

Quality of life, school performance, treatment adherence and gender differences in asthma

Rosita Sundberg

Institute of Medicine
at Sahlgrenska Academy
University of Gothenburg



Quality of life, school performance, treatment adherence and gender differences in asthma.

Rosita Sundberg

**Dept of Internal
Medicine/Respiratory Medicine
and Allergology Institute of Medicine
Sahlgrenska Academy
University
2009**



UNIVERSITY OF GOTHENBURG

© Rosita Sundberg 2009

All rights reserved. No part of this publication may be reproduced or transmitted, in any form or by any means, without written permission.

ISBN 978-91-628-7926-6

Printed by Geson Hylte Tryck, Göteborg, Sweden 2009



Quality of life, school performance, treatment adherence and gender differences in asthma.

Rosita Sundberg RN, Dept of Internal Medicine/Respiratory Medicine and Allergology, Institute of Medicine, the Sahlgrenska Academy at Göteborgs University, Göteborg, Sweden.

Abstract

The aims of this thesis were to estimate the effectiveness of a computerized asthma education program designed to suit young people (I), to analyze whether quality of life changed over a five year period and whether young adults with asthma had impaired quality of life compared with a control group of the same age (II), to explore the association between current asthma, current rhinitis, current eczema and final grade for adolescents in comprehensive school (III), and to compare men and women with asthma with special emphasis on reported adherence, anxiety, and quality of sleep (IV).

A hundred adolescents (17-18 years) from an asthma outpatient clinic for young adults were randomly assigned to either active education (intervention group) or normal care (control group). The intervention group completed an interactive computer program of 30 minutes' duration providing information about asthma, mechanisms, trigger factors, allergies, and medication use, which was followed by a discussion with a specialized asthma nurse (I). A follow-up study was conducted among the cohort of young adults with asthma (n=64) and 248 general population controls, using a respiratory questionnaire and quality of life questionnaires (II). In the autumn of 2000, 10 837 schoolchildren aged 15 in Västra Götalandsregionen were investigated with a respiratory questionnaire (III). The second European Community Respiratory Health Survey (ECRHS II) was a follow-up study, performed between 1999 and 2002, among the participants in the second stage of ECRHS I. From among the ECRHS II participants living in the Nordic countries, 470 individual with current asthma were investigated with a structured clinical interview, including questions on the presence of respiratory symptoms and therapy. They were also asked to fill in the self-reported Hospital Anxiety Depression scale and the Basic Nordic Sleep Questionnaire (IV). Limited asthma education had no effect on asthma symptoms, asthma knowledge, or quality of life parameters among young adults with asthma. The prevalence of respiratory symptoms decreased in both the intervention group, and in the control group, and quality of life and knowledge about asthma increased in both groups. However, the educational program did appear to be associated with a significant improvement in FEV₁. Young women with asthma seemed to have lower quality of life compared to young men with asthma, in spite of no difference in age of onset or severity of the disease. Adolescents with nasal symptoms severe enough to affect daily activity were at risk for low grades. Women with asthma had a more positive attitude towards their medication, had a higher reported adherence and used inhaled corticosteroids more often than men with asthma. At the same time women had more problems with anxiety and insomnia than men.

Computerized education program did not show an effect on asthma symptoms, asthma knowledge or quality of life in specialist care. Young women with asthma seemed to have lower quality of life compared with young men with asthma. Nasal symptoms severe enough to affect daily activity were associated with low grades. Women with asthma had a more positive attitude towards their medication, have a higher reported adherence, and use inhaled corticosteroids more often than men. At the same time women report more often anxiety and insomnia than men.

Key words: Asthma, quality of life, females, young adults, adolescents, patient education, allergy, school performance, asthma control, adherence, insomnia, anxiety, depression.

List of publications

- I Sundberg R, Tunsäter A, Palmqvist M, Ellbjär S, Löwhagen O, Torén K.
A randomized controlled study of a computerized limited education program among young adults with asthma
Respir Med 2005;99:321-328.
- II Sundberg R, Palmqvist M, Tunsäter A, Torén K.
Health-related quality of life in young adults with asthma
Respir Med. 2009;103:1580-1585
- III Sundberg R, Torén K, Höglund D, Åberg N, Brisman J.
Nasal symptoms are associated with school performance in adolescents.
Journal of Adolescent Health 2007;40:581-583
- IV Sundberg R, Torén K, Franklin KA, Gisslasson T, Omenaas E, Svanes C, Janson C.
Asthma in men and women: treatment adherence, anxiety and quality of sleep. Submitted

Abbreviations

ARIA	Allergic Rhinitis and its Impact on Asthma
BP	Bodily pain
BNSQ	Basic Nordic Sleep Questionnaire
BMI	Body mass index
CI	Confidence interval
DIS	Difficulty initiating sleep
DMS	Difficulty in maintaining sleep
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4 th edition
ECRHS	European Community Respiratory Health Survey
EDS	Excessive daytime sleep
FEV ₁	Forced expiratory volume in one second
FVC	Forced vital capacity
GH	General health
GINA	Global Initiative for Asthma
HAD	Hospital Anxiety Depression scale
HRQoL	Health-related quality of life
MH	Mental health
NRS	Non-restorative sleep
OR	Odds ratio
PF	Physical functioning (SF-36)
RHINE	Respiratory Health in Northern Europe
RE	Role-functioning-emotional
RP	Role-functioning-physical
SE	Standard Error
SF-36	Short Form 36 Health Survey
SF	Social functioning
SPT	Skin prick test
VT	Vitality
WHO	World Health Organization

1. Introduction	9
Adherence	10
Patient education	11
Asthma control	12
Health Related Quality of life (HRQoL)	13
School performance	13
Anxiety and depression	14
Insomnia and excessive daytime sleepiness	14
Epidemiology: asthma and rhinitis	15
Gender differences in asthma	16
2. Aims	16
3. Study populations and methods	17
Study I	17
Study II	19
Study III	19
Study IV	20
4. Definitions	21
Ethical aspects	22
Statistical analyses	22
5. Results	23
Paper I	23
Paper II	24
Paper III	26
Paper IV	27
6. Discussion	28
Paper I	28
Paper II	29
Paper III	30
Paper IV	31
7. Conclusions	32
Acknowledgements	33
Swedish summary	35
Svensk sammanfattning	35
References	37

Introduction

Asthma is a common chronic disease in people of all ages. It affects daily activities in many patients and is also a major public health problem with a great influence on both the health-economic costs of medical care (1, 2, 3) and the quality of life of the patients (4, 5).

Despite improved pharmaceutical treatment regimens, clinical and epidemiological studies have demonstrated that many patients with asthma have not achieved asthma control (6) and problems still exist with poor adherence to medical advice, resulting in a suboptimal effect of prescribed treatments (7). Non-adherence to inhaled steroids has been ascribed to various causes including the facts that asthma is a chronic illness requiring prolonged treatment, the prescribed medications are used as prophylactics, and the consequences of cessation of treatment are delayed (8).

The goal of modern asthma treatment is to achieve and maintain total asthma control in a long-term perspective (9) as such control is beneficial not only to the management of clinical manifestations but also to the improvement of health-related quality of life (HRQoL)(10). Many asthma patients also have an allergic rhinitis. Asthma and rhinitis are known to influence each other in terms of control and HRQoL, and the control of rhinitis in asthma patients can lead to an optimization of HRQoL (11).

Children with moderate to severe asthma are generally treated in paediatric specialist care especially if they also have other allergic manifestations. These children will probably continue to have some degree of airway hyperresponsiveness, and will be at risk for the long-term effects of asthma throughout life (12). Therefore the transition from paediatric to adult care requires careful planning. In Sweden, this will occur when the teenagers are 17-18 years old. Chronic illness and daily treatment have negative implications for peer relationships, as they cause functional limitations, frequent interruptions of daily activities, and differences in lifestyle. Allergic disease also has a significant impact on school attendance (13).

The special needs of adolescents with asthma have been largely ignored or neglected. Asthma is both underdiagnosed and undertreated in this age group. The concerns that adolescents with asthma have about their illness and its treatment are often not recognised or addressed by health professionals (14). Although it is widely recognised that asthma is often difficult to manage in adolescence, there is relatively little guidance for clinicians on the best way of working with this age group.

In addition to this, we have only limited knowledge of whether young adults with moderate to severe childhood asthma have impaired quality of life and of how quality of life changes as young adults: grow older. There is a lack of studies conducted among young adults, most of the studies about quality of life are carried out in older or much younger populations.

Another aspect is the cost of preventive asthma treatment, although the cost seems high, the cost of not treating asthma correctly is even higher (12). The presence of psychological problems along with attitudes, feelings, and beliefs about asthma and its treatment may affect patient behaviour. Characteristics which adversely affect self-care, including compliance with treatment, should be identified and addressed so that morbidity due to asthma can be reduced (15).

Three different definitions of how a patient follows the advice and ordinations that he or she is given.

Compliance – Adherence – Concordance

Compliance is “the extent to which a person’s behaviour, in terms of taking medications, following diets, or executing lifestyle changes, coincides with medical or health advice” (16). There is no agreement between the clinician and the patient: there is instead only loyalty towards the clinician from the patient who is a passive receiver.

Adherence is defined by the World Health Organization (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 (17).

Concordance in clinical care, is defined as agreement between physician and patient. In all senses, concordance is as opposed to discordance. The word comes from the Latin *concordare*, to agree (18).

The work described in this thesis used the concept of adherence.

Adherence is a complex, multidimensional, dynamic phenomenon that is influenced by many factors connected to the patients, doctors, disease, and therapy. Kelly et al. found that asthma treatment at all ages was generally inadequate (19). To reach optimal asthma control, it is important to identify factors that contribute to non-adherence (20, 21, 22).

Becker has described a model of health belief in which the likelihood of patients following a health regimen is related to their motivation and incentive to do so. Patients must believe that they are vulnerable or susceptible to the disease or its consequences, and that they actually have the disease (23).

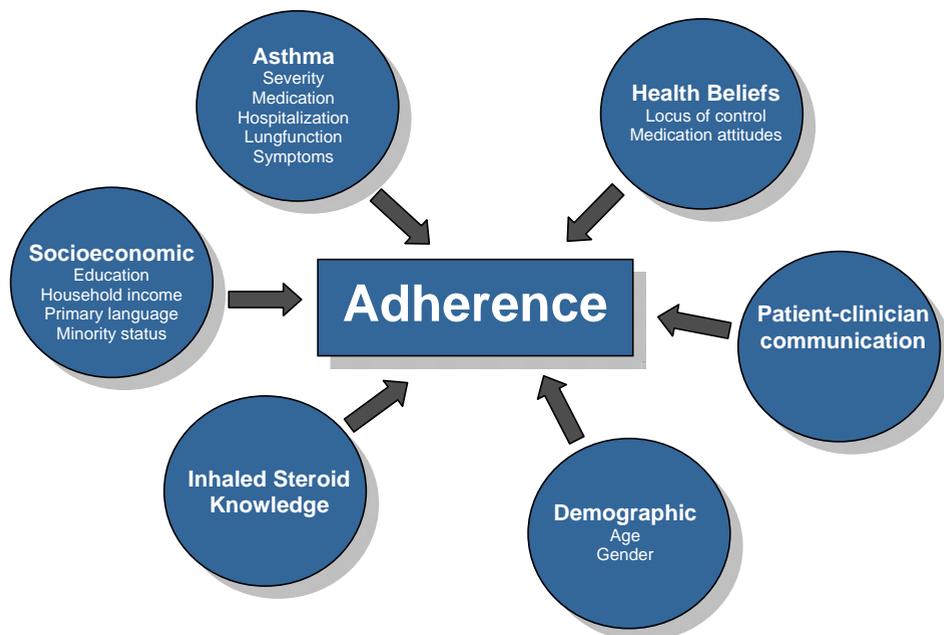
There is some evidence that both depression and risk-taking behaviour such as smoking, sex, alcohol and substance use, driving, or poor diet are associated with non-adherence to medications, poor treatment outcomes, and death (24). A study of individuals aged 18-75 years with severe asthma suggested that the morbidity and costs of asthma might be related to the level of psychological dysfunction rather than to asthma severity (25).

Although it is widely recognized that asthma in adolescents is often difficult to manage, there is relatively little knowledge about the predictors of low medication adherence in this age group (14). Most of our knowledge is about younger children or adults.

Medication regimens for asthma care in all ages of patients are particularly vulnerable to adherence problems because of the duration of the disease, the use of multiple medications mostly delivered as inhalation, and the periods of symptom remission. In order to determine the best way to intervene and to increase the control of asthma, it is essential to identify the specific reasons for non-adherence (26, 27, 28, 29, 30). Patients’ attitudes towards their treatment and medication play a major part in the management of asthma. Patients want treatments that are fast-acting and long lasting, and have minimal side effects (31). More time in asthma care must be allowed for focusing on adherence especially in those patients with

low educational achievement, not only for the benefit of the patient at hand but also for a better understanding of the underlying patient motivation for various patterns of non-adherence (27) See Figure1.

Fig 1. Patient characteristics as influences on adherence.



Interpreting Apter et al. Am J Respir Crit Care 1998

Patient education

One way to increase adherence to medical advices is to improve knowledge about asthma together with attitudes and beliefs, knowledge is recognized as being a major determinant of health behaviour, including adherence (13). Studies have shown conflicting data on whether limited asthma education has any effect on asthma morbidity, asthma knowledge, or quality of life (32, 33). This was the reason for the study of young adults described in Paper 1.

Two studies by Marabini et al. showed that while an education programme improved quality of life over one year (34), this improvement was not maintained in the second year (35). The Cochrane Collaboration has also concluded that limited asthma education does not improve health outcomes in adults with asthma (33, 32). However, providing information about asthma and its treatment is seen as necessary to the development of a successful therapeutic alliance between the person with asthma and their health professional (33). The evidence is strong that there should be a collaborative relationship between the patient and provider, and that the patient should be an active participant in establishing their own self-management goals and the asthma action plan (36). A programme with a focus on asthma management problems particular to women can significantly assist female asthma patients (37).

There is a real need to also provide care and advice for children with asthma once they become adolescents. Programmes for adolescents with asthma should serve a bridge between paediatric and adult care, and should offer advice about smoking and career choice (38). Support of self-management in adolescents with poorly controlled asthma can be achieved by the application of novel information and communication technologies, and hence internet-based self-management should target adolescents with poor asthma control (39)

Asthma control

Table1. Definition of asthma control according to Global Initiative for Health (GINA) guidelines.

<i>Asthma was considered controlled if all the following features were present</i>	
Asthma symptoms	Less than once a week
No asthma attacks	In the last 3 months
No activity limitations	In the last 12 months
No nocturnal symptoms	In the last 3 months
Short-acting beta-2agonists twice or less per week	In the last 3 months
No use of oral steroids	In the last 12 months
FEV ₁ of 80 % of predicted value or greater	
<i>Asthma was considered partly controlled if 1 or 2 of the above features were absent</i>	
<i>Asthma was considered uncontrolled if more than 2 features were absent or:</i>	
Asthma , shortness of breath, or wheezing had caused hospital/emergency department admission	In the last 12 months
Oral steroids were used	In the last 12 months
More than 12 asthma attacks	In the last 3 months

Health Related Quality of life (HRQoL)

Asthma control remains as a strong predictor of HRQoL, even when underlying differences in severity classification are taken into account (40).

The WHO has defined quality of life (QoL) as *individuals' perception of their 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* (41). HRQoL has achieved increased attention as an important outcome in medicine. One reason for this is the great number of people with chronic diseases for whom freedom from disease is an impossible goal. In these patients the goal must therefore be to help them to live as well as possible, that is to achieve good HRQoL (42).

The conventional clinical parameters of lung function, symptoms, and use of reliever medication predict HRQoL differently depending on the level of asthma severity, and these traditional measures of asthma severity and asthma control explain only half of the variance of HRQoL (43). Subjects with persistent symptoms have lower HRQoL scores than subjects with incident symptoms (44). A major variable relating to HRQoL is perceived stress, and hence stress management might improve their quality of life of patients with asthma (45). There are data which suggest that personality can influence how asthma patients adhere to asthma medication treatment, and how they report their control and HRQoL (46). Besides clinical and functional measures, evaluation of overall health status must also incorporate HRQoL measures (47).

Allergic rhinitis has a considerable negative impact on children's physical, social, and psychological well-being, as well as academic performance (48), and so investigators should ensure that the results are not biased by confounding factors that may affect quality of life (49).

HRQoL can be measured with generic instruments or disease-specific instruments. Generic instruments are broader measures that offer the possibility of comparing the scores between asthma and other diseases, whereas disease-specific instruments are designed to measure the impact of a specific disease on HRQoL. The work described here made use of both types of instrument. The disease-specific instrument was the Living with Asthma Questionnaire (50, 51, 52) chosen because it was the only asthma-specific instrument available in Sweden at the time of our first study. The generic questionnaire was the Short Form 36 Health Survey (SF-36) (53) one of the most common generic instruments for measurement of chronic disease.

School performance

Allergic disease has a significant impact on school attendance among high school students (13). In addition patients with allergic rhinitis complain of not sleeping well and of feeling sleepy and fatigued during the day (54). Allergic rhinitis has a negative impact on learning, cognitive function, and classroom performance, and affects the quality of life in children and adolescents (48). It can also cause mood disturbance and psychosocial problems (55). The

Allergic Rhinitis and its Impact on Asthma working group (ARIA) recommends that asthma patients must be evaluated for rhinitis, and vice versa (56).

However, the relationship of symptoms from allergy and asthma to school performance such as grades among children and adolescents is less clear.

Anxiety and depression

People with a chronic somatic disease are relatively more at risk of psychological distress than physically healthy people (57). Chronically medically ill people have more psychological distress than the average population, even after controlling for age and sex. Generic disease characteristics can be held responsible for this mental distress, as far as physical functioning of the patients is concerned (58). Two types of panic-fear have been identified, both with a unique association with asthma morbidity. Illness-specific panic-fear refers to anxiety elicited in response to asthma symptoms, while generalized panic-fear is a stable personality construct that reflects trait anxiety extending beyond asthma symptoms (59). Feldman found that asthma patients with panic disorder have higher rates of both illness-specific panic-fear and generalized panic-fear in comparison to patients with only asthma, despite no differences in asthma severity (60). The two panic-fear constructs were associated differently with asthma outcomes. Illness-specific panic-fear mediated the relationship between panic disorder and health-related quality of life, including emotional disturbance by increasing the perceived emotional burden attributed to asthma. Generalized panic-fear was associated with activity limitations due to asthma and use of quick-relief medication; this might reflect over-reliance on quick relief medication. These findings show the importance of distinguishing between anxiety that mobilizes appropriate asthma self-management, and panic that is mistaken as an asthma exacerbation (60). Health care providers should also consider the presence of anxiety and /or depression among asthma patients who report poor control over their asthma but consistently display normal lung function (58).

Psychological factors such as depression and anxiety play a significant role in asthma. Furthermore, three specific symptoms are associated with depression; dyspnoea, waking at night with asthma symptoms, and morning symptoms. These symptoms not only show the important co-morbidity of depression with asthma, but also confirm other evidence about severity symptoms of asthma and their impact on quality of life (61, 62, 63)

Anxiety and depression can be measured with the self-reported Hospital Anxiety Depression scale (HAD) questionnaire. The questionnaire has been found to discriminate effectively between possible and definite cases of anxiety and depression.

Insomnia and excessive daytime sleepiness

Insomnia can be described as a perception by the patient that their sleep is insufficient or inadequate. According to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition (DSM-IV), insomnia is divided into difficulty in initiating sleep (DIS) difficulty in maintaining sleep (DMS), and non-restorative sleep (NRS). To be diagnosed as

having insomnia, the disturbance must have been present for at least one month and have caused suffering and/or decreased functioning in social, occupational, or other important areas of functioning (64). Insomnia is the most prevalent sleep disorder affecting 10-15% of the general population, and has a significant negative impact on an individual's daily functioning including impaired work performance, lower physical and social functioning, an overall lower quality of life, and an increased risk for subsequent development of psychiatric disease (65). Insomnia represents serious sleep and/or mental disorders that require medical attention and inadequate treatment of insomnia has several important and under-recognized consequences including subsequent development of psychiatric disease. Insomnia is related to lifestyle factors such as smoking and excessive use of alcohol as well as somatic and psychiatric disorders (66, 67). There is a great need for educational programs regarding insomnia assessment, diagnosis, and treatment from the perspective of both the patient and the clinician (68, 65).

Excessive daytime sleepiness (EDS) is a major symptom of a sleep disorder that can be described as a propensity to fall asleep during wakefulness in situations of diminished attention. However, there is still no uniform operational definition of EDS, and there is no distinction between EDS and fatigue. Fatigue can be described as weariness, weakness or loss of energy, but it has still not been clarified whether or not fatigue is a part of EDS (69).

Asthma is a disease that can significantly affect an individual's physical and psychosocial functioning. Diurnal variability in lung function and symptom presentation mean that it is important to understand the effects of the disease on both daytime wakefulness and sleep quality (70). Sleep disturbances are associated with asthma control and quality of life. Clinicians may need to complete a more detailed sleep history in patients with poorly controlled asthma (71). Given this background, we decided to examine the importance of sleep disturbance in our study of adherence. Sleep disturbance can be measured with the Basic Nordic Sleep Questionnaire (BNSQ).

Epidemiology: asthma and rhinitis

Over the last few decades, the prevalence of asthma and allergic rhinitis has increased in many countries. These are now the most common group of diseases in children, teenagers and young adults (72, 73, 74, 75). Swedish studies have estimated the incidence of asthma among schoolchildren and teenagers to be 1 per 100 per year (76), and the prevalence of physician-diagnosed asthma in the total population has been reported to be 7-10% (77, 78). Many epidemiological studies suggest that women are at increased risk for developing adult-onset asthma and also suffer from more severe disease than men (79, 80).

During the last decade some reports have suggested that the almost monotonic increases in asthma prevalence reported over the last quarter of a century may be coming to an end, though these reports are not universal (81, 82, 83, 84, 85). Allergic rhinitis is still increasing (84) and remains as a significant health problem because of the high burden of symptoms and the resulting impact on general well being (86). The presence of rhinitis as a co-morbidity should always be taken into account in the management of asthma (5).

Gender differences in asthma

In early childhood, asthma is more common among males, but after puberty the incidence increases in females (87, 88, 89) and decreases in males (90). In addition, asthma after childhood is more severe in females than in males, and is more frequently underdiagnosed and undertreated in females (91). In general, there is a sex difference among adults presenting to emergency departments with acute asthma (92). The female majority present with specific and important pathophysiological features; however the observed differences may also represent sex differences in use of health care (92). Several studies suggest that men and women respond differently to their asthma disease, and that gender differences in various measures of asthma such as symptoms, hospital admissions, and quality of life may be explained by this response to disease, rather than to real differences in disease characteristics between men and women (87, 93, 94).

Aims

The aims of this thesis were:

To estimate the effectiveness of a limited computerized asthma education program, designed to suit young people with asthma.

To analyze whether quality of life changed over a five year period in a group of young adults, whether young adults with asthma had impaired quality of life compared with a control group of the same age and to analyze if there were any gender differences.

To explore the association between current asthma, current rhinitis, current eczema, and final grades for adolescents in comprehensive school.

To compare adult men and women with asthma, with special emphasis on reported adherence, anxiety, and quality of sleep.

Study populations and methods

Study I

Study I was conducted at the asthma outpatient clinic of the Department of Respiratory Medicine and Allergology, Sahlgrenska University Hospital, Göteborg, Sweden. The subjects were asthma patients between the ages of 18 and 25 (mean age 18.3) who were referred to the special asthma outpatient clinic for young adults during 1998. All patients were referred from the Children's Hospital at the University Hospital, Göteborg. The inclusion criterion was asthma diagnosed by a paediatrician, and the severity was classified according to the Global Initiative for Health (GINA) guidelines (95).

The first 100 patients who met the inclusion criterion were informed about the purpose and design of the study, and invited to participate. All patients agreed to participate and were randomly assigned to either active education (intervention group) or to normal care (control group) using the envelope technique. Three patients were excluded due to social reasons; hence the study group comprised 97 patients, 48 in the intervention group and 49 in the control group.

Study design

All patients included in the trial were followed as outpatients in a specialist clinic for young adults. The clinic had an allergist and a specialist nurse and both groups in the trial were attended by the same team. Team visits took place in the afternoon when the patients were free from school or work and were willing to come and visit the clinic. Parents did not attend these visits, though if they had any questions they were welcome to contact the team after the visit. All patients had the opportunity to contact the team by telephone if they had questions about symptom exacerbation, medication or anything else.

All outcome measures were obtained from all the patients at the start of the study and after 12 months. The outcomes of the study were number of hospital admissions, unscheduled visits, asthma symptoms, knowledge about asthma, lung function, and quality of life.

Questionnaires

A self-administered questionnaire was constructed based on previous questionnaires (96, 97). It included 41 items divided into three parts. The first part covered asthma symptoms over the last 3 months including nocturnal symptoms and the perceived disability due to asthma. The second part covered knowledge about triggers and physical activities, asthma as a disease, how to use medication and the potential side effects of such medication. The final part contained one item about paramedical treatment. The physician completed a structured questionnaire about patients' symptoms and status at the first visit and after 12 months. The physicians' questionnaire covered frequency of symptoms registered for the previous 4 weeks, hospital admissions and unscheduled visits in the previous 6 months.

Quality of life was assessed with the Living with Asthma Questionnaire (50, 52), translated into Swedish and adapted to Swedish conditions (51). The questionnaire included 11 domains: (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. There were 68 questions in the questionnaire, each with a three-point scale for responses; untrue, slightly true and very true. There was also an alternative “not applicable”. Each question carried a score of up to 3 points, giving a maximum overall score of 204. Quality of life was calculated according to Hyland (50) as the sum of the points in each item divided by the sum of the points in each area, (i.e. the mean scores), and analyzed as continuous variables. Responsiveness was expressed either as the ratio of the mean change in the score to the SD of the baseline score (‘effect size’), or as the ratio of the mean change in the score to the SD of that change (‘standardized response mean’) (49).

Skin pricktest (SPT) and spirometry

All the patients were investigated with SPT and spirometry (Vitalograph). The SPT was a standard panel with 10 allergen sources common in Sweden: cat, horse dog, two house dust mites, two moulds, birch, grass and mugwort. Histamine and blank tests were used as controls. A wheal and flare response of 3 mm or more was regarded as a positive SPT. Spirometry was performed by a the specialist nurse; the measures taken were forced exhaled volume in one second (FEV₁), forced vital capacity (FVC) and FEV₁/FVC ratio of predicted value (98).

The intervention

The intervention consisted of an interactive 30-minute computer program based on Teach your patients about asthma: a clinician’s guide (99). The program provided; basic information about asthma; information about medication use, and how to use inhalers and peak flow meters and information about asthma triggers, allergens and allergies (100). The program was developed at the Department of Respiratory Medicine and Allergology.

The program was constructed with different groups of asthma patients. Before the present study began, the finalized version was tested on 10 subjects with asthma. This pilot study resulted in only minor improvements to the program. The final program consisted of 30 questions with 3–6 alternative answers. Each question had an accompanying graphic that further illustrated the message. Subjects were not permitted to proceed to the next question until they had given the correct answer, and feedback about the answer was given after each question. At the end of the program, the nurse led a structured discussion with each subject about his/her results. Each of these discussions lasted approximately 30 min and so the intervention took 1 h in total per subject.

The patients assigned to the intervention group completed the interactive computer program, and were then scheduled to visit the clinic team every six months, or according to individual needs. The control group followed the routine schedule of the outpatient clinic for young adults, in which the next follow-up took place after six months or as needed.

Study II

Study II included the 97 subjects with asthma from study I along with 500 randomly selected controls from the same source population in the same age interval. The controls were selected from the general population in the year of the follow-up (2003).

Study design

The study consisted of a postal self-administered questionnaire with two reminders. The questionnaire consisted of two parts. One part was developed from previous questionnaires (101, 102, 103, 104, 105) and included items about asthma, rhinitis, eczema, use of medication, smoking, professional experience, physical activity, and family history of asthma and allergy. The second part consisted of two quality of life questionnaires, one generic and one asthma-specific. The asthma-specific questionnaire was sent only to the asthma cohort.

The generic questionnaire was the Short Form 36 Health Survey (SF-36), which consists of 36 items on eight health scales related to daily life activities (53). Four of these health scales represent the physical dimension: (1) physical functioning, (2) role functioning-physical, (3) bodily pain, and (4) general health, while the remaining four scales represent the mental dimension: (5) vitality, (6) social functioning, (7) role-functioning-emotional, and (8) mental health. All of these health scales are scored on a range from 0 to 100, with 100 representing the highest level of functioning and well-being. It is generally understood that an effect size of 5 points on the 0 – 100 scale of SF-36, represents clinical significance (106). The asthma-specific questionnaire was the Living with Asthma Questionnaire (presented in Study I).

Study III

All 15-year-old children in Västra Götaland (n = 18,158) were invited together with their parents to participate in a cross-sectional study of allergic diseases in the year 2000. The questionnaire addressed asthma, rhinitis, eczema, and use of medication. The response rate was 52% (n=10,837)

Study design

The questions were obtained from well-established questionnaires such as ISAAC (102) and The Health of youth (107). Data on foreign descent, and parents' education were obtained from Statistics Sweden, and psychosomatic symptoms, were also asked about in the questionnaire, being potential confounders to the association between grade sum and allergic symptoms (108).

The 2001 spring semester total grade of each respondent who provided a full unique personal identification number was obtained from national registers (n=9538). Total grade is calculated as the sum of the student's grades in 16 subjects; each subject can be graded at 0, 10, 15 or 20 points, and so on the maximum total grade sum is 320. Summation of grades is the standard way in Sweden to express the cumulative knowledge of nine years in elementary school, and is used as the entrance criterion to senior high school.

Study IV

The first European Community Respiratory Health Survey (ECRHS I) (109) was a multicentre study on the prevalence, determinants, and management of asthma performed in 48 centres during 1991–1993. ECRHS II (110) was a follow-up study, performed between 1999 and 2002, of the participants in the second stage of ECRHS. ECRHS I documented treatment and self-reported adherence (111, 112), while ECRHS II gave the opportunity to study the factors affecting adherence to asthma treatment.

The analyses in study IV included data from Sweden, Iceland, and Norway covering 470 subjects with current asthma who took part in the ECRHS II.

Study design

Each participant underwent a structured clinical interview including questions on the presence of asthma, respiratory symptoms, and therapy. The full questionnaire can be found at www.ecrhs.org/quests. Participants were also asked to fill in the self-reported Hospital Anxiety Depression (HAD) scale (113) and the Basic Nordic Sleep Questionnaire (BNSQ) on sleep disturbances (114).

The HAD questionnaire consists of fourteen questions, seven related to anxiety and seven related to depression. Each item is rated on a four-point scale from 0 to 3, giving maximum subscale scores of 21 for anxiety and 21 for depression. In the validation of the questionnaire, a score of 0-7 in the two subscales has been found to discriminate non cases, from doubtful cases with a score of 8-10 and scores of 11 or more for definite cases of anxiety and depression, respectively (113). The seven questions on sleep disorders were derived from the Basic Nordic Sleep Questionnaire and had been used previously in the Respiratory Health in Northern Europe (RHINE) study (29). Participants were asked to estimate the frequency of different symptoms during the last month on a five point scale: 1, never; 2, less than once a week; 3, 1-2 nights per week; 4, 3-5 nights per week; and 5, almost every night.

Table 2. Summary of the baseline characteristics for the various populations in the thesis.

	Paper I		Paper II		Paper III	Paper IV
Setting	Hospital based asthma cohort				General population	General population
	Intervention	Control	Asthma Cohort	Control group		
Participants	48	49	64	248	9538	470
Age group	18-25	18-25	25-26	26	15	35-49
Sex (women %)	52	45	56	56	51	60

Definitions

The following terms were defined as positive responses to the respective yes/no questions and refined as indicated by the accompanying comments.

Physician-diagnosed asthma: “Have you been diagnosed by a physician as having asthma?” Paper I-III or “Have you ever had asthma?” and “Was this confirmed by a doctor?” (116) (Paper IV)

Prescribed asthma medication: “Have you used any asthma medication during the last 12 months?” If the answer was “yes”, the following questions were asked: “Have you used rapid-acting inhaled beta₂-agonist?” and “Have you used inhaled corticosteroids?” (Papers I-III)

Current asthma: Affirmative answer to the question, “Have you been diagnosed by a physician as having asthma?” and either “Have you had asthma symptoms during the last 12 months?”, or “Have you used asthma medication during the last 12 months?” (Papers I-II)

Symptomatic asthma: was defined as physician-diagnosed asthma and asthma-related symptoms or attacks of asthma in the previous 12 months. (Paper IV)

Current rhinitis: “Have you had symptoms of runny nose, sneezing, nasal congestion, without having a cold, during the last 12 months?” (Paper III)

Severe nasal symptoms (SNS): “In the past 12 months, did your nasal problem interfere significantly with your daily activities?” (Paper III)

Psychosomatic symptoms: “Do you frequently have pain in your stomach?” or “Do you frequently have a headache?” or “Do you have difficulty getting to sleep?” (Paper III)

Smoking: Subjects were classified into either two categories, never smoked or ex-smoker/smoker (Paper I-II) or three categories never smoked, ex-smoker or smoker (Paper IV)

Adherence in normal situations: “When you have been prescribed medicine for your breathing, do you normally take: all the medicine, most of the medicine, some of the medicine, or none of the medicine?” *Adherence during exacerbations* was assessed by the question: “When your breathing gets worse, and you are prescribed medicine for your breathing, do you normally take all of the medicine, most of the medicine, some of the medicine or none of the medicine?” Patients answering “all of the medicine” were defined as being adherent (112, 30). (Paper IV)

Subjective impression of therapy: “Do you think it is bad for you to take medicine all the time to help your breathing?” and “Do you think you should take as much medicine as you need to get rid of all your breathing problems?”(112) (Paper IV)

Adherence-related variables were: smoking habits, having taken inhaled corticosteroids in the previous 12 months, having regular appointments for asthma with a doctor or a nurse, having written instructions from a doctor, having a personal peak expiratory flow (PEF) meter, and having had spirometry during the previous 12 months (30) (Paper IV)

Asthma control was defined as diurnal symptoms less than once a week and no asthma attacks in the last 3 months, no activity limitations in the last 12 months, no nocturnal symptoms in the last 3 months, short-acting beta-₂ agonists twice or less per week in the last 3 months, no use of oral steroids in the last 12 months, and FEV₁ of 80% of predicted value or greater (117, 6) (Paper IV)

Insomnia and excessive daytime sleepiness: Insomnia was defined as reporting at least one of three aspects: “difficulty in falling asleep at night”, “waking up repeatedly during the night”, and “waking up too early and having difficulty in getting sleep again” with a frequency of at least 3 nights a week (115). Excessive daytime sleepiness was defined as reported problems with daytime sleepiness at least 3 days/week (118).

Ethical aspects

Informed consent was obtained from all participants. Studies I-III were approved by the Regional Ethical Review Board of Gothenburg, Sweden; Dnr 408-95 (I), Dnr Ö 235-2 (II), Dnr S 279-00 (III). In study IV, the local ethics committees at each centre approved the study protocols .

Statistical analyses

The SAS statistical package (version 8.0) was used for the analyses in papers I-III. Paper I. The results were analyzed as the difference between follow-up and the start of the study. For continuous variables, the mean values of the difference at baseline and at follow-up were calculated and the statistical significances were analyzed with a non-parametric test (Kruskall-Wallis). The categorical variables were analyzed as the fraction of subjects in each group showing an improvement, and the statistical significance was analyzed with a chi square based method. Lung function values and quality of life outcomes were also analyzed using multiple linear regression models. (PROC GLM). The appropriate sample size was calculated based on the standardized difference for categorical data as described by Altman (119).

Paper II. A chi square test was used in the univariate analyses of differences regarding characteristics. Student's t-test was used for continuous variables, with p-values <0.05 were considered significant. In the multivariate analyses, generalized linear multiple regression models (PROC GLM) were used to estimate the associations between dependent and independent variables.

Paper III. P-values for differences were calculated by t-test, and multiple linear regressions (PROC GLM) were used to estimate the association between dependent (total grade sum) and independent variables (current asthma, current rhinitis, current eczema, and severe nasal symptoms). A logistic regression (PROC Logist) was performed to evaluate the consistency of the GLM results.

Paper IV. Statistical analyses were performed using the STATA 9 software (Stata Corp., College Station, Texas, USA). Chi squared tests and unpaired t-tests were used to compare characteristics between men and women. Logistic regression was used to analyze determinants for adherence, insomnia and daytime sleepiness. A p-value <0.05 was considered to be statistically significant.

Results

Paper I

Table 3. The basic data of the subjects included in the study.

	Intervention group (n=48)	Control group (n=49)
Females (%)	52	45
Age (yr)	18.3 (0.2)	18.5 (0.2)
Age of asthma onset (yr)	6.9 (0.8)	5.6 (0.8)
Severe asthma (%)	38	37
Moderate asthma (%)	57	60
Positive skin prick test (%)	91	85
Daily dose of inhaled steroids		
Budesonide (µg)	735	533
Fluticasone propionate (µg)	583	633
Beclometasone dipropionate (µg)	418	475
Never smokers (%)	63	76

Subjects in a randomized controlled study of asthma education among adolescents, divided into intervention group and control group.

Standard error (SE) within brackets.

Based on the physician's questionnaire and the self-administered questionnaire the prevalence of nocturnal and daily respiratory symptoms decreased in both the intervention group and in the control group, and there was no statistically significant difference between the two groups. The same situation occurred for knowledge about asthma and asthma triggers, which increased among both the intervention subjects and the controls. The only change that was statistically significant was a decreased positive response to the question "Do you know what asthma is?" This decreased from 81% to 73% in the intervention group, and increased from 84% to 94% among controls ($p=0.02$)

After the intervention FEV₁ increased significantly in the intervention group compared to the controls. The improved FEV₁ was observed mainly among the atopic subjects. The improvement in FEV₁ in the intervention group was significant in a multiple linear regression model adjusting for age, sex, skin prick test, smoking habits, and baseline value of FEV₁. The intervention did not result in any statistically significant changes in quality of life parameters, and quality of life increased in both groups.

The analysis of baseline quality of life revealed a gender difference (table 3) which was still present at year 1..

Table 3. Quality of life outcomes before the intervention among females and males assessed with the “Living with Asthma Questionnaire”.

	Females (n=44)	Males (n=48)	P-value
Overall score	151.4	163.3	0.01
Social and leisure activities	2.3	2.7	0.004
Sports	2.5	2.8	0.003
Holidays	2.3	2.6	0.04
Sleep	2.6	2.8	0.008
Work	2.3	2.6	0.007
Colds	2.0	2.3	0.002
Mobility	2.4	2.8	0.0001
Effects on others	2.5	2.5	>0.5
Medication usage	2.3	2.4	0.16
Sex	2.9	2.9	0.23
Dysphoric states and attitudes	2.5	2.7	0.008

Paper II

A high proportion of young adults with asthma had symptomatic asthma at the five-year follow-up, 87.5 % had current asthma but only 65.6 % reported use of inhaled steroids and 17.2 % (n = 11, all female) denied ever having made regular use of any asthma medication. After the intervention (paper I) 97 % (n=94) were using inhaled steroids.

The overall quality of life score at follow-up in the asthma cohort assessed with the Living with Asthma Questionnaire was 162.3 (SE = 3.7). Multiple linear regression modeling analysis showed that female gender ($p = 0.01$) and a low FEV₁ at baseline ($p = 0.002$) predicted a lower quality of life at follow-up. We also analyzed the change in quality of life in the asthma cohort (Table 4).

Table 4. Quality of life parameters in year 6 and the differences between year 6 and year 1 in the asthma cohort assessed with Living with Asthma Questionnaire.

Domain	Whole cohort in year 6 (n=60) **	Differences in the whole asthma cohort between year 6 and year 1 (n=57)	Differences between year 6 and year 1 among the males (n=26)	Differences between year 6 and year 1 among the females (n=31)
Overall score	162.3 (3.7)	-3.32 (3.77)	-2.81	-3.74
Social and leisure activities	2.6 (0.06)	-0.02 (0.04)	-0.05 (0.05)	-0.00 (0.07)
Sports	2.6 (0.07)	-0.04 (0.08)	-0.02 (0.05)	-0.08 (0.13)
Holidays	2.0 (0.06)	-0.44 (0.06)*	-0.51 (0.09)*	-0.39 (0.08)*
Sleep	2.8 (0.05)	-0.02 (0.04)	-0.02 (0.06)	-0.03 (0.06)
Work	2.6 (0.05)	0.03 (0.05)	0.02 (0.06)	0.03 (0.07)
Colds	2.3 (0.07)	0.00 (0.05)	0.02 (0.08)	-0.01 (0.07)
Mobility	2.7 (0.04)	0.03 (0.05)	0.06 (0.08)	0.00 (0.06)
Effects on others	2.6 (0.05)	0.08 (0.05)	0.11 (0.07)	0.05 (0.08)
Medication usage	2.5 (0.05)	0.02 (0.05)	-0.05 (0.08)	0.09 (0.07)
Sex	3.0 (0.03)	0.05 (0.03)	0.04 (0.45)	0.05 (0.05)
Dysphoric states and attitudes	2.7 (0.04)	0.04 (0.03)	0.00 (0.04)	0.07 (0.05)

Standard error (SE) within bracket

*Difference in the “Holidays” domain were significant ($p < .0001$)

**4 subjects failed to answer the instrument

In the univariate analysis of the generic instrument (SF-36) the asthma cohort scored significantly lower compared to the general population controls regarding the physical dimension (52.7 vs. 54.0, $p = 0.04$), especially in physical functioning (PF) ($p = 0.004$) and general health (GH) ($p = 0.0001$). Within the asthma cohort, females scored lower in the physical dimension than males ($p = 0.0009$) this was most obvious in the domain of general health ($p = 0.0002$).

Paper III

The GLM analysis showed statistically significant associations between grade sum and both current rhinitis ($p=0.01$) and nasal symptoms severe enough to affect daily activity ($p=0.009$), but no such association was found with current asthma or eczema (Table 5). The association with current rhinitis was positive — adolescents reporting rhinitis had higher grade sum— whereas the association with to nasal symptoms severe enough to affect daily activity was negative.

Table 5. Association between total grade sum and current asthma, current rhinitis, current eczema, and nasal symptoms severe enough to affect daily activity in the GLM model with adjustment for psychosomatic symptoms, sex, parental education, and foreign descent.

Independent variable (Yes=1, No=0)	Parameter estimate	SE	p-value
Current asthma	-3.1	2.3	0.2
Current rhinitis	4.1	1.6	0.01
Current eczema	-1.0	1.8	0.6
Severe nasal symptoms	-12.1	4.6	0.009

ORs calculated by the logistic regression analysis for current asthma, current rhinitis and current eczema were close to 1.0 with 95% confidence intervals including unity. The OR for nasal symptoms severe enough to affect daily activity was 1.6 (95% CI 1.04-2.6).

Among subjects using anti-allergy medication, there was a statistically significant association between grade sum and nasal symptoms severe enough to affect daily activity ($p=0.0005$). Among subjects not using such medication, this association was weak and not significant (Table 6).

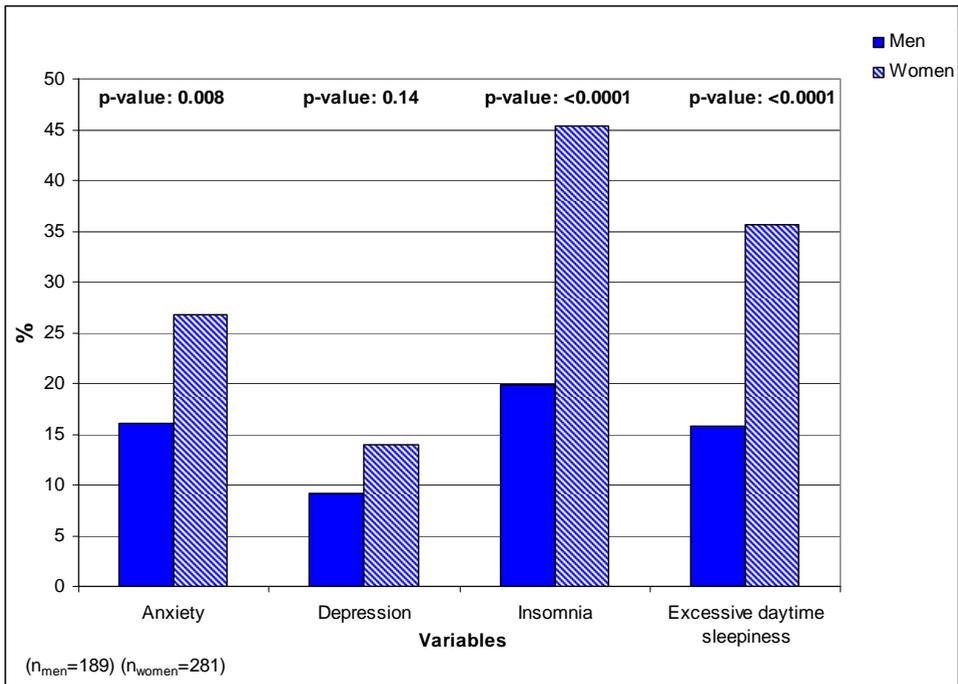
Table 6. Association between total grade sum and current asthma, current rhinitis, current eczema, and nasal symptoms severe enough to affect daily activity in the GLM model, stratified according to medication use, and adjusted for psychosomatic symptoms, gender, parental education, and foreign descent.

Independent variable	Not using medication			Using medication		
	Parameter estimate	SE	p-value	Parameter estimate	SE	p-value
Current asthma	-5.7	3.8	0.2	-5.6	3.0	0.07
Current rhinitis	0.9	2.3	0.7	2.4	2.4	0.3
Current eczema	-0.2	2.3	0.9	-3.0	2.9	0.3
Severe nasal symptoms	-4.5	6.9	0.5	-22.7	6.5	0.0005

Paper IV

There were no differences in age and body mass index between the sexes. Men were more likely to be atopic than women, and also had a lower age of asthma onset. Women with asthma were more likely than men to be smokers, to have a PEF-meter, to use inhaled corticosteroids and to have seen a doctor in the last 12 months. There was no difference in asthma control between men and women. In comparison to men, women with asthma had a higher self-reported adherence and a less negative attitude towards their medication. However, women with asthma had a higher prevalence of anxiety, insomnia, and daytime sleepiness (Fig 2). No significant sex difference was found in the association between risk factors and reported non-adherence.

Fig 2 Anxiety, depression, and insomnia in the asthma cohort at the Nordic centres of ECHRS.



Chi square tests were used to compare characteristics between men and women.

Discussion

Paper I

The limited computer-supported education program evaluated in this study had no effect on admittance to hospital, emergency department visits, prevalence of respiratory symptoms, and knowledge of asthma, or quality of life. However, it did seem to be associated with a significant improvement in FEV₁. Kauppinen et al. who assessed 162 newly diagnosed asthma patients (aged 18-76), reported that after intensive patient education their patients showed the same improvement in FEV₁ and PEF at the three-year follow-up, but that other lung functions and HRQoL assessed with the generic 15 D instrument and St George's Respiratory Questionnaire (SGRQ) did not differ between intervention and control groups (120). Kauppinen et al. concluded that the outcome variables covered by generic 15 D and SGRQ indicated that HRQoL scores may measure factors largely unrelated to lung functions, but airway hyperresponsiveness may have an influence on the personal assessment of HRQoL (121).

It is, however, possible that in the present study the subjects allocated to the intervention group had lower FEV₁ simply by chance, and therefore also had the greatest potential for improving. Another possible explanation is that any intervention effect may have been lost in the overriding of the general management and active care in this setup: it may have been better to test the intervention in relation to a non-specialist treatment. The fact that the patients were referred to a new clinic may also have increased adherence in both the intervention and the control group.

One important aspect of an adolescent's life is the need to become part of a peer group with the same lifestyle and the same rules. Chronic illness and daily treatment have negative implications for peer relationships, as they cause functional limitations, frequent interruptions of daily activities, and differences in lifestyle. It is important to discuss these things with the young adults and try to reconcile these differences.

The only difference between the intervention group and the control group was the limited education program, and we have now learnt that there is more to asthma management, than education. However, these patients were referred to a recently started asthma outpatient clinic for young adults. All the patients in the trial had been patients since they were very young, and had been admitted to the children's hospital several times together with their parents. The parents felt that they were responsible for medication and everything else for their children. When the patients entered adolescence and were considered old enough to take responsibility for their own asthma care, there were some difficulties as they had been used to leaving everything to their parents. At that point in adolescence it was more important to be a part of a peer group with the same lifestyle and hence their asthma was of secondary importance. One of the most important things when the patients came to the outpatient clinic for young adults with asthma was to get them to understand their own responsibility for the disease. Their parents did not attend the clinic visits, though they were welcome to contact the asthma team if they had any questions. Similarly, the patients were also able to contact the team outside the visit if they wished.

A review by the Cochrane collaboration concluded that culture-specific programmes for adults and children from minority groups with asthma, are more effective than generic programmes in improving quality of life, asthma knowledge, asthma exacerbations and

asthma control: however, only four studies were eligible for inclusion in the review, and the authors concluded that further studies are needed to answer that question (122). A study of internet-based self-management in adults with asthma resulted in improvements in asthma control and lung function but did not reduce exacerbations, and gave no significant improvement in quality of life (123). Emotional and behavioural symptoms rather than disease severity, predicted quality of life of children and adolescents with asthma (124).

A review by Kyngäs et al. concluded that adolescents need frequent support, encouragement, and positive feedback as they strive to manage their chronic illness and normal developmental crises (125). Asthma self-management education involves a collaborative partnership between the education provider and the patient. An asthma action plan facilitates asthma self-management and improves patient outcomes. The 2007 asthma guidelines from the National Asthma Education and Prevention Program emphasize that all types of healthcare providers should teach and reinforce asthma self-management education at every opportunity and in all settings (36).

The accessibility and continuity in the special out-patient clinic for young adults with asthma in this paper could have contributed to good asthma control both in the intervention group and in the control group.

Paper II

The most important result from this study of young adults with asthma five years after intervention, was that females seemed to have decreased asthma-related quality of life compared to males. This was also seen in the generic quality of life questionnaire, where females with asthma scored lower in the physical dimension. The gender difference in quality of life was already evident at baseline, and was still apparent after intervention year 1.

The asthma cohort consisted of a group of early-onset asthma patients who had been patients at the Children's Hospital at the University Hospital from the beginning of the disease and whose disease severity had been classified as moderate to severe when they were referred to The Department of Respiratory Medicine and Allergology. There were no significant gender differences regarding asthma symptoms, hospital admission, and unscheduled visits during childhood. One explanation for the fact that asthmatics females reported worse quality of life than asthmatic males could be that females perceive the same level of airflow obstruction differently than males, and that this impacts their daily living (87). Another explanation could be that this reflects biological, psychological or cultural distinctions between men and women. Mancuso et al. found that asthma patients with more depressive symptoms reported worse quality of life than asthma patients with similar disease activity but fewer depressive symptoms (126). Hommel et al. found in a study of older adolescents and young adults that depression and anxiety play a significant role in subjective assessment of asthma-specific quality of life. Anxiety had an independent main effect on asthma-specific quality of life after the influence of depression had been statistically controlled (62).

Wijnhoven et al. concluded that women with asthma report poorer HRQoL than men, but this is not due to a more severe disease state in terms of pulmonary obstruction, instead seeming to be related to a more severe subjective disease state in women than in men (127).

Many family, social, and behavioral factors contribute to asthma disparities both directly and indirectly. The relationships between these factors and the mechanisms by which they contribute to disparities are complex. Physical, economic, psychological, and social factors indirectly affect disparities by affecting the resources to which a person has access and the health behaviours they perceive to be important versus those which they neglect (128).

A study of women receiving education focused on the particular management problems of a woman with asthma showed that after one year there were significant improvements in their symptoms, health-care use, quality of life, days of missed work or school, and their self-confidence in managing asthma compared to women receiving conventional asthma education (37).

It is important to consider the difference in quality of life between men and women especially among adolescents and young adults.

Paper III

There was a difference in the association between grade and current rhinitis and between grade and severe nasal symptoms (SNS) in the GLM analysis. The logistic ORs implied that SNS was a significant determinant for grade, while current rhinitis was much less important. However, it is unlikely that our findings were due to sedation by pollen exposure, as the study was performed at the beginning of the year, before the pollen season.

It is known that allergic rhinitis has a considerable negative impact on children in terms of both their physical, social, and psychological well-being and their academic performance (129, 130, 131). If symptoms such as sneezing, itching, rhinorrhea, and congestion are not well controlled during the day, a child's ability to learn in the classroom may be affected (132). The results of this study indicate that rhinitis which is not well controlled, has an influence on the grade sum. The subjects were not using medication. Another explanation or contributing phenomenon may be adverse effects of the medication. A low degree of drowsiness taints even most modern antihistamines, and antihistamine medication was the treatment correlating most strongly with low grades (133). Therefore, it is important not only to recognize and aggressively manage allergic rhinitis, but also to evaluate the possible complications that may follow the disease (134). A recently presented expert report suggested that severe chronic upper airway diseases should be considered differently from mild chronic upper airway disease and that there is need for better understanding, prevention, and management of severe chronic upper airway diseases (135).

Conversely, eczema and asthma were not found to be associated with the final-year grades in the comprehensive school grades. This is in agreement with a study by Rietvald et al. (136), which concluded that children with asthma adapt well to living with the disease. Moreover, Celano et al (137) concluded that there is insufficient evidence to suggest that children with asthma are at significantly higher risk for poor school performance than children without asthma. Factors that may contribute to poor school performance among children with asthma include the iatrogenic effects of oral steroids, poor medical management of the disease, and psychological problems. Taras (138) found in a review of 66 articles examining the impact of asthma on school performance no clear evidence that the presence of asthma affected achievement or ability. Millard reported recently from the Dallas Independent School District

that 353 sixth-grade students with asthma missed no more school than their classmates without asthma (139). Moonie et al. concluded that children with asthma perform the same academically as their non asthmatic peers, but students with persistent asthma show a trend of performing worse on standardized test scores and have more absence days compared with other students (140). The asthma in study III was mostly mild asthma.

Paper IV.

The main finding was that in comparison to men, women with asthma had a higher self-reported adherence and a less negative attitude towards their medication and were more likely to have used inhaled corticosteroids and had appointments with a doctor in the last 12 months. Women with asthma also had a higher prevalence of anxiety, insomnia, and daytime sleepiness than men with asthma. No significant sex difference was found in asthma control.

Good communication skills, listening to the patient's needs and tailoring treatment to each individual are all aspects of good clinical practice (15). The relationship between psychological manifestation and respiratory symptoms is a point to consider in the management of asthma (141, 142). Anxiety is higher in women than in men, and increases with age (143). Neuman et al. found that symptoms related to anxiety and especially depression are important determinants for the development of dyspnea, while there was less evidence that dyspnea induces psychological symptoms (144). Studies have shown a positive correlation between both increased anxiety and depression and a higher dose of corticosteroids in asthmatics and impaired health-related quality of life (145, 146, 147).

In our study, female asthmatics were much more likely to have problems with insomnia and excessive daytime sleepiness. Asthma is a chronic inflammatory disease that can significantly affect the individual's physical and psychosocial functioning, for example in terms of daytime wakefulness and sleep quality (70). The increased insomnia seen in adult women may begin to manifest in early adolescence as excessive daytime sleepiness (148).

The reported sex differences could be related to differences in asthma phenotypes between men and women. Women had a later asthma onset and were less likely to have allergic asthma. Non-allergic asthma may be less responsive to inhaled corticosteroid treatment (149) and thus more difficult to treat.

The fact that so many symptoms of anxiety (e.g. shortness of breath, hyperventilation) overlap with many symptoms related to asthma mean that it is important to help the patient towards accurate symptom perception and appropriate self-management. Impairment in asthma-related quality of life in patients with anxiety and depressive disorders suggests that the impact of psychiatric co-morbidity on quality of life measures may be more general than specific (150).

Conclusions

Limited asthma education program did not show an effect on asthma symptoms, asthma knowledge or quality of life parameters among young adults with asthma. The prevalence of respiratory symptoms decreased in both the intervention group and in the control group and quality of life and knowledge about asthma increased in both groups. However, the educational program did seem to be associated with a significant improvement in FEV₁. Asthma management involves a collaborative partnership between the health care professionals and the patient. Adolescents need frequent support, encouragement, and positive feedback as they strive to manage their chronic illness and normal development.

A follow-up of young adults with asthma demonstrated that females seem to have lower quality of life compared with young males, even though there were no difference in age of onset of the disease or disease severity (moderate to severe), and they had all been patients at specialist care since the asthma debut. This gender difference may be important to consider when managing children and young adults with asthma in clinical practice.

The cross-sectional study of allergic disease among 15-year-old schoolchildren in Västra Götaland revealed that nasal symptoms severe enough to affect daily activity were strongly and significantly associated with final-year grades in comprehensive school. Conversely, eczema and asthma were not found to be associated with these final-year grades. The mean grade of those reporting nasal symptoms was lower than of those without these symptoms, and those using medication had a lower mean grade than those not using medication. Adolescents with severe chronic upper airway diseases are at risk of low grade-sum.

The follow-up study ECHRS II showed that women with asthma had a more positive attitude towards their medication, had a higher reported adherence, and used inhaled corticosteroids more often than men with asthma. At the same time, women had more problems with anxiety and insomnia than men. Awareness of gender differences in the manifestations and attitudes towards treatment of asthma is important in order to improve asthma management

Acknowledgements

I wish to express my sincere gratitude to everyone who has contributed in so many aspects to this thesis. I thank all of you patients who participated in the asthma outpatient clinic for young adults, all teenagers and their parents in the ALLOOO study, and all the people from the Nordic countries (Iceland, Norway and Sweden) who took part in the studies and answered the questionnaires.

A large number of colleagues and friends have contributed to this thesis, and supported me in many ways; thank you all. In particular I wish to express my thanks to:

Kjell Torén, my scientific teacher and supervisor, for your valuable support and continuous advice during this long process. You have always asked good critical questions and forced me to change my way of thinking. I would not say that this was an easy process – it was sometimes exhausting – but in the end it provided useful lessons and I have always felt inspired and encouraged to move on with my studies after our discussions.

Jonas Brisman, my co-supervisor for your inspiration, encouragement, and constant support. I am grateful for all our constructive discussions and for all your good advice and help.

Mona Palmqvist, head of the department of Respiratory Medicine and Allergology, and my chief and co-author, for constant encouragement, support, and enthusiasm, for enjoyable discussion and lots of laughs, for your great concern and patience, and for always having time for me.

Christer Janson, my co-author, at the Department of Medical Sciences: Respiratory Medicine and Allergology, Uppsala University for giving me the opportunity to become a part of ECRHS II, and for all your valuable help and advice and always being available to answer my questions

Alf Tunsäter, my co-author, for all your great support and friendship. I am grateful for all our constructive discussions about quality of life and for your generous hospitality during my visit to Borby.

Olle Löwhagen, my former chief department head and co-author, for support and valuable discussions.

Nalle Lindholm, former head of the department, for introducing me into the field of science, for your positive attitude towards new ideas and for the freedom I was given, to do things in my own way.

Susanne Ellbjär, asthma team member. I am very grateful for the time we had together in the outpatient clinic for young adults with asthma. It is thanks to you that I could start the first study.

My co-authors, Nils Åberg, Dag Höglund, Sten-Axel Wikenstedt, Thorarinn Gislason, Karl Franklin, Ernst Omenaas, and Cecilie Svanes for valuable co – operation and stimulating discussions.

Bengt-Eric Skoogh, for valuable advice and encouragement.

Gunnar Boman, for inspiration to start my doctoral studies.

Birgitta Aronsson, for friendship and discussions about everything important in life.

Christina Kristensson, for valuable help with all the references Desirée Wise, for keeping various papers in order, and Cina Holmer, for assisting me in editing this thesis.

All my friends and colleagues at Allergimottagningen, Elevhemmet, the former Allergilaboratoriet and Luftvägsgruppen at Occupational and Environmental Health.

My friends and colleagues at the the Swedish Society of Asthma and Allergy Nursing (ASTA) and especially the Allergikonulentgruppen.

Harrieth Thunberg-Sjöström, for your friendship: it is a great fun to work with you at the Institute of Health Care Sciences.

My mother Lillie, my brother Hans and his family Marita, Rasmus and Lovisa, thank you for your love and support. Invaluable friends and relatives, thank you for remembering me when I needed it most.

Most of all, to my beloved family for always being there for me during all these years. Inge, the man in my life and dearest friend, for your never-ending support, believing in me, and for all your love. Johanna, our wonderful daughter, who has so much energy and provides so much happiness in helping me to see what is important in life.

This work was financially supported by The Vårdal Foundation, the Department of Public Health, Västra Götalandsregionen, the Swedish Council for Worklife Research (FAS) and the Swedish Heart and Lung Foundation.

Swedish summary

Svensk sammanfattning

Syfte

Avhandlingens syfte var att hos patienter med astma undersöka kunskap om sjukdomen, astmakontroll, livskvalitet och följsamhet till behandling.

Frågeställningar i respektive delarbete:

Leder en pedagogisk modell av patientutbildning anpassad för ungdomar till förbättrad livskvalitet och minskad vård konsumtion hos ungdomar med astma? (I)

Ger ett optimalt omhändertagande av ungdomar med astma förändrad livskvalitet efter fem år och har dessa ungdomar sämre livskvalitet än en kontrollgrupp i samma ålder? (II)

Leder astma, rinit eller eksem bland ungdomar i årskurs nio till lägre meritvärde? (III)

Att jämföra kvinnor och män med astma med särskild tonvikt på rapporterad följsamhet, ångest och sömnsvärigheter.

Hundra ungdomar i ålder 17-18 år med astma, som remitterats till Allergisektionens ungdomsmottagning slumpades i en behandlingsgrupp och en kontrollgrupp.

Behandlingsgruppen fick genomgå patientutbildning utformad som interaktiv inläring med särskilt konstruerat datorprogram med efterföljande resultatdiskussion (I).

Fem år senare fick hela gruppen besvara frågor om symtom, medicinering, utbildning, fysisk aktivitet, rökning och livskvalitet. Gruppen jämfördes med 500 slumpmässigt utvalda kontrollpersoner i samma ålder (II).

Vid en tvärsnittsundersökning i årskurs nio i Västra Götaland 2000 besvarade 10 837 ungdomar frågor om astma, allergi och eksem. Från Statistiska centralbyrån inhämtades elevernas meritvärde. Multiple regression användes för att analysera sambandet mellan meritvärdet och astma, rinit, eksem och svåra näsbesvär som stör daglig aktivitet (III).

The European Community Respiratory Health Survey II är en uppföljningsstudie av ECRHS I som gjordes mellan 1999-2002. 470 patienter med astma från Sverige, Norge och Island har undersökts med avseende följsamhet till behandling, ångest och depression. Dessutom har sambanden mellan astma och sömnlöshet och dagtrötthet undersökts.

Vi fann ingen skillnad mellan behandlingsgruppen och kontrollgruppen avseende sjukhusvård, akutbesök, luftvägssymtom, kunskap om astma eller livskvalitet.

Luftvägssymtomen minskade och livskvaliteten förbättrades i både behandlingsgruppen och kontrollgruppen. Där fanns en signifikant förbättring i lungfunktionen mätt med FEV₁ (I).

Unga kvinnor med astma tycks ha en sämre livskvalitet än unga män med astma trots samma svårighetsgrad av sjukdom. Det fanns ingen skillnad mellan astmagruppen och kontrollgruppen avseende generell livskvalitet.

Svåra näsbesvär som stör dagliga aktiviteter har en påverkan på meritvärdet hos ungdomar i årskurs nio, det fanns inget samband mellan meritvärdet och astma, rinit eller eksem.

Kvinnor med astma har en bättre följsamhet till behandling både i normala och akuta situationer än män med astma. Inhalationssteroider och läkarbesök de senaste 12 månaderna reducerar risken för dålig följsamhet i normala situationer hos patienter med astma. Det fanns ett samband mellan ångest och dålig följsamhet i akuta situationer. Kvinnor med astma rapporterar en högre förekomst av ångest, sömnlöshet och dagtrötthet än män med astma.

Slutsatser

Intervention med ett datoriserat utbildningsprogram visade ingen effekt avseende astmasymtom, kunskap om sjukdomen eller livskvalitet hos ungdomar med astma. Lungfunktionen mätt med FEV1 förbättrades signifikant. Unga kvinnor med astma förefaller ha sämre livskvalitet än unga män med astma vid en femårsuppföljning. Svåra näsbesvär som stör dagliga aktiviteter påverkar meritvärdet hos ungdomar i årskurs nio, detta samband fanns inte vid astma och eksem. Kvinnor med astma rapporterar en mer positiv syn till medicinering, bättre följsamhet till behandling och använder mer inhalationssteroider än män med astma. Kvinnor med astma rapporterar mer ångest, sömnlöshet och dagtrötthet än män med astma.

References

1. Rutten-van Molken MP, Postma MJ, Joore MA, Van Genugten ML, Leidl R, Jager JC. Current and future medical costs of asthma and chronic obstructive pulmonary disease in *The Netherlands*. *Respir Med*. 1999 Nov;93(11):779-87.
2. Accordini S, Corsico A, Cerveri I, et al. The socio-economic burden of asthma is substantial in Europe. *Allergy*. 2008;63:116-124.
3. Bahadori K, Doyle-Waters MM, Marra C, Lynd L, Alasaly K, Swiston J, et al. Economic burden of asthma: a systematic review. *BMC Pulm Med*. 2009;9:24.
4. Matheson M, Raven J, Woods R K, Thien F, Walters E H, Abramson M. Wheeze not current asthma affects quality of life in young adults with asthma. *Thorax* 2002;57:165-167.
5. Baiardini I, Braido F, Brandi S, Tarantini F, Bonini S, Bousquet PJ, et al. The impact of GINA suggested drugs for the treatment of asthma on Health-Related Quality of Life: a GA(2)LEN review. *Allergy*. 2008 Aug;63(8):1015-30.
6. Cazzoletti L, Marcon A, Janson C, Corsico A, Jarvis D, Pin I, et al. Asthma control in Europe: a real-world evaluation based on an international population-based study. *J Allergy Clin Immunol*. 2007 Dec;120(6):1360-7.
7. Gavin LA, Wamboldt MZ, Sorokin N, Levy SY, Wamboldt FS. Treatment alliance and its association with family functioning, adherence, and medical outcome in adolescents with severe, chronic asthma. *J Pediatr Psychol*. 1999 Aug;24(4):355-65.
8. Griffith S. A review of the factors associated with patient compliance and the taking of prescribed medicines. *Br J Gen Pract*. 1990 Mar;40(332):114-6.
9. *Global Strategy for Asthma Management and Prevention*. Global initiative for asthma (GINA). Available at: www.ginasthma.org;2007 [accessed 12.22.08].
10. Katz PP, Yelin EH, Eisner MD, Blanc PD. Perceived control of asthma and quality of life among adults with asthma. *Ann Allergy Asthma Immunol* 2002;89:251-8
11. Braido F, Baiardini I, Balestracci S, Ghiglione V, Stagi E, Ridolo E, et al. Does asthma control correlate with quality of life related to upper and lower airways? A real life study. *Allergy*. 2009 Jun;64(6):937-43.
12. Global Initiative For Asthma. Global strategy for asthma management and prevention. NHLB/WHO Workshop Report, National Institutes of Health, National Heart, Lung, and Blood Institute Publication Number 02-3659, Revised 2002.
13. Gibson PG, Henry RL, Vimpani GV, Halliday J. Asthma knowledge, attitudes, and quality of life in adolescents. *Arch Dis Child*. 1995 Oct;73(4):321-6.
14. Couriel J. Asthma in adolescence. *Paediatr Respir Rev*. 2003 Mar;4(1):47-54.

15. Bosley CM, Fosbury JA, Cochrane GM. The psychological factors associated with poor compliance with treatment in asthma. *Eur Respir J*. 1995 Jun;8(6):899-904.
16. Haynes RB, Determinants of compliance: *The disease and the mechanics treatment. In Compliance and health care*. Baltimore, John Hopkins University Press, 1979.
17. Sabate E, ed. Adherence to long-term therapies: evidence for action. *Genev, world Health organization*, 2003.
18. Britten N, Stevenson FA, Barry CA, Barber N, Bradley CP. Misunderstandings in prescribing decisions in general practice: qualitative study. *Bmj*. 2000 Feb 19;320(7233):484-8.
19. Kelly WJW, Hudson I, Phelan PD, Pain MCF, Olinsky O. Childhood asthma in adult life: a further study at 28 years of age. *British Medical Journal* 1987;294:1059-1062.
20. Lee JH, Haselkorn T, Chipps BE, Miller DP, Wenzel SE, Tenor Study G. Gender differences in IgE-mediated allergic asthma in the epidemiology and natural history of asthma: Outcomes and Treatment Regimens (TENOR) study. *J Asthma*. 2006 Apr;43(3):179-84.
21. Baiardini I, Braido F, Giardini A, Majani G, Cacciola C, Rogaku A, et al. Adherence to treatment: assessment of an unmet need in asthma. *J Investig Allergol Clin Immunol*. 2006;16(4):218-23.
22. Janson SL, Earnest G, Wong KP, Blanc PD. *Predictors of asthma medication nonadherence. Heart Lung*. 2008 May-Jun;37(3):211-8.
23. Becker MH, Maiman LA. Sociobehavioral determinants of compliance with health and medical care recommendations. *Med Care*. 1975 Jan;13(1):10-24.
24. Bender BG. Risk taking, depression, adherence, and symptom control in adolescents and young adults with asthma. *Am J Respir Crit Care Med*. 2006 May 1;173(9):953-7.
25. ten Brinke A, Ouwerkerk ME, Zwiderman AH, Spinhoven P, Bel EH. Psychopathology in patients with severe asthma is associated with increased health care utilization. *Am J Respir Crit Care Med*. 2001 Apr;163(5):1093-6.
26. Birkhead G, Attaway NJ, Strunk RC, Townsend MC, Teutsch S. Investigation of a cluster of deaths of adolescents from asthma: evidence implicating inadequate treatment and poor patient adherence with medications. *J Allergy Clin Immunol*. 1989 Oct;84(4 Pt 1):484-91.
27. Apter AJ, Reisine ST, Affleck G, Barrows E, ZuWallack RL. Adherence with twice-daily dosing of inhaled steroids. Socioeconomic and health-belief differences. *Am J Respir Crit Care Med*. 1998 Jun;157(6 Pt 1):1810-7.
28. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther*. 2001 Oct;26(5):331-42.
29. Janson C, de Marco R, Accordini S, Almar E, Bugiani M, Carolei A, et al. Changes in the use of anti-asthmatic medication in an international cohort. *Eur Respir J*. 2005 Dec;26(6):1047-55.

30. Corsico AG, Cazzoletti L, de Marco R, Janson C, Jarvis D, Zoia MC, et al. Factors affecting adherence to asthma treatment in an international cohort of young and middle-aged adults. *Respir Med*. 2007 Jun;101(6):1363-7.
31. Dockrell M, Partridge MR, Valovirta E. The limitations of severe asthma: the results of a European survey. *Allergy*. 2007 Feb;62(2):134-41.
32. Gibson PG, Coughlan J, Wilson AJ, Hensley MJ, Abramson M, Bauman A, et al. Limited (information only) patient education programs for adults with asthma. *Cochrane Database Syst Rev*. 2000(2):CD001005.
33. Gibson PG, Ram FS, Powell H. Asthma education. *Respir Med*. 2003 Sep;97(9):1036-44.
34. Marabini A, Brugnami G, Curradi F, Casciola G, Stopponi R, Pettinari L, et al. Short-term effectiveness of an asthma educational program: results of a randomized controlled trial. *Respir Med*. 2002 Dec;96(12):993-8.
35. Marabini A, Brugnami G, Curradi F, Siracusa A. Does an asthma education program improve quality of life? A two-year randomized trial. *J Asthma*. 2005 Sep;42(7):577-81.
36. Jones MA. Asthma self-management patient education. *Respir Care*. 2008 Jun;53(6):778-84; discussion 84-6.
37. Clark NM, Gong ZM, Wang SJ, Lin X, Bria WF, Johnson TR. A randomized trial of a self-regulation intervention for women with asthma. *Chest*. 2007 Jul;132(1):88-97.
38. Cowie RL, Underwood MF, Little CB, Mitchell I, Spier S, Ford GT. Asthma in adolescents: a randomized, controlled trial of an asthma program for adolescents and young adults with severe asthma. *Can Respir J*. 2002 Jul-Aug;9(4):253-9.
39. van der Meer V, van Stel HF, Detmar SB, Otten W, Sterk PJ, Sont JK. Internet-based self-management offers an opportunity to achieve better asthma control in adolescents. *Chest*. 2007 Jul;132(1):112-9.
40. Chen H, Gould MK, Blanc PD, Miller DP, Kamath TV, Lee JH, et al. Asthma control, severity, and quality of life: quantifying the effect of uncontrolled disease. *J Allergy Clin Immunol*. 2007 Aug;120(2):396-402.
41. The World Health Organization Quality Of Life assessment (WHOQOL): Position paper from The World Health Organization. *Soc. Sci. Med*. 1995;41:1403-1409.
42. Holmes CA. Health care and the quality of life: a review. *J Adv Nurs*. 1989 Oct;14(10):833-9.
43. Moy ML, Israel E, Weiss ST, Juniper EF, Dube L, Drazen JM. Clinical predictors of health-related quality of life depend on asthma severity. *Am J Respir Crit Care Med*. 2001 Mar;163(4):924-9.
44. Voll-Aanerud M, Eagan TM, Wentzel-Larsen T, Gulsvik A, Bakke PS. Changes in respiratory symptoms and health-related quality of life. *Chest* 2007;131:1890–1897

45. Kimura T, Yokoyama A, Kohno N, Nakamura H, Eboshida A. Perceived stress, severity of asthma, and quality of life in young adults with asthma. *Allergol Int* 2009;58:1–9.
46. Axelsson M, Emilsson M, Brink E, Lundgren J, Torén K, Lötval J. Personality, adherence, asthma control and health – related quality of life in young adult asthmatics. *Respir Med* 2009; doi10.1016/j.rmed.2009.01.013.
47. Lobo FA, Lobo BA. Quality of life in asthmatics outpatients. *Journal of asthma*. 2008;45:27-32.
48. Blaiss MS. Allergic rhinitis and impairment issues in schoolchildren: a consensus report. *Curr Med Res Opin*. 2004 Dec;20(12):1937-52.
49. Leynaert B, Soussan D. Monitoring the quality-of-life in allergic disorders. *Curr Opin Allergy Clin Immunol*. 2003 Jun;3(3):177-83.
50. Hyland ME, Finnis S, Irvine SH. A scale for assessing quality of life in adult asthma sufferers. *J Psychosom Res*. 1991;35(1):99-110.
51. Tunsäter A, Sundberg R, Lindholm N. A Swedish questionnaire for assessment of quality of life among adults with asthma (In Swedish). *Hygiea* 1992;101:97.
52. Hyland ME, Ley A, Fisher DW, Woodward V. Measurement of psychological distress in asthma and asthma management programmes. *Br J Clin Psychol*. 1995 Nov;34 (Pt 4):601-11
53. Sullivan M, Karlsson J, Ware JE, Jr. The Swedish SF-36 Health Survey--I. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden. *Soc Sci Med*. 1995 Nov;41(10):1349-58.
54. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol*. 2001 Jul;108(1 Suppl):S2-8.
55. Jáuregui I, Mullol J, Dávila I. et al. Allergic rhinitis and schoolperformance. *J Investig Allergol Clin Immunol*. 2009;19:32-39.
56. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008 Apr;63 Suppl 86:8-160.
57. Verhaak P F M, Heijmans J W M, Peters L, Rijken M. Chronic disease and mental disorder. *Social Science & Medicine* 2005;60:789-797
58. Feldman JM, Siddique MI, Morales E, Kaminski B, Lu SE, Lehrer PM. Psychiatric disorders and asthma outcomes among high-risk inner-city patients. *Psychosom Med*. 2005 Nov-Dec;67(6):989-96.
59. Kinsman RA, Dirks JF, Jones NF. Levels of psychological experience in asthma: general and illness-specific concomitants of panic-fear personality. *J Clin Psychol*. 1980 Apr;36(2):552-61.

60. Feldman JM, Siddique MI, Thompson NS, Lehrer PM. The role of panic-fear in comorbid asthma and panic disorder. *J Anxiety Disord.* 2009 Mar;23(2):178-84.
61. Mancuso CA, Rincon M, McCulloch CE, Charlson ME. Self-efficacy, depressive symptoms, and patients' expectations predict outcomes in asthma. *Med Care.* 2001 Dec;39(12):1326-38.
62. Hommel KA, Chaney JM, Wagner JL, McLaughlin MS. Asthma-specific quality of life in older adolescents and young adults with long-standing asthma: The role of anxiety and depression. *Journal of Clinical Psychology in Medical Settings.* 2002;:185-192.
63. Goldney RD, Ruffin R, Fisher LJ, Wilson DH. Asthma symptoms associated with depression and lower quality of life: a population survey. *MJA* 2003;178:437-441.
64. American Psychiatric Association. Diagnostic and statistical Manual of Mental disorders 4th ed. Washington DC: American Psychiatric Association 1994.
65. Drake CL, Roehrs T, Roth T. Insomnia causes, consequences, and therapeutics: an overview. *Depress Anxiety.* 2003;18(4):163-76.
66. Harma M, Tenkanen L, Sjoblom T, Alikoski T, Heinsalmi P. Combined effects of shift work and life-style on the prevalence of insomnia, sleep deprivation and daytime sleepiness. *Scand J Work Environ Health.* 1998 Aug;24(4):300-7.
67. Janson C, Lindberg E, Gislason T, Elmasry A, Boman G. Insomnia in men-a 10-year prospective population based study. *Sleep.* 2001 Jun 15;24(4):425-30.
68. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev.* 2002 Apr;6(2):97-111.
69. Ohayon MM. From wakefulness to excessive sleepiness: what we know and still need to know. *Sleep Med Rev.* 2008 Apr;12(2):129-41.
70. Krouse HJ, Yarandi H, McIntosh J, Cowen C, Selim V. Assessing sleep quality and daytime wakefulness in asthma using wrist actigraphy. *J Asthma.* 2008 Jun;45(5):389-95.
71. Mastrorarde JG, Wise RA, Shade DM, Olopade CO, Scharf SM. Sleep quality in asthma: results of a large prospective clinical trial. *J Asthma.* 2008 Apr;45(3):183-9.
72. Larsson L. Incidence of asthma in Swedish teenagers: relation to sex and smoking habits. *Thorax* 1994;50:260-264.
73. Pearce N, Sunyer J, Cheng S, Chinn S, Bjorksten B, Burr M, et al. Comparison of asthma prevalence in the ISAAC and the ECRHS. ISAAC Steering Committee and the European Community Respiratory Health Survey. International Study of Asthma and Allergies in Childhood. *Eur Respir J.* 2000 Sep;16(3):420-6.
74. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med.* 2006 Nov 23;355(21):2226-35.

75. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet*. 2006 Aug 26;368(9537):733-43.
76. Ronmark E, Jonsson E, Platts-Mills T, Lundback B. Incidence and remission of asthma in schoolchildren: report from the obstructive lung disease in northern Sweden studies. *Pediatrics*. 2001 Mar;107(3):E37.
77. Lundback B. Epidemiology of rhinitis and asthma. *Clin Exp Allergy*. 1998 Jun;28 Suppl 2:3-10.
78. Larsson ML, Frisk M, Hallstrom J, Kiviloog J, Lundback B. Environmental tobacco smoke exposure during childhood is associated with increased prevalence of asthma in adults. *Chest*. 2001 Sep;120(3):711-7.
79. Becklake MR, Kauffman F. Gender differences in airway behaviour over the human life span. *Thorax*. 1999;54:1119-1138.
80. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma. *Eur Respir J*. 2003 Sep;22(3):470-7.
81. Fleming DM, Sunderland R, Cross KW, Ross AM. Declining incidence of episodes of asthma: a study of trends in new episodes presenting to general practitioners in the period 1989-98. *Thorax*. 2000;55:657-661
82. Ronchetti R, Villa MP, Barreto R et al. Is the increase in childhood asthma coming to an end? Findings from three surveys of schoolchildren in Rome, Italy. *Eur Respir J*. 2001;17:881-886.
83. Burney P. The changing prevalence of asthma? *Thorax*. 2002 Oct;57 Suppl 2:II36-II9.
84. Robertson CF, Roberts MF, Kappers JH. Asthma prevalence in Melbourne schoolchildren: have we reached the peak? *Med J Aust*. 2004 Mar 15;180(6):273-6.
85. Braun-Fahrlander C, Gassner M, Grize L, Takken-Sahli K, Neu U, Stricker T, et al. No further increase in asthma, hay fever and atopic sensitisation in adolescents living in Switzerland. *Eur Respir J*. 2004 Mar;23(3):407-13.
86. Canonica GW, Bousquet J, Mullol J, Scadding GK, Virchow JC. A survey of the burden of allergic rhinitis in Europe. *Allergy*. 2007;62 Suppl 85:17-25.
87. Osborne ML, Vollmer WM, Linton KLP, Buist AS. Characteristics of patients with asthma within a large HMO. A comparison by age and gender. *Am J Respir Crit Care Med* 1998;157:123-128.
88. Nicolai T, Pereszlenyiova-Bliznakova L, Illis S, Reinhardt D, von Mutius E. Longitudinal follow-up of the changing gender ratio in asthma from childhood to adulthood: role of delayed manifestation in girls. *Pediatr Allergy Immunol* 2003;14:280-283.

89. Torén K, Gislason T, Omenaas E, Svanes C, Jögi R, Forsberg B, Olin A-C, Janson C. A prospective study of asthma incidence and its predictors: *the RHINE study Eur Respir J* 2004;24:942-946.
90. de Marco R, Locatelli F, Sunyer J, Burney P and the European Community Respiratory Health Survey Study Group. Differences in incidence of reported asthma related to age in men and women. *Am J Respir Crit Care Med* 2000;162:68-74.
91. Almqvist C, Worm M, Leynaert B. for the working group of GA²LEN WP 2.5'Gender'. Impact of gender on asthma in childhood and adolescence: a GA²LEN review. *Allergy* 2008;63:47-57.
92. Singh AK, Cydulka RK, Stahmer SA, Woodruff PG, Camargo CA; for the multicenter asthma research collaboration investigators. Sex differences among adults presenting to the emergency department with acute asthma. *Arch intern Med* 1999;159:1237-1243.
93. Naleway AL, Vollmer WM, Frazier A, O'Connor E, Magid DJ. Gender differences in asthma management and quality of life. *Journal of Asthma* 2006;43:549-552.
94. Prescott E, Lange P, Vestbo J, and The Copenhagen City Heart Study Group. Effect of gender on hospital admissions for asthma and prevalence of self reported asthma: a prospective study based on a sample of the general population. *Thorax* 1997;52:287-289.
95. Global Initiative For Asthma. Global strategy for asthma management and prevention. NHLB/WHO Workshop Report, *National Institutes of Health*, National Heart, Lung, and Blood Institute Publication Number 95-3659, January 1995.
96. Heringa P, Lawson L, Reda D. The effect of a structured education program on knowledge and psychomotor skills of patients using beclomethasone dipropionate aerosol for steroid dependent asthma. *Health Educ Q.* 1987 Fall;14(3):309-17.
97. Wigal JK, Stout C, Brandon M, Winder JA, McConaughy K, Creer TL, et al. The Knowledge, Attitude, and Self-Efficacy Asthma Questionnaire. *Chest.* 1993 Oct;104(4):1144-8.
98. Knudson RJ, Slatin RC, Lebowitz MD, Burrows B. The maximal expiratory flow-volume curve. Normal standards, variability, and effects of age. *Am Rev Respir Dis.* 1976 May;113(5):587-600.
99. National Asthma Education Program, Office of prevention, education and control, National, Heart, Lung and Blood Institute. *Teach your patients about asthma: a clinician guide.* Bethesda, MD: *National Institutes of Health*, Publication 92-7237; 1992.
100. Sundberg R. *The knowledge of disease among subjects with asthma* [In Swedish]. Institutionen för vårdlärarutbildning, Göteborg, Sweden: Göteborgs Universitet, 1991.

101. Toren K, Brisman J, Jarvholm B. Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review. *Chest*. 1993 Aug;104(2):600-8.
102. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J*. 1995 Mar;8(3):483-91.
103. de Marco R, Zanolin ME, Accordini S, Signorelli D, Marinoni A, Bugiani M, et al. A new questionnaire for the repeat of the first stage of the European Community Respiratory Health Survey: a pilot study. *Eur Respir J*. 1999 Nov;14(5):1044-8.
104. Ekerljung L, Rönmark E, Larsson K, et al. No further increase of incidence of asthma: incidence, remission and relapse of adult asthma in Sweden. *Respir Med* 2008;102:1730–1736.
105. Ronmark E, Perzanowski M, Platts-Mills T, Lundback B. Incidence rates and risk factors for asthma among school children: a 2-year follow-up report from the obstructive lung disease in Northern Sweden (OLIN) studies. *Respir Med*. 2002 Dec;96(12):1006-13.
106. Ware JE Jr, Snow KK, Kosinski M, Gandek B. SF-36 *Health survey manual and interpretation guide*. Boston: New England Medical Center: The Health Institute; 1993
107. King A, Wold B, Tudor-Smith C, Harel Y. The health of youth. A cross-national survey. *WHO Reg Publ Eur Ser*. 1996;69:1-222.
108. Forero R, Bauman A, Young L, Booth M, Nutbeam D. Asthma, health behaviors, social adjustment, and psychosomatic symptoms in adolescence. *J Asthma*. 1996;33(3):157-64.
109. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J*. 1994 May;7(5):954-60.
110. The European Community Respiratory Health Survey II. *Eur Respir J*. 2002 Nov;20(5):1071-9.
111. Janson C, Chinn S, Jarvis D, Burney P. Physician-diagnosed asthma and drug utilization in the European Community Respiratory Health Survey. *Eur Respir J*. 1997 Aug;10(8):1795
112. Cerveri I, Locatelli F, Zoia MC, Corsico A, Accordini S, de Marco R on behalf of the ECRHS. International variations in asthma treatment compliance. The results of the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1999;14:288-294.
113. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983 Jun;67(6):361-70.
114. Partinen M, Gislason T. Basic Nordic Sleep Questionnaire (BNSQ): a quantitated measure of subjective sleep complaints. *J Sleep Res*. 1995 Jun;4(S1):150-5.

115. Janson C, Norbäck D, Omenaas E et.al. Insomnia is more common among subjects living in damp buildings. *Occup Environ Med* 2005;62:113-118.
116. Torén K, Palmqvist M, Löwhagen O, Balder B, Tunsäter A. Self-reported asthma was biased in relation to disease severity while reported year of asthma onset was accurate. *Journal of Clinical Epidemiology* 2006;59:90-93.
117. National Heart Lung and Blood Institute. Global initiative for asthma. Global strategy for asthma management and prevention. NHLBI/WHO workshop report. Bethesda (MD): *National Institutes of Health*; 1995. National Heart lung and Blood Institute publication no. 95-3659 Revised 2006.
118. Janson C, De Backer W, Gislason T, Plaschke P, Björnsson E, Hetta J, Kristbjarnason H, Vermeire P, Boman G. Increased prevalence of sleep disturbances and daytime sleepiness in subjects with bronchial asthma: a population study of young adults in three European countries. *Eur Respir J* 1996; 9:2132-2138.
119. Altman DG. *Practical statistics for medical research*. London: Chapman & Hall;1991.
120. Kauppinen R, Sintonen H, Vilkkä V, Tukiainen H. Long-term (3-year) economic evaluation of intensive patient education for self-management during the first year in new asthmatics. *Respir Med*. 1999 Apr;93(4):283-9.
121. Kauppinen R, Sintonen H, Vilkkä V, Pekurinen M, Tukiainen H. Quality-of-life measures and clinical parameters in asthmatics during three year follow-up. *Monaldi Arch Chest Dis*. 1998 Aug;53(4):400-4.
122. Bailey EJ, Cates CJ, Kruske SG, Morris PS, Chang AB, Brown N. Culture-specific programs for children and adults from minority groups who have asthma. *Cochrane Database Syst Rev*. 2009(1):CD006580.
123. van der Meer V, Bakker MJ, van den Hout WB, Rabe KF, Sterk PJ, Kievit J, et al. Internet-based self-management plus education compared with usual care in asthma: a randomized trial. *Ann Intern Med*. 2009 Jul 21;151(2):110-20.
124. Goldbeck L, Koffmane K, Lecheler, J, Thiessen K, Fegert JM. *Disease severity, mental health, and quality of life of children and adolescents with asthma*. DOI 10.1002/ppul.20509 Published online in Wiley InterScience 2006 www.interscience.wiley.com
125. Kyngäs HA. Compliance of adolescents with asthma. *Nurs Health Sci*. 1999 Sep;1(3):195-202.
126. Mancuso CA, Peterson MG, Charlson ME. Effects of depressive symptoms on health-related quality of life in asthma patients. *J Gen Intern Med*. 2000 May;15(5):301-10.
127. Wijnhoven HAH, Kriegsman DMW, Snoek FJ, Hesselink AE, de Haan M. Gender differences in health-related quality of life among asthma patients. *Journal of asthma*. 2003;40:189-199.
128. Mangan JM, Wittich AR, Gerald LB. The potential for reducing asthma disparities through improved family and social function and modified health behaviors. *Chest*. 2007 Nov;132(5 Suppl):789S-801S.

129. Blaiss M. Current concepts and therapeutic strategies for allergic rhinitis in school-age children. *Clin Ther.* 2004 Nov;26(11):1876-89.
130. Fisher L, Ghaffari G, Davies M, Craig T. Effects of poor sleep in allergic rhinitis. *Curr Opin Allergy Clin Immunol.* 2005 Feb;5(1):11-6.
131. Craig TJ, McCann JL, Gurevich F, Davies MJ. The correlation between allergic rhinitis and sleep disturbance. *J Allergy Clin Immunol.* 2004 Nov;114(5 Suppl):S139-45.
132. International Conference on Allergic Rhinitis in Childhood. *Allergy* 1999;54 (Suppl 55):7-34.
133. Shamsi Z, Hindmarch I. Sedation and antihistamines: a review of inter-drug differences using proportional impairment ratios. *Hum Psychopharmacol.* 2000 Oct;15(S1):S3-S30.
134. Blaiss MS. Pediatric allergic rhinitis: physical and mental complications. *Allergy Asthma Proc.* 2008 Jan-Feb;29(1):1-6.
135. Bousquet J, Bachert C, Canonica GW, et al. on behalf of the extended Global Allergy and Asthma European Network, World Allergy Organization and Allergic Rhinitis and its Impact on Asthma. *J Allergy Clin Immunol* 2009 in press
136. Rietveld S, Colland VT. The impact of severe asthma on schoolchildren. *J Asthma.* 1999 Aug;36(5):409-17.
137. Celano MP, Geller RJ. Learning, school performance, and children with asthma: how much at risk? *J Learn Disabil.* 1993 Jan;26(1):23-32.
138. Taras H, Potts-Datema W. Childhood asthma and student performance at school. *J Sch Health.* 2005 Oct;75(8):296-312.
139. Millard MW, Johnson PT, Hilton A, Hart M. Children with asthma miss more school: fact or fiction? *Chest.* 2009 Feb;135(2):303-6.
140. Moonie S, Sterling DA, Figgs LW, Castro M. The relationship between school absence, academic performance, and asthma status. *J Sch Health.* 2008 Mar;78(3):140-8.
141. Cluley S, Cochrane GM. Psychological disorder in asthma is associated with poor control and poor adherence to inhaled steroids. *Respir Med.* 2001 Jan;95(1):37-9.
142. Rimington LD, Davies DH, Lowe D, Pearson MG. Relationship between anxiety, depression, and morbidity in adult asthma patients. *Thorax.* 2001 Apr;56(4):266-71.
143. Cooper CL, Parry GD, Saul C, Morice AH, Hutchcroft BJ, Moore J, et al. Anxiety and panic fear in adults with asthma: prevalence in primary care. *BMC Fam Pract.* 2007;8:62.
144. Neuman A, Gunnbjornsdottir M, Tunsater A, Nystrom L, Franklin KA, Norrman E, et al. Dyspnea in relation to symptoms of anxiety and depression: A prospective population study. *Respir Med.* 2006 Oct;100(10):1843-9.

145. Bonala SB, Pina D, Silverman BA, Amara S, Bassett CW, Schneider AT. Asthma severity, psychiatric morbidity, and quality of life: correlation with inhaled corticosteroid dose. *J Asthma*. 2003 Sep;40(6):691-9.
146. Kullowatz A, Kannies F, Dahme B, Magnussen H, Ritz T. Association of depression and anxiety with health care use and quality of life in asthma patients. *Respir Med*. 2007 Mar;101(3):638-44.
147. Strine TW, Mokdad AH, Balluz LS, Berry JT, Gonzalez O. Impact of depression and anxiety on quality of life, health behaviors, and asthma control among adults in United States with asthma, 2006. *Journal of Asthma*. 2008;45:123-133.
148. Camhi SL, Morgan WJ, Pernisco N, Quan SF. Factors affecting sleep disturbances in children and adolescents. *Sleep Med*. 2000 Apr 1;1(2):117-23.
149. de Marco R, Marcon A, Jarvis D, Accordini S, Bugiani M, Cazzoletti L, et al. Inhaled steroids are associated with reduced lung function decline in subjects with asthma with elevated total IgE. *J Allergy Clin Immunol*. 2007 Mar;119(3):611-7.
150. Lavoie KL, Bacon SL, Barone S, Cartier A, Ditto B, Labrecque M. What is worse for asthma control and quality of life: depressive disorders, anxiety disorders, or both? *Chest*. 2006 Oct;130(4):1039-47.

