the multiple regression model was employed to analyze possible correlations between log PD<sub>20</sub> at the time of the entry and the independent factors described above, female gender ( $p < 0.01$ ), sensitization to furry animals ( $p < 0.003$ ) and “poor adherence” to treatment ( $p < 0.0022$ ) were all found to exert a significant negative. At the time of the five-year follow-up treatment with ICS ( $p = 0.0026$ ), “poor adherence” ( $p = 0.0032$ ) and atopy ( $p = 0.011$ ) exerted similar negative impacts, whereas regular exercise was associated with a more favorable PD<sub>20</sub> ( $p = 0.0041$ ).

### Working capacity and BMI

The exercise test was performed by 123 subjects at the time of their entry into the study and repeated by 91 of these in connection with the five-year follow-up. Mean total oxygen uptake decreased from 3.1 l to 2.9 l/min ( $p = 0.047$ ) and in relation to weight, from 48.3 (SD 10.6) to 40.6 ml/kg/min ( $p < 0.001$ ) between these two time-points. No significant correlation between oxygen uptake and lung function, the histamine challenge, atopy, gender or any of the other risk factors examined (see above) was observed. Participation in regular exercise outside of school or work (>2 hours/week) declined from 28% at the time of entry to 16% at the five-year follow-up.

At the time of entry their mean BMI was 22.4 and 24 patients (19%) had a BMI >25 (including 12 (19%) of the women). At the five-year follow-up the mean BMI had increased to 23.8 (SD 3.8) and was >25 in 32 (35%) of the subjects (including 13 (28%) of the women).

## **Drop-outs**

Of the 150 patients initially included in the study, 116 (77.3%) and 104 (69%) performed both HRQOL, lung function test and histamine challenge in connection with the two- and five-year follow-ups respectively (Table 1). The total of 46 subjects (30.7%) who dropped out during the course of our investigation included 35.3% (n=30) of the men and 24.6% (n=16) of the women. The characteristics of these 46 and those subjects who finished the study showed no significant differences at the time of the entry, except that a positive skin prick test to pollen allergens was less frequent among the drop-outs ( $p=0.03$ , Pearson Chi-square test), although the response to perennial allergens was similar.



## 5 DISCUSSION

Our major findings from the clinical investigations were that, with a few exceptions, adolescents with asthma who are leaving pediatric care exhibit normal lung function and that most of those with impaired lung-function (as reflected in their FEV<sub>1</sub>) have improved five years later. Lung function and HRQOL did not correlate during the five year study period which is in line with earlier investigations of asthma and HRQOL [53, 54]. The present study also demonstrates that severe asthma in young women had a negative impact on HRQOL. This may be explained by increased bronchial hyper-responsiveness in this group. The gender differences in HRQOL in our study are also consistent with results in a previous study on the same age group [55] and in line with other studies concerning females with asthma and HRQOL[54].

It is known that HRQOL-measurements in general show lower HRQOL in females than in males independent of a specific disease [55, 56]. This could reflect a gender specific way of coping with chronic diseases that may be important in the interaction between patients and caregivers.

Depression and anxiety in patients with chronic somatic diseases is common and in adolescents with asthma, psychiatric disorders such as depression as well as emotional and/or behavioral problems is more common compared to adolescents with other chronic diseases. [57-59]. Several studies have shown how this can affect asthma control and quality of life [58, 60]. Even in our cohort we found this but only in females indicated by their response to the “Living with Asthma Questionnaire” Domain 11 ”*Dysphoric states and attitudes*” and its subgroups ( *activities and avoidance*) and (*distress and preoccupation*). This significant gender difference disappeared during the five year study period. However earlier investigations concerning gender differences in QOL in adults with asthma and other lung diseases show the impact of anxiety on the control of the disease [53, 54, 61, 62]. This gender aspect should be taken into account in the total care of the asthma patient. Furthermore there is also a need of discussion concerning how young boys with severe asthma may be denying there chronic disease and therefore are at risk of non-adherence and under treatment of their asthma symptoms.

As the clinical results in Paper II did not correlate with “The Living with asthma Questionnaire” which is in line with the authors below. Physiological investigations such as spirometry, skin prick and bronchial challenge tests do not tell us all about how patients with asthma experience their disease. Evaluation of overall health status should also incorporate HRQOL measures [63].

Careful preparation regarding the transition from pediatric to adult health care is suggested by us and others as it is expected that the adolescent patient will gradually be taking over the responsibility for treatment and asthma control from the parents [49, 64]. As asthma and allergy today affect a large part of the population, most of the patients are handled in the primary care system. National as well as international management guidelines are developed for patients with this chronic disease [65-68]. Asthma severity plays a decisive role when deciding if the patient should be handled in the primary care system or at a specialist asthma clinic. However asthma in the

adolescent period seems to give less symptoms and often patients in the transition from pediatric to adult health care are referred to a general practitioner. All of the adolescent asthma patients in our study had received treatment in the pediatric clinic as they suffered from asthma and allergy since they were very young. In our study, patients randomized to primary care or to a specialist asthma clinic did not differ from each other concerning the clinical investigations or HRQOL at the five year follow up. This finding suggests that follow-ups required by young adults with mild/moderate asthma can be handled by the primary health care system which also is in line with the present guidelines.

It is well known that regular physical exercise does increase psychosocial well-being and has positive effects on mental health. There are several studies on children and adolescents confirming the importance of promotion and access to sport facilities [36, 69]. In the present study we found that regular physical activity had a positive effect on HRQOL but only for the young women. We do not know why this did not apply to the young men. One explanation could be a gender difference in coping with chronic diseases such as asthma and diabetes. Williams (2000) showed that gendered meanings of stigma can impact on strategies for dealing with chronic illness. In their study the majority of girls showed greater adaption, incorporating their conditions and the associated treatment regimens into their social and personal identities. In contrast the boys made every effort to keep asthma and diabetes out of their personal and social identities, attempting to ignore it out of existence [70]. The lack of a similar positive effect of regular exercise on the HRQOL of our adolescent men may reflect that these men do not expect asthma to affect their HRQOL. As a consequence they may not consider this condition to be a hinder for physical activity, an attitude of ignoring asthmatic symptoms that might result in under-treatment.

Regular exercise was in our study group associated with less pronounced BHR which may be an important indicator that suffering from asthma exerts a negative influence on both the motivation for and possibility of performing physical activity [49]. We also found with the multiple regression model that female gender correlated with more pronounced BHR at the time of entry into the study whereas regular exercise was associated with a more favorable PD<sub>20</sub>. The fact that working capacity decreased in our study group over the five year period could probably be explained by the decrease in regularly performed exercise when entering adulthood and leaving regular sport activities which are more common among younger adolescents. Furthermore this can also explain why the HRQOL-domain 2 “sports” among the women no longer was affected. It is also possible that regular exercise actually ameliorates BHR with subsequently beneficial effect on asthma as suggested by Rasmussen et al [69]. Support for continuing with regular performed exercise in young adults with asthma could therefore be of importance.

An association between obesity and asthma has been discussed in several studies that included adolescents. Some authors found a correlation while other did not [2, 7, 71, 72]. In our study group the mean BMI values increased significantly during the five year period without any apparent deleterious impact on lung function or any influence

on BHR. However this lack of correlation should be interpreted cautiously, since only three of our participants had a BMI >30.

When managing asthma in adolescents all the diverse aspects of an adolescent's everyday life must be taken into account. If the present study has been designed today we probably would have used both a generic and a disease specific instrument to measure HRQOL to compare asthma with other chronic diseases and its impact on HRQOL. Despite the specific challenge measuring HRQOL in adolescent period the "Living with Asthma Questionnaire" gives us information about asthma and its impact of HRQOL during the short but critical period of transition from adolescence to adulthood and transfer from pediatric to adult health care. Our results concerning asthma and its impact of HRQOL are also in line with a recently presented study of the same age group [55].

The mean age in our study group was 17.7 years and the "Living with Asthma" questionnaire is validated for a population from the age of 18 years. However there is a concern about available HRQOL-instruments appropriate for adolescents that include topics that are specific to adolescent development and functioning. Body image, peer relations are topics that are very important and rarely included in adult measures [73, 74]. There are instruments developed for children or adults, hence there could be questions or items in these instruments not suitable for this age group. Voll-Anerud et al have shown in a study using the generic instrument SF12[75] among a general study population that asthma does affect the physical component scores as well as the mental component scores [76]. As previously discussed by Frisen, when studying adolescents HRQOL it is essential to acknowledge the specific aspects of adolescent's HRQOL, than regarding these individuals as either children or adults [77].

In contrast to most previous prospective studies concerning adolescent asthma, we have focused on the age period from late adolescent to adulthood when a chronic disease such as asthma may exert considerable impact on future life in several ways. Our findings reveal that suffering from asthma in the beginning of the transition (i.e. between the ages 16-19) may have negative consequences on HRQOL, which should not be overlooked. Further research with long term follow up is needed to study the consistence and effects of our findings over time.

## 6 CONCLUSIONS

Suffering from asthma during the late adolescent period is associated with lower HRQOL for women than for men. This negative impact on adolescent women is enhanced when asthmatic symptoms are more severe. Among young women regular physical activity seems to increase HRQOL. HRQOL improves in young men and women when they grow older and enter adulthood.

Despite persistent BHR, increasing BMI and a decline in working capacity, lung function and HRQOL improves in adolescents with mild/moderate asthma regardless of whether they are treated at a specialist clinic or in the primary care system. Female gender, atopy and poor adherence to asthma treatment exert negative impact on bronchial hyper-responsiveness and HRQOL.

The negative impact of poor adherence to asthma treatment on HRQOL emphasizes the importance of health care programs that include patient education and support for adolescents as they are transferred from pediatric to adult health care. This support should include awareness of the need of special approaches suitable for young women. The gender difference in HRQOL and the asthma disease reveal that awareness of the manifestations and attitudes towards treatment of asthma is important in order to improve asthma management.

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