Untreated asthma, final height and sitting height/leg length ratio in Chile

Roberto J. Rona[a,*], Nigel C. Smeeton[a], Claudio Vargas[b], Patricia Bustos[b], Hugo Amigo[b]

[a]Department of Public Health Sciences, King's College London, 5th Floor Capital House, 42 Weston St, London SE1 3QD, UK
[b]Department of Nutrition, School of Medicine, University of Chile, Independencia 1027, Santiago, Chile

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Summary
Objective: There is uncertainty as to whether asthma has an effect on final height. We investigated using subjective and objective assessments whether untreated asthma is associated with final height, leg length and sitting height to leg length ratio in an area of Chile in which almost no one received asthma treatment.
Methods: We collected data on 1232 males and females aged 22–28 years in a semi-rural area of Chile. Information on asthma was collected using the European Community Respiratory Health Survey (ECRHS) questionnaire. We assessed sensitisation to eight allergens and bronchial hyper-responsiveness (BHR) to methacholine as a dichotomous variable and as a log slope. Information on possible confounders in terms of smoking, birth weight, number of siblings and socio-economic factors such as household possessions, car ownership and education was available.
Results: Regardless of the asthma assessment used, there was no association between asthma symptoms, diagnosis of asthma, atopy, BHR as log slope, binary or categorical and height, leg length or the ratio of sitting height to leg length. The latter was used as a potentially more appropriate measure to assess a detriment of growth.
Conclusion: Asthma as assessed in community studies is unrelated to final height or body proportions.

Introduction

Early studies on the association between asthma and height demonstrated that asthma rarely, if at all, was the cause of severe height deterioration,[1,2] but asthma was associated with some loss of height

*Corresponding author. Tel.: +44 20 7848 6618; fax: +44 20 7848 6605.
E-mail address: Roberto.rona@kcl.ac.uk (R.J. Rona).

in children,[3] especially during adolescence.[4,5] This decrease of height was unrelated to steroidal treatment.[6] However, Balfour-Lynn[7] concluded that asthma had no direct influence on growth in height but was associated with delay in the onset of puberty.

The studies in the 1970s were carried out before standardised questionnaires for assessing asthma became available.[8,9] As there is no gold standard for asthma, standardised tools to assess asthma are of great value in making comparisons between studies. In addition, since 1970 there has been a movement away from associating asthma with stigma and diagnostic practices have changed. As a result there is not a clear equivalence between subjects diagnosed as having asthma and those diagnosed in the 1970s. In more recent studies of height, there have been serious methodological problems in disentangling the effects of asthma from the effects of steroidal treatment. The current understanding is that asthma results in a delayed puberty and that would explain most of the short-lived height deficit.[10] However, the conclusion was based on the early-published work.[4,5,7,11] Most recent studies of height have tried to assess the possible effect of inhaled preventives of asthma such as budesonide and nedocromil.[12,13] Inhaled steroids may have no lasting effect on height and their effect may be restricted to the early period of treatment.[12] The current understanding is that if asthma and inhaled steroids have an effect on height, their effect is small.

We carried out a community study of young adults living in a semi-rural area of Chile. The population is highly interesting because asthma symptoms are prevalent in Chile,[14] but outside the larger cities very few subjects have received appropriate management for their condition. It is a suitable population for assessing whether asthma on its own affects the final height of young adults, as a large percentage would have started their symptoms in childhood. We also assessed the sitting height/leg length ratio as it has been indicated that in nutritional stress leg length is more susceptible to growth interruption than the upper segment.[15–17] We are unaware of any asthma studies that have assessed this ratio as an outcome variable of asthma.

Methods

Subjects

This was a non-concurrent longitudinal study centered on Limache, a semi-rural area of approximately 50,000 inhabitants about 120 km north-west of Santiago in Chile. Between 2001 and 2003, we collected information on 1232 subjects randomly selected using the birth register which included 3096 men and women born in the hospital of Limache between 1974 and 1978. We chose Limache for our study because of the high quality of the hospital birth registry and medical records in the first year of life, as these data were essential for other aims of the study. The low emigration rate in this population ensured that a large proportion of those born in Limache would remain in the area and could be found.

Respiratory symptoms, atopy and pulmonary function assessments

Participants completed the Spanish version of the European Community Respiratory Health Survey (ECRHS) questionnaire adapted to Chile.[9] Skin test sensitisations to cat fur, dog hair, cockroach, *Dermatophagoides Pteronyssinus*, *Alternaria Alternata*, and blends of grass pollens, trees, and weeds and shrubs common in Chile were assessed (samples obtained from Allergy Therapeutics). A wheal size of 3 mm or over was considered positive. Following advice, this was unadjusted for histamine control.[18] We assessed bronchial hyper-responsiveness (BHR) to methacholine using the tidal breathing methodology.[19] 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 period of 2 min. Forced expiratory volume at 1 s (FEV_1) was measured using a Vitalograph 2120 and software Spirotrac IV following the American Thoracic Society norms.[20] An FEV_1 decrease of 20% in comparison to baseline FEV_1 at any concentration up to 16 mg/ml (PC_{20}) was considered to have positive BHR. We also subdivided BHR response into three groups: positive response at a methacholine concentration up to 8 mg/l, positive response to a concentration between 8.1 and 16 mg/l and negative BHR status. Participants were advised not to smoke, or take asthma relievers and preventives before the test for at least 1 and 6 h, respectively. Those with an expected FEV_1 below 70% of the predicted value, and those with a heart condition, epilepsy, current pregnancy or breast-feeding were excluded (2% of the sample). The tests and measurements were carried out in a health setting with ready access to medical facilities. Three university nurses trained for the study administered the questionnaire and carried out the tests. The Ethics Committee of the Faculty of

Medicine of the University of Chile approved the study.

Height was measured as recommended by Habicht and sitting height was measured in all respects as height, but the thighs were in a horizontal plane, the feet firmly on the ground and the two measurements were taken to the nearest 1 mm below.[21] We also collected information on gender, age, current smoking, participant's education, number of household possessions, car ownership and number of brothers and sisters. The household possessions were a gas-fuelled water-heating device known as a calefont, refrigerator, washing machine and microwave oven. Education, household belongings and car ownership were used as indicators of socio-economic level. We also obtained birth weight from the hospital birth registry. Midwives measured weight following norms published by the Ministry of Health. The norms describe the equipment and advise staff to adjust for the weight of any garment put on the scales to protect the baby. The measurement techniques are illustrated, and summarily explained.

Analysis

The current analysis is cross-sectional, except that adjustment for birth weight used information collected at birth. The main aim was assessed by carrying out a series of multiple regression analyses in which the outcome variables were height, leg length or sitting height/leg length analysed separately and the main explanatory variables were asthma symptoms, BHR or atopy. The asthma variables assessed were wheeze in the last 12 months, waking with breathlessness in the last 12 months, the two asthma symptoms together, diagnosed asthma, diagnosed asthma in childhood, atopic status, wheeze and atopic status, BHR status, BHR response divided into three categories and BHR log slope. In all our analyses we adjusted for number of cigarettes smoked per day, gender, birth weight, number of household belongings, car ownership, participant's level of education and number of siblings in the family.

In the ECRHS, a dose–response slope was adopted as a measure of BHR.[21] This method has the advantage of minimising censored information in comparison with the BHR status as defined by a 20% fall in FEV_1. We estimated an equivalent BHR slope by regressing percentage fall in FEV_1 on $\log_{10}$ concentration, referred to as BHR log slope. The BHR log slope satisfied the statistical requirements of normality and homocedasticity. We excluded 55 participants from the analysis related to BHR log slope because their values represented extreme deviations to the left or right of the distribution.

The ratio of sitting height to leg length was used as a measure of proportional contribution to total height, as it might be more relevant in terms of undernutrition. Leg length was calculated as the difference between height and sitting height.

Results

Altogether, 10.5% of the selected sample did not participate in the study because they refused to participate, were serving a custodial sentence or had a learning disability and were randomly replaced using the original sampling frame. Two per cent were excluded from the BHR test. Eight participants failed to perform the lung function test satisfactorily. Data for all variables in the analyses were almost 100% complete for each participant, with the exception related to BHR log slope explained in the analysis section.

Woken by breathlessness ($P = 0.002$), positive BHR ($P < 0.001$), and diagnosed asthma ($P = 0.018$) among the asthma variables were more common in women than men (Table 1). Wheeze and waking with breathlessness in the last 12 months, and atopy were highly prevalent. Only two subjects have ever received steroidal treatment for their asthma in our study, and it was sporadic. The proportion of participants reporting asthma was very low (4.5%). Of those who had been diagnosed with asthma, 79% of males and 71% of females were diagnosed as such in childhood. These percentages exclude three currently asthmatic women who did not give information on asthma in childhood, two males who gave information on childhood asthma but not on current asthma and two males who were in remission. Families tended to have a large number of siblings and current smoking was highly prevalent in comparison to the US and northern Europe (Table 1). Adult height was well below norms for developed countries.

Height was highly correlated with leg length and sitting height (Table 2). Leg length and the sitting height to leg length ratio were highly correlated negatively. The other correlations were of intermediate magnitude.

Height was unrelated to asthma symptoms, diagnosed asthma, diagnosed asthma in childhood, wheeze and atopic status, HBR status and BHR log slope (Table 3). It was also unrelated to BHR status divided into three categories (not shown). Unsurprisingly, given the high correlation between height and leg length, there was also no association

Table 1 Prevalence of asthma variables, mean height, prevalence of smoking and family size by gender.

Variable	Males ($N = 556$)	Females ($N = 676$)
Wheeze in last 12 m (%)	147 (26.4)	189 (28.0)
Woken by breathlessness (%)	58 (10.4)	111 (16.4)
Positive BHR (%)	45 (8.1)	111 (16.4)
BHR (log slope and SD)	−0.318 (1.945)	0.488 (2.209)
Atopic to at least one allergen (%)	159 (28.6)	186 (27.5)
Diagnosed asthma (%)	14 (2.5)	35 (5.2)
Diagnosed asthma in childhood (%)	15 (2.7)	25 (3.7)
Adult height (cm and SD)	168.2 (6.0)	156.3 (5.5)
Leg length (cm and SD)	79.0 (4.1)	71.9 (3.7)
Current smokers (%)	379 (68.2)	344 (50.9)
Number of siblings		
0 or 1 (%)	77 (13.9)	90 (13.4)
2 or 3 (%)	242 (43.6)	281 (41.8)
⩾4 (%)	236 (42.5)	301 (44.8)

Table 2 Pearson's correlations between the anthropometric measurements in the analysis.

	Height	Leg length	Sitting height	Sitting height to leg length ratio
Height	1.00			
Leg length	0.91	1.00		
Sitting height	0.83	0.52	1.00	
Sitting height to leg length ratio	−0.41	−0.75	0.16	1.00

Table 3 Association between asthma in terms of subjective and objective assessments and height, leg length and sitting height to leg length ratio adjusted for gender, number of siblings, number of household belongings, birth weight, smoking, car ownership, and last year of fulltime education.

	Height No = 1190* Coefficient‡(95% CI)	Leg length No = 899* Coefficient‡(95%CI)	Sitting height to leg length ratio No = 899* Coefficient‡(95%CI)
Wheeze†	0.58 (−0.12, 1.28)	0.39 (−0.18, 0.96)	−0.007 (−0.017, 0.003)
Waking with breathlessness†	0.54 (−0.35, 1.44)	0.41 (−0.30, 1.13)	−0.002 (−0.014, 0.010)
Wheeze and waking with breathlessness†	1.07 (−0.15, 2.28)	0.89 (−0.10, 1.88)	−0. 011 (−0.028, 0.006)
Diagnosed asthma	0.44 (−1.13, 2.01)	0.04 (−1.18, 1.26)	0.003 (−0.018, 0.025)
Diagnosed asthma in childhood	−0.26 (−1.99, 1.47)	0.10 (−1.24, 1.44)	0.003 (−0.021, 0.026)
Atopic	−0.35 (−1.04, 0.33)	−0.55 (−1.10, 0.01)	0.007 (−0.003, 0.016)
Wheeze† and atopic	−0.20 (−1.23, 0.84)	−0.57 (−1.41, 0.27)	0.003 (−0.012, 0.017)
Positive BHR	−0.26 (−1.19, 0.68)	−0.43 (−1.20, 0.34)	0.004 (−0.009, 0.017)
BHR (log slope)	0.03 (−0.13, 0.18)	−0.06 (−0.17, 0.06)	0.002 (−0.0005, 0.004)

*Minimum number for some variables had two less subjects, except for BHR (log slope) in which 1122 subjects were included for height and 848 for the other two outcomes.
†In the last 12 months.
‡All coefficients were statistically insignificant.

between leg length and our asthma outcomes. The ratio of sitting height to leg length was also unrelated to the explanatory variables.

Discussion

In a population in which inhalers have been seldom used, we were able to confirm that asthma in the community, regardless of type of assessment, was unrelated to final height, leg length and the sitting height to leg length ratio.

The strengths of this study are that it was community based, asthma was assessed using standardised tools and the assessments were based on subjective and objective measurements, anthropometric measurements were taken using standardised protocols,[22] final height should have been achieved in the total sample at the age of 22–28 years and a large suitable control group was available similar in all characteristics, except their asthma status. As participants were young adults, physical shrinkage, if any, was minimal. As this was a community study, we suspect that most of the asthmatic subjects had either mild or moderate asthma. It is possible that in a study including only patients with severe asthma an effect on height could have been found. However, such a study would have selected patients known to physicians, who might be more likely to receive steroidal treatment thus making it difficult to distinguish the asthma from the steroids effect on height or other anthropometric measurement.

The cross-sectional design of our study should not have affected our results because we were able to measure our outcomes accurately, recall bias would have been unlikely because the fieldworkers and the participants supplying the information on asthma were unaware of the hypothesis being tested and reverse causality, say height causing asthma, would be less likely after adjusting for gender, birth weight, smoking and socio-economic factors. The main weakness of this study was that asthma might have started in adulthood in a proportion of the subjects and this would have increased the risk of misclassification, as asthma onset in adulthood could not have influenced our anthropometric measurement outcomes. As most of the questions on asthma symptoms did not explore early onset, and atopy and BHR were assessed in adulthood, we were uncertain about the percentage of participants whose asthma symptoms, atopy and positive BHR started in childhood. Approximately three quarters of those with diagnosed asthma reported having their asthma since childhood. Unfortunately in semi-rural areas in developing countries, only a small proportion of individuals with asthma symptoms receive a recorded diagnosis of asthma from a doctor. This is the reason why the number of subjects with asthma symptoms in our study was disproportionately high in comparison to subjects with physician-diagnosed asthma. We believe that approximately between 65% and 80% of those with asthma symptoms started their symptoms in childhood. These percentage would broadly correspond to a longitudinal study carried out in a different setting in Australia.[23] Wheeze on its own was probably a less useful variable in our study because many of those with current wheeze might have experienced it only recently in adulthood thus having little chance of influencing height. The suggestion that a large proportion of wheeze started in adulthood in our study is plausible because the prevalence of smoking in young adults in Chile is approximately 50%.[24] Thus a large percentage of individuals with wheeze may be developing chronic bronchitis and some may in the future develop chronic obstructive pulmonary disease rather than asthma. It is difficult to distinguish between the three conditions in young adults. Those with atopy and wheeze are more likely to have started their condition in childhood, but it is possible that some had atopy in childhood and wheeze later in adulthood.[23] We speculate that the percentage who started their symptoms in childhood was higher in those who reported waking with breathlessness compared to those who said they had wheeze.

Undernutrition in infancy was common in Chile in the 1970s. Although at the time infant mortality was decreasing, the levels were 60–40 per 1000 in the period 1974–1978, when our subjects were born.[25] The participants are a random sample of those who survived childhood and their average height in males is 6 cm less than the Spanish population in the 1990s, a population of partially similar genetic endowment to the Chilean population.[26] We would have expected that if asthma has an effect on height it would be more noticeable in a population already nutritionally vulnerable. However, regardless of the outcome measure of asthma chosen or the measure of length included, there was not a single significant association. Gunnell et al.[15] have contrasted results related to height and leg length trying to disentangle the association between anthropometric measurements and specific cause mortality based on their contention that leg length is more related to nutrition than height. However, we have demonstrated in this study that the correlation between height and leg length is so high that a distinction between these two measures in aetiological studies is unfruitful. If anything the ratio of sitting height to leg length might have provided a different perspective from height because it has been proposed that when growth in children is being threatened, the head and the body are protected in detriment to the limbs. However, in our study the asthma variables were unrelated to the sitting height to leg length ratio.

Our study is compatible with the view that asthma may have a small detrimental effect on height in childhood,[27] a greater effect during adolescence through delayed puberty,[4,11] but its effect is transient and will disappear in adulthood. Such a conclusion would have been suspected from the results presented by Agertorf and Pedersen,[12] in a mostly inhaled steroid-treated population. The fact that our population was conversely mostly untreated enhanced the view that asthma itself has a small effect on final height. Hauspie et al.[4] in their mixed-longitudinal analysis were able to demonstrate this pattern of growth in asthmatic children. However, they were unable to demonstrate that the final height of asthmatic subjects would be similar to non-asthmatics as reference values based on children born before their study were used for controls. Thus the lack of a significant difference may not have accounted for the secular trend of height in Belgium,[28] but also their slightly lower height may have been caused by steroidal treatment in their sample. We did not have these two limitations because our non-asthmatic subjects were born at the same time and the asthmatics seldom received steroidal treatment.

Large studies based on military drafts in Sweden and Israel did not reach similar conclusions.[29,30] The Israeli study did not find any difference in height, if anything non-asthmatics were slightly shorter while the Swedish study found that asthmatics were slightly shorter. These studies had the same limitation as our study, i.e. that the onset of asthma may have been recent in a subset of asthmatic subjects. In addition, there is uncertainty about the effect of inhaled steroids on the height of asthmatics.

In conclusion, our study demonstrates that final height is unlikely to be affected by mild or moderate asthma even in a population which may have suffered moderate levels of undernutrition in childhood.

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References

1. Lacey KA, Parkin JM, editors. *Growth retardation in chronic asthma (letter to the editor). Lancet* 1974;**i**:42.
2. Vimpani GV, Vimpani AF, Farquhar JW, editors. *Growth retardation in chronic asthma (letter to the editor). Lancet* 1976;**ii**:422.
3. Murray AB, Fraser BM, Hardwick DF, Pirie GE, editors. *Growth retardation in chronic asthma (letter to the editor). Lancet* 1976;**ii**:197.
4. Hauspie R, Susanne C, Alexander F. Maturational delay and temporal growth retardation in asthmatic boys. *J Allergy Clin Immunol* 1977;**59**:200–6.
5. Hauspie RC, Gyenis G, Alexander F, Simon G, Susanne C, Madách A. Heights and weights of Hungarian and Belgian asthmatic boys. *Hum Biol* 1979;**51**:507–21.
6. Falliers CJ, Tan LS, Szentivanyi J, Jorgensen J, Bukantz SC. Childhood asthma and steroid therapy influences on growth. *Am J Dis Child* 1963;**105**:127–37.
7. Balfour-Lynn L. Growth and childhood asthma. *Arch Dis Child* 1986;**61**:1049–55.
8. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;**8**:483–91.
9. Burney P, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994;**7**:954–60.
10. Doull IJ. The effect of asthma and its treatment on growth. *Arch Dis Child* 2004;**89**:60–3.
11. Martin AJ, Landau LI, Phelan PD. The effect on growth of childhood asthma. *Acta Paediatr Scand* 1981;**70**:683–8.
12. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonine on adult height in children with asthma. *N Engl J Med* 2000;**343**:1064–9.
13. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;**343**:1054–63.
14. ISAAC Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998;**351**:1225–32.
15. Gunnell DJ, Davey Smith G, Frankel SJ, Kemp M, Peters TJ. Socio-economic and dietary influences on leg length and trunk length in childhood: a reanalysis of the Carnegie (Boyd Orr) survey of diet and health in prewar Britain (1937–39). *Paediatr Perinatal Epidemiol* 1998;**12**(Suppl. 1):96–113.
16. Leitch I. Growth and health. *Br J Nut* 1951;**5**:142–51.
17. Mitchell HS. Nutrition in relation to stature. *J Am Diet Assoc* 1962;**40**:521–4.
18. Chinn S, Jarvis D, Luczynska CM, et al. Measuring atopy in a multi-centre epidemiological study. *Eur J Epidemiol* 1996;**12**:155–62.
19. American Thoracic Society. Standardization of spirometry. 1987 update. *Am Rev Respir Dis* 1987;**136**:1285–98.
20. American Thoracic Society. Guidelines for methacholine and exercise challenge testing-1999 (official statement). *Am J Respir Crit Care Med* 2000;**161**:309–29.
21. Chinn S, Burney P, Jarvis D, Luczynska C. Variation in bronchial responsiveness in the European Community Re-

spiratory Health Survey (ECRHS). *Eur Respir J* 1997;**10**:2495–501.

22. Habicht JP. Standardization of quantitative epidemiological methods in the field. *Bol Oficina Sanit Panam* 1974;**76**: 375–84.
23. Xuan W, Marks GB, Toelle BG, Belousova E, Peat JK, Berry G, et al. Risk factors for onset and remission of atopy, wheeze and airway responsiveness. *Thorax* 2002;**57**:104–9.
24. Ministry of Health. [National Survey of Health] 2003 accessed on 21 October 2004, http://www.minsal.cl/ici/destacados/Folleto%20FINAL.pdf
25. INE-CELADE Chile. 1.22-02: Tasa de natalidad, mortalidad, nupcialidad, mortalidad infantil, neonatal y mortinatalidad 1971–2001, http://www.ine.cl/29-producto/anuariovitales2001/122-02.pdf accessed on 2 September 2004.
26. Rebato E. The studies on secular trend in Spain: a review. In: Bodzsár BE, Susanne C, editors. *Secular growth changes in Europe*. Eötvös University Press: Budapest; 1998. p. 297–317.
27. Sommerville SM, Rona RJ. Respiratory conditions, including asthma, and height in primary school. *Ann Hum Biol* 1993;**20**:369–80.
28. Vercauteren M, Hauspie RC, Susanne C. Biometry of Belgian boys and girls: changes since quételet. In: Bodzsár BE, Susanne A, editors. *Secular growth changes in Europe*. Eötvös University Press: Budapest; 1998. p. 47–63.
29. Norjavaara E, Gerhardsson de Verdier M, Lindmark B. Reduced height in Swedish men with asthma at the age of conscription for military service. *J Pediatr* 2000;**137**:25–9.
30. Shojat M, Shohat T, Kedem R, Mimouni M, Danon YL. Childhood asthma and growth outcome. *Arch Dis Child* 1987;**62**:63–5.