

Prevalence of asthma, atopy and bronchial hyperresponsiveness and their interrelation in a semi-rural area of Chile

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SUMMARY

OBJECTIVE: To assess the prevalence of asthma symptoms and their association with sensitisation to eight allergens and bronchial hyperresponsiveness (BHR) to methacholine.

SETTING: A random sample of 1232 adults, aged 22 to 28 years, studied in a Chilean semi-rural area.

DESIGN: A cross-sectional design for the purpose of this analysis.

RESULTS: The prevalence of wheeze was 27.4% (95%CI 24.9–29.9) and waking with breathlessness 13.7% (95%CI 11.8–15.6), higher than the results of a multi-centre European study. Only 7.8% (95%CI 6.3–9.3) had a positive BHR (≤ 8 mg/ml) and 26.3% (95%CI 23.8–28.8) were atopic. The Youden index of

asthma symptoms in non-atopic subjects varied from 0.184 to 0.259 when using BHR as gold standard for asthma, and increased from 0.379 to 0.504 among those with positive atopy. Only 4.5% reported asthma, and the Youden index was slightly higher in comparison to the asthma symptom groups.

CONCLUSION: The prevalence of asthma symptoms in young adults was high, but only a small proportion of these were sensitised or had a positive BHR. We believe that aetiological studies of asthma should analyse subjects with asthma symptoms separately from those with positive atopic status or positive BHR.

KEY WORDS: asthma symptoms; atopy; bronchial hyperresponsiveness; epidemiology; adults

ASTHMA PREVALENCE STUDIES based on standardised questionnaires in Latin American adults, including Chileans are scarce. The prevalence of wheeze in Chilean children ranged from 7% to 21% depending on centre and age in the International Study of Asthma and Allergies in Childhood (ISAAC),^{1,2} and another study confirmed this high prevalence.³ Most studies of asthma prevalence around the world have been carried out in children through the ISAAC umbrella.¹ The European Community Respiratory Health Survey (ECRHS) has focused their efforts in Europe, Australia, New Zealand and the United States to study the prevalence and aetiology of asthma.⁴ Large community studies in adults in developing countries using a standardised questionnaire are infrequent.⁵

There is a degree of scepticism about the interpretation of asthma symptoms based on questionnaires, as they are not specific to a condition and participants may not understand the characteristics of the symptoms asked. Agreement between symptoms reported in a questionnaire before and after watching a video on asthma symptoms was only fair or low, as the kappa statistics ranged from nearly 0.00 to 0.66 in a

study based on 99 study centres.⁶ Asthma symptoms and psychological illness are interrelated, and it is possible that respiratory symptoms elicited in questionnaires may correspond partly to somatisation and psychological distress.^{7,8} Culture and fashion also have an influence on the response to the assessment of asthma.⁹

Studies using several criteria of asthma to estimate prevalence, such as symptoms, bronchial-hyperresponsiveness (BHR) to a challenge and skin tests, are rare in developing countries. In these countries, access to good quality medical care is more limited than in industrialised countries. Although not exempt of bias, information on asthma diagnosed by a physician can also be obtained from questionnaires, and such a proxy of prevalence can be used in industrialised countries.⁹ In emerging economies, good quality medical care is mainly restricted to large cities, and many subjects with asthma remain undiagnosed and untreated.

We report on the prevalence of asthma symptoms and diagnosed asthma as reported by the participants in a study of young adults in a semi-rural area of Chile in which we used the standardised ECRHS questionnaire,⁴ and assessed skin reactivity and BHR

to methacholine. We also assessed the interrelation between asthma, sensitisation and positive BHR.

STUDIED POPULATION AND METHODS

This is a follow-up study, but for the purposes of the current analysis, it is cross-sectional. It was carried out from January 2001 until April 2003 in a sample of 1232 subjects randomly selected from a total of 3096 men and women born in the hospital of Limache, Chile, between 1974 and 1978. Thus the participants were aged between 22 and 28 years when assessed. Subjects in the sample who emigrated from Limache, refused to participate, were serving a custodial sentence or had a learning disability were randomly replaced using the original sampling frame, altogether 21.6%. The process of accounting for each randomly selected subject took place during the survey; however, the event causing a subject not to participate may have occurred at any time from birth. Limache has a population of 50 000. Many of its agricultural products are exported and its poverty level corresponds to the median for Chile.¹⁰ We chose this city and rural surroundings for our study.

Participants completed the Spanish version of the ECRHS questionnaire adapted for Chile.⁴ Skin test sensitisation to cat fur, dog hair, cockroach, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, and blends of grass pollens, trees, and weeds and shrubs common in Chile, manufactured by Allergy Therapeutics, was assessed. Fourteen participants who reacted to the control sample were omitted from the analysis. A wheal size reaction of at least 3 mm to any of the eight allergens was considered positive.

We assessed BHR challenge to methacholine using the tidal breathing method.¹¹ Increasing concentrations of 0.5, 1.00, 4.00, 8.00 and 16 mg/ml were used with a Hudson nebuliser at a flow rate of 0.13 l/min over a 2 min period. One second forced expiratory volume (FEV₁) was measured using a Vitalograph 2120 (Vitalograph Ltd, Buckingham, UK) and software Spirotrac IV (Vitalograph Ltd) following the American Thoracic Society norms.¹² A participant with an FEV₁ decrease of 20% in comparison to baseline FEV₁ at any concentration up to 8 mg/ml (PC₂₀) was considered to have a positive BHR. We also considered a cut-off point of 16 mg/ml in the initial analysis. Participants were advised not to smoke or take asthma relievers and preventives before the test for at least 1 h and 6 h, respectively.

Those with an expected FEV₁ below 70% at baseline, and those with a heart condition, epilepsy, current pregnancy or breast-feeding, were excluded from the study (2%) and nine people failed to perform the lung function test. The tests and measurements were carried out in medical facilities. Participants with a fall in FEV₁ of at least 20% were kept until full recovery.

Three university nurses especially trained for the study administered the questionnaire and conducted the tests. The ethics committee of the Faculty of Medicine of the University of Chile approved the study.

The current analysis was based on information collected in a survey. Data for all variables were available for all the participants. We assessed the prevalences and 95% confidence intervals (95%CI) of asthma symptoms, reported asthma ever, mostly physician-diagnosed asthma, and BHR to methacholine. We also looked at the association between asthma symptoms and BHR stratified by atopic status. We assessed sensitivity, specificity, and the Youden index, a summary measure which combines sensitivity and specificity (sensitivity plus specificity minus 1): a value of 1 indicates perfect validity and a value of 0 lack of validity.¹³ We also assessed the positive predictive value (PPV) of each symptom stratified by atopic status using BHR to methacholine as the gold standard, as an objective measure of asthma in epidemiological studies is unavailable.¹⁴ These calculations were made in relation to those without asthma symptoms and a negative sensitisation. We are aware that BHR is not the gold standard for asthma, but BHR is a factor strongly associated with asthma and serves as a convenient marker to ascertain the relative value of each of the respiratory symptoms and reported asthma.

RESULTS

The prevalence of asthma symptoms varied from 10.4% to 35.5% in men and 16.5% to 40.7% in women; significantly more women experienced waking at night with a feeling of chest tightness, breathlessness at rest, waking at night with breathlessness and waking with cough (Table 1). Reported asthma ever in their life showed a prevalence of 3.2% in men and 5.6% in women ($P = 0.043$). The prevalence of positive BHR based on PC₂₀ of ≤ 8 mg/ml was higher in women than men ($P < 0.001$). A change of cut-off point to PC₂₀ of ≤ 16 mg/ml increased the prevalence by 63%. The prevalence of atopy was 26.3% (95%CI 23.8–28.8).

Each of the main asthma symptoms was subdivided into those who had a positive response to at least one of the eight allergens and those who did not. A large percentage of those reporting asthma symptoms did not react to common allergens. For each of the asthma symptoms, the prevalence of BHR was much higher in those who were also atopic (Table 2). The prevalence of BHR was at least as high in those without asthma symptoms with a positive atopic status as in those with an asthma symptom and a negative atopic status. The same results were observed with a combination of asthma symptoms (Table 2). A much higher prevalence of BHR was observed in those with asthma, and the prevalence was even higher in those with a positive skin test. FEV₁ was lower in

Table 1 Prevalence of asthma symptoms in the last 12 months, asthma ever and BHR to methacholine

Symptoms	Total		Men		Women		P value
	n (%)	95%CI	n (%)	95%CI	n (%)	95%CI	
Wheeze	337 (27.4)	24.9–29.9	151 (27.1)	23.4–30.8	186 (27.6)	24.2–31.0	0.83
Waking with a feeling of tightness in the chest	313 (25.4)	23.0–27.8	117 (21.0)	17.6–24.4	196 (29.1)	25.7–32.5	<0.001
Breathlessness at rest	244 (19.8)	17.6–22.0	93 (16.7)	13.6–19.8	151 (22.4)	19.2–25.6	0.012
Breathlessness after exercise	467 (37.9)	35.2–40.6	198 (35.5)	31.5–39.5	269 (39.9)	36.2–43.6	0.111
Waking with breathlessness	169 (13.7)	11.8–15.6	58 (10.4)	7.9–12.9	111 (16.5)	13.7–19.3	0.002
Waking with cough	452 (36.7)	34.0–39.4	178 (31.9)	28.0–35.8	274 (40.7)	37.0–44.4	0.002
Asthma ever	56 (4.5)	3.3–5.7	18 (3.2)	1.7–4.7	38 (5.6)	3.9–7.3	0.043
Positive BHR (≤ 8 mg/ml)	96 (7.8)	6.3–9.3	25 (4.5)	2.8–6.2	71 (10.5)	8.2–12.8	<0.001
Positive BHR (≤ 16 mg/ml)	155 (12.6)	10.7–14.5	46 (8.0)	5.7–10.3	109 (16.2)	13.4–19.0	<0.001
Total	1232		558		674		

BHR = bronchial hyper responsiveness; CI = confidence interval.

terms of expected FEV₁ in those with a positive BHR (98.0%, 95%CI 96.2–99.8) than those with a negative BHR (105.8%, 95%CI 105.2–106.4); the difference was similar in males and females. There were no differences in FEV₁ between the contrasting groups, except in those with wheeze and waking at night with breathlessness ($P < 0.05$) (Table 2).

The sensitivity was slightly higher in those with asthma symptoms and positive sensitisation than those with asthma symptoms only, and the specificity was markedly higher in those with asthma symptoms and sensitisation in comparison to those with asthma

symptoms only (Table 3). This was reflected by a higher Youden index in those with a positive skin test for each symptom. In those who reported asthma, the Youden index was slightly higher than in those with asthma symptoms, regardless of atopic status (Table 3). The PPVs were markedly higher in atopics than in non-atopics, regardless of asthma symptoms. The PPVs were generally low, except for asthma ever.

DISCUSSION

The prevalence of asthma symptoms in this study was higher than reported in Chilean children.^{1–3} A large percentage of those reporting asthma symptoms do not react to common allergens, and a minority had a positive BHR to methacholine. Those who reported asthma (4.5%) had a high percentage of sensitisation and positive BHR. As in other studies,^{14,15} most asthma symptoms and positive BHR were more frequent in females than males.

The strengths of this study are that it was a large community study involving especially trained nurses and using standardised methods. Very few patients, if any, had ever been treated appropriately for asthma, so symptoms were not attenuated. We used BHR as the gold standard for asthma because a precise definition of asthma is unavailable in community studies and BHR status provides an approximation that has been used by others.^{14,17} The number of men in our study is lower than women, as men are usually more reluctant to participate in health studies and they also tended to be working in the fields. We considered whether to adjust BHR for FEV₁ and gender, but there are many difficulties in taking such an approach. When using PC₂₀ to assess BHR status, the majority of the data would be censored because the exact methacholine concentration for a 20% fall can be estimated only in a minority, 7.8% in our study. If we had adjusted BHR as a dichotomous variable we would have converted it into a continuous variable and we would have lost the dichotomous characteristic of BHR that allowed us to estimate validity. If we had

Table 2 Asthma symptoms and asthma ever by atopy* status and BHR to methacholine (≤ 8 mg/ml) and mean FEV₁ in 1232 subjects

	n	Positive BHR		FEV ₁ [†]
		n (%)	95%CI	
Wheeze				
Atopic	114	22 (19.3)	12.1–26.5	103.3
Non-atopic	223	16 (7.2)	3.8–10.6	105.3
Waking with breathlessness				
Atopic	48	9 (18.8)	7.8–29.8	105.3
Non-atopic	121	7 (5.8)	1.6–10.0	104.7
Breathlessness at rest				
Atopic	60	9 (15.0)	6.0–24.0	105.3
Non-atopic	184	11 (6.0)	2.6–9.4	107.7
Asthma				
Atopic	23	11 (47.8)	27.4–68.2	99.56
Non-atopic	33	7 (21.2)	12.5–29.9	104.4
Wheeze and waking with breathlessness				
Atopic	27	7 (25.9)	9.4–42.4	103.0
Non-atopic	58	3 (5.2)	0.5–10.9	107.9
Two of three symptoms above				
Atopic	52	11 (21.2)	10.1–32.3	104.6
Non-atopic	134	7 (5.2)	1.5–8.9	105.9
No asthma symptoms				
Atopic	94	11 (11.7)	5.2–18.2	104.6
Non-atopic	297	8 (2.7)	0.9–4.5	105.0

* A positive skin reaction to at least one allergen.

[†] As percentage of expected FEV₁ for age, sex and height.BHR = bronchial hyperresponsiveness; FEV₁ = one second forced expiratory volume; CI = confidence interval.

Table 3 Sensitivity, specificity, Youden index and PPV of asthma symptoms when BHR to methacholine is used as the gold standard

Symptoms	Sensitivity		Specificity		Youden index		PPV	
	Atopic %	Non-atopic %	Atopic %	Non-atopic %	Atopic %	Non-atopic %	Atopic %	Non-atopic %
Wheeze	73.3	66.7	75.8	58.3	0.491	0.250	19.3	7.2
Waking with feeling of tightness in the chest	69.2	66.7	81.2	57.7	0.504	0.244	21.2	7.0
Breathlessness at rest	52.9	57.9	85.0	62.6	0.379	0.205	15.0	6.0
Breathlessness after exercise	71.4	77.8	73.0	48.1	0.444	0.259	15.7	8.2
Waking with breathlessness	52.9	46.7	88.1	71.7	0.410	0.184	18.8	5.8
Waking with an attack of cough	74.2	71.4	73.2	48.8	0.474	0.202	17.8	6.2
Asthma ever	57.9	46.7	96.0	91.7	0.539	0.384	47.8	21.2

PPV = positive predictive value; BHR = bronchial hyperresponsiveness.

used the BHR 'slope' we would have converted BHR into a continuous variable,¹⁸ and the whole point of our analysis was to use BHR as a dichotomous variable. Although BHR is associated with FEV₁ and gender, we know that asthma is also associated with FEV₁ and gender, and we believe that adjustment for FEV₁ and gender would have overadjusted BHR.

The levels of prevalence of asthma symptoms in our study were above the 75th percentile of participating centres in the first ECRHS,⁴ above the prevalence reported for the US,¹⁹ well above the low prevalences reported for rural Beijing,⁵ and similar to those of Canada.²⁰ The high levels of prevalence in our study are compatible with those in Chilean children.³ The high percentage of asthma symptoms contrasts with the relatively low percentage of BHR in comparison to the ECRHS.²⁰ As we used methacholine concentration and not dose, as in most epidemiological studies, it is difficult to compare BHR in our study and other epidemiological studies. However, an approximate equivalence would indicate that our BHR prevalence might be slightly below the median of the ECRHS centres.¹⁸ The percentage of participants with an allergen wheal of ≥ 3 mm was also lower than in industrialised countries.^{21,22}

The perception of asthma symptoms may be too high in our study. This is suspected due to the low specificity and Youden index to a positive BHR to methacholine in those with asthma symptoms and negative reactivity to skin tests. The specificity and Youden index greatly increased in those with asthma and symptoms of asthma and atopic reaction. Our results are the opposite of those reported by Burney et al., who showed that the Youden index was higher in those with wheeze in the last 12 months than in those reporting an attack of asthma in the last 12 months,¹⁶ but are similar to those reported by Remes et al.¹⁷ The specificity of asthma symptoms in our study is lower than reported by others.^{16,23,24} This may be due to the perception of asthma or because all participants were tested for atopy and BHR to methacholine in our study. The other studies used a two-stage design, and it is possible that the perception of symptoms among

those who were challenged differ from those who were not challenged in the initial survey. Smoking may also partly explain the low Youden index, as smoking is highly prevalent in Chileans, especially in our age group (60% in males and 45% in females).²⁵ We have shown in separate analyses that smoking is highly related to asthma symptoms, but less so to positive BHR. Our results are not explained by asthma treatment, as treatment of the condition was rare, and it is unlikely that air pollution can explain our results because in Limache, unlike Santiago,²⁶ the levels of air pollution should be low, as heavy traffic is low and there are few industrial settings.

Studies of the aetiology of asthma and the assessment of levels of prevalence have been hampered by the lack of consistency between them. The ISAAC Steering Committee recognises that the identification of asthma based on questionnaire remains a contentious issue.¹ Based on our results, we believe that aetiological analyses should be carried out separately for those with asthma symptoms alone and those with positive sensitisation or positive BHR. Likewise, Wieringa et al. showed that increases in the prevalence of asthma are based mostly, but not entirely, on subjective symptom assessments alone.²⁷ We do not dispute that some individuals with symptoms of asthma only might be asthmatics, but the lack of specificity of asthma symptoms alone introduces a high degree of uncertainty into the nature of the condition. Cross-cultural perceptions of asthma symptoms vary using the same standardised asthma questionnaire. This has been partly explored with the large variation in Cohen statistics (kappa) before and after seeing a video.⁶ The variation might correspond to differences in the appreciation of the characteristics of asthma symptoms between and within countries. In that study, Latin American countries were in the middle, with kappa statistics usually below 0.35.

It should be stressed that corroboration or otherwise of our results would be important for developing common strategies in the study of the aetiology of asthma in emerging economy countries.

CONCLUSIONS

This study has shown a high prevalence of asthma symptoms, but a relatively low percentage of those with asthma symptoms have a positive BHR and/or atopy. We suggest that there are large differences in the perception of asthma symptoms between and possibly within countries. Thus aetiological studies should aim to analyse individuals with symptoms of asthma separately from those with a positive atopic status or positive BHR.

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RÉSUMÉ

OBJECTIF : Évaluer la prévalence des symptômes d'asthme et leur association avec une sensibilisation à l'égard de huit allergènes ainsi qu'avec l'hyperréactivité bronchique (HRB) à la méthacholine.

CONTEXTE : Un échantillon aléatoire de 1.232 adultes âgés de 22 à 28 ans, étudiés dans une zone semi-rurale du Chili.

SCHEMA : Pour cette analyse, on a recouru à un schéma transversal.

RÉSULTATS : La prévalence des sifflements a été de 27,4% (IC95% 24,9–29,9) et celle de la dyspnée à l'éveil de 13,7% (IC95% 11,8–15,6), chiffres plus élevés que la médiane d'une étude européenne multicentrique. Un test d'hyperréactivité bronchique positif (≤ 8 mg/ml) n'exis-

taut que chez 7,8% (IC95% 6,3–9,3) et une atopie chez 26,3% (IC95% 23,8–28,8). L'index de Youden concernant les symptômes de l'asthme chez les sujets non atopiques a varié de 0,184 à 0,259 lorsqu'on utilise le HRB comme standard de qualité pour l'asthme, et elle a augmenté de 0,379 à 0,504 parmi ceux ayant des signes positifs d'atopie. L'asthme n'a été signalé que chez 4,5% des sujets, et l'index de Youden a été légèrement supérieur par comparaison avec les groupes avec symptômes d'asthme.

CONCLUSION : La prévalence de symptômes d'asthme est élevée chez les jeunes adultes, mais une faible proportion seulement d'entre eux présente des signes d'atopie ou un test de HRB positif. Nous croyons que les études étiologiques de l'asthme devraient analyser séparément les sujets n'ayant que des symptômes asthmatiques et ceux ayant en outre un statut atopique ou une HRB.

RESUMEN

OBJETIVO : Evaluar la prevalencia de síntomas de asma y su asociación con la sensibilización a ocho alérgenos y la hiperreactividad bronquial (HRB) a la metacolina.

MUESTRA : Una muestra aleatoria de 1232 adultos de 22 a 28 años de un área semi-rural de Chile.

DISEÑO : Estudio de cohorte transversal.

RESULTADOS : La prevalencia de sibilancias fue de 27,4% (95%IC 24,9–29,9) y despertar con falta de aire de 13,7% (95%IC 11,8–15,6), frecuencias que fueron mayores que las del estudio multicéntrico europeo. Solo 7,8% (95%IC 6,3–9,3) presentó HRB (≤ 8 mg/ml) y 26,3% (95%IC 23,8–28,8) fueron atópicos. El índice de Youden para síntomas de asma en no atópicos varió en-

tre 0,184 a 0,259, la que se incrementó entre 0,379 a 0,504 en los atópicos. Solo 4,5% refirieron ser asmáticos y el índice de Youden fue significativamente mayor en comparación con el grupo de sujetos con síntomas aislados.

CONCLUSIÓN : La prevalencia de síntomas de asma fue alta para adultos jóvenes, pero solo una pequeña proporción de ellos estaba sensibilizado o tenía HRB. Nosotros creemos que los estudios etiológicos debieran analizar separadamente a los sujetos con síntomas de asma aislados de los que tienen atopía o HRB.