Secondary exposure to inhaled tobacco products
To Marie
Matz Larsson

Secondary exposure to inhaled tobacco products
ABSTRACT

Secondary exposure to inhaled tobacco products can influence health and development in a variety of ways. The aim of this thesis was to investigate a variety of health effects of secondary exposure to inhaled tobacco products, encompassing both airborne and in utero exposures. Specific investigations included:

- Childhood exposure to environmental tobacco smoke (ETS) and associations with respiratory symptoms and allergic sensitisation.
- Adult exposure to ETS and exacerbation of respiratory symptoms
- Workplace exposure to ETS and associations with respiratory symptoms
- The influence of smoke-free workplace legislation on respiratory symptoms
- In utero exposure due to maternal smoking and associations with physical control and coordination at age 11 years

ETS exposure during childhood was shown to be associated with an increased risk of asthma and allergic sensitisation. ETS exposure in adult non-smokers was associated with a dose-dependent increase in the prevalence of respiratory symptoms. The frequency of respiratory and sensory symptoms in hospitality workers declined substantially in non-smokers following the introduction of smoke-free legislation. Maternal smoking during pregnancy was associated with poorer physical control and coordination among offspring, particularly in the left – usually non-dominant- hand and most pronounced in boys, consistent with a modest adverse influence on neurological development.

These findings help to characterize several adverse outcomes associated with secondary exposure to inhaled tobacco products and emphasise the importance of preventing such exposures.

Keywords: passive smoking, smoking in pregnancy, asthma, allergy, hospitality workers, respiratory symptoms, physical control.
LIST OF PAPERS


(5) Larsson ML, Montgomery SM. Does maternal smoking during pregnancy influence physical control and coordination among offspring? (in preparation)

Reprints were made with the kind permission of the publishers.
### CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABBREVIATIONS</td>
<td>11</td>
</tr>
<tr>
<td>SUMMARY IN SWEDISH (SVENSK SAMMANFATTNING)</td>
<td>13</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>15</td>
</tr>
<tr>
<td>AIMS</td>
<td>21</td>
</tr>
<tr>
<td>MATERIALS AND METHODS</td>
<td>23</td>
</tr>
<tr>
<td>Study areas and populations</td>
<td>23</td>
</tr>
<tr>
<td>Measures and methods</td>
<td>26</td>
</tr>
<tr>
<td>Statistical Analysis</td>
<td>32</td>
</tr>
<tr>
<td>RESULTS</td>
<td>37</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>43</td>
</tr>
<tr>
<td>What is new in this thesis, and discussion of main results</td>
<td>58</td>
</tr>
<tr>
<td>Concluding remarks</td>
<td>59</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>61</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>63</td>
</tr>
<tr>
<td>APPENDIX</td>
<td>71</td>
</tr>
</tbody>
</table>
ABBREVIATIONS

4-ABP = 4-aminobiphenyl
ANOVA = analysis of variance
BMRC = British Medical Research Council
COPD = Chronic Obstructive Pulmonary Disease
EFSQ = Estonian FinEsS study questionnaire
ERS = European Respiratory Society
ETS = Environmental tobacco smoke
FEV1 = Forced Expiratory Volume in one second
FinEsS = Finnish, Estonian and Swedish respiratory survey
FSQ = FinEsS study questionnaire
FVC = Forced Vital Capacity
IARC = International Agency for Research in Cancer
LAWI = Lower airway irritant
NCDS = National Child Development Study
OLIN = Obstructive Lung Disease in Northern Sweden Study
OR = Odds ratio
RR = Relative risk
SFSQ = Swedish FinEsS study questionnaire
SPT = Skin prick testing
T2DM = Type 2 Diabetes Mellitus
WHO = World Health Organisation
SAMMANFATTNING PÅ SVENSKA

Skadliga effekter i rökarens omgivning

Även andra individer än rökaren kan påverkas av tobaksrökning. Syftet med denna avhandling var att undersöka några sådana effekter. Studierna omfattar såväl passiv rökning som exponering under graviditet. Mer specifikt handlar studierna om:

- Exponering för passiv rökning under barndomen och samband med luftvägssymtom och allergi senare i livet.
- Passiv rökning i vuxen ålder och samband med luftvägssymtom.
- Exponering hos serveringspersonal och effekter av lagstiftning mot tobaksrökning.
- Rökning under graviditet och kontroll och koordination av handrörelser hos barn.


Ett flertal oönskade effekter kan således drabba dem som är nära rökare under någon period i livet och resultaten understryker vikten av att förebygga sådan exponering.
INTRODUCTION

History of tobacco use

Tobacco plants, *Nicotiana tabacum* and *Nicotiana rustica*, were used for ceremonial purposes among Native Americans as early as 5,000 years BC. Tobacco was introduced to Europeans when two of Columbus’ crew observed Tainos Indians smoking the rolled leaves, and used tobacco as snuff or by chewing it\(^1\). The role of tobacco for most of the 16th Century was limited in Europe as it was considered largely as a botanical oddity, an exotic medicine or for recreation. In London, tobacco was introduced in 1565 (one year after William Shakespeare’s birth) as a luxury, but gained such popularity that at the end of the century that there were no less than 7,000 tobacconists in London. It was used not only for pleasure but also as treatment against venereal disease, migraine, bad breath, and as prophylaxis against plague. Even small children were persuaded to use it. For a time pupils at Eaton faced a thrashing if it was discovered that they had neglected their tobacco\(^1\).

The Spanish brought tobacco plants to the Philippines, where tobacco became common and from where its use spread to China, rapidly becoming popular. The Portuguese introduced the plant to western Africa around the beginning of the 17th century and also took it to India, Java, Japan and Iran, from where its use soon spread to surrounding countries. By 1620 the tobacco plant was widely cultured and used in most parts of the world\(^1\).

During the 1880s, cigarette-making machines began to replace hand-rolling in The United States and in Europe, dramatically reducing production cost. When the American Tobacco Company monopoly in the US was abolished in 1911, new independent companies began to compete and prices fell. Promotion and advertising increased, and cigarette consumption rose rapidly\(^3\). In the mid-1990s consumption of cigarettes was equivalent to a pack per week for every man, woman, and child on the planet\(^1\).

Tobacco smoking can seriously damage the health of smokers and is associated with an average reduction in life expectancy of ten years\(^4\). At present, approximately five million deaths annually are associated with tobacco use worldwide. Estimates based on
current trends indicate that this number will increase to 10 million by 2030, with 70% of deaths taking place in low- and middle-income nations\textsuperscript{44}.

**Exposure to Environmental tobacco smoke (ETS)**

Tobacco smoke also has the potential to cause disease in non-smokers. Secondary exposure to inhaled tobacco products can influence the human body in various ways and outcomes can vary by age at exposure. Exposure to ETS has been reported to have health effects similar to those of active smoking, including lung cancer and cardiovascular and respiratory diseases. ETS usually results in considerably lower exposure levels than active smoking, and effects are, in general, less pronounced\textsuperscript{32}. ETS has been classified as a class I carcinogen by the International Agency for Research in Cancer (IARC, 2002). More than 3,800 different compounds, including nicotine, carbon monoxide, benzene, formaldehyde, and acrolein are produced by a burning cigarette\textsuperscript{14}. No safe level of ETS exposure has been established. ETS was classified as a known human carcinogen by the US Environmental Protection Agency in 1993, by the U.S. Department of Health and Human Services in 2000, and by the WHO International Agency for Research on Cancer in 2002. In addition, it has been classified as a workplace carcinogen by the governments of Finland (2000) and Germany (2001).

The organs most exposed to ETS are those of the respiratory system, as well as the skin and the eyes. Respiratory tract symptoms associated with ETS have been extensively reported in scientific literature\textsuperscript{41, 42}. Acute exposure to ETS is associated with respiratory symptoms in people with asthma\textsuperscript{95}. Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements are involved. The chronic inflammation causes an associated increase in airway hyper-responsiveness leading to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. The episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment\textsuperscript{7}. There is evidence that secondary tobacco smoke exposure increases the prevalence of wheezing, cough, and phlegm, and that household ETS exposure may exacerbate symptoms of asthma in children\textsuperscript{16, 17, 30}.
Acute exposure to ETS has also been reported to increase bronchial reactivity to histamine. 

Studies have identified an association between ETS and respiratory symptoms as well as lung function in children. The evidence for associations of secondary exposure to inhaled tobacco products with asthmatic symptoms and impaired lung function is persuasive. The evidence that exposure to ETS increases risk of allergic disease is less conclusive. As reviewed by Strachan and Cook, several large studies failed to confirm early reports of an association of maternal smoking with concentrations of total serum IgE in neonates or in older children. Studies of parental smoking during pregnancy or infancy were broadly consistent in showing no adverse effect on the risk of allergic sensitisation as measured by skin prick testing (pooled odds ratio 0.87, 95% confidence interval 0.62 to 1.24). The conclusion of Strachan and Cook was that parental smoking, either before or immediately after birth, is unlikely to increase the risk of allergic sensitisation in children. This review, however, dealt primarily with studies of comparatively small size, which often were not longitudinal and there were some contradictory reports. For example, while the German Multicentre Allergy Study found no association between prenatal or postnatal exposure to tobacco smoke and IgE sensitisation to inhalant allergens at the 3 year follow-up, there was an association with food allergens. Some studies have reported a weak negative association between parental smoking and the risk of allergic sensitisation in children, for instance a study of young adults from the general population in Denmark. Many of the previous studies lack objective measures of allergic sensitisation like skin prick test and most of the studies have only examined maternal smoking or have examined maternal and paternal smoking combined.

Effects of anti-smoking legislation
Tobacco is an addictive substance, and its use is extremely common worldwide, but complete elimination of smoking in the short or medium term is impractical. Clarification of risks associated with ETS exposure is therefore important.
Several European countries, including Ireland, Norway, Italy, and Spain, have introduced a policy to eliminate smoking from workplaces and public buildings, including bars and restaurants. Sweden extended its smoke-free workplace policy to include hospitality workers, such as bar and restaurant personal, on 1 June 2005.

Workers in the hospitality sector may experience particularly high levels of exposure to ETS. It is therefore important to assess the effects of the smoke-free legislation in this sector. Previous research has mainly investigated bar workers while other groups for example casino and bingo hall workers, have not been examined.

The rate of respiratory symptoms among hospitality workers is notably elevated due to exposure to ETS. It is important to establish whether the introduction of legislation is accompanied by a real reduction in environmental tobacco smoke and if there is an accompanying reduction in the rate of respiratory symptoms. Attitudes towards the legislation may also be important in determining its long-term success, so it is of value to assess these and whether they change following introduction of the legislation.

In addition to associations with acute respiratory and sensory symptoms, it is possible that the reduced exposure to ETS following introduction of legislation may have more profound health effects. Some studies indicate that a reduction in exposure to ETS can result in modest improvements in respiratory function. Airborne nicotine concentrations have been used to estimate mutagenicity risk, so it is of value to assess any change in risk that legislation may bring.

**In utero exposure to inhaled tobacco products**

Inhaled tobacco products can affect foetal development. Notably, *in utero* exposure to tobacco smoke is associated with low birth weight. *In utero* exposures differ from inhalation exposure, whether passive or active, in that toxic substances dissolved in the blood of the mother reach the body of the foetus through placental circulation instead of the lungs. In addition, inhaled tobacco smoke could mediate effects on the foetus through its action on the mother’s vascular, immune, endocrine, central nervous system, or through other routes. Examples include reduced placental circulation resulting in a form of foetal malnutrition, and suppression of the immune system.
leading to increased risk of infection. Evidence that smoking might harm the development of the foetal brain has been found in animal studies. Some human studies have also indicated possible effects on foetal brain development. Maternal smoking during pregnancy has been linked with increased risks of type 2 diabetes mellitus (T2DM) and obesity in offspring. It has been observed that poorer neurological function – indicated by poorer motor competence and cognitive function in childhood – pre-dates the onset of these diseases. This suggests the possibility that poorer neurological development or function and diseases such as obesity and T2DM may share common risks in early life. It is therefore plausible that smoking during pregnancy may result in poorer neurological function among offspring. While some studies have demonstrated association between maternal smoking during pregnancy and poorer cognitive function in offspring, it has been argued that such studies may be confounded by a variety of social and material factors.

Thus it may be that the children of mothers who smoke during pregnancy are more likely to grow up in relatively disadvantaged circumstances and it is this that accounts for their poorer cognitive function. Performance in cognitive function tests can be to a certain extent affected by learning, so results may reflect social rather than neurological mechanisms. Therefore it is desirable to examine the putative association of maternal smoking during pregnancy with neurological development and function using markers that are less susceptible to confounding by social factors, such as measures of motor competence. Prenatal exposure to tobacco has been associated previously with deficits in design memory, as well as slowed responses in tests of eye-hand coordination. However, the aforementioned study was limited in size, and the results may have been confounded by illegal drug use, as this was common among mothers in the study.
AIMS

The goal of the thesis was to identify associations of secondary exposure of inhaled tobacco with health outcomes and to quantify health benefits of smoke-free legislation. The specific aims were to:

- Determine associations between ETS-exposure during childhood and the prevalence of physician-diagnosed asthma and respiratory symptoms (Paper I).
- Determine associations between ETS-exposure during childhood and allergic sensitisation in adults (Paper II).
- Identify associations of respiratory symptoms with ETS-exposure in adults at home, and in other localities (Paper III).
- Evaluate effects of legislation against smoking in the workplace by monitoring levels of ETS-exposure as well as airway and sensory symptoms in hospitality workers before and after the introduction of smoke-free legislation (Paper IV).
- Identify associations of maternal smoking during pregnancy with physical control and coordination in offspring at age 11 years (Paper V).
MATERIALS AND METHODS

Papers I and II are based on the Örebro, Sweden component of the FinEsS (Finland, Estonia and Sweden) studies, while Paper III is based on the Estonia component. Paper IV is based on the Swedish Hospitality Workers Study (SHW). Paper V uses data from the British National Child Development Study (NCDS), an ongoing longitudinal birth cohort study.

FinEsS was a general population-based study, conducted in three nations, investigating putative risks for asthma, chronic bronchitis, type-1 allergy and respiratory symptoms. The postal questionnaire used in FinEsS was developed in 1985 for the OLIN studies, adapted from a revised version of the BMRC questionnaire. It included questions about respiratory symptoms and other disease symptoms in a variety of situations such as exposure to cold air, exercise, and in relation to other exposures, such as strong smells, dust, pets, pollen, car-exhaust fumes, and cigarette smoke. Information was also collected on smoking habits, occupation, and family history of asthma, allergic rhino-conjunctivitis disease, and Chronic Obstructive Pulmonary Disease (COPD). A question about childhood exposure to ETS at home was added to the FinEsS study in Örebro.

Study areas and populations

Paper I (Childhood ETS and asthma)

Paper I is based on the portion of the FinEsS study conducted in Örebro, Sweden in the winter of 1995-96. Örebro is a medium-sized city in central Sweden, situated at low altitude and covering 1,360 square kilometres. In 1994 the population was 118,606 with a population density of 87 per square kilometre. Approximately 87% of the population was living in an urban/suburban area. The annual mean temperature is 6.1°C. The mean temperature in January is 4.0°C and in July it is 16.8°C. The main occupations are public services (78%) and industrial labour.

From the population of inhabitants aged 15 to 69 years (80,569), a sample of 8008 was randomly selected. Subjects were stratified into 10-year age bands. The
sample size was based on a predicted response rate of 75%, which would provide 80% power to detect a difference of 2-3% in each stratum in prevalence of allergic disease between Örebro and Estonia. This thesis is not concerned with estimations of allergic disease prevalence. The Örebro County Council population register, which is updated fortnightly, was used to identify participants.

**Paper II (Childhood ETS and allergic sensitisation)**

From among the 6,732 responders to the FinEsS sample in Örebro (originally 8,008 subjects) described above, a stratified sample (by sex and age) of 1,200 respondents, aged 22–74 years, was randomly selected for skin prick testing (SPT).

A total of 720 (60%) participated in this sub-study, providing SPT data for 704 subjects after exclusions for illness and pregnancy or breastfeeding. Subject characteristics in the sample fell within 2 percent of the original sample for sex, smoking, and allergic rhinitis, but there was slight age variation, such that there was a 5% increase in the second oldest age category (50-59 years of age in 1995).

**Paper III (ETS and respiratory symptoms)**

Paper III is based on the Estonian section of the FinEsS studies. In the FinEsS Estonian study, a random sample of 24,307 individuals stratified by sex and 10-year age groups was selected from the populations of Tallinn (pop. 442,679), Narva (pop. 79,094) and Saaremaa (pop. 40,822). Of the 6,817 never-smokers included in the analysis, 4,995 (73%) were female.

**Paper IV (ETS and smoke-free legislation)**

Paper IV was based on a cohort of hospitality workers who volunteered to participate in a study at the time Sweden implemented legislation against tobacco smoking in the work environments of hospitality industries.

Criteria for inclusion were working as a waiter, bar-staff, or croupier in a restaurant, bar, nightclub, casino or bingo hall where a smoke-free policy was not in place before the legislation came into force.
When recruiting volunteers, the specification was for daily smokers and non-smokers, while occasional smoking was an exclusion criterion. Snuff use was permitted (a snuff user could be classified as a non-smoker).

Other exclusion criteria were an already smoke-free working place prior to implementation of the law, and a work period shorter than three consecutive days. We accepted all workers who volunteered in time to allow for completion of testing before the introduction of the ban.

The subjects were hospitality workers in nine communities throughout Sweden: Stockholm (21 participants), Gothenburg (19), Malmö (6), Uppsala (5), Västerås (13), Linköping (5), Örebro (6), Östersund (7), and Skövde (9).

A total of 91 subjects (26% smokers, 74% non-smokers) were investigated at the start of the study. Seventy-one of these (20% smokers, 80% non-smokers) participated in the 12-month follow-up. The proportion of females was 70% at both sweeps. Since ETS-exposure of staff working in gaming areas such as bingo and casinos has rarely been investigated, the sample was stratified into two subgroups: gaming workers and other workers. At both sweeps gaming workers represented approximately 40% of the total sample and other workers approximately 60%. Gaming workers were employed in bingo halls or casinos. Other workers consisted of waiters and waitresses, bar-staff, bar owners, and disc jockeys, as well as those who had a combined role as both bar-worker and waiter.

**Paper V (physical control and coordination)**

The National Child Development Study (NCDS) has followed all those born in the Great Britain from 3-9 March 1958, with data collection at various ages throughout childhood and adult life. The study originally comprised 17,000 individuals, but the subsequent exclusion of Northern Ireland, along with death, emigration and other causes of attrition, reduced the sample size, although the cohort has remained broadly representative of the target population.
The outcome data used in this study were recorded in 1969, when subjects were 11 years of age. The NCDS collected data from 15,303 subjects at this time, and 13,207 children received a full medical examination, which included a series of functional assessments, conducted by a Local Authority Medical Officer.

After exclusion of subjects with incomplete data the number of subjects ranged from 9,615 for the copying designs test to 10,247 for the ticking of squares test.

The majority (67.5%) of the mothers were non-smokers. Of the 32.5% smokers, 7% were considered variable smokers, 15.0% medium smokers (1-9 cig/d), and 11.8% heavy smokers. Birth weight, breast-feeding, pubertal development of child, social class, household crowding, and mother’s education level differed significantly in relation to smoking habits, so these were potential confounding factors, while laterality of child was not associated with maternal smoking.

**Measures and methods**

**Papers I-III**

**Postal FinEsS Questionnaire**

The Swedish (SFSQ) and Estonian (EFSQ) versions of the FinEsS questionnaire used in Papers I and III were based on the OLIN questionnaire, which has been used in several Nordic studies and was developed from the British Medical Research Council Committee (BMRC) questionnaire from 1960.

The SFSQ in Örebro contained questions on 23 subjects, each of which comprised between 1 and 9 questions. The questionnaire contained a total of 44 questions requiring “yes” or “no/don’t know” responses and an additional four questions on work history and current main occupation. The SFSQ and EFSQ included questions about respiratory symptoms and diagnoses of asthma and chronic bronchitis. They also recorded the presence of symptoms that occurred in specific circumstances, the use of asthma medication, smoking habits, and profession. Questions about family history of asthma, COPD and allergy were also included.
In Örebro, a question was added concerning tobacco smoke in the home environment during childhood and adolescence. In Estonia, two additional questions concerning duration of ETS exposure at home and in localities outside of the home were added. The questions about smoking and work history were modified from the OLIN questionnaire. Questions about respiratory symptoms and diseases required either “yes”, or “no/don’t know” responses.

Smoking habits were classified to identify non-smokers, ex-smokers (those who had stopped more than 12 months prior to the study), or current smokers. In some analyses the categories were never-smokers and ever-smokers (the sum of ex-smokers and current smokers). Current smokers were asked to rank their cigarette usage as < 5, 5-14, or > 14 cigarettes/day.

The questionnaire also included a question on exposures or circumstances with the potential to cause lower airway irritation (LAWI):

**LAWI questions**

Do you become breathless or wheeze, or do you have attacks of coughing, when exposed to…

1) exercise?
2) cold air?
3) exercise in cold air?
4) dust?
5) tobacco smoke?
6) car exhaust fumes?
7) strong smells, e.g. perfume, spices, printers ink?
8) pollen from plants or trees?
9) pets?

If a positive response was given, the factor or circumstance was defined as being associated with LAWI.
**Paper II (Childhood ETS and allergic sensitisation)**

**Structured FinEsS Interview**

Paper II used data collected using an expanded version of the OLIN interview schedule\(^{59,77}\). A trained research nurse conducted the interview.

Skin prick tests (SPT) were performed in duplicate on the volar aspects of the forearms using fifteen allergen extracts (appendix II).

The following allergen extracts were used: two house dust mites (Dermatophagoides pteronyssinus and Dermatophagoides farinae), two storage mites (Lepidoglyphus destructor and Acarus siro), cat, dog, cow, horse, birch pollen, timothy, mugwort, Alternaria alternata, Cladosporium herbarum, latex and German cockroach.

The prick tests were carried out by three trained nurses following procedures according to the position paper “Allergen standardisation and skin tests by EAACI Subcommittee on Allergen Standardisation and Skin Tests”\(^{1}\).

A SPT was regarded as positive if the wheal was greater or equal to 3mm, calculated as the sum of the longest and the midpoint orthogonal diameters divided by two. The size of both wheals for each allergen was recorded, whereas only the size of the first wheal (the first produced of the two) was used for analysis. A subject was classified as sensitised if at least one positive SPT for any allergen was observed.

**Paper IV (ETS and smoke-free legislation)**

**Questionnaire**

A questionnaire specifically designed for the Swedish Hospitality Workers Study was used in both sweeps. The first sweep was conducted in April-May 2005, approximately one month before the introduction of legislation on June 1st 2005, while the second sweep was conducted between April-May 2006. The following questions about symptoms were included:

1. Have you had whistling/wheezing in your chest?
2. Have you felt short of breath?
3. Do you usually cough first thing in the morning?
4. Do you cough at all during the rest of the day?
5. Do you bring up phlegm?
6. In the past 4 weeks have your eyes been red or irritated?
7. Have you had a running nose, sneezing or nose irritation?
8. Have you had a sore or irritated throat?

The questions were developed by the International Union against Tuberculosis and Lung Disease to quantify symptoms and have been used in similar studies\(^3, 27, 62\). Participants reported the presence or absence of symptoms in two domains (respiratory and sensory) in the preceding four weeks. The same questions were used at baseline and at follow-up. Information on tobacco use was also recorded. Exposure to ETS at work, at home and in other localities over the previous seven days was recorded, including information on whether participants lived with a smoker. At both surveys subjects reported their attitude to the legislation using a scale of 0-100, where a higher score indicated a more positive response. The four questions were: What is your opinion about how members of each of the following persons or groups are affected by the tobacco smoking legislation? The areas were: yourself; hospitality workers in general; the employer; and the guests.

**Diary**
A diary developed for the Hospitality Workers Study was used during both surveys. Subjects recorded own smoking, nicotine, and snuff use during the previous 24 hours. Exposure to ETS during working hours and during leisure time and the periods the nicotine-sampler had been used were recorded after each work-shift for three consecutive days.

**Urine sampling**
Screening for unreported tobacco use by urine cotinine testing was conducted at both sweeps. Urine samples, obtained at the end of a work shift, were frozen immediately and sent to the laboratory, where cotinine assays were performed using liquid extraction gas chromatography–mass spectrometry\(^39\). We defined non-tobacco users as those who reported being currently non-smokers (and non snuff users) with a urine-cotinine concentration below 100 ng/ml.
Nicotine in the air

Nicotine vapour phase was measured using detectors composed of a 37mm diameter plastic filter cassette (with a windscreen in one side), containing a sodium bisulphate treated, Teflon coated, fibreglass filter\textsuperscript{34, 35, 40}. The subgroup of non-smokers wore detectors placed on the clothing on the left side of the body approximately over the pectoral muscle throughout the workday for two to four days. Among smokers, the detectors were placed in the workplace for a similar duration but were not worn on the body, in order to avoid contamination by participants’ smoking. Analysis was performed at the Department of Occupational and Environmental Medicine, Örebro University Hospital, Sweden. The limit of detection was 0.0025 μg/sample. The air nicotine concentration (μg/m\textsuperscript{3}) was calculated by using the uptake rate (24 ml/min) and the time the filter was exposed (recorded in the diary), thus extrapolating for the duration of exposure. The method has previously been fully described and has been validated in several studies\textsuperscript{33-35, 40}.

The number of subjects exceeding the level of nicotine in the air, which has been determined to be consistent with disease risk was recorded. A potent bladder carcinogen, 4-aminobiphenyl (4-ABP), is present in ETS and has been shown to bond covalently with hemoglobin\textsuperscript{34}. We chose a cut-off level for nicotine in the air (greater or equal to 0.5 μg/m\textsuperscript{3}), previously identified as indicating potentially hazardous levels of 4-ABP\textsuperscript{34}.

Spirometry

All subjects were assessed in one of the nine recognized pulmonary function clinics used by the study. All clinics followed written instructions from the study coordinator, which were based on ERS-guidelines\textsuperscript{85} and included instructions on calibration and Forced Expiratory Volume in one second (FEV1) and Forced Vital Capacity (FVC) measurements. The same spirometer was used pre- and post-ban for all participants. The Forced Expiratory Flow One Second (FEV1) value, as well as Forced Vital Capacity (FVC), were recorded prior to and 15 minutes after inhalation of 0.4 mg salbutamol (or 1.0 mg terbutalin). The highest FEV1 and FVC from at least three attempts were recorded.
**Paper V (physical control and coordination)**

Maternal smoking during pregnancy was recorded by midwives at birth (using data from medical records collected during the fifth month of pregnancy). Mothers were grouped according to daily cigarette consumption and divided into non-smokers, medium (1-9 cigarettes/day), heavy (>9), and variable smokers (a combination of medium and heavy smokers). In addition, smoking habits before pregnancy were recorded.

Midwives also recorded information on: the baby’s sex, weight in ounces, gestational age in weeks, mother’s age, mother’s age at leaving full time education, household crowding defined as persons per-room (up to 1, > 1 to 1.5, > 1.5 to 2, > 2 to 2.5, >2.5 to 3, >3 persons). The Registrar General’s social class based on the father’s occupation, was categorised as I, II, III non-manual, III manual, IV, V or ‘Not assigned’ (where the father was not present or not working).

At age 11 years, children were examined by a local authority medical officer who administered a series of functional assessments. Three tests were selected as measures of physical control and coordination:

1. Time in seconds (maximum 99 seconds) to pick up 20 matches with the left hand (n=10,223) and with the right hand (n=10,230). (Unlike the other tests, a higher score indicates poorer performance.)
2. Marking squares (a maximum of 200) on paper in one minute with the left hand (n=10,193) and with the right hand (n=10,247).
3. Copying a simple geometric design (n=9,615). The accuracy of the copy was scored 0-12.

Children with incomplete or equivocal information on mothers smoking habits during pregnancy (7.4% of the original sample) were excluded from the analysis, as were those with a disability not allowing participation in tests at age 11 years. Participants were free from major disabilities and in mainstream schools.

The medical officer assessed laterality by observing which hand the children used when throwing a ball. Disabilities were assessed by physical examination and from review of medical records. Disabilities were categorised by function, defined as whether the condition was present and whether it affected daily living. Pubertal
development was assessed using scores for breast development and pubic hair density assessments in girls and genitalia development and pubic hair density in boys (0-5 for each measure). The scores were summed for boys and girls separately and were then converted into standard deviation units and combined.

Ethnic origin was categorized as: White British (over 96%), Irish, White other, White and Black Caribbean, White and Black African, White and Asian, other mixed race, Indian, other Asian, Caribbean, African, other Black, or other ethnic group.

**Statistical Analysis**

**Paper I (Childhood ETS and asthma)**

Analysis was based on participants who had never smoked. The question concerning tobacco smoke exposure in the home environment during childhood and adolescence was a binary variable. The question about physician diagnosed asthma (that was answered in the same manner) was used to define the outcome. Relative risks of physician diagnosed asthma, and airway symptoms were estimated using odds ratios and Fisher’s double-sided Exact Test was used where appropriate. Separate analyses were performed for the sub-group with no family history of asthma in parents or siblings. Risk factors for physician-diagnosed asthma and symptoms in specific circumstances among never-smokers without a family history of asthma were calculated using multiple logistic regression analysis.

**Paper II (Childhood ETS and allergic sensitisation)**

The subjects, stratified by age and sex, were randomly selected from SFSQ responders in Örebro (see paper I).

A SPT was regarded as positive if the wheal was at least 3mm, and participants were classified as sensitised if at least one positive SPT was registered.

Allergic sensitisation (defined as at least one positive SPT) was used as the dependent variable with mutual simultaneous adjustment for potential confounding factors.
(maternal and paternal smoking, the subjects’ smoking habits, older siblings, younger siblings, shared bedroom with sibling, pets, type of home (flat or house), place of residence at birth, age at SPT and sex), modelled as series of dummy variables.

Earlier observations suggested that there might be contrasting associations with allergic sensitisation for maternal and paternal smoking\textsuperscript{84}. Therefore, we stratified the analysis so that maternal smoking could be examined among those with non-smoking fathers and paternal smoking could be examined among those with non-smoking mothers. We then modelled maternal and paternal smoking as separate variables, which were adjusted for each other. We also analysed associations with smokers in the household, other than the parents.

**Paper III (ETS and respiratory symptoms)**

The outcomes in this study were self-reported respiratory symptoms. The two exposures we investigated were ETS exposure outside the home, and ETS exposure at home. Multiple logistic regression was used to calculate associations with respiratory symptoms. In the adjusted model we controlled for age, sex, family history of asthma, bronchitis, emphysema, and geographic region. Two measures for ETS-exposures were included in the model simultaneously, one measuring ETS-exposure at home, and the other ETS-exposure outside home.

Analyses were based only on the participants who had never smoked (n= 6,817). We estimated effect modification by sex for ETS outside the home using interaction testing. Dose-dependent associations were analyzed by examining an ordinal ETS exposure effect. In this analysis, ETS exposure was coded from 1 to 4, where 1 was “nearly never,” and 4 was “more than 5 hours of ETS exposure outside home”.

**Paper IV (ETS and smoke-free legislation)**

We examined and compared characteristics of participants approximately one month before the smoking ban and eleven months after its introduction, using cross-tabulation. All analyses were performed for the total sample as well as stratified by occupation. *Gaming workers* were those employed in bingo halls and casinos while the remainder of the hospitality workers are described here as *other workers*. 
To measure change in respiratory and sensory symptoms between data collection sweeps, we used the xtlogit procedure provided by Stata software. This is a form of logistic regression specifically developed for panel data where there is an explicit time component. When individuals participate at multiple points in time, this technique links the data and estimates individual change. This technique also made it possible to use data from those that only participated at the first survey. Baseline data from all 91 subjects could then be used in analyses comparing the population at the two time points.

We limited a complimentary analysis to the 71 subjects who participated in both sweeps to ensure that results were not influenced by attrition-associated selection bias. The xtlogit models were adjusted for age, sex and smoking. The analysis was also stratified by smoking behaviour.

To estimate reduction in ETS exposure following the introduction of legislation, we calculated the number of subjects exposed to nicotine in the air above the cut-off value of >0.5 μg/m³ using logistic regression. Where it was not possible to report odds ratios due to empty cells, relative risks were reported.

A similar analysis examined the dichotomised attitude scores. In analysis of attitudes to the legislation, we defined a score of 75 or greater as indicating general satisfaction. Pulmonary function tests were recorded pre-ban and post-ban and analysed for each changes in FEV1 and FVC. We compared the predicted score for the pre- and post-ban periods using the paired sample t test procedure. We also used potentially more sensitive analyses to identify differences in lung function between data collection times, by assessing differences in reversible bronchial reactivity during the study-period. Delta-FEV1 indicated the difference in capacity before and after a beta-2 agonist was administered, and linear regression assessed differences in this measure, with adjustment for sex, age and height. A similar analysis was conducted for FEV1. Smokers were excluded from the analysis of lung function.

**Paper V (physical control and coordination)**

The test scores [*Time to pick up 20 matches* (left and right hand), *Marking squares on paper* (left and right hand), *Copying design*] were dependent variables in linear
regression analysis, with adjustment for sex, birth weight, gestational age, breast-feeding, social class, parental education, mother’s age, handedness, and pubertal development (age 11 years). The potential confounders, ethnicity and diseases or disability of the CNS and motor function, were added to the models but removed for reasons of parsimony, as they did not influence associations with the outcome.

Covariates were selected on theoretical grounds and represent maternal and family material and cultural characteristics, as well as child characteristics. Measures that were categorical (smoking, mother’s education, mother’s age, laterality, puberty score, and breast-feeding) were modelled as series of binary dummy variables. All of the measures that were included in the model are presented in Table 1 of paper V.

All analyses were stratified by sex. A further (non-stratified) model included the interaction term for sex with prenatal smoking adjusted for the main effects (i.e. sex of offspring and smoking during pregnancy).
RESULTS

Paper I (Childhood ETS and asthma)

Approximately 84% (6,732) of 8,008 mailed questionnaires were completed and returned. The total comprised 3,556 never-smokers (52.8%), 1,676 smokers (24.9%), 1,257 ex-smokers (18.7%), and 243 subjects (3.6%) giving no answer about their smoking habits. Among the 3,556 never-smokers, 1,625 (45.6%) reported exposure to ETS in childhood, and 1,926 (54.0%) reported no exposure. The prevalence of physician-diagnosed asthma was 7.6% in exposed subjects compared with 5.9% in unexposed subjects (p =0.036).

Sub-sample with no family history of asthma

In the sub-sample with no family history of asthma, the prevalence of physician-diagnosed asthma in subjects reporting childhood ETS exposure was almost twice as common, 6.8% compared with 3.8% in unexposed subjects corresponding to an OR of 1.82 (95% Confidence Interval 1.28 to 2.58).

This association remained virtually unchanged in a multiple logistic regression analysis adjusted for sex, age, and socio-economic position. ETS-exposed subjects also reported more breathing difficulties associated with current exposure to tobacco smoke, exercise, and pets.

Lower airway irritants (LAWI)

ETS was the most common LAWI, reported by 21% of participants. An even higher number of subjects with asthma; 50%, reported ETS to be a LAWI. It is also notable that females more frequently reported all nine LAWI than did males.

Paper II (Childhood ETS and allergic sensitisation)

We found a weak association between allergic sensitisation and paternal smoking in the univariate analysis OR 1.37(1.00 to 1.89). After adjustment for maternal smoking and all of the other measures, the odds ratio for allergic sensitisation associated with
paternal smoking increased with enhanced statistical significance: OR 1.48 (1.04–2.10). In contrast, maternal smoking after corresponding adjustments was associated with a non-significant decreased risk of allergic sensitisation in offspring. A sub-group analysis of families with a non-smoking mother produced an odds ratio for paternal smoking and risk for allergic sensitisation 1.61 (1.09–2.37). This provides evidence of effect modification through maternal smoking, such that maternal smoking seems to be associated with a reduced risk of allergic sensitisation which may mask a positive association with paternal smoking.

Analysis of smokers in the same household other than parents produced an odds ratio similar in magnitude to paternal smoking, although not statistically significant (probably due to low statistical power as only 51 subjects reported this exposure). Subject’s age (birth cohort) was significantly associated with both likelihood of parental smoking and allergic sensitisation. Among measures other than parental smoking, only subject’s age and number of older siblings were observed to have a statistically significant association with allergic sensitisation in the adjusted model.

**Paper III (ETS and respiratory symptoms)**

ETS exposure outside the home was related to almost all reported respiratory symptoms in a dose-dependent manner. If exposure exceeded 5 hours daily, the odds ratios (and 95% confidence intervals) were 2.67 (1.98 to 3.61) for wheeze and 1.79 (1.02 to 3.16) for physician-diagnosed asthma compared with the group that reported no or almost no ETS exposure.

ETS exposure in Estonian homes was more common in females, 31% compared with 19% for males, while exposure outside the home was more common in males, 53% compared with 37%. The reported duration of ETS exposure was associated with positive responses for all types of LAWI. In common with Örebro, Sweden (paper I) LAWI was more frequently reported by females. For example, 37% of females and 22% of males reported tobacco smoke to be a LAWI. Tobacco smoke was also the most commonly reported LAWI among the Estonian population.
Paper IV (ETS and smoke-free legislation)

Some 91 subjects participated in the first data collection sweep with 71 of these participating in the second. Females predominated and there were relatively few smokers. Subjects lost to follow-up were somewhat younger and more likely to be smokers, but did not differ from the overall group by sex and (pre-ban) attitudes to the legislation. The implementation of smoke-free legislation was associated with a substantial reduction in respiratory and sensory symptoms among non-smoking hospitality workers.

All reported symptoms in the study population declined. The decrease was statistically significant for cough in the morning, cough during the rest of the day, eye irritation, nasal irritation, and throat symptoms.

The xtlogit program made it possible to include subjects that didn’t participate twice and this analysis showed that the frequency of reported symptoms was approximately halved among non-smokers one year following introduction of the ban. The reduction in symptoms was observed both in gaming workers (who have not usually been included in studies of ETS exposure), and in other hospitality workers. Restricting the analyses to those who participated in both sweeps gave similar results.

Nicotine in the air

There was a reduction in the median level of nicotine measured in the air between baseline and 12-month follow-up from 7.50 g/m$^3$ to 0.16 g/m$^3$. (In smokers the median declined from 12.6µg/m$^3$ to 0.2µg/m$^3$ and in non-smokers from 6.2µg/m$^3$ to 0.2µg/m$^3$). In terms of risk reduction, before the ban 87% of subjects were exposed to ETS exceeding the nicotine cut-off level of 0.5 µg/m$^3$, while after the ban it was 22%, representing a relative risk (RR) of 0.25 (95% Confidence Interval 0.15 to 0.41) in the total sample (RR was presented as OR could not be calculated due to an empty cell). The samplers worn by non-smoking subjects showed that nicotine in the air before the ban was under the detection limit for 1/54 (2%), while after the ban it was under the limit for 17/54 (31%).
Self-reported exposure
Before the ban, 59 of 91 subjects (65%) reported ETS exposure for 75% or more of the working time, while at follow-up this was the case for only 1 of 71 (1%), \( p < 0.001 \). The reported duration of ETS-exposure at home was unchanged (data not shown). In other localities (not work or home) 35 of 71 subjects (49%) reported ETS exposure exceeding 1 hour prior to legislation, while following the ban the figure was reduced to 7 of 71 (10%), \( p < 0.001 \).

At work prior to the ban, there was a statistically significant longer ETS exposure time among gaming workers compared with other workers. Duration of exposure exceeding 75% of the working-time was reported by 81% of gaming workers, while it was 54% of other workers. Post-ban ETS-exposure duration was similar in both occupational groups (data not shown).

Paper V (physical control and coordination)
Lower social class, crowding, mother’s education level, breastfeeding, and lower birth weight were all strongly associated with maternal smoking during pregnancy. There was no association between laterality and maternal smoking during pregnancy, indicating that this cannot be a confounding factor.

Picking up matches: Compared with non-smoking mothers, smoking over 9 cigarettes per day during pregnancy was associated with poorer performance in physical control and coordination, indicated by a longer duration for picking up matches, particularly in the left hand. In the left hand there were only modest reductions in the magnitude of the associations after adjustment for multiple potential confounding. In the right hand associations were more notably reduced but remained statistically significant after adjustment.

Stratification by sex (in the adjusted model) showed that in offspring of heavily smoking mothers the association was of greater magnitude in boys and was not statistically significant among girls. The corresponding analysis for right hand showed almost no difference by sex.
Number of squares marked: Both in the left and right hand tests, heavy maternal smoking was associated with a modest reduction in ability, which did not remain statistically significant in the adjusted model.

Stratification by sex showed that in offspring of heavy smoking mothers the associations for both hands were more notable in boys, (and in left hand achieved borderline statistical significance).

Copying designs: Heavy smoking during pregnancy was associated with a reduced test score among offspring. There was a reduction in the magnitude of the associations in the adjusted model but they remained statistically significant.

Stratification by sex showed that in offspring to heavily smoking mothers the association was much more notable in boys, while in girls, there was almost no association. The interaction test for heavy maternal smoking by sex was statistically significant.

Less than 4% (394/11,348) of subject were not white British, and when these were excluded, the results were almost entirely unaffected (data not shown).
DISCUSSION

The research encompassed by this thesis includes participants from several countries who experienced different modes of secondary exposure to inhaled tobacco products in a variety of settings and at various ages. Such exposure in childhood was associated with increased risk of asthma in adults, and paternal smoking during childhood showed an association with allergic sensitisation in adults, indicating the potential to influence health several decades after the exposure. An association between maternal smoking during pregnancy and poorer physical control and coordination in 11-year-old children was described, providing another example of how secondary exposure to inhaled tobacco products may have the potential to influence health and development over the course of life. An aim of this body of work was to examine tobacco-related exposures at different life stages to demonstrate the diversity of outcomes and risks that may accumulate with age and different forms of exposure. This emphasises that effectively addressing problems associated with secondary exposure to inhaled tobacco products; requires that interventions be planned around a variety of exposures and outcomes.

The life-course approach adopted by this thesis introduces both strengths and potential weaknesses to the research. Paper I was limited somewhat as it collected retrospective information on whether other members of the household smoked when the participant was a child. Thus, these data could not tackle the issue of potential differences in association for maternal and paternal smoking. Paper II tackled this problem by collecting data on maternal and paternal smoking separately. This approach indicated that combining maternal and paternal smoking may mask an association with allergic sensitisation in offspring. A number of explanations are possible but a negative association with maternal smoking may reflect factors not directly due to ETS exposure and this may mask a positive association with ETS from other sources. Both papers I and II were based on retrospective data, which may introduce recall bias, although the second paper may have reduced reporting bias somewhat, by using an objective measure of allergic sensitisation, SPT.
Paper III reported airway symptoms associated with current ETS exposure, removing some problems of recall bias related to exposure.

The research for paper IV asked hospitality workers about symptoms and benefited from measures of ETS exposure: nicotine levels in the air before and after the introduction of smoke-free legislation in Sweden. This study objectively demonstrated a dramatic reduction in the level of ETS exposure and showed a major reduction in symptoms. While the respiratory and sensory symptoms that constituted outcome measures were based on subjective reports, the design used repeated measures in the same individuals, thus eliminating selection bias and some forms of reporting bias.

The longitudinal design of the final study (paper V) benefited from prospectively collected data for both the exposure: smoking during pregnancy and the outcome: measures of physical control and coordination at age 11 years. In addition to using standardised doctor-administered tests at age 11 to improve precision, a wealth of background information was available to address potential confounding by social and material factors.

The studies were performed in three nations (Sweden, Estonia and Great Britain) and involved data collection spanning a period of nearly 50 years beginning in 1958 and ending in 2006. With the exception of the Swedish Hospitality Workers Study (paper IV), which was made up of volunteers, the studies were general population based. The research was conducted with participants of varying ages, living in different countries, and this emphasises the extent of some risks associated with secondary exposure to inhaled tobacco products, demonstrating that the problem is not limited by region or age at exposure. The contribution of each paper is discussed in greater detail below.

**Paper I (Childhood ETS and asthma)**

The aim of this questionnaire study of adult never-smokers in Örebro, Sweden was to investigate associations between exposure to ETS during childhood and physician-diagnosed asthma. A modest increase in asthma risk was associated with earlier ETS exposure during childhood. Sweden has a low prevalence of daily smokers, but despite
this, ETS was the most commonly reported LAWI (a factor related to shortness of breath, wheezing, or coughing) among the general public.

Strength of this study is its large sample size (n=8,008) drawn from the general population, and the high participation rate (84%) of those initially contacted. Postal questionnaires are commonly used in respiratory epidemiological studies due to their relatively low cost and rapid data acquisition, but how reliable is a diagnosis of asthma identified by a postal questionnaire? Clinical validation of self-reported asthma has supported the ability of questionnaires to correctly identify asthma, for example by the OLIN and FinEsS studies.\(^9\)

**Limitations**

Identification of asthma was based on the question about physician-diagnosed asthma, and a single question has limitations. However, if only one question is used, the question concerning physician-diagnosed asthma is thought to be the most valid measure of asthma.\(^9\) Reporting bias is another possible concern. For example subjects with asthma or other respiratory symptoms may be more prepared to participate in this kind of study, and smokers may be less likely to complete questionnaires on smoking habits. However, detailed analyses have been carried out in the FinEsS and OLIN studies showing non-responders to have similar characteristics compared with respondents.\(^5\), and the relatively high participation rate (85%) may also limit selection bias.

The question about physician-diagnosed asthma did not identify when the diagnosis was made. As a positive response could indicate both current disease and previous childhood asthma, this could influence the reported prevalence. The range in age of participants from 20-65 years may influence precision. Older people may under-report asthma they had in early life. Also, the diagnostic criteria, and doctors’ and subjects’ awareness of asthma may have changed with time. Changes in the environment, urbanisation, and work and housing conditions may have resulted in changes in the distribution of asthma phenotypes leading to alterations in symptoms and degree of allergic sensitisation and influencing the likelihood of diagnosis.
Our ETS-exposure data were collected using retrospective reports in a questionnaire. As asthma problems may influence the reporting of ETS-exposure, the possibility of bias exists. The association between respiratory symptoms and ETS may be spuriously strengthened if subjects with childhood asthma were more likely to have suffered symptoms as a result of ETS-exposure and therefore were more likely to report this exposure compared with others who were exposed but did not experience symptoms. But opposing effects are also possible if subjects who had an asthma diagnosis (or asthmatic symptoms) in childhood influenced the smoking behaviour of people around them. It is possible that family members may have given up smoking due to asthma symptoms in the child. If that happened in early childhood, the child may be unaware of early ETS exposure, thus diminishing the associations that a study such as this could detect.

ETS-exposure during childhood was mainly an effect of the smoking behaviour of parents, which is related to a variety of factors like income, housing, education, family size and household crowding. Such factors could possibly also be associated with the risk of developing asthma, so confounding is a distinct possibility. The educational level of parents might also have influenced the awareness and the likelihood of an asthma diagnosis being made, as well as being associated with smoking behaviour. Smoking and its association with social class has changed during the last decades, for example in 1969, almost 50% of doctors in Sweden smoked compared with around 5% in 2001. Awareness in respondents of an association between asthma and ETS exposure could have influenced their reporting. However in 1995-96 when the postal questionnaire was distributed, scientific reports about such associations were scarce, consequently awareness in the general public should have been low.

A father or mother with asthma may be more likely to give up, or never start, smoking due to increased airway sensitivity. Thus a genetic predisposition (parents with asthma or allergy) may be linked to a reduced likelihood of being exposed to parental ETS. The risk of a child developing asthma is strongly related to asthma in parents, and may be 5-10 times higher if both parents have asthma. Thus, if parents with asthma or increased airway sensitivity were more likely to be non-smokers, it could
have reduced associations substantially. The stronger association between physician-diagnosed asthma and ETS-exposure during childhood in subjects without a family history of asthma could indicate that a family history of asthma and allergy may reduce the likelihood of family members smoking producing an overall masking effect in the study.

An important potential weakness is that the questionnaire did not separately identify smoking in mothers, fathers, and other inhabitants of the household. Such lack of precision may influence the results. In the clinical investigation in Paper II, paternal smoking showed a significantly positive association with the outcome (allergic sensitisation) while maternal smoking did not. This may be an important weakness since differing, possibly even opposing, effects of maternal and paternal smoking could mask an association.

**Assessing family history**

Paper I considered family history of asthma and how it may influence associations between ETS exposure and asthma. The postal FinEsS questionnaire included the following question: Have any of your parents, brothers or sisters had asthma? yes no/don’t know.

Some possible problems in analysing responses to this question might be:

- The number of siblings, *per se*, might be associated with the risk of developing allergic sensitisation (this was shown in paper II, where the number of older siblings was associated with a reduced OR for having a positive SPT).
- A greater number of siblings will increase the likelihood that at least one of them had an allergic disease; hence, the likelihood of having a positive family history may be influenced by family size.
- As discussed, public awareness, diagnostic criteria, and diagnostic methods relevant to asthma have varied among decades and generations. That may influence the reporting of family history in different age-groups (birth cohorts).
General conclusions

The stronger association between physician-diagnosed asthma and ETS-exposure during childhood in subjects without a family history of asthma is an interesting finding. Perhaps parents with a greater genetic predisposition to asthma were less likely to take up smoking or continue to smoke, due to increased airway reactivity. Thus, their children, who would also share a greater genetic predisposition to develop asthma, were less exposed to parental ETS.

Paper II (Childhood ETS and allergic sensitisation)

The FinEsS study in Örebro, Sweden, investigated associations between ETS-exposure during childhood and allergic sensitisation in adults, using a structured interview and SPT. A significant positive association of paternal smoking during the subject’s childhood with subsequent allergic sensitisation was observed, while maternal smoking was not associated with allergic sensitisation in offspring. A strength of the study is the general population based nature of the sample, and, importantly, SPT represents an objective measurement of the outcome. Parental smoking during the subjects’ childhood was also highly unlikely to influence the participation rate. The SPT was performed after the interview, thus its results could not have influenced reporting of ETS exposure.

We were also able to adjust for potential confounding factors, independent risks, and potential effect modifiers, including markers of material and cultural circumstances, to reduce the possibility that the results reflect parental smoking as a marker for other exposures.

Limitations

The participation rate was lower than is optimal (60%) which may result in selection bias: for example, people with airway disease or allergy may have been less likely to participate. However it is unlikely that parental smoking would have influenced participation directly, so this potential source of differential bias is not a major concern. Information on parental smoking during the subjects’ childhood was collected by retrospective interview and had a potential for recall error. However, the difference in association with allergic sensitisation for maternal and paternal smoking
suggests that the findings are not driven by a systematic tendency for allergic individuals to have reported parental smoking.

A problem similar to that discussed for Paper I would arise if subjects with allergic symptoms in childhood were more irritated by tobacco smoke and therefore more likely to remember and report ETS-exposure. That could have strengthened the association between allergy (positive SPT) and ETS-exposure. Again, the opposing associations for maternal and paternal smoking suggest that this is unlikely to offer a complete explanation for the results.

A commentary about this article (paper II) by van der Wouden et al. raised several issues. The first was whether we investigated individual allergens and the association of these allergens with parental smoking. We investigated the 15 allergens separately, but as there was no notable variation in their association with parental smoking, we combined them to create a measure of allergic sensitization to include all subjects with evidence of sensitisation to maximise statistical power, rather than examining a subset. Another question was if the risk of allergen exposure could be associated with the likelihood that parents smoke. If so it would suggest a possible source of confounding as parental smoking could be a marker for the offspring’s allergen exposure rather than being directly involved in the causal pathway for allergic sensitisation. However, this explanation alone seems rather unlikely given the divergent nature of the association of parental smoking with allergic sensitisation in offspring: paternal smoking is associated with an increased risk but there is evidence of a decreased risk with maternal smoking. If parental smoking was only a proxy marker for another exposure, we would expect similar associations with allergic sensitisation in offspring for smoking in both parents.

Dr van der Wouden and colleagues also found it unsurprising that modelling maternal and paternal smoking together altered the results of our analysis, suggesting that paternal smoking will play a much larger role in families where the mother does not smoke. However, we found evidence of opposing associations with allergic sensitisation for maternal and paternal smoking. Maternal smoking may be associated with a lower incidence of sensitisation through mechanisms different to passive smoke
exposure, thus masking the direct effects of this exposure. Therefore studies assessing
the association of parental smoking with allergic sensitisation must take into account
the potential masking influence of maternal smoking.

**Parental allergy, smoking behaviour and allergic sensitisation among offspring**
It is possible that parents with allergic disease may be less likely take up or continue
smoking due to the symptoms that smoking provokes, even among those with mild and
undiagnosed disease. As a higher proportion of females tend to experience symptoms
of allergic disease, one might speculate that females with a genetic predisposition for
allergic disease may be more likely to avoid smoking than are males. Such a
phenomenon is another possible explanation for the weak inverse association between
maternal smoking and allergic sensitisation among offspring. Mothers with a genetic
predisposition for allergy may be less likely to smoke and more likely to have a child
with allergic sensitisation. Such a mechanism could mask an association of ETS
exposure in childhood to a risk of allergic sensitisation.

**General conclusions**
A statistically significant positive association of paternal smoking during the subject’s
childhood with subsequent allergic sensitisation was observed, while maternal
smoking was not associated with allergic sensitisation in offspring. It is speculated that
the association with allergic sensitisation for childhood ETS exposure resulting from
maternal smoking may be confounded by factors such as pre-natal maternal smoking
or the effect of maternal genetic predisposition for allergic disease on her smoking
behaviour.

**Paper III (ETS and respiratory symptoms)**
This postal questionnaire study investigated associations of respiratory symptoms with
ETS exposure at home and in other localities among adult never-smokers in Estonia. It
showed a dose-dependent relationship between ETS exposure outside the home and
respiratory symptoms. The results indicated ETS exposures outside the home to be
associated with more pronounced effects than ETS exposures at home. This may be
because it is easier to avoid ETS exposure at home for those with respiratory
symptoms. Twice as many females as males reported that tobacco smoke caused breathlessness, wheezing, and coughing.

The strengths of the study were the sample size of approximately 18,000, of whom approximately 7,000 were never-smokers, the random selection from a general population, and a high participation rate (77%). Furthermore, a high smoking prevalence in Estonia, and almost no societal restrictions on tobacco smoking in public areas at the time of the study, gave a high number of exposed subjects. As discussed in paper I, clinical validations of self-reported asthma\(^{90}\), and analyses of non-response support the validity of questionnaire data\(^{50, 57, 77}\).

**Limitations**

A potential weakness is the lack of validation regarding smoking status and ETS exposures. Smoking status was self-reported, which increased the risk of misclassification. However, a meta-analysis\(^{68}\), of the validity of self-reported smoking suggested a high sensitivity (87%) and specificity (89%). Riboli et al.\(^{74}\) estimated that the proportion of females misreporting active smoking habit was approximately 2%. It is unlikely that misclassification could have been of sufficient magnitude to explain the strong ETS effects observed in both females and males in this study. Some non-smokers may not have reported ETS exposure even if they were exposed and could have been misclassified as unexposed, which would have diminished the association. Of course, an opposite effect is possible, which would have spuriously strengthened the associations.

Owing to increased bronchial reactivity, subjects with asthma or chronic obstructive pulmonary disease might be more aware of ETS exposure and overestimate the length of exposure, leading to an overestimation of the risk\(^{10}\).

This potential reporting bias is difficult to rule out as levels of ETS exposure were not measured directly. This is a limitation this study shares with paper I and II.

Subjects with airway disorders might be more likely to avoid ETS and, if successful, will report less exposure, leading to an underestimation of the potential risk. This may partly explain the lack of association between ETS in the home and respiratory
symptoms. Individuals in a family might be more likely (compared with workmates) to stop or reduce smoking if a family member develops respiratory symptoms. Lam et al.\textsuperscript{54} concluded that “stronger effects were observed at work where the risk of ETS exposure was much greater, because subjects spent more time among a larger number of smoking co-workers at work than at home.” Our question did not distinguish ETS exposure at work from other sources of ETS exposure outside the home. It seems likely that a high proportion of ETS exposure outside the home was related to work, as most of the subjects were of working age, but we cannot exclude the possibility that spending leisure time in bars and other smoky environments contributed to the ETS-exposure. Anderson et al. showed that the level of a tobacco smoke-specific carcinogen in urine was six times higher among females exposed to ETS at home than among non-exposed females\textsuperscript{4}. As paper III and Lam’s\textsuperscript{54} research has indicated that ETS exposure in the workplace might represent a significant risk, a future study of tobacco smoke-specific carcinogens in urine after ETS exposure at work was proposed.

**General conclusions**

In summary, the reported duration of daily passive smoking outside the home was associated with an increased prevalence of respiratory symptoms. The dose-dependent association is consistent with a causal interpretation.

**Paper IV (ETS and smoke-free legislation)**

The implementation of smoke-free legislation in Sweden was associated with a substantial reduction in respiratory and sensory symptoms among non-smoking hospitality workers.

Due to enrolment of participants from nine different geographical areas, the sample represented a range of climates and living conditions throughout Sweden. We were able to enrol many gaming workers, who, prior to this, had scarcely been studied in relation to ETS-exposure\textsuperscript{46}.

Pre- and post-ban data were collected from the same individuals, employed at the same workplace, and the symptoms were recorded at the same time of year, thereby eliminating seasonal variations and some other possible sources of bias. We used
xtlogit analysis, which is specifically designed for longitudinal data when there is an explicit time component (panel data), so that repeated measures can be examined, even if some subjects are lost to follow-up. One advantage of this design will be almost perfect control for exposure levels. Subjects not followed up did not differ from the overall group in terms of sex and attitudes towards the ban prior to its introduction, reducing the risk of selection bias.

Papers I-III used subjective reports, questionnaire data and interviews to assess subjects’ recall of ETS-exposure. As questionnaire data about ETS exposure can lack precision and objectivity, we attempted to complete ETS-exposure assessments with measures of nicotine levels in the air. It was also specific to ETS exposure at work. Sampling of cotinine from bodily fluids has been used in similar studies of hospitality workers. However, urinary cotinine is influenced by individual physiological (respiration, absorption, metabolism and excretion), temporal (exposure duration) and physical (exposure concentration) parameters. Factors other than exposure at work (such as leisure time exposure) could confound urinary cotinine measures. Assessment of ETS-exposure in smokers or snuff-users is not possible with urinary cotinine testing due to the masking effect of their own tobacco use. Among non-smokers in this study, 35% had pre-ban urinary cotinine values below the detection threshold making it impossible to detect a further reduction in a substantial part of the subjects using this method. However, the large reduction of nicotine detected in the air confirms a reduction in ETS levels. Non-smokers wore the detectors but smokers did not. By placing the air nicotine detectors in the locality when we investigated smokers we attempted to avoid spuriously high values caused by the subjects own smoking (when he or she hold a cigarette close to the nicotine sampler).

In the Swedish Hospitality Workers Study, we did not estimate tobacco smoke-specific carcinogens in urine, as was discussed in Paper III. However, the nicotine in air measure offered a proxy method. To evaluate the potential value of the ban on future health of participants, we estimated the proportion exposed to nicotine in the air above a specified level. A potent bladder carcinogen, 4-aminobiphenyl (4-ABP), is present in ETS and has been shown to bond covalently to haemoglobin. We chose a cut-off
level (0.5 μg/m³), previously identified as indicating potentially hazardous levels of 4-ABP³⁴.

Limitations
The voluntary nature of the recruitment process is likely to have resulted in selection bias. We do not have data on the characteristics or number of potential participants, as recruitment was through a form of advertising. Volunteers may have been less likely to smoke and have characteristic attitudes to smoking and the legislation, so the population may not be entirely representative of the target working population. The loss to follow-up may have further selected non-smokers and may also have implications for the representativeness of non-smokers. The somewhat complicated and time-consuming procedures may have selected subjects that were more positive to legislation, thus introducing potential bias. A larger decline in symptom prevalence has been shown among workers with a positive attitude²⁶, possibly reflecting bias. The large proportion of women, which according to papers I and III, may be more reactive to tobacco smoke, may have influenced the prevalence of reported symptoms. However the proportion of males to females in the study was the same pre- and post-ban.

Pre-ban as well as post-ban we were able to assess urine cotinine in 79% of the subjects, thus there was a risk of smoking status misclassification in the remaining subjects. This could underestimate the benefits of legislation as the greatest change was seen among non-smokers. Although the attrition rate of 21% between sweeps is not negligible, it is not unexpected, as this type of work is often casual and seasonal and frequent job changes are common³, ⁶². Thus the results are more likely to reflect the characteristics and views of those workers in more stable employment.

General conclusions
The smoke-free workplace law in Sweden has reduced ETS levels for some of the most heavily exposed occupational groups, as indicated by an objective exposure measure. It was also associated with a reduction of symptoms, some of which, such as cough, are likely to have an impact on quality of life¹⁵. In the long term, a reduction
in hospitality workers’ ETS exposure may result in other important health effects as ETS contains carcinogens\textsuperscript{34} and it is also a recognised cause of atherosclerotic disease\textsuperscript{6} and other smoking related diseases\textsuperscript{22,93,98}.

This study of hospitality workers in Sweden before and after legislation indicates that this form of prevention on a societal level may have beneficial effects, both improving quality of life and dramatically reducing potentially toxic exposures.

**Paper V (physical control and coordination)**

In this British cohort study we found an association between maternal smoking during pregnancy and poorer performance in measures of physical control and coordination in 11-year-old children. In the unadjusted analyses, the five investigated measures were associated with maternal smoking, and in three (picking up matches with right and left hand, and copying design) the association remained statistically significantly independent of multiple markers of social and material conditions in childhood.

As in paper I and III, the sample size was large (> 10,000 children and mothers) and it represented a general population-based group. The material and methods used in this study had major advantages. The exposure data (smoking during pregnancy) were collected prospectively. We were able to adjust for a variety of important indicators of material and social circumstances.

**Limitations**

A potential weakness of this study is the possibility that the association of maternal smoking in pregnancy with poorer motor competence at age 11 years reflects social factors rather than a more direct biological mechanism. However, we have attempted to tackle this issue. The measure of exposure was recorded prospectively and the outcome was assessed in a medical examination. We adjusted for a variety of indicators of material and social circumstances, but this did not eliminate statistical significance. Indeed, adjustment for measures such as birth weight may represent over-adjustment, as maternal smoking could influence them. This would result in more conservative estimates of association, but we opted to do this as birth weight is also an important predictor of current and future socioeconomic disadvantage and so any association independent of this is less likely to be confounded by such factors.
The associations of poorer neurological function in children with greater risk of T2DM and obesity in later life cannot be explained entirely by maternal smoking during pregnancy. The associations between maternal smoking and poorer motor competence are more modest than that seen between motor competence and later obesity previously observed using these data\textsuperscript{67}. However smoking during pregnancy may be one of several exposures over the course of life that adversely influences neurological function as well as increasing the risk of diseases such as T2DM and obesity.

In general the associations were more pronounced in tests of the left hand. This finding is consistent with an earlier study indicating the most pronounced association between maternal smoking in pregnancy and poorer coordination is in the non-dominant side\textsuperscript{20}. Laterality was not associated with maternal smoking, thus should not be a confounding factor.

The majority of associations between tests and maternal smoking were more pronounced or were solely found in male rather than female offspring. While this could be due to socially determined sex differences, we believe this finding is consistent with a biological mechanism. Animal studies have shown that in utero exposure to nicotine result in a variety of sex-specific effects in brain development and behaviour\textsuperscript{25, 47, 69, 70, 75, 79}. Furthermore nicotine reduces plasma testosterone in male offspring\textsuperscript{97}.

The impact of prenatal nicotine exposure on neurological performance in humans is scarcely studied, and, to our knowledge, there is only one previous study suggesting sex-specific differences\textsuperscript{38}. However that study included less than 200 subjects, was non-prospective, and investigated combined prenatal and adolescent exposures to tobacco smoke\textsuperscript{56}. 

56
General conclusions
Maternal smoking during pregnancy may influence neurological development and function as reflected in physical control and coordination. The association is clearly stronger for the left hand, and males are most affected.

What is new in this thesis and discussion of the main results
Several studies have indicated that childhood exposure to ETS is associated with an increased prevalence of asthma. Paper I indicated this association is stronger in subjects without a family history of atopic disease. The suggestion was that a family history of asthma indicating genetic predisposition is associated with reduced ETS exposure as affected parents are less likely to smoke.

Paper II indicates opposing associations for maternal and paternal smoking with allergic sensitisation in offspring. Maternal smoking would, for many subjects, have included in utero exposure as well as ETS exposure in childhood. An opposite effect of such exposure may be possible; exposure in utero may affect the immune system in a different way from inhalation of ETS. An alternative explanation is that a genetic predisposition to allergic disease may encourage females to avoid smoking to a greater extent than it does males. Such mothers may be less likely to smoke but more likely to have offspring inheriting a higher risk of allergic disease. Such associations could mask a causal role of ETS exposure in childhood for allergic disease if mothers are a source of ETS.

A work by Lam et al. failed to show a dose-dependent relationship between ETS exposure and respiratory symptoms in females\(^5\); however, paper III showed a clear dose-dependent association and indicated that never-smoking females were at least as sensitive as males to ETS exposure. Females also reported irritation to cigarette smoke more often. Females have smaller airways than men, which could be one potential explanation. Also, during adulthood, women are more susceptible to the effects of smoking and more likely to develop asthma than men\(^7\).

The fourth paper included a majority of female subject. It also included gaming workers, an occupational area in which ETS-exposures had rarely been studied. More
gaming workers than other hospitality workers were exposed to a potentially hazardous level of ETS exposure before legislation, and our study showed that gaming workers gained as much as other hospitality workers in reduction of ETS exposure levels and symptom relief. There may also be a notable reduction in exposure outside work, probably because hospitality workers visit bars and restaurants as customers.

The thesis also suggests that measuring nicotine levels in the air to assess ETS exposures in workplaces has the following advantages.

- It can serve as a method to measure workplace specific ETS exposure (since measurements will not be influenced by smoking during leisure time).
- Oral tobacco users can be included (only a slight modification of the sampling technique is required to include smokers).
- Assessing reduction in ETS exposure of subjects with low to moderate exposure levels was possible.

Paper V provides the strongest evidence to date that maternal smoking during pregnancy subtly influences neurological development or function relevant to motor competence in offspring. In all tests, the strongest associations were in children whose mothers smoked most, thus indicating a dose-dependent relationship.

It is notable that in general the associations were more pronounced in tests of the left rather than the right hand. This is most likely to be because left is the non-dominant side in the majority of individuals. This finding is consistent with an earlier, in comparison small study, indicating the most pronounced association between maternal smoking in pregnancy and poorer coordination in the non-dominant side\textsuperscript{20}. Laterality was not associated with maternal smoking, eliminating it as a confounding factor.

Paper V provided another example how health-outcomes in males and females may vary. The majority of associations between tests of motor competence and maternal smoking were more pronounced or were solely found in male offspring. This may be because in utero exposure to nicotine may result in sex-specific effects in brain development in humans as has been demonstrated using animal models\textsuperscript{25, 47, 69, 70, 75, 79}.
Concluding remarks

The spread of tobacco use in Europe and most other parts of the world started some five hundred years ago, but began earlier among Native Americans. Little was known about health effects at that time, children were even forced to use tobacco. We know much more now, particularly about effects on the smoker, but this has not prevented widespread tobacco use and attendant damage to health. Tens of thousands of scientific reports concerning the detrimental effects by tobacco smoking have accumulated over recent decades, but at the same time the number of smokers in the world has increased, especially in developing countries\textsuperscript{44}.

The studies in this thesis have shown that exposure to ETS during childhood was associated with an increased prevalence of asthma, and allergic sensitisation. ETS exposure in adult non-smokers was associated with a dose-dependent increase in the prevalence of respiratory symptoms. The frequency of symptoms in hospitality workers declined substantially in non-smokers after the introduction of non-smoking legislation. Maternal smoking during pregnancy was associated with a modest reduction in motor competence among offspring and may suggest an adverse influence on neurological development or function.

It is hoped that it will be impossible to ignore expanding knowledge about the effects of secondary exposure to inhaled tobacco products, and appropriate prevention methods will continue to develop.
ACKNOWLEDGEMENTS

I would like to offer my thanks to all the persons and colleagues involved in the various projects and all others who have shared their knowledge and experience with me, and who have supported and encouraged me on the way to this thesis.

First I want to say a cordial thank you to Professor Scott M. Montgomery, my senior supervisor during my time at the Department of Health Sciences, Örebro University. I admit I did not giggle all the time I wrote, but we had many a good laugh during the (long) way to the coffee machine. Thank you for your deep knowledge, creativity, humour, patience, and enthusiasm while advising, correcting, supporting, contradicting, focusing me. You warned me several times for an excessive use of exclamation marks. At last I understood when to use them - Thank you!

Thank you to my secondary supervisors Professor Kjell Larsson and Professor Bo Lundbäck. Thank you for your deep expertise, knowledge, helpfulness, and patience.

To Jaak Kiviloog, without whom I would never have been on the track to this thesis.

Last but not least, my sincere thanks to Göran Boethius, for your patience, and the gigantic work to initiate and happily fulfil The Swedish Hospitality Workers Study.

I would also like to offer special thanks to:

- Marianne Alton the former head of the Department of Respiratory Medicine, Örebro University Hospital. You facilitated in all ways the first struggling steps on the hard scientific road and you encouraged me to go on with tobacco prevention. For your deep interest in the research, your humour, patience, kindness and everything you gave us - Thank you!
- Lennart Nilholm, the present head of the Department of Respiratory Medicine, Örebro University Hospital. Thank you for continuing in the same way.
- Margaret Landin, the medical Library, Örebro University Hospital. Thank you for patiently teaching me Endnote, and for all other help I got from you and your colleagues.
- The FinEsS-team; Iréne Eriksson, Lotta von Friesendorff, Margot Frisk, Jan Hallström, and Silvia Assi, and all the staff at the Department of Respiratory Medicine, Örebro University Hospital. Anders Magnuson, statistician at the Department of Health Sciences, Örebro University.
• Ing-Liss Bryngelsson, Håkan Westberg and all the other helpful and expertise
people at the Occupational and Environmental Medicine, Örebro University
Hospital.
• Lucidus Consultancy for professional help with the language.

• Finally a warm thank to my beloved family.

• Financial support for these studies has come from:
  • Hjärt-Lungfonden
  • Folkhälsoinstitutet
  • Cancerfonden
  • The Department of Respiratory Medicine, Örebro University Hospital.
References


Errata in Paper III

Abstract: …

In original paper it is written:
…ETS exposure at home was more common in females (31% versus 19%), while exposure outside of the home was more common in males (53% versus 7%).

Should be:
…ETS exposure at home was more common in females (31% versus 19%), while exposure outside of the home was more common in males (53% versus 37%).
APPENDIX I

The FinEsS Study

During the Finnish Chest Physicians’ meeting at Oulu in 1994, research co-operation between northern Sweden (OLIN studies) and northern Finland (Länsi-Pohja Central Hospital) was initiated. At the same time, colleagues from Örebro Central Hospital in Sweden and the Pneumonology Department at the Clinical and Experimental Research Centre of Tallinn, Estonia, were about to start similar co-operation. It became apparent that broader co-operation could be of mutual benefit, and the FinEsS study co-operation began among these four centres.

Soon after, Helsinki and Stockholm were invited to participate.

Organisation

Participants on the steering committee of the FinEsS study were Associate Professor Bo Lundbäck (chair), Stockholm and Luleå, Professor Anssi Sovijärvi, Helsinki, Professor Lii Jannus-Pruljan (Tallinn), Professor Kjell Larsson, Stockholm, and Associate Professor Jaak Kiviloog, Örebro. In the initial phase, Professor Lauri A. Laitinen, Helsinki, Professor Markku M. Nieminen, Tampere, and Professor Per Malmberg, Stockholm, also participated. During recent years, Eva Rönmark, PhD, has participated in data management and supervision of data analyses of asthma and allergy.

The statisticians, docent Elsy Jönsson, Umeå, and Docent Matti Kataja, Tampere, have been responsible for data management for statistical analyses in the FinEsS study, assisted by the statisticians Anders Magnusson, Örebro, and Ola Bernhoff, Haparanda. Associate Professor Anders Oden, Göteborg, participated in special analyses of smoking-associated risks for COPD.

Co-ordinators were, when the study was conducted, Mai Lindström, PhD, Luleå (questionnaires), Britt-Marie Sundblad, PhD, Stockholm (lung function), and Irene Eriksson, SRN, Örebro (skin prick tests). In Estonia, Associate Professors Helle-Mai Loit and Jaak Pölluste led the study, and statistician Tanja Veidebaum the data management.
APPENDIX II

Allergens and SPT methods in paper II

Allergen extracts were labelled in histamine equivalent prick units (HEP), weight/volume (w/v), or biologic units (BU). Otherwise other stated, the allergens were provided by ALK, Hørsholm, Denmark.

Allergens:

Two house dust mites (Dermatophagoides pteronyssinus (10 HEP) and Dermatophagoides farinae (10 HEP); two storage mites (Lepidoglyphus destructor (10000 BU/ml) and Acarus siro (10000 BU/ml, Laboratorium Diephuis, Netherlands); four furred animals (cat (10 HEP), dog (10 HEP), cow (1:100 w/v), and horse (10 HEP)); pollen from birch (10 HEP), timothy (10 HEP), and mugwort (10 HEP); two moulds (Alternaria alternata (1:20 w/v) and Cladosporium herbarum (1:20 w/v)); latex (100 IR/ml, Alyostal ST-IR, Stallergenes SA, France); and German cockroach (1:10 w/v, Bayer, Elkhart, IN, USA). Lancets from ALK were used. Histamine dihydrochloride (10 mg/ml) was used as positive control and 50% glycerol as negative control.
Environmental Tobacco Smoke Exposure During Childhood Is Associated With Increased Prevalence of Asthma in Adults*

Matz L. Larsson, MD, FCCP; Margot Frisk; Jan Hallström, MD; Jaak Kiviloog, MD, PhD; Bo Lundbäck, MD, PhD

Objective: To examine if exposure to environmental tobacco smoke (ETS) during childhood has an impact on asthma prevalence in adults, and to identify the amount of nuisance from ETS and other lower airway irritants (LAWIs) in a city population.

Design: A postal survey.

Setting: The municipality of Örebro, Sweden.

Participants: A total of 8,008 randomly selected inhabitants aged 15 to 69 years.

Measurements: Exposures, airway symptoms, and respiratory history were assessed using a questionnaire.

Results: The response rate was 84%. In never-smokers with childhood ETS exposure, the prevalence of physician-diagnosed asthma was 7.6% vs 5.9% in nonexposed subjects (p = 0.036). In never-smokers without a family history of asthma, the prevalence of physician-diagnosed asthma in subjects reporting childhood ETS exposure was 6.8% vs 3.8% in nonexposed subjects (p < 0.001). Subjects with childhood ETS exposure were more likely to start smoking in adulthood. The prevalence of ever-smokers was 54.5% vs 33.8% (p < 0.0001) in nonexposed subjects. ETS was the most commonly reported LAWI in the total sample (21%), followed by exercise in cold air (20%), dust (19%), exercise (16%), perfume (15%), cold air (12%), pollen (10%), and pets (8%). All LAWIs were more frequently reported by women.

Conclusions: Childhood exposure to ETS is associated with an increased prevalence of asthma among adult never-smokers, especially in nonatopic subjects. Children exposed to ETS are also more likely to become smokers. ETS is as a major LAWI.

(CHEST 2001; 120:711–717)

Key words: asthma; environmental tobacco smoke; respiratory symptoms

Abbreviations: CI = confidence interval; ETS = environmental tobacco smoke; LAWI = lower airway irritant; OR = odds ratio

In spite of educational campaigns, stricter tobacco control laws, and a declining number of daily smokers in Sweden, which is currently approximately 20% of the adult population,1 environmental tobacco smoke (ETS) is still a major health problem in workplaces, public areas, and many homes.

ETS is a risk factor for lung cancer2 and coronary heart disease.3 More than 3,800 different compounds, including nicotine, carbon monoxide, benzene, formaldehyde, and acrolein, are produced from a burning cigarette.4 In a Danish study,5 55% of nonsmokers and 25% of smokers experienced discomfort when exposed passively to tobacco smoke, with severe discomfort reported by 9% of Danish men and 17% of women.

The eyes are the most common site for irritation, and the nose is the second most common site.6 For many subjects with asthma, short-term exposure to ETS is associated with respiratory symptoms,7 and it has also been reported to increase bronchial reactivity to histamine.8 The role of ETS as a subjective lower airway irritant (LAWI) in a general population, however, has not been well studied.

*From the Department of Lung Medicine (Drs. Larsson, Hallström, and Kiviloog), Örebro Medical Center Hospital, Örebro, Sweden; the Department of Public Health and Caring Sciences (Ms. Frisk), Uppsala Universitet, Sweden; and the Respiratory Unit (Dr. Lundbäck) Department of Occupational Medicine, National Institute for Working Life, Stockholm, Sweden. Financial support was provided from The Cancer Fund, Sweden, and The Research Committee of Örebro County Council. Manuscript received May 23, 2000; revision accepted April 11, 2001.

Correspondence to: Matz Larsson, MD, FCCP, Department of Lung Medicine, Örebro Medical Center Hospital, SE-701 85 Örebro, Sweden; e-mail: matz.larsson@orebro.se
Children are more vulnerable to ETS than adults, since the respiratory and immune systems are not fully developed; additionally, children spend more time at home.9 Many studies10–12 have shown ETS to be associated with respiratory symptoms in children. The relative risk of asthma in children with smoking mothers has been reported to be 1.2 to 2.6.11 The pooled odds ratio (OR) for asthma prevalence from 14 case-control studies was 1.37 (95% confidence interval [CI], 1.15 to 1.64) if either parent smoked, and the association between parental smoking and asthma appeared to be stronger in nonatopic children.12 The available literature13,14 concerning childhood exposure for ETS and the rates of asthma later in life is limited and focused on young adults.

The aim of this study was to investigate if ETS exposure during childhood at home was associated with a higher prevalence of asthma and respiratory symptoms later in life. A second aim was to compare ETS with other environmental factors or circumstances with a known potential to cause breathing problems.

**Materials and Methods**

This study was a part of the FinEsS studies: epidemiologic studies in Finland, Estonia, and Sweden on the prevalence of asthma, chronic bronchitis, COPD, type-1 allergy, respiratory symptoms, and risk factors for those conditions. This article is based on the Örebro portion of the study material. The study was approved by the Research Ethics Committee of Örebro County Council.

**Study Area**

The municipality of Örebro is a medium-sized city in the middle of Sweden, situated at low altitude and covering 1,360 square kilometers. The population was (in 1994) 118,606 inhabitants, with a population density of 87 per square kilometer. Approximately 87% of the population was living in an urban/suburban area. The mean January temperature is −4.0°C, and the mean July temperature is 16.8°C. The annual mean temperature is 6.1°C. The main occupations are public services (78%) and industrial labor.

**Study Population**

From the population in Örebro (80,569 inhabitants aged 15 to 69 years), a random total sample of 8,008 individuals stratified on 10-year age bands and gender was selected. The study dimension was determined based on a predicted response rate of 75%, which would provide an 80% probability in every strata to detect a difference in prevalence between Örebro and Estonia of approximately 2 to 3%. We used the Örebro County Council population register, which updates its register at fortnightly intervals, to identify subjects.

**Questionnaire**

The questionnaire was developed from a revised version of The British Medical Research Council questionnaire15 and had been previously used in several Swedish studies.16 The postal questionnaire with an explanatory note, envelope, and a stamp was sent to the study sample during the winter from 1995 to 1996. In case there was no response, two reminders were sent to the subjects. The questionnaire included questions about respiratory symptoms and diseases, including recurrent wheeze, attacks of shortness of breath, long-standing cough, sputum production, asthma, allergic rhinitis, chronic bronchitis, use of antiasthmatic drugs, and symptoms in special circumstances and varying exposures. Furthermore, the questionnaire included questions about smoking habits, occupation, and family history of the above-mentioned diseases. Depending on special interest, an extra question about childhood exposure to ETS at home was added in the study in Örebro: “Do or did any of your parents/relatives smoke at home when you grew up?” All questions were answered with either “yes,” or “no,” not as far as I know.”

**Definitions**

Ever-asthma was defined as a positive response to the question, “Have you ever had asthma?” Physician-diagnosed asthma was defined as a positive response to the question, “Have you been diagnosed as having asthma by a doctor?” Childhood exposure to ETS at home was defined as a positive response to the question, “Do or did any of your parents/relatives smoke at home when you grew up?” Childhood ETS exposure was used as an exposure variable.

**LAWI**

There were nine questions about factors and/or circumstances with a potential to cause LAWI: “Do you become breathless, wheeze, or have attacks of cough when exposed to (1) exercise; (2) cold air; (3) exercise in cold air; (4) dust; (5) tobacco smoke; (6) car exhaust fumes; (7) strong smells, eg, perfume, spices, printers ink; (8) pollen from plants and/or trees; (9) pets?” If a positive response was given, the factor and/or circumstance was defined as a LAWI. Ever-smokers were defined as active smokers or ex-smokers. Ex-smokers were defined as subjects who successfully had stopped smoking ≥12 months prior to the survey.

**Statistical Analysis**

Statistical analysis was performed using software (Statistical Package for the Social Sciences; SPSS; Chicago, IL). Fisher’s double-sided Exact Test was used for bivariate calculations. Risk factors for physician-diagnosed asthma among never-smokers without a family history of asthma were calculated by using multiple logistic regression analysis.

**Results**

**Participation and Smoking Habits**

The response rate was 84% (n = 6,732). In addition, 3% (n = 243) returned a blank questionnaire, and these were not included in the analyses. Data for the smoking habits in the main sample are shown in Table 1. There were 3,556 never-smokers (52.8%), 1,676 smokers (24.9%), and 1,257 ex-smokers (18.7%) in the total sample, and 243 subjects (3.6%) gave no answer about their smoking habits.
Childhood ETS Exposure and Smoking Habits Later in Life

Exposure to childhood ETS was most common among subjects aged 30 to 49 years (Fig 1). The part of the sample reporting childhood ETS exposure included significantly more ever-smokers, 54.5%, compared to 33.8% (p < 0.0001) among “nonexposed” subjects (Fig 2). The difference between exposed and nonexposed subjects was most clearly seen in the 15-year to 19-year age group, where the smoking prevalence was 36.9% vs 13.1%.

Table 1—Smoking Habits in the Total Sample

<table>
<thead>
<tr>
<th>Smoking Habits</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never-smoker</td>
<td>1,657 (50.5)</td>
<td>1,899 (55.0)</td>
<td>3,556 (52.8)</td>
</tr>
<tr>
<td>Smoker</td>
<td>821 (25.0)</td>
<td>855 (24.8)</td>
<td>1,676 (24.9)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>701 (21.4)</td>
<td>556 (16.1)</td>
<td>1,257 (18.7)</td>
</tr>
<tr>
<td>No answer about smoking</td>
<td>101 (3.1)</td>
<td>142 (4.1)</td>
<td>243 (3.6)</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%).

Childhood ETS exposure was a risk factor for physician-diagnosed asthma, with a prevalence of 7.6% in exposed subjects vs 5.8% in nonexposed subjects (p = 0.035). Data on never-smokers with or without a family history of asthma are shown in Table 3. In never-smokers without a family history of asthma, the prevalence of physician-diagnosed asthma in subjects reporting childhood ETS exposure was 6.8% vs 3.8% in nonexposed subjects (p < 0.001). Also, breathing difficulties during exercise, in cold air, and from tobacco smoke were more common if subjects had been exposed to childhood ETS (Table 3). In never-smokers with a family history of asthma, no significant differences in prevalence of asthma, or breathing difficulties in special circumstances or due to different exposures were found (Table 3). The difference in asthma prevalence between subjects exposed and not exposed to childhood ETS was more pronounced in the younger half of the population (Table 4).

Multivariate Relationships

Risk factors for physician-diagnosed asthma and symptoms in special circumstances among never-smokers without a family history of asthma were calculated by using multiple logistic regression analysis (Table 5). ETS was a significant risk factor for physician-diagnosed asthma (OR, 1.82), breathing difficulties at exercise (OR, 1.45), breathing difficulties from cigarette smoke (OR, 1.25), and breathing difficulties from pets (OR, 1.41). Breathing difficulties during exercise were significantly more common in younger persons. Physician-diagnosed asthma was
significantly more common among manual workers in industry (OR, 1.97) and self-employees other than professionals (OR, 2.81).

ETS and Other LAWIs

The proportion of subjects reporting ETS to be a LAWI is shown for the general population and for asthmatic subjects in Figure 3. In the whole sample, 21% of the subjects reported ETS to be a LAWI. When excluding active smokers from the total sample, the frequencies for ETS and the second most frequent answer, exercise in cold air, were 22% vs 19%, respectively.

Among asthmatic subjects, ETS was a common LAWI (50%), although it was less commonly reported than exercise in cold air (69%), dust (62%), exercise (58%), and cold air (55%). All LAWIs were more frequently reported by women. The prevalence rates were as follows: ETS (women, 24%; men, 18%), exercise in cold air (women, 22%; men, 19%), dust (women, 20%; men 18%), exercise (women, 17%; men, 15%), strong smells (women, 18%; men, 12%), cold air (women, 14%; men, 10%), car exhaust fumes (women, 13%; men, 9%), pollen (women, 11%; men, 10%), and pets (women, 9%; men, 7%).

Discussion

Parental ETS has a strong association to childhood asthma.2,9–12 Our study showed that ETS exposure in childhood was also associated with a higher asthma prevalence in adult never-smokers. Especially in never-smokers without a family history of asthma, ETS exposure in childhood seems to be an important risk factor for asthma. This is in accordance with previous reports.12 The result for the reverse set of conditions, never-smokers with a family history of asthma, although not statistically significant, appears

Table 2—Prevalence of Asthma and Other Conditions in Never-Smokers in Relation to ETS Exposure at Home During the Growing-Up Period

<table>
<thead>
<tr>
<th>Diseases or Conditions</th>
<th>Exposed (n = 1,625), %</th>
<th>Not Exposed (n = 1,926), %</th>
<th>Difference by Exposure p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician-diagnosed asthma</td>
<td>7.6</td>
<td>5.8</td>
<td>0.035</td>
</tr>
<tr>
<td>Ever-asthma</td>
<td>8.6</td>
<td>7.1</td>
<td>0.059</td>
</tr>
<tr>
<td>Use of asthma medicines</td>
<td>8.2</td>
<td>7.2</td>
<td>0.283</td>
</tr>
<tr>
<td>Wheezing</td>
<td>4.5</td>
<td>4.7</td>
<td>0.792</td>
</tr>
<tr>
<td>Attacks of shortness of breath during the night</td>
<td>8.5</td>
<td>7.0</td>
<td>0.089</td>
</tr>
<tr>
<td>Breathing difficulties during exercise</td>
<td>15.1</td>
<td>12.7</td>
<td>0.038</td>
</tr>
<tr>
<td>Breathing difficulties in cold air</td>
<td>12.2</td>
<td>9.4</td>
<td>0.006</td>
</tr>
<tr>
<td>Breathing difficulties from cigarette smoke</td>
<td>25.0</td>
<td>21.4</td>
<td>0.011</td>
</tr>
</tbody>
</table>
to differ from previous reports. We believe this could be explained by a sickness-related tendency for asthmatic parents to give up or never start smoking, and of course that asthma heredity is by far a more important risk factor than ETS exposure. There is no doubt that asthma heredity is a major risk factor for asthma, but this fact also provokes the question, What role does heredity play in asthmatic parents with asthma because of former childhood ETS exposure? And another question is posed, Could children exposed to ETS give their future child an increased risk of asthma?

During the 1950s and 1960s, smoking habits in Sweden reached a peak level. In 1963, approximately 50% of Swedish men and 25% of women were daily smokers. During last 3 decades, the prevalence of daily smokers has been reduced in Sweden, especially in men. The trend to reduce smoking habits in women started some years later than among men and progressed to a lesser extent, leading to a somewhat higher prevalence of smoking women than men nowadays.

One possible conclusion is that the older cohorts have been relatively more exposed to paternal ETS and younger cohorts relatively more to maternal ETS, which is known to give more severe effects. The questionnaire that was employed provided only yes or no/do-not-know answers about ETS exposure during childhood at home. Therefore, we lack more detailed information about the nature and the duration of the childhood ETS exposure. If low-degree exposure was common in our exposed group, or if the unexposed group was widely exposed to ETS sources outside the home, the result would be an underestimation of the risk for ETS-associated asthma. We cannot exclude the possibility of reporting bias where asthmatics are more prone than nonasthmatics to report ETS exposure, which would give an overestimation of the risk. In any event, the ETS-associated risk for asthma in adults observed in our study is similar to that reported in many studies of childhood asthma.

The diagnosis of asthma was based on the question about physician-diagnosed asthma, and of course a single question may have some limitations. However, the question concerning physician-diagnosed asthma was the most valid measure of asthma if only one question was used in order to identify asthma. Our study clearly demonstrates the importance of collecting data about childhood ETS exposure in epidemiologic studies of asthma prevalence, where childhood exposure could otherwise be an important confounder. Further questions about whether or not the ETS exposure was maternal, paternal, or both may also be relevant.

Current and former smokers were excluded from the part of the study concerning childhood ETS exposure and asthma prevalence because the association between active smoking and asthma is uncertain in the current literature. This might partly be explained by a tendency for asthmatics to stop smoking. Secondly, a period of active smoking may be a confounder; for instance, smoking is associated with an increased sensitization against occupational allergens. In addition, active or former smoking could cause respiratory symptoms and deterioration.

### Table 3—Prevalence of Asthma and Other Conditions in Never-Smokers With and Without a Family History of Asthma in Relation to ETS Exposure at Home During the Growing-Up Period

<table>
<thead>
<tr>
<th>Diseases or Conditions</th>
<th>Never-Smokers With a Family History of Asthma</th>
<th>Never-Smokers Without a Family History of Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposed (n = 273), %</td>
<td>Not Exposed (n = 300), %</td>
</tr>
<tr>
<td></td>
<td>Difference by Exposure p Value</td>
<td>Difference by Exposure p Value</td>
</tr>
<tr>
<td>Physician-diagnosed asthma</td>
<td>11.4</td>
<td>16.0</td>
</tr>
<tr>
<td>Ever-asthma</td>
<td>13.2</td>
<td>19.0</td>
</tr>
<tr>
<td>Use of asthma medicines</td>
<td>13.6</td>
<td>17.7</td>
</tr>
<tr>
<td>Wheezing</td>
<td>8.1</td>
<td>8.7</td>
</tr>
<tr>
<td>Attacks of shortness of breath during the night</td>
<td>10.3</td>
<td>11.0</td>
</tr>
<tr>
<td>Breathing difficulties during exercise</td>
<td>18.3</td>
<td>24.0</td>
</tr>
<tr>
<td>Breathing difficulties in cold air</td>
<td>17.9</td>
<td>17.7</td>
</tr>
<tr>
<td>Breathing difficulties from tobacco smoke</td>
<td>29.3</td>
<td>29.7</td>
</tr>
</tbody>
</table>

### Table 4—Prevalence of Asthma Among Never-Smokers in Relation to ETS Exposure at Home During the Growing-Up Period When Dichotomized Into Age Classes 15 to 39 yr and 40 to 69 yr

<table>
<thead>
<tr>
<th>Asthma Type and Age Groups, yr</th>
<th>Exposed, %</th>
<th>Not Exposed, %</th>
<th>Difference by Exposure p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician-diagnosed asthma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–39</td>
<td>8.8</td>
<td>6.3</td>
<td>0.025</td>
</tr>
<tr>
<td>40–69</td>
<td>6.3</td>
<td>5.4</td>
<td>0.234</td>
</tr>
<tr>
<td>Ever-asthma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–39</td>
<td>10.8</td>
<td>8.2</td>
<td>0.039</td>
</tr>
<tr>
<td>40–69</td>
<td>7.5</td>
<td>6.4</td>
<td>0.238</td>
</tr>
</tbody>
</table>
in lung function of a magnitude that overshadows the effects of former ETS exposure. The difference in asthma prevalence between subjects exposed and nonexposed to childhood ETS was more pronounced in the younger half of the population. Asthma developing later in life may have other more important risk factors, such as environmental exposure in the workplace.20

Our study includes many cohorts growing up during periods when different attitudes and tolerance to tobacco prevailed. The importance of parental smoking as a predictor for children starting the smoking habit has been uncertain.21 In a review,22 parental smoking was a predictor in only half of the published prospective studies. In our study, the risk for an individual to take up the smoking habit was

Table 5—Effects of Different Independent Variables on Prevalence of Physician-Diagnosed Asthma and Respiratory Symptoms in Never-Smokers Without a Family History of Asthma*

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Physician-Diagnosed Asthma</th>
<th>Breathing Difficulties During Exercise</th>
<th>Breathing Difficulties From Cigarette Smoke</th>
<th>Breathing Difficulties From Pets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Women</td>
<td>1.16 0.80–1.68</td>
<td>1.23 0.96–1.58</td>
<td>1.78 1.45–2.18</td>
<td>1.05 0.76–1.45</td>
</tr>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–19</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>20–29</td>
<td>1.98 0.96–4.09</td>
<td>0.72 0.45–1.15</td>
<td>1.57 1.04–2.37</td>
<td>1.57 0.83–2.96</td>
</tr>
<tr>
<td>30–39</td>
<td>1.10 0.45–2.66</td>
<td>0.46 0.26–0.84</td>
<td>1.26 0.78–2.08</td>
<td>0.90 0.42–1.95</td>
</tr>
<tr>
<td>40–49</td>
<td>1.07 0.43–2.68</td>
<td>0.45 0.24–0.82</td>
<td>1.66 1.00–2.74</td>
<td>1.26 0.59–2.73</td>
</tr>
<tr>
<td>50–59</td>
<td>1.18 0.48–2.90</td>
<td>0.48 0.27–0.87</td>
<td>2.05 1.25–3.36</td>
<td>0.81 0.37–1.80</td>
</tr>
<tr>
<td>60–69</td>
<td>1.24 0.51–3.01</td>
<td>0.61 0.35–1.08</td>
<td>1.92 1.18–3.14</td>
<td>0.92 0.42–2.01</td>
</tr>
<tr>
<td>Socioeconomic groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professionals and higher civil servants</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Manual workers in industry</td>
<td>1.97 1.10–3.54</td>
<td>1.63 1.06–2.50</td>
<td>1.31 0.94–1.84</td>
<td>1.25 0.74–2.11</td>
</tr>
<tr>
<td>Manual workers in service</td>
<td>1.23 0.71–2.12</td>
<td>1.34 0.92–1.94</td>
<td>1.36 1.04–1.78</td>
<td>1.18 0.76–1.84</td>
</tr>
<tr>
<td>Assistant nonmanual employees</td>
<td>1.30 0.71–2.40</td>
<td>1.50 1.21–2.67</td>
<td>0.98 0.72–1.36</td>
<td>0.77 0.44–1.37</td>
</tr>
<tr>
<td>Housewives</td>
<td>0.82 0.19–3.64</td>
<td>1.29 0.56–3.03</td>
<td>0.83 0.42–1.63</td>
<td>1.76 0.70–4.42</td>
</tr>
<tr>
<td>Self-employees other than professionals</td>
<td>2.81 1.09–7.21</td>
<td>1.59 0.72–3.53</td>
<td>0.93 0.48–1.80</td>
<td>0.53 0.12–2.27</td>
</tr>
<tr>
<td>Students</td>
<td>1.56 0.76–3.19</td>
<td>1.32 0.78–2.21</td>
<td>1.76 1.16–2.66</td>
<td>1.08 0.57–2.04</td>
</tr>
<tr>
<td>Childhood ETS exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>1.82 1.28–2.58</td>
<td>1.45 1.14–1.83</td>
<td>1.25 1.04–1.51</td>
<td>1.41 1.04–1.90</td>
</tr>
</tbody>
</table>

*To examine the influence of different possible determinants, ORs were calculated by multiple logistics regression analysis.
increased 60% if a smoking person was in the household during childhood. A similar pattern was seen in almost all age and gender groups, with one alarming exception seen in the youngest cohort. Nowadays, growing up in a “smoking family” increases the risk threefold of becoming a smoker! From our data, it is impossible to evaluate if this depends on social influence, low nicotine exposure during childhood, a combination of this, or something else. Regardless, this study indicates the importance of giving the children of smokers extra resources to prevent future tobacco dependence!

ETS and other LAWIs seem to be associated with more frequent airway problems in women. This gender difference may be caused by differences in perception, or there may be anatomic or physiologic reasons.

Sweden has a low prevalence of daily smokers, nowadays 20% in the adult population, and there are some laws prohibiting smoking in public areas. In spite of this, ETS was the most commonly reported factor causing attacks of shortness of breath, wheezing, or attacks of cough in the general public. Such acute effects of ETS, together with our finding that childhood ETS exposure was associated with a higher asthma prevalence also in adults, clearly indicates the need for further campaigns and legislation against ETS.

ACKNOWLEDGMENT: We thank Elsy Jönsson, Department of Occupational Health Medicine at National Institute for Working Life, Umeå, and Håkan Ka¨n, Stockholm, for valuable support with the statistical analyses; and Irene Eriksson, Department of Lung Medicine, O¨rebro, for help with the collection of data. We also thank David M. Mammio, National Center for Environmental Health, Atlanta, GA, for valuable comments.

REFERENCES
4 Committee on Passive Smoking, Board of Environmental Studies and Toxicology, National Research Council (NRC). Environmental tobacco smoke: measuring exposures and assessing health effects. Washington, DC: National Academy Press, 1986
5 Nielsen P. Passiv rygning og overforlo¨sommenhed (Passive tobacco smoke and hypersensitivity) [in Danish]. ¨Kopenhagen, Danmark: Tobaksskader˚alet, 1993
13 Conluras DB. Health effects of passive smoking: passive smoking and risk of adult asthma and COPD; an update. Thorax 1998; 53:381–387
21 Reid DJ, McNeill AD, Glynn TJ. Reducing the prevalence of smoking in youth in Western countries: an international review. Tob Control 1995; 4:266–277
Short Communication

Parental smoking and allergic sensitization in offspring defined by skin prick testing


Investigations of parental smoking during childhood and allergic sensitization have produced contradictory results, but this may be because of variations in the definition of allergy and other influences. We investigated associations of parental smoking with an objective measure of allergy, skin prick testing (SPT), and considered associations with maternal and paternal smoking, independently of each other. A stratified random sample, aged 22–74 yr, of 720 Swedish FinEsS-study members were skin prick tested for 15 allergens. Subjects with at least one positive SPT were defined as atopic. Data on childhood exposures, including parental smoking, were collected by structured interview. Logistic regression used atopy as the dependent variable. After adjustment, paternal smoking was statistically significantly associated with an increased risk and maternal smoking a non-statistically significant decreased risk in offspring, with odds ratios (and 95% confidence intervals) of 1.48 (1.04–2.10) and 0.73 (0.48–1.12), respectively. Analysis of families with a non-smoking mother produced an odds ratio for paternal smoking of 1.61 (1.09–2.37). The negative association between maternal smoking and atopy may not operate through passive smoke exposure and could conceal a significant increased risk associated with passive exposure to tobacco smoke in childhood.

Reported associations of parental smoking with offspring’s allergy are contradictory, (1, 2) possibly because of at least two potential confounding or modifying factors. The first is failure to separate maternal and paternal smoking. Some studies looking specifically at maternal smoking reported a protective association (3, 4). Therefore, potentially different associations with allergy for maternal and paternal smoking should be considered. Another potential source of error and variation in association is the use of symptoms and diagnoses such as wheeze and asthma to define allergy. Such symptoms have been associated with passive exposure to tobacco smoke in childhood (5) but do not represent allergy and may result from smoke-induced exacerbation of symptoms such as wheezing. Such a definition of allergy may obtain false positive associations with parental smoking. Here, we investigated associations of maternal and paternal smoking during offspring’s childhood separately and used skin prick testing (SPT) as an objective measure of allergic sensitization.

Methods

A stratified random sample of 1200 Swedish FinEsS (5, 6), respondents, aged 22–74 yr, was selected for SPT. The FinEsS study was designed as a general population-based study investigating putative risks for asthma, chronic bronchitis, type-I allergy and respiratory symptoms; and details of the sample have been described in full elsewhere (5). Some 720 (60%) participated in this sub-study, providing SPT data for 704 subjects after exclusions for illness, pregnancy or breastfeeding. The variations in proportion in the attained sample compared with the original population were within two percent for sex, smoking and allergic rhinitis, but there was a slight age shift such that there was 5% increase in second oldest age category.

Standardized SPT (7, 8), was performed on the forearm for 15 allergens: *Dermatophagoides pteronyssinus, Dermatophagoides farinae, Lepidoglyphus destructor, Acarus siro*, cat, dog, cow,
horse, birch pollen, timothy, mugwort, Alternaria alternata, Cladosporium herbarum, latex and German cockroach. The definition of atopy used here is a positive test to at least one allergen. Subjects reacting to the negative reference (n = 12) were excluded, leaving 692 for analysis.

A structured interview conducted by a research nurse, recorded information on exposures and characteristics during childhood, including parental smoking behaviour (whether mother or father regularly smoked at home), urban or rural place of residence, bedroom sharing with a sibling, house type and the presence of pets during the first 5 yr of life. Other information recorded by the interview included: number of older and younger siblings and own smoking behaviour.

Multiple logistic regression in SPSS used atopy as the dependent variable with mutual adjustment for all of the measures shown by the Table 1, modelled as binary dummy variables.

| Table 1. Skin prick tests for atopy by parental smoking and potential confounding factors |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                  | Skin prick      | Odds ratios with 95% CI |                  |                  |                  |
|                                  | Positive        | Negative        | Unadjusted      | p-value          | Adjusted*        | p-value          |
| Mother smoked                    |                 |                 |                  |                  |                  |                  |
| No                               | 173 (76.2)      | 357 (76.8)      | 1               | 0.71–1.50        | 0.870            | 0.73 (0.48–1.12) | 0.148 |
| Yes                              | 54 (23.8)       | 108 (23.2)      | 1.03             | 0.69–1.50        | 0.938            | 0.94 (0.61–1.46) | 0.798 |
| Father smoked                    |                 |                 |                  |                  |                  |                  |
| No                               | 107 (47.1)      | 256 (55.1)      | 1               | 0.56–1.19        | 0.927            | 1.09 (0.74–1.61) | 0.684 |
| Yes                              | 120 (52.9)      | 209 (44.9)      | 1.37             | 1.00–1.89        | 0.051            | 1.48 (1.04–2.10) | 0.029 |
| Subject’s smoking                |                 |                 |                  |                  |                  |                  |
| Never smoked                     | 115 (50.7)      | 224 (48.2)      | 1               |                   | 1.05             | 1.12 (0.94–1.36) | 0.686 |
| Ex-smoker                        | 69 (30.4)       | 140 (30.1)      | 0.96             | 0.67–1.38        | 0.927            | 1.09 (0.74–1.61) | 0.684 |
| Current smoker                   | 43 (19.9)       | 101 (21.7)      | 0.83             | 0.54–1.26        | 0.865            | 0.90 (0.58–1.40) | 0.640 |
| Older siblings                   |                 |                 |                  |                  |                  |                  |
| None                             | 124 (54.6)      | 199 (42.8)      | 1               |                   |                  | 0.79 (0.55–1.13) | 0.201 |
| 1                                | 61 (26.9)       | 120 (25.8)      | 0.92             | 0.56–1.19        | 0.938            | 0.94 (0.61–1.46) | 0.798 |
| 2                                | 22 (9.7)        | 59 (12.7)       | 0.60             | 0.35–1.02        | 0.927            | 1.09 (0.74–1.61) | 0.684 |
| 3 or more                        | 20 (8.8)        | 87 (18.7)       | 0.37             | 0.22–0.63        | <0.001           | 0.42 (0.23–0.75) | 0.003 |
| Younger siblings                 |                 |                 |                  |                  |                  |                  |
| None                             | 94 (41.4)       | 197 (42.4)      | 1               |                   |                  |                  |                  |
| 1                                | 63 (27.8)       | 130 (28.0)      | 1.02             | 0.69–1.50        | 0.938            | 0.94 (0.61–1.46) | 0.798 |
| 2                                | 40 (17.6)       | 78 (16.8)       | 1.08             | 0.68–1.69        | 0.755            | 1.06 (0.64–1.76) | 0.820 |
| 3 or more                        | 30 (13.2)       | 60 (12.9)       | 1.05             | 0.63–1.73        | 0.955            | 1.12 (0.94–1.36) | 0.686 |
| Pets from birth to age 5 yr      |                 |                 |                  |                  |                  |                  |
| No                               | 116 (51.1)      | 201 (43.2)      | 1               |                   |                  |                  |                  |
| Yes                              | 111 (48.9)      | 264 (56.8)      | 0.73             | 0.53–1.00        | 0.951            | 0.79 (0.55–1.13) | 0.201 |
| Home from birth to age 5 yr      |                 |                 |                  |                  |                  |                  |
| House                            | 102 (44.9)      | 248 (53.3)      | 1               |                   |                  |                  |                  |
| Flat                             | 99 (43.6)       | 174 (37.4)      | 1.38             | 0.99–1.94        | 0.060            | 1.02 (0.66–1.56) | 0.938 |
| Both                             | 26 (11.5)       | 43 (9.2)        | 1.47             | 0.86–2.52        | 0.161            | 1.18 (0.66–2.10) | 0.568 |
| Place of residence birth to age 5 yr |                 |                 |                  |                  |                  |                  |
| Urban                            | 142 (62.6)      | 256 (55.1)      | 1               |                   |                  |                  |                  |
| Rural                            | 85 (37.4)       | 209 (44.9)      | 0.73             | 0.53–1.02        | 0.061            | 0.99 (0.65–1.51) | 0.957 |
| Age at SPT (yr)                   |                 |                 |                  |                  |                  |                  |
| 20–29                            | 24 (10.6)       | 33 (7.1)        | 0.89             | 0.46–1.72        | 0.725            | 0.87 (0.44–1.70) | 0.685 |
| 30–39                            | 45 (19.8)       | 55 (11.8)       | 1               |                   |                  |                  |                  |
| 40–49                            | 42 (18.5)       | 102 (21.9)      | 0.50             | 0.30–0.86        | 0.012            | 0.48 (0.28–0.84) | 0.010 |
| 50–59                            | 53 (23.3)       | 116 (24.9)      | 0.56             | 0.34–0.93        | 0.025            | 0.50 (0.29–0.87) | 0.013 |
| 60–69                            | 54 (23.8)       | 139 (29.9)      | 0.48             | 0.29–0.79        | 0.004            | 0.44 (0.25–0.77) | 0.004 |
| 70                               | 9 (4.0)         | 20 (4.3)        | 0.55             | 0.23–1.33        | 0.183            | 0.52 (0.21–1.32) | 0.168 |
| Sex                              |                 |                 |                  |                  |                  |                  |
| Male                             | 113 (49.8)      | 232 (49.9)      | 1               |                   |                  |                  |                  |
| Female                           | 114 (50.2)      | 233 (50.1)      | 1.00             | 0.73–1.38        | 0.978            | 1.02 (0.73–1.42) | 0.922 |
| Shared a bedroom with siblings from birth to age 5 yr | | | | | | |
| Yes                              | 96 (42.3)       | 167 (35.9)      | 1.32             | 0.95–1.82        | 0.101            | 1.03 (0.69–1.54) | 0.876 |
| No                               | 125 (55.1)      | 285 (61.5)      | 1               |                   |                  |                  |                  |
| Uncertain                        | 6 (2.1)         | 12 (2.6)        | 1.14             | 0.42–3.12        | 0.792            | 0.80 (0.28–2.34) | 0.689 |
| Total                            | 227             | 465             |                  |                  |                  |                  |                  |

The measures of parental smoking are for smoking during the subject’s childhood. *Adjustment is for all variables shown.
Results

In univariate analysis, maternal smoking was not associated with offspring’s atopy risk, while paternal smoking was associated with a marginally statistically significant increased risk of atopy among offspring. Mutual adjustment for maternal and paternal smoking clarified their associations with offspring’s atopy. After adjustment for maternal smoking and all of the other measures, the odds ratio for atopy associated with paternal smoking increased with enhanced statistical significance. A non-statistically significant negative association between maternal smoking and offspring’s atopy was observed after adjustment.

Evidence of effect modification through maternal smoking comes from the higher odds ratio for offspring’s atopy associated with paternal smoking in families where the mother was a non-smoker. Analysis of paternal smoking in families without a smoking mother produced an odds ratio for offspring’s allergy of 1.61 (1.09–2.37). After adjustment for the main effects the interaction of maternal and paternal smoking was not statistically significantly associated with atopy, with an odds ratio of 0.65 (0.27–1.50).

Another source of evidence for a positive association with smoke exposure comes from analysis of smokers in the same household other than parents. Although not statistically significant and underpowered (only 51 subjects reported sharing a household with a smoker other than their parents), this produced and odds ratio of 1.32 (0.69–2.54), similar in magnitude to paternal smoking.

Subject’s age (birth cohort) was significantly associated with both likelihood of parental smoking (data not shown) and atopy and this potential confounding factor had a notable influence on associations of paternal smoking with allergy risk, somewhat increasing statistical significance. Among measures other than parental smoking, only subject’s age and number of older siblings were observed to have a statistically significant association with atopy in the adjusted model.

Discussion

Using an objective measure of atopy – SPT – a statistically significant positive association was observed with paternal smoking during the subject’s childhood. Maternal smoking was not positively associated with atopy in offspring. Adjustment for maternal smoking clarified that the positive association with paternal smoking may have been partly concealed by a modifying effect of maternal smoking, compounded by the tendency of smokers to have smoking partners. Further evidence of this modifying effect comes from the stronger association of atopy with paternal smoking in families where the mother was a non-smoker. Variation in risk of allergy by maternal or paternal smoking may help to explain inconsistencies in previous research into passive tobacco smoke exposure in childhood and allergic sensitization.

This phenomenon could explain variation by country. Passive smoking during infancy was associated to atopic sensitization in Estonia but not Sweden (2). In Estonia smoking prevalence is about two times higher among men (6), while more Swedish women smoke than men (5). The lower proportion of male smokers in Sweden may account for the reduced risk of allergic sensitization among infants with smoking parents. A recent Danish study(9) reported a negative association between passive tobacco smoke exposure in childhood and atopy defined by SPT. However, this study did not differentiate between maternal and paternal smoking so it is possible that the influence of maternal smoking concealed a positive association with passive exposure to tobacco smoke.

Perinatal and prenatal maternal smoking has been associated with reduced allergy risk (4) and one study (3) found this reduced risk among the whole sample, but not in a sample restricted to atopic mothers, suggesting complex mechanisms other than passive exposure to tobacco smoke, such as a differential effect of smoking on maternal immune function. If passive exposure to tobacco smoke in childhood increases the risk of allergic sensitization, but perinatal or perinatal maternal smoking decreases this risk through another mechanism, the conflicting effects of maternal smoking may lead to an overall reduction in association of maternal smoking with atopy, depending on the mother’s smoking pattern. Also, just as maternal smoking may conceal a raised risk of allergic sensitization in offspring because of paternal smoking, paternal smoking may conceal a reduced risk associated with prenatal or perinatal maternal smoking. The positive association with paternal smoking reported here more plausibly reflects an increased risk of allergy associated with exposure to particulates, possibly explained by mechanisms such as the adjuvant effect proposed for diesel exhaust particles (10).

While avoidance of smoking by allergic mothers offers a potential explanation operating although inheritance, this cannot explain the positive association with paternal smoking. If
maternal smoking prior to, or during pregnancy, is associated with a reduction in offspring’s allergy risk, this may mask any increased risk associated with passive smoke exposure because of maternal smoking after birth. Although non-statistically significant, probably because of small numbers, the positive association with atopy for another individual (non-parent) smoking in the household found by our study lends further support to a causal role for passive exposure in childhood to tobacco smoke.

Through use of an objective measure of allergy – SPT – the possibility of reporting or diagnostic bias through exacerbation of symptoms by cigarette smoke exposure was eliminated. Information on parental smoking during the subject’s childhood was collected by retrospective interview and this is a potential source of recall error. However, the difference in association with atopy for maternal and paternal smoking, suggests that the findings are not driven by a systematic tendency for allergic individuals to have reported parental smoking.

We were able to adjust for potential confounding factors, independent risks and potential effect modifiers, including markers of material and cultural circumstances, to reduce the possibility that parental smoking is a marker for other exposures. The associations with parental smoking are not because of subjects’ own smoking behaviour as this was not associated with atopy, nor did adjustment for this influence the association of parental smoking with atopy risk. Among all of the exposures, potential confounding factors and other measures, only paternal smoking during the subjects childhood remained as a risk for atopy in the adjusted model, while having more older siblings and older age at SPT (earlier birth cohort) are significantly protective. The only important factor potentially concealing a positive association of atopy with paternal smoking was effect modification associated with maternal smoking.

The results of this study are consistent with a putative causal role for early life passive tobacco smoke exposure in increasing allergy risk. Future studies should take into account the possible modifying influence of maternal smoking that may operate through a mechanism other than passive tobacco smoke exposure, thus masking an allergenic effect of passive tobacco smoke exposure in childhood.

Acknowledgments
We thank the National Health Institute, Sweden, The Heart and Lung Foundation, Sweden, and the Research Committee of Örebro County Council.

References
Passive smoking and respiratory symptoms in the FinEss Study


ABSTRACT: The aim of the present study was to examine the relationship between reported environmental tobacco smoke (ETS) exposure and respiratory symptoms.

In 1996, a postal questionnaire was randomly distributed in three areas of Estonia to a population-based sample, of which 4,995 females and 1,822 males had never smoked. The main outcome measures were current respiratory symptoms and the amount of reported ETS exposure outside the home.

ETS exposure at home was more common in females (31% versus 19%), while exposure outside of the home was more common in males (53% versus 7%). Females reported more symptoms from tobacco smoke than males (37.7% versus 21.6%). If ETS exposure outside of the home exceeded 5 h daily, the risk for wheeze (odds ratio (OR) 2.67, 95% confidence interval (CI) 1.98–3.61) and physician-diagnosed asthma (OR 1.79, 1.02–3.16) were increased. ETS exposure outside of the home was shown to be strongly related to almost all respiratory symptoms in a dose–response manner, ETS exposure at home did not show significantly elevated ORs for any respiratory symptoms.

This study shows that females seem to be more troubled by environmental smoke exposure than males and provides further evidence of the serious health hazards associated with environmental smoke exposure. Indeed, the findings of this study support a ban on smoking in the workplace and public areas.

*Dept of Lung Medicine and +The Research Unit, Örebro University Hospital, Örebro, +The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, and §The OLIN studies, Dept of Medicine, Sunderby Central Hospital of Norrbotten, Luleå, Sweden. #Dept of Pulmonology, Institute of Experimental and Clinical Medicine, Tallinn, Estonia.

Correspondence: M.L. Larsson, Dept of Lung Medicine, Örebro University Hospital, SE-701 85 Örebro, Sweden.
Fax: 46 19186526 E-mail: matz.larsson@orebrol.se

Keywords: Asthma, epidemiology, passive smoking, respiratory symptoms

Received: April 25 2002 Accepted after revision: November 28 2002

This study was supported by grants from the Estonian Science Foundation, The National Health Institute, The Heart and Lung Foundation, and The Research Committee of Örebro County Council, Sweden.

The 1992 US Environmental Protection Agency (EPA) review [1] on passive smoking confirmed that exposure to environmental tobacco smoke (ETS), i.e. passive smoking, can cause respiratory illness in children. There is also increasing evidence of ETS causing respiratory illness in adults [2–11]. The US EPA review also includes reports on a relationship between ETS, respiratory symptoms and sickness in adults [1]. White et al. [7] showed that workplace ETS is more strongly related to respiratory symptoms than household exposure, a finding which has also been shown in other studies [8, 9]. There are almost 4,000 chemical agents in ETS, including nicotine, carbon monoxide, benzene, formaldehyde, and acrolein, all of which are emitted from a burning cigarette and could cause respiratory symptoms [12]. For many subjects with asthma, acute exposure to ETS is associated with respiratory symptoms [13] and ETS exposure has been reported to increase bronchial reactivity to histamine in asthmatics [14]. Leuenberger et al. [8] reported on the increasing risk and dose relationship for respiratory symptoms related to total ETS exposure. In November 1999 the US National Cancer Institute published an extensive report [10] on health risks of ETS exposure. In the report, no definite conclusion on the association between ETS and chronic respiratory symptoms in adults was reached. Since this report, a dose relationship between exposure to ETS at work and respiratory symptoms in never-smokers, an important criterion for causal association, has been shown by others [9, 11]. In the study by Lam et al. [11], performed on police officers with a small proportion of females, the association was clear among males but less clear among females. Studies concerning ETS and chronic respiratory symptoms in adults have mainly been performed on selected groups or with pooled data from many different countries [9].

This study was conducted as a result of conflicting results in previous studies, lack of data from population-based random samples, lack of data from Eastern Europe and the scarcity of knowledge concerning females. The study’s main aim was to examine the respiratory effects of ETS exposure in a random sample of adult never-smokers from a general population. A further aim was to study whether the respiratory effects of ETS exposure are different in males and females.

Materials and methods

Participants and survey

This study was a part of the epidemiological studies performed in Finland, Estonia, and Sweden (FinEss) on the prevalence of and risk factors for asthma, chronic bronchitis, type-I allergy, and respiratory symptoms. The present investigation was based on the Estonian part of the study, which was approved by the Tallinn Medical Research Ethics Committee.

Study population

A random sample of 24,307 individuals stratified on a 10-yr age band and sex were selected from the populations of Tallinn (442,679 inhabitants), Narva (79,094 inhabitants) and Saaremaa (40,822 inhabitants). The Estonian State Computing Centre population register was used to identify subjects.
This register is updated on a fortnightly basis. Smokers, former smokers, and subjects reporting "I don’t leave home" were excluded. Prevalence rates of respiratory symptoms in this population have recently been reported [15].

Questionnaire

The questionnaire [16] was developed from a revised version of the British Medical Research Council questionnaire [17] and had been previously validated and used in several Scandinavian studies. The postal questionnaires were sent to the study sample with an explanatory note, an envelope, and a stamp during November 1995. In a case in which there was no response, two reminders were sent to the subject. In Estonia, two versions of the questionnaire were used, a Russian and an Estonian version. The Russian version was mailed to subjects with Russian names and the Estonian version to subjects with Estonian names. In cases in which the subject’s language was uncertain, both versions were sent. The questionnaire included questions about respiratory symptoms and diseases, for example recurrent wheeze, attacks of shortness of breath, long-standing cough, sputum production, asthma, allergic rhinitis, chronic bronchitis and symptoms in special circumstances with varying exposures. The questionnaire also included questions about smoking habits, occupation, and family history of the above mentioned diseases. Two questions concerning exposure to ETS at home and outside the home were added in the Estonian study, exclusively, and were as follows. 1) "Does somebody of your family member smoke at home in living rooms?" This question was answered with either "yes" or "no (don’t know)" as were all questions concerning symptoms. 2) "How many hours per day do you spend in smoky rooms outside your home?" The reply had to be one of the following alternatives: >1-5 h day-1, 1-5 h day-1, <1 h day-1, "nearly never", "I don’t leave home".

Definitions

Exposure to ETS at home was defined as a positive answer to the first ETS question seen above. Exposure to ETS outside home was estimated by the answer to the second ETS question seen above. A never-smoker was defined as someone giving a negative reply ("no (don’t know)") to the two following questions: 1) "Do you smoke? (smokers also include those who smoke a few cigarettes or pipe fills a week, and those who have stopped during the last 12 months)"; and 2) "Have you been a smoker but have stopped smoking >1 yr ago?"

The following definitions of the dependent variables were used for respiratory symptoms or conditions. Long-standing cough: having had a long-standing cough during the last few years. Increased sputum production: often having phlegm when coughing or having difficulties in bringing up phlegm. Chronic productive cough: bringing up phlegm when coughing on most days during periods of >3 months during at least 2 successive yrs. Wheeze: wheezing, whistling or a noisy sound in the chest when breathing. Wheezing during the last 12 months or having had wheezing or whistling in the chest at any time during the last 12 months. Woken with chest tightness or having woken with chest tightness at any time in the last 12 months. Dyspnoea grade 2: getting short of breath or having to walk more slowly when walking with other people of the same age on level ground at a normal pace. Physician-diagnosed chronic bronchitis: having been diagnosed as having chronic bronchitis or emphysema by a physician. Physician-diagnosed asthma: having been diagnosed as having asthma by a physician.

Lower airway irritant

The questionnaire also included the following nine questions concerning exposures and/or circumstances with the potential to cause lower airway irritation: "Do you become breathless or wheeze, or do you have attacks of cough when exposed to 1) exercise, 2) cold air, 3) exercise in cold air, 4) dust, 5) tobacco smoke, 6) car exhaust fumes, 7) strong smells, e.g. perfume, spices, printers ink, 8) pollen from plants and/or trees, or 9) pets?" If a positive response was given, the factor and/or circumstance were defined as a lower airway irritant. Odds ratios (ORs) for giving a positive response to questions concerning various lower airway irritants were calculated in relation to reported ETS-exposure duration. This was performed in an identical manner to the calculations of OR for respiratory symptoms (see Data analysis).

Data analysis

The analyses were based only on the participants who had never smoked. When estimating the effects of ETS exposure outside the home on respiratory symptoms, multiple logistic regression was used to calculate OR values with 95% confidence intervals (CIs), adjusted for age, sex, heredity for asthma and/or bronchitis/emphysema, community and ETS exposure at home. Males and females were analysed together, but an interaction between the subject factor sex and the within factor ETS exposure outside home was tested with a likelihood ratio test [18]. This was obtained as minus twice the difference between log-likelihood for the models with and without the interaction term. Dose/response was also analysed in the same way with a likelihood ratio test, by comparing a linear ETS exposure effect coded from 1 to 4, where 1 was "nearly never" and 4 was ">5 h".

Results

From the 24,307 subjects eligible to join the survey a total of 17,725 (77.6%) completed the questionnaire. Amongst the respondents, 8,022 subjects were never-smokers and from these 1,205 were excluded because of missing entries for ETS exposure. In total 6,817 never-smokers were included in the survey, 4,995 of which were female. The demographical characteristics and exposure to ETS at home or work are shown in table 1. Exposure at home was more common in females (31%) than in males (19%). In contrast, exposure outside the home was more common in males (53%) than in females (37%) and 23% of the males reported ≥1 h of ETS exposure outside of the home compared to 16% of females.

Exposure times to ETS outside of the home showed a significant dose/response relationship with all respiratory symptoms and conditions (table 2), except for physician-diagnosed asthma, where only a slight increase was observed. The reported duration of ETS exposure was associated with positive responses for all types of lower airway irritants (table 3).

There were no significant interactions by sex on the dose/response for ETS exposure duration, respiratory symptoms, or the lower airway irritants, except for tobacco smoke which showed a significant interaction by sex (p=0.02). The ORs gave positive responses meaning tobacco-smoke was reported as a lower airway irritant; for example, when reporting tobacco smoke to be a lower airway irritant, they were 1.50 (CI 1.28–1.77), 1.96 (1.57–2.45) and 1.53 (1.18–1.97) for low, medium and high exposures, respectively, in females, and 1.12 (0.83–1.52), 1.11 (0.77–1.59) and 1.77 (1.11–2.80) for low,
Table 1. – Demographical characteristics and pattern of environmental tobacco smoke (ETS) exposure in the never-smoking population

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects n</td>
<td>1822</td>
<td>4995</td>
</tr>
<tr>
<td>Age yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–24</td>
<td>628 (34.5)</td>
<td>1015 (20.3)</td>
</tr>
<tr>
<td>25–34</td>
<td>331 (18.2)</td>
<td>845 (16.9)</td>
</tr>
<tr>
<td>35–44</td>
<td>289 (15.9)</td>
<td>983 (19.7)</td>
</tr>
<tr>
<td>45–54</td>
<td>270 (14.8)</td>
<td>1046 (20.9)</td>
</tr>
<tr>
<td>55–64</td>
<td>304 (16.7)</td>
<td>1106 (22.1)</td>
</tr>
<tr>
<td>ETS exposure at home</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1472 (80.8)</td>
<td>3431 (68.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>350 (19.2)</td>
<td>1564 (31.3)</td>
</tr>
<tr>
<td>Daily ETS exposure time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>outside of the home</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nearly never</td>
<td>864 (47.4)</td>
<td>3148 (63.0)</td>
</tr>
<tr>
<td>&lt;1 h</td>
<td>545 (29.9)</td>
<td>1050 (21.0)</td>
</tr>
<tr>
<td>1–5 h</td>
<td>295 (16.2)</td>
<td>474 (9.5)</td>
</tr>
<tr>
<td>&gt;5 h</td>
<td>118 (6.5)</td>
<td>323 (6.5)</td>
</tr>
</tbody>
</table>

Data presented as n (%) unless otherwise stated.

medium and high exposures, respectively, in males (exposures are as defined in table 3).

All respiratory symptoms and conditions were more common in females than in males, except physician-diagnosed asthma, where the OR for females was 0.93 (0.62–1.39) (table 4). The female predominance was most clearly observed in dyspnea grade 2 (OR 2.88 (2.13–3.90)), followed by increased sputum production (OR 1.67 (1.45–1.93) and least pronounced physician-diagnosed chronic bronchitis (OR 1.29 (1.04–1.60)).

Tobacco smoke was the most commonly reported lower airway irritant, followed by dust, amongst both males and females together and females only (fig. 1). Dust was the most commonly reported lower airway irritant in males, followed by tobacco smoke. Females more frequently gave positive responses to all questions concerning lower airway irritants.

ETS exposure at home showed no significant increase in ORs for respiratory symptoms. If the group exposed to ETS at home was considered a reference category (OR 1.0), the OR for nonexposed was 1.03 (0.89–1.18) for long-standing cough, 1.13 (0.92–1.38) for wheeze, 1.05 (0.90–1.23) for wheezing in the last 12 months, and 1.32 (1.12–1.56) for being woken up during the night with chest tightness.

Discussion

This study shows a clear association and a strong dose/response relationship between ETS exposure outside the home and respiratory symptoms. This study also suggests that ETS exposures outside the domestic area brought about more serious effects than ETS exposures at home. The study found

Table 2. – Adjusted odds ratios (ORs) for different respiratory symptoms by daily exposure time to environmental tobacco smoke (ETS) outside of the home

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>ETS outside home</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1 h</td>
</tr>
<tr>
<td>Long-standing cough</td>
<td>1.25 (1.07–1.45)</td>
</tr>
<tr>
<td>Increased sputum production</td>
<td>1.32 (1.14–1.52)</td>
</tr>
<tr>
<td>Chronic productive cough</td>
<td>1.32 (1.01–1.72)</td>
</tr>
<tr>
<td>Wheeze</td>
<td>1.25 (0.99–1.59)</td>
</tr>
<tr>
<td>Wheezing in last 12 months</td>
<td>1.15 (0.97–1.37)</td>
</tr>
<tr>
<td>Woken up with tightness in chest</td>
<td>1.11 (0.92–1.35)</td>
</tr>
<tr>
<td>Dyspnoea grade 2</td>
<td>1.02 (0.80–1.30)</td>
</tr>
<tr>
<td>Physician-diagnosed asthma</td>
<td>0.85 (0.54–1.34)</td>
</tr>
<tr>
<td>Physician-diagnosed chronic bronchitis or emphysema</td>
<td>2.24 (1.01–1.53)</td>
</tr>
</tbody>
</table>

All data presented as OR (95% confidence interval) unless otherwise stated. The ORs were adjusted for age, sex, heredity for asthma or bronchitis/emphysema, community, and ETS exposure at home and were calculated using subjects reporting almost no ETS exposure outside of the home as a reference category; *: linear dose/response relationship.

Table 3. – Adjusted odds ratios (ORs) for reporting problems from different lower airway irritators by daily exposure time to environmental tobacco smoke (ETS) outside of the home

<table>
<thead>
<tr>
<th>Lower airway irritating factors/ circumstances</th>
<th>ETS outside home</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1 h</td>
</tr>
<tr>
<td>Exercise</td>
<td>1.06 (0.86–1.31)</td>
</tr>
<tr>
<td>Cold</td>
<td>1.22 (1.03–1.46)</td>
</tr>
<tr>
<td>Exercise in cold air</td>
<td>1.15 (0.97–1.36)</td>
</tr>
<tr>
<td>Dust</td>
<td>1.28 (1.11–1.48)</td>
</tr>
<tr>
<td>Tobacco smoke</td>
<td>1.39 (1.21–1.60)</td>
</tr>
<tr>
<td>Car exhaust fumes</td>
<td>1.35 (1.16–1.58)</td>
</tr>
<tr>
<td>Perfume, etc.</td>
<td>1.38 (1.17–1.63)</td>
</tr>
<tr>
<td>Pollen</td>
<td>1.32 (1.00–1.75)</td>
</tr>
<tr>
<td>Pets</td>
<td>1.30 (0.92–1.84)</td>
</tr>
</tbody>
</table>

All data are presented as OR (95% confidence interval) unless otherwise stated. The ORs were adjusted for age, sex, heredity for asthma or bronchitis/emphysema, community, and ETS exposure at home and were calculated using subjects reporting almost no ETS exposure outside of the home as a reference category; *: linear dose/response relationship.
Table 4. – Odds ratios (ORs) for respiratory symptoms by sex

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-standing cough</td>
<td>1.57 (1.35–1.83)</td>
</tr>
<tr>
<td>Increased sputum production</td>
<td>1.67 (1.45–1.93)</td>
</tr>
<tr>
<td>Chronic productive cough</td>
<td>1.52 (1.16–1.99)</td>
</tr>
<tr>
<td>Wheeze</td>
<td>1.36 (1.07–1.73)</td>
</tr>
<tr>
<td>Wheezing in last 12 months</td>
<td>1.31 (1.10–1.55)</td>
</tr>
<tr>
<td>Woken up with tightness in chest</td>
<td>1.57 (1.29–1.93)</td>
</tr>
<tr>
<td>Dyspnoea grade 2</td>
<td>2.88 (2.13–3.90)</td>
</tr>
<tr>
<td>Physician-diagnosed asthma</td>
<td>0.93 (0.62–1.39)</td>
</tr>
<tr>
<td>Physician-diagnosed chronic bronchitis or emphysema</td>
<td>1.29 (1.04–1.60)</td>
</tr>
</tbody>
</table>

All data are presented as ORs (95% confidence interval) with males as the reference category and adjusted for age, heredity for asthma or bronchitis/emphysema, community, ETS exposure at home and exposure time to ETS outside the home.

no significant interactions by sex in the dose/response for ETS exposure duration and respiratory symptoms. However, with almost twice as many females as males reporting that tobacco smoke caused breathlessness, wheezing, and attacks of cough, females seem to be more irritated by ETS exposure. Irrespective of ETS exposure, females in general report more respiratory symptoms, suggesting that when exposed to equal amounts of ETS, females will have more symptoms than males.

LAM et al. [11] did not show dose/response relationships between ETS exposure and respiratory symptoms as clearly in females as in males, but the present study did show females to be at least as sensitive as males to ETS exposure. The strengths of the present study are the sample size, the random selection from the general population and the high participation rate. Furthermore, the smoking prevalence in Estonia is high as ~ 50% of the males are smokers (data not presented). Almost no restrictions on ETS existed at the time of the study, giving a reasonable number of exposed subjects for calculations. A potential weakness of this study is the lack of validation regarding smoking status and ETS exposures. Smoking status was self-reported by the participants, which increased the risk of smokers being misclassified as nonsmokers. However, a meta-analysis [19] of the validity of self-reported smoking suggested a high sensitivity (87%) and specificity (89%) for self-report. Indeed, Rinjou et al. [20] estimated that the proportion of females misreporting their active smoking habit was between 1.9–3.4% in 13 centres from 10 countries. If a misclassification of 3.5% is assumed, misclassification of smoking status does not explain the excess risks associated with ETS. Thus, possible misclassification cannot explain the strong ETS effects observed in both females and males. However, it is possible that some nonsmokers did not report ETS exposure even if they were exposed and, therefore, could have been misclassified as unexposed. A validation of outcome measures for respiratory symptoms was not performed, but these measures have been tested in several other studies and been found to have a high level of validity [21].

Another potential weakness is that the levels of ETS exposure were not directly measured. However, the self-reported ETS exposure can be accepted as a valid measure in the study as clear dose/response relationships were observed between the reported time with ETS exposure outside the home and most respiratory symptoms. The respondents were anonymous and would have found no advantages, real or expected, to giving falsified reports. The participants reported respiratory symptoms first and ETS exposure later in the questionnaire, which makes it less likely that reported respiratory symptoms would be biased by reported exposure to ETS. Subjects with asthma or chronic obstructive pulmonary disease might be more aware of ETS exposure, owing to an increased bronchial reactivity, and might therefore overestimate the length of exposure, leading to an overestimation of the risk [22]. Alternatively, subjects with airway disorders like asthma might be more likely to avoid ETS and, if successful, will report less exposure, leading to an underestimation of the risk. This perhaps partly explains the lack of association between passive smoking at home and respiratory symptoms, i.e. family members may be more likely to stop or reduce smoking if one of their family members develops respiratory symptoms.

ETS exposure at home slightly increased ORs for some respiratory symptoms, but were not statistically significant. LAM et al. [11] concluded that “stronger effects were observed at work where the risk of ETS exposure was much greater because subjects spent more time among a larger number of smoking co-workers at work than at home”. The present study did not separate ETS exposure at work from other sources of ETS exposure outside of the home. It seems reasonable, however, that ETS exposure outside of the home was mainly related to work, since most of the subjects were of working age. Therefore, this study supports the hypothesis that ETS exposures outside the domestic area have more serious effects than ETS exposure at home. A recent study [23] showed that the amount of metabolites in a tobacco smoke-specific carcinogen in urine was six times higher among females exposed to ETS at home than amongst nonexposed females. As studies concerning airway symptoms and ETS exposure imply that ETS exposure in the workplace is more harmful, a study of tobacco smoke-specific carcinogens in urine after ETS exposure at work is urgently required. There is also a lack of epidemiological data concerning workplace ETS exposures and lung cancer [24].

In Estonia the level of awareness about the effects of ETS is currently low and few workplaces have smoking restrictions or have banned smoking. In the present study, ~20% of the subjects were exposed to ETS outside home for >1 h·day⁻¹. This level of exposure was associated with a ~50% higher prevalence of symptoms like phlegm, cough and dyspnoea. The present data indirectly supports many studies [9, 25, 26], indicating that ETS exposure is associated with small deficits in adult lung function.

![Fig. 1. – Prevalence of positive responses to the questions concerning lower airway irritants in females (♀) and males (♂).](image-url)
Cigarette smoke was the most commonly reported cause of lower airway irritation in the present study and a previous Swedish study [28]. The present authors also found a clear association between ETS exposure outside the home and airway symptoms from a variety of lower airway irritants. Most of these were known, unspecific airway irritants, e.g. cold air and strong-smelling scents. However, some were found to be rather surprising agents, commonly related to immunoglobulin (Ig)E-mediated allergies, e.g. pollen and animals with fur. From the present data it cannot be determined whether ETS exposure just triggers unspecific airway sensitivity or increases the risk of IgE-mediated allergy, which has been shown in active [28] but not passive smokers [9].

The high prevalence of chronic respiratory symptoms clearly represents a major public health problem. Exposure to ETS in society is preventable. Banning smoking in the workplace can significantly and rapidly improve the respiratory health of employees [29] and has also been reported to reduce the number of daily smokers and the number of cigarettes consumed in prevailing smokers. Implementation of stronger legislation in Estonia and all other countries with few regulations against ETS should be of high priority.

In summary, the reported duration of daily passive smoking outside of the home was associated with an increased prevalence of respiratory symptoms and a clear dose/response. This strongly supports the finding of a causal association.

Acknowledgements. The authors would like to thank E. Jönsson for valuable support with the statistical analyses and J. Kiviloog for his encouraging support.

References

Exposure to environmental tobacco smoke and health effects among hospitality workers in Sweden—before and after the implementation of a smoke-free law

by Matz Larsson, MD, Göran Boëthius, MD, Sara Axelsson, MSc, Scott M Montgomery, PhD


Objectives This study attempted to identify changes in exposure to environmental tobacco smoke, as well as symptoms and attitudes among hospitality workers after the introduction of extended smoke-free workplace legislation.

Methods A total of 37 volunteers working in bingo halls and casinos (gaming workers) and 54 bars and restaurant employees (other workers) in nine Swedish communities participated in the study. Altogether 71 of 91 persons (14 daily smokers and 57 nonsmokers) participated in both the preban baseline survey and the follow-up 12 months after the ban. Exposure to environmental tobacco smoke, smoking habits, respiratory and sensory symptoms, and attitudes towards the ban were recorded, and spirometry was carried out.

Results The frequency of reported respiratory and sensory symptoms was approximately halved among the nonsmokers in both occupational groups after the introduction of the ban. Initially 87% had exposure to environmental tobacco smoke that was over the nicotine cut-off level chosen to identify possible health risk (<0.5 μg/m³), while, after the ban, it was only 22%, a relative risk of 0.25 (95% confidence interval 0.15–0.41). The risk decreased in both occupational groups, but gaming workers experienced the highest preban exposure levels. Attitudes towards the legislation were largely positive, particularly after the ban. However, there was no notable change in lung function, and there was no notable reduction in the number of cigarettes consumed by smokers.

Conclusions The introduction of smoke-free legislation was associated with a substantial reduction in respiratory and sensory symptoms, as well as reduced exposure to environmental tobacco smoke at work, particularly among gaming workers.

Key terms cotinine; gambling; hospitality venue; legislation; nicotine in air; passive smoking; spirometry; symptom.
frequency of respiratory and sensory symptoms among bar workers (2, 7–9), a similar benefit may be observed among Swedish hospitality workers. In the context of examining the change in the rate of such symptoms, it is important to establish whether the introduction of the legislation is accompanied by a real reduction in environmental tobacco smoke. In Norway, similar legislation (12) was associated with a reduction in particulate levels from an average of 262 μg/m³ to 77 μg/m³, a 70% reduction. Mulcahy et al (13) measured changes in airborne nicotine levels as a result of the Irish smoke-free legislation, and they found a reduction of approximately 83%. Attitudes towards the legislation may also be important in determining its long-term success.

In addition to associations with acute respiratory and sensory symptoms, it is possible that the reduced exposure to environmental tobacco smoke that is associated with legislation may have more profound health effects. Some studies indicate that a reduction in exposure to environmental tobacco smoke can result in modest improvements in respiratory function (2, 7, 9). There is some evidence that exposure to environmental tobacco smoke is linked with an increased risk for a variety of diseases, including coronary artery disease (14, 15), obstructive lung disease (16–18), stroke (19), and lung cancer (20, 21).

This study evaluated the influence of the smoke-free legislation among a sample of hospitality workers in Sweden by examining the change in the rate of respiratory and sensory symptoms among the same persons before and 12 months after its introduction. As part of the assessment of compliance, the levels of environmental tobacco smoke were monitored at the workplaces involved in the study. As airborne nicotine concentrations may be important in determining mutagenicity (10, 22), we set cut-off levels that have been estimated as risk relevant to a potent bladder carcinogen, 4-aminobiphenyl (4-ABP) (22), as a general marker of potential disease risk. Spirometry was used to assess any change in lung function, and questionnaires recorded information on tobacco use and exposure to environmental tobacco smoke at work and during leisure time, as well as attitudes towards the legislation.

### Study population and methods

The sample was broadly representative of Sweden, and staff were enrolled who were working in bars, restaurants, and bingo halls in nine communities throughout Sweden. A baseline survey was performed 1 month before the ban (April–May 2005), and data were again collected 12 months later (April–May 2006). Both nonsmokers and daily smokers were included. The research ethics committee of the Faculty of Medicine, Umeå, Sweden, approved the study.

**Participant selection**

The characteristics of the participants are described in Table 1. The volunteers were recruited through two routes. A trade union (Hotell och Restauranganställdas Förbund) forwarded information to members about the study, asking them to contact the research team if they were interested in participating. A restaurant and hotel chain (Scandic) also helped to recruit volunteers from among its staff.

The inclusion criteria included working as a waiter, bar staff, or croupier in a restaurant, bar, nightclub, casino, or bingo hall, where a smoke-free policy was not implemented before the legislation came into force.

Smokers and nonsmokers were included, but occasional smoking was an exclusion criterion (smoking in the last 12 months but not daily), as high variation may confound associations with symptom frequency. Snuff

### Table 1. Characteristics of the participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preban a (N=91)</th>
<th>12 months postban b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Female</td>
<td>64</td>
<td>70</td>
</tr>
<tr>
<td>Male</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>Smoker</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>67</td>
<td>74</td>
</tr>
<tr>
<td>Daily snuff use</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Irregular snuff use</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Profession</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gaming worker</td>
<td>37</td>
<td>41</td>
</tr>
<tr>
<td>In bingo hall</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>In casino</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Other worker</td>
<td>54</td>
<td>59</td>
</tr>
<tr>
<td>Waiter or waitress</td>
<td>28</td>
<td>31</td>
</tr>
<tr>
<td>Bar staff</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Other function d</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Participation rate e</td>
<td>91</td>
<td>100</td>
</tr>
<tr>
<td>Completed the questionnaire</td>
<td>83</td>
<td>91</td>
</tr>
<tr>
<td>Completed the diary</td>
<td>90</td>
<td>99</td>
</tr>
<tr>
<td>Spirometry</td>
<td>83</td>
<td>91</td>
</tr>
<tr>
<td>Urine cotinine</td>
<td>72</td>
<td>79</td>
</tr>
</tbody>
</table>

a Mean 33.3 years and range 18–65 years for age; mean 33 hours and range 0–65 hours for working the week before.

b Mean 36.5 years and range 18–65 years for age; mean 33 hours and range 0–78 hours for working the week before.

c All of the smokers were daily smokers.

d For example, owner, discjockey, both bar worker and waiter.

e Altogether 43 participants filled out a questionnaire, kept a diary, and underwent spirometry, nicotine sampling, and urine cotinine sampling at both times.
use was permitted. Other exclusion criteria were an already smoke-free workplace prior to implementation of the law and a work period shorter than three consecutive days per week. We accepted all eligible volunteers able to participate before the introduction of the ban. Altogether 91 persons were investigated at the start of the study and 64 (70%) of these were women. A total of 71 (79%) persons participated at the 12-month follow-up. At the follow-up, at least two attempts were made to contact the earlier participants. Of those participating at both times, 44 of the 67 nonsmokers and 10 of the 14 smokers provided air samples for nicotine on both occasions.

Data collection

Institutions, predominantly pulmonary clinics, were contacted by mail or telephone, and those willing to participate were involved as data collection centers. They were situated throughout Sweden, including in its seven largest communities (with the number of participants investigated) as follows: 21 in Stockholm, 19 in Gothenburg, 6 in Malmö, 5 in Uppsala, 13 in Västerås, 5 in Linköping, 6 in Örebro, 7 in Östersund, and 9 in Skövde. The participants visited their local participating clinic to complete the questionnaire and diary and undergo spirometry, both before and after the introduction of the legislation. Nicotine samplers and test tubes for urine samples were also issued at these times. It was planned that spirometric data would be collected at the end of the workday, but, due to irregular shift times, the collection at this time was only possible for approximately 50% of the participants, and the remaining data were collected the following day.

Screening of unreported tobacco product use by urine cotinine

Samples of urine, obtained at the end of a workshift, were immediately frozen and sent to the laboratory, where cotinine assays were performed using liquid extraction—gas chromatography–mass spectrometry (23). Data on smoking and wet snuff use, as well as nicotine replacement therapy, were collected from the questionnaires. The time and duration of workshifts and the time of the collection of the urine samples were also recorded. Cut-off values for cotinine levels distinguishing smokers from nonsmokers vary in the literature; a national survey of the United States population used 15 ng/ml (85.2 nmol/l) of serum cotinine as the cut-off (24). Heavy exposure to environmental tobacco smoke may produce serum cotinine concentrations as high as 31.3 ng/ml (25, 26). The corresponding urinary cotinine value is approximately 6.5 times as high (27). We defined nontobacco users as those who reported being currently nonsmokers (or nonsnuff users) with a urinary cotinine concentration below 100 ng/ml.

Respiratory and sensory symptoms

We used questions (presented in table 2) developed by the International Union Against Tuberculosis and Lung Disease to quantify symptoms; they have been used in similar studies (1, 7, 28). The participants reported the presence or absence of symptoms in two domains (respiratory and sensory) in the preceding 4 weeks. The same questions were used in the baseline and follow-up examinations.

Measurement of exposure to environmental tobacco smoke

Nicotine in the air. The nicotine vapor phase was measured using passive samplers for environmental tobacco smoke, which are composed of a 37-mm diameter plastic filter cassette (with a windscreen on one side) that contains a Teflon-coated glass-fiber filter treated with sodium bisulfate (22, 29, 30). In the subgroup of nonsmokers, the samplers were placed in the breathing zone on the left-hand side of the participants, who wore them during the workday for a period of 2 to 4 days. Among the smokers, the samplers were placed in the workplace for a similar duration rather than being worn so that contamination by the participants’ smoking would be avoided. The samplers were placed according to written instructions given to the participants (30). The analysis of the samplers was performed at the Department of Occupational and Environmental Medicine, Örebro University Hospital, Sweden. The limit of detection was 0.0025 μg/sample. The nicotine air concentration (μg/m³) was obtained by using the sampler uptake rate (24 ml/minute) and the time the filter had been exposed; thus the duration of exposure was standardized. The method has previously been fully described, and it has been validated and used in several studies (22, 29–31).

We estimated how many participants were over a cut-off level for nicotine in the air relevant to previously defined disease risk. A potent bladder carcinogen, 4-aminobiphenyl (4-ABP), is present in environmental tobacco smoke and has been shown to bond covalently to hemoglobin (22). We chose a cut-off level for nicotine in the air (≥0.5 μg/m³), previously identified as indicating potentially hazardous levels of 4-ABP (22).

Self-reported exposure. Exposure to environmental tobacco smoke at work, at home, and in other localities over the previous 7 days was recorded in the questionnaire, including information on whether the participants lived with a smoker. Exposure during workhours was...
Legislation, environmental tobacco smoke and health effects

Symptoms of the hospitality workers before and after the ban. (OR = odds ratio, 95% CI = 95% confidence interval, Question 1: Have you had whistling or wheezing in your chest?, Question 2: Have you felt short of breath?, Question 3: Do you usually cough the first thing in the morning?, Question 4: Do you cough at all during the rest of the day?, Question 5: Do you bring up phlegm?, Question 6: In the past 4 weeks, have your eyes been red or irritated?, Question 7: Have you had a runny nose, sneezing, or nose irritation?, Question 8: Have you had a sore or irritated throat?)

<table>
<thead>
<tr>
<th>Question</th>
<th>Total sample at preban baseline (N=91)</th>
<th>Preban sample with postban data (N=71; 78%)</th>
<th>Preban sample with postban data (N=14; 18%)</th>
<th>All</th>
<th>Nonsmokers (N=57)</th>
<th>Smokers (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ques. 1</td>
<td>10 14.9 9 37.5 9 15.8 3 21.4 6 10.5 5 35.7</td>
<td>A 0.64 B 0.85</td>
<td>A 0.23–1.80 B 0.28–2.52</td>
<td>A 0.58 B 0.56</td>
<td>A 0.17–1.97 B 0.16–1.91</td>
<td>A 26.5 B 143</td>
</tr>
<tr>
<td>Ques. 2</td>
<td>11 16.4 4 16.7 11 19.3 3 21.4 6 10.5 3 21.4</td>
<td>A 0.53 B 0.44</td>
<td>A 0.16–1.71 B 0.13–1.42</td>
<td>A 0.50 B 0.64</td>
<td>A 0.13–1.93 B 0.11–1.63</td>
<td>A 0.66 B 0.52</td>
</tr>
<tr>
<td>Ques. 3</td>
<td>25 37.3 9 37.5 23 40.4 3 21.4 9 15.8 6 42.9</td>
<td>A 0.44 B 0.46</td>
<td>A 0.14–0.90 B 0.22–0.97</td>
<td>A 0.36 B 0.33</td>
<td>A 0.14–0.87 B 0.13–0.81</td>
<td>A 0.72 B 0.52</td>
</tr>
<tr>
<td>Ques. 4</td>
<td>33 46.3 14 58.3 31 54.4 8 57.1 12 21.1 6 42.9</td>
<td>A 0.28 B 0.25</td>
<td>A 0.12–0.62 B 0.11–0.56</td>
<td>A 0.22 B 0.19</td>
<td>A 0.08–0.63 B 0.06–0.55</td>
<td>A 0.40 B 0.37</td>
</tr>
<tr>
<td>Ques. 5</td>
<td>22 32.8 8 33.3 20 35.1 3 21.4 12 21.1 5 35.7</td>
<td>A 0.36 B 0.38</td>
<td>A 0.12–1.13 B 0.12–1.22</td>
<td>A 0.22 B 0.21</td>
<td>A 0.05–1.01 B 0.04–0.96</td>
<td>A 1.51 B 2.03</td>
</tr>
<tr>
<td>Ques. 6</td>
<td>34 50.7 9 37.5 29 50.9 5 35.7 9 15.8 2 14.3</td>
<td>A 0.12 B 0.11</td>
<td>A 0.04–0.38 B 0.03–0.38</td>
<td>A 0.09 B 0.09</td>
<td>A 0.02–0.39 B 0.02–0.40</td>
<td>A 0.24 B 0.21</td>
</tr>
<tr>
<td>Ques. 7</td>
<td>44 65.7 14 58.3 39 68.4 9 64.3 21 36.8 9 64.3</td>
<td>A 0.37 B 0.31</td>
<td>A 0.18–0.79 B 0.14–0.69</td>
<td>A 0.32 B 0.28</td>
<td>A 0.13–0.76 B 0.11–0.68</td>
<td>A 0.70 B 0.50</td>
</tr>
<tr>
<td>Ques. 8</td>
<td>37 55.2 7 29.2 32 56.1 3 21.4 12 21.1 7 50.0</td>
<td>A 0.36 B 0.35</td>
<td>A 0.17–0.75 B 0.16–0.76</td>
<td>A 0.18 B 0.18</td>
<td>A 0.06–0.51 B 0.08–0.52</td>
<td>A 1.31 B 1.66</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N %</th>
<th>N %</th>
<th>OR a</th>
<th>95% CI</th>
<th>OR a</th>
<th>95% CI</th>
<th>OR a</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ques. 1</td>
<td>10 14.9 9 37.5</td>
<td>A 0.64</td>
<td>B 0.85</td>
<td>A 0.23–1.80</td>
<td>B 0.28–2.52</td>
<td>A 0.58</td>
<td>B 0.56</td>
</tr>
<tr>
<td>Ques. 2</td>
<td>11 16.4 4 16.7</td>
<td>A 0.53</td>
<td>B 0.44</td>
<td>A 0.16–1.71</td>
<td>B 0.13–1.42</td>
<td>A 0.50</td>
<td>B 0.64</td>
</tr>
<tr>
<td>Ques. 3</td>
<td>25 37.3 9 37.5</td>
<td>A 0.44</td>
<td>B 0.46</td>
<td>A 0.14–0.90</td>
<td>B 0.22–0.97</td>
<td>A 0.36</td>
<td>B 0.33</td>
</tr>
<tr>
<td>Ques. 4</td>
<td>33 46.3 14 58.3</td>
<td>A 0.28</td>
<td>B 0.25</td>
<td>A 0.12–0.62</td>
<td>B 0.11–0.56</td>
<td>A 0.22</td>
<td>B 0.19</td>
</tr>
<tr>
<td>Ques. 5</td>
<td>22 32.8 8 33.3</td>
<td>A 0.36</td>
<td>B 0.38</td>
<td>A 0.12–1.13</td>
<td>B 0.12–1.22</td>
<td>A 0.22</td>
<td>B 0.21</td>
</tr>
<tr>
<td>Ques. 6</td>
<td>34 50.7 9 37.5</td>
<td>A 0.12</td>
<td>B 0.11</td>
<td>A 0.04–0.38</td>
<td>B 0.03–0.38</td>
<td>A 0.09</td>
<td>B 0.09</td>
</tr>
<tr>
<td>Ques. 7</td>
<td>44 65.7 14 58.3</td>
<td>A 0.37</td>
<td>B 0.31</td>
<td>A 0.18–0.79</td>
<td>B 0.14–0.69</td>
<td>A 0.32</td>
<td>B 0.28</td>
</tr>
<tr>
<td>Ques. 8</td>
<td>37 55.2 7 29.2</td>
<td>A 0.36</td>
<td>B 0.35</td>
<td>A 0.17–0.75</td>
<td>B 0.16–0.76</td>
<td>A 0.18</td>
<td>B 0.18</td>
</tr>
</tbody>
</table>

* a OR for symptoms when comparing postban to preban period.
* A includes panel data on all of those who participated in the preban examination, while B is restricted to those who participated in both the pre- and postban examinations.
* b Not presented due to low precision (not statistically significant).
* c The XT-logit model did not converge; hence an estimate could not be made. Therefore, we provided an estimate using logistic regression.

recorded in a diary for three consecutive days during both periods.

Attitudes towards the legislation on environmental tobacco smoke

At both examinations, the participants reported their attitude towards the legislation on environmental tobacco smoke using a scale from 0 to 100, on which a higher score indicated a more positive response. In our analyses, we dichotomized the score at 75 to define general satisfaction with the legislation. The question was “What is your opinion of the tobacco smoking legislation?”, with requested comments on the participant him- or herself, hospitality workers in general, the employer, and the clients.

Spirometry

All of the participants underwent a spirometric examination; they were assessed in one of the nine recognized pulmonary function clinics used by the study. All of the clinics followed written instructions from the study coordinator, which were based on guidelines of the European Respiratory Society (32), and it included instructions about calibration and measurements of forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). The same spirometer was used pre- and postban for all of the participants. The FEV1 value, as well as the FVC, was recorded before and 15 minutes after the inhalation of 0.4 mg of salbutamol (or 0.8 mg of terbutaline). The highest FEV1 and FVC values from at least three attempts were recorded.

Statistical analysis

We examined the characteristics of the participants using cross-tabulation, and statistical significance was assessed by the chi-square test. The test for trend was used to estimate changes in tobacco consumption. All of the analyses were performed for the total sample, as well as
for two subgroups based on occupation. Gaming workers were employed in bingo halls (N=22) and casinos (N=15), while the remainder of the hospitality workers have been identified as “other workers” (N=54).

To measure the change in respiratory and sensory symptoms between the data collections, we used the XT-logit procedure provided by Stata software (Stata Corporation, College Station, TX, USA). This is a form of logistic regression specifically developed for panel data for which there is an explicit time component. When workers participate at both time points, this technique links the data and estimates individual change. It can also use estimates from those who participated only once. Data from the 91 participants who were included at baseline could be used in the analyses comparing the population at the two time points. We also limited the analysis to the 71 persons who participated in both examinations to ensure the results were not influenced by attrition-associated bias. The XT-logit models were adjusted for age, gender, and smoking. The analysis was also stratified by smoking behavior.

To estimate the reduction in the exposure to environmental tobacco smoke after the introduction of legislation, we used logistic regression to estimate how many participants were exposed above the cut-off value of <0.5 μg/m$^3$ of nicotine in the air. A similar analysis examined the dichotomized attitude scores. Where it was not possible to report odds ratios, with 95% confidence intervals (95% CI) due to empty cells, relative risks were reported in their place.

Pulmonary function tests were recorded preban and postban and analyzed for each parameter (FEV1 and FVC). We compared the predicted score for the pre- and postban periods using the paired-sample t-test procedure. We also used potentially more sensitive analyses to identify differences in lung function between the time points. To assess differences in reversible bronchial reactivity during the study period, delta-FEV1 was calculated for the difference in capacity before and after a beta-2 agonist was administered. Linear regression was used to assess the differences in this measure, with adjustment for gender, age, and height. A similar analysis was conducted for FEV1. Smokers were excluded from these analyses.

The analysis was conducted using SPSS (SPSS Inc, Chicago, IL, USA) and Stata software.

**Results**

**Hospitality workers’ characteristics**

Table 1 summarizes the characteristics of the participants. A total of 91 persons volunteered and fulfilled the inclusion criteria. Women predominated, and there were relatively few smokers. Persons lost to follow-up were somewhat younger and were more likely to be smokers, but they did not differ from the overall group by gender, and (preban) attitudes towards the legislation.

**Tobacco habits**

Table 1 shows that most of the participants were nonsmokers. One smoker, as well as one nonsmoker, used moist snuff regularly at the follow-up. No one changed their smoking status, and the average daily consumption among the smokers decreased slightly from a median of 17 to 15 cigarettes/day, but this reduction was not statistically significant (P for trend=0.788).

Preban, the number of smokers among the gaming workers was 11 of 37 (30%), and postban the number was 6 of 27 (22%); among the other workers, 13 of 54 (24%) and 8 of 44 (18%) preban and postban, respectively, were smokers. There was no statistically significant decline in the number of cigarettes smoked per day when the two occupational groups were examined separately.

**Screening of unreported smoking or snuff use according to urinary cotinine level**

We were able to analyze urinary cotinine for 79% of the participants in both the preban and postban periods. Storage and transportation problems were the main reasons that we were unable to analyze all of the urine samples. Three persons who reported no tobacco use had urinary cotinine values exceeding the cut-off level of 100 ng/ml [one at baseline (195 ng/ml) and two others at follow-up (283 ng/ml)]. All three were included in the analyses but were reclassified as smokers. Before the ban, urinary cotinine was under the detection limit for 16 of 43 (37%) nontobacco users, while, after the ban, it was below this limit in 29 of 43 (67%) of those who did not use tobacco.

**Respiratory and sensory symptoms**

Table 2 shows the prevalence of respiratory and sensory symptoms among the smokers and nonsmokers before and 12 months after the introduction of the ban. In the entire study population, all of the reported symptoms declined, and the decline was statistically significant for questions about cough in the morning, cough during the rest of the day, eye irritation, nose irritation, and throat symptoms. Using data for all of the nonsmokers (N=67) participating in the preban sweep gave approximately the same results as the analyses using only those who completed the questionnaire both in the preban and postban examination (N=54). Among the smokers, there was no notable association between symptoms and period,
but the small number of smokers makes this result difficult to interpret.

Table 3 shows the prevalence of the respiratory and sensory symptoms presented in table 2 divided into gaming workers and other workers. Among the gaming workers, the odds ratio declined more for cough in the morning, cough the rest of the day, and bringing up phlegm, while the remaining five symptoms declined somewhat more among the other workers. None of the difference between these groups was statistically significant.

**Exposure to environmental tobacco smoke**

*Nicotine in the air.* There was a reduction in the median level of nicotine measured in the air between the baseline and the 12-month follow-up from **7.50 μg/m³** to **0.16 μg/m³** (12.6–0.2 μg/m³ among the smokers and 6.2–0.2 μg/m³ among the nonsmokers). When quantified in terms of risk reduction, before the ban, 87% of the participants had exposure to environmental tobacco smoke over the nicotine cut-off level of <0.5 μg/m³, while, after the ban, it was only 22%, representing a reduced relative risk of 0.25 (95% CI 0.15–0.41) in the total sample. Nicotine in the air, before the ban, was under the detection limit in 1 of 54 (2%) of the nontobacco users, while, after the ban, it was under the limit in 17 of 54 (31%) of the nontobacco users.

Table 3. Symptoms among the gaming and other workers before and after the ban.

<table>
<thead>
<tr>
<th>Group</th>
<th>Preban Total sample at the preban baseline</th>
<th>Preban sample with postban data</th>
<th>Postban Preban sample with postban data</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gaming workers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Question 1: Have you had whistling or wheezing in your chest?</td>
<td>37</td>
<td>100</td>
<td>27</td>
<td>100</td>
<td>27</td>
</tr>
<tr>
<td>Question 2: Have you felt short of breath?</td>
<td>9</td>
<td>24.3</td>
<td>6</td>
<td>22.2</td>
<td>6</td>
</tr>
<tr>
<td>Question 3: Do you usually cough the first thing in the morning?</td>
<td>15</td>
<td>40.5</td>
<td>13</td>
<td>48.1</td>
<td>5</td>
</tr>
<tr>
<td>Question 4: Do you cough at all during the rest of the day?</td>
<td>20</td>
<td>54.1</td>
<td>18</td>
<td>66.7</td>
<td>9</td>
</tr>
<tr>
<td>Question 5: Do you bring up phlegm?</td>
<td>14</td>
<td>37.8</td>
<td>12</td>
<td>44.4</td>
<td>8</td>
</tr>
<tr>
<td>Question 6: In the past 4 weeks, have your eyes been red or irritated?</td>
<td>15</td>
<td>40.5</td>
<td>10</td>
<td>37.0</td>
<td>4</td>
</tr>
<tr>
<td>Question 7: Have you had a runny nose, sneezing, or nose irritation?</td>
<td>23</td>
<td>62.2</td>
<td>19</td>
<td>70.4</td>
<td>14</td>
</tr>
<tr>
<td>Question 8: Have you had a sore or irritated throat?</td>
<td>20</td>
<td>54.1</td>
<td>14</td>
<td>51.9</td>
<td>9</td>
</tr>
<tr>
<td><strong>Other workers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Question 1: Have you had whistling or wheezing in your chest?</td>
<td>54</td>
<td>100</td>
<td>44</td>
<td>100</td>
<td>44</td>
</tr>
<tr>
<td>Question 2: Have you felt short of breath?</td>
<td>6</td>
<td>11.1</td>
<td>6</td>
<td>13.6</td>
<td>3</td>
</tr>
<tr>
<td>Question 3: Do you usually cough the first thing in the morning?</td>
<td>19</td>
<td>35.2</td>
<td>13</td>
<td>29.5</td>
<td>10</td>
</tr>
<tr>
<td>Question 4: Do you cough at all during the rest of the day?</td>
<td>27</td>
<td>50.0</td>
<td>21</td>
<td>47.7</td>
<td>9</td>
</tr>
<tr>
<td>Question 5: Do you bring up phlegm?</td>
<td>16</td>
<td>29.6</td>
<td>11</td>
<td>25.0</td>
<td>9</td>
</tr>
<tr>
<td>Question 6: In the past 4 weeks, have your eyes been red or irritated?</td>
<td>28</td>
<td>51.9</td>
<td>24</td>
<td>54.5</td>
<td>7</td>
</tr>
<tr>
<td>Question 7: Have you had a runny nose, sneezing, or nose irritation?</td>
<td>35</td>
<td>64.8</td>
<td>29</td>
<td>65.9</td>
<td>16</td>
</tr>
<tr>
<td>Question 8: Have you had a sore or irritated throat?</td>
<td>24</td>
<td>44.4</td>
<td>21</td>
<td>47.7</td>
<td>10</td>
</tr>
</tbody>
</table>

<sup>a</sup> For symptoms when the postban period is compared with the preban period (A includes panel data of all those participating in the preban examination, while B is restricted to those who participated in both the pre- and postban examinations).
There was a reduction in the median nicotine level measured in the air between the baseline and 12-month follow-up among the gaming workers from 11.0 μg/m³ to 0.22 μg/m³ and among other workers from 2.95 μg/m³ to 0.12 μg/m³. Among the gaming workers, 100% were exposed over the cut-off value before the legislation, but only 22% were so exposed at the follow-up. This difference can be estimated as a relative risk of 0.29 (95%CI 0.15–0.55), P-value <0.001 (odds ratio not calculated due to an empty cell). Among the other workers, 78% of the participants were over the cut-off level before the ban, while 23% were over the ban at the follow-up, giving a relative risk of 0.29 (95%CI 0.15–0.55), P-value <0.001.

Self-reported exposure. Before the ban, 59 of 91 (65%) persons reported exposure to environmental tobacco smoke for 75% or more of their worktime, while at the follow-up such exposure was the case for only 1 of 71 (1%) persons, P<0.001. The duration of exposure to environmental tobacco smoke at home was unchanged (data not shown).

In other localities (not at work or at home), 35 of 71 (49%) participants reported exposure to environmental tobacco smoke in excess of 1 hour, while, after the ban, it was 7 of 71 (10%) persons, P<0.001.

Preban, there was longer exposure to environmental tobacco smoke at work among the gaming workers than among the others, P-value for trend 0.029. The duration of postban exposure to environmental tobacco smoke was similar in both groups (data not shown).

Attitudes towards the legislation on environmental tobacco smoke. Table 4 indicates that the number of participants reporting that they thought that both employers and clients were satisfied in this respect (a score of 75 or over) showed a statistically significant increase over the pre- and postban periods.

The gaming and other workers’ attitudes on how the employer would be affected by the legislation differed before the ban. The proportion satisfied was 19 of 37 (51%) among the gaming workers and 39 of 51 (76%) among the other workers (OR 3.1, 95% CI 1.2–7.7, P=0.014). This difference was independent of age and gender, as indicated by the multivariate logistic regression analysis. After the ban, this difference was reduced. Some 89% of the gaming workers, compared with 93% of other workers, were satisfied in this respect (P=0.528).

Spirometry. The mean FEV₁ for the nonsmokers (percentage of the expected value) was defined as 100% at the baseline, and, after 12 months, it had declined slightly to 99%. Among the smokers, it fell from 93% to 90%. The mean FVC of the nonsmokers was 93% at the baseline and 92% after 12 months, and, among the smokers, it fell from 94% to 92%.

The delta-FEV₁ did not change notably or statistically significantly over the study period. The regression analysis produced adjusted coefficients of 0.020 (95%CI -0.050–0.090, P=0.566) for the nonsmokers and -0.004 (95%CI -0.144–0.137, P=0.957) for the smokers. Similar analyses for FEV₁ and FVC did not reveal any notable or statistically significant association with period (data not shown).

Discussion

Main findings

The fact that the implementation of the smoke-free legislation was associated with a substantial reduction in respiratory and sensory symptoms among nonsmoking hospitality workers was the main finding of this study. The frequency of reported symptoms was approximately halved among the nonsmokers 1 year after the introduction of the ban. A reduction in symptoms was observed for both the gaming workers (who tended not to have been included in previous studies of exposure to environmental tobacco smoke) and the other hospitality workers. Before the implementation of the legislation, a higher proportion of gaming workers than other hospitality workers was exposed to a potentially hazardous level of exposure to environmental tobacco smoke, but this level was substantially reduced in both occupational groups after the ban; this finding indicates that the legislation was successful in preventing smoking at these workplaces. Although the workers’ attitudes towards the legislation were broadly positive before the ban, the proportion that was positive increased during the year following its introduction.

There is evidence that exposure to environmental tobacco smoke represents a health risk (22, 33–37). It has
been shown that environmental tobacco smoke may be a risk for diseases such as bladder cancer among women who have never used tobacco products (22, 35). The cut-off level for nicotine related to environmental tobacco smoke (<0.5 μg/m³) was chosen for use in this study because, above this level, the associated 4-ABP exposure may notably increase cancer risk (22). The proportion that was exposed above this level was substantially reduced after implementation of the legislation.

**Comparisons with other studies**

There is an increasing number of studies on the effects of smoke-free legislation on hospitality workers; however, many of these studies have been limited to bar workers (1, 7–9, 28). Studies in San Francisco in the United States and in Ireland (7, 9) found substantial decreases in self-reported exposure to environmental tobacco smoke at work and also reductions in respiratory and sensory symptoms. The reductions in salivary cotinine concentrations among nonsmoking hospitality workers in New York State (8) were of a similar magnitude as in the Irish study (1), but no notable changes in the frequency of symptoms were found in the former study. Self-reported symptoms decreased in our study by approximately 50%; this level is in accordance with the findings of studies from California and Ireland (7, 9).

Our study differed from some previous studies that identified changes in lung function (1, 2, 7), which we did not detect. This difference may be because the previous studies performed measurements during or shortly after the workshift. Due to the centralized spirometry measurements in our study, that approach was not possible, and approximately 50% of the spirometry tests were performed either before the workshift or the next day. Therefore, the influence of environmental tobacco smoke on pulmonary function prior to the ban may have been underestimated if there is a close temporal relationship between exposure to environmental tobacco smoke at work and lung function.

Skogstad et al measured lung function before and after shifts (2) and reported a lower cross-shift decrease in some spirometric values postban compared with the preban period. Even when we examined the delta-FEV1 as a potentially more-sensitive measure of the influence of environmental tobacco smoke on lung function, we saw no notable change between the pre- and postban periods.

In contrast with some recent studies (1, 38–40), we found no evidence of a reduction in exposure to environmental tobacco smoke at home, but the number of participants living with a smoker was small. The reduction of reported exposure to environmental tobacco smoke outside home and work may be due to leisure time spent in bars and restaurants that were also smoke-free due to the legislation. In contrast with the study by Braverman et al, who reported a significant decline of the prevalence of daily smoking among Norwegian hospitality workers (41), the slight decrease in the median number of cigarettes smoked by a daily smoker (from 17 to 15/day) in our study was not statistically significant. However, the low number of smokers in our study makes it difficult to draw any firm conclusions.

**Limitations of the study**

The voluntary nature of the recruitment process is likely to have resulted in selection bias. We do not have data on the characteristics or number of potential participants, as recruitment was through a form of advertising. Volunteers may have been less likely to smoke and have different attitudes towards smoking and the legislation; therefore, the population may not have been entirely representative of the target working population. The loss to follow-up may have further caused a selection of nonsmokers and may also have implications for the representativeness of nonsmokers. A larger decline in symptom prevalence has been shown for workers with a positive attitude (42); therefore, it is possible that selection bias in our study could have had this effect. We were able to assess the urinary level of cotinine for 79% of the participants, and therefore some of the participants could have been smokers but reported themselves as nonsmokers, thus underestimating the benefits of smoke-free legislation as the greatest associations were found for the nonsmokers. Although the attrition of 21% is not negligible, it is not unexpected, as this form of work is often casual, seasonal, and frequent job changes are common (1, 28). Thus the results will be more likely to reflect the characteristics and views of those with a more stable position.

**Strengths of the study**

We were able to enroll gaming workers, an occupational area hitherto very scarcely studied in this respect (10). The participants were enrolled from nine different geographic areas in Sweden, from cities with varying population sizes, thus representing a range of climates and living conditions throughout Sweden. The pre- and postban data collection took place among the same persons, employed at the same workplace, and the symptoms were recorded at the same time of year, thereby eliminating seasonal variations and some other possible sources of bias. We used XT-logit analysis, which is specifically designed for longitudinal data when there is an explicit time component so that repeated measures can be examined, even if some participants are lost to follow-up. The participants who were not followed up
did not differ from the overall group in terms of gender and attitudes towards the ban prior to its introduction, reducing the risk of bias. The reduction of exposure to environmental tobacco smoke was confirmed by an objective measurement—nicotine in the air. In this case, using a specific method for measuring work-related exposure to environmental tobacco smoke meant that only exposure at work was recorded. Previous studies have mainly used indirect assessment methods of exposure to environmental tobacco smoke, including subjective reports (9), particle sampling, or exhaled carbon monoxide (43). The sampling of cotinine from bodily fluids is a more direct measurement of environmental tobacco smoke, and it was also used (8, 9). However, urinary cotinine is influenced by individual physiological (respiration, absorption, metabolism, and excretion), temporal (exposure duration), and physical (exposure concentration) parameters (27). Thus factors other than exposure at work (such as leisure-time exposure) could have confounded the urinary cotinine measures. The assessment of exposure to environmental tobacco smoke among smokers or snuff users is not possible with the use of urinary cotinine due to the masking effect of their own tobacco use. Among the nonsmokers, 35% had preban urinary cotinine values below the detection threshold, and this level may reflect a somewhat lower exposure level than in previous studies (1, 2, 9), making it difficult to detect a further reduction with this method. However, the very large reduction in nicotine in the air in our study confirms a reduction in the levels of environmental tobacco smoke. By placing air nicotine samplers in different locations for smokers and nonsmokers, we attempted to avoid confounding from the participants’ smoking behavior. The nonsmokers wore samplers, but the smokers did not, as smoking during breaks could have masked the true measurement of environmental tobacco smoke for their workplace.

Recommendations for further research

Our results indicate that gaming workers—previously investigated very little in relation to exposure to environmental tobacco smoke—may have had the most substantial reduction in such exposure, and therefore the effects are worthy of further study.

In our sample, the exposure to environmental tobacco smoke at home remained about the same, while self-reported exposure in other nonwork localities dropped to one-fifth of the preban level; therefore research into the effects of this reduction in exposure is of potential interest.

The benefits and limitations of using portable samplers for nicotine or locality-bound samplers as an alternative to other methods of assessing exposure to environmental tobacco smoke should also be investigated.

Implications for public health

In conclusion, the legislation on smoke-free workplaces in Sweden has reduced the levels of environmental tobacco smoke for some of the most heavily exposed occupational groups, as indicated by an objective exposure measure. There may also be a notable reduction in exposure outside work when these workers visit bars and restaurants as customers. Implementation of the ban was associated with a reduction in respiratory and sensory symptoms among the nonsmokers. Some of these symptoms, such as cough, are likely to have an impact on the quality of life (44). In the long term, a reduction in hospitality workers’ exposure to environmental tobacco smoke may result in other important health effects as such smoke contains carcinogens (22) and is also a recognized cause of atherosclerotic disease (33) and other smoking-related diseases (34, 36, 37). The health and comfort of hospitality workers may be improved by the smoke-free policy.

Acknowledgments

We thank Siv Karlsson and Gunnel Löw, RN, from the Tobacco Control Unit, The Department of Respiratory Medicine, Örebro University Hospital, Örebro, Sweden, for coordinating the study, recruiting participants, and collecting data from nine study sites throughout the country. We thank the Occupational and Environmental Health Department at the Stockholm Centre for Public Health, Department of Respiratory Physiology at the Sahlgrenska University Hospital in Göteborg, The Environment Administration in Göteborg, and the pulmonary medicine departments of the Linköping University Hospital, the Malmö University Hospital, Kärnsjukhuset in Skövde, the Uppsala University Hospital, the Västerås Hospital, the Örebro University Hospital, and the Östersund Hospital. We especially thank the hospitality workers who participated in the study. We thank Ing-Liss Bryngelsson, from the Department of Occupational and Environmental Medicine Örebro, University Hospital of Örebro, Sweden, for her help with the data collection, entry, and editing.

A grant was obtained from the Swedish National Institute of Public Health.

References


Received for publication: 13 December 2007
Does maternal smoking during pregnancy influence physical control and coordination among offspring?

Matz Larsson (MD)¹,²,³ and Scott M Montgomery (Professor)²,⁴,⁵

1. Department of Respiratory Medicine, Örebro University Hospital, Örebro, Sweden.
2. Clinical Research Centre, Örebro University Hospital, Örebro Sweden.
3. The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.
4. Department of Primary Care and Social Medicine, Charing Cross Hospital, Imperial College, London.
5. Clinical Epidemiology Unit, Department of Medicine at Karolinska University Hospital, Karolinska Institutet, Stockholm Sweden.

Word count: abstract 246; main text 2948

Abbreviations:

NCDS= The National Child Development Study

Time taken to pick up 20 matches (PUM)

Number of squares marked (NSM)

Copying designs (CD)

Type 2 diabetes mellitus (T2DM)

Financial disclosure:

Conflict of interest: Non reported

Correspondence to:

Dr Matz Larsson
Department of Respiratory Medicine
Örebro University Hospital
SE-701 85 Örebro
Sweden

Telephone: +46 19 6025596 / +46 738090228
Fax: +46 19 186526
E-mail: matz.larsson@orebroll.se
ABSTRACT

OBJECTIVE. Smoking during pregnancy is a plausible exposure explaining poorer childhood motor competence among those at risk of obesity in later life. We examine whether this exposure is associated with poorer neurological function or development indicated by motor competence. The chosen measures may be less susceptible to socioeconomic confounding than tests of cognitive function.

SUBJECTS AND METHODS. The analysis was of 13,207 members of the National Child Development Study, who were born in Great Britain between the 3rd and 9th of March 1958. Maternal smoking during pregnancy was recorded prospectively. Physical control and coordination was tested by a school doctor at age 11 years: time taken to pick up 20 matches (PUM), number of squares marked (NSM) and copying designs (CD). PUM and NSM were tested for left and right hand. Test scores were dependent variables in linear regression analysis, with inclusion of: maternal smoking during pregnancy sex, birth weight, gestational age, breast-feeding, social class, parental education, mother’s age, laterality and pubertal development.

RESULTS. Maternal smoking of over 10 cigarettes per day was associated with poorer performance among offspring, indicated by a longer duration for PUM or a lower CD score. Adjusted regression coefficients (95% confidence interval and p value): PUM left hand 1.271 (0.55 to 1.99; p=0.001); PUM right hand 0.745 (0.02 to 1.47 p=0.045); CD -0.116 (-0.21 to – 0.03 p=0.010). The associations were more pronounced among boys. CONCLUSIONS. Smoking during pregnancy may be responsible for a subtle reduction in motor competence, particularly among boys.

Key Words: motor competence • pregnancy smoking • laterality • cohort studies • sex.
BACKGROUND.

Adult-onset obesity and type 2 diabetes mellitus (T2DM) are associated with poorer motor competence and cognitive function in childhood.[1,2] Some socially patterned early life exposures may increase both the risk of these diseases and impair neurological development or function. Several processes may explain these associations, including maternal smoking during pregnancy as this has been linked with T2DM and obesity in offspring.[3,4] Smoking during pregnancy is also associated with poorer cognitive function test scores among offspring so it may also impair some aspects of neurological development or function.[5-9] Tests of cognitive function are influenced directly by social and cultural factors, so may not indicate a neurological mechanism.[10-14] We attempted to tackle this issue by investigating whether smoking during pregnancy was associated with tests of physical control and coordination in offspring during children. These measures are less subject to confounding by social factors than many tests of cognition, so an association with maternal smoking in pregnancy would provide more evidence of a direct biological mechanism rather than social pathway.

Previous studies of smoking in pregnancy and physical control and coordination in offspring are few and tend to have been limited by small population sizes or other methodological constraints. Smoking in pregnancy was associated with a small adverse effect on balance at age 5 years in a study of 362 children.[15] Research involving 593 children found maternal
smoking during pregnancy was associated with a modest decrease in coordination on the non-dominant side of the body and the ability to reproduce geometric designs from memory.[6]

This study investigated the association of maternal smoking during pregnancy with doctor-administered tests of physical control and coordination at 11 years of age, among a large and representative British longitudinal birth cohort with the possibility to take multiple potential confounding factors into account. The same tests and population were previously used to establish the association of smoking during pregnancy with type 2 diabetes risk and the association of poorer motor competence in childhood with adult obesity.[2,3] Some tests were performed for the left and right hand separately, allowing us to investigate whether any associations are more pronounced on the non-dominant side, as previously reported.[6] We also stratified our analyses by sex, as several animal studies have demonstrated different and usually greater neurological influence of in utero exposures to nicotine among males.[16-19] Sex-specific differences have also been demonstrated in humans.[20]

MATERIALS AND METHODS

The National Child Development Study (NCDS) is following all those born between 3rd-9th March 1958 and living in Great Britain, with data collection sweeps throughout childhood and in adult life.[14] The study was originally of approximately 17,000 births, but the subsequent exclusion of Northern Ireland, death, emigration and other causes of attrition reduced the sample size, although the cohort has remained broadly representative of the target population.[15]

At birth midwives recorded maternal smoking habits during pregnancy (after the fourth month), using data from the medical records. This measure was divided into non-smokers, medium (1-9 cigarettes/day), heavy (>10), and variable smokers (a balance of medium and
heavy smokers). Children with incomplete or equivocal information on mother’s smoking habits during pregnancy represented (7.4%) of the original sample, and were not included in this study.

At birth, midwives also recorded: sex, birth weight in ounces, gestational age in weeks, mother’s age, her age on leaving full time education, number of persons per room at birth (up to 1, > 1 to 1.5, > 1.5 to 2, > 2 to 2.5, >2.5 to 3, >3 persons per room). The Registrar General’s social class based on the father’s, occupation, was categorised as I, II, III non-manual, III manual, IV, V and ‘Not assigned (where the father was not present or not working).

In 1969 at age 11 years (when the outcomes of this study were measured) information was collected for 15,303 cohort members. Some 13,207 received a medical examination from a Local Authority medical officer. Three tests were selected as indicating hand control and coordination, and they have been used in a previous study on neurological functions and obesity later in life [2]:

1. The time in seconds (maximum 99 seconds) that it took to pick up 20 matches with left (n=10223), or right hand (n=10230). (Unlike the other tests, a higher score indicated poorer performance.)

2. Marking squares (maximum 200) on paper within one minute with left (n=10193), or right hand (n=10247).

3. Copying a simple design with the dominant hand (n=9615). The accuracy of the copy was scored from 0 to 12.

During the sweep at age 11 years, the medical officer assessed laterality. Chronic illness and disability were assessed from the medical records and by medical examination. Conditions were characterised by the major functional domains: if the condition was present, and the
degree to which it impaired daily living. Pubertal development was assessed using scores for breast development and pubic hair assessments in girls and genitalia development and pubic hair density in boys (0-5 for each measure). The scores were summed for boys and girls separately and were then converted into standard deviation units (for standardisation) and combined.

Ethnic origin was categorised as: White British (over 96%), Irish, White other, White and Black Caribbean, White and Black African, White and Asian, other mixed race, Indian, other Asian, Caribbean, African, other Black, or other ethnic groups.

Ethical permission was not required for this analysis of anonymous data, although it was obtained to cover the original data collection.

**Statistical Analysis:**

Linear regression estimated associations with each test of physical control and coordination with separate analyses for left and right hand as appropriate. The following continuous covariates were included in the model: puberty score in standard deviation units (Z score), sex of child, and the person-per-room ratio (crowding) The categorical measures were maternal smoking during pregnancy, mothers education, social class, mothers age, breast-feeding, birth weight-gestational age for sex in standard deviation groups, laterality of the child and sex. These measures were modelled as series of binary dummy variables.

All analyses were stratified by sex. Effect modification was assed by interaction testing with adjustment for the main effects. [21] The main analyses were repeated excluding the minority
non-white UK ethnic groups. Similarly, all those with a recorded chronic illness at age 11 years were excluded, irrespective of severity.

The analyses were conducted using SPSS for windows version 16.3.

RESULTS:

Table 1 shows the distributions by maternal smoking behaviour during pregnancy for the main covariates. Lower social class, crowding, mother’s education level, breastfeeding, as well as lower birth weight were all strongly associated with maternal smoking during pregnancy (p<0.001). It is important to note that there was no association between laterality and maternal smoking during pregnancy (P=0.859), indicating that this cannot be a confounding factor.

Time picking up matches

Table 2 presents the results for time picking up matches with left, and right hand. In contrast with the other tests, a higher score in the picking up matches test indicates worse performance (a longer time). In both the left and right hand tests there was a statistically significant association of reduced motor competence with heavy maternal smoking during pregnancy. Notably, the strongest association was in the left hand. There were only modest reductions in the magnitude of the associations after adjustment for multiple potential confounding factors. Stratification by sex showed that in offspring to heavy smoking mothers the association remained statistically significant for the left hand in boys Beta 1.593, 0.60 to 2.59, p=0.002, however not for girls 1.007, -0.03 to 2.04, p=0.056). The corresponding values for right hand showed almost no sex difference: boys 0.719, –0.29 to 1.73, p= 0.164, and girls 0.844, –0.20
to 1.89, p= 0.114. The interaction test for sex with prenatal smoking, adjusted for the main effects, was not statistically significant for either hand (data not shown.)

**Number of squares marked**

Table 3 presents the results for number of squares marked with left, and right hand. In heavy smoking mother’s group, left and right hand tests showed a modest reduction in ability with prenatal tobacco exposure (indicated by a negative coefficient) in the unadjusted model, which however did not remain in the adjusted model. Stratification by sex showed that in offspring of heavy smoking mothers the associations for both hands were stronger in boys. **Left hand** in boys: Beta value –1.687, 95% CI: –3.40 to 0.03, p= 0.054; girls 0.359, –1.55 to 2.27, p= 0.713. **Right hand** in boys -1.278, –3.15 to 0.59, p= 0.180, and in girls 0.110, 95% CI: –2.02 to 2.24, p= 0.920. The interaction test for sex with prenatal smoking was not statistically significant for either hand (data not shown.)

**Copying designs**

Table 4 presents the results for Copying designs. In the unadjusted model, heavy smoking during pregnancy was associated with a reduced test score In the adjusted model there was a reduction in the magnitude of the associations but it remained statistically significant. Stratification by sex showed that in offspring to heavy smoking mothers the association was much more notable in boys: Beta – 0.216, 95%CI: –0.35 to –0.08; p=0.001 while in girls, there was almost no association: -0.021, -0.15 to 0.10; p=0.743. The interaction test for heavy maternal smoking by sex was statistically significant for Copying designs: Beta 0.196, 95%CI: 0.02 to 0.37, p=0.029.
To assess possible confounding by disability, we excluded those with conditions associated with test scores: any CNS-condition, general motor handicap or epilepsy. There was almost no notable difference in the results, except a slight influence on the already modest association with picking up matches using the right hand where the modest statistical significance was eroded: 0.691 (-0.04 to 1.42, p=0.065).

Excluding the small minority that did not have white UK ethnic origin (n=394, <4%) did not alter any of the results (data not shown).

**DISCUSSION**

We found an association between maternal smoking during pregnancy and poorer performance in physical control and coordination in 11-year-old children. In the unadjusted analyses all the five investigated measures were associated with maternal smoking, and in three - picking up matches with right, left hand, and copying design - the association remained statistically significantly independent of multiple markers of social and material conditions in childhood. In all five outcomes the strongest association was in children whose mothers smoked most. Smoking during pregnancy showed a stronger association to reduced performance in picking up matches with the left hand compared to the right.[6] Stratification by sex indicated that the associations with prenatal smoking were more pronounced in boys. The sex difference was most notable for Copying designs where there was statistically significant effect modification.

We examined smoking during pregnancy, as this is one of the exposures that may help to explain why there may be poorer neurological function in children at greater risk of T2DM
and obesity in later life. Maternal smoking during pregnancy has been linked with T2DM, and obesity as well as with poorer performance in cognitive function tests.[2,3][5] However, associations with cognitive function tests can be confounded by social factors, such that they reflect social pathways rather than a more direct biological mechanism.[10-14] By focusing on markers of motor competence we attempted to reduce the risk of confounding by social factors in our examination of the influence of smoking during pregnancy on neurological function or development among offspring. The same study individuals and tests of physical control and coordination were recently used to establish that poorer motor competence in childhood is associated with subsequent adult-onset obesity.[2] This is therefore a particularly suitable population to assess the potential role of maternal smoking during pregnancy in limiting motor competence.

It is notable that in general the associations were more pronounced in tests of the left rather than the right hand. This is most likely to be because left is the non-dominant side in the majority of individuals. This finding is consistent with an earlier study indicating the most pronounced association between maternal smoking in pregnancy and poorer coordination in the non-dominant side.[6] It is worthy of note that laterality was not associated with maternal smoking, so this is not a confounding factor.

The majority of associations between tests and maternal smoking were more pronounced or were solely found in male rather than female offspring. While this could in theory be due to socially determined sex differences, we believe this finding points to a biological mechanism. Animal studies have shown that in utero exposure to nicotine result in a variety of sex-specific effects in brain development and behaviour [16,18] [22-25].
The impact of prenatal nicotine exposure on neurological performance in humans is scarcely studied, and, to our knowledge there is only one study before that has suggested sex-specific differences.[20] However that study was limited in size (181 subjects), non-prospective, and it investigated combined (prenatal and adolescent) exposures to tobacco smoke.[26] Many studies have investigated smoking in pregnancy and cognitive function, but as previously discussed, these may be more likely to be confounded by social factors.[7-9] Reports about maternal smoking during pregnancy and physical control and coordination among offspring are scarce, but there has been at least two previous studies.[6,15] The first study showed that smoking in pregnancy was associated with a small but demonstrable adverse effect on the child's balance at 5 years of age. That study was also prospective but limited in size (n=362 children).[15] Arguably, measures of balance may be more confounded than hand control by socially patterned factors including exercise and body mass.[2] In the second earlier study, neuropsychological development among 593 10-year-old children was followed prospectively from the fourth month of gestation. Maternal smoking during pregnancy was associated with a small, statistically significant, decrease in eye-hand coordination on the non-dominant side, and to reproduce geometric designs from memory [6]. These relationships persisted after adjusting for a variety of maternal prenatal and current substance abuse measures, as well as maternal and child demographic, psychosocial, and environmental characteristics. However the study also had some potential limitations as the participants were predominantly from a disadvantaged population. A more specific concern is the high proportion smoked marijuana (approximately 20%) and crack-cocaine and other cocaine use was also substantial. Therefore, associations with smoking during pregnancy could have been confounded by other drug use.
Our study is less likely to be confounded by maternal illicit substance abuse in pregnancy and also benefits from a far larger and representative population. The large number of prospectively recorded measures in almost every life domain is another major advantage.

It is plausible that maternal smoking during pregnancy has a direct influence on neurological development and function among offspring. Accumulating evidence from preclinical studies has identified nicotine as the major teratogenic component of tobacco smoke contributing to adverse neurodevelopment consequences associated to prenatal exposure to maternal smoking.[19,20,27] Nicotinic acetylcholine receptors, which nicotine binds to, play a key role in the regulation of brain development.[27-30] Maternal smoking may result in a form of foetal malnutrition, but it is not clear why this should influence male more than female offspring.

A potential weakness of this study is that it remains possible that the association of maternal smoking in pregnancy with poorer motor competence at age 11 years reflect confounding by social factors rather than a more direct biological mechanism. However, this is somewhat unlikely for several reasons. The measure of exposure was recorded prospectively and the outcome was assessed in an examination conducted by doctors. We were able to adjust for a variety of important indicators of material and social circumstances, but this did not eliminate statistical significance. Indeed, adjustment for measures such as birth weight may represent over-adjustment, as they could be outcomes of maternal smoking. This would result in more conservative estimates of association, but we opted to do this as birth weight is also an important predictor of current and future socioeconomic disadvantage and so any association independent of this is unlikely to be confounded by such factors. It is possible that some mothers falsely reported they were non-smokers in pregnancy (false reports of smoking are
unlikely), thus providing more conservative estimates of association. Insulin metabolism can influence the timing of puberty and as maternal smoking during pregnancy may have an effect on this, this could be a potential confounding factor. We adjusted for pubertal development at the time of testing, but again this may represent an over-adjustment, as maternal smoking during pregnancy may be associated with age at puberty; this is likely to have resulted in more conservative estimates of association.[31] Smoking during pregnancy may be associated with other unmeasured behaviours that could have injured the foetus, but as these tend to be socially patterned our adjustment for multiple social and cultural factors could have gone some way to tackling this potential source of bias.

This study provides some of the strongest evidence to date that maternal smoking during pregnancy influences neurological development or function in offspring, as indicated by poorer motor competence. This finding is consistent with the hypothesis that smoking during pregnancy is one of the exposures responsible for the increased risk of neurological complications among individuals who will develop obesity or T2DM in later life.[2,3] The associations between maternal smoking and poorer motor competence are more modest than seen between motor competence and later obesity previously observed using these data.[2] This indicates that smoking during pregnancy is only one of several exposures that occur across the life-course that could help explain the natural history of neurological complications in those at greater risk of obesity and T2DM. Other in utero exposures as well as factors in later life may also be relevant. Very early life exposures such as maternal smoking during pregnancy may influence neurological development and function as relevant to physical control and coordination. If maternal smoking during pregnancy does influence childhood motor competence directly, the effects appear modest and males are most affected.
Acknowledgements

Professor Montgomery received funding from Economic and Social Research Council grant RES – 596-28-0001 to the International Centre for Life-Course Studies in Society and Health. We thank Margareta Landin at the medical Library, Örebro University Hospital for assistance in the literature research.

What is already known about this topic?

Poorer physical control and coordination in childhood is associated with adult obesity and as smoking during pregnancy is related to obesity risk among offspring, this is as plausible exposure that may also impair motor competence.

What this study adds?

Smoking during pregnancy is associated with poorer physical control and coordination among offspring, particularly in boys. The magnitude of the association is modest, so smoking during pregnancy cannot fully explain poorer motor competence among those who will become obese, but it may be one of several relevant exposures.
Table 1. Distribution of variables in relation to Maternal Smoking During Pregnancy
(Total; \(N=10247\))

<table>
<thead>
<tr>
<th>Number (%)</th>
<th>Non-smoker</th>
<th>Variable smoker</th>
<th>Medium smoker</th>
<th>Heavy smoker</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6920 (67.5)</td>
<td>582 (5.7)</td>
<td>1539 (15.0)</td>
<td>1206 (11.8)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Social class of mother's husband at birth</th>
<th>Non-smoker</th>
<th>Variable smoker</th>
<th>Medium smoker</th>
<th>Heavy smoker</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unempl., sick</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>339 (79.0)</td>
<td>6 (1.4)</td>
<td>49 (11.4)</td>
<td>35 (8.2)</td>
<td></td>
</tr>
<tr>
<td>I I</td>
<td>1077 (77.8)</td>
<td>48 (3.5)</td>
<td>142 (10.3)</td>
<td>117 (8.5)</td>
<td></td>
</tr>
<tr>
<td>I I I nonmanual</td>
<td>776 (74.4)</td>
<td>50 (4.8)</td>
<td>140 (13.4)</td>
<td>77 (7.4)</td>
<td></td>
</tr>
<tr>
<td>I I I manual</td>
<td>3420 (65.8)</td>
<td>316 (6.1)</td>
<td>819 (15.8)</td>
<td>642 (12.4)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>781 (61.7)</td>
<td>84 (6.6)</td>
<td>229 (18.1)</td>
<td>172 (13.6)</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>527 (56.9)</td>
<td>77 (8.3)</td>
<td>160 (17.3)</td>
<td>162 (17.5)</td>
<td></td>
</tr>
</tbody>
</table>

| No. persons/room | 1.42(0.869)# | 1.69(1.049)# | 1.62(1.029)# | 1.66(1.054)# | <0.001 |

| Birth weight in gram | 3724(1931) # | 3605(1946) # | 3464(1578) # | 3542(1982) # | <0.001 |

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3520(67.2)</td>
<td>315(6.0)</td>
<td>766(14.6)</td>
<td>632(12.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.242</td>
</tr>
</tbody>
</table>

| Puberty | 0.0031(1.0009)# | -0.0159(1.0402)# | -0.0276(0.9686)# | -0.0301(0.9710)# | 0.015 |

<table>
<thead>
<tr>
<th>Handedness of child</th>
<th>right</th>
<th>left</th>
<th>right</th>
<th>left</th>
<th>right</th>
<th>left</th>
<th>right</th>
<th>left</th>
<th>right</th>
<th>left</th>
<th>right</th>
<th>left</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6264(67.7)</td>
<td>1384(14.9)</td>
<td>1085(11.7)</td>
<td>525(5.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.859</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mother’s education</th>
<th>Did stay at school</th>
<th>Did not stay</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2036(77.3)</td>
<td>87(3.3)</td>
<td>279(10.6)</td>
</tr>
<tr>
<td></td>
<td>4883(64.1)</td>
<td>495(6.5)</td>
<td>1260(16.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Breastfed</th>
<th>No</th>
<th>Under 1 month</th>
<th>Over 1 month</th>
<th>Don’t know</th>
<th>Mother’s age</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1917(62.5)</td>
<td>197(6.4)</td>
<td>507(16.5)</td>
<td>455(14.8)</td>
<td>1620(63.9)</td>
<td>158(6.2)</td>
</tr>
<tr>
<td></td>
<td>3352(73.1)</td>
<td>221(4.8)</td>
<td>586(12.8)</td>
<td>424(9.3)</td>
<td>31(60.8)</td>
<td>6(11.8)</td>
</tr>
</tbody>
</table>

| No | 2723(68.2) | 250(6.3) | 611(15.3) | 408(10.2) | 731(68.0) | 51(4.7) | 159(14.8) | 134(12.5) | 0.011 |
|    | 5(50.5) | 1(10.0) | 3(30.0) | 1(10.0) |    |        |      |        |      |     |

* Pearson Chi-Square  
# Standard Deviation
Table 2. Relation of Maternal Smoking During Pregnancy with time picking up matches

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>Unadjusted</th>
<th>95% CI</th>
<th>P</th>
<th>Adjusted</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>B</td>
<td></td>
<td></td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Left hand (N=10230)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>6906 (67.5)</td>
<td>Ref</td>
<td>-</td>
<td>-</td>
<td>Ref</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Variable smoker</td>
<td>583 (5.7)</td>
<td>1.111</td>
<td>0.13 to 2.99</td>
<td>0.026</td>
<td>0.744</td>
<td>0.24 to 1.73</td>
<td>0.138</td>
</tr>
<tr>
<td>Medium smoker</td>
<td>1539 (15.0)</td>
<td>0.386</td>
<td>-0.25 to 1.02</td>
<td>0.237</td>
<td>0.148</td>
<td>-0.50 to 0.79</td>
<td>0.652</td>
</tr>
<tr>
<td>Heavy smoker</td>
<td>1202 (11.7)</td>
<td>1.590</td>
<td>0.88 to 2.30</td>
<td>&lt;0.001</td>
<td>1.271</td>
<td>0.55 to 1.99</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Right hand (N=10234)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>6909 (67.5)</td>
<td>Ref</td>
<td>-</td>
<td>-</td>
<td>Ref</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Variable smoker</td>
<td>584 (5.7)</td>
<td>0.869</td>
<td>-0.13 to 1.85</td>
<td>0.089</td>
<td>0.445</td>
<td>-0.55 to 1.44</td>
<td>0.381</td>
</tr>
<tr>
<td>Medium smoker</td>
<td>1539 (15.0)</td>
<td>0.512</td>
<td>-0.14 to 1.16</td>
<td>0.122</td>
<td>0.235</td>
<td>-0.42 to 0.89</td>
<td>0.481</td>
</tr>
<tr>
<td>Heavy smoker</td>
<td>1202 (11.7)</td>
<td>1.114</td>
<td>0.39 to 1.83</td>
<td>0.002</td>
<td>0.745</td>
<td>0.02 to 1.47</td>
<td>0.045</td>
</tr>
</tbody>
</table>

*Model adjusted for social class of mothers’s husband, number of persons living per room, birth weight, sex of child, puberty score, laterality, mothers education, breast-feeding, mother’s age
Table 3. Relation of Maternal Smoking During Pregnancy with number of squares marked

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>Unadjusted B</th>
<th>95% CI</th>
<th>P</th>
<th>Adjusted† B</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left hand (N=10244)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>6918 (67.5)</td>
<td>Ref</td>
<td>-</td>
<td>-</td>
<td>Ref</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Variable smoker</td>
<td>582 (5.7)</td>
<td>-0.621</td>
<td>-2.32 to 1.27</td>
<td>0.570</td>
<td>0.253</td>
<td>-1.47 to 1.97</td>
<td>0.773</td>
</tr>
<tr>
<td>Medium smoker</td>
<td>1539 (15.0)</td>
<td>-0.151</td>
<td>-1.32 to 1.02</td>
<td>0.801</td>
<td>0.245</td>
<td>-0.88 to 1.37</td>
<td>0.671</td>
</tr>
<tr>
<td>Heavy smoker</td>
<td>1205 (11.8)</td>
<td>-1.337</td>
<td>-2.63 to -0.04</td>
<td>0.044</td>
<td>-0.794</td>
<td>-2.05 to 0.46</td>
<td>0.214</td>
</tr>
<tr>
<td><strong>Right hand (N=10247)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>6920 (67.5)</td>
<td>Ref</td>
<td>-</td>
<td>-</td>
<td>Ref</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Variable smoker</td>
<td>582 (5.7)</td>
<td>-0.869</td>
<td>-2.84 to 1.10</td>
<td>0.387</td>
<td>0.826</td>
<td>-1.27 to 2.52</td>
<td>0.518</td>
</tr>
<tr>
<td>Medium smoker</td>
<td>1539 (15.0)</td>
<td>-0.850</td>
<td>-2.14 to 0.44</td>
<td>0.196</td>
<td>0.171</td>
<td>-1.07 to 1.41</td>
<td>0.787</td>
</tr>
<tr>
<td>Heavy smoker</td>
<td>1206 (11.8)</td>
<td>-1.875</td>
<td>-3.30 to -0.45</td>
<td>0.010</td>
<td>-0.616</td>
<td>-2.00 to 0.78</td>
<td>0.382</td>
</tr>
</tbody>
</table>

† Model adjusted for social class of mothers’s husband, number of persons living per room, birth weight, sex of child, puberty score, laterality, mothers education, breast-feeding, mother’s age.
Table 4. Relation of Maternal Smoking During Pregnancy with copying design test score.
(Total; $N=9655$)

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
<th>Unadjusted B</th>
<th>95% CI</th>
<th>P</th>
<th>Adjusted$^1$ B</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smoker</td>
<td>6576(68.1)</td>
<td>Ref</td>
<td>-</td>
<td>-</td>
<td>Ref</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Variable smoker</td>
<td>534(5.5)</td>
<td>-0.199</td>
<td>-0.32 to -0.07</td>
<td>0.002</td>
<td>-0.075</td>
<td>-0.20 to 0.05</td>
<td>0.258</td>
</tr>
<tr>
<td>Medium smoker</td>
<td>1431(14.8)</td>
<td>-0.127</td>
<td>-0.21 to -0.04</td>
<td>0.002</td>
<td>-0.024</td>
<td>-0.11 to 0.06</td>
<td>0.557</td>
</tr>
<tr>
<td>Heavy smoker</td>
<td>1112(11.5)</td>
<td>-0.238</td>
<td>-0.33 to -0.14</td>
<td>&lt;0.001</td>
<td>-0.116</td>
<td>-0.21 to -0.03</td>
<td>0.010</td>
</tr>
</tbody>
</table>

$^1$ Model adjusted for social class of mother’s husband, number of persons living per room, birth weight, sex of child, puberty score, laterality, mothers education, breast-feeding, mother’s age.
REFERENCES


