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Epidemiological studies of asthma and allergic diseases in teenagers:

methodological aspects and tobacco use

The Obstructive Lung Disease in Northern Sweden Studies – Thesis X

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To Johan, Ida & Tyra

"Nobody said it was easy. No one ever said it would be this hard."

The Scientist, Coldplay

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ABSTRACT

Parental reports are often used in studies of asthma and allergic diseases in children. A change in respondent from parent to index subject usually occurs during adolescence. Little is known about the effects this change in method might have on the outcomes of a longitudinal study. Smoking is a major cause of respiratory symptoms among adults and environmental tobacco smoke (ETS) is a risk factor for asthma among children. Less is known about these associations among teenagers. In order to improve prevention of smoking, it is important to identify populations at risk of becoming smokers.

The aim of this thesis were to 1) evaluate the methodological change from parental to self-completion of a questionnaire about asthma and allergic diseases, and 2) to study determinants for, and respiratory health effects of ETS and personal smoking in teenagers.

In 1996, a longitudinal study of asthma and allergic diseases among schoolchildren started within the Obstructive Lung Disease in Northern Sweden (OLIN) studies. All children in first and second grades (aged 7-8 years) in three municipalities, Luleå, Kiruna and Piteå (n=3,525) were invited and 97% participated by parental completion of a questionnaire. The cohort has been followed with annual questionnaires until age 16-17 years and with high participation rates (>91%). From age 12-13 years, the teenagers were the respondents and questions about their tobacco use were included. In addition to the questionnaire completed by the teenagers at age 13-14 years, a questionnaire was also distributed to a random sample of 10% of the parents and 294 participated (84%).

The parents and the teenagers reported a similar prevalence of asthma, respiratory symptoms, rhinitis, eczema and environmental factors. Two statistically significant differences were found: the teenagers reported a higher prevalence of wheezing during or after exercise (14% vs 8%, $p<0.05$), and having a dog in the home in the last 12 months (42% vs 29%, $p<0.001$). Answer agreement between parents and teenagers on questions about asthma was *almost perfect* with kappa values of 0.8-0.9. Corresponding kappa values for questions about respiratory symptoms and rhinitis were 0.3-0.6 and for eczema 0.5-0.6. Agreement about environmental factors varied from 0.2-0.9. Kappa values for parental smoking were 0.8-0.9. The risk factor pattern for allergic diseases was similar regardless of respondent, ie parent or teenager.

The prevalence of smoking increased from 3% at 12-13 years to 6% at 14-15 years. Smoking was more common among girls, while the use of snus was more common among boys. Significant risk factors related to smoking

among teenagers were smoking family members, female sex and living in an apartment. Having physician-diagnosed asthma did not prevent the teenagers from becoming smokers. Factors related to using snus were a smoking mother and male sex.

Daily smokers aged 16-17 years (9%) reported a significantly higher prevalence of wheezing and physician-diagnosed asthma compared to non-smokers. There was a significant dose-response association with higher prevalence of wheeze among those who smoked ≥11 cigarettes per day compared to those who smoked ≤10 per day. In multivariate analyses, maternal environmental tobacco smoke exposure was a significant risk factor for ever wheeze and physician-diagnosed asthma at age 16-17 years, while daily smoking was a risk factor for current wheeze.

In conclusion, the methodological change of questionnaire respondent from parent to index subject did not substantially alter the findings of this longitudinal study. There were significant sex differences in the tobacco use: smoking was more common among girls and snus was more common among boys. The most important factor related to tobacco use was presence of family members who smoke. Both maternal ETS exposure and personal smoking was associated with asthma and wheeze in adolescence. ETS was associated with lifetime symptoms but daily smoking was more strongly associated with current symptoms.

SVENSK SAMMANFATTNING

Studier om astma och allergiska sjukdomar bland barn baseras ofta på frågeformulär som besvaras av föräldrarna. En förändring av metoden från föräldra- till självrapportering kan bli aktuell i tonåren. Vilken effekt denna förändring kan ha på resultaten i en longitudinell studie är inte väl studerad.

Rökning är en starkt bidragande orsak till luftvägssymtom bland vuxna och miljötobaksrök (ETS) är en riskfaktor för astma bland barn. Bland tonåringar är dessa samband mindre studerade. För att kunna förbättra rökprevention är det viktigt att identifiera de grupper som löper risk att bli rökare under tonåren.

Syftet med denna avhandling var att 1) utvärdera en metodologisk förändring från föräldra- till självbesvarade enkäter om astma och allergiska sjukdomar, och 2) att studera faktorer relaterade till rökdebut samt ETS och egen rökning i relation till astma och luftvägssymtom bland tonåringar.

1996 påbörjades inom ramen för Obstruktiv Lungsjukdom I Norrbotten (OLIN-studierna) en longitudinell studie om astma och allergiska sjukdomar bland skolbarn. Samtliga barn i första och andra klass (7-8 år) i tre kommuner, Luleå, Piteå och Kiruna (n=3525) bjöds in och 97% deltog genom att föräldrarna besvarade en enkät. Kohorten har följts upp med årliga enkäter till och med 16-17 års ålder och deltagandet har varit högt (>91%). Från och med 12-13 års ålder besvarades enkäten av barnen själva och frågor om deras tobaksvanor lades till. Utöver den årliga enkäten till tonåringarna vid 13-14 års ålder, förmedlades enkäten även till ett slumpmässigt urval om 10% av föräldrarna och 294 besvarade den (84%).

Föräldrar och tonåringar rapporterade lika förekomst av astma, luftvägssymtom, rinit, eksem och miljöfaktorer. I två frågor skiljde sig tonåringarnas och föräldrarnas enkätsvar signifikant åt. Förekomsten av pip i bröstet i samband med ansträngning var högre enligt tonåringarnas enkätsvar (14% vs 8%, p=0,02). Även förekomst av hund i hemmet under de senaste 12 månaderna rapporterades av fler tonåringar än föräldrar (42% vs 29%, p<0,001). Samstämmigheten mellan föräldrar och tonåringar i frågor om astma var mycket bra, med kappa-värden på 0,8-0,9. Motsvarande kappa-värden i frågor om luftvägssymtom och rinit var 0,3-0,6 samt för eksem 0,5-0,6. Samstämmigheten i frågor om miljöfaktorer varierade från 0,2-0,9. Kappa-värden avseende föräldrars rökning var 0,8-0,9. Riskfaktormönstren för allergiska sjukdomar var lika oavsett om föräldrar eller tonåringar användes som respondenter.

Andelen rökare ökade från 3% vid 12-13 års ålder till 6% vid 14-15 års ålder. Rökning var signifikant mer vanligt bland flickor, medan snusning

var vanligare bland pojkar. Signifikanta riskfaktorer för att vara rökare var att ha rökande familjemedlemmar, att vara flicka och att bo i lägenhet. Att ha astma hindrade inte tonåringarna från att bli rökare. Faktorer relaterade till snusning var att ha en rökande mamma samt att vara pojke.

Förekomsten av astma och pip i bröstet var signifikant högre bland dagligrökare jämfört med icke-rökare vid 16-17 års ålder. Ett dos-respons förhållande förelåg där prevalensen av pip i bröstet var högre bland de som rökte ≥11 cigaretter per dag jämfört med de som rökte ≤10 per dag. I multivariata analyser var exponering för miljötobaksrök från mamman relaterat till läkardiagnostiserad astma och att någonsin ha haft pip i bröstet medan egen dagligrökning var relaterat till nuvarande luftvägssymtom vid 16-17 års ålder.

Således visar denna avhandling att den metodologiska förändringen från föräldrar till tonåringar som respondenter inte påverkade utfallet i denna longitudinella studie. Det fanns signifikanta könsskillnader i tobaksbruk, där rökning var vanligare bland flickor och snusning vanligare bland pojkar. Den viktigaste faktorn relaterat till tobaksanvändning var att ha rökande familjemedlemmar. Både exponering för miljötobaksrök från mamman och egen rökning var relaterat till astma och pip i bröstet i tonåren. Att någonsin ha haft luftvägssymtom var relaterat till miljötobaksrök, medan nuvarande symtom var starkare relaterat till tonåringarnas egen rökning.

ABBREVIATIONS

BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
EAACI	The European Academy of Allergy and Clinical Immunology
ETS	Environmental tobacco smoke
GYTS	Global Youth Tobacco Survey
HBSC	Health Behaviour in School-aged Children
ISAAC	International Study of Asthma and Allergies in Childhood
OLIN	Obstructive Lung Disease in Northern Sweden studies
OR	Odds ratio
RSV	Respiratory synctial virus
SES	Socioeconomic status
SPT	Skin prick test
WHO	World Health Organisation

ORIGINAL PAPERS

I **Hedman L**, Lindgren B, Perzanowski M, Rönmark E. Agreement between parental and self-completed questionnaires about asthma in teenagers. *Pediatr Allergy Immunol* 2005;16:176-181.

II **Hedman L**, Bjerg A, Perzanowski M, Rönmark E. Good agreement between parental and self-completed questionnaires about allergic diseases and environmental factors in teenagers. *J Clin Epidemiol* 2009. Epub ahead of print.

III **Hedman L**, Bjerg-Bäcklund A, Perzanowski M, Sundberg S, Rönmark E. Factors related to tobacco use among teenagers. *Respir Med* 2007;101, 496-502.

IV **Hedman L,** Bjerg A, Sundberg S, Forsberg B, Rönmark E. Both environmental tobacco smoke and personal smoking are associated with asthma and wheeze among adolescents. *In manuscript.*

INTRODUCTION

The transition from childhood to adolescence involves personal, physiological and social changes. During this time, teenagers develop a stronger personal identity and independence from their parents. They will also take more responsibility for themselves and make their own choices, about education, social activities and medical treatment, for example.

Teenagers spend less time with their parents compared to when they were younger, and identification with peers becomes more important. By observing family members and friends, teenagers adopt and develop both positive and negative behaviours. Risk taking behaviours such as experimentation with alcohol, tobacco or drugs, often start during adolescence. Smoking cigarettes has been a part of teen culture since the 1950s, when icons such as James Dean, Marlon Brando, Marilyn Monroe and Elvis Presley were often pictured while smoking a cigarette. Although tobacco advertisement in the media is regulated, smoking is perceived by many teenagers as an adult habit that increases social status, rather than the addictive and harmful habit it actually is.

An early tobacco antagonist was King James I of England. He wrote about smoking in *A Counterblaste to Tobacco* from 1604 (1):

> *"A costume lothsome to the eye, hatefull to the Nose,*
> *harmefull to the braine, dangerous to the Lungs, and*
> *in the blacke stinking fume thereof, nearest resembling*
> *the horrible Stigian smoke of the pit that is bottomlesse."*

Although this statement may seem overly dramatic, it shows that smoking has been a subject for debate since its introduction in Europe in the 16th century. Smoking remains a controversial topic of which many have a strong opinion.

BACKGROUND

The word *epidemiology* is Greek and includes the terms *epi* – among, *demos* – people, and *logos* – study. The term epidemic was first used by Hippocrates (460-377 BC), who attempted to explain the association between environmental factors and diseases with observation rather than intuition (2).

Historically, investigations of epidemics and causes of infectious diseases have been described. Some examples include investigations of the 19th century London cholera epidemic by John Snow, mortality of Austrian childbirth fever during the 1840s by Ignaz Semmelweiss, and the association between poor living conditions and high mortality rates among wounded soldiers observed by Florence Nightingale during the Crimean war. However, the profession of epidemiology was not established until the 20th century.

Rothman et al have defined epidemiology as *"the study of the distributions and determinants of disease frequency in human populations"* (3). The objective of epidemiologic research is to acquire valid and reliable measurements of disease and exposure and to study the causal relationship between them. There are different ways of conducting epidemiologic research and the most suitable design depends on the research question (3). The studies included in the present thesis are cross-sectional and cohort studies.

In *cross-sectional studies*, or *prevalence studies*, the outcome is expressed as prevalence of disease and exposure in a population at a defined time or period. Such studies can be used to measure how disease and exposure prevalence changes over time. In measures of association between exposure and disease, also retrospective questions can be included. However, cross-sectional studies have limitations in determining the time order of cause and effect.

In a *cohort study*, a defined group of individuals, or cohort, are followed over time. Cohort studies are used to measure prevalence, incidence and remission of disease and to study the associations between exposure and disease. Cohort studies can be retrospective or prospective, open or closed. In a closed cohort new members cannot be added to the cohort. In an open cohort, new members can be added as they move into the study area or in other ways become eligible for the study.

Asthma and allergic diseases

Asthma is characterised by bronchial inflammation and hyper-responsiveness that results in respiratory symptoms caused by variable and reversible airway obstruction (4-7). Asthma is a common chronic respiratory disease where symptoms such as chest wheezing, chest tightness, cough or episodes of shortness of breath (dyspnoea) usually are induced by viral infections, physical exercise, allergen exposure or environmental triggers such as tobacco smoke or other strong scents (5, 6). Recent literature describes asthma as a syndrome rather than a single disease entity, and several phenotypes have been described (7-9).

Asthma and allergic diseases among children increased substantially during the second part of the 20th century (10-12). However, recent studies of time trends in asthma prevalence report a plateau (13, 14) and even a decrease in asthma and respiratory symptoms (15). The decrease in asthma has been seen in countries with high prevalence of asthma, while asthma was still increasing in countries with low prevalence of asthma (16).

The relationship between asthma and wheezing is complex. Among teenagers and young adults, asthma is a common cause of wheeze. Among middle aged and elderly there are several other causes of wheezing, for instance chronic bronchitis, chronic obstructive pulmonary disease (COPD) (17, 18), and cardiovascular diseases. The prevalence of wheeze is high in early childhood (19-23), however not all wheeze are asthma and many children only experience wheezing during infections and never develop asthma (19, 24).

Besides asthma, the other primary allergic diseases are eczema and rhinitis. Eczema is characterised by an itchy rash, commonly located at the folds of the elbows, behind the knees, on the front of the ankles, under the buttocks or around the neck, ears or eyes. Rhinitis is an inflammation of the nose, usually presenting with a runny or stuffy nose and sneezing, and often accompanied by conjunctivitis with itchy watery eyes. Symptoms of allergic rhinitis, or hay fever, is usually caused by airborne allergens such as pollen. The first allergic disease to appear in childhood is typically eczema, followed by asthma, with rhinitis coming later (6, 25). This natural history of allergic diseases is sometimes referred to as "the atopic march". In northwestern European countries, the prevalence of current rhino-conjunctivitis was 10-17% and the prevalence of current eczema 7-16% in

early adolescence according to surveys within the International Study of Asthma and Allergies in Childhood (ISAAC) (16).

Natural history of asthma

Obstructive respiratory symptoms such as chest wheezing that present during pre-school ages are often not allergic, but are triggered by viral infections and not present between infections (24). These wheezing episodes are most often transient. A prospective American birth cohort study reported that the majority of children less than 3 years of age who had lower respiratory tract illnesses with wheezing reported no wheezing by the age of six (19) or eleven years (26). Although these transient wheezers had lower levels of lung function than the asymptomatic children, they did not have an increased risk of asthma later in life (26). However, others have found early transient wheezing caused by respiratory synctial virus (RSV) to be a risk factor for asthma later in life (27).

The allergic asthma phenotype is more common after preschool age and is often associated with sensitization to pollen, furry animals and house dust mites (26, 28, 29). This type of asthma usually persists into adolescence. From childhood until middle age, the association between asthma and allergic sensitization becomes stronger with increasing age (5, 30).

In northwestern European countries, the prevalence of current wheeze varied between 7-21% among children aged 6-7 years and 8-25% at age 13-14 years according to ISAAC surveys, with the highest prevalence in the UK (16). The prevalence of ever asthma among 13-14 year olds was reported to be 12% in Linköping, Sweden, 7-9% in other northern European countries, while it was 25% in the UK (31). Before adolescence, both the prevalence and incidence of asthma and wheezing are usually higher among boys than girls (28, 32, 33). At the age of 11-12 years, the prevalence of asthma was significantly higher among boys (9%) than girls (7%) in northern Sweden (30). The incidence rate of asthma or wheezing illness between birth and age 7 was estimated at 2.9/100 per year among boys and 2.3/100 per year among girls in a British birth cohort (32). Although the incidence of new onset wheezing decreases with age, the incidence of asthma is still high in early adolescence (32, 33). Anderson et al found that the incidence rate of asthma or wheezing illness from age 12-16 years was 0.9/100 per year among boys and 0.6/100 per year among girls. At age 17-23 years, it was 0.6/100 per year among boys and 0.9/100 per year among girls (32) – a reversal in incidence. Among pre-teen school children in northern Sweden, the incidence of

asthma was 0.7-0.9/100 per year (34-36). This can be compared to the stable incidence of 0.2-0.3/100 per year among Swedish adults since the 1980s (37-40).

Exercise-induced wheezing or dyspnoea is common among adolescents. Causes other than asthma, such as poor physical condition, restrictive lung function impairment and vocal cord dysfunction, have been suggested (41). During the late teen years, some individuals might have mild asthma symptoms or be in remission but relapse during early adulthood is common (33, 42). Children with asthma or respiratory symptoms who experience more frequent symptoms and severe disease are more likely to have asthma that persists into adolescence and adulthood (24, 43). Further, those with respiratory symptoms early in life that persist into adolescence more often have a family history of asthma, are sensitized, or have another allergic disease such as eczema or food allergy (6, 24, 32, 44). Having obstructive spirometry, airway hyper-responsiveness or atopy at age 8-12 years predicts asthma in adulthood (43, 45).

Risk factors for asthma and wheeze

The most important risk factors for asthma are family history of asthma (8, 30, 32, 37, 46, 47) and allergic sensitization (4, 8, 30, 32, 47). Among younger children where the non-allergic asthma phenotype is common, risk factors are often environmental and include viral infections (4, 44), dampness in the home (8, 48, 49), and exposure to tobacco smoke (8, 48). Premature birth or low birth weight has been identified as risk factors for asthma and wheeze both among children (34, 50), adolescents (47, 51) and adults (52).

The relationship between overweight and asthma is inconsistent in the literature. Some studies show significant associations only among girls (26), some only among boys (53), and others only among the non-allergic (53). An increased body mass index (BMI) was significantly related to new onset asthma among adults, independent of sex and allergic status, in a study from northern Sweden (54).

Asthma and respiratory symptoms in relation to environmental tobacco smoke (ETS)

Among adults a causal dose-response relationship between ETS exposure and respiratory disorders has been suggested (55). Among small children, numerous studies have found that exposure to environmental tobacco

smoke (ETS) in early life or *in utero* is a risk factor for asthma and wheezing (50, 56-59). ETS exposure, especially from the mother, is strongly related to transient wheeze at pre-school ages (19, 60). Some studies suggest that ETS exposure *in utero* and in early life has an adverse effect on respiratory health into adulthood (61-63). There are only a few studies that have evaluated the effects of both early and recent ETS exposure on adolescent respiratory health. Some found stronger independent effects of exposure to maternal smoking *in utero* than ETS during childhood (59, 64). Gilliland et al reported that *in utero* exposure was related to both asthma and wheezing among school children, while postnatal ETS exposure was related only to wheezing (65). Among adolescents or young adults, some studies found an increased prevalence of wheezing and asthma among those with current ETS exposure (55, 66, 67), while others did not find such associations (57, 68).

Asthma and respiratory symptoms in relation to smoking

Smoking is the single most important and preventable risk factor for all respiratory symptoms. While several studies among adults have shown a strong association between smoking and Chronic Obstructive Pulmonary Disease (COPD) and chronic bronchitis (69-73), the relationship between smoking and asthma is not as strong or consistent (74, 75). Several cross-sectional studies found significant associations between ex-smoking or ever smoking and asthma (76-79), while others show no or a weak association (80, 81). Prospective studies more often report significant associations between smoking and adult onset of asthma (37, 82-85).

Among adolescents, several studies have found significant associations between smoking and asthma and wheezing (57, 66, 68, 86-90). However, there are only a few studies that have assessed both the independent and combined effects of ETS and adolescent smoking. These studies found significantly higher risk for current wheezing among active smokers compared to both non-smokers and those exposed to ETS (66). The highest risk for both asthma and wheezing was among smokers with current ETS exposure (66, 87) or exposure *in utero* (59). Genuneit et al reported that ETS was not a significant risk factor for incident asthma or wheezing among non-smoking adolescents, while active smoking increased the incidence of both asthma and wheezing (68).

Smoking

Before the 20th century, tobacco was usually smoked in pipes. The sale of cigarettes increased dramatically at the beginning of the 20th century (91). However, although harmful health effects were suspected as a result of smoking, major actions into the research of lung and airway diseases did not start until after the London fog catastrophe in December 1952 (92). Attention was initially paid to bronchitis symptoms and chronic bronchitis (92, 93) and British researchers found the association to smoking. In the 1950s a prospective study of smoking and its health effects was begun in the UK among male physicians. Doll and his colleagues found a causal relationship between smoking and lung cancer (94) which became increasingly strong over time (91). Several early Nordic epidemiologic studies could verify mainly cough, sputum production and wheezing to be considerably more common among smokers than non-smokers (95, 96). During the 1970s and 1980s the focus changed from symptoms to include also lung function impairment. One of the most important studies in this topic was a longitudinal study of British post office workers (97). Fletcher et al quantified the smoking exposure and described the longitudinal effects of smoking on lung function and also the benefits of smoking cessation (92, 97). Several large scale studies in USA and Europe, including the Nordic countries, contributed to the strong evidence of the association between smoking and lung function impairment (92, 98-100).

Not until the mid 1960s were public health efforts to reduce the prevalence of tobacco use initiated (101). Shortly thereafter the number of smokers started to decline. Still, smoking remains a major preventable cause of illness and death. The World Health Organisation (WHO) estimates that 500 million people alive today will die due to tobacco use (102). The tobacco epidemic is still growing, especially in developing countries. In 2004, the WHO rated COPD as the fourth most common cause of death in the world. The burden of disease and tobacco-related deaths will increase in countries of high population-growth and where health care is less available.

Worldwide tobacco use

Smoking among adults has decreased during the past decades in most parts of Europe. This downward trend was also seen during the beginning of the 21th century (103). Although the overall prevalence of daily smoking was higher among European men than women, the prevalence among men decreased while the prevalence among women was level. The decrease in

smoking prevalence was not seen among adolescents, particularly not among girls in developed countries (103, 104). Strong et al predicted an increase in daily smoking among women in all European regions except for Northern Europe (103). These tobacco use trends are also described by Lopez et al (105). Retrospective observations of smoking trends in developed countries show an increasing prevalence of smoking followed by an increase of smoking related deaths 30-40 years later. The pattern is similar among men and women, however the increase in smoking occurs 10 to 20 years later among women compared to men. In the final stage of the tobacco epidemic, the number of smokers and smoking-related deaths decline. To date, the final stage has only been seen in some developed countries, including Sweden (105).

A worldwide comparison of prevalence of current smokers in ages 13-15 years found major sex differences. Current smoking was more common among boys in Africa, the eastern Mediterranean region, southeast Asia, and the western Pacific region. In the Americas and Europe no sex differences were found (106). However, the prevalence of current smokers in Western and Northern European countries was not presented in this report.

The prevalence of adolescent smokers in Sweden has decreased during the last 25 years (107). Since 1983, the Swedish Council for Information on Alcohol and Other Drugs (CAN) has performed annual surveys of tobacco use among school children at 15 years of age. Daily smoking among boys was 7-13% during the 1980s and 1990s and 4-7% during the 2000s. Among girls, daily smoking decreased from 10-17% during the 1980s and 1990s to 7-12% in the 2000s (107).

Tobacco control

A key factor for successful prevention is long term collaborations between international, national, regional and local organisations. The WHO has introduced the MPOWER package to decrease the number of smokers and tobacco-related diseases and deaths: (102)

- Monitor tobacco use and prevention policies
- Protect people from tobacco smoke
- Offer help to quit tobacco use
- Warn about the dangers of tobacco
- Enforce bans on tobacco advertising, promotion and sponsorship
- Raise taxes on tobacco

These are some of the most effective tobacco control policy interventions. In order to be effective, the strategies have to be implemented at both international and local levels. However, not all countries participating in the WHO have fully adopted them. The WHO´s Tobacco Free Initiative (TFI) in collaboration with the Centers for Disease Control and Prevention (CDC) initiated the Global Youth Tobacco Survey (GYTS) in 1999 (108). Since then, the survey has been conducted in over 140 countries and across all six WHO regions. The aim of the GYTS is to monitor tobacco use among youth, enable comparison of tobacco use at the national and international levels, and enhance the capacity of countries to design, implement and evaluate tobacco control and prevention programmes (106, 108). In the first worldwide report, the GYTS requested further research about the patterns of tobacco use among adolescents, the interaction of the different determinants of tobacco use, and the differences between countries and cultures. With this information, subpopulations at high risk of becoming smokers can be targeted and prevention efforts can be improved. Campaigns targeted with respect to sex, age, sexual orientation, socioeconomic, racial and ethnical groups might be more successful than "one size fits all" approaches (109).

On the national and regional levels, mandatory bans against smoking in schools (110), public service announcements (111), as well as combination approaches that include policies, media campaigns and school-based programmes (112, 113) are effective in decreasing smoking rates among adolescents. Although many European countries have age limits for the purchase of tobacco products, usually set at 16 or 18 years, the association between age limit and reduced smoking prevalence is weak (110). One of the objectives for the Swedish National Institute of Public Health (Folkhälsoinstitutet) is to reduce tobacco use. The prevention of tobacco use among children and adolescents is a high priority task (114).

Tobacco legislation in Sweden

The Swedish tobacco act (SFS 1993:581) was adopted in 1993 and has been extended with new restrictions (115). In short, the act currently bans smoking in:

1. All premises used for child care, including both indoor and outdoor schools and day care environments.
2. All premises used for health care.
3. Collective localities in apartment buildings and service homes
4. Public transportation
5. Restaurants and bars, since 2005

The act states that no employee should be involuntarily exposed to tobacco smoke. All packaging of tobacco products must be labelled with information about health risks and a declaration of content. Furthermore, the age limit to buy tobacco products is 18 years and there are restrictions about who is allowed to import and sell tobacco products and the way tobacco products are advertised.

Predictors of becoming a smoker

In order to reduce the number of teenage smokers, it is important to identify at-risk populations. There is a complex interaction between societal, social and personal factors that may predict who becomes a smoker. The most common factors are presented below.

Societal factors

Tobacco use among teenagers is influenced by the media and marketing. A review by DiFranza et al found a strong and consistent relationship between tobacco promotion and smoking initiation among teenagers (116). Although tobacco advertising is prohibited in printed and broadcast media, tobacco brands and logos were recognised by children aged three to eight years (117). Exposure to tobacco marketing and promotional items was significantly related to smoking among teenagers in Norway, despite a ban on tobacco advertising and promotion since 1975 (118). Besides national tobacco control policies, such as bans against the sale of tobacco products to minors (110), other societal factors that influence the tobacco use are taxes and price of tobacco products (119), and school-based efforts such as enforcement of smoking bans and policies (110, 120) and antismoking classes (121).

Social factors

A teenager´s risk of becoming a smoker increases if there are smokers in the environment (104, 121, 122). Several studies found an increased risk of becoming a smoker among those with mothers (87, 123) or fathers (121, 124) who smoke. Children living in a two-parent household are less likely to become smokers compared to other family structures (104, 125). Other family-related predictors of smoking are parental indifference to their child´s smoking, a poor parent/child relationship, lack of support, and having a sibling who smokes (104, 122). The association between having friends who smoke and becoming a smoker is consistent (123, 126). Ellickson

et al found that having friends who smoked has a stronger relationship with becoming a smoker in early and late teenage years, compared to having parents who smoked, which was a risk factor only among early teens (125).

Low socioeconomic status (SES) is strongly related to smoking among adults and influences smoking initiation among teenagers. Sotariades et al found smoking prevalence to be higher among teenagers with a personal income (127). In a longitudinal study of a British birth cohort, low paternal SES during childhood and adolescence was significantly related to persistent smoking in adulthood (128). However, after adjusting for SES in adulthood the associations were weakened and childhood SES was only a risk factor for persistent smoking among women only.

Personal factors

Sex differences in smoking habits vary between cultures (104). Generally, a higher prevalence of smoking among girls is found in developed countries (120, 121, 129), while smoking among boys is more common in developing countries and Eastern cultures (106). There are several studies where no sex differences in smoking prevalence were found (122, 125, 130).

Lower prevalence of smoking has been found among those with good school performance and commitment (125), high educational aspirations, and those who follow a healthy lifestyle and participate in physical exercise (104, 130, 131). Inversely, those with risk-taking behaviour, stress, depression, and high susceptibility to peer-pressure are more likely to smoke (104, 126). Aveyard et al found that smoking was less prevalent among those engaged in a student-centred anti-tobacco program compared to those who reported disengagement from the intervention program and from school (132). Several studies have reported a higher prevalence of smoking among asthmatic compared to non-asthmatic teenagers (133-135). In a Danish study, teenagers with asthma reported a higher prevalence of daily smoking and heavy smoking (>15 cigarettes/day), and boys with asthma started smoking at an earlier age compared to non-asthmatic teenagers (134).

Snus

In addition to cigarettes, there are various smokeless tobacco products, eg chewing tobacco, snuff and snus. Snus is a smokeless, moist grounded tobacco that is placed under the upper lip. Sweden is the only country in the European Union where snus is allowed. Using snus is significantly more

common among men than women (136). Among Swedish 15-16 year old boys, using snus has become more common than smoking cigarettes (137). In a study about the behavioural influence of parental tobacco use it was found that maternal smoking increased the risk of becoming a smoker, while paternal snus use increased the risk for snus use among boys (138).

Methodological aspects of cohort studies

In longitudinal studies that follow cohorts of children through adolescence, a change of methods from parental report to child self-reports will be necessary as the children get older. There are epidemiologic cohort studies of asthma and respiratory health among children followed throughout adolescence. Some examples of cohort studies include the British National Child Development Study (32, 57), the Dunedin Multidisciplinary Health and Development Study (23), and the Tucson Children´s Respiratory Study (26). The transition in respondent from parents to index subject have been actualised in all of these studies. However, the transition occurred at different ages and the effects it might have on the results have not been evaluated.

The International Study of Asthma and Allergies in Childhood (ISAAC) started in 1994 and has provided standardised methods to estimate the prevalence and severity of wheezing, asthma, rhinitis and eczema among school children (139). The study has been performed worldwide and has a large number of participants in both developed and developing countries (16). The protocol includes two questionnaires: one for distribution to parents of 6-7 year old children and one for distribution to adolescents aged 13-14 years (139).

The prospective OLIN paediatric study I of asthma and allergies started in 1996 when all 3,525 children aged 7-8 years in three municipalities in Norrbotten were invited to participate and 97% of the parents completed a questionnaire (28). Until graduation from high school, annual questionnaires were distributed and extensive studies of asthma, allergic diseases and measures of environmental factors have been performed (30, 140). From the age of 12-13 years, the adolescents have completed the questionnaire themselves.

Agreement between parentally and self-completed questionnaires

When data are nominal, as in the ISAAC questionnaire, common methods to assess the agreement between observers or responders are to compare the prevalence reports from the two information, calculate the absolute agreement (or observer agreement) and to use kappa statistics (141, 142). There are only a few studies of the parent-child agreement in questionnaire reports of allergic diseases (143-146), and none of these are evaluations within longitudinal studies. These comparative studies have all used the ISAAC questionnaire designed for 13-14 year old adolescents.

The results of these comparative studies showed that parent-child agreement was very good for asthma and slightly lower for respiratory symptoms. Kappa values were 0.7-0.8 for "ever asthma"; 0.4-0.5 for "ever wheeze"; and 0.2-0.5 for "current wheeze". Generally, the prevalence rates were significantly higher in adolescent reports compared to parental reports and all studies found significantly higher rates of current wheeze in the teenager reports (143-146). The prevalence of wheezing during or after exercise was also higher by teenager report in two of the studies (143, 146).

In the two available comparative studies, the agreement in questions about rhinitis and eczema was lower compared to questions about asthma and respiratory symptoms (144, 145). Kappa values were 0.3 for "ever rhinitis", 0.2 and 0.6 for "ever hay fever", 0.3 for "current rhinitis", and 0.3 and 0.4 for "current eczema".

Comparative studies between parental and teenager questionnaire reports of environmental factors are limited. However, there are some studies that compare reports of parental smoking. Generally, the agreement between parents and teenagers was very good with kappa values of 0.6-0.9 (147-149).

It has been suggested that adolescents at the ages of 11-14 years can be considered a reliable source of information (150). A study of asthmatic children found that symptoms reported by children aged 11 years and older correlated better with measures of lung function and quality of life than those from parental reports (151). In an additional study, the authors conclude that teenager questionnaire reports regarding asthma and respiratory symptoms are useful measures for population-based prevalence estimates (152).

The OLIN-studies

The Obstructive Lung Disease in Northern Sweden (OLIN) Studies is an ongoing epidemiological and clinical research programme that began in 1985. The overall aims are to study prevalence, incidence and remission of obstructive lung diseases (asthma, chronic bronchitis, COPD and obstructive sleep apnoea), and allergic sensitization and their main determinants, health economics and quality of life. Since the initiation more than 50,000 people in representative population samples from Norrbotten have participated in cross-sectional, case-control, cohort or clinical studies. To date, nine doctoral theses are based entirely on data from the OLIN studies (153-161), and data from the OLIN studies and close collaborative studies are included in 16 theses.

AIMS

The overall aims of this thesis were:

- To evaluate a methodological change in questionnaire respondent from parent to index subject in a longitudinal study of asthma and allergies.
- To study smoking in adolescence, its predictors and respiratory health effects.

The specific aims were:

- To study the agreement between parental and teenager questionnaire reports of asthma and respiratory symptoms.
- To study the agreement between parental and teenager questionnaire reports of rhinitis, eczema and environmental factors related to allergic diseases.
- To study factors related to smoking and use of snus among teenagers.
- To study asthma and respiratory symptoms in relation to environmental tobacco smoke and personal smoking among teenagers.

MATERIAL AND METHODS

Study area

Norrbotten County (Norrbottens Län) is situated in the northernmost part of Sweden and borders Finland and Norway (Figure 1). The county covers one fourth of the Swedish land mass (98,000km^2), and is divided by the Arctic Circle (162). In 2008, the population was 249,677 (136) with the majority living in cities on the coast of the Gulf of Bothnia. The population density is low with only 2.5 inhabitants per square kilometre (162). The average temperature is between 11 to 15 degrees Celsius in July and -9 to -17 degrees in January (163). Three of the 14 municipalities in Norrbotten County were selected as the study area: Luleå and Piteå are situated by the coast and Kiruna is in the inland mountain region.

Luleå is the largest city and the capital of Norrbotten County. The regional theatre and museum are located in Luleå and cultural events are frequently attended. The major employers are Luleå University of Technology (LTU) and the SSAB steelworks.

Piteå is located on the coast of the Gulf of Bothnia. Local industry and trades are mainly forestry, paper and saw mills, and small and mid-sized businesses related to tourism, energy and computer communications.

Kiruna is located in the Lapland province and is the northernmost city of Sweden. Iron ore mining is the key area industry. Major employers are the LKAB mining company, tourism and industries related to space science.

In 1996, the number of inhabitants was as follows: 71,238 in Luleå, 40,859 in Piteå and 25,575 in Kiruna (136). All three municipalities include both urban and rural areas.

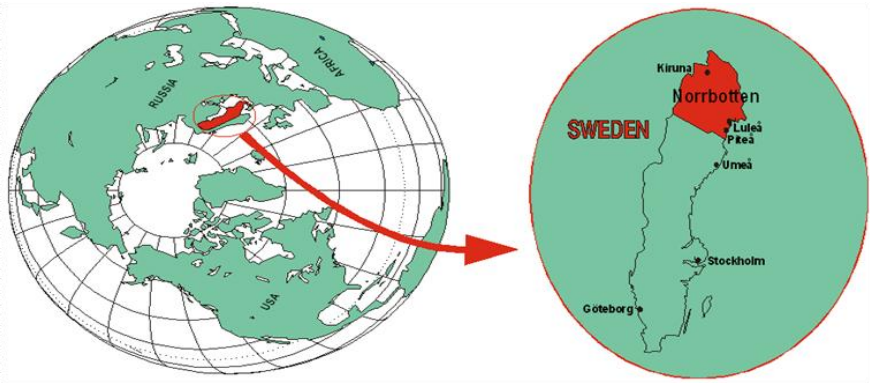

Figure 1. Study area of Norrbotten, Sweden.

A summary of the OLIN Paediatric Study I

Within the OLIN studies, a prospective paediatric study of asthma and allergic diseases started in 1996. The overall aim was to longitudinally study the prevalence, incidence and remission of asthma, type 1 allergy, rhinitis and eczema, as well as their risk factors. The starting point of the study was a questionnaire survey performed in February 1996. All children aged 7-8 years, ie enrolled in first and second grades (n= 3,525), in Luleå, Piteå and Kiruna in Norrbotten County were invited to participate. The cohort was followed by annual questionnaires until the participants graduated from high school. In this thesis data from age 7-8 to 16-17 years have been used. The questionnaires were distributed to all children enrolled in the classes at each time of follow-up, ie an open cohort. Skin prick tests (SPT), spirometry, and BMI were measured in two of the municipalities, Luleå and Kiruna. Other measurements performed in subsamples include blood samples for IgE analysis and dust samples from homes and schools. The OLIN Paediatric Study I has been recently summarised in a review article (164). This is the fourth thesis based on data from this cohort (154, 157, 160).

During the first years of the study, parents were the respondents and source of information about their child´s health. From 2001, at 12-13 years of age, the adolescents completed the questionnaires. An overview of the participation is presented in Table 1. All studies in this thesis were approved by the Ethics Committee at Umeå University, Sweden.

Table 1. Participation in the 1996 OLIN Paediatric Study I, and follow-up studies in 2000-2005 in the open and the closed cohorts.

	Year	1996	2000	2001	2002	2003	2004	2005
	Age	7-8	11-12	12-13	13-14	14-15	15-16	16-17
Open	Invited	3,525	3,512	3,516	3,512	3,511	3,917	3,916
cohort	Participated	3,430	3,389	3,217	3,342	3,327	3,698	3,619
		97%	96%	91%	95%	95%	94%	92%
Closed	Invited		3,229	3,192	3,142	3,134	3,097	3,012
cohort	Participated		3,151	2,941	3,013	2,989	2,985	2,805
			98%	92%	96%	95%	96%	93%
% of participants 1996			92%	86%	88%	87%	87%	82%

Study population

Papers I and II

In 2002, at age 13-14 years, 3,512 children were re-invited to the questionnaire study and 3,342 (95%) participated; 51% were boys. In addition to the annual questionnaire distributed to the teenagers at school, the questionnaire and a pre-paid envelope was also sent home to a random sample of the parents. The subsample of 10% (n=350) was selected from all responders in 2002. Two hundred ninety-four (84%) questionnaires were completed and returned by parents. The majority of the questionnaires were completed by mothers (86%), 10% were completed by fathers and 4% were completed by other guardians. The 294 teenagers in the comparative study sample were 13-14 years old; 52% were boys, and 274 (93%) belonged to the closed cohort.

In Paper II data from previous surveys were also used. Results from SPT performed in 2000 at age 11-12 years, and data about family history of allergic diseases reported by parents in the 1996 questionnaire were used in risk factor analyses. Of the 294 teenagers in the comparative study, 64% also participated in the SPT. All SPT participants were living in Luleå and Kiruna. (Children in Piteå were not invited to SPT).

Paper III

Paper III included questionnaire data from 1996 (age 7-8 years), 2001 (12-13 years), 2002 (13-14 years) and 2003 (14-15 years). Paper III was based on the open cohort. For specific analyses using longitudinal variables related to tobacco use, only subjects from the closed cohort were included in the analyses. Among the participants in the 2001-2003 surveys, 89-91% of the children belonged to the closed cohort. Mean ages were the same in the closed and the open cohorts.

Paper IV

Paper IV was based on questionnaire data from all surveys from 1996 to 2005. The analyses were based on the closed cohort; 2,805 (82%) of the original responders in 1996 remained as follow-up participants at age 16-17 years.

The questionnaire

During the first years of the study when the parents were responders, the ISAAC protocol was used for parental completion regarding children aged 6-7 years (139, 165). From 2002, at the age of 12-13 years and subsequently when the children became the respondents, the ISAAC protocol for self-completion by 13-14 year olds was used (Appendix 1). In 1996, the 13-page questionnaire consisted of 87 questions. In addition to the core ISAAC protocol questions, questions about symptoms, use of medication, diagnoses, heredity of asthma, rhinitis and eczema, demographic characteristics, living circumstances, participation in sports activities, past and present pets in the home, signs of dampness, and smoking habits among the parents were also included. Most of the additional questions were in the same format as the ISAAC protocol and used a fixed set of responses. Questions regarding early life events were not repeated in the follow-up questionnaires. Family history of asthma, rhinitis and eczema questions were included only in the parental questionnaires. Questions about the teenagers´ smoking habits were only included in their questionnaires.

Data collection

The questionnaire and a cover letter were distributed to the parents by the teachers, completed at home and returned in a sealed envelope to the teacher, who sent them to the OLIN study group. When the children became the respondents, the questionnaires were completed in the classrooms. The teachers were instructed to distribute an informational letter and a questionnaire to all children in the classroom. After completion, the teachers placed the questionnaires in a envelope, sealed it and sent them to the OLIN study group. Nonparticipants were sent two reminders by regular mail, including an informational letter, a questionnaire and a pre-paid envelope. The procedure for the nonparticipants was the same for parents and teenagers.

Skin prick tests (SPT)

SPT performed in 2000 was used in risk factor analyses in Paper III. The methods and results have been described previously (28, 166). In short, the children living in Luleå and Kiruna were invited to SPT at the age of 11-12 years and 2,148 (88%) participated. The tests followed the guidelines from the European Academy of Allergy and Clinical Immunology (EAACI) (167). Allergen extracts included a Swedish standard panel with ten common airborne allergens (Soluprick, ALK, Hørsholm, Denmark). A mean wheel diameter of 3 mm and larger was regarded as positive. Parental consent was obtained via the questionnaire.

Questions about smoking

Questions regarding current smoking habits among family members were included in all questionnaires. In the parentally completed questionnaires, smoking habits were based on information about the number of cigarettes smoked per day. Information on parental smoking during the child´s first two years of life and whether the mother smoked during pregnancy were included in the 1996 baseline questionnaire. In the questionnaires completed by the teenagers, it was asked whether mother, father or other family member smoked currently or not.

From 2001, at age 12-13 years, questions regarding their own tobacco use (ie smoking and snus) were added when the questionnaire was completed the first time by the teenagers (Papers III and IV). The questions were the same as those used in the Swedish Council for Information on Alcohol and Other

Drugs (CAN) recurring surveys of tobacco use among Swedish teenagers (107). They include one main question that is completed by all: "Do you smoke (use snus)?" Two follow-up questions are directed to smokers: "How often do you smoke?" and "How much do you smoke?"

Smoke prevention program

A smoking prevention program was performed during 1999 and 2000. The aim and effect of the program are presented in Paper III. Half of the schools in Luleå and Kiruna (n=1,255) were randomly selected as intervention schools, while the other half and all schools in Piteå acted as control schools (n=2,681). Students at the control schools had the ordinary curriculum education about tobacco use. The prevention program included a special theatre performance developed for the study, discussions about smoking and its health effects, and group projects that were presented publicly. The initial objective was for the program to continue over time. Due to organisational changes the students from the control and intervention schools were mixed and therefore the program was cancelled after the year 2000.

Definitions

Below, the operationalisation of the key terms used in this thesis is presented.

*Ever wheeze: "*Have You ever had wheezing or whistling in the chest at any time in the past?"(139)

*Wheeze in the last 12 months: "*Have You had wheezing or whistling in the chest in the last 12 months?"(139)

Current wheeze: "yes" to any of the following: "Have You had wheezing or whistling in the chest in the last 12 months?"(139), "In the last 12 months, has Your chest sounded wheezy during or after exercise?"(139), "In the last 12 months, have You had wheezing or whistling in the chest without having a cold?"(165), or those reporting more than one attack in the question: "How many attacks of wheezing have You had in the last 12 months?"(139)

Physician-diagnosed asthma (Paper I, II and IV); *Asthma* (Paper III)*: "*Have You been diagnosed by a physician as having asthma?"(165)

Use of asthma (rhinitis) medicine: "Sometimes", "often/periodically", or "every day" to the question: "How often have You had to use asthma (allergic rhinitis or conjunctivitis) medications in the last 12 months?"(165)

Current asthma: physician-diagnosed asthma and either current wheeze or current use of asthma medicines.

Ever rhinitis: "Have You ever had a problem with sneezing, or a runny, or a blocked nose when You did not have a cold or the flu?"(139)

Current rhinitis: "In the past 12 months, have You had a problem with sneezing, or a runny, or a blocked nose when You did not have a cold or the flu?"(139)

*Current rhino-conjunctivitis: "*In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?"(139)

*Ever hay fever (eczema): "*Have You ever had hay fever (eczema)?"(139)

Current eczema: "Have You had this itchy rash at any time in the last 12 months?"(139)

Physician-diagnosed rhinitis (eczema): "Have You been diagnosed by a physician as having allergic rhinitis or hay fever (eczema)?"(165)

ETS: Having a smoking mother (father).

Continuous ETS: ETS exposure from the mother (father) reported in all questionnaires from 1996-2005.

Smoker (snus users) (Paper III)*:* "Yes" to the question: "Do You smoke (use snus)?"(107)

Occasional smokers (Paper IV)*:* Smoking on weekends or at parties.

Daily smokers (Paper IV)*:* smoking daily or almost daily.

Participation in sports: participation in sport activities outside school physical education.

Socioeconomic indicator: Two measures of socioeconomic indicators were included: 1) living in an apartment or both an apartment and a house versus living only in a house as reported at age 14-15 years, and 2) living in a single parent household versus a two-parent household reported in the baseline questionnaire at 7-8 years.

Cat(dog) at home: Having had a cat (dog) in the home during the last 12 months.

House dampness: Report of past or present dampness at home in any of the questionnaires from 1996-2005.

Family history of asthma: Mother, father or sibling reported as having asthma in the 1996 questionnaire.

Statistical methods

The statistical analyses were performed using two software programmes: Statistical Package for the Social Sciences (SPSS) Version 10.0 (Papers I and III), 16.0 (Paper II) and 17.0 (Paper IV), Chicago, Illinois U.S.A.; and EpiInfo Version 6.0, Centers for Disease Control and Prevention, Atlanta, Georgia U.S.A.

Comparison of prevalence between groups was performed using the χ^2 test. P-values of <0.05 were regarded as statistically significant.

Multiple logistic regressions were used for multivariate analyses and the results presented as odds ratios (OR) with 95% confidence intervals (CI). Independent variables were manually entered in the models based on the research question and statistical significance in bivariate analyses.

For nominal binary data, a common way to measure agreement between subjects is to calculate the observed (or absolute) agreement and use the kappa statistic (168). Absolute agreement is the proportion of pairs of positive and negative responses that are in agreement. As described by Dawson & Trapp, the observed agreement overestimates the agreement since the observers might agree by chance (141). The kappa statistic is the adjusted agreement beyond the level of chance.

The formula for kappa is:

$$Kappa = \frac{Observed - Expected\ agreement}{1 - Expected\ agreement}$$

The following definitions of kappa values suggested by Landis & Koch (169) were used:

<0.2	slight or poor agreement
0.21-0.4	fair agreement
0.41-0.6	moderate agreement
0.61-0.8	substantial agreement
>0.81	almost perfect agreement

If the kappa-value is negative it indicates that the observed agreement was less than expected by chance alone (141). Kappa values are presented with 95% confidence intervals.

In calculations of prevalence of symptoms and diseases, missing answers to individual questions (0-5%) were treated as negative responses. However, in the calculations of kappa, missing answers in individual questions were excluded from the analyses. In questions about smoking habits in Paper IV, missing answers (0-7%) were assigned the response from the previous year´s questionnaire, while in Paper III missing answers were regarded as missing and excluded from the analyses. Missing answers in other questions about exposures were regarded as missing and excluded from the analyses.

Power calculations were performed to determine the subsample size in the comparative studies of parental and teenager reports (Paper I and II). Given an alpha level of 0.05, a beta level of 0.2, a population of 3,500, and a difference of three percentage points between groups (7-10%) to be regarded as a significant difference, a sample size of 250 was estimated. If five percentage points was used instead (15-20%), a sample size of 190 was estimated. A random sample of 10% (n=350) of the cohort was selected and n=294 participated.

RESULTS

Method aspects: Agreement between parental and teenager questionnaire reports (Papers I & II)

Prevalence comparisons

Overall, parents and teenagers reported similar prevalence of asthma, respiratory symptoms, rhinitis and eczema. There was a tendency of higher prevalence of lifetime symptoms in the parental reports and higher prevalence of current respiratory symptoms in the teenagers reports, although only "wheeze during or after exercise in the last 12 months" was statistically significant. That prevalence was 14% according to the teenagers, and 8% according to the parents ($p<0.05$) (Paper I).

The concordance between parents and teenagers was good for report of physician-diagnosed asthma. Although prevalence estimates for physician-diagnosed rhinitis and eczema were similar based on parental and teenager reports, they were less concordant compared to asthma (Figure 2; Figure 1 in Paper II).

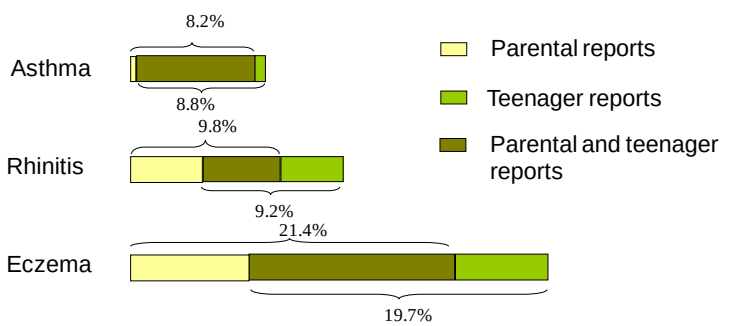

Figure 2. Concordance between parental and teenager reports for physician-diagnosed asthma, rhinitis and eczema. Adapted from Paper II.

The prevalence estimates of environmental factors, ie house dampness and parental smoking, were similar in parental and teenager reports. While there was no difference between parents and teenagers in reports of having a cat at home, 29% of parents versus 42% of teenagers reported having a dog at home in the last 12 months ($p<0.001$) (Paper II).

Level of agreement

The agreement between parental and teenager reports was *almost perfect* for questions about asthma, physician-diagnosed asthma and use of asthma medicines. Agreement on questions about symptoms was *fair* to *substantial* (Figure 3). The absolute agreement for the asthma variables were 96-99% and the kappa values were 0.8-0.9. Corresponding values for respiratory symptoms were 86-94% and 0.3-0.6 (Paper I)

The agreement between parents and teenagers was *fair* to *moderate* for questions about rhinitis and eczema. For reports of rhinitis, the absolute agreement ranged from 78-92% and kappa values from 0.3-0.6. The absolute agreement regarding eczema was 77-86% and kappa values were 0.5-0.6 (Paper II).

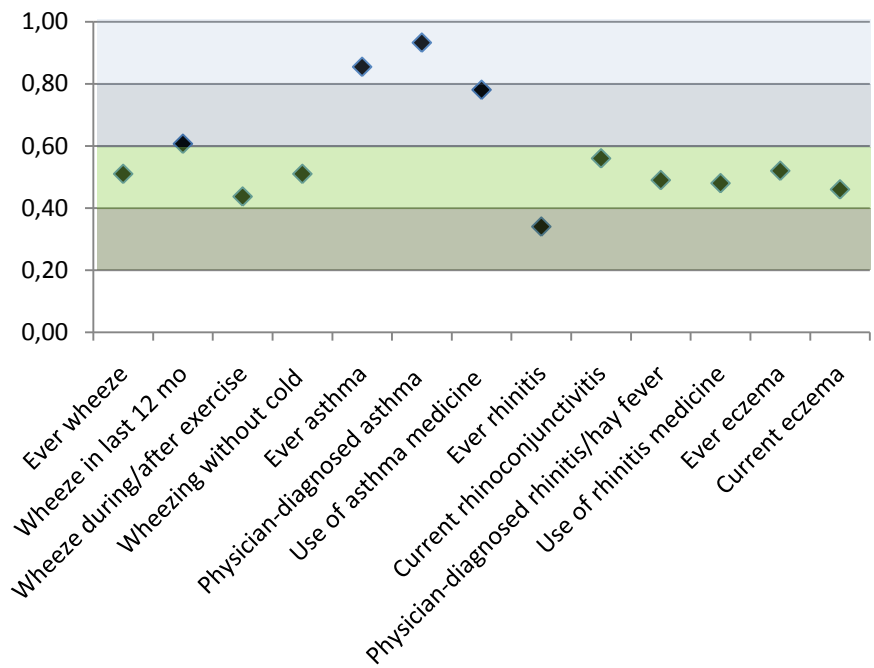

Figure 3. Agreement between parents and teenagers for questions about wheeze, asthma, rhinitis and eczema, expressed as kappa values.

For reports of environmental factors, the agreement between parents and teenagers was *almost perfect* for questions about parental smoking, with kappa values of 0.8-0.9. Agreement on questions of having a cat or a dog or participating in horseback riding was *substantial* to *almost perfect* with absolute agreement ranging from 85-97% and kappa values from 0.7-0.9. House dampness had a high absolute agreement but low kappa value of 93% and 0.2 respectively (Paper II).

Multiple logistic regression analyses

Since parental and teenager reports of rhinitis and eczema were less concordant and yielded lower kappa values compared to questions regarding asthma, we performed risk factor analyses for rhinitis and eczema. Two separate multiple logistic regression analyses were done. One used the teenager reports of the outcome variables rhinitis and eczema, and the other used the parental reports. The risk factor analyses were adjusted for sex, allergic sensitization and family history of rhinitis or eczema, respectively. The results were similar regardless of the respondent. However, some small differences were seen. The ORs were somewhat higher when the analyses were based on parental reports. Family history of rhinitis was a significant risk factor for *ever rhinitis* in the parental analyses with an OR of 2.3, (95% CI 1.1-5.0), but not in the teenager analyses with an OR of 1.3 (95% CI 0.6-2.7; Paper II).

Tobacco use and ETS (Paper III & IV)

Tobacco use in relation to age and sex

Smoking prevalence increased with age, from 3% at 12-13 years to 6% at 14-15 years. Similarly, the use of snus increased from 3% at 12-13 years, to 10% at 14-15 years. At all ages, smoking was significantly more common among girls, and use of snus was more common among the boys. The overall prevalence of any tobacco use was higher among boys than girls at 14-15 years, 17% versus 12% ($p<0.001$) (Paper III). At 16-17 years, daily smoking was more common among girls, while occasional smoking was equally common among girls and boys (Paper IV). Changes in the prevalence of tobacco use by age are presented in Figures 4 and 5.

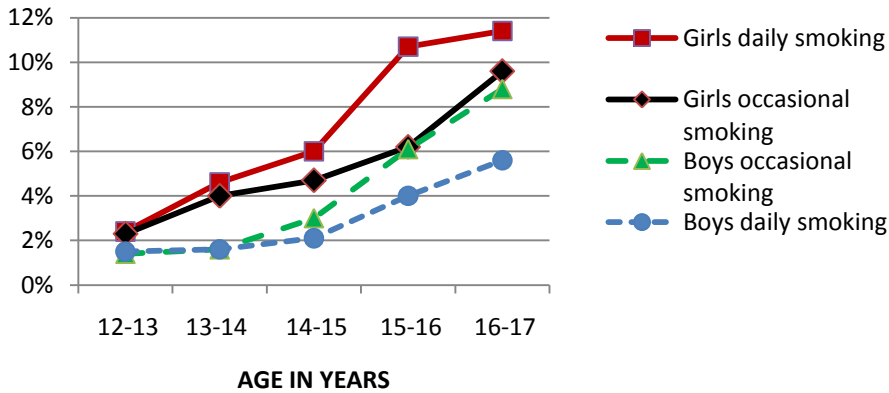

Figure 4. Prevalence of daily and occasional smoking, stratified by sex and age.

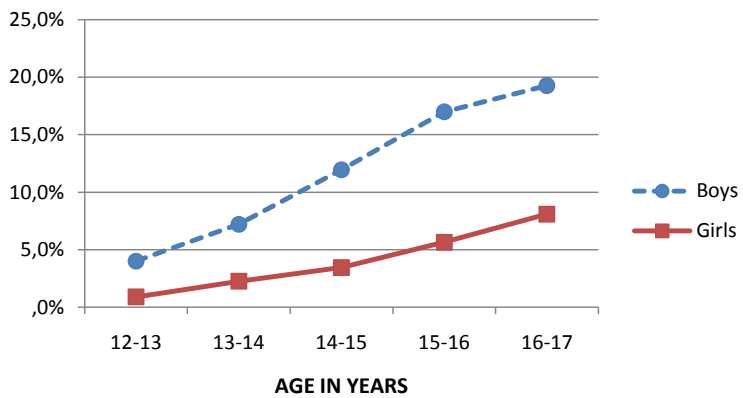

Figure 5. Prevalence of snus use, stratified by sex and age.

Factors related to tobacco use (Paper III)

The most important risk factor for being a smoker at 14-15 years was having smoking family members. There was a dose-response relationship between the number of smoking family members and the prevalence of smokers. Among those without any smoking family members, only 2% smoked themselves, while 33% among those with three or more smokers in the family were smokers.

Significant associations between smoking and socioeconomic indicators were found. Smoking was more common among those who were living in an apartment (10%) compared to living in a house (4%), and even higher among those who lived in both (15%; $p<0.001$). Smoking was also more common among those who lived in a single parent household at the age of 7-8 years (10%) compared to a two-parent household (5%; $p<0.001$).

Results from multiple logistic regression analyses showed that significant risk factors for being a smoker at 14-15 years were female sex, living in an apartment, living in both an apartment and a house, having smoking family members, and having physician-diagnosed asthma. Significant risk factors for snus use were male sex, living in Piteå or Kiruna, having a smoking mother, and having a smoking family member other than parent. Participation in sports activity outside of school was protective against both smoking and snus use.

No significant effect of the intervention program was seen. However, at the age of 12-13 years, the prevalence of smoking was slightly lower in the intervention group (2%) than the control group (3%) ($p=0.06$). This difference was not found at age 14-15 years when the prevalence of smoking was 6% in both groups.

Prevalence of ETS exposure (Paper IV)

The prevalence of smoking among parents decreased significantly from the age of 7-8 to 16-17 years. Maternal smoking decreased from 29% to 24% ($p<0.001$) and paternal smoking decreased from 21% to 19% ($p<0.05$). More girls than boys had been continuously exposed to maternal ETS from age 7-8 to 16-17 years; 16% versus 13% ($p<0.05$).

Asthma and wheezing in relation to ETS and smoking (Paper IV)

All ETS variables concerning maternal smoking were significantly associated with physician-diagnosed asthma, ever wheeze and current wheeze reported at age 16-17 years (Paper IV; Table 2). The prevalence of physician-diagnosed asthma and current wheeze was higher among teenagers whose mothers smoked during pregnancy. In general, there were no significant associations between paternal smoking and the prevalence of asthma or wheeze.

Daily smokers reported a significantly higher prevalence of physician-diagnosed asthma, ever wheeze and current wheeze compared to non-smokers. There was a dose-response relationship with the prevalence of ever wheeze and current wheeze higher among those who smoked ≥11 cigarettes per day compared to those who smoked ≤10 per day (Figure 6).

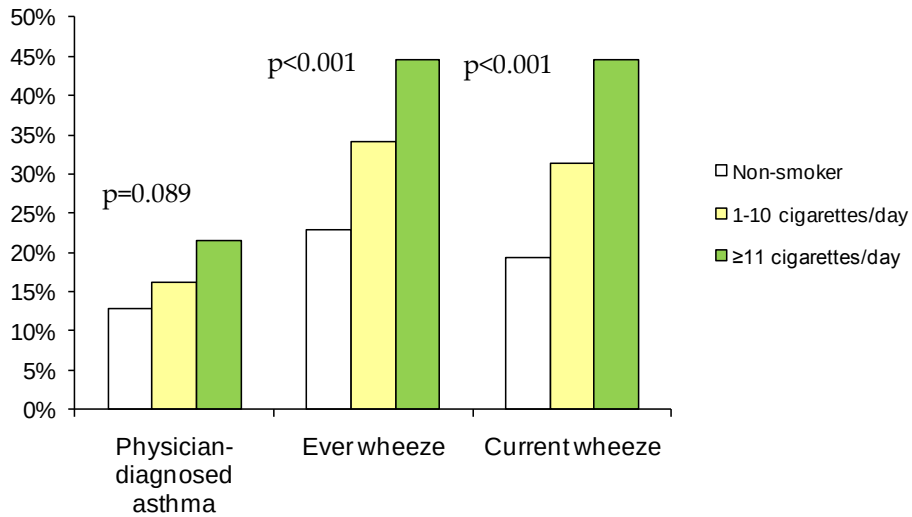

Figure 6. Prevalence of asthma and wheeze at age 16-17 years in relation to number of cigarettes per day.

In multivariate analyses, daily smoking was a significant risk factor for current wheeze (OR 1.9-2.0) and ever wheeze (OR 1.9) after adjustment for covariates including maternal ETS exposure. Most of the significant associations between ETS and asthma and wheeze found in the bi-variate analyses remained statistically significant in the multivariate analyses. After adjusting also for daily smoking among the adolescents, some of the ETS associations became borderline significant. ETS exposure from the mother at the age of 7-8, and continuous ETS exposure from 7-8 to 16-17 years remained significant risk factors for physician-diagnosed asthma and ever wheeze after adjustment for daily smoking.

In order to study the independent and combined effect of ETS exposure and personal smoking on asthma and wheeze, we used different models. First, we created a variable with four mutually exclusive categories based on daily smoking and current maternal ETS exposure. The prevalence of physician-diagnosed asthma, ever wheeze and current wheeze were highest among the

daily smokers who were exposed to ETS. When this categorised variable was included in multivariate analyses, daily smoking was a significant risk factor for ever wheeze (OR 1.7 95% CI 1.1-2.5) and current wheeze (OR 2.0 95% CI 1.3-2.9), while ETS from the mother alone was not (Table 3; Paper IV).

In further analyses, daily smokers were excluded in multiple logistic regression analyses in order to study the independent effect of ETS in adolescence. The analyses of non-smokers had similar results as the analyses based on the whole sample, and ETS exposure from the mother remained a significant risk factor for physician-diagnosed asthma (Figure 7).

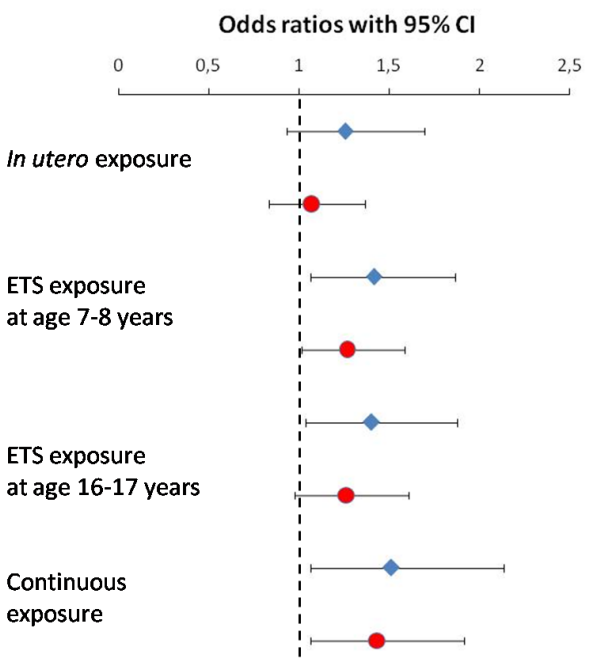

Figure 7. Maternal ETS exposure at different ages as risk factor for physician-diagnosed asthma and ever wheeze, respectively, in non-smokers at age 16-17 years. Expressed as odds ratios with 95% confidence interval by multiple logistic regression analyses adjusted for sex, family history of asthma, current place of residence, house dampness and birthweight.

DISCUSSION OF METHODOLOGY

Validity and reliability

Validity, or accuracy, is the ability of a study to measure what it is supposed to measure according to certain criteria. Validity is usually discussed in terms of internal and external validity. *Internal* validity is how well results from the study population reflect the source population. *External* validity is whether the results of the study can be applied to other populations, ie the generalisability. Reliability is the consistency of the results, ie the ability of the study to obtain similar results with repeated measures using the same methods.

An aspect of validity that is important for both internal and external validity is the representativeness of the study population. In the present cohort, the population consists of all the children enrolled in first and second grades in all of the schools in the study area during 1996. The study area includes more than half of the population in Norrbotten. Since school attendance is mandatory and participation rates have been very high throughout the study, the study population is highly representative of children in Northern Sweden and the risk of selection bias is small. By using the validated and internationally used ISAAC questionnaire, we can compare our results with other studies. The prevalence of asthma and allergic diseases in this cohort is similar to studies performed in comparable ages in Sweden and other parts of northern Europe (16, 31, 170), which supports external validity of the results.

After the first year of the OLIN Paediatric Study I, the questionnaire was validated against predefined asthma criteria. Structured interviews were performed in a subsample and the results have been reported elsewhere (8). Specificity of the question about physician-diagnosed asthma was 99.9% and sensitivity was 70.3%. Validation of the teenager questionnaire responses has not been studied in detail. However, since parental and teenager reports of asthma were very similar at age 13-14 years, it can be assumed that the specificity is high.

Bias

Bias is a systematic error that might affect the study results. Three types of bias will be discussed: selection bias, information bias and confounding.

Selection bias

Cohort studies can be influenced by selection bias, such as errors in the selection process or the loss of study participants during follow-up. The selection of the cohort was discussed above in the section about validity. In order to evaluate whether there was bias in selection of the subsample used for the studies in Paper I and II, the randomly selected subsample was compared to the entire cohort. The two groups reported similar prevalence of asthma, respiratory symptoms, rhinitis, eczema, and environmental factors. Since the subsample had adequate power and did not differ from the entire cohort, it can be considered a representative sample.

Sim & Wright have tabulated sample size requirements for the kappa statistics that are based on the minimum acceptance level of agreement (142). Using this, a sample size of 190 was estimated for a study with two observers, an alpha level of 0.05, beta level of 0.2 and a null hypothesis with a kappa value of 0.4. Thus, our sample size of 294 in Papers I and II was large enough.

In the studies of tobacco use, Paper III was based on the open cohort and Paper IV on the closed cohort. In Sweden, school attendance is compulsory the first nine years, until the age of 15 years. Children are most often enrolled in the school closest to their home. In Table 1 in Materials and Methods, it is shown that the number of invited school children in the open cohort was almost identical up to age 14-15 years and that almost 90% of the participants in the original cohort from 1996 participated also in the 2001-2003 surveys. Thus, the migration of children to and from the schools is unlikely to influence the outcome. Therefore, we chose to use the open cohort in the analyses in Paper III. At the age of 16 years the teenagers start high school and they can attend a school in another town if the educational program they wish to enter could not be provided for in their hometown. All three municipalities included in the study area offered exclusive programmes and a considerable increase in the number of teenagers in the open cohort during years 2004 and 2005 could be seen (Table 1). In order to avoid systematic selection bias only the closed cohort was used in Paper IV. Also, the analyses in Paper IV included data on ETS exposure from age 7-8 years which was available only among subjects in the closed cohort. Few subjects were lost to follow-up, and 88% of the cohort was available for follow-up. Eighty-two percent of those who participated in the initial 1996 study participated at the age of 16-17 years. Two possible reasons for the loss to follow-up were high school drop-outs or high school attendance in

another town. The study population in the closed cohort and those lost to follow-up at age 16-17 years reported almost identical prevalence of asthma and wheezing at age 7-8 years. However, ETS exposure at the age of 7-8 years was significantly different between the groups. Those lost to follow-up reported a higher prevalence of ETS exposure (Paper IV). Several studies of non-responders in Sweden, Finland and Norway have found that smokers are less likely to respond (171-174). Thus, as we found a positive correlation between parental smoking and personal smoking we may have underestimated the smoking prevalence among the adolescents. However, since the number of lost to follow-up was low and the response rate was high in the present study this type of selection bias probably had no effect on the results.

Information bias

Recall bias is one type of information bias which is a common problem in epidemiologic surveys. By using annual questionnaires and asking for symptoms and exposure to environmental factors in the last 12 months, the risk for recall bias was reduced. However, the prevalence of ever wheeze was slightly higher in the parental compared to the teenager questionnaire reports at age 13-14 years. This trend was seen in other studies where parental and teenager reports of symptoms were compared (143-146). Wheezing in early childhood is often transient (19) and the teenagers have likely forgotten or have never been aware of its occurrence and the parents probably have never informed their child about early life events.

As previously mentioned, the question about physician-diagnosed asthma was validated at the beginning of the study. In a further validation study, dust samples were collected in homes and schools in order to confirm the parental reports of furry pets. The allergen levels in homes without cats or dogs were substantially lower than homes with pets and were also lower compared to the levels found in the schools (140). The prevalence of having a dog in the home in the last 12 months was significantly higher by teenager versus parental report (Paper II). A corresponding difference was not seen in the question about having a cat. The question about dogs was most likely misunderstood by the teenagers, and visitors with a dog may have been included into their reports. This question to teenagers should be used carefully until further validation.

Confounding

A confounding factor is a factor that affects both the outcome and the exposure in a study. Rothman et al have described confounding as *"the confusion or mixing of extraneous effects with the effect of interest"* (3). In studies about asthma and smoking, SES may be a confounding factor as low SES have been associated with both asthma (175, 176) and smoking (128). Common measures of SES among children and young adolescents are parental education and household income. These factors were not asked about in the questionnaire used in the present studies because they might be perceived as intrusive. We did not want to risk nonresponse due to the questionnaire content. Therefore we used other socioeconomic indicators that included living in an apartment versus in a house, and living in a single parent household versus a non-single parent household. In Norrbotten at the time of the study, there were few expensive apartments that required high income. Thus, families that could afford living in a house can be assumed to have higher income and more secure employment. Single parent households can also be regarded as a socioeconomic indicator. Although a single parent might have high income and educational level, the household income is most likely lower compared to a household with two incomes. In a study by Bolte & Fromme, the authors argue that more socioeconomic determinants than just parental education should be used and include single parent household as an important measure (177).

Treatment of data

Missing answers for questions about smoking and ETS exposure were regarded as missing in cross-sectional analyses. Thus, prevalence estimates and associations between exposure and outcome were probably not overestimated. Annual questionnaires may have increased the reporting of symptoms, which in turn may cause bias in longitudinal studies (3). However, when the prevalence of asthma and respiratory symptoms from a longitudinal study was compared to those obtained from a cross-sectional study within the same population, no difference was found (178).

Three methods of comparing parental and teenager reports were used: prevalence comparison, absolute agreement and kappa statistics. The prevalence comparisons were essential for the cohort study, however prevalence gives little information of the agreement between the two sources of information. This is seen in Figure 2. Absolute agreement is based

on the proportion of parents and teenagers that responded identically, but it is a crude measurement that is difficult to interpret (142). The kappa value takes the expected agreement into account and is a quantitative measure of the agreement between observers. Expected agreement depends on the prevalence of the variable under study. Both low and high prevalence might decrease the kappa value (179). Further, the kappa value can sometimes be low despite a high absolute agreement (180), which was seen in the question about house dampness (Paper II; Table 2). Thus, a moderate kappa value would not necessarily indicate poor agreement between observers. In these situations, absolute agreement is useful in assessing the level of agreement (168). Furthermore, by using prevalence, absolute agreement and kappa statistics, we were able to provide extensive information about the similarities and differences between the parental and teenager reports.

In this thesis, both cross-sectional and longitudinal data are presented. All papers include cross-sectional data, while Papers III and IV also include longitudinal data about ETS exposure. The annual incidence of asthma from age 7-8 to 11-12 years in this cohort has previously been reported at 0.7-0.9/100 per year (35, 36). During adolescence the incidence has been reported to be around 1/100 per year in Sweden (89, 181), and 0.7-0.8/100 per year in Great Britain (32). Thus, due to the limited numbers of new cases with asthma in combination with the relatively low prevalence of daily smoking, the study lacks power to analyze smoking in relation to incidence of asthma. In a few years, when the subjects under study have smoked for a longer time, it will be possible to study this relationship.

Parental ETS exposure is often measured by asking whether it occurred *in utero*, during childhood or currently. However, teenagers currently exposed to parental ETS, were most likely exposed in childhood and *in utero*. We had annual information about the prevalence of parental smoking and we were able to identify those who had been exposed to ETS continuously from age 7-8 to 16-17 years. In this cohort, among the mothers who smoked when their child was 16-17 years old, 60% had smoked continuously since the child was 7-8 years as well as during the pregnancy (Paper IV). Future analyses of this cohort could focus on the isolated effect of ETS exposure at different time periods.

We have shown a strong relationship between having smoking family members and becoming a smoker in adolescence (Paper III). In order to study the independent and combined effect of ETS exposure and personal smoking on asthma and wheeze, we used different models (Paper IV). First,

we created a variable with four mutually exclusive categories based on daily smoking and current maternal ETS exposure. Second, daily smokers were excluded in multiple logistic regression analyses in order to study the independent effect of ETS in adolescence. To date, only a few studies have performed similar analyses (66, 68, 87).

Although questions about smoking habits were identical in all the questionnaire surveys, different definitions of smokers were used in Papers III and IV. The aim of Paper III was to study factors related to tobacco use. Thus, smoking was regarded as a habit and behaviour and it was more relevant to include all smokers in the definition, regardless of how often or how much they smoked. In Paper IV, on the other hand, we separated the smokers into two groups, occasional and daily smokers, since smoking was regarded as an exposure rather than a behaviour. In analyses of associations, smokers were defined as daily smokers since occasional smoking was not related to asthma or wheeze. If the Paper III definition of smokers had been used the associations between smoking and asthma would have been underestimated.

In this thesis, questions about tobacco use were taken from the Swedish Council for Information on Alcohol and Other Drugs (CAN), which have been used in annual surveys in Sweden since the 1980s (107). Among teenagers, smokers is sometimes defined as daily (66), weekly (86, 87), or monthly smoking (108). Gilliland et al also defined smokers as those who smoked any cigarettes during the last year (86). In epidemiologic studies among adults, smokers are often defined as daily smokers (182, 183) or weekly smokers (77, 184, 185).

Validation of questions about smoking has not been performed among parents or teenagers. Parents might underreport smoking since it is socially unacceptable to expose a child to tobacco smoke. However, the validity of the question about parental smoking is supported by the very good agreement between parents and teenagers (Paper II). Teenagers might underreport because they often smoke in secret and are not allowed to buy tobacco products. However, the teenagers completed the questionnaire at school without parental supervision. Furthermore, when self-reported smoking has been compared to biochemical measures such as cotinine levels, the agreement is good (186-188). In a Danish cohort study, reports of parental smoking during pregnancy and in the child´s early life were validated by measuring exhaled CO and the specificity was >96% (189).

DISCUSSION OF MAIN RESULTS

Papers I & II

During early adolescence, there might be changes in the manifestation of asthma symptoms and the management of asthma is often transferred from the parents to the teenager (190). In epidemiologic studies of small children, the parents are a reliable source of information about the child´s health, but with increased age the children will probably become a more reliable source. In the OLIN Paediatric Study I, the children became the respondents at age 12-13 years. There is no consensus regarding the appropriate age to begin using self-reports. Studies of the parent-child agreement that include children younger than 11 years, have found poor agreement and significant differences between parental and child reports (151, 191). Wittich et al concluded that reports from 7-10 year old children can be used to detect cases of physician-diagnosed conditions, however they were a less reliable source of symptom reports (192). In a case-control study of risk factors for melanoma among children aged 10-14 years, the agreement between parental and self-reports depended more on the type of questions than age or sex of the respondents (150). Stable conditions had the highest level of agreement and this corresponds well with the findings of Sweeting & West (193). They found the highest agreement between parents and 11 year old children in questions about conditions that were regarded as common, visible or diagnosed. Thus, depending on the research question, children aged 11 years or younger could give reliable reports about their health. However, in studies about asthma and respiratory symptoms, the parent-child agreement was better among children aged 13 and older than 11-year old children (Table 2).

This thesis shows that the agreement between parents and teenagers aged 13-14 years was highest for questions about physician-diagnosed asthma, ever asthma and use of asthma medication (Figure 3). Although the agreement on questions about wheeze and respiratory symptoms were very good, they were not as high as for the asthma questions. Wheezing may occur due to many reasons and is a less specific condition than asthma. In reports of wheeze, a noticeable trend was found with prevalence of lifetime symptoms higher by parental report and prevalence of currents symptoms was higher in the teenagers report. These results are in accordance with other studies (143-146). The teenagers had likely forgotten early life events or had not at all been aware of early life events. Parents have less insight into the daily life of their teenage child, who will probably not tell the parents every time they wheeze. The parents have to rely on the teenager´s

information for occurrence of symptoms, use of medicines and perception of disease severity. Guyatt et al argue that for children over 11 years parental information about the child´s asthma provides limited complementary information beyond that given by the child (151).

Table 2. Different studies showing agreement between parental and teenager reports of asthma and respiratory symptoms using the ISAAC protocol*.

		Ever asthma	Ever wheeze	Current wheeze	Current wheeze during/after exercise	Attacks of wheeze
Braun-Fahrländer, et al 1998(143)	Absolute agreement	93%	83%	92%	85%	93%
	Kappa	0.7	0.5	0.5	0.4	0.5
Decker, et al 2008 (146)	Absolute agreement	95%	75%	60%	81%	48%
	Kappa	0.8	0.4	0.2	0.4	0.0
Hedman, et al (Paper I)	Absolute agreement	97%	86%	94%	89%	93%
	Kappa	0.9	0.5	0.6	0.4	0.6
Mallol, et al 2006 (145)	Absolute agreement	94%		86%	75%	
	Kappa	0.7		0.3	0.3	
Renzoni, et al 1999** (144)	Absolute agreement	73/97%	55/88%	47/96%		
	Kappa	0.7	0.4	0.4		

*All studies were among teenagers aged 13-14 years except the study by Decker et al which was among children aged 11 years.

**Absolute agreement presented as positive and negative agreement

The agreement between parents and teenagers on questions about rhinitis and eczema were lower than for asthma (Table 3). These results are in accordance with Renzoni et al (144) and Mallol et al (145). One possible explanation for this is that symptoms of rhinitis and eczema are less specific than symptoms of asthma. For instance, a runny or stuffy nose and itchy, watery eyes might be perceived as symptoms of a common cold.

The agreement between parents and teenagers in Papers I & II was better than other similar studies (Tables 2 and 3). This might be explained by the fact that they were based on single cross-sectional surveys. All participants

in the OLIN paediatric study completed annual questionnaires and a large number of them have taken part in clinical examinations since they were 7-8 years old. Therefore they might be more aware and have more knowledge about allergic diseases compared to average teenagers. This cohort effect might bias the results in a positive direction, and it is difficult to assess whether it occurred. However, this is a consequence of most prospective studies. An advantage of the prospective study is that cohort members learn more about the disease under study.

Table 3. Different studies showing agreement between parental and teenager reports of rhinitis and eczema using the ISAAC protocol*.

		Ever rhinitis	Current rhinitis	Ever hay fever	Ever eczema	Current eczema
Hedman, et al (Paper II)	Absolute agreement	78%	84%	87%	77%	83%
	Kappa	0.3	0.4	0.4	0.5	0.5
Mallol, et al 2006 (145)	Absolute agreement		76%	87%	94%	86%
	Kappa		0.3	0.2	0.2	0.3
Renzoni, et al 1999** (144)	Absolute agreement	53/77%	47/85%	63/93%		43/95%
	Kappa	0.3	0.3	0.6		0.4

*All studies were among teenagers aged 13-14 years

**Presented as positive and negative agreement

There were no significant differences in prevalence of rhinitis or eczema between parental and teenager reports. However, different subjects were identified by the questionnaire depending on the respondent (Figure 2). This discrepancy had limited consequences in cross-sectional analyses of prevalence. However, in longitudinal analyses and in risk factor analyses, the outcome might be affected. Therefore, we performed multivariate risk factor analyses based on parental and teenager reports of rhinitis and eczema, respectively. The odds ratios were similar regardless of respondent. However, there was a tendency of slightly higher odds ratios of known risk factors in the analyses based on cases identified by the parents. Hence, the specificity of the allergic diseases reported by the parents might be higher compared to the teenager reports.

There are few studies that compare parent and teenager reports of environmental factors. These studies found very good agreement between parents and teenagers on questions about parental smoking (147-149). This is similar to our findings in Paper II. Questionnaire reports of environmental factors such as parental smoking, house dampness or having cats or dogs are often used in risk factor analyses regarding asthma. However, a change of respondent may affect the outcome in risk factor analyses. Thus, in studies of the agreement between parental and teenager reports of allergic diseases, it is important to also include questions about risk factors.

This thesis suggests that questionnaire reports from adolescents aged 13-14 years can be used in epidemiologic studies of asthma, allergic diseases and related determinants. Although the questionnaire reports were not validated against a "gold standard", the similar prevalence rates between parents and teenagers, the overall high level of agreement in key questions and the unchanged risk factor pattern between parental and teenager reports, all support the validity and reliability of the results.

Papers III & IV

There were significant sex differences in tobacco use patterns (Paper III). Although the prevalence of smoking was higher among girls, the prevalence of any tobacco use was significantly higher among boys who used snus to a greater extent (Figures 4 and 5). Studies that include both smoking and snus use among teenagers have found similar patterns of tobacco use. For instance, among Finnish 16-year olds in 2001, using snus was more common among boys (43%) than girls (13%), while weekly smoking was more common among girls (37%) versus boys (33%) (194). In 2003, the prevalence of using snus among Swedish 15-16-year olds was 13% among boys and 1% among girls, while the prevalence of smoking was 15% among girls and 4% among boys (137).

Although the prevalence of smoking has decreased in Sweden during past decades, overall tobacco use has remained at approximately the same level due to a parallel increase in snus use. There is some evidence that snus is used as a substitute for cigarettes, as many snus users are ex-smokers (195). Compared to studies about the harmful effects of smoking, there are fewer studies about the health effects of snus. Using snus has not been shown to increase the risk for myocardial infarction (196, 197). However, higher risk of hypertension (198) and fatal ischemic stroke (199) were found among Swedish snus users. In a Norwegian study, an increased risk of pancreatic

cancer was found among adult snus users (200). The sale of snus is forbidden in the European Union, except in Sweden (201).

Although Sweden is often mentioned as a country with a low prevalence of smokers, prevention of tobacco use is still an important task, especially among teenagers (114). Anti-smoking campaigns have successfully reduced the number of smokers in the general population. But among teenagers the reduction has been smaller (107). Suggested smoking prevention methods aimed at teenagers are complete bans on tobacco advertising and promotional items (118), and an increased price of cigarettes (119). Prevention efforts targeting subpopulations at risk of becoming tobacco users might decrease the number of smokers and snus users also among teenagers.

The smoking prevention program in the present cohort may have delayed the age of smoking initiation, but no effect could be seen at the age of 14-15 years (Paper III). The initial idea was for a long-term prevention program with active engagement of program participants, which has been shown to be a successful concept (132). Although the prevention program was cancelled due to organisational changes in the schools, the prevalence of smoking in the cohort was slightly lower compared to similar ages in whole Sweden (107). Further, the prevalence of any tobacco use was significantly lower in Luleå and Kiruna compared to Piteå (Paper III; Table 1), where the cohort members have only been included in the questionnaire surveys but not in any intervention efforts or clinical examinations. Furthermore, the prevalence of parental smoking decreased during the study period (Paper IV). It has been shown that the prevalence of smoking parents decreases when their teenager is included in a smoking prevention program (202).

Similar to the findings of other studies, having smoking family members is strongly related to being a smoker and to use snus at the age of 14-15 years (Paper III) (104, 123, 138). Rosendahl et al reported that having at least one smoking parent increased the likelihood of early escalation to heavy consumption of cigarettes among girls (203). Taylor et al found that when the number of family members and friends who smoked increased, so did the risk for becoming a smoker among American teenagers (123). This is similar to the findings in Paper III. There are even studies that have found significant associations between maternal smoking during pregnancy and smoking behaviour among teenagers (204, 205). However, this association may be explained by the fact that mothers who smoke during pregnancy often continue to smoke after the child is born.

The girls in our cohort were more often smokers and more commonly exposed to maternal ETS compared to the boys (Paper IV). One explanation for this gender difference may be related to bidirectional role modeling between mothers and daughters; having a smoking mother increase smoking among adolescent girls and having a smoking daughter could increase the likelihood that the mother continues to smoke. Some have suggested that vulnerability to ETS exposure (206), and to personal smoking (207, 208) is stronger among girls compared to boys, similar to studies among adults (209). These results provide further evidence of the importance of informing parents of the effect their smoking behaviour has on their child´s respiratory health and likelihood of becoming a smoker in adolescence.

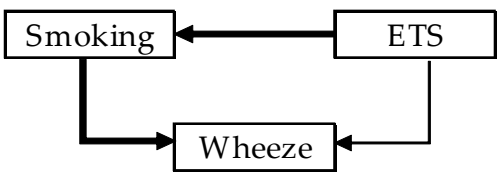

Figure 8. The association between environmental tobacco smoke (ETS) and personal smoking to wheeze among teenagers.

Besides age, sex and smoking family members, other factors related to smoking were having asthma and the SES indicator of living in an apartment. There are other studies that show an increased prevalence of smokers among asthmatic teenagers (134, 135). However, the association is complicated by the fact that both asthma and smoking is more common among those with smoking family members (Figure 8). In a study of directionality of smoking and asthma, having asthma was a risk factor for becoming a smoker only among those with a smoking mother (87). SES among children and teenagers is usually based on parental education or household income. In order to further characterize social circumstances, a recent study suggests taking other SES indicators into account, such as family structure and size, parental occupation and parental employment status (177). Results in Paper III show that living both in an apartment and a house or in a single parent household was associated with being a smoker in adolescence. These variables probably identify those who have divorced parents and alternate between homes, and this was related to smoking in other studies (104, 125). Participation in sports activities was a protective factor of tobacco use (Paper III), a finding that is similar to other studies

(130, 131). Sports participation probably identifies teenagers who have chosen a healthy lifestyle that excludes smoking.

Regardless of which exposure variable was used, maternal ETS exposure was associated with asthma and wheeze among teenagers (Paper IV). After adjustment for covariates, ETS exposure remained a significant risk factor for lifetime history of wheeze and physician-diagnosed asthma. The analyses among the non-smoking adolescents further support these findings. Exposure *in utero* or lifetime exposure during childhood are common measures of ETS. However, analyses of current ETS exposure in relation to asthma or wheeze in studies among teenagers are limited. Some studies have found an independent effect of current ETS exposure and respiratory symptoms among adolescents (66, 67), whereas others have found no such associations (57). In our study, current ETS exposure from the mother was related to asthma in the stratified analyses among the non-smokers. However, the association between current maternal ETS and lifetime asthma may be explained by a lasting effect of ETS exposure earlier in life.

In utero and early life exposure compared to later life exposure has been suggested to be more strongly related to impaired lung function, asthma and wheeze (59, 65, 210). A possible explanation for these results could be that teenagers are less exposed to parental ETS since they spend less time in the home compared to a younger child. A study by Irvine et al assessed ETS exposure by measuring cotinine level among children aged 2-12 years (211). The oldest children had substantially lower levels of cotinine compared to the preschool age children. Another possible explanation may be that young children are more sensitive to ETS than teenagers. Children whose mothers smoked during pregnancy are more likely to have low birth weight and impaired lung function in early life which in turn predicts development of asthma (60, 212).

The prevalence of wheeze was significantly increased among daily smokers, and the association remained after adjustment for covariates, including ETS. Several other studies have found similar associations (23, 68, 87). Already at the age of 16-17 years, we found a significant dose-response association between number of cigarettes and prevalence of wheeze (Figure 6), in accordance with other studies (68, 86, 87). These results suggest an adverse effect of smoking after only a few years.

CONCLUSIONS

- The agreement between parents and teenagers was good for reports about respiratory symptoms, rhinitis, eczema and environmental factors, and it was very good for reports of asthma and parental smoking.

- The methodological change from parents to teenagers as questionnaire responders did not substantially alter the outcome in this longitudinal study about asthma and allergic diseases.

- There were significant sex differences in tobacco use among the teenagers. Overall, the prevalence of any tobacco use was higher among boys who used snus to a greater extent, while smoking was more common among girls.

- The most important factor related to tobacco use was having smoking family members. Other factors related to tobacco use were living in an apartment, and not participating in sport activities. Having asthma did not prevent the teenagers from becoming a smoker.

- Maternal ETS exposure was significantly related to ever wheeze and physician-diagnosed asthma, but being a daily smoker was more strongly related to current wheeze at the age of 16-17 years.

PERSPECTIVES

In early adolescence parents are still responsible and make decisions on their child´s behalf. Only a few years later, the children will be fully responsible for themselves as they go from adolescence into adulthood. In epidemiologic studies performed during the time between childhood and adulthood the decision must be made about whether to use a parent or the index person as the respondent. Parents may provide more accurate reports of events in early life, while teenagers may be more reliable when it comes to current events. In longitudinal studies where a cohort of children is followed throughout adolescence, it is possible to change the methodology from parents to index person as the respondent. However, it is important to evaluate the effect of this change, not only in questions about diseases but also in questions about exposures. This thesis suggests that 13-14 years is an appropriate age for self-completion of questionnaires.

Although the prevalence of smoking has generally decreased during the last decades, smoking prevention and intervention are still important tasks and should not be forgotten in public health efforts. Smoking is still common among teenagers and many continue to smoke despite the widespread knowledge of its harmful effects. Adults need to understand their important role concerning smoking among teenagers. Smoking cessation among parents may be an important step towards reduced number of adolescent smokers. By identification and characterisation of smokers but also populations at risk of becoming smokers, efforts to reduce smoking might be improved.

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