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SMOKING AND THE INCIDENCE OF ASTHMA DURING ADOLESCENCE: RESULTS OF A LARGE COHORT STUDY IN GERMANY.

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ABSTRACT

Background: The association between smoking and asthma or wheeze has been extensively studied in cross-sectional studies but evidence from large prospective cohort studies on asthma incidence during adolescence is scarce.

Methods: We report data from a cohort study in two German cities, Dresden and Munich. The study population (n=2,936) was first studied in 1995/96 at age 9-11 years as part of Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II) and followed-up in 2002/03. At baseline, parents completed a questionnaire and children underwent clinical examination, and blood sampling. At follow-up, the young adults completed questionnaires on respiratory health, living and exposure conditions. We calculated incidence risk ratios (IRR) and adjusted for potential confounders using a modified poisson regression approach.

Results: The adjusted IRR for incident wheeze comparing active smokers with non-smokers was 2.30 (95% confidence interval: 1.88-2.82). The adjusted IRR was slightly higher for incident wheeze without a cold (2.76;1.99-3.84) and incidence of diagnosed asthma (2.56;1.55-4.21). The analyses of duration and intensity of active smoking indicated dose dependent associations. Stratified analyses showed that among atopic smokers the risk of incident wheeze without cold increased with decreasing α_1-antitrypsin plasma levels at baseline (1.64;1.22-2.20; per interquartile range).

Conclusions: Active smoking is an important risk factor for the incidence of asthma during adolescence. Relatively lower α_1-antitrypsin plasma levels, although well above currently accepted thresholds, may increase susceptibility to respiratory disease among atopic smokers.

INTRODUCTION

Determinants of asthma and wheeze have been extensively studied in cross-sectional studies. However, this study design has a major limitation in the inability to establish a temporal sequence between exposure and disease. Evidence from birth cohort studies on risk factors for the incidence of asthma is currently emerging from several countries, but most cohorts are still relatively young. Evidence from cohort studies on risk factors for asthma incidence during adolescence is scarce.

The results from available cohort studies on the role of active smoking are conflicting. While some studies observed an increased incidence of asthma among smokers,[1] [2] [3] [4] [5] [6] some found no effect or weak associations,[7] [8] and one group reported an inverse relation.[9] Only two of these studies provide data on adolescents.[1] [6] Exposure to environmental tobacco smoke (ETS) is also thought to be a risk for the incidence of respiratory disease. ETS exposure seems to cause an increase in non-atopic wheezy bronchitis in children, whereas among children with established asthma parental smoking is associated with a more severe disease.[10] [11] In addition, ETS exposure seems to be a risk factor for chronic bronchitis and asthma in adults.[12] However, longitudinal data on adolescents are again limited and only one study showed a significant association between maternal smoking and the incidence of asthma in their children.[11]

Apart from the lack of longitudinal data concerning risk factors for asthma there is also rising interest in interactions of environmental exposures with genetic predisposition and in markers for susceptibility. Recently, attention has been drawn to the harmful effect of glutathione-S-transferase deficiency and of low α_1-antitrypsin plasma levels in combination with exposure to ETS.[13] [14] Alpha-1-antitrypsin is a serine protease inhibitor primarily

binding elastase produced by neutrophils during inflammation. Thus, it prevents elastic tissue like the lung from degeneration.[15]

In this paper, we present data from a large population based cohort study in Germany. The study population comprises 2,936 children, aged 9-11 years at baseline and followed for about seven years through adolescence. The objective was to investigate the role of active and passive smoking on the incidence of asthma. In addition, we examined differences in susceptibility to respiratory disease associated with atopy, smoking and α_1-antitrypsin blood plasma levels.

METHODS

Study population and study design

The baseline population consisted of 9-11 year old participants in Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II) in Munich and Dresden in 1995/96.[16] Details of the surveys have been described elsewhere.[17] Briefly, parents of random samples of fourth grade pupils in Munich (n=3354, response rate 87.5%) and in Dresden (n=3045, response rate 83.0%) responded to a written questionnaire. We assessed detailed information on respiratory health, living and exposure conditions.

Characteristics of the participants in the follow-up survey (n=3785) and the study population we included in the analyses (n=2936) are given in figure 1 and table 1. We excluded 849 participants from the analyses for the following reasons: 1. Non-German nationality (n=293). In Germany, nationality reflects ethnicity rather than place of birth. It is known, that in Germany the prevalence of asthma and allergies is much higher among children with German nationality than in those without.[18] The proportion of participants without German nationality differed substantially between the two study centres (Dresden 0.2%, Munich 13.5%). 2. Reported wheeze or asthma during the baseline survey (n=494), since this study was on the incidence of wheeze and asthma. 3. Missing values for wheeze or asthma at baseline or wheeze at follow up (n=62).

The studies at baseline were approved by the ethics committee of the University of Münster, Germany, and the follow-up study has been approved by the Ethical Committee of the Bavarian Chamber of Physicians and the Ethical Committee of the Department of Medicine, Technical University of Dresden.

Table 1: Characteristics of the study population (n=2936)

	at baseline n (%) *	at follow-up n (%) *
age (mean ± SD)	9.6 ± 0.56	17.1 ± 0.62
sex		
female	1592 (54.2)	1592 (54.2)
male	1344 (45.8)	1344 (45.8)
symptoms and diagnosis of respiratory disease		
incident wheeze (yes)	n.a.	388 (13.2)
incident wheeze without a cold (yes)	n.a.	158 (5.8)
incidence of diagnosed asthma (yes)	n.a.	66 (2.6)
parental history of		
allergic disease (yes)	1258 (43.2)	n.a.
asthma (yes)	241 (9.0)	n.a.
clinical examination		
bronchial hyperreactivity (yes)	186 (15.2)	n.a.
atopy † (yes)	780 (36.6)	n.a.
α_1-antitrypsin plasma levels in mg/dl (median (IQR))	152.0 (25.0)	n.a.
active smoking during adolescence (yes)	n.a.	993 (34.1)
age at onset of smoking (mean ± SD)	n.a.	14.1 ± 1.54
duration of active smoking		
never	n.a.	1922 (66.4)
≤2 yrs		395 (13.6)
2–4 yrs		422 (14.6)
>4 yrs		156 (5.4)
duration of active smoking (mean ± SD)	n.a.	2.6 ± 1.35
intensity of active smoking		
never	n.a.	1922 (66.1)
occasionally		169 (5.8)
daily≤10 cigarettes		440 (15.1)
daily>10 cigarettes		378 (13.0)
exposure to environmental tobacco smoke (ETS) (yes)	1094 (38.9)	1863 (63.9)
exposure to environmental tobacco smoke (ETS) at home (yes)	1094 (38.9)	920 (40.2)
duration of ETS exposure		
never	n.a.	997 (34.4)
≤1 hr/d		560 (19.3)
1–5 hrs/d		863 (29.8)
>5 hrs/d		478 (16.5)

abbreviations: n = cases, % = prevalence, SD = standard deviation, IQR = interquartile range, n.a. = not applicable / assessed

* unless otherwise specified

† atopy is defined as either at least one positive skin prick test (wheal size ≥3 mm after subtraction of negative control) or specific serum IgE levels greater than 0.7 kU/l (a panel of common aeroallergens tested for both)

Questionnaires and clinical examination, blood sampling and laboratory analysis

The baseline questionnaire consisted of the questionnaire from the German ISAAC Phase II study described in detail elsewhere.[17] The follow-up questionnaire consisted mainly of items from the European Community Respiratory Health Survey (ECRHS) and ISAAC.[19] [16] The items in question were respiratory symptoms and disease as well as allergies among participants and their families, socio-demographic characteristics, active and passive smoking, present and previous living conditions, and several occupational aspects.

At baseline, measurements (n=2088; 71.1%) of specific serum IgE-antibodies directed against a panel of common aeroallergens (mixed grass pollen, birch pollen, mugwort pollen, *Dermatophogoides pteronyssinus*, cat dander, dog dander, *Cladosporium herbarum*) were conducted by Flourescence Enzyme Immuno Assay (SX1 CAP; Pharmacia, Lund, Sweden). Skin prick tests (n=2500; 85.1%) were performed using extracts of six common aeroallergens (*D. pteronyssinus*, *D. farinae*, *Alternaria tenius*, cat hair, mixed tree and mixed grass pollen). A random subsample underwent spirometry and bronchial challenge using hypertonic saline (n=1227; 41.8%).[14] Alpha-1-antitrypsin blood plasma levels were measured in samples of 2015 children (68.6%) using the rate-nephelometric Immuno-Chemistry System (ICS Aray; Beckman Instruments, Fullerton, CA, USA).[16] C-reactive Protein (CRP) was measured in plasma (n=2018; 68.7%) by standard densiometry (Vitro 250; Johnson & Johnson, Rochester, NY, USA).

Definitions of variables

Outcome variables

We defined *wheeze* as either presence of "wheezing or whistling in the chest" or asthma medication use in the past 12 months. W*heeze without a cold* was an affirmative response to the question "Have you had this wheezing or whistling when you did not have a cold?". Subjects were defined as having *diagnosed asthma* if they had *wheeze* and reported that a doctor had either diagnosed "asthma" at least once or "spastic/asthmatic bronchitis" at least twice. *Atopy* was assessed only at baseline and defined as either at least one positive skin reaction (wheal size ≥3 mm after subtraction of negative control) to the six tested aeroallergens or specific serum IgE levels greater than 0.7 kU/l.[20]

Explanatory variables

Active smoking was determined by responses to "Have you ever smoked for as long as a year? ['YES' means at least 20 packs of cigarettes in a lifetime, or at least one cigarette per day or one cigar a week for one year]" (yes/no). Age at the onset of active smoking and age at quitting were reported in years. Duration of active smoking was calculated as the difference of the age at onset smoking and the age at follow-up or, if applicable, the age at quitting. Intensity of active smoking was obtained by responses to "How often have you smoked cigarettes in the last month?" and combined into four categories for analyses (never, occasionally, daily ≤10 cigarettes, daily >10 cigarettes), to conform WHO Guidelines and smoking definitions widely used in the medical literature.

Exposure to environmental tobacco smoke (ETS) was evaluated by "Does anybody, at present, smoke inside your child's home?" (yes/no) at baseline and by "Have you been regularly exposed to tobacco smoke in the last 12 months? ['Regularly' means on most days or nights]" (yes/no) at follow-up. The duration of ETS exposure at follow-up was determined as reported hours/day at home, at the workplace, in bars, restaurants, movie theatres, or similar places, and at other places. For analyses the sum of all responded hours was categorised in never, ≤1 hr/d, 1-5 hrs/d, and >5 hrs/d.

Putative confounding variables

The following variables were assessed at baseline and tested as putative confounders in the models: atopy, bronchial hyperreactivity, sex, study centre, age (at follow-up, continuously), parental history of allergies (at least one parent reporting a lifetime history of asthma, hayfever, or atopic dermatitis), parental history of asthma, socio-economic status (SES), dampness or mould in the dwelling, exposure to heavy truck traffic, body mass index (BMI), and ETS exposure. BMI and ETS exposure at follow-up were also tested as putative confounders. BMI was computed as weight (kg) divided by the square of height (m^2). Cut points for underweight and overweight were the 10^{th} and the 90^{th} percentile, respectively, according to the distribution of BMI among the German population.[21] SES was considered high if either parent had attended school for at least 12 years.

Statistical methods

Participants with missing values were excluded from analyses involving the respective variable. Three subjects reported extreme ages at onset of smoking (seven years and earlier) and were excluded from the analyses of onset and duration of active smoking. Subjects with CRP plasma levels higher than 1 mg/dl (sensitivity of laboratory analyses to detect CRP was 0.6 mg/dl) were regarded to have acute inflammation and were excluded from the analyses of α_1-AT plasma levels (n=48).

Incidence risk ratios (IRR) were estimated using a modified poisson regression approach.[22] [23] The comparison was always made between incident cases and participants who never reported the respective outcome. P-values from a Chi-Square-Test are denoted as $p_{\chi 2}$. Confounding or interaction with the main exposure variable was tested for the confounding variables mentioned above. Confounding was defined by change of ≥15% in the estimated coefficient of the main exposure variable by one or joint confounders. Interaction was presumed if the interaction term was significant with a $p_{\chi 2}<0.05$ and found consistently for the three outcomes. All multivariate models included sex, age, and study centre regardless of the confounding effect. Generally, adjustments did not alter the direction of the observed effect and only changed statistical significance of estimates in three models. Therefore, we do not report crude IRR in the interest of brevity. Information on number of cases and non-cases, however, is given in the tables. All computations were performed using SAS Software Version 8.02 (SAS Institute Inc.,Cary, NC, USA).

RESULTS

The study population had almost equal numbers in Dresden and Munich and consisted of more females than males (table 1). At baseline, the prevalence of atopy was 36.6% and the prevalence of bronchial hyperreactivity was 15.2%. About one third was classified as active smokers at follow-up. At baseline 38.9% experienced exposure to environmental tobacco smoke (ETS) at home and 40.2% at follow-up. Almost 30% reported daily exposure to ETS between one and five hours at follow-up.

Table 2 shows the incidence of wheeze and asthma in relation to active smoking during adolescence. The adjusted IRR (95%CI) for active smokers compared with non-smokers for incident wheeze was 2.30 (1.88-2.82). The adjusted IRR was higher for more severe outcomes, e.g. 2.76 (1.99-3.84) for incident wheeze without a cold, and 2.56 (1.55-4.21) for incidence of diagnosed asthma. The analyses of duration and intensity of active smoking showed dose dependent associations, before and after adjustment for covariates.

There was significant interaction between atopy and active smoking for incident wheeze (p=0.0016), but not for incident wheeze without a cold (p=0.1556) or for incident asthma (p=0.9696). Due to the observed interaction and the potential for a better understanding of the disease etiology we performed the analyses of smoking effects on

Table 2: Incidence (%) of wheeze or asthma between age 9 and 17 in relation to active smoking during adolescence

	incident wheeze		incident wheeze without a cold		incidence of diagnosed asthma	
	% (n/N) *	adjusted IRR (95%CI) †	% (n/N) *	adjusted IRR (95%CI) †	% (n/N) *	adjusted IRR (95%CI) †
active smoking during adolescence						
no	8.4 (160/1907)		3.2 (58/1805)		1.6 (27/1739)	
yes	22.6 (222/983)	2.30 (1.88-2.82)	11.4 (98/859)	2.76 (1.99-3.84)	4.7 (37/780)	2.56 (1.55-4.21)
duration of active smoking in years						
never	8.4 (160/1907)		3.2 (58/1805)		1.6 (27/1739)	
≤2 yrs	16.8 (65/388)	1.82 (1.38-2.40)	8.0 (28/351)	2.13 (1.37-3.33)	2.5 (8/323)	1.43 (0.65-3.17)
2–4 yrs	24.3 (102/419)	2.45 (1.92-3.11)	10.7 (38/355)	2.55 (1.69-3.85)	5.7 (19/331)	3.11 (1.71-5.65)
>4 yrs	31.6 (49/155)	3.10 (2.32-4.15)	22.1 (30/136)	4.95 (3.24-7.57)	7.3 (8/110)	3.97 (1.84-8.57)
intensity of active smoking						
never	8.4 (160/1907)		3.2 (58/1805)		1.6 (27/1739)	
occasionally	14.3 (24/168)	1.58 (1.06-2.36)	7.7 (12/156)	2.13 (1.17-3.87)	2.7 (4/146)	1.63 (0.58-4.58)
daily≤10 cig	19.5 (85/435)	2.13 (1.66-2.74)	9.3 (36/386)	2.42 (1.61-3.64)	4.3 (15/352)	2.46 (1.31-4.63)
daily>10 cig	29.7 (111/374)	2.95 (2.31-3.77)	16.0 (50/313)	3.66 (2.47-5.43)	6.5 (18/278)	3.34 (1.80-6.19)

abbreviations: n = cases, N = total of exposed, IRR = incidence risk ratio, CI = confidence interval

* the population comprizes subjects without missing values for the outcome, exposure, and confounding variables

† all models adjusted for sex, age, study centre, and duration of exposure to environmental tobacco smoke (ETS) at follow-up (for further detail see methods)

Table 3: Incidence (%) of wheeze or asthma between age 9 and 17 in relation to active smoking during adolescence by atopy at baseline

	incident wheeze		incident wheeze without a cold		incidence of diagnosed asthma	
	% (n/N) *	adjusted IRR (95%CI) †	% (n/N) *	adjusted IRR (95%CI) †	% (n/N) *	adjusted IRR (95%CI) †
atopic subjects						
active smoking during adolescence						
no	13.8 (71/515)		6.3 (30/474)		3.4 (15/442)	
yes	25.8 (65/252)	1.63 (1.20-2.22)	18.3 (42/229)	2.07 (1.35-3.18)	9.7 (19/196)	2.16 (1.15-4.06)
duration of active smoking in years						
never	13.8 (71/515)		6.3 (30/474)		3.4 (15/442)	
≤2 yrs	18.1 (19/105)	1.18 (0.74-1.87)	12.2 (12/98)	1.44 (0.79-2.64)	3.5 (3/85)	0.84 (0.26-2.69)
2–4 yrs	26.7 (27/101)	1.59 (1.08-2.34)	17.8 (16/90)	1.86 (1.07-3.23)	13.4 (11/82)	2.90 (1.35-6.21)
>4 yrs	40.5 (15/37)	2.51 (1.58-3.99)	35.3 (12/34)	3.87 (2.16-6.91)	16.7 (4/24)	3.71 (1.39-9.94)
intensity of active smoking						
never	13.8 (71/515)		6.3 (30/474)		3.4 (15/442)	
occasionally	14.9 (7/47)	1.01 (0.50-2.05)	7.0 (3/43)	0.98 (0.33-2.89)	2.4 (1/41)	0.64 (0.09-4.42)
daily≤10 cig	23.5 (27/115)	1.55 (1.04-2.32)	18.5 (20/108)	2.18 (1.28-3.71)	10.1 (9/89)	2.42 (1.11-5.27)
daily>10 cig	34.8 (31/89)	2.19 (1.48-3.23)	24.7 (19/77)	2.63 (1.54-4.49)	13.8 (9/65)	3.05 (1.32-7.02)
non-atopic subjects						
active smoking during adolescence						
no	5.5 (45/825)		1.9 (15/795)		0.8 (6/778)	
yes	20.8 (104/500)	3.25 (2.22-4.76)	9.2 (40/436)	3.92 (2.01-7.65)	2.3 (9/399)	2.16 (0.79-5.93)
duration of active smoking in years						
never	5.5 (45/825)		1.9 (15/795)		0.8 (6/778)	
≤2 yrs	14.2 (26/183)	2.42 (1.48-3.98)	6.5 (11/168)	3.13 (1.34-7.33)	1.9 (3/158)	1.91 (0.50-7.32)
2–4 yrs	23.3 (50/215)	3.67 (2.39-5.63)	9.3 (17/182)	4.06 (1.90-8.68)	2.4 (4/167)	2.27 (0.64-8.06)
>4 yrs	28.4 (27/95)	4.38 (2.70-7.11)	15.0 (12/80)	5.98 (2.68-13.35)	2.9 (2/68)	2.84 (0.59-13.58)
intensity of active smoking						
never	5.5 (45/825)		1.9 (15/795)		0.8 (6/778)	
occasionally	14.6 (12/82)	2.46 (1.34-4.51)	6.7 (5/75)	3.11 (1.12-8.63)	2.9 (2/70)	2.92 (0.61-14.03)
daily≤10 cig	15.8 (35/222)	2.72 (1.73-4.30)	5.6 (11/198)	2.68 (1.14-6.27)	1.6 (3/187)	1.63 (0.42-6.30)
daily>10 cig	28.9 (56/194)	4.41 (2.86-6.79)	14.8 (24/162)	6.24 (2.94-13.22)	2.8 (4/141)	2.42 (0.70-8.36)

Table 3: Footnotes

abbreviations: n = cases, N = total of exposed, IRR = incidence risk ratio, CI = confidence interval

* the population comprizes subjects without missing values for the outcome, exposure, and confounding variables

† all models adjusted for sex, age, study centre, and duration of exposure to environmental tobacco smoke (ETS) at follow-up (for further detail see methods)

wheeze and asthma stratified by atopy (table 3). The pattern of associations resembled those of the unstratified analysis and most associations were statistically significant. The estimated IRR tended to be lower for atopic subjects. Table 4 shows the observed associations of ETS exposure with the incidence of wheeze and asthma for non-smokers. After adjustment none of the associations reached statistical significance.

The relation between decreasing α_1-antitrypsin (α_1-AT) plasma levels at baseline and the incidence of wheeze and asthma are depicted in Figure 2. Alpha-1-antitrypsin plasma levels ranged from 52.2 mg/dl to 254.0 mg/dl and had a median of 152.0 mg/dl. The IRR were calculated for a 25 mg/dl decrease in α_1-AT plasma levels which reflects the interquartile range (IQR, i.e. the difference between the 25th and 75th percentile) within the total study population.

In the total cohort decreasing α_1-AT plasma levels were not associated with the incidence of wheeze, wheeze without a cold, and diagnosed asthma. Smoking has been shown to be an important risk factor for respiratory disease in subjects with α_1-AT deficiency. Decreasing α_1-AT plasma levels carried no statistically significant risk for the incidence of wheeze, wheeze without a cold, and diagnosed asthma among active smokers. The same was true for non-smoking subjects exposed to ETS at follow-up. An interaction between active smoking and α_1-AT plasma levels, which was at least of borderline statistical significance, was observed only in relation to the incidence of diagnosed asthma ($p_{\chi 2}$=0.066).

However, given the significant interaction between active smoking and atopy in relation to the incidence of wheeze, we also explored the effects of α_1-AT stratified by atopy. The multiplicative interaction between the three variables α_1-AT plasma levels, smoking and atopic sensitisation had a $p_{\chi 2}$=0.001 for the incidence of wheeze, a $p_{\chi 2}$=0.057 for the incidence of wheeze without a cold, and a $p_{\chi 2}$=0.730 for the incidence of diagnosed asthma. The estimated relative risks for wheeze and asthma with decreasing α_1-AT plasma levels are therefore presented stratified for atopy and smoking status in figure 2. There was a statistically significant association between decreasing α_1-AT plasma levels and the incidence of wheeze (1.33;1.02-1.73) and wheeze without a cold (1.64;1.22-2.20) among atopic smokers. The incidence of diagnosed asthma was found to be related to decreasing α_1-AT plasma levels in non-atopic smokers, but the statistical significance was only borderline (1.72;0.96-3.06).

DISCUSSION

Our data provide strong evidence that active smoking increases the incidence of wheeze and asthma during adolescence. As expected, the increase depended on the duration and intensity of smoking. The effect of smoking was stronger among non-atopic compared with atopic subjects. There was no statistically significant association between the exposure to environmental tobacco smoke (ETS) and the respiratory outcomes. Our findings suggest that incidence of wheeze increases with decreasing alpha-1-antitrypsin (α_1-AT) plasma levels among subjects who were atopic at baseline and started active smoking during adolescence.

Participation bias is one of the most important biases in longitudinal studies. In our study, 2614 participants of the baseline survey had to be classified as non-respondents at follow-up. However, half of them had initially denied further contact and 197 could not be located for follow-up (figure 1). Thus, the participation rate of those with contact agreement who could be located was 77.4%, which is reasonable considering the follow-up time of seven years.

A limitation of our study, like in most epidemiologic studies following childhood through adolescence, is that information regarding the child's health in early life was reported

Table 4: Incidence of wheeze or asthma between age 9 and 17 in relation to exposure to environmental tobacco smoke (ETS) during adolescence for non-smokers

	incident wheeze		incident wheeze without a cold		incidence of diagnosed asthma	
	% (n/N) [*]	adjusted IRR (95%CI) [†]	% (n/N) [*]	adjusted IRR (95%CI) [†]	% (n/N) [*]	adjusted IRR (95%CI) [†]
ETS exposure at home at baseline [‡]						
no	7.8 (96/1234)		2.8 (33/1171)		1.2 (14/1136)	
yes	9.5 (57/597)	1.22 (0.87-1.72)	3.9 (22/562)	1.39 (0.79-2.46)	2.2 (12/534)	2.00 (0.84-4.76)
ETS exposure at follow-up						
no	8.0 (71/888)		3.3 (20/599)		1.4 (12/841)	
yes	8.8 (84/952)	1.04 (0.74-1.46) [ll]	3.7 (25/677)	1.19 (0.68-2.10) [**]	1.7 (15/888)	1.25 (0.57-2.73) [††]
duration of ETS exposure at follow-up in hours per day						
never	8.0 (70/877)		3.0 (25/832)		1.5 (12/809)	
≤1 hr/d	7.0 (28/399)	0.88 (0.58-1.34)	2.6 (10/381)	0.88 (0.43-1.82)	1.4 (5/369)	0.93 (0.33-2.64)
1–5 hrs/d	10.5 (48/459)	1.31 (0.92-1.86)	4.0 (17/428)	1.35 (0.74-2.48)	2.2 (9/406)	1.53 (0.63-3.70)
>5 hrs/d	8.1 (14/172)	1.01 (0.58-1.77)	3.7 (6/164)	1.24 (0.52-2.97)	0.6 (1/155)	0.45 (0.05-3.75)

abbreviations: n = cases, N = total of exposed, IRR = incidence risk ratio, CI = confidence interval

[*] the population comprizes subjects without missing values for the outcome, exposure, and confounding variables

[†] all models adjusted for sex, age, and study centre (for further detail see methods)

[‡] additionally adjusted for duration of ETS exposure at follow up

[ll] additionally adjusted for ETS exposure at home at baseline

[**] additionally adjusted for atopy

[††] additionally adjusted for intensity of active smoking and duration of active smoking

by the parents whereas information regarding adolescence is given by the participants themselves. Subjects with a parental history of allergies were more likely to participate at follow-up. However, there was no significant association between participation at follow-up and parental history of asthma, which is probably more relevant as a determinant of asthma incidence (figure 1). Wheeze and diagnosed asthma at ages 9-11 were not associated with the uptake of smoking during adolescence (IRR;95%CI: 1.04;0.90-1.20 and 1.08;0.90-1.30, respectively). Active smoking was assessed at follow-up and strictly speaking it cannot be assumed that it preceded the onset of wheeze or asthma in all cases. Nevertheless, there was a clear dose-response relationship between duration or intensity of active smoking and the incidence of wheeze or asthma. Therefore we believe that it is unlikely that the observed associations are due to reverse causation.

The analyses gave no evidence for differences in the observed associations between females and males and all estimates are adjusted for gender. We could not identify a significant association between exposure to ETS and the incidence of wheeze or asthma among adolescents. This is in line with some earlier publications. Nevertheless, data on this association among adolescents are still limited and the results so far are conflicting.[11]

The role of active smoking on the incidence of respiratory disease has been investigated previously. Data on duration and intensity of active smoking were only reported by Strachan *et al.*.[4] In a study among young adults (age 17-33) they observed a positive dose-response-relation of both with the incidence of asthma or wheezing illness. Larsson examined the incidence of asthma between ages 16-19, Withers *et al.* the incidence of wheeze between ages 7-15 [1] [6]. Both reported a positive association between active smoking and the incidence of wheeze or asthma. The effects reported by Larsson were only adjusted for sex. Withers *et al.* did not report associations with the incidence of diagnosed asthma. Our study on almost 3,000 adolescents goes beyond previous reports in that it describes the effect of active smoking on the incidence of wheeze and asthma, taking objective markers of atopic disease and numerous possible confounders into account.

The comparative epidemiology of atopic and non-atopic wheeze with regard to different patterns of risk factors has gained attention.[24] [25] To contribute to this pivotal distinction, we have displayed the associations of smoking as well as α_1-AT plasma levels with the incidence of wheeze and asthma stratified for atopy.

The effect of active smoking on the incidence of wheeze was stronger among non-atopic subjects compared with atopic subjects. This interaction between smoking and atopy has been reported previously by others for the association of smoking with the prevalence of wheeze,[24] with bronchial responsiveness,[26] and with incidence of asthma or wheezing illness.[4] The proposed explanations include self-selection of smokers or biological antagonism between atopy and smoking. In our study, non-atopic subjects took up smoking more often than atopics (IRR;95%CI: 1.19;1.06-1.32). This small effect, however, is unlikely to fully explain the differences in the stratified analyses. The interaction between atopy and active smoking could not be seen for incidence of diagnosed asthma, but it has to be taken into account that the number of diagnosed asthma cases was small. The number of participants with incidence of diagnosed asthma might be underestimated owing to mild disease that had not been recognised. Furthermore, current smoking and ETS exposure at home were found to be associated with undiagnosed frequent wheezing among adolescents in the USA.[27] Likewise, in Europe underdiagnosis of asthma with its implications on treatment of the disease is still common.[28] [29]

We present new data on the association of α_1-AT plasma levels with the incidence of wheeze and asthma stratified by atopy and active smoking. Unlike other studies we did not investigate α_1-AT deficiency using genetic alterations, but rather analysed α_1-AT plasma levels independent of the genetic background and within the normal range. To provide a quantification of the observed effects the IRR are given for a 25 mg/dl decrease in α_1-AT

plasma levels which reflects the interquartile range within the study population. The National Heart, Lung and Blood Institute registry of α_1-AT deficiency has used a threshold level that was set by convention to 11 µmol/L (approx. 60 mg/dl) to identify subjects with α_1-AT deficiency.[30] In our study, only one subject had an α_1-AT plasma level below this threshold and more than 97% had plasma levels within the normal range of 90-200 mg/dl.

An effect of α_1-AT deficiency on respiratory disease has been investigated closely recently and α_1-AT deficiency with its genetic alterations was subject to a review series in 2004.[31] It seems that Z and S alleles, leading to low α_1-AT plasma levels, are associated with an increased risk of developing lung and liver disease whereas null variants, with no detectable α_1-AT plasma levels, may be associated with an increased risk of developing emphysema.[32] However, some data of a national birth cohort study in Great Britain did show an association between α_1-AT deficiency and infant lower respiratory tract infections but not impaired adult respiratory health.[33]

In children with genetically determined α_1-AT deficiency active smoking seems to be a risk factor for lung function decline in young adults.[15] [34] Cross-sectional analyses of our cohort at baseline suggest that children with low levels of α_1-AT ($\leq$116 mg/dl) are at increased risk of developing pronounced decrements in pulmonary function, particularly if they are exposed to ETS.[14] Further analysis showed no association between low levels of α_1-AT and the prevalence of asthma but suggested an increase in the vulnerability for lung function decrements among children with low levels of α_1-AT and asthma.[35] Data on the genetic background of our study population was assessed at baseline but could not be accessed for the cohort due to ethical reasons.

Since smoking has been shown to be an important risk factor for respiratory disease in subjects with α_1-AT deficiency, we explored a potential interaction between α_1-AT plasma levels and smoking for the respiratory outcomes in our study population. The analyses of the incidence of diagnosed asthma but not wheeze suggested an interaction between decreasing α_1-AT plasma levels and active smoking. It could be speculated that higher levels of α_1-AT protect active smokers from respiratory disease via the effects of α_1-AT against the degeneration of elastic tissue during inflammation. In our study, decreasing α_1-AT plasma levels were associated with the incidence of wheeze and wheeze without a cold among atopic smokers and, although only of borderline statistical significance, with the incidence of diagnosed asthma in non-atopic smokers. We have no immediate explanation for this discrepancy between wheeze and diagnosed asthma. The relatively small number of cases of diagnosed asthma or chance may have played a role. The mechanisms by which smoking, atopy and α_1-AT may interact during chronic inflammation of the lung are not fully understood. To our knowledge this is the first study relating relatively lower α_1-AT plasma levels within the normal range in combination with smoking and atopy to the incidence of wheeze and asthma. If our results are confirmed, children with low α_1-AT plasma levels may be a target group for smoking prevention programs.

In conclusion, our data indicate that active smoking is an important risk factor for the incidence of wheeze and asthma during adolescence. The relative risk increases with the duration and intensity of active smoking and seems to be higher among non-atopic compared to atopic subjects. Relatively lower plasma levels of α_1-antitrypsin, although well above currently accepted thresholds, may increase susceptibility to respiratory disease among atopic smokers.

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Figure 2: Incidence risk ratios (IRR) relating the incidence of wheeze (A), wheeze without a cold (B) and diagnosed asthma (C) between ages 9 and 17 years to the plasma level[*] of α_1-antitrypsin (α_1-AT) at baseline stratified by atopy at baseline and active smoking during adolescence

abbreviations: % = incidence, n = cases, N = subjects in category, IRR = incidence risk ratio, CI = confidence interval

[*] IRR refer to a 25 mg/dl decrease in α_1-AT plasma levels, i.e. the interquartile range in the study population

[†] the population comprizes subjects without missing values for the outcome, exposure, and confounding variables

[‡] all models adjusted for sex, age, and study centre (for further detail see methods)

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Figure 1:

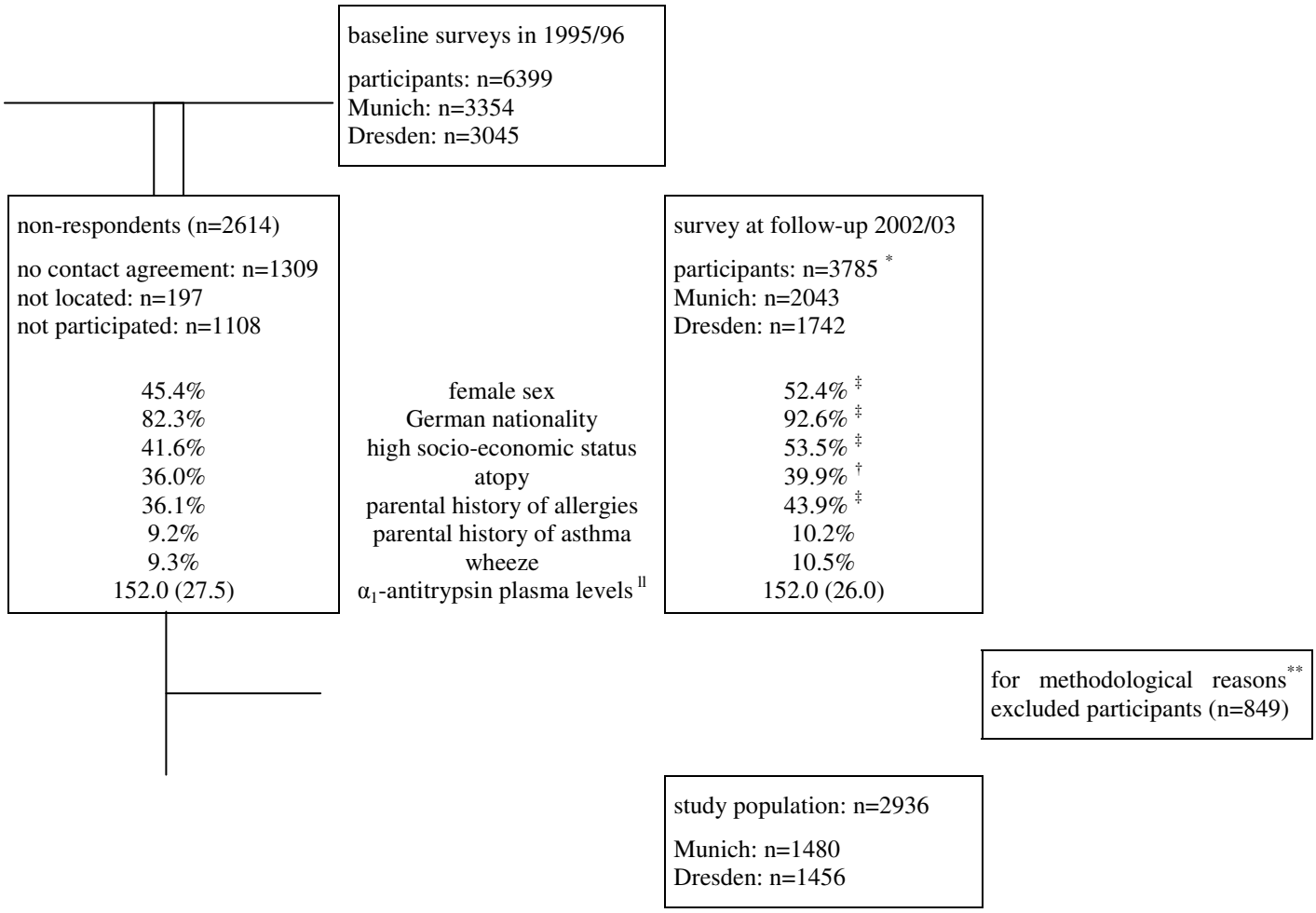


Figure 1: Characteristics of non-respondents (n=2614) and follow-up participants (n=3785)

abbreviations: n = cases, % = prevalence

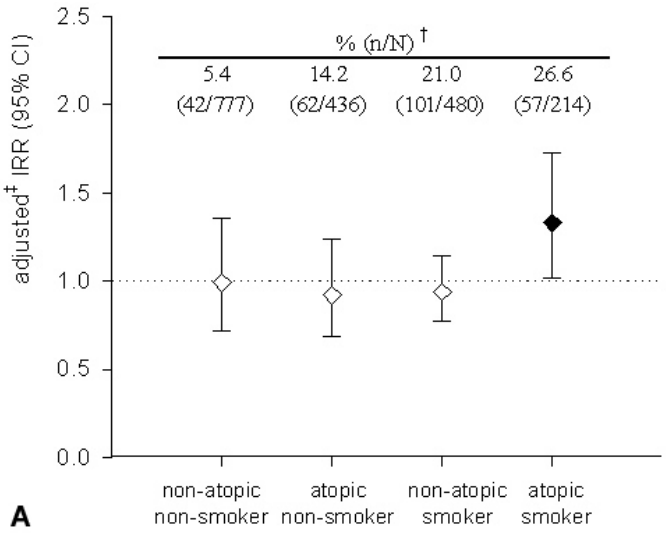
* participation rate: 77.4% of those located

† $p<0.05$

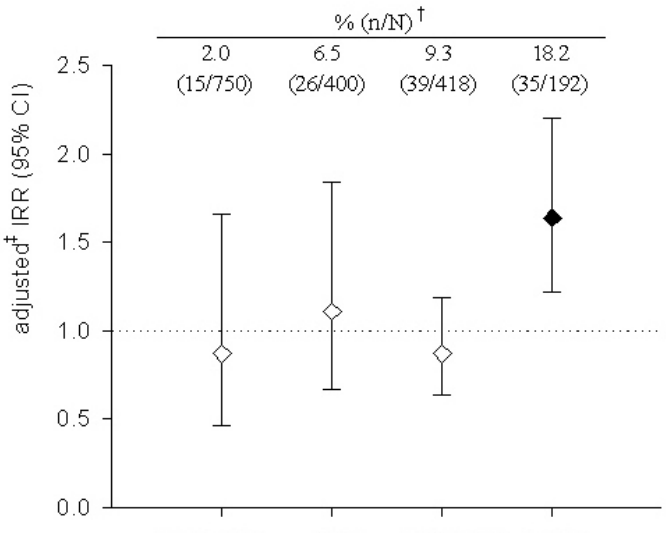
‡ $p<0.001$

ll in mg/dl, median (interquartile range) given

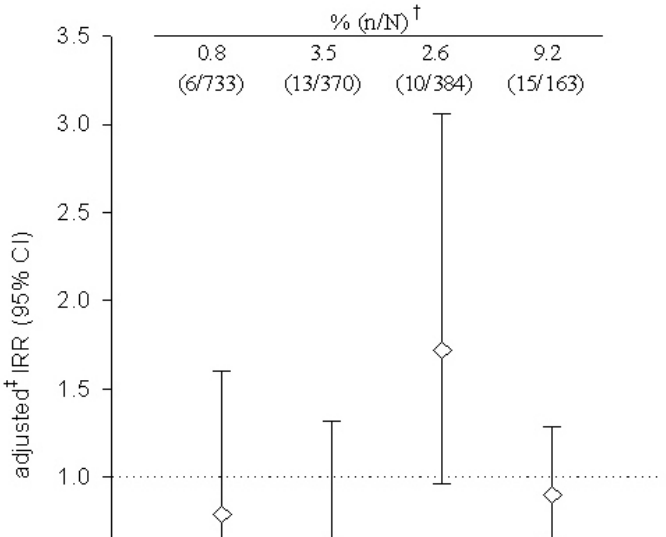
** details are given in methods section


% (n/N) †
5.4 (42/777)
14.2 (62/436)
21.0 (101/480)
26.6 (57/214)
adjusted‡ IRR (95% CI)
2.5
2.0
1.5
1.0
0.5
0.0
non-atopic non-smoker
atopic non-smoker
non-atopic smoker
atopic smoker

A


% (n/N) †
2.0 (15/750)
6.5 (26/400)
9.3 (39/418)
18.2 (35/192)
adjusted‡ IRR (95% CI)
2.5
2.0
1.5
1.0
0.5
0.0
non-atopic non-smoker
atopic non-smoker
non-atopic smoker
atopic smoker

B


% (n/N) †
0.8 (6/733)
3.5 (13/370)
2.6 (10/384)
9.2 (15/163)
adjusted‡ IRR (95% CI)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
non-atopic non-smoker
atopic non-smoker
non-atopic smoker
atopic smoker

C