

ORIGINAL ARTICLE

BRONCHIAL HYPERRESPONSIVENESS IN A POPULATION OF NORTH FINLAND WITH NO PREVIOUS DIAGNOSIS OF ASTHMA OR CHRONIC BRONCHITIS ASSESSED WITH HISTAMINE AND METHACHOLINE TESTS

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Received 22 October 2007; Accepted 22 February 2008

ABSTRACT

Objectives. To assess the prevalence of bronchial hyperresponsiveness (BHR) in a population of north Finland among subjects with no previous diagnosis of asthma or chronic bronchitis by using histamine and methacholine challenges. The agreement between the methods was also evaluated.

Study design. An epidemiological study assessing the prevalence of BHR measured with 2 direct dosimetric challenge methods.

Methods. Seventy-nine randomly selected subjects (21–73 years) were studied; 67% had respiratory or allergic symptoms. The baseline spirometry was normal or showed mild obstruction. Bronchial challenges to methacholine and histamine were performed on each subject in a randomized order. Provocative doses inducing the decrease of FEV₁ by 15% and 20% (PD₁₅FEV₁ and PD₂₀FEV₁) and dose response ratios (DDR) were calculated for both tests.

Results. BHR with the methacholine test (PD₂₀FEV₁ ≤ 2.6 mg) was found in 20% and with the histamine test (PD₁₅FEV₁ ≤ 1.6 mg) in 28% of subjects; the agreement was 80% (kappa 0.45; 95% CI 0.23–0.68). In staging the severity of BHR the methods had a good agreement (weighted kappa 0.64; CI 95% 0.46–0.82). Prevalence of BHR fulfilling the criteria of the both methods was 14%.

Conclusions. The findings suggest that the prevalence of BHR in the population of north Finland with no previous diagnosis of asthma or chronic bronchitis is at least 14%, probably around 20%, assessed by histamine and methacholine challenge methods. The methods have a good agreement to be used for classifying the severity of BHR. (*Int J Circumpolar Health* 2008; 67(4):308-317)

Keywords: bronchial hyperreactivity (BHR), histamine, methacholine, respiratory symptoms, non-asthmatics

INTRODUCTION

The population living close to the Arctic Circle live in a cold climate, which may interfere with airway hyperresponsiveness (BHR) by different mechanisms (1). Differences in the prevalence of respiratory symptoms and diseases in these surroundings have been studied (2–4), but no data are available for the prevalence of BHR in subjects drawn from an Arctic population with no previous diagnosis of asthma or chronic bronchitis. The clinical use of BHR tests is most often focused on this type of subject for diagnostic purposes. Therefore, a comparison of commonly used dosimetric methods by using methacholine (5) and histamine (6) in such a population has clinical and methodological importance. The present study is a part of the FinEsS-study, a large epidemiological study of respiratory symptoms of asthma, allergy and chronic obstructive pulmonary disease (COPD) in Finland, Estonia and Sweden which has been underway since 1995.

BHR can be assessed through several different methods (7). Standardization of protocols is necessary to produce comparable results between provocative agents and methods (8–11). For that purpose the European Respiratory Society (ERS) (7) and the American Thoracic Society (ATS) (12) guidelines for BHR testing have made a serious attempt to integrate the variety of tools for measuring BHR. As well, methacholine and histamine challenges have been compared, but mainly among asthmatics (13–16).

The aim of this study was to assess the prevalence of BHR and its severity in a north Finland population with no previous diagnosis of asthma and chronic bronchitis by using 2 in

Finland commonly used dosimetric challenge methods, one with methacholine (5) and the other with histamine (6). Another aim was to evaluate the agreement of these 2 methods for assessment of BHR in such a population. The study population contained subjects mostly with respiratory symptoms or with a family history of asthma, thus having an increased pre-test probability of asthma (12,17–19). To our knowledge, no comparison studies of the dosimetric methacholine and histamine methods in this kind of population have been published.

MATERIAL AND METHODS

Seventy-nine voluntary adults participated in the study. All of them took part in the FinEsS postal questionnaire survey in Finnish Lapland in 1996 (3,20). The subjects were selected from those FinEsS participants who had reported that they did not have asthma or chronic bronchitis. They had answered “NO” to the following questions (2): “Have you now or have you had any of the following diseases: (a) asthma? and/or (c) chronic bronchitis or emphysema?” “Have you been diagnosed as having asthma by a physician?” “Have you been diagnosed as having chronic bronchitis or emphysema by a physician?”

Lung function measurements were performed on 683 randomly selected subjects out of a population sample of 6,633 postal questionnaire responders (20). Bronchial challenge tests with histamine and methacholine were administered to 86 subjects selected using a random procedure; from consecutive subjects recruited to lung function assessment in the FinEsS Lapland study every third subject with no diagnosis of asthma or

chronic bronchitis or emphysema was selected for BHR tests. Seven subjects were excluded from the analyses since their baseline FEV₁ differed $\geq 10\%$ on the BHR testing days.

The age range of subjects (n=79; 37 women) was 21–73 years. Anthropometric data are presented in Table I and baseline spirometric values in Table II. In 8% of the subjects, forced expiratory volume in the first second

(FEV₁) was below the normal range ($\leq 81\%$ of predicted), in 20% the ratio FEV₁ to forced vital capacity (FVC) (FEV₁/FVC) was $\leq 88\%$ of predicted and in 35% any of the following spirometric variables, FEV₁, FEV₁/FVC, peak expiratory flow (PEF) or maximal expiratory flow at 50% of the FVC (MEF₅₀), was decreased according to the predicted values of Viljanen et al. (21).

Table I. Anthropometric data and smoking history of study subjects (n=79).

	Men (n=42)	Women (n=37)	Total (n=79)
Age (yrs)	50.4 \pm 15.7 (21–71)	48.5 \pm 12.7 (22–73)	49.5 \pm 14.3 (21–73)
Height (m)	174.3 \pm 5.59 (1.61–1.86)	162.9 \pm 6.86 (1.46–1.74)	1.69 \pm 8.4 (1.46–1.86)
Weight (kg)	80.0 \pm 12.6 (43–110)	70.6 \pm 13.8 (48–105)	75.6 \pm 14.0 (43–110)
Body mass index (kg/m ²)	26.8 \pm 3.1 (21.3–32.2)	26.4 \pm 5.2 (19.7–42.2)	26.6 \pm 4.2 (19.7–42.2)
Pack years ^a	13.0 \pm 14.4 (0–55.0)	5.4 \pm 8.9 (0–31.8)	9.4 \pm 12.6 (0–55.0)
Smoking ^a (%) non-smokers	38 (n=16)	62 (n=23)	49 (n=39)
ex-smokers	31 (n=13)	8 (n=3)	20 (n=16)
smokers	31 (n=13)	29 (n=11)	30 (n=24)

Values are given as mean \pm SD (range).

^aAccording to Kotaniemi et al. (4).

Table II. Baseline spirometric values. Forced expiratory volumes in the first second (FEV₁), forced vital capacity (FVC), FEV₁/FVC ratio, peak expiratory flow (PEF) and maximal expiratory flow at 50% of FVC (MEF₅₀) are presented.

	Men (n=42)	Women (n=37)	Total (n=79)
FEV ₁ (L)	3.40 \pm 0.68	2.56 \pm 0.48	3.01 \pm 0.73
FEV ₁ of predicted (%) ^a	96.5 (77.5–119.5)	92.8 (77.4–118.5)	94.8 (77.4–119.5)
FVC (L)	4.52 \pm 0.95	3.31 \pm 0.58	3.95 \pm 1.00
FVC of predicted (%) ^a	98.8 (77.3–122.6)	97.4 (78.2–124.0)	98.2 (77.3–124.0)
FEV ₁ /FVC (%)	72.7 \pm 7.4	74.0 \pm 7.1	73.3 \pm 7.2
FEV ₁ /FVC % of predicted (%) ^a	97.5 (68.1–123.9)	94.3 (75.8–116.7)	96.0 (68.1–123.9)
MEF ₅₀ (L/s)	3.47 \pm 1.16	2.74 \pm 0.89	3.13 \pm 1.10
MEF ₅₀ of predicted (%) ^a	92.7 (35.7–159.8)	81.2 (52.4–132.5)	87.3 (35.7–159.9)
PEF (L/s)	8.55 \pm 1.56	6.46 \pm 1.12	7.57 \pm 1.72
PEF of predicted (%) ^a	93.5 (70.5–128.9)	97.2 (72.5–125.1)	95.2 (70.5–128.9)

Values are given as mean \pm SD, and in values of the predicted * [%] as mean and range.

^aLower limits in men: FEV₁ = 81%; FEV₁/FVC = 88%; PEF = 78%; MEF₅₀ = 62%; lower limits in women:

FEV₁ = 80%; FEV₁/FVC = 88%; PEF = 74%; MEF₅₀ = 63%. Predicted values according to Viljanen et al. (1982).

According to questionnaire replies (2), 20% of subjects reported having a family history of asthma, 24% a long-standing cough, 24% wheezing during the last 12 months, 33% allergic rhinitis or conjunctivitis and 67% any respiratory or allergic symptoms. When asked about shortness of breath (SOB) or wheezing or cough, 21% reported having them during exercise, 8% in cold weather and 26% during exercise in cold weather. Forty-nine percent of subjects were non-smokers, 20% ex-smokers and 30% smokers (classification according to Kotaniemi et al.) (4). Approval of the study protocol was obtained from the Länsi-Pohja Central Hospital Ethics Committee, with all patients giving written informed consent.

Lung function and bronchial challenge tests were performed at the Department of Pulmonary Medicine, Länsi-Pohja Central Hospital, Kemi, Finland, from August 1997 to June 1998. Of the subjects, 38 started with the histamine test and 41 with the methacholine test. In the latter group the mean interval between BHR tests was 7.8 (range 6–18) days, and in the former group 7.2 (range 6–10) days. The tests were performed between 8:20 a.m. and 3:30 p.m.

Before the challenge tests, a flow-volume spirometry with a Vmax22 Spirometer (SensorMedics Corporation, Yorba Linda, CA, USA) was performed according to the criteria of ATS 1994 (22). A nose clip was used. Inclusion criteria for BHR tests were as follows: a pre-test value of FEV₁ over 70% of predicted or over 2.0 L or the FEV₁/FVC ratio over 78% of predicted (21), no respiratory infection within 4 weeks prior to the tests, no severe heart diseases (myocar-

dial infarction within 3 months, unstable coronary disease, dysfunction, arrhythmia) and no stroke. Subjects using asthma medication were excluded. Smoking was not allowed within 4 hours before the tests.

The methacholine test followed the protocol by Nieminen (5). An inhalation-synchronized, dosimetric jet nebulizer (Spira Elektro 2, Respiratory Care Centre, Hämeenlinna, Finland) was used. Subjects breathed with a tidal volume of 0.5±0.1 L, and the peak inspiratory flow was 0.5 L/s during the administration of aerosols. The nebulization was set to start 100 mL after the beginning of inspiration and the nebulization time was 0.5 seconds. The nebulization of saline was followed by 5 increasing doses of methacholine chloride at 5-minute intervals (0.018 mg; 0.072 mg; 0.270 mg; 0.810 mg; 2.600 mg as cumulative doses). FEV₁ was measured with the flow-volume spirometer. The end-point of the test was a decline of FEV₁ by 20% or more from the post-saline value or a completed protocol.

The histamine test was performed according to the method by Sovijärvi et al. (6). The same nebulizer was used as in the methacholine test. The nebulization was set to start 100 mL after the beginning of inspiration and the nebulization time was 0.4 seconds. Subjects breathed with tidal volume of 0.5±0.1 L in the limit of peak inspiratory flow of 0.5 L/s during the administration of the histamine diphosphate aerosol. Subjects inhaled buffered histamine diphosphate aerosol according to the protocol with 4 doses (0.025 mg; 0.1 mg; 0.4 mg; 1.6 mg as the maximum non-cumulative dose), at 5-minute intervals. FEV₁ was measured with

the flow-volume spirometer. The end-point of the test was a decline of FEV₁ by 20% or more or a completed protocol.

During both challenge tests all symptoms were recorded and lung sounds were listened to with a stethoscope. After the provocation, 400 µg of salbutamol aerosol was given via a spacer (Volumatic®, Glaxo Wellcome Production, Evreux, France). Post-bronchodilatation FEV₁ was measured after 10 minutes. The provocative doses inducing a decline of FEV₁ of 15% and 20% (PD₁₅FEV₁; PD₂₀FEV₁ values) were calculated for methacholine and histamine tests by interpolation (23). The duration of each challenge test was about 30 minutes.

A majority of the subjects did not achieve a 15% or 20% decline in FEV₁ at the highest dose of histamine or methacholine, respectively. Their PD values were censored, that is, they were extrapolated using the one-point and two-point estimation methods (23–25) if the decline in FEV₁ was between 10% and 15% for histamine or between 13% and 20% for methacholine after the highest dose. For the final analysis, the one-point estimation method was chosen. The number of extrapolated PD values was 11 for the histamine test and 7 for the methacholine test. Regression analysis was applied to describe the possible linear association between the provocative doses (mg) of histamine (PD₁₅FEV₁) and methacholine (PD₂₀FEV₁), including also extrapolated PD values when appropriate.

The classification of BHR severity used in this study, in terms of PD₁₅FEV₁, is based on an earlier clinical validation of the histamine challenge test (6,26): severe ≤0.100 mg; moderate 0.101–0.400 mg; mild 0.401–1.600

mg; no BHR ≥1.601 mg. For the methacholine challenge, the limits were adapted from the distribution of PD₂₀FEV₁ methacholine in a population with asthmatic symptoms (5,27). In terms of PD₂₀FEV₁, the classes used were as follows: severe, ≤0.150 mg; moderate, 0.151–0.600 mg; mild, 0.601–2.600 mg; and no BHR, ≥2.601 mg. The dose response ratio (DRR) to methacholine and histamine was calculated according to the formula $DRR = \text{last FEV}_1 \text{ decline (\%)} / \text{last dose administered (28)}$.

Statistical analyses

The conventional crossover analysis, ANOVA for repeated measures, was used to compare the continuous variables of baseline FEV₁ between challenges. The McNemar test was applied to compare the dichotomous variables between histamine and methacholine tests. A chi-square test was used to assess the effect of demographic categorical variables on the BHR and agreement between challenges. The DRR in histamine and methacholine tests was compared using the method of Altman and Bland (29), and limits of agreement were calculated (30) to indicate the level of agreement. Weighted kappa was applied in calculating the agreement of BHR severity between the 2 challenge methods (31). Agreement (%) and kappa coefficients were also assessed using different PD histamine and methacholine cut-off points with non-censored PD values. Logistic and nominal regressions were used to assess the correlation of answers of the questionnaire and BHR (32). SPSS (version 12.0 for Windows, Chicago, IL, USA) and StatXact 6 (Cytel Software Corp., MA, USA, 2003) were used for statistical analyses.

RESULTS

The proportion of subjects with abnormal BHR (responders) assessed by the histamine test ($PD_{15}FEV_1 \leq 1.6$ mg) was 28% and 20% by the methacholine test ($PD_{20}FEV_1 \leq 2.6$ mg) (Table III). Fourteen percent of the subjects fulfilled the responder criteria with both methods. The results of abnormal BHR agreed in 80% of cases ($\kappa=0.45$; 95% CI 0.23–0.67), indicating moderate agreement. The agreement was good (96%; κ 0.65; CI (0.28–1.02) for moderate or severe BHR.

Classification of BHR according to PD values in the histamine and methacholine tests is presented in Figure 1; good agreement was observed between the tests (weighted kappa 0.64; 95% CI 0.46–0.82). At least moderate BHR was found in 6.3% of subjects ($n=5$) with the histamine challenge and in 5.1% ($n=4$) with the methacholine challenge, while mild BHR appeared in 21.5% ($n=17$) and 15.2% ($n=12$), respectively (Fig. 1).

Table III. Number and rate of appearance (%) of responders and non-responders in the selected population ($n=79$).

Histamine	Methacholine Non-responders ($PD_{20}FEV_1 > 2.6$ mg)	Responders ($PD_{20}FEV_1 \leq 2.6$ mg)	Total
Non-responders ($PD_{15}FEV_1 > 1.6$ mg)	52 65.8%	5 6.3%	57 72.2%
Responders ($PD_{15}FEV_1 \leq 1.6$ mg)	11 13.9%	11 13.9%	22 27.8%
Total	63 79.7%	16 20.3%	79 100.0%

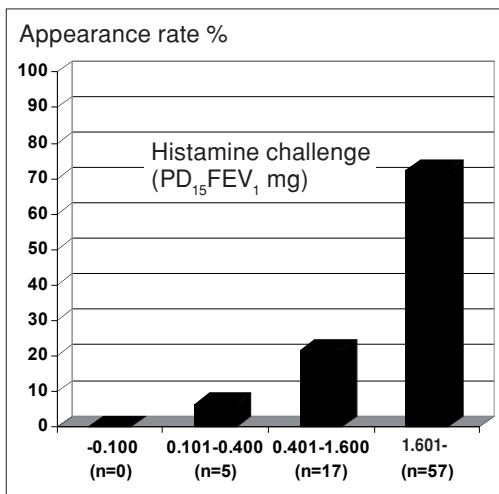


Figure 1A. Frequency distribution of bronchial hyperresponsiveness (BHR) in terms of histamine $PD_{15}FEV_1$; the BHR severity classes used were as follows: severe, ≤ 0.100 mg; moderate, 0.101–0.400 mg; mild, 0.401–1.600 mg; no BHR, ≥ 1.601 mg.

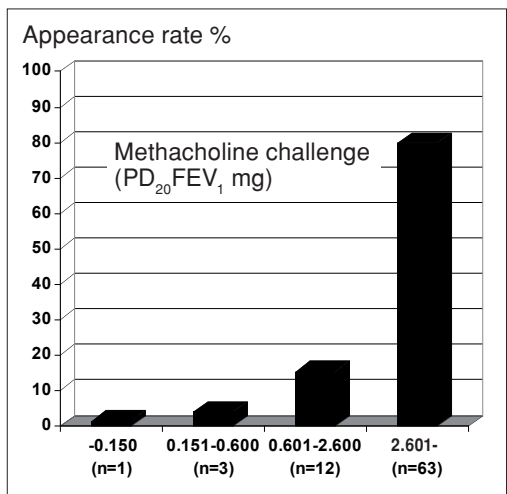


Figure 1B. Frequency distribution of bronchial hyperresponsiveness (BHR) in terms of methacholine $PD_{20}FEV_1$; the BHR severity classes used were as follows: severe, ≤ 0.150 mg; moderate, 0.151–0.600 mg; mild, 0.601–2.600 mg; and no BHR, ≥ 2.601 mg.

A linear association between methacholine $PD_{20}FEV_1$ and histamine $PD_{15}FEV_1$ was estimated, including extrapolated PD values in the analysis. The regression line was $PD_{20}=1.088 + 0.967 \times PD_{15}$ ($R^2=0.17$, $n=19$). No significant difference was found in DRR values obtained from the methacholine (mean -7.97 [%/mg]) and histamine (mean -8.40 [%/mg]) challenges ($p=0.751$).

In subjects with normal lung functions (FEV_1 , FEV_1/FVC , PEF, MEF_{50}) at baseline, agreement of positive BHR in the histamine and methacholine challenges was 86%. Decreased baseline FEV1 (<80% of predicted) did not significantly affect the agreement (67% vs. 81%, $p=0.407$). Smoking history ($p=0.468$) and body mass index (BMI) neither had any significant impact ($p=0.455$).

There was no seasonality in positive findings for BHR. The tests were done during the months of August, May and June, except for 1 subject in early September. There was no significant difference in BHR between subjects tested during birch pollen season (May–June) and during the other months. There was no significant difference in between the 2 methods in measuring the BHR.

Based on the replies of the questionnaire, no significant association was found between the BHR and any of the respiratory symptoms, and the same was found with the smoking history, baseline FEV_1 and the body mass index. Nor were the cold-related symptoms, outdoor working conditions or cross country-skiing activities risk factors for BHR. The risk ratio (RR) for a “yes” answer to the question concerning asthma in parents or siblings was 2.25 (CI 95%: 1.09–4.63), and the corresponding odds ratio (OR) was 3.5 (CI 95%: 1.1–11.0). Female gender ($p=0.049$) and

the family history of asthma were the only significant factors associated to BHR in this study population.

The histamine test induced minor respiratory symptoms, such as loss of voice, throat irritation, cough and dyspnoea in 63% of the subjects ($n=50$). During the methacholine test the incidence of symptoms was slightly lower; 47% of subjects ($n=37$) reported one or more respiratory symptom ($p=0.047$). No difference was present between the tests concerning the appearance of adventitious lung sounds by lung auscultation; 9% of subjects showed either expiratory or inspiratory wheezing sounds during both tests.

DISCUSSION

We found that in a population with no previous diagnosis of asthma or chronic bronchitis the prevalence of non-specific BHR was 20% to 28%. These subjects fulfilled the criteria of abnormally increased bronchial responsiveness either for inhaled histamine or for inhaled methacholine. The prevalence of subjects fulfilling the both BHR criteria was 14%. The results of the European Respiratory Health Survey (ECRHS) population study (33) conducted in 3 parts of Sweden showed that the prevalence of BHR by using a methacholine cut-off level $PD_{20}FEV_1 < 1.6$ mg in general population was 12.7%, reflecting a lower prevalence of BHR than in this study's selected population in north Finland. The difference is probably due to the use of a different methodological threshold of BHR ($PD_{20}FEV_1$ 1.6 mg vs. 2.6 mg).

We found that asthma in parents or siblings significantly increased the risk of BHR in the

present study population who had no previous diagnosis of asthma or chronic bronchitis. Previous studies have shown some evidence of genetic background for BHR; Koh et al. (34) reported about adolescents in asthma remission to have a higher prevalence of BHR in adolescents with a positive family history of BHR, and Holroyd et al. (35) demonstrated a gene-linked expression of BHR. The Italian Po Delta epidemiological study (36) reported a significant father–son correlation of the methacholine dose response curve, but did not find any major gene causing the BHR.

The northern climate (e.g., exposure to the cold) did not have a significant association to BHR. There was no seasonality in positive findings for BHR. The birch pollen season in May and June was not associated to BHR. There wasn't any difference between the methacholine and histamine methods and the used cut-off values ($PD_{15}FEV_1$ or $PD_{20}FEV_1$) in terms of the BHR.

Comparing the appearance of symptoms between our study, in which the diagnosed/self-reported asthma and chronic bronchitis were excluded along with the original randomized population studies of Finnish Lapland and Helsinki (2,20), the prevalence of reported respiratory symptoms as well as the smoking history of the subjects are similar. The prevalence of any respiratory symptoms within a year in population studies from northern Sweden has also been reported fairly high (37). In terms of the validity of the results, the final number of subjects accepted in the study was big enough for the method comparison, and no bias in the selection procedure was found. For purpose of finding determinants for the BHR the number subjects having abnormally increased BHR were too small.

The dosimetric histamine and methacholine methods tested had a good agreement for staging BHR severity in randomly selected subjects without diagnosed asthma or chronic bronchitis when using the previously published classification criteria of BHR severity (6,26–27). The agreement of methacholine and histamine test results was inversely related to the PD values; better agreement was found in more pronounced BHR, i.e. in subjects with clearly sensitive airways to direct stimuli. However, since subjects with diagnosed asthma were excluded, the majority of patients did not show abnormally increased BHR. Anthropometric factors, gender, smoking history and baseline FEV_1 did not diminish the agreement between the challenge tests.

The methods used here have shown good day-to-day repeatability (6,27,38–39) and high intraclass correlation coefficients (0.95 for histamine test and 0.87 for methacholine test), as evaluated recently (40). Although the time interval between the histamine tests was around 7 days, we do not believe that a shorter interval would have improved the agreement significantly due to good day-to-day repeatability of the tests and the use of randomized order of the tests. The subjects did not use any asthma medication; by this fact drug-induced modification of airway responsiveness between repeated tests was avoided.

Intraindividual variation in PD values of histamine versus methacholine could be partly due to differences in the position and form of the dose-response curves of FEV_1 to histamine and methacholine. The curves are typically more sigmoid than linear, which hinders the procurement of repeatable PD results for less hyperreactive subjects (41–43). Another factor involved in the variation may be the validity of

the cut-off levels used in the analysis. We found better agreement between PD₁₅ histamine (<1.6 mg) and PD₁₅ methacholine (<2.6 mg) than with PD₁₅ histamine (<1.6 mg) and PD₂₀ methacholine (<2.6 mg), the kappa values being around 0.64 and 0.45, respectively. This finding supports the view that the PD₂₀ limit, originally applied for the methacholine test (38), could be substituted by PD₁₅, in population studies. The small size and selection of our study population allow no extrapolation of the results on the prevalence or severity of BHR to normal population.

The findings suggest that the prevalence of BHR in subjects with no previous diagnosis of asthma or chronic bronchitis in north Finland is at least 14%, probably around 20%. The agreement of dosimetric methacholine and histamine methods used for assessment of BHR was good for classification of the severity of BHR.

Acknowledgements

This part of the FinEss study was supported by the University of Helsinki (Project TYH1235) and by grants from the Finnish Cultural Foundation, the Finnish Society of Clinical Physiology and the Väinö and Laina Kivi Foundation. We are grateful to the staff Länsi-Pohja Central Hospital for data collection and to Docent Matti Kataja for help with the primary data files. Special thanks to Information Specialist Tuula Boström for assistance at the Jorvi Scientific Research Library and to Biostatistics Professor Seppo Sarna at the Department of Public Health, University of Helsinki, for invaluable discussions and teaching.

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