AN EPIDEMIOLOGICAL STUDY
OF OCCURRENCE, PROGNOSIS AND
PREDISPOSING FACTORS OF
ADULT ASTHMA

by

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ACADEMIC DISSERTATION

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HELSINKI 2002
CONTENTS

ABSTRACT ............................................................................................................................ 5
ABBREVIATIONS .................................................................................................................. 6
LIST OF ORIGINAL PUBLICATIONS ................................................................................... 7
1 INTRODUCTION ............................................................................................................. 8
2 REVIEW OF LITERATURE ............................................................................................. 10
   2.1 Definition of asthma in epidemiological studies ......................................................... 10
   2.2 Occurrence of adult asthma ....................................................................................... 11
   2.3 Mortality .................................................................................................................... 19
   2.4 Predictors of adult asthma ......................................................................................... 20
      2.4.1 Genetic factors ................................................................................................... 20
      2.4.2 Atopy and respiratory symptoms ......................................................................... 21
         2.4.2.1 Atopy ........................................................................................................ 21
         2.4.2.2 Respiratory diseases and symptoms ......................................................... 22
      2.4.3 Social and life-style factors ............................................................................... 23
         2.4.3.1 Smoking .................................................................................................... 23
         2.4.3.2 Social class ............................................................................................... 24
         2.4.3.3 Physical activity ....................................................................................... 26
      2.4.4 Psychological factors ......................................................................................... 29
      2.4.5 Psychosocial factors ........................................................................................... 39
3 AIMS OF THE STUDY ..................................................................................................... 32
4 MATERIALS AND METHODS ......................................................................................... 33
   4.1 The Finnish Twin Cohort Study ............................................................................... 33
      4.1.1 Compilation of the cohort ................................................................................ 33
      4.1.2 Questionnaires ................................................................................................. 33
      4.1.3 Determination of zygosity ............................................................................... 34
   4.2 Registers .................................................................................................................... 35
      4.2.1 Register of the Social Insurance Institution ......................................................... 35
      4.2.2 The Finnish Hospital Discharge Register ............................................................. 35
      4.2.3 Other registers ................................................................................................. 36
   4.3 Study variables and definitions ................................................................................ 36
      4.3.1 Asthma .............................................................................................................. 36
      4.3.2 Allergic and respiratory symptoms ................................................................. 36
      4.3.3 Social and life-style factors ............................................................................... 37
      4.3.4 Psychological factors ....................................................................................... 38
   4.4 Study design .............................................................................................................. 40
   4.5 Statistical methods .................................................................................................. 40
      4.5.1 Prevalence and incidence ............................................................................... 40
      4.5.2 Mortality ......................................................................................................... 42
      4.5.3 Logistic regression ........................................................................................... 42
ABSTRACT

Objective: To study the occurrence, prognosis and risk factors of adult onset asthma.

Subjects and Methods: This study is based on the Finnish Twin Cohort Study, which consists primarily of adult twin pairs born before and with both members alive in 1967. All pairs of persons with the same date of birth, sex, surname at birth and locality of birth were identified from the Central Population Registry of Finland. A postal questionnaire was sent in 1975 (31 133 persons responding) and follow-up questionnaires in 1981 and 1990, with questions that covered twinship, medical history, symptoms, state of health, social factors and psychological traits. The question about asthma: "Have you ever been told by a physician that you have or have had asthma?" was identical in all questionnaires. In addition, register-based data on asthma medication and hospital treatment were collected. Logistic regression was used to assess the effect of selected social, life-style and psychological factors on the onset of asthma in adulthood. A proportional hazard regression model was used to compare mortality rates of asthmatic subjects with those of non-asthmatic ones. In addition, twin pairs discordant for asthma (one twin has asthma, while the twin sibling does not) were studied to determine whether the risk of asthma in cases in relation to chosen determinants differed from the risk of their twin siblings without those determinants.

Results and Discussion: The 15-year cumulative incidence of asthma was 2.3% among men and women. The prevalence of asthma remained steady from 1975 to 1981 (2%), increasing slightly in 1990 (3%) among adults aged 30 years or older. The overall mortality was higher among adult asthmatics compared with non-asthmatics. Excess deaths due to respiratory diseases explain a great part of this poorer survival of persons with asthma. Low social class, measured by educational level as well as low levels of physical activity, was associated with asthma risk among twin pairs discordant for reimbursed asthma medication as was also. In contrast to previous studies, obesity was significantly associated with increased asthma risk only among men, while both under- and overweight women had slightly increased asthma risk compared with normal-weight women. Higher adult height conferred protection against adult onset asthma. While no typical personality profile was found among asthmatics, women with a high extroversion score and men with neuroticism had an elevated risk of asthma.

Conclusions: The occurrence of asthma has increased slightly among adult Finns. Sedentary life-style and obesity are associated with increased risk of asthma. Personality may play a role in the onset of adult asthma, although different features affect asthma risk in men and women.

Key words: Asthma, adult onset, twins, prevalence, incidence, mortality, allergic rhinitis, chronic bronchitis, social class, smoking, physical activity, weight, height, personality, psychological factors
ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\chi^2$</td>
<td>chi-square</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index; weight (kg)/ height (m)$^2$</td>
</tr>
<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>DZ</td>
<td>dizygotic</td>
</tr>
<tr>
<td>EAACI</td>
<td>European Academy of Allergy and Clinical Immunology</td>
</tr>
<tr>
<td>ECRHS</td>
<td>European Community Respiratory Health Survey</td>
</tr>
<tr>
<td>FEV</td>
<td>forced expiratory volume</td>
</tr>
<tr>
<td>FHDR</td>
<td>Finnish Hospital Discharge Register</td>
</tr>
<tr>
<td>FinEsS study</td>
<td>Comparative Survey between Finland, Estonia and Sweden</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>IgE</td>
<td>immunoglobulin E</td>
</tr>
<tr>
<td>IRR</td>
<td>incidence rate ratio</td>
</tr>
<tr>
<td>MZ</td>
<td>monozygotic</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>RR</td>
<td>risk ratio</td>
</tr>
<tr>
<td>SII</td>
<td>Social Insurance Institution</td>
</tr>
<tr>
<td>Th$_1$</td>
<td>T-helper 1 lymphocyte</td>
</tr>
<tr>
<td>Th$_2$</td>
<td>T-helper 2 lymphocyte</td>
</tr>
</tbody>
</table>
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following articles referred to in the text by their Roman numerals.


V Huovinen E, Kaprio J, Koskenvuo M. Factors associated to life-style and risk of adult onset asthma. Respiratory Medicine, in press.
1 INTRODUCTION

Asthma is one of the most common chronic diseases in Finland. The proportion of persons with asthma is estimated to be up to 5% depending on the definition of asthma, with about half of these needing regular asthma medication (Sosiaali- ja terveysministeriö, 1994). Since 1970 National Sickness Insurance of Finland has covered 75-100% of the costs of drug treatment for asthma, if it has been diagnosed accurately (Vesterinen et al. 1993). In 1997, this right to reimbursed asthma medication was granted to 169 200 asthma patients in Finland (Sosiaali- ja terveysministeriö, 1998). The clinical features of asthma vary significantly and classification of asthma severity is difficult. At the end of the 1980s, most adult asthma patients (60%) in Finland were categorized as having mild and every fifth patient as having severe or very severe asthma (Sosiaali- ja terveysministeriö, 1994). The definition of adult asthma is often confused with other respiratory symptoms and diseases such as chronic bronchitis.

While the occurrence of asthma has been low in Finland, it has been increased during the last decades (Haahtela et al. 1990; Reijula et al. 1996). In recent studies, its prevalence has been reported to be somewhat lower than in some other western countries, but higher than in eastern Europe (The International Study of Asthma and Allergies in Childhood, 1998; Pekkanen, 1999). Epidemiological twin and family studies have offered evidence for familial aggregation of asthma (Jenkins et al. 1997; Laitinen et al. 1998). However, the observed increase in the occurrence of asthma cannot be explained by changes in genetic susceptibility, instead environmental explanations are needed. The westernized life-style and associated factors have been suggested as one reason for the increasing prevalence of asthma (von Mutius et al. 1994). Another explanation may lie in a more hygienic environment and its effect on immunity developed during early childhood (Holgate, 1999). In developing countries, asthma has also become more common as life-styles become more urbanized or “western” (von Mutius et al. 1998).

Although asthma is a public health problem that is increasing in prevalence in most developed countries, its aetiology and prognosis remain obscure. Previous studies have focused on childhood asthma, and research on the incidence and risk factors of adult onset asthma is limited. This thesis is based on the Finnish Twin Cohort Study, which examines both predisposing and possible confounding
factors of asthma. In addition, because the cohort consists mainly of twins, genetic and familial factors are considered.
2 REVIEW OF LITERATURE

2.1 Definition of asthma in epidemiological studies

According to the International Consensus Report on the diagnosis and treatment of asthma: “Asthma is a chronic inflammatory disorder of the airways in which many cells play a role, including mast cells and eosinophils. In susceptible individuals, this inflammation causes symptoms which are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment and causes an associated increase in airway responsiveness to a variety of stimuli.” (International Asthma Management Project, 1992). This definition cannot however be used directly in epidemiological studies. Clinical diagnosis of asthma is usually based on self-reported symptoms, patient’s medical history, clinical examination and lung function and laboratory tests measuring bronchial hyperreactivity, airway narrowing, atopy and inflammation. Although reversible airway obstruction is the main diagnostic criterion, other features may differ widely.

The absence of a single clear-cut definition of asthma is a basic problem in studies dealing with asthma (Toelle et al. 1992). In addition, no test has been found to be both specific and sensitive (Siersted et al. 1996). In epidemiological studies, asthma is often defined by questions of diagnosis or symptoms of asthma. Reliability of a questionnaire can be tested by repeating the questionnaire among the same individuals (Torén et al. 1993). Translations of questions may affect the reliability of the questionnaire (Burney et al. 1989). Validity testing of asthma questionnaires is difficult since no gold standard of asthma diagnosis exists (Pekkanen and Pearce, 1999; Peat et al. 2001).

Questionnaires are commonly validated by bronchial challenge tests, by clinical diagnosis of asthma or by comparing a new questionnaire with an old one (Torén et al. 1993). When validated by bronchial challenge tests, questions on ‘physician-diagnosed asthma’ have been shown to have very high specificity (up to 99%) (Torén et al. 1993). In a Finnish study of young adults, questionnaire reports of doctor-diagnosed asthma have had high positive predictive value and specificity but lower sensitivity when validated against the doctor’s interview and lung function tests (Kilpeläinen et al. 2001). A high positive predictive value (proportion of the truly diseased among positive questionnaire respondents) is
important when studying risk factors of a disease (Pekkanen and Pearce, 1999). High specificity means a small number of false-positive answers and is especially important in studies of diseases with a low prevalence (Torén et al. 1993). Questionnaire diagnosis of asthma is a valid method for epidemiological studies, and particularly useful in studies on risk factors of asthma.

2.2 Occurrence of adult asthma

The European Community Respiratory Health Survey (ECRHS 1996) found a wide geographical variation in the prevalence of asthma among adults. The lowest prevalence was found in Estonia (2.0%) and the highest in Australia (11.9%) (European Community Respiratory Health Survey, 1996). Recent studies in Finland show the prevalence of doctor-diagnosed asthma among adults in the 1990s to be 4.4% to 8.0% (Table 1). These prevalences are higher than in studies from the 1980s, although a study of elderly Finns in 1986 showed relatively high prevalences (7.0-8.6%) (Isoaho et al. 1994a). In the 1960s and 1970s, asthma prevalences were even lower (0.3-1.4%) (Table 1). However, comparison between previous Finnish studies is difficult due to varying asthma definitions used.

The International Study of Asthma and Allergies in Childhood (ISAAC 1998) has shown a large variation of the prevalence of atopic diseases between countries also among children. The prevalence of asthma in Finnish children is somewhat higher than in many eastern European countries but is lower than in the UK or Australia (The International Study of Asthma and Allergies in Childhood, 1998).

An increase in prevalence of asthma has been reported during recent decades in several countries. In 1968, over 16 000 Tasmanian adults were surveyed and the prevalence of asthma was found to be as high as 10.9% (Hopper et al. 1995). Since then, prevalence has increased in Tasmania to 23.2% in 1991-1993 (Hopper et al. 1995). Increases in asthma prevalence have also been reported in other Australian studies (Peat et al. 1992; Adams et al. 1997; Woods et al. 2001).
<table>
<thead>
<tr>
<th>Study</th>
<th>Year 1</th>
<th>Age (years)</th>
<th>Study population</th>
<th>Number of subjects</th>
<th>Definition of asthma</th>
<th>Occurrence of asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huhti 1965</td>
<td>1961</td>
<td>40-64</td>
<td>Harjavalta population</td>
<td>1620</td>
<td>Q + LFT</td>
<td>0.5% M 1.6% F</td>
</tr>
<tr>
<td>Alanko 1970</td>
<td>1967-68</td>
<td>10-59</td>
<td>Harjavalta population</td>
<td>5862</td>
<td>Q: Dg by doctor</td>
<td>1.2% M 1.6% F</td>
</tr>
<tr>
<td>Luoma and Koivikko</td>
<td>1971-75</td>
<td>≥15 (mean 26)</td>
<td>Population-based (Turku and Kuopio)</td>
<td>5630</td>
<td>Q: self-report</td>
<td>1.8%</td>
</tr>
<tr>
<td>Haahtela and Jokela</td>
<td>1977</td>
<td>18-19</td>
<td>Men of conscription age in Imatra</td>
<td>295</td>
<td>Q: Dg by doctor or PE</td>
<td>2.7% cumulative prevalence 1.7% active asthma</td>
</tr>
<tr>
<td>Vesterinen et al. 1988</td>
<td>1975 1981</td>
<td>18-64</td>
<td>Finnish Twin Cohort</td>
<td>14 359 10 604</td>
<td>Q: Dg by doctor + R: hospital</td>
<td>1.35% 1.80%</td>
</tr>
<tr>
<td>Haahtela et al. 1990</td>
<td>1966 1989</td>
<td>19</td>
<td>Men of conscription age men</td>
<td>98% of conscription age men</td>
<td>PE: call-up examination for military service</td>
<td>0.29% 1.79%</td>
</tr>
<tr>
<td>Nieminen et al. 1991</td>
<td>1985 1988</td>
<td>≥28</td>
<td>Finnish Twin Cohort</td>
<td>27 776 (13 888 twin pairs)</td>
<td>Q: Dg by doctor + R: hospital + R: reimbursed medication</td>
<td>Cumulative prevalence 1.8% MZ, 1.7% DZ M 1.9% MZ, 2.2% DZ F</td>
</tr>
<tr>
<td>Keistinen et al. 1993</td>
<td>1972 1986</td>
<td>all</td>
<td>National</td>
<td>Whole Finnish population</td>
<td>R: hospital</td>
<td>1.14/1000/year 1.15/1000/year</td>
</tr>
<tr>
<td>Isoaho et al. 1994</td>
<td>1986</td>
<td>≥64</td>
<td>Lieto population</td>
<td>1196</td>
<td>Q: self-report PE</td>
<td>Cumulative prevalence 7.0% M, 8.6% F Current asthma 2.9% M, 3.8% F</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Age Range</td>
<td>Population Type</td>
<td>Population Size</td>
<td>Diagnosis Method</td>
<td>Prevalence/Incidence Rate</td>
</tr>
<tr>
<td>----------------------------</td>
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</tr>
<tr>
<td>Reijula et al. 1996</td>
<td>1993</td>
<td>15-64</td>
<td>National</td>
<td>~ 2 million</td>
<td>R: reimbursed medication</td>
<td>Incidence rate 0.4%</td>
</tr>
<tr>
<td>Kujala et al. 1996</td>
<td>1985</td>
<td>not reported</td>
<td>Male former elite athletes Controls</td>
<td>1 282/777</td>
<td>Q:Dg by doctor + R: reimbursed medication</td>
<td>Life-time occurrence 2.4% (athletes)/3.5% (controls)</td>
</tr>
<tr>
<td>Kilpeläinen 2001</td>
<td>1995</td>
<td>18-24</td>
<td>All first year university students</td>
<td>10 667</td>
<td>Q: Dg by doctor</td>
<td>Life-time occurrence 5.1% M/4.2% F</td>
</tr>
<tr>
<td>Pallasaho et al. 1999</td>
<td>1996</td>
<td>20-69</td>
<td>Population-based (Helsinki) FinEsS-study</td>
<td>6 062</td>
<td>Q:self-report Q:Dg by doctor</td>
<td>Self-reported 5.7% (20-44yr)/6.8% (45-69yr) M/7.5% (20-44yr)/8.7% (45-69yr) F Doctor-diagnosed 5.2% (20-44yr)/6.1% (45-69yr) M/6.9% (20-44yr)/8.0% (45-69yr) F</td>
</tr>
<tr>
<td>Hedman et al. 1999</td>
<td>1996</td>
<td>18-65</td>
<td>Population-based (Päijät-Häme)</td>
<td>3 102</td>
<td>Q: Dg by doctor</td>
<td>Prevalence 5.3% (observed)/5.1% (age-standardized)/4.4% (non-response adjusted)</td>
</tr>
<tr>
<td>Kotaniemi et al. 2001</td>
<td>1996</td>
<td>20-69</td>
<td>Population-based (Lapland) FinEsS-study</td>
<td>6 633</td>
<td>Q: Dg by doctor</td>
<td>Prevalence 6.0%</td>
</tr>
<tr>
<td>Karjalainen et al. 2001</td>
<td>1986-98</td>
<td>25-59 employed</td>
<td>National sample All employed Finns</td>
<td>1 852 848</td>
<td>R: reimbursed medication</td>
<td>Incidence rate 1.65/1000/yr men/2.47/1000/yr women</td>
</tr>
<tr>
<td>Pekkanen et al. 2001</td>
<td>1997</td>
<td>31</td>
<td>Birth cohort</td>
<td>5 192</td>
<td>Q: Dg by doctor</td>
<td>Prevalence 8.0% (ever diagnosed asthma)</td>
</tr>
</tbody>
</table>

Q=questionnaire, PE=physical examination, R=register based data, M=male, F=female
Physician-diagnosed asthma increased in all age groups in the UK between 1970 and 1981 (Fleming and Crombie, 1987), in Canada between 1980 and 1990 (Manfreda et al. 1993) and in USA during the last few decades (Senthilselvan, 1998; Vollmer et al. 1998). These large population studies are based on physician diagnoses obtained from medical records. Because no objective measurements of asthma were used, altered diagnostic practices over time may affect the results.

Many studies have been done among young adults, students and conscripts. Among Swedish conscripts, the prevalence of asthma was higher in 1981 (2.8%) than in 1971 (1.9%) (Åberg, 1989), and among Belgian conscripts, prevalence was 7.2% in 1991 compared with 2.4% in 1978 (Dubois et al. 1998). In Denmark, self-reported asthma prevalence among young adults in 1976-1978 was 1.5% and 15 years later 4.8% (Hansen et al. 2000), and among students from Belfast University, the 12-month period prevalence of asthma increased from 1.3% in 1972 to 2.8% in 1989 (Bruce et al. 1993). The elevated prevalences found in these studies of young adults may reflect raised asthma prevalences during childhood rather than an increase in adult asthma. However, in an American study, the prevalence of treated asthma increased in all age groups and both genders, excluding men over 65 years, during a 20-year follow-up (Vollmer et al. 1998). Finnish studies applying similar methods at different times also show an increase in asthma prevalence during the last decades (Haahtela et al. 1990; Reijula et al. 1996). Better awareness of asthma and a diagnostic shift from chronic bronchitis towards asthma may explain part of the higher asthma prevalences (Peat et al. 1992; Hansen et al. 2000), but the increase is too steep to be explained fully by changes in diagnosing asthma.

Although the evidence of increased prevalence of asthma among children and young adults was found to be weak in a meta-analysis (Magnus and Jaakkola, 1997), studies using objective measurements of asthma reflect the true increase in prevalence (Auerbach et al. 1993; Dubois et al. 1998). Dubois and co-workers found the proportion of asthmatics with airway hyperresponsiveness to remain stable with increasing asthma prevalence, thus indicating that the increase was not due to diagnostic bias. (Dubois et al. 1998). In addition, Vollmer and co-workers showed in their 20-year follow-up that an increase in asthma prevalence paralleled an increase in the broader category of chronic airway obstruction, suggesting that a diagnostic shift towards asthma is not a likely explanation for increased asthma prevalence (Vollmer et al. 1998). However, a gender difference in diagnostic practice is possible. A Tucson study showed that with
same symptoms and taking into account smoking habits, women were more likely to be diagnosed as asthmatics, while men were more likely to be diagnosed as having emphysema (Dodge et al. 1986). Among Finnish university students, the occurrence of physician-diagnosed asthma was higher among boys than among girls, although both lifetime and current wheezing were more common among girls (Kilpeläinen, 2001). Asthma may be under-diagnosed in girls or women may more easily report symptoms.

The occurrence of other atopic diseases has also increased over time. Among Swedish conscripts, the prevalence of allergic rhinitis was 4.4% in 1971 and almost two fold (8.4%) ten years later. In Scotland, the prevalence of hay fever among middle-aged adults increased from 5.4% to 15.5% in 20 years, and in Tasmania, the lifetime occurrence of hay fever in young adults was twice as high as in their parents 25 years earlier. However, Peat and co-workers found little change in the prevalence of atopy, measured by skin prick tests, during a ten-year period among adults (Peat et al. 1992) as well as among children (Peat et al. 1994). That objective measurement used by Peat and co-workers did not show a significant increase suggests that at least part of the rise in prevalence of allergic rhinitis found in other studies is due to improved awareness of this disease.

Incidence studies on adult onset asthma are relatively few (Table 2). In the ECRHS study, yearly incidences of subjects aged 16-44 years varied from 0.3/1000 persons in Belgium and the Netherlands to 2.9/1000 persons in Australia, with an increase by birth cohort (Sunyer et al. 1999). Studies from USA including subjects of all ages (Broder et al. 1974; Dodge and Burrows, 1980; Yunginger et al. 1992) as well as studies focusing only on adults (McWhorter et al. 1989; Ownby et al. 1996) indicate annual incidence rates of 1-4/1000 person years. Incidence of asthma among young adults is found to be similar (Kivity et al. 1995) or somewhat higher (Strachan et al. 1996) than among older adults. From puberty, the incidence of asthma is more common among women (Anderson et al. 1992; Larsson, 1995), and this pattern was consistent in all countries studied in the ECRHS (deMarco et al. 2000). A Swedish study shows the importance of the methods used to measure asthma incidence, especially the significance of defining the population at risk (Rönmark et al. 1997; Lundbäck et al. 2001). Incidence of physician-diagnosed asthma was halved, from 8/1000 to 4/1000 person years, when those not reporting asthma themselves but who were diagnosed as asthmatics in clinical examination at the beginning of follow-up were excluded (Rönmark et al. 1997).
Table 2. Incidence studies of asthma in adult populations.

<table>
<thead>
<tr>
<th>Country/study</th>
<th>Time of study (years)</th>
<th>Average follow-up (years)</th>
<th>Age at baseline (years)</th>
<th>Study population</th>
<th>Number of subjects</th>
<th>Exclusion criteria</th>
<th>Definition of incident asthma</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA Broder et al. 1974</td>
<td>1959-65</td>
<td>4</td>
<td>All</td>
<td>Population-based</td>
<td>6563</td>
<td>Q&amp;PE</td>
<td>Q&amp;PE</td>
<td>2.5/1000/yr</td>
</tr>
<tr>
<td>USA Dodge and Burrows 1980</td>
<td>1972-76</td>
<td>3.5</td>
<td>All</td>
<td>Population-based</td>
<td>3432</td>
<td>Q:Have seen doctor for asthma or own report of asthma</td>
<td>Q:Have seen doctor for asthma</td>
<td>4/1000/yr</td>
</tr>
<tr>
<td>USA McWorther et al. 1989</td>
<td>1971-84</td>
<td>9.1</td>
<td>25-74</td>
<td>Population-based</td>
<td>14404</td>
<td>Q:asthma diagnosis</td>
<td>Q:asthma diagnosis +hospital register (no chr.bronchitis or emphysema)</td>
<td>2.1/1000/yr (age-standardized)</td>
</tr>
<tr>
<td>USA Younginger et al. 1992</td>
<td>1964-83 (retrospective)</td>
<td>20</td>
<td>All</td>
<td>Population-based</td>
<td>~60 000</td>
<td>MR:diagnosis or symptoms</td>
<td>MR:diagnose or symptoms</td>
<td>1.38/1000/yr</td>
</tr>
<tr>
<td>UK Anderson et al. 1992</td>
<td>1975-81</td>
<td>7</td>
<td>17</td>
<td>Birth cohort</td>
<td>5452</td>
<td>History of asthma or wheezy bronchitis</td>
<td>Q: asthma and wheezy bronchitis</td>
<td>5.6/1000/yr M 9.4/1000/yr F</td>
</tr>
<tr>
<td>Israel Kivity et al. 1995</td>
<td>1987-89</td>
<td>Not reported</td>
<td>18</td>
<td>3 national cohorts of conscripts (male and female)</td>
<td>107 636</td>
<td>Asthma diagnosis in call-up examination</td>
<td>PE,LFT</td>
<td>2.75/1000/yr (-87) 2.45/1000/yr (-88) 2.43/1000/yr (-89)</td>
</tr>
<tr>
<td>Location</td>
<td>Study Period</td>
<td>Age Range</td>
<td>Study Design</td>
<td>Sample Size</td>
<td>Questionnaire</td>
<td>Cumulative Incidence Rate</td>
<td></td>
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<td>USA</td>
<td>1987-93</td>
<td>young adults mean 28.7</td>
<td>Population-based</td>
<td>1031</td>
<td>Q: dg by doctor</td>
<td>Q:dg by doctor 1.5/1000/yr M 5.2/1000/yr F</td>
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<td>Sweden</td>
<td>1986-96</td>
<td>36-67</td>
<td>3 birth cohorts</td>
<td>4754</td>
<td>Q: asthma dg or suspected asthma or concomitant COPD or symptoms PE: asthma or chr.bronchitis</td>
<td>Q:dg by doctor 1.7/1000py M 2.9/1000py F</td>
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<td>USA</td>
<td>from 1993 backwards</td>
<td>20-50</td>
<td>Population sample</td>
<td>15813</td>
<td>Q: asthma dg before age 16</td>
<td>Q:dg by doctor 1.0/1000 py M 1.3/1000 py F</td>
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<td>USA</td>
<td>1977-92</td>
<td>27-87</td>
<td>Non-smokers</td>
<td>3091</td>
<td>Q: asthma in first questionnaire Or asthma before age 16</td>
<td>Q:dg by doctor 2.1/1000yr M 2.9/1000yr F</td>
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<td>Spain</td>
<td>1991-99</td>
<td>20-44</td>
<td>Population-based (ECRHS)</td>
<td>1640</td>
<td>Q:ever asthma in first questionnaire or in 5 yrs before first questionnaire</td>
<td>Q:ever asthma 4.04/1000py M 6.88/1000py F</td>
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Q=questionnaire, PE=physical examination, LFT=lung function tests, MR=medical records, M=male, F=female

*calculated from the reported cumulative incidence during follow-up
Further, the incidence decreased to 2.3/1000 person years when the incidence calculations were corrected by excluding subjects reporting symptoms, use of asthma medication or diagnosis of chronic bronchitis prior to follow-up, but not having been diagnosed before the start of follow-up (Lundbäck et al. 2001).

Previous asthma incidence studies in Finland are based on either hospital discharge registers (Keistinen et al. 1993) or on reimbursed asthma medication (Reijula et al. 1996; Karjalainen et al. 2001). Asthma incidences are similar to those found in other countries (Tables 1 and 2). Among the Finnish twin cohort, the annual incidence of doctor-diagnosed asthma was 1.3/1000 for men and 1.7/1000 for women during 1976-1981, and the incidence of hospital admissions was 0.7/1000/year (Vesterinen et al. 1988). Asthma-induced treatment periods among Finns aged 25 to 64 years increased with age; middle-aged women used hospital services more than men, while among older patients no sex difference was present (Tuuponen, 1993). A regional difference also exists between hospital treatment related to asthma, with the highest increase occurring in Northern Finland and smallest in Western Finland during 1972-1986 (Tuuponen et al. 1993b). This same trend was seen in new hospital treatments due to asthma (Tuuponen et al. 1993b). First hospital treatment periods for asthma were found also among the elderly, and in addition to new asthma cases, this may demonstrate exacerbations of existing asthma needing hospital treatment for the first time at an older age (Tuuponen et al. 1993a; Harju et al. 1996).

Prevalence of asthma is related to prognosis. The course of asthma and existing symptoms vary with time both spontaneously and depending on medication. Remission in childhood and in young adulthood is common. Of children with wheezing or asthma by seven years of age, at least 25% are shown to have wheezing at 33 to 35 years of age (Jenkins et al. 1994; Strachan et al. 1996). Those with more severe symptoms during childhood are at increased risk of having asthma as adults (Jenkins et al. 1994; Oswald et al. 1994). Disappearance of asthma symptoms was common also among young adults (Panhuysen et al. 1997; Settipane et al. 2000), while studies among middle-aged subjects with asthma show very low remission rates (Bronnimann and Burrows, 1986; Rönmark et al. 1999). Among asthmatic subjects with severe symptoms, reduced lung function or concomitant diagnosis of chronic bronchitis or emphysema, remissions are rare (Bronnimann and Burrows, 1986).
2.3 Mortality

A wide international variation has been found in asthma mortality rates among children and young adults (Jackson et al. 1988). A gradual increase has occurred in most countries from the mid-1970s to the mid-1980s. In Finland, the annual number of asthma deaths has been small during this period and no increase has occurred (Kinnula et al. 1988; Jackson et al. 1988). Asthma deaths have remained rare in Finland; less than 100 asthma patients per year died from asthma in the late 1980s and early 1990s (Harju et al. 1998). Recent studies show decreasing asthma mortality rates since the late 1980s (Campbell et al. 1997; Goldman et al. 2000).

Data on overall survival of adult patients with asthma are inconsistent. In the general population, asthma is associated with slight excess of mortality, asthmatic subjects having 1.5 times the risk of those without asthma in two large studies in Denmark (Lange et al. 1996) and the UK (Markowe et al. 1987), while an American study found no increase in mortality of asthma patients unless asthma was associated with chronic obstructive pulmonary disease (COPD) (Silverstein et al. 1994). Furthermore, asthma with onset after age 65 was not associated with reduced survival (Bauer et al. 1997). Studies on patients referred to chest clinics or hospitals show raised mortality among asthmatic patients, relative risks varying from 1.2 to 2.4 (Alderson and Loy, 1977; Almind et al. 1992; Ulrik and Frederiksen, 1995; Sunyer et al. 1998), but these results may not be generalizable. In addition, most of these studies compared survival of asthmatic patients with standard mortality rates of the regional population or with national death rates. (Alderson and Loy, 1977; Almind et al. 1992; Sunyer et al. 1998). Therefore, the effect of possible confounding factors, such as smoking and socio-economic class could not be taken into account.

The predominant cause of excess mortality among asthmatics is a respiratory disease, including asthma (Markowe et al. 1987; Ulrik and Frederiksen, 1995). Asthma was the underlying cause of death in 4% of patients who died in an American study (Silverstein et al. 1994), while only 1% of the total asthmatic cohort died from asthma over the follow-up period in another study (Markowe et al. 1987). Prognosis of COPD has been shown to be worse than that of asthma (Burrows et al. 1987; Sunyer et al. 1998; Keistinen et al. 1998), but survival of asthma patients also depends on lung function (Ulrik and Frederiksen, 1995; Lange et al. 1996). To control misclassification between self-reported asthma
and COPD, Lange et al. (1996) performed separate analyses among never-smokers. Among these excessive mortality risk associated with asthma was similar to that of the whole study population (Lange et al. 1996).

The association between allergy and cancer is complex (Eriksson et al. 1995), depending on the type of allergy and the organ site (Mills et al. 1992). Although history of asthma is reported to increase risk of lung cancer (Vesterinen et al. 1993), especially among non-smoking women (Alavanja et al. 1992; Wu et al. 1995), some studies do show a reduced risk of cancer among asthmatic patients (Alderson, 1974; Osann, 1991).

2.4 Predictors of adult asthma

2.4.1 Genetic factors

Asthma has a strong genetic component according to family studies (Panhuysen et al. 1998) and twin studies (Koppelman et al. 1999; Räsänen, 2000). Molecular genetic studies provide insights into relevant genes (Holgate et al. 1998; Kauppi, 2001). The heritability of asthma among the Finnish twin cohort was estimated to be 35.6% (Nieminen et al. 1991). Among the younger twin cohort, the genetic effect accounted for 79% of the variance in the development of asthma (Laitinen et al. 1998). Heritability estimates from other countries were similar, although somewhat higher than among adult Finnish twins (Edfors-Lubs, 1971; Hopper et al. 1990; Duffy et al. 1990; Harris et al. 1997; Lichtenstein and Svartengren, 1997; Skadhauge et al. 1999). However, this genetic susceptibility for asthma is unlikely to explain the observed increase in asthma prevalence, and environmental explanations are needed.
2.4.2 Atopy and respiratory symptoms

2.4.2.1 Atopy

Definitions of atopy and allergy have evolved with improved understanding of the pathophysiology of these conditions. The European Academy of Allergy and Clinical Immunology (EAACI) position statement defines atopy as follows: "a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis, or eczema/dermatitis” (Johansson et al. 2001). In Anglosaxon literature, atopy is defined as specific IgE (Matricardi et al. 1994) or positive skin prick test for common allergen(s) (The European Academy of Allergology and Clinical Immunology, 1993). However, the clinical disease is not associated with the results of these tests consistently. Use of this kind of definition may underestimate by excluding symptomatic patients with negative tests or overestimate by including asymptomatic subjects with positive tests prevalent allergic diseases. Thus, questionnaire-based definitions of atopy (either allergic rhinitis or eczema) are also widely used. Questions about physician-diagnosed allergic rhinitis have been found to be valid in risk factor studies (Sibbald and Rink, 1991; Braun-Fahrländer et al. 1999; Kilpeläinen et al. 2001).

Although atopy is commonly associated with asthma, this association is less strong than generally assumed (Pearce et al. 1999). Many studies have demonstrated atopy to be strongly associated with asthma in childhood (von Mutius et al. 1994; Remes and Korppi, 1996) and adolescence (Anderson et al. 1992; Norrman et al. 1998), but not all studies show this association (Penny et al. 2001). The relation between asthma and atopy is different in urban and rural areas, indicating a more heterogeneous association between these entities (Yemaneberhan et al. 1997). Studies among adults also show atopy to be a strong predictor of asthma (Siracusa et al. 1997; Sunyer et al. 1997a; Bodner et al. 1998). In longitudinal studies, atopy has been demonstrated to be related to persistence of asthma into adulthood (Strachan et al. 1996). However, on the population level, asthma cases attributable to atopy have been estimated to be less than 50% of all asthma cases (Pearce et al. 1999).
2.4.2.2 Respiratory diseases and symptoms

Chronic bronchitis is defined as chronic production of mucus in the lungs for at least three months during at least two consecutive years, with no other underlying pulmonary or cardiac disease (Rose and Blackburn, 1968). Chronic bronchitis can occur with or without airway obstruction, while slowly progressing, generally irreversible airway obstruction and a decreased expiratory flow rate are characteristic of COPD.

In a Tucson study, adult onset asthma was often associated with chronic bronchial irritation (Dodge and Burrows, 1980), and among older subjects occurrence of symptoms (wheezing, dyspnoea and attacks of shortness of breath) was surprisingly similar in groups diagnosed as having chronic bronchitis, asthma or even emphysema (Dodge et al. 1986). Littlejohns and co-workers also found a considerable clinical and physiological similarity in asthma and chronic bronchitis (Littlejohns et al. 1989). Moreover, evidence exists of a common allergic basis of adult onset wheezing (Burrows et al. 1989; Tollerud et al. 1991; Postma and Lebowitz, 1995; Bodner et al. 1998). A Dutch hypothesis was put forward in 1961 that asthma, chronic bronchitis and emphysema should not be considered as separate diseases but rather as expressions of one disease entity known as “chronic non-specific lung disease” (Orie et al. 1961). Both endogenous (host) and exogenous (environmental) factors are thought to play a role and diffuse airway obstruction is considered to be the common pathophysiological characteristic according to the above-mentioned Dutch hypothesis (Orie et al. 1961).

Clinically, distinguishing between severe, long-lasting asthma and COPD is difficult. In a Finnish study, 11% of elderly men with COPD also had current asthma, while among women almost half of COPD patients had concurrent asthma (Isoaho et al. 1994b). In a Swedish study, the prevalence of a combined diagnosis of both asthma and chronic bronchitis was highest among the oldest age cohort (65-66 years), and no cases occurred in the youngest age cohort (35-36 years) (Lundbäck et al. 1993).

The differential diagnosis between asthma and chronic bronchitis is difficult to make. A patient’s age, gender and smoking habits may direct the diagnosis towards either condition. Therefore, symptom-based definitions of chronic bronchitis are widely used in questionnaire studies. However, chronic cough and
phlegm production are also characteristic symptoms of asthma, thus causing definition problems.

Breathlessness or dyspnoea is a common symptom of many different diseases. Although it can be described in various ways, patients with different underlying conditions experience distinct qualities of breathlessness (Simon et al. 1990; Elliott et al. 1991; Mahler et al. 1996). Reporting chest tightness and shortness of breath at rest are shown to predict asthma (Bai et al. 1998). Breathlessness at rest is also a widespread symptom among older adults with untreated asthma (Dow et al. 2001), while among children, breathing trouble is more common among those diagnosed with asthma than among the undiagnosed (Siersted et al. 1998).

2.4.3 Social and life-style factors

2.4.3.1 Smoking

Smoking is a well-known risk factor of overall mortality (Jacobs et al. 1999). Smoking cessation has been shown to improve the survival of smokers despite their pulmonary function (Pelkonen et al. 2000). The harmful effects of maternal smoking during pregnancy or passive smoking during childhood on children’s lung function are also well known (Cook and Strachan, 1997; Cook et al. 1998; Strachan and Cook, 1998). However, the association between adult asthma and smoking is complex (Strachan et al. 1996). The definition of asthma varies in different studies, and subjects with smoking related airway obstructions may also be included (Strachan et al. 1996). Current smoking is shown to be a risk factor for asthma among young adults (Larsson, 1995; Strachan et al. 1996; Norrman et al. 1998). Studies among adults of all ages have also demonstrated this relationship (Dodge and Burrows, 1980; Sparrow et al. 1993; Bodner et al. 1998; Toren and Hermansson, 1999). However, other studies found no or weak associations (Higgins et al. 1977; Vesterinen et al. 1988; McWhorter et al. 1989) or even an inverse relationship (Troisi et al. 1995a; deMarco et al. 2000) between smoking and asthma. Recently, environmental tobacco smoke has also been shown to be associated with an increased asthma risk among adults (Coulitas, 1998; Thorn et al. 2001; Bousquet and Vignola, 2001).
Self-selection may partly explain the lack of association between asthma and smoking in cross-sectional studies. Subjects with asthma or atopy may not begin smoking, and smokers developing symptoms of asthma tend to give up smoking. However, among active smokers, non-atopic subjects are found to be at greater risk of adult onset wheezing (Strachan et al. 1996), and increased bronchial hyperresponsiveness associated with smoking has only been found among non-atopic subjects (Sunyer et al. 1997b), possibly due to changes in immunological and inflammatory functions caused by smoking (Sunyer et al. 1996). This negative interaction between smoking and atopy on wheezing or bronchial responsiveness may partly account for the heterogeneous role of smoking on asthma in previous studies. However, evidence that smoking is an independent risk factor for adult onset asthma is lacking.

2.4.3.2 Social class

An increase in the prevalence of respiratory disease with decreasing socio-economic position has been reported (Pincus et al. 1987; Marmot et al. 1991; Payne et al. 1993). COPD is also strongly associated with social class (Prescott and Vestbo, 1999) as well as greater respiratory symptom prevalence and severity, which are linked with low socio-economic status (Erzen et al. 1997; Trinder et al. 2000). However, little consistency has been found in the relation between social class and childhood asthma in a review of over 20 studies (Mielck et al. 1996). Studies on the effect of social class on adult asthma are fewer, and the results are also inconsistent. Some studies show greater asthma prevalence in individuals of relatively low socio-economic class (Littlejohns and MacDonald, 1993; Salmond et al. 1999) or with low income (McWhorter et al. 1989), while others found no association (Higgins et al. 1977; Montnemery et al. 2001) or found an association only among women (Eachus et al. 1996).

In a Norwegian study, educational level was associated with self-reported respiratory symptoms or a physician’s diagnosis of obstructive lung disease, while no difference in prevalence of asthma was found (Bakke et al. 1995). Bodner and co-workers found an increased risk of adult onset wheezing in the manual social class (Bodner et al. 1997), while in their other study, socio-economic status was not associated with doctor-diagnosed asthma (Bodner et al. 1997).
Use of different asthma definitions as well as different definitions of social class makes comparison of studies difficult. In addition, subjects from the same social class may face different exposures in different populations. There is also some evidence that adults in lower socio-economic groups are less likely to receive a diagnostic label of asthma (Littlejohns et al. 1989); therefore, diagnostic bias in studies on social class and risk of asthma is a concern. Social class may to a certain extent affect access to health services and treatment, while in some countries, such as Finland, public health services offer medical services quite equally to all citizens. Although a history of asthma may increase the risk of unemployment, the effect is small (Sibbald et al. 1992), suggesting that asthma does not lower ones’ social status.

Occupational factors were estimated to affect of 9% of attributable risk of adult onset asthma in a review study (Blanc and Toren, 1999), while in a recent Finnish study, the corresponding attributable fraction was found to be as high as 29% for men and 17% for women (Karjalainen et al. 2001). In Finland, the incidence rate of occupational asthma has been 17.4 cases/100 000 employed workers during 1989-1995, with most cases being caused by sensitizing agents, animal epithelia and flour dust (Karjalainen et al. 2000). Working conditions may differ significantly in professions classified under the same social class.

The effect of farming on asthma risk is not unambiguous. Childhood farm environment seems to have a protective effect against allergies (Kilpeläinen et al. 2000; Lewis, 2000), while farming as an occupation is shown to be a risk factor of asthma, especially among grain farmers (Senthilselvan et al. 1993). Farmers are exposed to dominant allergens, such as storage mites and animal epithelia (Kronqvist et al. 1999), one of the main causes of occupational asthma (Karjalainen et al. 2000). Most farmers have lived on a farm in their childhood and those with allergic or respiratory symptoms have more likely chosen a profession other than farming. Increased asthma risk among farmers despite the protective effect of a childhood farm environment indicates that the underlying mechanism of adult onset asthma is heterogeneous.
2.4.3.3 Physical activity

Population-based studies on the association of asthma and average levels of physical activity are rare (Camargo et al. 1999; Beckett et al. 2001), as previous studies have mostly focused on athletes (Kujala et al. 1996; Helenius et al. 1997; Weiler et al. 1998). Top-ranking athletes have been shown to have higher asthma prevalences than the general population (Weiler et al. 1998), while former elite athletes show no increase in lifetime occurrence of asthma (Kujala et al. 1996). In two prospective studies of young adults (Beckett et al. 2001) and female nurses (Camargo et al. 1999), the degree of physical activity was not associated with an increased risk of asthma.

Low physical activity with consequent reduction in deep breathing may decrease the extent to which bronchial muscle is stretched, thus leading to airway narrowing (Platts-Mills et al. 1997; Shaheen et al. 1999). However, the effect of physical activity on onset of asthma is difficult to measure. Exercise-induced asthma symptoms may affect one’s physical activity. A substantial rate of untreated asthma, manifested in a higher rate of exercise-induced bronchospasm, was found among high school athletes (Kukafka et al. 1998). Low physical activity may also lead to underdiagnosis of asthma due to misinterpretation of asthma symptoms as caused by lack of physical fitness (Siersted et al. 1998).

Chen and co-workers examined energy expenditure in leisure-time activities among asthmatics and non-asthmatics (Chen et al. 2001). They found a heterogeneous association between asthma and energy expenditure across different age groups, younger asthmatics having increased and older asthmatic decreased energy expenditure compared with non-asthmatics (Chen et al. 2001). The clinical course of asthma varies between individuals and also within the same individual over time both spontaneously and depending on medication and treatment. Self-report of physician-diagnosed asthma was used by Chen et al. (2001), and thus, subjects defined as having asthma may differ significantly, from asymptomatic subjects to patients with severe symptoms. There seems to be a complex relation between exercise and respiratory symptoms, but evidence of causality between level of physical activity and asthma is lacking.
2.4.3.4 Obesity

Obesity has been increasing world-wide (Seidell and Rissanen, 1998). In Finland, 60% of men and 50% of women aged 30-59 years in 1972-1990 were overweight (body mass index (BMI) over 25 kg/m²) and close to 20% were obese (BMI >30 kg/m²) (Pietinen et al. 1996). Furthermore, during the 1980s and the 1990s in Finland, the average BMI has increased among both sexes as well as the proportion of obese (BMI > 30 kg/m²) people (Lahti-Koski, 2001). Health risks associated with obesity are shown to grow with an increasing degree of obesity (Bray, 1998). The high prevalence of asthma has been reported to be accompanied by an elevated prevalence of obesity.

Cross-sectional studies have demonstrated an association between obesity and prevalence of asthma (Young et al. 2001), more strongly among women than men (Chen et al. 1999; Shaheen et al. 1999). In a few prospective studies on the association between BMI and risk of adult onset asthma, obesity was related to development of asthma only among women (Beckett et al. 2001; Chen et al. 2002). The incidence of asthma was higher among women than among men in a Canadian study regardless of BMI (Chen et al. 2002). This is in accordance with other studies showing higher incidences of asthma among women than men (Anderson et al. 1992; Larsson, 1995; deMarco et al. 2000). In addition to the strong positive association between BMI and risk of adult onset asthma, women who gained weight since age 18 were revealed to be at increased risk of developing asthma in a large study of American nurses (Camargo et al. 1999).

A Chinese study of over 700 adults among families of subjects with asthma found an U-shaped curve of association between BMI and symptomatic airway hyperresponsiveness (Celedon et al. 2001). Moreover, in a follow-up study of 18 to 30-year-olds, in which subjects were divided to five equal-sized groups according to BMI, the ten-year asthma incidence was lowest in the second quintile and greatest in the highest quintile, showing a J-shaped pattern (Beckett et al. 2001). The underweight group of the study of Schachter and co-workers had more respiratory problems than those with normal weight (Schachter et al. 2001), corresponding to the J- and U-shaped associations between BMI and asthma found elsewhere (Beckett et al. 2001; Celedon et al. 2001). These studies suggest that the relation between BMI and asthma is complex and that no linear dose-response curve exists.
Whether the association between obesity and asthma is true is still debatable, as are the causality and mechanism of this association (Shaheen, 1999; Wilson and Irwin, 1999). In addition to mechanical effects of obesity on lung function, co-factors associated with obesity, such as physical activity, may explain the connection between obesity and asthma (Stenius-Aarniala et al. 2000; Tantisira and Weiss, 2001). However, the association of BMI increase with asthma incidence was independent of reported level of physical activity in a ten-year follow-up of young adults (Beckett et al. 2001) and physical activity itself was not associated with asthma risk (Camargo et al. 1999). Indirect mechanisms, such as diet (Weiss, 1997), gastroesophageal reflux (Wilson and Irwin, 1999) and immunological mechanisms (Varner, 2000), have also been suggested to explain the association between asthma and obesity. The relation between asthma and obesity may be more complex among women than among men because of hormonal factors, especially oestrogen. Postmenopausal hormone replacement therapy for instance is associated with increased asthma risk (Troisi et al. 1995b).

The prevalence of respiratory symptoms is shown to increase with increasing BMI (Lean et al. 1999), causing diagnostic problems. Schachter and co-workers found no increased prevalence of airway hyperresponsiveness or atopy among the obese group of their study despite raised wheezing and asthma medications, suggesting that the elevated rate of asthma diagnoses among obese people reflects an increase in symptoms rather than an increase in asthma (Schachter et al. 2001). Nevertheless, many other studies show a relation between obesity and asthma (Chen et al. 1999; Shaheen et al. 1999; Young et al. 2001; Beckett et al. 2001; Chen et al. 2002), and plausible mechanisms, including mechanical and genetic effects, immune modification and the effect of foetal circumstances, have been cited (Tantisira and Weiss, 2001).

2.4.3.5 Body height

Body height has been found to correlate with health, specifically with cardiovascular diseases (Silventoinen et al. 1999). An association between overall childhood living conditions and poor health has been suggested to explain at least part of the better health of taller people (Silventoinen et al. 1999), and this may be relevant for adult onset asthma as well.
Literature regarding on adult height and adult onset asthma is limited, with most studies focusing on the association between growth and childhood asthma. A relation between asthma and shorter height in childhood was found in a national study in England and Wales (Rona and du V Florey, 1980), and this relationship was independent of social and biological factors affecting height. In a Scottish study, children with asthma were of normal height, except for those with severe disease receiving high doses of inhaled steroids (McCowan et al. 1998). By contrast, Agertoft and co-workers have shown that children with asthma who have received long-term treatment with inhaled budesonide attained normal adult height (Agertoft and Pedersen, 2000). However, if asthma in childhood is sufficiently severe to affect adult height and then goes into remission for years, a relapse in adulthood may be considered as new asthma, leading to a conclusion of causality between height and adult onset asthma.

An alternative explanation, based on Barker’s hypothesis, associates certain diseases in later life with foetal and early infant growth (Barker, 1990; Barker, 1992). Birth length has been correlated with adult height (Ijzerman et al. 2001), but it is not clear whether this association is genetic or due to environmental factors (Pietiläinen et al. 2001). One previous epidemiological study found a positive association between birth length and risk of asthma in childhood (Leadbitter et al. 1999), while others found no relation (Fergusson et al. 1997; Hagstrom et al. 1998). Although growth retardation during pregnancy may affect the Th1/Th2 lymphocyte balance, thus predisposing to atopic diseases (Godfrey et al. 1994), the evidence is too weak to make conclusions about an association between birth length and later asthma.

2.4.4 Psychological factors

Quality of life in asthma patients seems to be impaired both in younger (Gibson et al. 1995) and in elderly people (Dyer et al. 1999). Thus, it is necessary to distinguish the consequences of asthma on patients’ psychological condition from the role of psychological factors in the genesis of asthma.

The relationship between asthma and psychological traits is complicated. Recent studies have not found a specific personality profile of asthmatic patients (Michel, 1994; Chetta et al. 1998). A population-based study which compared
asthmatic children and children with bronchial hyperreactivity to controls also found no remarkable psychosocial differences (Wjst et al. 1996). Janson and co-workers demonstrated an association between respiratory symptoms and psychological status, although asthma patients were not shown to have more anxiety or depression than those without an asthma diagnosis (Janson et al. 1994). However, a Finnish study did find more psychic disturbances among asthmatic patients than among controls; those with acute asthma were often neurotic and those with chronic asthma had depression (Salminen, 1985). Centanni and co-workers also found increased incidence of anxiety and depression among asthmatic patients when compared with patients with liver disease. Although these liver patients were asymptomatic, they had to live with the fears and restrictions of chronic disease (Centanni et al. 2000). Evidence also points to an association between atopic illness and depression (Wamboldt et al. 2000) and between asthma with positive skin prick tests and anxiety (Belloch et al. 1994).

In addition, psychic disorders seem to influence the course of asthma (Salminen, 1985). Psychological disturbances are more common among asthma patients with more severe disease (Chetta et al. 1998); among patients with near fatal asthma attacks, mental illness has been found to be common (Yellowlees and Ruffin, 1989; Campbell et al. 1995). Healthy subjects are also more likely to report respiratory symptoms if they have an abnormal psychological status (anxiety, depression, anger and cognitive disturbances) (Dales et al. 1989)

Previous studies have focused on the personality of asthmatic subjects and the effect of physical disturbances on the clinical course of asthma. Research on the effect of personality on asthma onset is lacking. Although many personality characters are relatively stable, chronic diseases probably change them. Prospective studies are therefore needed to determine the role of psychological factors in developing asthma.

Although the association between stress and asthma has been studied previously, a causal link has not been established (Busse et al. 1995; Wright et al. 1998). Some retrospective studies report an association between onset of asthma and stressful life events (Teiramaa, 1979; Levitan, 1985; Salminen, 1985), and a prospective study has shown an increased risk of asthma attacks among children who have recently experienced negative life events (Sandberg et al. 2000). A recent study among Finnish university students found more stressful life events during childhood, adolescence and early adulthood among subjects with asthma.
compared with non-asthmatics (Kilpeläinen et al. 2002). Both concomitant and subsequent events were associated with asthma, suggesting that the time between stressful events and onset of asthma is short and stress probably affects the manifestation of the disease (Kilpeläinen et al. 2002).
3 AIMS OF THE STUDY

The aims of the study were to:

1. estimate the prevalence and incidence of asthma among Finnish adults from 1975 to 1990
2. estimate the survival of adult patients with asthma
3. identify potential social and life-style risk factors for adult onset asthma
4. study the relation between adult asthma and personality, stress and life satisfaction
4 MATERIALS AND METHODS

4.1 The Finnish Twin Cohort Study

4.1.1 Compilation of the cohort

The Finnish Twin Cohort was initially compiled to study genetic and environmental determinants of chronic diseases and risk factors in the Finnish population (Kaprio et al. 1990). The data base from the Central Population Registry of Finland was used as the foundation of the study. All pairs of persons with the same date of birth, sex, surname at birth and locality of birth were identified from the registry. This selection procedure yielded the base population of the Finnish Twin Cohort, 17,357 twin pairs born before 1958 and alive in 1967. In addition, these selection criteria also captured a small number of unrelated individuals (Kaprio et al. 1978a; Kaprio et al. 1978b; Kaprio et al. 1979).

4.1.2 Questionnaires

A postal questionnaire was sent in autumn 1975 to pairs with both members alive in 1974 (Fig 1). Questionnaire comprised 97 questions on twinship, zygosity, height, weight, life-style, health behaviour, psychosocial factors, medical symptoms, and disease history. The medical questions included one that asked whether asthma had ever been diagnosed by a physician. A total of 31,133 persons responded (response rate 89%), of which 26,567 were twins and 4,217 were singletons. Detailed information on the questionnaire and the compilation has been presented elsewhere (Kaprio et al. 1978a; Kaprio et al. 1978b; Kaprio et al. 1979).

Follow-up questionnaires were posted to both members of each twin pair in 1981 and 1990 (Fig 1). The 1981 questionnaire was sent to all cohort members, not only to those who had responded to the 1975 baseline questionnaire (N=31,110).
For the 1990 questionnaire, members of the cohort born between 1930 and 1957 and living in Finland in 1987 were selected. And questionnaire was sent to those who had responded to the previous questionnaires (N=17,876 individuals, 8,938 pairs). The 1981 questionnaire was nearly identical to that of 1975, whereas the 1990 questionnaire consisted of 103 multiple choice questions. The question about asthma was identical in all three questionnaires. The response rates were 84% in 1981 and 77% in 1990.

4.1.3 Determination of zygosity

Zygosity was assessed in the 1975 study by responses to two questions about the similarity of appearance of co-twins at early school-age. Based on this question, 93% of the pairs could be classified as monozygotic (MZ) or dizygotic (DZ) pairs. The accuracy of zygosity testing by questionnaire was ascertained by testing 11 blood markers in a random subsample of 104 MZ and DZ pairs living
in Southern Finland (Sarna et al. 1978). Agreement between the blood tests and the questionnaire was 100%. The possibility of misclassified zygosity was estimated to be 1.7% (Sarna et al. 1978).

4.2 Registers

4.2.1 Register of the Social Insurance Institution

In Finland, all residents are covered by National Sickness Insurance (NSI). Since 1970 NSI has covered 75-100% of the costs of drug treatment for chronic bronchial asthma (including corticosteroids, corticotrophins, cromoglycate, sympathomimetics, theophyllin and its derivatives, hydroxyzine, ipratropium, oxytropium, nedocromil and some combinations). Patients eligible for this benefit have been registered by the Social Insurance Institution (SII). A prerequisite for being registered is an accurate diagnosis of asthma, as given in a special certificate signed by a specialist in allergy, pulmonary diseases, internal medicine or paediatrics, or based on a appropriate hospital examination. This certificate is reviewed and must be accepted by a consultant physician of the Social Insurance Institution (Vesterinen et al. 1993).

4.2.2 The Finnish Hospital Discharge Register

The National Research and Development Centre for Welfare and Health maintains a register of all patients discharged from the hospital in Finland since 1969, including their diagnoses. In hospitals, medical records are abstracted for the Finnish Hospital Discharge Register according to the guidelines issued by the National Research and Development Centre for Welfare and Health, using a standardized sheet (Keskimäki and Aro, 1991). It is possible to extract all treatment periods for which the main diagnosis is asthma, including acute exacerbation stages, diagnostic examinations, and check-up visits (Keistinen et al. 1993).
4.2.3 Other registers

The Finnish Cancer Registry contains information about all cancer cases diagnosed in Finland since 1953. The Finnish Death Register contains data on deaths, including date of death and causes of death. Statistics Finland, which maintains information on current addresses, deaths and emigration, was used to update persons’ vital status.

4.3 Study variables and definitions

4.3.1 Asthma

Definition of asthma was based on different sources for the purposes of each original study. For the mortality study (II) asthma was used as an exposure and defined based on the answer to the 1975 study question: "Have you ever been told by a doctor that you have or have had asthma?"

For the other studies, asthma was the outcome variable. Depending on whether the outcome of interest was prevalence or incidence, different questionnaire constructions were used. The asthma definition based on the reimbursed asthma medication registered by the Social Insurance Institution (hereafter called medicated asthma) was used for the discordant pair study (III). Asthma diagnoses defined by the Finnish Hospital Discharge Register, in addition to questionnaire answers and data from the Social Insurance Institution, were used mainly in exclusions of asthma cases at baseline, when needed (III,V).

4.3.2 Allergic and respiratory symptoms

Each questionnaire asked whether allergic rhinitis (including hay fever), allergic eczema, urticaria (only in 1975 questionnaire), prolonged bronchitis (called also chronic bronchitis) or emphysema had ever been diagnosed by a physician. The question was similar to that of asthma and was identical in all three questionnaires. Symptoms of chronic bronchitis and dyspnoea were assessed by
a mailed questionnaire adaptation of the London School of Hygiene respiratory questionnaire (Rose and Blackburn, 1968). Symptoms of chronic bronchitis were based on cough and phlegm production, and dyspnoea on the subjects report of whether they get short of breath during different physical activities.

Atopy was defined as the presence or absence of allergic rhinitis and allergic eczema (V) and urticaria (III), and a respiratory index as the presence or absence of emphysema, prolonged bronchitis, symptoms of chronic bronchitis or dyspnoea (IV, V). Allergic rhinitis (I,II,IV), prolonged bronchitis (I,II) and symptoms of chronic bronchitis and dyspnoea (II) were also used as such.

4.3.3 Social and life-style factors

Smoking habits were classified with respect to cigarette smoking: non-smokers (had never smoked more than ten packs of cigarettes in their lifetime), occasional smokers (had never smoked on a daily or almost daily basis), former smokers (had stopped smoking) and current smokers (regular (daily) smokers) (II). In studies III and V, occasional smokers were included in non-smokers and a three-category classification (reporting never smoking in 1975 and 1981, reporting current smoking in 1975 and 1981 and changing reports) was used in study IV as a confounding variable. The number of daily smoked cigarettes was asked of regular smokers, separately for former and current smokers.

The classification of social class was based on occupation using the 1970 Finnish census classification (Central Statistical Office of Finland, 1974). Six categories were used: 1. upper-level professionals, 2. lower-level professionals, 3. skilled workers, 4. unskilled workers, 5. farmers, 6. unclassified (students, conscripts, housewives, etc.) (II) or both professional groups were combined as well as both groups of workers (III). Physical activity at work was assessed by a question about one’s present work. Education was measured by enquiring what schooling the respondent had completed (nine alternatives) (Koskenvuo et al. 1979) and was divided into 1. lower (at most primary school and possibly some vocational training) and 2. higher (at least junior high school) (III, V). In study IV, social class was defined by years of education and physical activity at work and classified into the following three categories: 1. upper class, 2. middle class and 3. lower class. Upper class consisted of those with at least a high school diploma.
(12-13 years) and sedentary work, the lower class of those with primary school (6-7 years) or less education and work involving at least standing and walking, and the middle class of the remaining subjects.

Respondent’s physical activity at leisure time was assessed by using a series of questions about frequency, duration and intensity of leisure-time physical activity as well as a subjective estimate of physical activity (Kujala et al. 1998). Different combinations of question were used to define the respondent as 1. sedentary, including respondents estimating their leisure-time physical activity as practically non-existent, 2. conditioning exercisers, including those participating in exercise at least six times a month for a mean duration of at least 30 minutes with a mean intensity corresponding to alternate walking and jogging or 3. occasional exercisers, including the remainder. In study III, sedentary and occasional exercisers were combined into one group.

With regard to domestic animals and pets, it was asked what animals, if any, were included in the household (II, III).

Body mass index (BMI, weight (kg) by height (m) squared) was used as a measure of relative body weight. Subjects were defined as 1. underweight (BMI<20), 2. normal weight (20 BMI<25), 3. overweight (25 BMI<30) and 4. obese (BMI 30). Absolute weight in kilograms was used to measure weight change. Height was recorded in centimetres, and when necessary, rounded off to the nearest integral number (V).

4.3.4 Psychological factors

The experienced stress was measured using the Reeder Stress Inventory (Reeder et al. 1968) including four items of self-report of stress in daily activities with four response alternatives. The items were the following:
1. In general, I am unusually tense and nervous.
2. There is a great deal of stress connected with my daily activities.
3. At the end of day, I am mentally and physically completely exhausted.
4. My daily activities are extremely trying and stressful.

The response alternatives (very well, well, not very well, not at all) were scored 1-4, with a sum score ranging from 4 to 16 (increasing score indicates decreasing
stress). This scale was divided into three groups: 1. little stress (16 points), 2. some stress (9-15 points) and 3. high levels of stress (4-8 points). In addition, score was used as a continuous variable. The face validity of this kind of measure of stress is supported by previous studies of the Finnish Twin Cohort, in which mental disorders (Kaprio et al. 1987), long-term weight gain (Korkeila et al. 1998) and peptic ulcers (Räihä et al. 1998), but not breast cancer (Lillberg et al. 2001) are predicted.

Life satisfaction was measured according to Allardt’s four-item scale on levels of interest, happiness, easiness and loneliness of life (Allardt, 1976). The item responses were scored on a scale of 1-5 in terms of intensity (e.g., 1=very interesting, 2=fairly interesting, 3=cannot say, 4=fairly boring, 5=very boring). The life satisfaction score was calculated as the overall sum of the four items (possible range 4-20, increasing score indicates decreasing life satisfaction). If the response was missing for at least three items, the total score was regarded as “missing data”, otherwise missing data for one or two items were each scored as a three. This scale was divided into three groups: 1. satisfied (4-6 points), 2. slightly dissatisfied (7-11 points) and 3. very dissatisfied (12-20 points). In addition, score was used as a continuous variable. This scale has been shown to predict mortality in the Finnish twin cohort (Koivumaa-Honkanen et al. 2000).

Extroversion and neuroticism were measured using the abbreviated Eysenck Personality Inventory (EPI) (Floderus, 1974) including nine items for the assessment of extroversion and nine items for neuroticism. The subjects were asked to mark the items in a “yes/no” format in terms how well they described one’s acts and feelings. The extroversion and neuroticism scores were then calculated as the overall sum of nine items (possible range 0-9) and the scales were divided into three groups: 1. low (0-2 points), 2. medium (3-6 points) and 3. high (7-9 points) levels of extroversion or neuroticism. In addition, scores were used as continuous variables. Extroversion and neuroticism are regarded as stable characteristics of personality and its central dimensions (Bouchard, 1993; Viken et al. 1994; Bouchard and Loehlin, 2001).
4.4 Study design

The study population consists of the responders of the Finnish Twin Cohort (Fig 1). Different sample constructions have been used according to the purposes of each original study. Study populations of original articles are shown in Table 3. Cohort study design is used in studies I, II, IV and V and co-twin case-control study design among discordant twin pairs in studies I, II and III.

4.5 Statistical methods

4.5.1 Prevalence and incidence

Prevalence refers to cases of a disease that exist at a specified time, and incidence to the number of new cases developing during some specified time interval. Thus, prevalence is a function of incidence and duration of the disease. Cumulative incidence provides an estimate of the probability, or risk, that an individual will develop a disease during a specified period of time.

Prevalences of asthma and allergic rhinitis in 1975, 1981 and 1990 were calculated for subjects with data available on the respective diseases in each questionnaire. The European standard population was used to calculate age-standardized prevalences by five-year age groups. Cumulative incidences of asthma, allergic rhinitis and chronic bronchitis during 1976-1990 and 1976-1981 were calculated for subjects free of the respective diseases in 1975. Age trend analyses were based on three birth-decade groups. In addition, cumulative incidence of asthma was calculated for subjects with and without history of allergic rhinitis or chronic bronchitis before follow-up.

To compare different sources of asthma diagnosis, cumulative asthma incidence in 1982-1990 was calculated based on questionnaire responses, data on reimbursed asthma medication and hospital treatment. Exclusion of asthma cases at baseline was based on both questionnaire and register information of asthma.
Table 3. Study populations of original publications.

<table>
<thead>
<tr>
<th>Study</th>
<th>Base population</th>
<th>Age at beginning of follow-up (years)</th>
<th>Exclusion criteria of asthma cases at baseline</th>
<th>Follow-up time</th>
<th>Subsets</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Incidence study</td>
<td>Subjects responding to all three questionnaires</td>
<td>19 - 46</td>
<td>Questionnaire responses</td>
<td>1976-90</td>
<td>Twin pairs discordant for incident asthma in the 1981 or 1990 questionnaire or in both 161 pairs</td>
</tr>
<tr>
<td></td>
<td>N=11 540</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II Mortality study</td>
<td>Responders to the baseline questionnaire in 1975</td>
<td>19 -</td>
<td></td>
<td>1976-91</td>
<td>Twin pairs discordant for asthma based in 1975 questionnaire 293 pairs</td>
</tr>
<tr>
<td></td>
<td>N=31 110</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III Discordant pair study</td>
<td>Twin pairs discordant for asthma based on SII-register data among responders to 1975 questionnaire</td>
<td>20 - 50</td>
<td>Questionnaire responses, SII-register data and hospital discharge register data</td>
<td>1977-93</td>
<td></td>
</tr>
<tr>
<td></td>
<td>262 pairs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV Psychological study</td>
<td>Subjects responding to all three questionnaires</td>
<td>25 - 52</td>
<td>Questionnaire responses</td>
<td>1982-90</td>
<td>Subjects free of symptoms of COPD</td>
</tr>
<tr>
<td>-prevalence study</td>
<td>N=11 540</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-incidence study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V Life-style-study</td>
<td>Subjects responding to all three questionnaires</td>
<td>25 - 52</td>
<td>Questionnaire responses, SII-register data and hospital discharge register data</td>
<td>1982-90</td>
<td>Subjects free of symptoms of COPD</td>
</tr>
<tr>
<td></td>
<td>N=11 540</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Incidences of asthma, allergic rhinitis and chronic bronchitis were calculated separately for two periods (1976-1981 and 1982-1990) to estimate possible changes in incidences over time. Person-years were calculated by multiplying the number of subjects at risk by years (6 or 9) followed. The European standard population was used to calculate age–standardized incidences by five-year age groups.

4.5.2 Mortality

Crude death rates were calculated by sex for both exposed (asthmatic) and unexposed (non-asthmatics) cohorts. A proportional hazards regression model was used to compare mortality rates among asthmatic and non-asthmatic persons. Analyses were controlled for smoking, social class, domestic animals, allergic trinities, chronic bronchitis and dyspnoea and stratified into 10-year age groups.

4.5.3 Logistic regression

Odds ratios (OR) with 95% confidence interval (95% CI) obtained by logistic regression were calculated to assess the effect of chosen determinants (symptomatic, social and life-style, and psychological variables) on adult onset asthma. Logistic regression was also used to assess the relation between psychological variables and prevalent asthma. Wald’s $X^2$-test was used to calculate whether any significant trend was present in the odds ratios for selected variables across categories. Each category with an assigned rank (1,2,...) was entered into the logistic regression model as a continuous variable and the significance level of the Wald statistic was used to assess significance of trend.

4.5.4 Effect of twin pair relationship

Because the study population included twin pairs with both twins of a pair included, individual observations may not be regarded as totally independent.
The number of independent observations is smaller than the total number of observations, and thus, the confidence limits may be too narrow when twins are positively correlated. Positive correlation of adult onset asthma between twin pairs is not very strong and mortality correlates only slightly. To account for the possible lack of independence, methods used in the analysis of complex survey data can be applied. In some analyses, the models controlled for twin pair structure by specifying that twins were clustered as twin pairs in the computation of confidence intervals, but the regression model standard errors were virtually unchanged compared with models not taking the twin pair relationship into account. In the mortality analyses, confidence intervals were corrected, excluding those twins whose co-twin was already included. This conservative method overcorrects for twinship as twins in a pair are neither fully concordant for asthma nor mortality.

4.5.5 Case-control analyses

Co-twins represent persons who have generally shared the same childhood environment and have part or all of their genes in common by descent. With case-control study design among twin pairs discordant for a disease, it is possible to examine whether the risk of the disease in relation to chosen determinants is different between age-matched siblings (co-twins) with and without that determinant. An estimate of relative risk is calculated from the ratio of the number of pairs in which the exposed twin, but not the unexposed co-twin, had suffered the outcome of interest to the number of pairs in which the opposite had occurred. Differences in determinants among affected and unaffected co-twins are assessed by McNemar’s two-sided test (dichotomous variables) and by Bowker’s test of symmetry (multicategorical variables). Risk ratios and their confidence limits are calculated by conditional logistic regression for 1-1 matched data (Duffy, 2000).

4.6 Statistical software

Analyses were done with SAS Release 6.03 and 6.12 (SAS Institute Inc., Cary, NC, USA) and STATA (StataCorp. 2001, Stata Statistical software: release 7.0.
College Station, TX: Stata Corporation). Confidence intervals were calculated by CIA (Confidence Interval Analysis; M.J. Gardner and British Medical Journal; London, UK). Incidence rate ratios (IRRs) were computed using the Rate Analysis Program.
5 RESULTS

5.1 Consistency and correspondence of asthma reports

The three questionnaires permitted assessment of stability of response to the asthma question (Fig 2). Altogether 77% of men and 90% of women reporting asthma in both previous questionnaires also reported asthma in the 1990 questionnaire. Among subjects reporting asthma in 1981, but not in 1975, the corresponding proportions were 62% and 58% (I). Partial overlap existed between register and questionnaire information. Asthma was reported the first time in the 1990 questionnaire by 73% (43/59) of men and 80% (57/71) of women with a register-based diagnosis during 1982-1990. In addition, 42% (31/74) of men and 39% (36/93) of women reporting asthma in the questionnaire did not have a register-based record (V, Fig. 3).

Figure 2. Stability of asthma diagnoses in questionnaires
5.2 Incidence and prevalence of adult onset asthma

The prevalence of asthma remained steady during 1975-1981, and a slight increase was seen in 1990 (I, Fig. 4). The pattern of increase in allergic rhinitis prevalence was similar, although the increase was larger (I, Fig. 4).

Cumulative incidence of asthma was similar among men (2.3%) and women (2.6%) from 1975 to 1990 (I). Asthma incidence increased with increasing age and age-trend analyses based on three birth decades (1950-1957, 1940-1949 and 1930-1939) showed significant age dependence both among men (p=0.0001) and women (p=0.0003) during 1975-1990 (I). In contrast, allergic rhinitis was more common among women (cumulative incidence 13.6%) than among men (9.4%) (Incidence rate ratio (IRR) 1.4; 95% CI 1.3-1.6), and no age dependence was seen (I). Asthma incidence showed only a non-significant increase when incidence during 1982-1990 was compared with figures for 1975-1981 (IRR 1.5; 95% CI 0.9-2.4 for men and IRR 1.2; 95% CI 0.8-1.8 for women) (I). Allergic rhinitis incidence was significantly lower during the later period among men (IRR 0.7; 95% CI 0.6-0.9), while no change was seen among women (I).
5.3 Mortality

Mortality from all natural causes was higher among asthmatic adults (Hazard ratios adjusted for age and smoking were 1.52; 95%CI 1.09-2.12 for men and 1.58; 1.12-2.21 for women) (II, Fig. 5). After also adjusting for chronic bronchitis, dyspnea and allergic rhinitis, mortality was no longer increased in asthmatic men (adj. HR 0.97; 0.66-1.43) and among women the increase became non-significant (adj. HR 1.38; 0.94-2.01) (II, Fig. 5). An excess of deaths due to COPD was seen in both sexes, explaining part of the increased mortality of asthmatics. The risk of death due to lung cancer was almost three-fold among asthmatic compared with non-asthmatic men. This increased risk was also seen after adjusting for age, smoking, social class and pets (adj. HR 2.81; 1.16-6.78) (II). The results of discordant pair analyses were consistent with results for the whole cohort. The overall relative risk for death during follow-up was 1.64 (95% CI 0.97-2.81) for an asthmatic twin compared with the non-asthmatic twin sibling, and the relative risk of death due to lung cancer was 1.8 (0.54-6.84) (II).
5.4 Predictors of adult onset asthma

5.4.1 Atopy and respiratory symptoms

Atopy, as well as allergic rhinitis alone, was a strong predictor of asthma. Depending on the definition, the risk of adult onset asthma was three- to six-fold among women with previous reports of atopic diseases. Among men, the risks were somewhat lower but remained significant. Within twin pairs discordant for questionnaire-based incident asthma, twins with a history of allergic rhinitis had significantly increased risk of asthma compared with their twin siblings without previous allergic rhinitis (RR 3.2; 95% CI 1.5-7.7). The risk of medicated asthma was also higher for twin with previous atopy compared with the twin sibling without atopy (RR 2.91; 95% CI 1.81-4.68).

The respiratory index predisposed adult onset asthma significantly (OR:s 2.01; 95% CI 1.23-3.29 for men and 3.07; 1.81-5.19 for women). However, respiratory symptoms cannot be considered as pure predictors of asthma but merely as symptoms of asthma.
5.4.2 Social and life-style factors

Higher education and conditioning physical activity were associated slightly, although non-significantly, with lower questionnaire-based asthma incidence (V, Table 4). However, among twins discordant for medicated asthma, twins with more education had a significantly lower asthma risk compared with their twin sibling with less education (RR 0.45; 95% CI 0.23-0.86) (III, Table 4), as did those participating in conditioning exercise compared with their more sedentary counterparts (RR 0.55; 95% CI 0.34-0.88) (III, Table 4). Smoking was not associated with adult onset asthma (Table 4).

Obese men had a significantly higher risk of asthma compared with those of normal weight (age-adjusted OR 3.95; 95% CI 1.79-8.73, after adjusting for age, smoking, education, physical activity and height OR 3.47 95% CI 1.56-7.72 and after adjusting for age, atopy and respiratory symptoms OR 3.13; 95% CI 1.41-6.97) (V, Fig. 6).

Table 4. Education, physical activity and smoking with respect to risk of adult onset asthma in different study designs.

<table>
<thead>
<tr>
<th></th>
<th>Questionnaire-based asthma among men and women</th>
<th>Twin pairs discordant for medicated asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N=9671</td>
<td>N=262 pairs</td>
</tr>
<tr>
<td>Education</td>
<td>OR (95% CI)(^1)</td>
<td>RR (95% CI)(^2)</td>
</tr>
<tr>
<td>- upper vs. lower</td>
<td>0.78 (0.53-1.15)</td>
<td>0.45 (0.23-0.86)*</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- occasional vs. sedentary</td>
<td>1.23 (0.71-2.16)</td>
<td>Conditioning vs. others</td>
</tr>
<tr>
<td>- conditioning vs. sedentary</td>
<td>0.87 (0.45-1.67)</td>
<td>0.55 (0.34-0.88)*</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ex-smokers vs. non-smokers</td>
<td>0.91 (0.58-1.42)</td>
<td>0.58 (0.31-1.06)</td>
</tr>
<tr>
<td>- current vs. non-smokers</td>
<td>1.15 (0.77-1.71)</td>
<td>0.88 (0.51-1.51)</td>
</tr>
</tbody>
</table>

1 adjusted for age, sex, height, weight and other factors in table
2 univariate analysis, adjusting for atopy or for other social factors did not change risk ratios
* Statistically significant
Figure 6. Effect of weight and height on the risk of adult onset asthma among men (A, B) and among women (C, D) adjusted for atopy and respiratory symptoms. Subjects were divided into weight categories by BMI (underweight BMI<20, normal weight 20≤BMI<25, overweight 25≤BMI<30 and obese BMI≥30) and into height quartiles separately for men and women.
There was also a significant trend for higher risk of asthma across four increasing weight groups among men \((p=0.024\) when adjusted for atopy and respiratory symptoms). The association between asthma and weight was different among women, with underweight women also having a higher asthma risk than women with normal weight \((V, \text{Fig. 6})\). Higher height was associated with lower asthma incidence among men \((p=0.03\) for trend over quartiles of height) \((V, \text{Fig. 6})\).

### 5.4.3 Psychological factors

Women with a high level of extroversion had an increased risk of incident asthma compared with women with a low extroversion level \((\text{OR } 2.69; 95\% \text{ CI } 1.42-5.12, \text{ adjusted for age, allergic rhinitis, and respiratory symptoms and diseases})\) \((IV, \text{Fig. 7})\). This effect of extroversion on new asthma was also seen when extroversion score was used as a continuous variable \((\text{age–adjusted OR } 1.14; 95\% \text{ CI } 1.04-1.24)\) \((IV)\). Among men, extroversion was not a significant predictor of asthma. In contrast, neuroticism was associated with incident asthma among men but not women. The risk of asthma was nearly two-fold \((\text{OR } 1.96; 95\% \text{ CI } 0.95-4.04)\) in men with a high level of neuroticism compared with their low-level counterparts, but this effect almost disappeared when adjusted for respiratory symptoms and allergic rhinitis \((\text{adj. OR } 1.36; 95\% \text{ CI } 0.64-2.87)\) \((IV, \text{Fig. 7})\). The effect of stress was similar to that of neuroticism \((IV, \text{Fig. 7})\) and life satisfaction did not predict asthma.

Prevalent asthma was associated with neuroticism \((\text{age- and sex-adjusted OR } 1.78; 95\% \text{ CI } 1.12-2.84 \text{ for those with a high level of neuroticism as compared with those with a low level})\) \((IV)\). Furthermore, low life satisfaction was associated with a higher asthma prevalence \((\text{age- and sex-adjusted OR } 1.85; 95\% \text{ CI } 1.07-3.18 \text{ for those most dissatisfied compared with those most satisfied})\) \((IV)\). Smoking habits and social class explained practically none of these associations, and adjusting for respiratory symptoms and allergic rhinitis weakened these associations \((IV)\).
Figure 7. Stress, neuroticism and extroversion as predictors of adult onset asthma separately among men and women.
6 DISCUSSION

6.1 Study population and methods

The study population comprises a nation-wide cohort of Finnish adult same-gender twin pairs, unselected except for twinship. Because the baseline and follow-up questionnaires covered multiple aspects of health, social situation and personality, overreporting of asthma is unlikely. The high response rates at baseline and follow-up make this study population representative. The advantage of using questionnaire-based diagnoses lies in the consistency of follow-up information provided by the identical questions posed in each questionnaire. Finns tend to be quite aware of what diseases they have, when their knowledge is compared with medical records (Haapanen et al. 1997). In this study, asthma was defined by self-report of doctor-diagnosed asthma and in some cases by register data on asthma medication and hospital treatment. The question on doctor-diagnosed asthma has been shown to be valid for the purposes of epidemiological studies (Torén et al. 1993; Kilpeläinen et al. 2001). Diagnosis- or treatment-based definitions may underestimate the occurrence of asthma compared with definitions based on symptoms. However, if the misclassification is non-differential, these underestimated occurrences tend to underestimate the real associations between the disease and potential risk factors (Torén et al. 1993).

The strength of using register data is that the diagnoses are independent of questionnaire responses; however milder cases are excluded. While consistent criteria exist on the basis for reimbursed asthma medication, social and administrative factors may affect these diagnoses. It is possible that some patients diagnosed as having asthma, especially according to the registry of reimbursement of asthma medicine costs, actually have COPD. According to the criteria of the Social Insurance Institution, these patients also benefitted from asthma medication, and thus, they probably had an asthmatic component in their disease.

The advantage of twin study design is that it allows comparison of twin pairs who are fully age-matched, have generally shared the same childhood environment and have part or all of their genes in common by descent. Whether twin studies are generalizable depends on the variable studied. Prenatal
circumstances and common childhood environment are the main differences between twins and singletons (de Geus et al. 2001; Phillips et al. 2001). We found no significant difference in rates of questionnaire-based asthma between twins and singletons aged 30-59 years among Finnish Twin Cohort (Huovinen and Kaprio, 2001). Moreover, studies among children and young adults from Finland (Räisänen et al. 1997), Denmark (Skadhauge et al. 1999) and Norway (Harris et al. 1997) report asthma rates corresponding to those found in the general population. On the other hand, there is evidence of reduced risk of wheezing and asthma among twins (Michie et al. 1996). In a study of Swedish conscripts, multiple gestation reduced the prevalence of asthma (Bråbäck and Hedberg, 1998), and a record linkage study from Scotland reported reduced risk of hospital admission for childhood asthma among twins (Strachan et al. 2000). More comparative studies are needed to determine differences between twins and singletons in allergic diseases. However, twins, with respect to adult onset asthma, may be regarded as representative of the general population.

6.2 Results

6.2.1 Incidence and prevalence

The prevalences of asthma in the present study are consistent with previous studies from the same time period (Haahtela and Jokela, 1979; Luoma and Koivikko, 1982; Kujala et al. 1996). Earlier studies show somewhat lower and recent studies higher prevalences. This study detected only a slight increase in asthma prevalences during the follow-up period, whereas a study among Finnish conscripts showed as much as a six-fold rise during 1966-1989 (Haahtela et al. 1990). The age distributions were different in these studies, with Haahtela and co-workers focusing on young men (Haahtela et al. 1990) and the prevalence calculations of the present study including only adults 30 years of age or older. Changes have also occurred in call-up examination practice during follow-up in Haahtela et al. (1990) and at least part of the elevated prevalence is probably caused by different attitudes towards diagnosing asthma and towards asthma itself. A diagnostic shift from COPD to asthma may explain part of the increase in asthma prevalence. The preference towards asthma diagnosis may be partly due to the medication reimbursement policy of the Social Insurance Institution of
Finland, which better subsidizes the costs of asthma medication than those of chronic bronchitis. An American study found increasing trends of asthma prevalences to parallel increases in the broader category of chronic obstructive airway diseases (Vollmer et al. 1998). A Danish study among young adults found no time trend in smoking habits or in mucus production prevalences of asthmatic patients, suggesting that misclassification may not be increasing (Hansen et al. 2000).

Sunyer and co-workers have recently reported a retrospective assessment of the incidence rates of asthma in Europe by using the ECRHS dataset (Sunyer et al. 1999). They found a higher incidence of asthma in the younger cohorts. In the present study, by contrast, cumulative incidence of asthma as well as asthma prevalences increased with age. The age ranges and the definition of asthma were different in these studies. Although a limitation of the present study is a lack of the exact time of asthma diagnosis, we also found age to be a strong risk factor for adult onset asthma in studies focusing on possible predictors of adult asthma.

While evidence exists for an increase in occurrence of asthma during the last decades, most of this increase is probably due to higher asthma prevalences in children, with the prevalence of adult onset asthma remaining relatively stable.

### 6.2.2 Mortality

The increase found in overall mortality of asthmatic adults was similar to previous studies of general adult populations (Markowe et al. 1987; Lange et al. 1996). Smoking explained practically none of the excess mortality of asthmatics. Lange and co-workers found also the survival of asthmatics to be similar within different smoking groups (Lange et al. 1996). However, we found no decrease in the survival of asthmatic men and the decrease was non-significant in women, when adjusted for allergic and respiratory symptoms, including chronic bronchitis. Misclassification of chronic bronchitis as asthma is possible, and these diseases may also occur concurrently. Exclusion of subjects with both asthma and chronic bronchitis or emphysema from a UK study changed the results of overall mortality only slightly (Markowe et al. 1987). In contrast, an American study excluding subjects aged over 50 years and those with reduced forced expiratory volyme (FEV) or dyspnoea with exercise found no effect of
asthma on overall mortality (Silverstein et al. 1994). These respiratory symptoms also provide information on the severity and nature of asthma, and exclusion of subjects with these symptoms may cause selection of only patients with mild asthma.

Asthma is associated with a slightly elevated mortality, mainly caused by respiratory diseases. This increased mortality risk is mostly mediated through lung function, and thus, patients with a permanent reduction in lung function in particular are at risk.

6.2.3 Risk factors

6.2.3.1 Atopy and respiratory symptoms

In other studies, as in the present study, prevalence of allergic rhinitis has increased alongside asthma during the last decades (Åberg, 1989; Hopper et al. 1995; Upton et al. 2000). Allergic rhinitis is commonly used as a marker of atopy in epidemiological studies. In this study, allergic rhinitis alone as well as in combination with allergic rhinitis and allergic eczema was a strong risk factor for asthma, in concordance with previous studies (Anderson et al. 1992; Upton et al. 2000).

Cough and phlegm production is used as a diagnostic symptom of chronic bronchitis (Rose and Blackburn, 1968), while severe dyspnoea may be a symptom of asthma as well. Prolonged bronchitis is a non-specific diagnosis, and in addition to chronic bronchitis, may also be a pre-existing symptom of asthma. The respiratory index, which includes prolonged cough, cough and sputum production, dyspnoea and diagnosis of chronic bronchitis or emphysema, used in the present study is a broad combination of both common and specific symptoms and diseases. Thus, the strong predictive value of this index for asthma mostly reveals the wide variation of pre-existing symptoms of adult onset asthma. Overall, the effect of respiratory symptoms on adult asthma is difficult to estimate, especially in follow-up studies, because in the large variability of these symptoms over time.
6.2.3.2 Social factors and life-style

Smoking was not consistently associated with asthma. However, among female twin pairs discordant for asthma, the amount of smoked cigarettes was significantly associated with increased asthma risk. Previous studies have indicated that women are more vulnerable to respiratory effects of smoking (Langhammer et al. 2000). In the present study, changes in smoking habits were not measured during follow-up, which can affect the risk estimates during a long follow-up. Moreover, those susceptible to smoking-induced asthma may have become ill earlier, and thus, no longer smoked as adults. Passive smoking during childhood also has an effect (Räsänen et al. 2000). An association of asthma risk and the amount of smoked cigarettes was seen in the present study among discordant twin pairs, who can be assumed to have been exposed to approximately the same amount of environmental cigarette smoke during childhood. The finding that former smokers did not have a higher asthma risk supports the importance of giving up smoking. The role of smoking in the onset of asthma in adulthood is still unclear (Vesterinen et al. 1988; Bodner et al. 1998; deMarco et al. 2000), and thus, smoking cannot be considered to be an independent risk factor of adult onset asthma.

Social class was measured by level of education. Income and social class based on occupation have also been used previously as indicators of socio-economic status. Occupation reveals information about one’s working conditions and possible working-related exposures, while educational level probably describes one’s life-style. Educational levels have changed during recent decades, especially among women. Education used in the present study was measured in 1975 and 1980, and thus, differences between various birth cohorts may be significant. Among women, socio-economic status has also been more dependent on husbands’ social class (Liberatos et al. 1988). In a Finnish study on cardiovascular risk factors, family income provided more information on the socio-economic status of women than of men (Luoto et al. 1994). Bakke and co-workers used the type of school completed instead of years of school as a measure of educational level and divided subjects into three classes: primary, secondary and university-educated (Bakke et al. 1995). They found a low educational level to be a risk factor for obstructive lung diseases, but no difference in asthma prevalences was present (Bakke et al. 1995). In the present study, years of education was used and only two categories were defined, and thus, the difference in education may be only marginal and have little effect on
social class. When the questionnaire-based asthma definition was used, asthma risk decreased only marginally with increasing education, while in discordant twin pair analyses in which reimbursed asthma medication was used, the effect of education was significant. Studies with more exact indicators of social class are therefore needed to clarify the association between socio-economic status and asthma and the factors affecting that relationship.

Corresponding to results of previous studies (Camargo et al. 1999; Beckett et al. 2001), asthma as defined by questionnaires was not associated with exercise. Furthermore, a protective effect of leisure-time physical activity was found only among twin pairs discordant for reimbursed asthma medication. Pre-existing symptoms of asthma may restrict physical activity and in this way affect results. Underdiagnosed exercise-induced asthma may also affect one’s leisure-time physical activity. Although there is evidence of an association between physical activity and asthma, causality has not been established.

Results concerning social and life-style factors obtained from discordant pair analyses differ somewhat from the results of the entire cohort. Although results are mostly parallel, discordant pair analyses indicate stronger associations. Co-twins share part or all of their genes, have generally shared a childhood environment and are fully age-matched. Another difference between these analyses is the definition of asthma, which is based on reimbursed asthma medication in the discordant pair study and on questionnaire responses for the whole cohort. The severity of asthma cases may therefore vary between these analyses. On the other hand, register based diagnoses may be more accurate. Further, questionnaire responses, although based on physicians’ diagnosis, are more or less subjective and not confirmed by medically trained person. In addition, a possible gene-environment interaction modifying the risk effect of social factors on asthma may affect results differently among the entire cohort and within a twin pair.

In contrast to previous findings associating obesity with increased asthma risk only among women (Beckett et al. 2001; Chen et al. 2002), men with BMI 30 had a significantly increased asthma risk compared to those with normal weight (BMI 20-25). Among women, no significant differences in asthma risk were found between BMI groups. However, the risk of asthma was lowest in women of normal weight and both under- and overweight women had slightly increased risks. This different effect of weight on asthma in men and women may be partly due to gender difference in the distribution of BMI. More men were obese than
women, while only 5% of men had BMI lower than 20, compared to 23% among women. Underweight persons have also been shown to have respiratory problems in previous studies (Beckett et al. 2001; Celedon et al. 2001; Schachter et al. 2001), suggesting that the relation between weight and asthma is not clear-cut. However, evidence for increased risk of asthma among obese people is quite strong.

Although the heritability of body height is high, environmental factors also have an effect on final height (Silventoinen et al. 2000). Adult height is also related to birth length (Ijzerman et al. 2001; Pietiläinen et al. 2001). When studying the association between body height and adult onset asthma, the effect of childhood living conditions and diseases, especially respiratory symptoms, should be taken into account. In the present study, a significant trend towards lower risk of asthma with increasing height was found among men, while in women, no such trend was evident. Recall bias may also affect results. Those who have had asthma during childhood but have been asymptomatic for years may report asthma as new onset disease in adulthood. However, evidence of growth retardation due to childhood asthma is inconsistent, and therefore, recall bias cannot explain this association wholly. Intrauterine circumstances may also affect adult health (Barker, 1990; Barker, 1992). Thus, devoting more time to studying the underlying mechanisms of the association between adult height and asthma is important. Variations in lung size and airways may be one explanation for the effect of height on adult onset asthma.

6.2.3.3 Psychological factors

Psychological characteristics and personality of asthma patients have been studied previously among small samples of patients of chest clinics, therefore focusing on more severe cases of asthma (Yellowlees et al. 1988; Chetta et al. 1998; Centanni et al. 2000). Population-based studies including also milder cases have not found significant differences in psychological characteristics of asthmatic and non-asthmatic children (Wjst et al. 1996) or adults (Janson et al. 1994). Chronic disease affects patients’ personality, and thus, a prospective study design, as in our study, has the advantage of distinguishing the effects of asthma on personality and the possible predisposing effect of personality features on asthma. We used an asthma definition based on questionnaire-reported doctor-
diagnosed asthma. Personality might affect reporting, as well as seeking of treatment for asthma. Another advantage of the present study was the possibility to control the effect of respiratory symptoms and social factors.

Measurement of psychological variables and comparisons between different scales are difficult. In the Finnish Twin Cohort, only validated scales were used. The personality traits used in this study (extroversion and neuroticism) are stable characteristics of personality formed in early life (Bouchard, 1993; Viken et al. 1994). The life satisfaction scale, by contrast, is associated with the current life situation as well as the stress measure used in this study, which assess subjects’ experiences of daily stress.

The only significant effect on onset of asthma was that of a high extroversion score among women. In contrast, men with a high neuroticism score were at increased risk of asthma, although this effect was statistically non-significant. Gender differences may occur in personality features associated with the inclination to seek treatment and this may partly contribute to the additional number of new asthma diagnoses among men with a high score in neuroticism. Personality affects one’s life-style and may have an effect on the observed association between extroversion and asthma. Although the relation of smoking and adult onset asthma is unclear, smoking habits associated with an extrovert personality may partly explain the increased risk of asthma seen in extroverted women. Personality may also affect one’s choice of profession, health habits and residential environment differently among men and women.

Asthma patients were more dissatisfied with their lives than those without asthma. Neuroticism was also associated with prevalent asthma. Treatment of asthma has improved markedly since since the 1970s and early 1980s, when the prevalent asthma cases of the present study were defined. Thus, findings need to be interpreted in this context.

Overall, no specific personality type seems to be associated with onset of adult asthma. However, different psychological factors are associated with asthma risk among men and women.
7 SUMMARY AND CONCLUSIONS

The aims of this study were to report incidence and prevalence of asthma among adult Finnish twins, to estimate the survival of adult asthma patients in comparison with non-asthmatics and to identify the role of life-style and social factors as well as certain psychological factors in predicting adult onset asthma.

The cumulative 15-year incidence of asthma among adults was 2.3% for men and 2.3% for women, with a higher incidence occurring in older age cohorts. Prevalence of asthma remained steady during 1975-1981 (2%), and was slightly higher in 1990 (3%) among adults aged 30 years or older. No increase in incidence rate was seen between the follow-up periods of 1975-1981 and 1982-1990 (I). These figures are similar to recent studies, although the increase was not as steep as that found previously. Prevalence of allergic rhinitis paralleled that of asthma, although incidence of allergic rhinitis decreased during follow-up. Allergic rhinitis and broader atopy index were strong predictors of asthma (I), which was seen also among asthma-discordant twin pairs (III).

The overall mortality of adults with asthma was higher than that of non-asthmatics, even when smoking habits were taken into account. Survival of the asthmatic twin was decreased compared with the twin sibling without asthma (II). This somewhat lower life expectancy of asthma patients is in keeping with previous studies of general adult populations.

Of social and life-style factors, education and conditioning exercise were associated with lower asthma risk only among twin pairs discordant for reimbursed asthma medication asthma (III). Smoking was not consistently associated with adult onset asthma (III, V). In contrast to previous studies, obesity was associated with a higher asthma risk among men, while both under- and overweight women had a slightly higher risk of asthma than normal-weight women (V), suggesting that the relation between weight and asthma is more complex among women possibly due to hormonal factors. Higher height in adulthood was protective against adult onset asthma among men (V). In addition to possible growth retardation due to childhood asthma, factors affecting to foetal growth may also explain this association.

Women with a high extroversion score had a higher risk of getting asthma, and among men neuroticism was associated with an increased asthma risk (IV).
Although personality might affect reporting and seeking of treatment for asthma, evidence also exists for the role of psychological factors on asthma onset.

In conclusion, the prevalence of asthma among adult twins corresponds to that found among singletons, indicating that twin studies of adult onset asthma are generalizable. A slight increase in asthma prevalence in adults and stable incidence rates of adult onset asthma points to the role of childhood asthma on elevated prevalences. Concomitant respiratory symptoms and diseases were common among adult asthmatics, confounding the definition of adult onset asthma. Detailed consideration of chronic bronchitis and other respiratory symptoms may offer more information on factors associated with adult onset asthma and on the underlying mechanisms.

Our results support previous findings of an association between sedentary lifestyle and asthma. However, our finding of a higher risk of asthma among obese men, in contrast to previous studies showing this association only among women, supports the theory of more complex association between asthma and weight. The role of personality on onset of asthma encourages to take psychological as well as physiological symptoms of asthma patients into consideration.
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