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Higher asthma occurrence in an urban than a suburban area: role of house dust mite skin allergy

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ABSTRACT: Understanding of geographical differences in asthma prevalence may be helpful in explaining recent increases in the occurrence of asthma. We wondered whether differences in allergic sensitization or other factors could explain differences in reported occurrence of asthma between an urban centre and a neighbouring suburban area.

From the European Community Respiratory Health Survey (ECRHS) questionnaire, responses on asthma symptoms and risk factors and results of 11 skin allergy tests were available from 656 young adults living in urban or south suburban Antwerp, Belgium. Answers to five asthma questions were selected as dependent variables, and eight personal or environmental risk factors, as well as house dust mite (HDM) allergy, as independent variables. The effect of each independent variable on the association of asthma variables with area was assessed.

Prior asthma diagnosis, present asthma symptoms, the selected risk factors and HDM allergy were all more frequently recorded in urban Antwerp. Difference in HDM allergy accounted for most of the difference in prior (mostly childhood) asthma diagnosis, since correction for it decreased the odds ratio from 2.10 to 1.65. On the contrary, the regional differences in recent asthma symptoms were not explained by HDM allergy differences nor by any other factor under study.

This urban-suburban comparison indicated that house dust mite allergy is a major determinant of prior (childhood) asthma, whereas factors contributing to higher urban prevalence of present asthma symptoms could not be identified. Furthermore, our results indicate that it may be inappropriate to combine data from neighbouring areas, when their similarity has not been verified.
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The results presented are from a national analysis of data collected from the ECRHS; any final international comparison may use a different form of analysis.

During recent decades, there has been a growing public health interest in asthma, induced by increasing prevalence rates in adults [1] and children [2, 3]. Large geographical differences in asthma prevalence have been reported [4], both between and within countries, for instance between urban and rural areas [5]. Explanations for the reported geographical and time-related differences in asthma occurrence are still lacking. It is not unreasonable to assume that both types of difference result from the same causes.

Evidence is accumulating for a major role of allergy, especially to house dust mite (HDM), in the childhood onset of asthma [6]. This was recently supported by VON MUTIUS *et al.* [7], who found that sensitization to aeroallergens accounted almost entirely for the differences in prevalence of asthma and hay fever between children of the former East and West Germany.

The European Community Respiratory Health Survey (ECRHS) was designed to provide a standardized comparison of asthma symptom prevalence and risk factors among young adults within a large number of countries inside and outside Europe [1]. In Belgium, the urban and south suburban areas of Antwerp were selected for participation in this survey. The main objective of the present analysis was to assess any differences in reported asthma occurrence between these areas, which are in close proximity but have different features, and to evaluate whether, by analogy to the German findings, a difference in sensitization to aeroallergens could account for any differences in asthma occurrence.

Materials and methods

Areas

This Belgian contribution to the ECRHS was carried out in the centre of Antwerp (urban), and in 13 municipalities at the southern border of the city (suburban). Antwerp, a city of 0.5 million inhabitants, located at some 100 km from the North Sea, has one of the world's largest harbours at its northern border. The historical city centre is several centuries old and has small streets and old houses. The 13 municipalities located at the southern border of the city present a mixture of suburban, residential and rural features. Each area has a total population of about 150,000 inhabitants. The two areas had a comparable degree of air pollution in 1992: in the

urban and suburban areas, the median (range) concentration of sulphur dioxide (SO_2) was 25 (10–750) and 15 (10–550) $\mu g \cdot m^{-3}$, and of nitrogen dioxide (NO_2) was 45 (0–230) and 40 (0–200) $\mu g \cdot m^{-3}$, respectively.

Questionnaires

According to the ECRHS protocol [1], random samples of approximately 4,000 subjects of Belgian nationality, aged 20–44 yrs, were selected from the municipality registers of each area. The stage I postal screening questionnaire [4] was mailed during the spring to the suburban subjects in 1991, and to the urban subjects in 1992. This questionnaire included only a few questions about symptoms of asthma. In both areas, the response rate was approximately 75%, the total response being 6,038 out of 8,051 subjects.

One out of five responders was subsequently randomly selected for stage II of the ECRHS, which was carried out mainly during the summer and autumn of 1991 in suburban Antwerp, and during the same seasons in 1992 in urban Antwerp. The subjects were interviewed by means of the translated [8] extended questionnaire of the survey [1] for asthma symptoms and risk factors in family and environment. The dependent variables selected in this report were "prior asthma diagnosis" resulting from the question, "Have you ever had asthma?", and the presence during the last 12 months (=recent) of the following asthma symptoms: wheezing, wheezing in the absence of a cold, dyspnoea at rest, and being woken by an attack of dyspnoea. Response rates to the extended questionnaire in the suburban and urban areas were 70% (558 out of 800) and 65% (563 out of 866), respectively.

To assess the presence of selection bias in the different stages of the study, prevalence of wheezing and being woken by an attack of dyspnoea were calculated for both areas, and the associations between symptoms and area in these different stages were compared.

Clinical measurements and assessment of home environment

The second stage also included skin-prick allergy testing for 11 common allergens using phasets (Farmacia Diagnostics AB, Uppsala, Sweden) and methacholine inhalation challenge testing. These tests were performed in a standardized manner, according to the ECRHS protocols.

Sixty per cent (337 out of 558) of the responders in the suburban area and 57% (319 out of 563) in the urban area agreed to have skin-prick allergy tests. The study population of the present analysis was the group of 656 subjects participating both in the extended questionnaire interview and the skin-prick allergy testing. Among them, there were more males in the suburban than in the urban area (52 and 43%, respectively) (χ^2= 5.64; p= 0.02). Suburban subjects were also slightly older (mean age suburban=34 yrs and urban=32 yrs; t-test (p=0.04)).

For the analyses of the results of skin-prick testing, subjects not reacting to positive control (histamine) were excluded. The mean wheal diameter to the negative control was subtracted from that elicited by the allergen. Sensitization was arbitrarily defined by a corrected wheal size to the allergen of at least 3 mm. Prevalence rates of the five most prevalent allergens will be shown for both areas.

For definition of airway hyperresponsiveness with methacholine challenge testing, the cut-off point for the provocative dose of agonist causing a 20% fall in forced expiratory volume in one second (PD_{20}) was arbitrarily set at 2.0 mg methacholine chloride, which is equivalent to 10 µmol or slightly above the recommended cut-off of 7.8 µmol [9].

In a random sample of 127 subjects, bed mattresses were vacuumed (1 m^2 for 2 min) and sampled for determination of *Dermatophagoides pteronyssinus* allergen (*Der p* I) concentration, using a hand-held portable vacuum cleaner equipped with an ALK (ALK Benelux, Houten, The Netherlands) dust sampling filter. Dust samples were processed and analysed for *Der p* I using an enzyme-linked immunosorbent assay (ELISA) [10]. Since the threshold of *Der p* I for sensitization to HDM is assumed to be 2 $\mu g \cdot g^{-1}$ dust [6, 11], this was taken as cut-off point for an increased level of HDM exposure. Additionally, a questionnaire concerning indoor dust avoidance measures was also completed by these subjects.

Statistical analysis

The associations between area of residence and the dependent variables were expressed as odds ratios (ORs), with a test-based 95% confidence interval (95% CI). ORs for the associations between respiratory symptoms and the selected threshold for airway hyperresponsiveness were also calculated.

Questionnaire variables and skin-prick results, considered as independent variables, were screened for possible associations with the dependent variables and with area of residence. Only variables for which these associations were considered relevant were taken into account as potential confounders in the analysis.

In addition, logistic regression analysis was performed to assess the effects of each potential confounder separately on the association of the dependent variables with area. Finally, all variables were brought into a full model. The statistical package Statistica (StatSoft) was used for the crude analysis; logistic regression analysis was performed on EGRET (SERC, CYTEL, Seattle, USA).

A p-value below 0.05 was considered to be statistically significant.

Results

Study population characteristics: associations with residence

Of the 656 subjects, 35 subjects had a prior diagnosis of asthma (table 1). In all but one, this had been confirmed by a physician and 31 (89%) had suffered their first attack before the age of 16 yrs. One hundred and eighty one (28%) subjects reported recent wheezing, whereas the more specific asthma symptoms, wheezing without a cold and shortness of breath at rest or at night, were less prevalent (15, 7 and 6%, respectively).

The risk for prior asthma diagnosis was found to be twice as high in subjects living in the city of Antwerp

Table 1. – Crude associations of dependent variables with area of residence: suburban area (n=337) and urban area (n=319)

Dependent variable	Suburban area positives		Urban area positives		OR# (95% CI)
	n	%	n	%	
Prior asthma diagnosis	12	4	23	7	2.10 (1.03–4.30)
Wheezing+	71	21	110	34	1.97 (1.39–2.80)
Wheezing without a cold+	31	9	70	22	2.77 (1.76–4.37)
Shortness of breath at rest+	14	4	35	11	2.84 (1.50–5.39)
Been woken by shortness of breath+	12	4	30	9	2.81 (1.41–5.59)

#: urban/suburban; +: in the last 12 months. OR: odds ratio; 95% CI: 95% confidence interval.

Table 3. – Associations of the potential confounders with area of residence: suburban area (n=337) and urban area (n=319)

	Suburban area		Urban area		OR# (95% CI)
	n	%	n	%	
Male	177	53	138	43	0.69 (0.51–0.94)
HDM allergy	56	17	83	26	1.76 (1.21–2.58)
Asthma in family (n=613)	37	12	50	17	1.48 (0.94–2.34)
RTI <5 yrs	29	9	43	13	1.66 (1.00–2.72)
Mother smoked	75	22	99	31	1.57 (1.11–2.23)
Smoked >1 year	183	54	197	62	1.36 (1.00–1.86)
Current smoking	99	29	134	42	1.74 (1.26–2.41)
Open fire	138	41	153	48	1.33 (0.98–1.81)
Moulds last 12 m	71	21	80	25	1.25 (0.87–1.79)

#: urban/suburban. OR: odds ratio; 95% CI: 95% confidence interval. For further abbreviations see legend to table 2.

(OR 2.10; 95% CI 1.03–4.30). Recent asthma symptoms also had ORs between 2.0 and 2.8 for being more prevalent in the urban area. Presence of selection bias during the study in relation to the area difference was assessed by calculating the associations between area and some symptoms throughout the different phases of the study. There was no indication of strong influence on the measures of effect studied. For wheezing, the OR for urban *versus* suburban area in the first stage was 1.75, in the second stage 1.76, and for responders to the allergy tests it was 1.97. For waking with an attack of dyspnoea, these ORs were 2.06, 2.17 and 2.81, respectively.

Clinical measurements and assessment of home environment

In urban Antwerp, more subjects had skin reactions to the allergens tested, and more males than females were found to react (fig. 1). These patterns were most

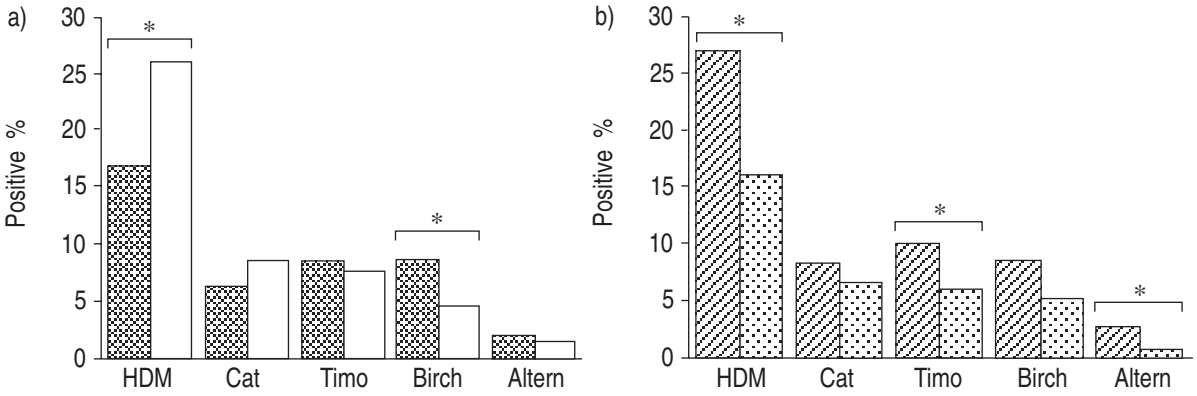

Fig. 1. – Results of skin-prick allergy testing to five prevalent allergens: a) in urban ( ) and suburban ( ) Antwerp; and b) in males ( ) and females ( ). It can be seen that HDM allergy is more prevalent in urban Antwerp and that allergies are more prevalent in males. *: p<0.05. HDM: house dust mite; Timo: Timothy; Altern: Alternaria.

Table 2. – Adjusted odds ratios of the potential confounders with the dependent variables‡

	Prior asthma diagnosis	Wheezing+	Wheezing without cold+	Shortness of breath at rest+	Woken by shortness of breath+
Male/female	0.72	0.86	0.96	0.76	0.38*
HDM allergy	11.0*	2.33*	2.15*	1.75	2.29*
Asthma in family	4.68*	1.49	1.87*	1.85	3.53*
RTI <5 yrs	6.55*	1.50	1.80	2.39*	2.71*
Mother smoked	0.72	0.96	0.78	1.02	1.16
Smoked >1 yr	0.42*	-	-	-	-
Current smoking	-	3.92*	3.05*	1.44	0.88
Open fire	1.50	1.05	1.06	1.08	1.15
Moulds last 12 m	1.05	1.10	1.48	1.34	1.40

‡: adjusted for all the other variables, including area and age; +: in the last 12 months. HDM: house dust mite; Asthma in family: asthma of the parents, brothers or sisters; RTI <5 yrs: serious respiratory tract infection before the age of 5 yrs; Mother smoked: mother smoked during pregnancy or childhood; Smoked >1 year: ever having smoked more than 1 yr; Open fire: open fire (coal, coke, wood or gas) for heating; moulds last 12 m: Moulds on any surface inside the home in the last 12 months. *: p<0.05.

Table 4. – Odds ratios of area of residence for the dependent variables adjusted for each potential confounder, separately and combined

	Prior asthma diagnosis	Wheezing+	Wheezing without cold+	Shortness of breath at rest+	Woken by shortness of breath+
Crude	2.10 (1.03–4.30)	1.97 (1.39–2.80)	2.77 (1.76–4.37)	2.84 (1.50–5.39)	2.81 (1.41–5.59)
Male/female	2.12*	2.00*	2.84*	2.81*	2.64*
HDM allergy	1.65	1.83*	2.57*	2.67*	2.63*
Asthma in family	1.95	1.95*	2.71*	2.83*	2.65*
RTI <5 yrs	1.93	1.92*	2.68*	2.69*	2.65*
Mother smoked	2.16*	1.95*	2.78*	2.79*	2.78*
Smoked >1 year	2.23*	1.89*	2.66*	2.79*	2.97*
Current smoking	2.11*	1.73*	2.47*	2.65*	2.82*
Open fire	2.05*	1.96*	2.76*	2.82*	2.78*
Moulds last 12 m	2.08*	1.92*	2.67*	2.71*	2.77*
All variables‡	1.41 (0.62–3.22)	1.49 (1.01–2.18)	2.15 (1.33–3.49)	2.22 (1.14–4.34)	2.09 (1.01–4.32)

The values presented are odd ratios, and 95% confidence intervals in parentheses. +: in the last 12 months; ‡: adjusted for the other variables, including age. For abbreviations see legend to table 2. *: $p<0.05$.

striking for HDM allergy, which was also the most prevalent allergy. Only for birch and Alternaria were more subjects sensitive in suburban Antwerp.

Five hundred and sixty of the 656 subjects also underwent methacholine inhalation challenge tests. PD_{20} was ≤2.0 mg methacholine in 27% of the subjects in urban and 15% in suburban Antwerp ($\chi^2=12.5$; $p=0.0004$). Airway hyperresponsiveness (AHR) was also strongly associated with respiratory symptoms. ORs for wheeze, wheeze without a cold, dyspnoea during rest, waking with an attack of dyspnoea and ever having had asthma when AHR was present were 3.9, 3.4, 3.8, 2.3 and 15.5, respectively (all significant).

Der p I concentrations exceeded 2.0 $\mu g \cdot g^{-1}$ in 27% of bed mattresses in urban *versus* 42% in suburban Antwerp ($\chi^2=2.82$; $p=0.09$). No differences were found between the two areas in application of avoidance measures. In urban and suburban Antwerp, absence of bedroom coverings was 49 and 58%, respectively; absence of blankets was 69 and 64%; washing of bedding at a temperature above 60°C was 35 and 30%; vacuuming the bedroom once a week or more was 69 and 78%; and mopping the bedroom once a week or more was 19 and 35% (all nonsignificant).

Assessment of confounding

The associations, expressed as adjusted odds ratios, of dependent variables with independent variables are presented in table 2. As many females as males had prior asthma diagnosis, but after adjusting for the other risk factors females had a higher risk for prior asthma diagnosis, although not significantly, and also for recent symptoms than males. HDM allergy was strongly associated with prior asthma diagnosis, but the associations with recent symptoms were again less strong. The associations of "asthma in the family", "having suffered a respiratory infection before the age of 5 yrs" and "having an open fire for heating" with prior asthma diagnosis were also much stronger than the associations with recent asthma symptoms. "Current smoking" was positively associated with recent wheezing and wheezing without a cold, but "ever having smoked >1 year" was negatively associated with prior asthma diagnosis. The associations of the dependent variables with age were very weak.

Crude associations of potential confounders with area of residence were assessed, in order to identify the presence of confounding (table 3). Almost all potential confounders were positively associated with area.

Associations of dependent variables with area, adjusted for potential confounders

The associations of the dependent variables with area of residence adjusted for only one potential confounder are presented in table 4. Correcting only for HDM allergy weakened the association between prior asthma diagnosis and area (ORs from 2.10 to 1.65; 95% CI 0.79–3.48), whilst correcting for only one of the other variables had little effect on the association. The ORs for recent symptoms of asthma hardly changed after correcting for one of the potential confounders, nor did the associations change notably when the model was extended with the other confounders.

Discussion

In this study, a prior diagnosis of asthma and recent asthma symptoms were recorded more frequently in urban Antwerp than south suburban Antwerp. Interestingly, it was found that the difference in HDM allergy accounted for most of the difference in prevalence of prior asthma diagnosis between the urban and suburban areas, whereas the difference in reporting of recent asthma symptoms could only be poorly explained by this allergy, or by any other risk factor considered. This finding is in accordance with that of Von Mutius *et al.* [7], who reported that more frequent sensitization to aeroallergens in children in Munich explained most of the difference in asthma prevalence compared to the former East German city of Leipzig. This similarity is not surprising, since prior diagnosis of asthma in the young

adults in the present study also generally implied childhood asthma, and it suggests that allergy, in particular to HDM, is a major determinant of regional differences in childhood asthma.

Higher occurrence of asthma in urban than in rural areas has been reported by others. As early as 1979, VAN NIEKERK *et al.* [5] found more asthma in subjects who had migrated from a rural to an urban area than in those remaining in the former area. LANG and POLANSKY [12] concluded that features of the urban environment increased both the severity and the prevalence of asthma. Children [13] and adolescents [14] living in an urban area were also found to have asthma more frequently. TURKELTAUB and GERGEN [15] and DEVEREUX *et al.* [16] did not find more asthma in adults in urban areas.

In the present study, the area compared with urban Antwerp was not a rural but a suburban area with mixed residential and rural features. This area is relatively close to the main city, since the mean distance from the centre of the 13 municipalities to Antwerp city centre is only 9 km. Accordingly, we did not expect *a priori* large differences between the areas, and the magnitude of the difference in asthma occurrence was therefore surprising. A real difference in symptom occurrence is obviously also supported by the difference found in prevalence of airway hyperresponsiveness.

It has not been well established which factors of urban life could be responsible for an increased risk for asthma. Given the relatively close proximity of the two areas studied, which was unique in the ECRHS, we considered that this would be an interesting group of subjects for investigating the factors associated with urban asthma. Among these, racial or genetic differences can at once be ruled out, since in both areas a homogeneous Flemish population was studied.

Any comparison of asthma occurrence is confronted with the lack of a clear and reliable epidemiological definition of asthma; we, therefore, concentrated on single (symptom) questions. Our first choice was to have a positive answer to the question, "Have you ever had asthma?", which was found to be specific for having the disease [8]; in the age group of subjects studied, this almost invariably implied having had childhood asthma. An accepted limitation is that patients may not have been given this diagnosis by their physician, but in the present group nearly all had asthma confirmed by a physician. The alternative choice for epidemiological definition was the presence of recent asthma symptoms; we mainly considered recent wheezing and dyspnoea, although such symptoms may lack specificity for asthma, at least in adults.

Among personal characteristics, age was poorly associated with the occurrence of asthma, probably because the occurrence of asthma hardly differs between the ages of 20 and 44 yrs [17]. Gender differences in childhood asthma have been repeatedly reported, *i.e.* more in boys than girls [18], but from adulthood the gender differences appear to decrease and even to reverse [17, 19]. The latter is consistent with the present findings, since females more frequently had asthma symptoms than males. We also found that, after correction for other variables, the risk for prior diagnosis of asthma was higher in females. A selection bias could have contributed to this, since in urban Antwerp a higher proportion of females with a prior diagnosis of asthma participated in the study.

Our results confirm that occurrence of asthma in siblings is associated with a higher risk [20–22], especially for prior diagnosis of asthma and waking with an attack of shortness of breath. With respect to smoking of the mother during childhood, several studies have found an increased risk of asthma [21, 23, 24], but this contrasts with our results and those of others [20, 25], who failed to find an association. This may be explained by parents with asthmatic children refraining from smoking. Our finding that a respiratory infection before the age of 5 yrs increased the risk for asthma was similar to that of others [20, 21]. This is in apparent contradiction with the hypothesis, based on recent studies, postulating that infections in early life may protect against asthma and allergies [26]. The most plausible explanation could be that these recalled infections were actually unrecognized symptoms of asthma.

We found quite strong positive associations between current smoking and asthma variables, with the exception of prior diagnosis of asthma and shortness of breath, for which a negative association was found, probably because more asthmatic subjects were not taking up the habit of smoking. Although some studies [25, 27–29] found associations between asthma occurrence and home characteristics, such as the presence of moulds and use of an open gas/wood fire for heating, in the present study these associations were only weak.

The role of socioeconomic status (SES) remains a subject of discussion, because SES affects several factors and it is still not clear which are the more important ones. In the present study, age on completing full-time education was used as a reliable parameter to reflect SES. The distribution of this parameter was comparable in both areas and the associations with respiratory symptoms were weak. Therefore, the influence of SES seemed negligible.

Atopy is a well-known risk factor for asthma, and in many Western countries, HDM is the main allergen [6, 30, 31]. In the present study, HDM was found to be the most prevalent allergen and the most strongly associated with the occurrence of asthma, whereas other allergies were only slightly associated with the disease. High prevalence of HDM allergy in an urban area, as reported in this study, was also found in children [32], but OMENAAS *et al.* [33] recently reported slightly (but not significantly) higher prevalence rates for immunoglobulin E (IgE) antibodies to HDM in adult subjects living in suburban and rural than in urban areas.

We found HDM allergy to be much less strongly associated with recent asthma symptoms. Increased current use of asthma medicines could have weakened these associations by reducing symptoms; however, this effect seems negligible, since only 17 (3%) subjects were taking asthma medication. Increased use of avoidance measures in HDM allergic individuals could have had a similar effect on the associations. This was studied in a random subsample of 127 subjects. Surprisingly, there were rather more high *Der p* I concentrations in suburban Antwerp, and from an additional questionnaire there was no indication of a difference in application of avoidance measures. Therefore, it seems unlikely

that the difference in respiratory symptoms resulted from higher exposure to HDM allergens in adulthood, although MARKS *et al*. [34] quantified a relationship between reduction in HDM allergen concentration and improvement in airway hyperresponsiveness and symptoms. Unfortunately, we cannot determine whether higher frequency of sensitization to HDM allergen in the urban area is a result of higher exposure during childhood, which probably plays a more important role in sensitization. The effect of migration between the two areas studied obviously needs to be considered. However, we have no indication that it occurred to a large extent. Any migration between areas probably occurs at random and, therefore, would only induce nondifferential misclassification, which should have attenuated the real differences.

Although the prevalence of several risk factors differed between the two areas, none of those considered, except HDM allergy, notably influenced the association between asthma variables and area of residence. HDM allergy explained most of the higher prevalence of "prior diagnosed asthma", but hardly influenced the association of recent asthma symptoms and area.

It is, thus, not clear from our analysis what factor(s) account for the marked differences in recent asthma symptoms found between urban and suburban Antwerp. Could this difference have been a result of selection bias as a consequence of relatively low response rates, for instance if more subjects with symptoms had been selected for participation in the second stage of the survey in urban Antwerp? This was investigated further and found to be true to only a minor extent. The response rate in both areas for the first stage was as high as 75%, but decreased in stage II, when clinical testing was involved, especially in urban Antwerp. Although prevalence of respiratory symptoms increased in the subsequent stages of the study, the associations with area of residence hardly changed. We therefore concluded that there was only a small effect of selection bias [35].

Differences in environmental air pollution between the two areas would be the obvious factor external to the present study to explain the difference in present symptoms. However, the annual median values and ranges of SO_2 and NO_2 were quite comparable in both areas. Although the measurements may not be quite representative for both areas, large differences are very unlikely. Unfortunately, we are not yet able to perform a valid further assessment, *e.g.* through personal sampling, of the role of environmental air pollution in our area. Therefore, the role of air pollution in causing asthma or eliciting symptoms in adults is still disputed [7, 36].

From the differences found between the urban and suburban areas in this study, we conclude that house dust mite allergy appears to be a major possible determinant for the regional difference in the onset of asthma in childhood. However, other factors responsible for the difference in the persistence of symptoms in adulthood could not be identified. Levels of mite allergens in mattress dust in the two areas studied did not explain the differences in asthma symptoms in young adults. Finally, we found that substantial differences in asthma prevalence and allergen sensitization could be present in neighbourhoods only a few kilometres apart; implying that, in practice, care should be taken in combining prevalence data from neighbourhoods around large cities, unless their similarity has already been established. Studies of differences in asthma prevalence within relatively small areas could prove as instructive as studies comparing differences between countries or continents.

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