Thorax Online First, published on October 21, 2005 as 10.1136/thx.2005.040881

Hormone replacement therapy, body mass index and asthma in peri-menopausal women. A cross-sectional survey.

Gomez Real F [1,2], Svanes C [2,3], Björnsson E H [4], Franklin K[5], Gislason D[4], Gislason T[4], Gulsvik A[2,3], Janson C[6], Jögi R[7], Kiserud T[1,10], Norbäck D[6], Nyström L [8], Torén K[9], Wentzel-Larsen T[11], Omenaas E [3,11]

[1]Department of Gynecology and Obstetrics, Haukeland University Hospital, 5021 Bergen, Norway
[2]Institute of Medicine, University of Bergen, Norway
[3]Department of Thoracic Medicine, Haukeland University Hospital, 5021 Bergen, Norway
[4]Department of Pulmonary Medicine, Landspitali University Hospital, 105 Reykjavik, Iceland
[5]Department of Pulmonary Medicine and Allergology, Umeå University, 90185 Umeå, Sweden
[6]Department of Medical Sciences, Uppsala University, 75185 Uppsala, Sweden
[7]Foundation Tartu University Clinics, Lung Clinic, 51014 Tartu, Estonia
[8]Department of Public Health, Clinical Medicine and Epidemiology, Umeå University, 90185 Umeå, Sweden
[9]Department of Occupational and Environmental Medicine, Sahlgrenska University Hospital, 41266 Gothenburg, Sweden
[10]Institute of Clinical Medicine, University of Bergen, Norway
[11]Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway

Corresponding author: Francisco Gómez Real, Department of Gynecology and Obstetrics, Haukeland University Hospital, 5021 Bergen, Norway

E-mail: francisco.real@med.uib.no

Running head: HRT, body mass index and asthma
Word count: 2556 words

Keywords: Asthma, HRT, body mass index, RHINE, ECRHS

ABBREVIATIONS:

BMI: body mass index

ECRHS: European Community Respiratory Health Survey

HRT: hormone replacement therapy

IR: insulin resistance

RHINE: Respiratory Health in Northern Europe

ABSTRACT

Background: Hormone replacement therapy (HRT) and obesity both appear to increase asthma risk. We wanted to investigate the association of HRT with asthma and hay fever in a population of peri-menopausal women, focusing on possible interaction with body mass index (BMI).

Methods: A postal questionnaire was sent to population-based samples in Denmark, Estonia, Iceland, Norway and Sweden in 1999-2001, and 8588 women aged 25-54 years responded (77%). Pregnant women, women using oral contraceptives, and women <46 years were excluded. Analyses included 2206 women aged 46-54 of which 884 were menopausal and 540 used HRT. Stratified analyses by BMI in tertiles were performed.

Results: HRT was associated with increased risk for asthma (OR= 1.57[95% CI=1.07-2.30]), wheeze (OR=1.60[1.22-2.10]) and hay fever (OR=1.48[1.15-1.90]). The associations with asthma and wheeze were significantly stronger among women with BMI in the lower tertile (asthma OR=2.41[1.21-4.77]; wheeze OR=2.04[1.23-3.36]) as compared with heavier women (asthma: $p_{interaction}$= 0.030; wheeze: $p_{interaction}$= 0.042). Increasing BMI was associated with more asthma (OR=1.08 [1.05-1.12] per kg/m^2). This effect was only found in women not taking HRT (OR=1.10 [1.05-1.14] per kg/m^2), while no such association could be detected in women taking HRT (OR=1.00 [0.92-1.08] per kg/m^2) ($p_{interaction}$ = 0.046). Menopause was not significantly associated with asthma, wheeze or hay fever.

Conclusions: In peri-menopausal women there was an interaction between HRT and BMI in effects on asthma. HRT-users among lean women had as high a risk for asthma as overweight women not taking HRT. The authors suggest that HRT and overweight increase asthma risk through partly common pathways.

INTRODUCTION

Hormonal replacement (HRT) as remedy to menopausal symptoms has long seemed to be biologically plausible, though solid assessment of its side-effects has been lacking. In the last years there has been an increasing awareness of the risks of HRT, mainly on cardiovascular diseases, stroke, venous thromboembolism and breast cancer, as a result of the Women's Health Initiative[1] and other trials[2]. Less attention has been paid to the effects of HRT on the airways, even though there is mounting, but somehow contradictory, evidence of the association of HRT with obstructive airways disease.

Data from the Nurses Health Study [3 4] and the Copenhagen City Heart Study [5] show that women taking HRT more often have asthma. In an elderly US Medicare population [6], HRT users had higher lung function. Small intervention and case-control studies in selected healthy women generally show improvement in asthma or lung function related to HRT intake [7 8]. The apparently contradictory findings may be caused by unrecognized sources of error in some studies [9]. Another possibility is that the effects of HRT differ between subgroups of women of different ages[9], metabolic condition [10-14] or menopausal status [15].

The association of asthma with BMI is well known, although not fully understood [16-18]. Sex hormones and body fat mass are closely interrelated; the levels of estrogens are related to body fat mass [9 12] and the subject's metabolic status [19]. Exogenous estrogens and body mass index are known to interact in effects on breast cancer; the increase in breast cancer risk related to HRT is stronger among lean women[20].

Initiation of menopause may possibly also play a role in the development of asthma; asthma may sometimes start or worsen around the age of menopause [15], but is also described to be less common among post-menopausal women[3].

We wanted to address the possible associations of HRT and menopause with symptoms of asthma and allergy among peri-menopausal women in general population samples from Northern European countries with different prescription practices[21]. In particular we wanted to address possible heterogeneity in effects of HRT according to body mass index.

METHODS

Design and subjects

This is a cross-sectional analysis of the Respiratory Health in Northern Europe (RHINE)[16 22] (www.rhine.nu). RHINE is a follow up study of subjects from seven Northern European centres who participated in the European Community Respiratory Health Survey (ECRHS) I stage 1 (www.ecrhs.org), a study that took place in 1990-1994 [23]. In stage 1 of the ECRHS men and women aged 20 to 44 years were randomly selected from population registers within specific boundaries of each participating centre. A postal questionnaire was sent to 3000 - 4300 subjects in each centre. The population included in the RHINE study was responders from Reykjavik in Iceland, Bergen in Norway, Umeå, Uppsala and Gothenburg in Sweden, Aarhus in Denmark and Tartu in Estonia (n=21,802, response rate 83.7%). The eligible subjects (excluding 264 deaths) were sent a postal questionnaire in 1999-2001. Subjects not responding to the first mailing were sent two reminders. In total 16,191 subjects answered the questionnaire, including 8588 women (response rate 77%) born between 1945 and 1973. Local ethics committees approved the study.

Analyses were restricted to women aged 46 to 54 years, since 45-46 years is the average age for onset of the perimenopausal transition[24]. Pregnant women (n=6) and women using oral contraceptives (n=72) were excluded, leaving 2206 women for analyses.

There were 121 women younger than 46 years that reported menopause, and 102 of these were taking HRT. The age group 26-45 was not included in further analyses because pathologic conditions underlying early menopause might introduce unknown confounders; and because the 19 younger menopausal women not taking HRT would constitute a small and possibly biased reference group.

Questionnaire

The first part of the questionnaire contained 12 questions identical with those asked in the ECRHS I stage 1. These items covered respiratory symptoms, asthma medication and hay fever. Asthma was defined as currently using asthma medication and/or having had asthma attacks during the last 12 months, wheeze as having had wheeze during the last 12 months, night symptoms as waking with tightness in chest or waking with shortness of breath, and hay fever as currently having hay fever or nasal allergies. Three or more asthma symptoms were defined based on the following eight symptoms: wheeze, wheeze with shortness of breath, wheeze without cold, waking with tightness in chest, waking with shortness of breath, waking with cough, asthma attacks, current asthma medication[25].

The second part of the questionnaire included 52 items covering various aspects including factors related to hormonal status in women. Menopause was defined as answering "yes" to the question "Have you reached the menopause? (six or more months since your last menstruation)". Hormonal replacement therapy (HRT) was defined as answering "yes" to the question "Are you using hormones/hormone replacement therapy?". In some centres HRT was only registered in women answering "yes" to having reached the menopause. The women were also asked about pregnancy, use of oral contraceptives, age of menopause, and date of the last menstrual bleeding.

Body mass index was based on self-reported weight and height, and calculated as weight in kilos per square of height in meters. Smoking history was assessed by two questions: "are you a smoker?" and "are you an ex-smoker?" Based on these, three groups were defined: never-, ex- or current smokers. Type of dwelling (detached, semidetached, apartment, other) was used as a proxy for social class, "detached" corresponding to upper social class, etc. A socio-economic index based on current occupation was available in four centres (Bergen, Gothenburg, Uppsala and Tartu). In these centres, type of dwelling was strongly correlated with socio-economic index ($p<0.001$), and analyses with adjustment for this variable gave similar results as when adjusting for type of dwelling.

Statistical analysis

Logistic regression models were used to assess the effects of menopause and of HRT on asthma and hay fever. Number at risk fluctuated slightly from outcome to outcome due to a varying number of missing for each variable. Adjustments were made for age (5-year categories), body mass index (kg/m^2), smoking habits (never, ex- and current smoking), study centre and social class (type of dwelling). Analyses of HRT were stratified according to BMI categorised in tertiles. Based on results from the stratified analyses the two upper tertiles were grouped together post hoc, and the differences in effects of HRT on asthma between lean and

heavier women were analysed by including interaction terms of BMI and HRT in the logistic regression models. Similarly, logistic regression models were used to assess the effects of BMI (as a continuous variable) on asthma and hay fever, analyses were stratified by HRT use, and an interaction term between BMI and HRT was included to assess the statistical significance of differences in BMI effects between subjects using or not using HRT. Potential heterogeneity between centres was studied by meta-analyses according to derSimonian and Laird. The analyses were carried out using the statistical software program Stata 7.0 (Stata Corporation, College Station, Texas, USA).

RESULTS

Among 2206 women aged 46-54 years, 540 (24 %) were using HRT at the time of study. There was some variation between centres, with HRT being more widely used in Reykjavik and Bergen and less used in Tartu and Aarhus as compared with the Swedish centres (table 1). In total, 844 women reported that they were menopausal (table 1). Women taking HRT were leaner, more often smokers and more often lived in a semi-detached house as compared with women not taking HRT.

Table 1 Characteristics of women aged 46 to 54 years participating in the RHINE study.

Centre	Study population	median age	median BMI	current smokers	menopausal*	HRT	asthma†	wheeze‡	hay fever§
	n	*years*	*kg/m^2*	*%*	*n (%)*	*n (%)*	*%*	*%*	*%*
Aarhus	328	49	23.5	34	92 (32)	37 (11)	9.2	17	23
Reykjavik	323	49	24.8	27	145 (51)	157 (49)	8.1	12	23
Bergen	345	49	23.4	39	191 (57)	103 (30)	7.3	22	23
Gothenburg	326	49	24.6	34	113 (43)	78 (24)	9	25	27
Umeå	398	49	24.5	24	154 (41)	79 (20)	8.1	21	22
Uppsala	375	49	24	19	123 (35)	81 (22)	6.8	19	26
Tartu	111	47	24.6	24	26 (24)	5 (4.5)	3.6	23	25
Total	*2206*	*49*	*24.2*	*29*	*844 (42)*	*540 (24)*	*7.8*	*20*	*24*

* Menopause as defined as answering “yes” to the following question: “have you reached the menopause? (six or more months since your last menstruation)“
† Current asthma medication and/or asthma attacks last 12 months.
‡ Wheeze in the last 12 months.
§ Current hay fever or nasal allergies.

Asthma, wheeze or hay fever did not differ significantly between premenopausal and postmenopausal women, while there was a borderline significant association between night symptoms and menopause (table 2).

Table 2 Asthma and hay fever according to menopause in 1527 women aged 46-54 years. Women using HRT were excluded.

	premenopausal *n=1103* %	postmenopausal *n=424* %	*OR (95 % CI)**	*p-value*
Asthma†	6.9	7.2	0.94 (0.57-1.55)	0.8
Wheeze‡	17	21	1.18 (0.85-1.14)	0.3
Three or more asthma symptoms§	13	16	1.11 (0.76-1.63)	0.6
Night symptoms**	13	17	1.36 (0.96-1.93)	0.088
Hay fever††	23	21	0.97 (0.71-1.32)	0.8
Allergic asthma‡‡	4.4	2.6	0.54 (0.26-1.13)	0.1

*From logistic regression models with adjustment for smoking, BMI, age, centre and social class.
†Asthma medication and/or asthma attacks last 12 months.
‡Wheeze in the last 12 months
§Symptoms included: wheeze, wheeze with shortness of breath, wheeze without cold, waking with tightness in chest, waking with shortness of breath, waking with cough, asthma attacks, current asthma medication
**Waking with tightness in chest or waking with shortness of breath
††Hay fever or nasal allergies
‡‡Asthma and hay fever

Asthma, asthma symptoms and hay fever, but not night symptoms, were significantly more common among women using HRT (table 3). There was no significant heterogeneity between centres in the association of HRT with asthma or wheeze (figure 1, asthma: $p_{heterogeneity} = 0.84$; wheeze: $p_{heterogeneity} = 0.35$).

Table 3 Asthma and hay fever according to use of HRT among 2206 women aged 46-54 years.

	no HRT *n=1666* *%*	HRT *n=540* *%*	*OR (95%CI)**	*p-value*
Asthma†	7.2	10.0	1.50 (1.03-2.20)	0.035
Wheeze‡	18.7	23.1	1.54 (1.17-2.02)	0.002
Three or more symptoms§	13.3	18.5	1.62 (1.20-2.20)	0.002
Night symptoms**	14.2	11.8	0.85 (0.61-1.18)	0.3
Hay fever††	23.0	27.4	1.47 (1.14-1.88)	0.003
Allergic asthma‡‡	3.9	5.8	1.77 (1.09-2.89)	0.022

*From logistic regression models with adjustment for smoking habits, BMI, age, centre and social class
†Asthma medication and/or asthma attacks last 12 months.
‡Wheeze in the last 12 months
§Symptoms included: wheeze, wheeze with shortness of breath, wheeze without cold, waking with tightness in chest, waking with shortness of breath, waking with cough, asthma attacks, current asthma medication
**Waking with tightness in chest or waking with shortness of breath
††Hay fever or nasal allergies
‡‡Asthma and hay fever

When stratifying by BMI in tertiles, HRT was significantly associated with higher risk for asthma, wheeze and hay fever only among lean women (table 4). The associations of HRT with asthma and wheeze among women in the lower BMI tertile were significantly stronger than the corresponding associations among women in the medium and upper tertiles ($p_{interaction}$=0.020 and $p_{interaction}$=0.026, respectively).

Table 4 Asthma and hay fever in women according to use of HRT, stratified by BMI in tertiles.

	No HRT	HRT		
	%	*%*	*OR (95%CI)**	*p-value*
lower tertile, *BMI<22.76 (n=716)*				
Asthma†	5.3	12.0	2.28 (1.18-4.40) **	0.014
Wheeze‡	14.9	25.8	1.85 (1.16-2.96) ††	0.010
Hay fever§	20.7	29.7	2.06 (1.33-3.19) ‡‡	0.001
medium tertile, *BMI=22.76-25.71 (n=736)*				
Asthma†	5.6	6.3	1.28 (0.61-2.71) **	0.513
Wheeze‡	15.0	19.7	1.56 (0.95-2.54) ††	0.076
Hay fever§	23.1	25.3	1.20 (0.79-1.84) ‡‡	0.395
upper tertile, *BMI>25.71 (n=709)*				
Asthma†	10.6	12.4	1.31 (0.71-2.42) **	0.382
Wheeze‡	24.1	26.7	1.28 (0.80-2.06) ††	0.302
Hay fever§	25.0	26.9	1.39 (0.89-2.17) ‡‡	0.153

* From logistic regression models with adjustment for smoking habits, BMI (within tertile), age, centre and type of dwelling (as a proxy for social class).
†Asthma medication and/or asthma attacks last 12 months.
‡Wheeze in the last 12 months
§Hay fever or nasal allergies
** Interaction in effect of HRT on asthma between lean and normal/overweight women $p_{interaction}$=0.020
††Interaction in effect of HRT on wheeze between lean and normal/overweight women $p_{interaction}$=0.026
‡‡ Interaction in effect of HRT on hay fever between lean and normal/overweight women $p_{interaction}$=0.076

Increasing BMI was associated with more asthma and asthma symptoms, but not with hay fever (table 5).

Table 5 Asthma and hay fever according to BMI in tertiles, and adjusted associations of BMI with asthma and hay fever.

	lower tertile *BMI<22.76* *n=716* *%*	medium tertile *22.76<BMI<25.71* *n=736* *%*	upper tertile *BMI>25.71* *n=709* *%*	*OR (95 % CI)** *per kg/m^2*
Asthma†	6.9	5.8	11	1.08 (1.05-1.12)
Wheeze‡	17.4	16.2	26.1	1.09 (1.06-1.12)
Three or more symptoms§	11.5	11.9	20.7	1.10 (1.07-1.13)
Night symptoms**	10.9	12.8	17.1	1.06 (1.03-1.09)
Hay fever††	22.8	23.7	25.5	1.02 (0.99-1.04)
Allergic asthma‡‡	4.1	3.7	5.1	1.04 (1.00-1.10)

*From logistic regression models with adjustment for smoking habits, BMI, age, centre and social class
†Asthma medication and/or asthma attacks last 12 months.
‡Wheeze in the last 12 months
§Symptoms included: wheeze, wheeze with shortness of breath, wheeze without cold, waking with tightness in chest, waking with shortness of breath, waking with cough, asthma attacks, current asthma medication
**Waking with tightness in chest or waking with shortness of breath
††Hay fever or nasal allergies
‡‡Asthma and hay fever

Stratifying by use of HRT, an association of asthma with BMI was observed in women not taking HRT (OR=1.10; 95%CI=1.05-1.14 per kg/m^2) (figure 2A), while no such association could be detected in women taking HRT (OR=1.00; 95%CI=0.92-1.08 per kg/m^2)(figure 2B). The difference in the associations of asthma with BMI according to use of HRT was significant ($p_{interaction}$ =0.046).

The associations of HRT with asthma, wheeze and hay fever were only significant among never smokers (table 6), however the differences between smoking groups were not significant (asthma: $p_{interaction}$=0.19; wheeze: $p_{interaction}$=0.6; hay fever: $p_{interaction}$=0.4)

Table 6 Asthma and hay fever according to use of HRT, stratified by smoking history.

	no HRT	HRT		
	%	*%*	*OR (95%CI)**	*p-value*
Never smokers *(n=907)*				
Asthma†	5.3	9.2	2.42 (1.24-4.72)	0.010
Wheeze‡	13.1	17.2	1.94 (1.18-3.19)	0.008
Hay fever§	23.6	30.4	1.85 (1.23-2.78)	0.003
Ex smokers *(n=684)*				
Asthma†	8.1	9.7	1.20 (0.61-2.33)	0.589
Wheeze‡	14.9	19.5	1.66 (0.99-2.77)	0.050
Hay fever§	23.4	27.2	1.39 (0.89-2.18)	0.143
Smokers *(n=649)*				
Asthma†	9.1	11.5	1.41 (0.74-2.71)	0.293
Wheeze‡	31.9	33.5	1.34 (0.87-2.06)	0.183
Hay fever§	22.1	24.1	1.18 (0.73-1.91)	0.488

* From logistic regression models with adjustment for smoking habits, BMI (within tertile), age, centre and type of dwelling (as a proxy for social class).
†Asthma medication and/or asthma attacks last 12 months.
‡Wheeze in the last 12 months
§Hay fever or nasal allergies

DISCUSSION

The prevalence of diagnosed asthma, asthma symptoms and allergy was higher among HRT users in a multi-centre population-based cross-sectional survey of Northern European peri-menopausal women. This was consistent between centres with different prescription practices. The risk for asthma related to HRT was significantly larger among lean women as compared with heavier women, and this interaction in effects of HRT and BMI on asthma was significant. The well-documented association of asthma with BMI was in this study observed only among women not taking exogenous sex hormones, while no significant association between asthma and BMI was found among HRT users. Thus, exogenous estrogens appear to interfere with the mechanism causing more asthma among overweight women, resulting in similar high prevalence of asthma in lean HRT users as that observed among obese women not taking HRT.

The observed higher prevalence of asthma among HRT-users is in agreement with findings from the two large cohort studies, the Copenhagen City Heart Study and the Nurses' Health Study [3-5]. The interaction between BMI and HRT in effects on asthma is supported by Nurses´ Health Study showing a RR for HRT on asthma of 3.09 among lean women as compared to 1.58 among heavier women[4]. The association of HRT with hay fever has not been reported previously. Our study supports the report from Lange et al. noting a stronger association of HRT and asthma among never-smokers[5], possibly due to anti-estrogen effects of smoking [26]. Our findings are not necessarily contradictory to those of Carlson et al. [6], as we did not have data on lung function and our study population comprises much younger women.

The main limitation of the present study is its cross-sectional design. Due to lack of information about when the women started using HRT, we do not know with certainty whether HRT preceded asthma or not. Self-reported use of HRT is considered to be reliable[27]. We did not have information about type of HRT; however, Barr et al. did not observe differences with regard to type of HRT [4]. Differential misclassification of asthma related to HRT is a possibility; women taking HRT might more often have their asthma diagnosed due to higher health awareness or more frequent contact with a doctor. The association of asthma and obesity might also be influenced by doctor's bias. However, it seems unlikely that these sources of error may explain our findings, because the associations were consistent between centers with different prescription practices, the findings were similar for doctor's diagnosed asthma and asthma symptoms like wheeze, adjustment for social class did not alter the effects, and the associations of asthma with HRT differed significantly between lean and normal weight women. This interaction of HRT with BMI is biologically plausible, but difficult to attribute to systematic error.

Women in the age group 46-54 years as included in this study are usually in the peri-menopausal transition. The average age of onset for the peri-menopausal transition is 46 years, and the average duration 5 years [24]. This is the age when the climacteric symptoms are most frequent and the use of HRT most relevant. There is a possibility for residual confounding by menopausal status, however, self-reported menopausal status is considered reliable even though some caution must be exerted [28] . Differential misclassification of respiratory night symptoms as related to menopause could be suspected; night symptoms as opposed to other asthma symptoms appeared to be more common in menopausal women and less common in those taking HRT. There are some discrepancies in the current available literature about the role the onset of menopause plays in the development of pre-existent or new asthma and allergy. There are studies showing less asthma risk in naturally menopausal

women [3], while other suggest start or worsening of asthma with the menopause [15]. In our study menopause in itself was not significantly associated with asthma or hay fever.

Our study reveals that the association of HRT with asthma appears to be modified by BMI. This is biologically plausible, as there is a close interplay between sex hormones, fatty tissue and metabolic status. A similar interaction is described for breast cancer, where the increase in relative risk among HRT users was greatest in lean women [20 29]. The association of asthma with BMI is well documented although not fully understood[16-18 30]. BMI is closely related to insulin resistance (IR) [31 32]. We suggest that the association of asthma with BMI is due to the pro-inflammatory effects of IR[32-34]. There is no direct evidence linking asthma with IR, but there are several studies showing associations of lung function with IR[34-36], and a previous analysis of the present population showed an association of asthma with menstrual irregularity which often is a manifestation of IR[22]. The effects of estrogens on the airways appear to be complex. Both direct pro-inflammatory effects[37 38] and indirect beneficial metabolic effects are described[39]. Estrogens are closely related to BMI, which is the strongest marker of estrogen levels in post-menopausal women[9 12]. IR is intimately involved in the regulation of local estrogen production[13 19]. Thus, we hypothesize that exogenous estrogens and BMI act on the airways in part through common pathways, where inflammation associated with IR might play an important role. Among lean women with low IR, direct pro-inflammatory effects of HRT could be predominant, while among heavier and more insulin resistant women such effects might be counterbalanced by estrogen-related reduction in IR.

In conclusion, our study shows an association of HRT with asthma and hay fever, and confirms the association of obesity with asthma. Further, this study reveals an interaction of HRT with BMI in effects on asthma, HRT increasing asthma risk in lean women to the same level as that observed in obese women. These findings are fairly convincing as the interaction with body mass index is biologically plausible and difficult to explain as error, even if the study design is not ideal. Thus, this study indicates that asthma and allergy may be side-effects to HRT, at least in subgroups of women. Further, the study indicates that obesity and exogenous estrogens may be involved in the pathogenesis of asthma through partly common pathways. Future studies about effects of HRT on the airways should be conducted in representative general population samples, taking into account the possibility that effects of estrogens might be dependent on BMI or metabolic status. Likewise, further studies of asthma and BMI should take into consideration hormonal status.

ACKNOWLEDGEMENTS

The author, FGR, was supported by a grant from the Norwegian Research Council.

The study was supported financially by the Icelandic Research Council, the Swedish Heart and Lung Foundation, the Vårdal Foundation for Health Care Science and Allergy Research, the Swedish Association against Asthma and Allergy, the Norwegian Research Council project 135773/330, the Norwegian Asthma and Allergy Association, the Danish Lung Association and the Estonian Science Foundation grant no 4350.

The following scientists in the Rhine study group are acknowledged for helpful contributions: Blöndal T, Björnsdottir US, Boman G, Forsberg B, Gislason D, Gulsvik A, Gunnbjörnsdottir M, Juel Jensen E, Ledin M-C, Lillienberg L, Lundbäck B, Lærum BN, Norrman E, Olin A-C, Rydén E, Spetz-Nyström U, Stenudd Cashelunge K, Söderberg M, Talvik J, Tunsäter A, Wieslander G.

ETHICAL APPROVAL

The study was approved by local ethics committees in all the study centres**.**

CONFLICT OF INTEREST STATEMENT

I hereby declare no conflict of interest.

LEGEND TO FIGURES

Figure 1 Odds ratios for the associations between A) HRT and asthma by centre (Tartu not included because of small numbers) and between B) HRT and wheeze by centre.
Adjustment within centre for smoking habits, BMI, age and social class. For each centre, horizontal lines indicate 95%CI. For combined OR, diamond indicates 95%CI from model with centre as random effect. The size of each square is proportional to the sample size.

Figure 2 Asthma prevalence according to BMI A) in 1648 subjects not taking HRT and B) in 535 subjects taking HRT.

REFERENCES

1. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *Jama* 2002;288(3):321-33.
2. Cushman M, Legault C, Barrett-Connor E, Stefanick ML, Kessler C, Judd HL, et al. Effect of postmenopausal hormones on inflammation-sensitive proteins: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study. *Circulation* 1999;100(7):717-22.
3. Troisi RJ, Speizer FE, Willett WC, Trichopoulos D, Rosner B. Menopause, postmenopausal estrogen preparations, and the risk of adult-onset asthma. A prospective cohort study. *Am J Respir Crit Care Med* 1995;152(4 Pt 1):1183-8.
4. Barr RG, Wentowski CC, Grodstein F, Somers SC, Stampfer MJ, Schwartz J, et al. Prospective study of postmenopausal hormone use and newly diagnosed asthma and chronic obstructive pulmonary disease. *Arch Intern Med* 2004;164(4):379-86.
5. Lange P, Parner J, Prescott E, Ulrik CS, Vestbo J. Exogenous female sex steroid hormones and risk of asthma and asthma-like symptoms: a cross sectional study of the general population. *Thorax* 2001;56(8):613-6.
6. Carlson CL, Cushman M, Enright PL, Cauley JA, Newman AB. Hormone replacement therapy is associated with higher FEV1 in elderly women. *Am J Respir Crit Care Med* 2001;163(2):423-8.
7. Kos-Kudla B, Ostrowska Z, Marek B, Ciesielska-Kopacz N, Kajdaniuk D, Kudla M. Effects of hormone replacement therapy on endocrine and spirometric parameters in asthmatic postmenopausal women. *Gynecol Endocrinol* 2001;15(4):304-11.
8. Pata Ö. The effects of hormone replacement therapy type on pulmonary functions in postmenopausal women. *Maturitas* 2003;46:213-218.
9. Grodstein F, Clarkson TB, Manson JE. Understanding the divergent data on postmenopausal hormone therapy. *N Engl J Med* 2003;348(7):645-50.
10. Fernandez-Real JM, Sanchis D, Ricart W, Casamitjana R, Balada F, Remesar X, et al. Plasma oestrone-fatty acid ester levels are correlated with body fat mass in humans. *Clin Endocrinol (Oxf)* 1999;50(2):253-60.
11. Carr MC. The emergence of the metabolic syndrome with menopause. *J Clin Endocrinol Metab* 2003;88(6):2404-11.
12. Figueroa A, Going SB, Milliken LA, Blew R, Sharp S, Lohman TG. Body composition modulates the effects of hormone replacement therapy on growth hormone and insulin-like growth factor-I levels in postmenopausal women. *Gynecol Obstet Invest* 2002;54(4):201-6.
13. Kalish GM, Barrett-Connor E, Laughlin GA, Gulanski BI. Association of endogenous sex hormones and insulin resistance among postmenopausal women: results from the Postmenopausal Estrogen/Progestin Intervention Trial. *J Clin Endocrinol Metab* 2003;88(4):1646-52.
14. Lindheim SR, Presser SC, Ditkoff EC, Vijod MA, Stanczyk FZ, Lobo RA. A possible bimodal effect of estrogen on insulin sensitivity in postmenopausal women and the attenuating effect of added progestin. *Fertil Steril* 1993;60(4):664-7.
15. Balzano G, Fuschillo S, Melillo G, Bonini S. Asthma and sex hormones. *Allergy* 2001;56(1):13-20.
16. Gunnbjornsdottir MI, Omenaas E, Gislason T, Norrman E, Olin AC, Jogi R, et al. Obesity and nocturnal gastro-oesophageal reflux are related to onset of asthma and respiratory symptoms. *Eur Respir J* 2004;24(1):116-21.
17. Shaheen SO, Sterne JA, Montgomery SM, Azima H. Birth weight, body mass index and asthma in young adults. *Thorax* 1999;54(5):396-402.

18. Camargo CA, Jr., Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Arch Intern Med* 1999;159(21):2582-8.
19. Simpson E, Rubin G, Clyne C, Robertson K, O'Donnell L, Jones M, et al. The role of local estrogen biosynthesis in males and females. *Trends Endocrinol Metab* 2000;11(5):184-8.
20. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet* 1997;350(9084):1047-59.
21. Topo P, Koster A, Holte A, Collins A, Landgren BM, Hemminki E, et al. Trends in the use of climacteric and postclimacteric hormones in Nordic countries. *Maturitas* 1995;22(2):89-95.
22. Svanes C, Real FG, Gislason T, Jansson C, Jogi R, Norrman E, et al. Association of asthma and hay fever with irregular menstruation. *Thorax* 2005;60(6):445-50.
23. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994;7(5):954-60.
24. Speroff L, Glass RH, Kase NG. Menopause and the Perimenopausal transition. In: Mitchell C, editor. *Clinical Gynecologic Endocrinology and Infertility*. 6th ed. Baltimore: Lippincott Williams&Wilkins, 1999:643-724.
25. Pekkanen J, Sunyer J, Anto J, Burney P. Operational definitions of asthma in studies on its aetiology. *Eur Resp J* 2005;26(1):1-9.
26. Key TJ, Pike MC, Brown JB, Hermon C, Allen DS, Wang DY. Cigarette smoking and urinary oestrogen excretion in premenopausal and post-menopausal women. *Br J Cancer* 1996;74(8):1313-6.
27. Espeland MA, Stefanick ML, Kritz-Silverstein D, Fineberg SE, Waclawiw MA, James MK, et al. Effect of postmenopausal hormone therapy on body weight and waist and hip girths. Postmenopausal Estrogen-Progestin Interventions Study Investigators. *J Clin Endocrinol Metab* 1997;82(5):1549-56.
28. Harlow SD, Crawford SL, Sommer B, Greendale GA. Self-defined menopausal status in a multi-ethnic sample of midlife women. *Maturitas* 2000;36(2):93-112.
29. Bruning PF, Bonfrer JM, Hart AA, van Noord PA, van der Hoeven H, Collette HJ, et al. Body measurements, estrogen availability and the risk of human breast cancer: a case-control study. *Int J Cancer* 1992;51(1):14-9.
30. [Sex hormones as risk factor? More asthma in cases of irregular menstrual periods]. *MMW Fortschr Med* 2002;144(44):14.
31. Barrett-Connor E, Frette C. NIDDM, impaired glucose tolerance, and pulmonary function in older adults. The Rancho Bernardo Study. *Diabetes Care* 1996;19(12):1441-4.
32. Dandona P, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. *Trends Immunol* 2004;25(1):4-7.
33. Fernandez-Real JM, Broch M, Richart C, Vendrell J, Lopez-Bermejo A, Ricart W. CD14 monocyte receptor, involved in the inflammatory cascade, and insulin sensitivity. *J Clin Endocrinol Metab* 2003;88(4):1780-4.
34. Engstrom G, Hedblad B, Nilsson P, Wollmer P, Berglund G, Janzon L. Lung function, insulin resistance and incidence of cardiovascular disease: a longitudinal cohort study. *J Intern Med* 2003;253(5):574-81.
35. Davis WA, Knuiman M, Kendall P, Grange V, Davis TM. Glycemic Exposure Is Associated With Reduced Pulmonary Function in Type 2 Diabetes: The Fremantle Diabetes Study. *Diabetes Care* 2004;27(3):752-757.

36. Lawlor DA, Ebrahim S, Smith GD. Associations of measures of lung function with insulin resistance and Type 2 diabetes: findings from the British Women's Heart and Health Study. *Diabetologia* 2004;47(2):195-203.
37. Kirsch EA, Yuhanna IS, Chen Z, German Z, Sherman TS, Shaul PW. Estrogen acutely stimulates endothelial nitric oxide synthase in H441 human airway epithelial cells. *Am J Respir Cell Mol Biol* 1999;20(4):658-66.
38. Keller AC, Rodriguez D, Russo M. Nitric oxide paradox in asthma. *Mem Inst Oswaldo Cruz* 2005;100 Suppl 1:19-23.
39. Simpson ER, Misso M, Hewitt KN, Hill RA, Boon WC, Jones ME, et al. Estrogen - the Good, the Bad, and the Unexpected. *Endocr Rev* 2005.

Figure 1a

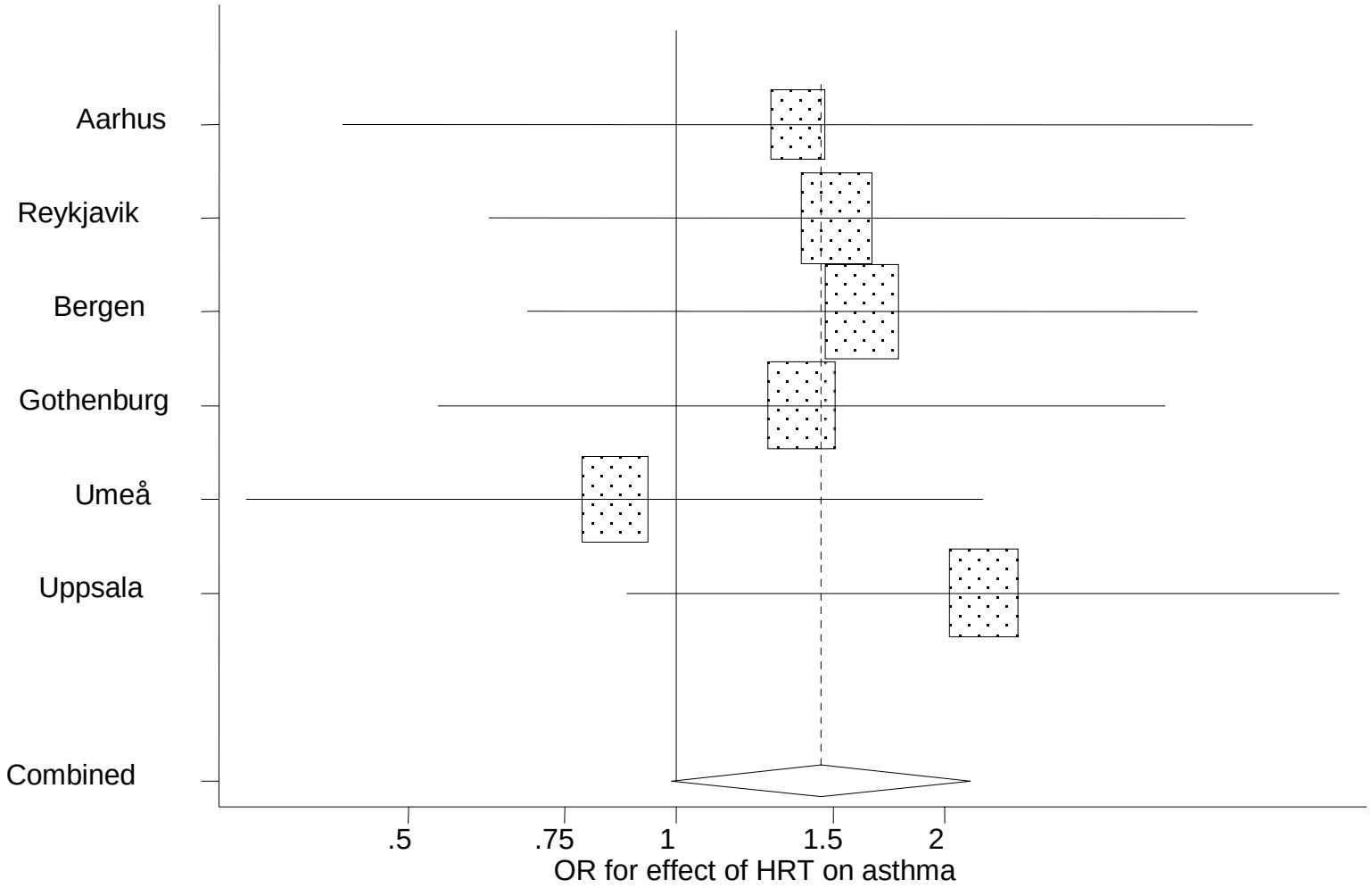

Figure 1b

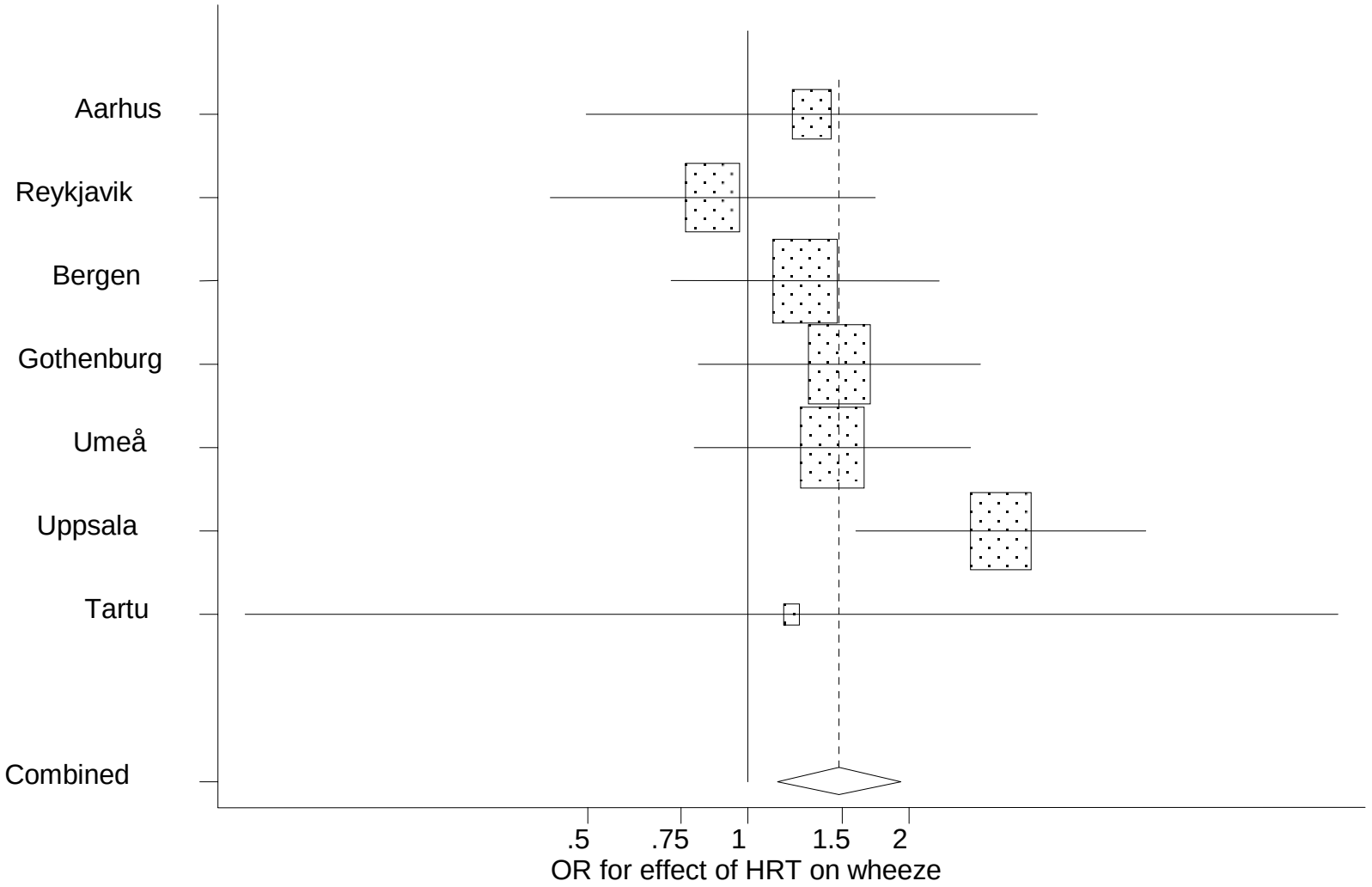

Figure 2a

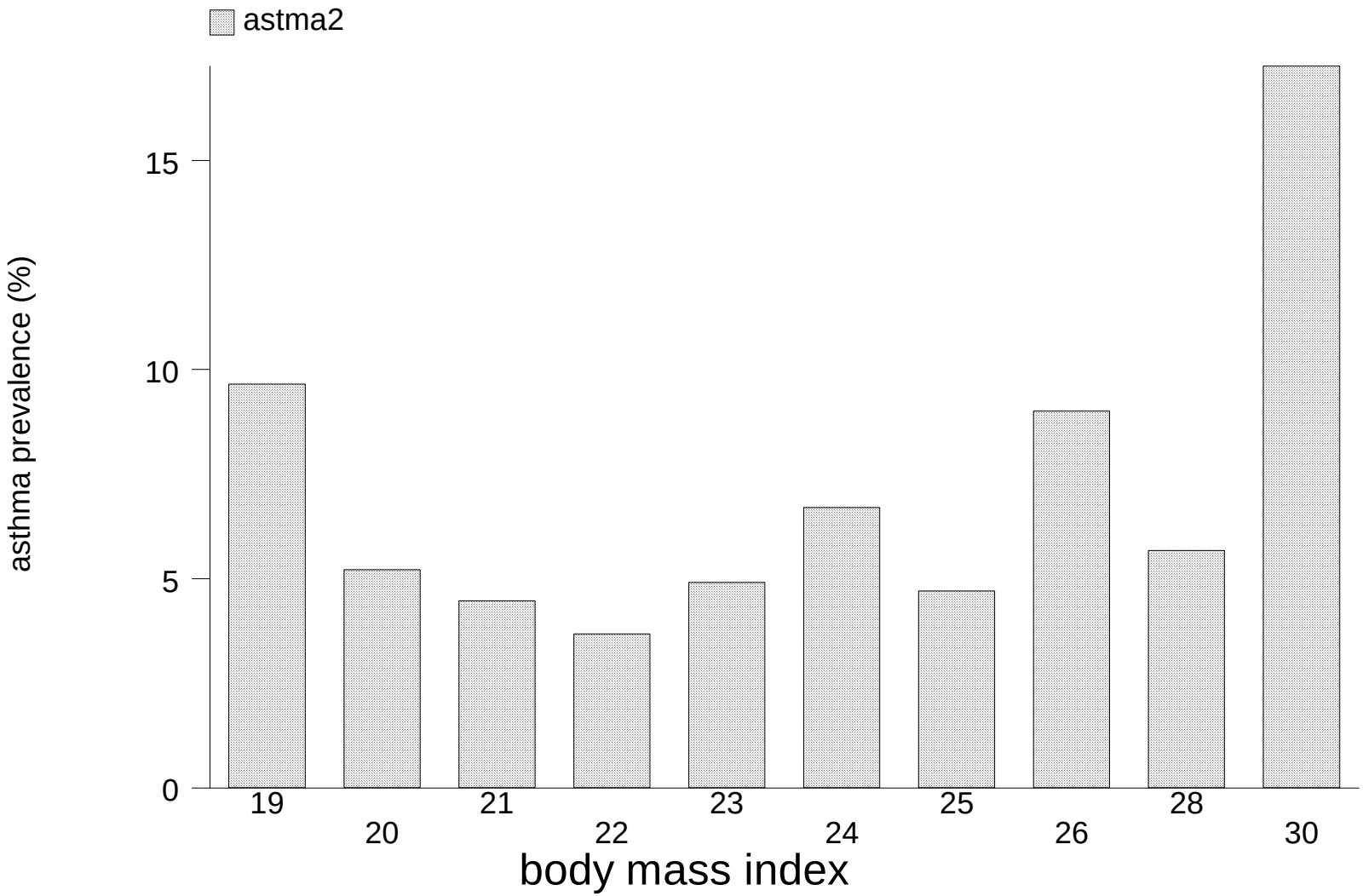

Figure 2b

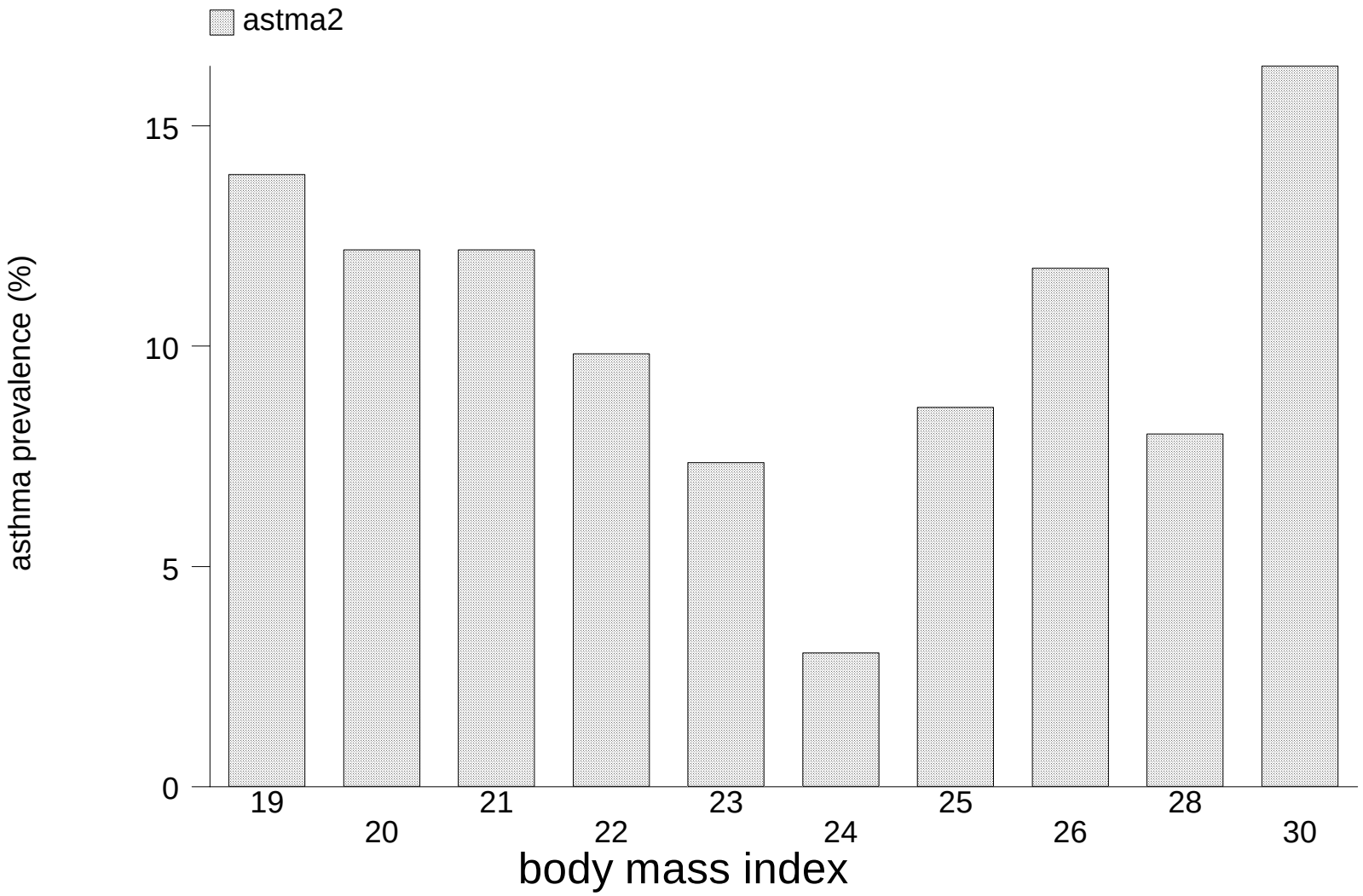

Table 1 Statistical analysis of the case-control study

	Co-dominant				Dominant (AA/AG *v* GG)				Recessive (AA *v* AG/GG)			
	AA	AG	GG	p value	AA/AG	GG	OR (95% CI)	p value	AA	GG/AG	OR (95% CI)	p value
Controls	84 (41%)	82 (41%)	36 (18%)		166	36			84	116		
Cases	99 (47%)	93 (44%)	18 (9%)	**0.021**	192	18	**2.31 (1.27 to 4.23)**	**0.006**	99	111	1.25 (0.85 to 1.85)	0.276
Acute	30 (42%)	32 (45%)	9 (13%)	0.576	62	9	1.49 (0.68 to 3.28)	0.358	30	41	0.99 (0.57 to 1.71)	0.97
Chronic	59 (52%)	47 (41%)	8 (7%)	**0.021**	106	8	**2.87 (1.29 to 6.42)**	**0.007**	59	55	0.67 (0.43 to 1.07)	0.095

Significant associations are shown in bold.

(95% CI 1.29 to 6.42), p<0.0069; table 1) with a PAR for AA homozygotes and AG heterozygotes of 50%.

This study underlines the importance of the association of *BTNL2* rs2076530 variant with the susceptibility to develop sarcoidosis in a German population. Furthermore, our data suggest that susceptibility is preferentially towards the chronic form of the disease.

Y Li, B Wollnik
Center for Molecular Medicine Cologne (CMMC) and Institute of Human Genetics, University of Cologne, Germany

S Pabst, M Lennarz
Medizinische Universitäts-Poliklinik, Rheinische-Friedrich-Wilhelms Universität Bonn, Germany

E Rohmann
Center for Molecular Medicine Cologne (CMMC) and Institute of Human Genetics, University of Cologne, Germany

A Gillissen
Städtisches Klinikum St Georg, Leipzig, Germany

H Vetter, C Grohé
Medizinische Universitäts-Poliklinik, Rheinische-Friedrich-Wilhelms Universität Bonn, Germany

Correspondence to: Professor Dr med C Grohé, Medizinische Universitäts-Poliklinik, Wilhelmstr, 35-37, D-53111 Bonn, Germany; c.grohe@uni-bonn.de

doi: 10.1136/thx.2005.056564

Competing interests: none.

References

1 **Newman LS**, Rose CS, Maier LA. Sarcoidosis. *N Engl J Med* 1997;**336**:1224–34.
2 **Rybicki BA**, Iannuzzi MC, Frederick MM, *et al*. ACCESS Research Group. Familial aggregation of sarcoidosis. A case-control etiologic study of sarcoidosis (ACCESS). *Am J Respir Crit Care Med* 2001;**164**:2085–91.
3 **Valentonyte R**, Hampe J, Huse K, *et al*. Sarcoidosis is associated with a truncating splice site mutation in BTNL2. *Nat Genet* 2005;**37**:357–64.
4 **Rybicki BA**, Walewski JL, Maliarik MJ, *et al*. ACCESS Research Group. The BTNL2 gene and sarcoidosis susceptibility in African Americans and Whites. *Am J Hum Genet* 2005;**77**:491–9.
5 **Costabel U**, Hunninghake GW. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executice Committee. *Am J Respir Crit Care Med* 1999;**160**:736–55.

Asthma and allergies in Germany

We read the study by Zöllner and colleagues published recently in *Thorax* about the levelling off of asthma and allergies among children in Germany between 1992 and 2001.[1] We have published a study looking at the same issue and using a similar protocol (ISAAC)[2] to assess the symptoms, diagnosis, and severity of asthma and allergies in more than 15 000 children aged 6–7 and 13–14 years between 1995 and 2000 in Münster, Germany.[3] We found a tendency towards an increase in current symptoms of asthma and allergies in both age groups, but more so among girls.[3]

Indices of diagnosis either remained the same or increased in parallel with the increase in symptoms, arguing against a change in diagnostic behaviour as an explanation for our results. Indices of severity also showed a homogenous increase in the 5 year study period, pointing towards an increase in the overall burden of asthma and allergies within the society.[3]

Regrettably, these results, coming from Germany, were not considered in either the discussion of Zöllner's report or in the affirmative title that no increase in asthma and allergies occurred in Germany in the 1990s. Even more regrettable is the fact that when our study was alluded to in the discussion and conclusion of the paper by Zöllner *et al*, it was cited—contrary to our results—as one of the studies showing a decrease or levelling off of asthma and allergies among children.[1]

W Maziak, U Keil
Institute of Epidemiology and Social Medicine, University Clinic of Muenster, Muenster, Germany; maziak@net.sy

References

1 **Zöllner IK**, Weiland SK, Piechotowski I, *et al*. No increase in the prevalence of asthma, allergies, and atopic sensitisation among children in Germany: 1992–2001. *Thorax* 2005;**60**:545–8.
2 **Asher MI**, Keil U, Anderson HR, *et al*. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;**8**:483–91.
3 **Maziak W**, Behrens T, Brasky TM, *et al*. Are asthma and allergies in children and adolescents increasing? Results from ISAAC phase I and phase III surveys in Münster, Germany. *Allergy* 2003;**58**:572–9.

Authors' reply

Unfortunately, the paper by Maziak *et al*[1] published in *Allergy* was listed as reference number 18 instead of number 21 in the reference list of our paper.[2] We apologise for any misunderstanding which may have arisen from this error. A correction is published below.

In the paper by Maziak *et al*[1] the prevalences in 1994/5 and 1999/2000 are compared. As we know from our own studies, trend analyses based on (only) two time points may be difficult and should be interpreted with caution. Indeed, in their investigation Maziak *et al* did not find a significant increase in the lifetime prevalence of asthma and hay fever, except in one subgroup. The effect found in 13–14 year old girls could also be due to a former underdiagnosis of asthma in girls, as discussed in their paper.

Since our results are based on six cross sectional surveys, we consider the title and the conclusion—that we did not see an increase in asthma and allergies from 1992 to 2001—to be appropriate.

I Zöllner
Department of Epidemiology and Health Reporting, Baden-Wuerttemberg State Health Office, Wiederholdstr 15, D-70174 Stuttgart, Germany; Iris.Zoellner@rps.bwl.de

Reference

1 **Maziak W**, Behrens T, Brasky TM, *et al*. Are asthma and allergies in children and adolescents increasing? Results from ISAAC phase I and phase III surveys in Münster, Germany. *Allergy* 2003;**58**:572–9.
2 **Zöllner IK**, Weiland SK, Piechotowski, *et al*. No increase in the prevalence of asthma allergics, and atopic sensitisation among children in Germany: 1992–2001. *Thorax* 2005;**60**:545–8.

CORRECTIONS

doi: 10.1136/thx.2005.029561corr1

In the paper entitled ''No increase in the prevalence of asthma, allergies, and atopic sensitisation among children in Germany: 1992–2001'' by I K Zöllner *et al* which appeared in the July 2005 issue of *Thorax* (2005;**60**:545–8), the authors apologise for a mistake which occurred in the reference list. Reference number 18 should be number 21 and references 19–21 should be listed as 18–20.

doi: 10.1136/thx.2005.040444corr1

The paper entitled ''Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis'' by G J Rodrigo and J A Castro-Rodriguez (10.1136/thx.2005.040444) has been published previously on 17 June 2005 as a *Thorax* Online First article but under the incorrect DOI (10.1136/thx.2005.047803). The publishers apologise for this error. The definitive version of the article can be found at the following citation: *Thorax* 2005;**60**:740–6.

doi: 10.1136/thx.2005.040881corr1

In the paper entitled ''Hormone replacement therapy, body mass index and asthma in perimenopausal women: a cross sectional survey'' by F Gómez Real *et al* published in the January 2006 issue of *Thorax* (2006;**61**:34–40), the fourth author should be **K A Franklin**, not K Franklin.

CORRECTION

doi: 10.1136/thx.2005.040881corr1

In the paper entitled ''Hormone replacement therapy, body mass index and asthma in perimenopausal women: a cross sectional survey'' by F Gómez Real *et al* published in the January 2006 issue of *Thorax* (2006;**61**:34–40), the fourth author should be **K A Franklin**, not K Franklin.