Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study

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Summary

Background **Incidence of asthma increases during early adulthood. We aimed to estimate the contributions of sex and early life factors to asthma diagnosed in young adults.**

Methods **1246 healthy newborn babies were enrolled in the Tucson Children's Respiratory Study. Parental characteristics, early-life wheezing phenotypes, airway function, and bronchial hyper-responsiveness to cold dry air and sensitisation to *Alternaria alternata* were determined before age 6 years. Physician-diagnosed asthma, both chronic and newly diagnosed, and airway function were recorded at age 22 years.**

Findings **Of 1246 babies enrolled, 849 had follow-up data at 22 years. Average incidence of asthma at age 16–22 years was 12·6 per thousand person-years. 49 (27%) of all 181 cases of active asthma at 22 years were newly diagnosed, of which 35 (71%) were women. Asthma remittance by 22 years was higher in men than in women (multinomial odds ratio [M-OR] 2·0, 95% CI 1·2–3·2, p=0·008). Age at diagnosis was linearly associated with the ratio of forced expiratory volume at 1 s to forced vital capacity at age 22 years. Factors independently associated with chronic asthma at 22 years included onset at 6 years (7·4, 3·9–14·0) and persistent wheezing (14·0, 6·8–28·0) in early life, sensitisation to *A alternata* (3·6, 2·1–6·4), low airway function at age 6 years (2·1, 1·1–3·9), and bronchial hyper-responsiveness at 6 years (4·5, 1·9–10·0). Bronchial hyper-responsiveness (6·9, 2·3–21·0), low airway function at 6 years (2·8, 1·1–6·9), and late-onset (4·6, 1·7–12·0) and persistent wheezing (4·0, 1·2–14·0) predicted newly diagnosed asthma at age 22 years.**

Interpretation **Asthma with onset in early adulthood has its origins in early childhood.**

Funding **National Heart Lung and Blood Institute.**

Introduction

Several lines of evidence indicate that most people diagnosed with asthma in the first two decades of life had recurrent episodes of wheezing in early childhood,[1] suggesting that the disease process might have started years before diagnosis. Prospective data from the 1958 British cohort[2] indicated an upsurge in incident cases of asthma and wheezing in early adulthood. This second wave of newly diagnosed disease has not been extensively studied but constitutes a high proportion of asthma in young adults and contributes to respiratory morbidity in this age group, especially in women.[3] Whether factors in early life contribute to the risk of this second wave of asthma, as they do for asthma developing during the school years, is unknown. Strachan and co-workers[2] reported that pre-existing allergic rhinitis was an important risk factor for new-onset asthma in early adult life; Guerra and colleagues[4] confirmed this finding and suggested that allergy-related factors might play a part. Whether respiratory events and changes in airway and immune reactivity before age 6 years affect the incidence and prevalence of asthma in early adulthood needs to be assessed.

Children who have lower respiratory tract illnesses in early life are at increased risk of wheezing and asthma.[5,6] In a longitudinal study of unselected children,[1] we showed that those who are wheezing at age 6 years are at increased risk of subsequent asthma up to the age of 16 years, whereas those with transient early wheezing (ie, those who wheeze with lower respiratory tract illnesses but do not report wheezing at age 6 years) are not. What the relation is between these early wheezing phenotypes and new-onset asthma in early adulthood is unknown.

Bronchial hyper-responsiveness, a central characteristic of asthma irrespective of age at onset,[7] is an abnormal bronchoconstrictive response to various stimuli. We previously showed in this same longitudinal cohort that non-asthmatic children with bronchial hyper-responsiveness at age 6 years were at increased risk of asthma by 11 years, but the association was not independent of allergic sensitisation and mild wheezing at 6 years.[8]

We aimed to determine whether potential risk factors for asthma measured during the preschool years predict prevalence, incidence, and remission of physician-diagnosed asthma and asthma-like symptoms in early adulthood.

Methods

Study design

Healthy infants were enrolled at birth in the Tucson Children's Respiratory Study in Tucson, AZ, USA,

	2–16 years	22 years
No asthma	–	–
Inactive	+	–
Newly diagnosed	–	+
Chronic	+	+

Table 1: **Definitions of asthma at 22 years on the basis of physician diagnosed asthma and current symptoms**

between 1980 and 1984.[9] Parents were contacted shortly after their children were born and completed a questionnaire describing their ethnicity, history of physician-diagnosed asthma, years of education, and current smoking habits. Informed consent was obtained from the parents for their children, or by the enrollees themselves if appropriate, and the Institutional Review Board of the University of Arizona approved the study.

Data collection

Parents were instructed at enrolment to bring their child to collaborating paediatricians at the first signs or symptoms of a lower respiratory illness before age 3 years.[10] Wheezing was identified by the physician. Physician-diagnosed asthma and current wheeze in the previous year were assessed from questionnaires completed for the children by their parents or adult carers at ages 2, 3, 6, 8, 11, 13, and 16 years. If a physician diagnosis of asthma with active symptoms was ever reported on a questionnaire, the participant was classified as having asthma by age 16 years.

Skin-prick tests for seven local aeroallergens (Bermuda grass, *Alternaria alternata*, careless weed, house-dust mix, and mesquite, mulberry, and olive-tree pollens) were done at age 6 years as previously described.[11] Tests were read at 20 min and the sum of the largest wheal diameter plus the perpendicular diameter recorded. We classified wheals greater than or equal to 3 mm, after subtracting the negative control, as positive.

	Adult data	No adult data	p value
Male	410/858 (48%)	203/388 (52%)	0·14
Ethnicity*	554/858 (65%)	180/388 (46%)	<0·0001
Early wheezing phenotypes			
Never	355/687 (52%)	70/139 (50%)	
Transient	138/687 (20%)	26/139 (19%)	
Late	108/687 (16%)	16/139 (12%)	
Persistent	86/687 (13%)	27/139 (19%)	0·1†
Any skin test‡	260/667 (39%)	34/95 (36%)	0·6
Alternaria skin test‡	114/666 (17%)	19/95 (20%)	0·5
Parental characteristics			
Mother asthmatic	90/845 (11%)	37/310 (12%)	0·5
Father asthmatic	98/812 (12%)	34/282 (12%)	0·9
Mother smoker	128/858 (15%)	92/385 (24%)	<0·001
Father smoker	235/846 (28%)	150/380 (40%)	<0·001
Mother educated >12 years	640/857 (75%)	207/384 (54%)	<0·001
Father educated >12 years	644/842 (77%)	212/375 (57%)	<0·001

Data are number (%). *Two non-Hispanic white parents. †3 df. ‡At age 6 years.

Table 2: **Characteristics of participants with data at age 22 years (n=858) and those without (n=388)**

Participants did a cold-air challenge at a mean age of 6·1 years (SD 0·5).[8] Children who were actively wheezing, who had used drugs to help their breathing in the past 48 h, who had had a lower respiratory illness during the previous 6 weeks, or who had had upper-respiratory-tract infection during the previous 3 weeks were rescheduled for testing. Those who required continuous treatment or could not be rescheduled were not tested. Baseline maximum expiratory flow at functional residual capacity ($\dot{V}_{max}FRC$) measured in millilitres per second was recorded from the best of three voluntary partial expiratory manoeuvres as previously described.[8] The children then breathed CO_2-enriched cold (–20°C) dry air for 6 min and the mean of the first two values of $\dot{V}_{max}FRC$ measured within 5 min was taken as the postchallenge value. Bronchial responsiveness was calculated as percentage fall in $\dot{V}_{max}FRC$. Cold-air bronchial hyper-responsiveness was defined as a drop greater than 41·1%, the 90th percentile of decline for reference children (those with negative skin-tests, classified as never wheezing, who had not been diagnosed with asthma by age 6 years).[8]

We included previously described early wheezing phenotypes as risk factors:[5] persistent wheezing (wheeze developed during lower respiratory tract infection before age 3 years and lasted to 6 years), late-onset wheezing (no lower respiratory tract infections with wheezing before age 3 years but wheezing by age 6 years), transient early wheezing (wheezing during infection in early life but not wheezing at 6 years), and never wheezing (no lower respiratory tract infections with wheezing and no wheezing at 6 years).

Data for the occurrence of respiratory symptoms during the previous year were obtained from questionnaires completed at the in-depth assessment at age 22 years, and, if no data were available at that age, data from questionnaires at ages 24 years or 18 years were used. Current wheeze was defined as having had at least one self-reported episode during the previous year. Shortness of breath with wheeze was defined as infrequent (one to three), frequent (four or more), or any (infrequent and frequent combined) episodes during the previous year. Current asthma at age 22 years was defined as having ever had a physician diagnosis with active symptoms (attacks, episodes, or wheeze) during the previous year. Current asthma at 22 years was subdivided into four categories (table 1). Those with current asthma were further subdivided into those who had taken any prescription drugs for asthma or wheeze in the past year and those who had not. Current cigarette smoking was determined from questionnaire responses.

	Before (Z scores)			After (Z scores)		Response* (Z scores)	
	n	Mean (SE)	p	Mean (SE)	p	Mean (SE)	p
No asthma	317	0·10 (0·05)	..	0·09 (0·05)	..	−0·08 (0·05)	..
Inactive	44	0·09 (0·15)	0·9	0·16 (0·14)	0·6	−0·07 (0·15)	0·9
Newly diagnosed	24	−0·49 (0·20)	0·005	−0·47 (0·19)	0·009	0·21 (0·30)	0·4†
Chronic	69	−0·37 (0·15)	0·004†	−0·33 (0·15)	0·009†	0·32 (0·15)	0·016†

Each lung function outcome was adjusted for sex in a linear regression and the standardised residuals from the regression (Z scores) were saved and used as the outcome measures for this table. A Z score of 1 represents one standard deviation from the group mean of zero. p values computed with linear regression for each outcome with the no asthma group as the reference group. *Bronchodilator response calculated with FEV_1 (mL) as 200x([after–before]/[after+before]). †Levene's test for equality of variances was significant for this comparison and so we used an unequal variances *t* test to compute the p value with reference to the no asthma group.

Table 3: **Prebronchodilator and postbronchodilator FEV1/FVC ratio and response to bronchodilator for asthma groups at age 22 years**

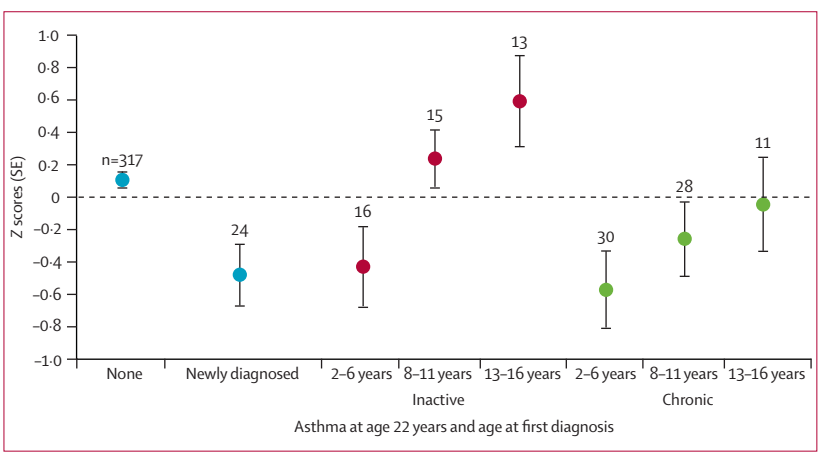

Figure: **FEV_1/FVC ratio and asthma at age 22 years by age at first asthma diagnosis**
FEV_1/FVC ratio was adjusted for sex in a linear regression and the standardised residuals from the regression (Z scores with SE) were saved and used as the outcome measure for this figure (a Z score of 1 represents 1 SD from the group mean of zero). Age at first diagnosis was divided into three groups on the basis of when the diagnosis was first reported. Age at diagnosis was significantly and linearly related to the FEV_1/FVC ratio (p=0·009) in people with inactive and chronic asthma at age 22 years, after adjusting for asthma status and sex.

Allergy skin-prick tests were done at age 22 years (n=462) for 17 local aeroallergens including: house-dust mix, cat hair, cat pelt, dog, cockroach, *Dermatophagoides farinae*, *Penicillium notatum*, *Aspergillus fumigatus*, *Hormodendrum cladosporioides*, *A alternata* (the main asthma-associated allergen in the Tucson area[11]), and the pollens of Bermuda grass, olive tree, careless weed, mesquite tree, mulberry tree, and ragweed. Methods were the same as for testing at age 6 years.

Spirometry was done at age 22 years (n=456) with a portable Schiller Spirovit SP-1 (Schiller AG, Baar, Switzerland).[1] Systems were calibrated with a Jones flow-volume calibrator (Model FVC-3000; Jones Medical Instrumentation Company, Oakbrook, IL, USA). No participants had used a bronchodilator within 6 h of testing. Study nurses recorded height, weight, and age at time of testing. Subsequent to baseline measurements, a fixed dose of two puffs of salbutamol (180 µg) was given from a metred-dose inhaler and aerochamber holding device (Monaghan Medical Corp, Plattsburgh, NY, USA) and postbronchodilator spirometry obtained after 15 min. Spirometry indices included forced vital capacity (FVC, mL) and forced expiratory volume in 1 s (FEV_1, mL). Response to bronchodilator was calculated as 200×([after–before]/[after+before]).

Statistical analysis

Proportions were compared with χ^2 analysis or Fisher's exact test as appropriate; odds ratios (ORs) were calculated with logistic regression. Multinomial logistic regression was used to estimate multinomial odds ratios (M-OR, also known as relative-risk ratios) for categorical outcomes. To allow for all participating patients to be included in the regression models, dummy missing categories were used when predictor variables had missing information. Full regression models included all variables, best-fitting models included those variables with p<0·1 in the full model. Attributable risk was calculated as ([OR–1]÷OR)×proportion of participants who had the risk factor. Significance was defined as two-tailed p-values less than 0·05. Statistical analyses were done with SPSS for Windows (v 15.0) and STATA (v 10.0).

Role of the funding source

The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

1246 children were enrolled. 858 had data at 22 years; mean age at final data collection was 21·7 years (SD 1·2)—735 collected at 22 years, 77 at 18 years, and 46 at 24 years. Of these 858, 835 completed questionnaires at 2 (mean age 1·6 years, SD 0·3), 769 at 3 (2·9, 0·5), 840 at 6 (6·2, 0·9), 727 at 8 (8·6, 0·7), 831 at 11 (10·9, 0·6), 646 at 13 (13·5, 0·6), and 712 at 16 (16·6, 0·6) years. Individuals who had information for asthma and respiratory symptoms at age 22 years were more likely to have non-smoking, non-Hispanic white parents with more years of education than those who did not have information (table 2). There were no differences in the proportion of men, early wheezing phenotypes, atopy or *Alternaria* sensitisation at age 6 years, or parental history of asthma between the two groups.

The number of participants who had complete data for all parts of each question about asthma, wheeze, shortness of breath, and smoking varied; those with incomplete data were excluded from analysis. Of 849 participants with data at age 22 years, 255 (30%) reported ever receiving a physician diagnosis of asthma. 22% (181) reported active asthma, and 19% (163) reported wheeze without a diagnosis of asthma. 163 (19%) of 850 reported shortness of breath with wheeze during the previous year and 61 (7%) had these symptoms frequently. 224 (26%) of 851 participants reported currently smoking cigarettes at 22 years.

Parental asthma and cold-air bronchial hyper-responsiveness at age 6 years, *Alternaria* skin-test reactivity and low V'maxFRC were all strongly associated with an increased risk for asthma and shortness of breath at 22 years (webtable 1). Ethnicity (data not shown) and eczema at age 2 years were unrelated to asthma symptoms at 22 years (webtable 2). People with persistent and late-onset wheeze in early childhood were more likely to have current asthma and shortness of breath with wheeze at age 22 years than were those who had no reporting of wheezing by 6 years (webtable 1). Smoking at 22 years was associated with increased reporting of asthma and wheeze at that age. When multinomial logistic regression was done with current asthma and wheeze only as the outcomes compared with the no asthma and no wheeze group, late and persistent wheezing, parental asthma, cold-air bronchial hyper-responsiveness at age 6 years, sensitisation to *A alternata*, and low V'maxFRC were all positively and independently associated with current asthma and shortness of breath with wheeze at age 22 years (webtable 2).

Of 849 individuals with information about asthma at age 22 years, 496 (58%) completed all seven questionnaires administered between age 2 years and 16 years, 335 (39%) completed four, five, or six questionnaires, and 18 (2%) completed up to three questionnaires. On average, participants completed six questionnaires. By age 16 years, 206 (24%) had reported a diagnosis of asthma at least once. Of 643 individuals who never reported physician diagnosed asthma by age 16 years, 412 (64%) had at least one report of wheezing at age 2–16 years.

49 patients had newly diagnosed asthma at age 22 years, average yearly incidence was 12·6 per thousand person-years. 74 had inactive asthma, 132 chronic asthma, and 594 no asthma. When compared with no asthma, newly diagnosed and chronic asthma were strongly associated with current shortness of breath and cough (webtable 3). All three asthma categories were associated with concurrent skin-test positivity.

To assess asthma severity, newly diagnosed and chronic asthma were further divided according to whether any prescription drugs were used to treat asthma or wheezing during the previous year (webtable 4). For newly diagnosed asthma, there was no difference in shortness of breath with wheezing, cough, or skin-test positivity between those using drugs and those who did not. By contrast, participants with chronic asthma who were using drugs were more likely to have shortness of breath with wheeze than those who did not (53 [76%] of 70 *vs* 25 [40%] of 62, respectively, p<0·0001). Prevalence of cough and skin test positivity was the same in both groups.

Similar values for prebronchodilator and post-bronchodilator ratio of FEV_1 to FVC and response to bronchodilator were recorded for the inactive asthma and no asthma groups at age 22 years (table 3). In contrast, the prebronchodilator and postbronchodilator FEV_1/FVC ratio was significantly lower in both newly diagnosed and chronic asthma than in no asthma. The response to bronchodilator was significantly higher in chronic asthma, but not in newly diagnosed asthma, than in no asthma. When current asthma was further subdivided by prescription drugs used for asthma during the previous year, different patterns were recorded for the newly diagnosed and chronic groups (webtable 5). Whereas patients with newly diagnosed asthma have a low FEV_1/FVC ratio irrespective of drug use, only patients with chronic asthma using drug treatment had a low FEV_1/FVC ratio compared with those not on drugs.

Participants with asthma at age 22 years were subdivided into three categories prospectively defined on the basis of age at diagnosis: 2–6 years, 8–11 years, and 13–16 years. There was no significant difference at age at

	No asthma	Inactive	p	Newly diagnosed	p	Chronic	p
Sex							
Male (404)	271	46 (15%)	..	14 (5%)	..	73 (21%)	..
Female (445)	323	28 (8%)	0·008	35 (10%)	0·023	59 (15%)	0·045
Parental asthma							
Neither (622)	468	51 (10%)	..	30 (6%)	..	73 (14%)	..
Either (179)	93	20 (18%)	0·018	17 (16%)	0·001	49 (35%)	<0·0001
Parental smoking							
No (565)	395	54 (12%)	..	31 (7%)	..	85 (18%)	..
Yes (273)	194	18 (9%)	0·18	17 (8%)	0·7	44 (19%)	0·8
Physician diagnosed eczema by 2 years							
No (696)	502	51 (9%)	..	43 (8%)	..	100 (17%)	..
Yes (79)	40	16 (29%)	<0·0001	4 (9%)	0·8	19 (32%)	0·004
Early wheezing phenotype							
Never (354)	297	19 (6%)	..	13 (4%)	..	25 (8%)	..
Transient (135)	99	11 (10%)	0·16	10 (9%)	0·055	15 (13%)	0·090
Late onset (107)	47	18 (28%)	<0·0001	8 (15%)	0·004	34 (42%)	<0·0001
Persistent (86)	27	17 (39%)	<0·0001	4 (13%)	0·044	38 (59%)	<0·0001
***Alternaria* skin-test positive at 6 years**							
No (546)	399	47 (11%)	..	31 (7%)	..	69 (15%)	..
Yes (113)	51	15 (23%)	0·006	3 (6%)	0·7	44 (46%)	<0·0001
CA-BHR at 6 years							
No (330)	262	25 (9%)	..	11 (4%)	..	32 (11%)	..
Yes (58)	29	7 (19%)	0·048	7 (19%)	0·001	15 (34%)	<0·0001
V'maxFRC quartiles at 6 years							
High (132)	106	10 (9%)	..	7 (6%)	..	9 (8%)	..
Med–high (132)	91	13 (13%)	0·4	3 (3%)	0·3	25 (22%)	0·005
Med–low (132)	91	16 (15%)	0·15	6 (6%)	0·9	19 (17%)	0·036
Low (132)	75	13 (15%)	0·17	10 (12%)	0·17	34 (31%)	<0·0001
Smoking at 22 years							
No (625)	439	62 (12%)	..	30 (6%)	..	94 (18%)	..
Yes (224)	155	12 (7%)	0·068	19 (11%)	0·058	38 (20%)	0·5

Data are number (%). Percentages for each asthma group were calculated with respect to the no asthma group after excluding the other two asthma groups. Significance (p values) for the association between each individual risk factor and the asthma groups were estimated using multinomial logistic regression with respect to the no asthma group. CA-BHR=bronchial hyper-responsiveness to cold air challenge at age 6 years.

Table 4: **Proportion of participants with early-life risk factors and current smoking by asthma group at age 22 years**

See Online for webtables 1–5

	Inactive		Newly diagnosed		Chronic	
	M-OR† (95% CI)	p	M-OR (95% CI)	p	M-OR (95% CI)	p
Parental asthma	2·0 (1·1–3·6)	0·030	2·7 (1·4–5·2)	0·004	3·2 (1·9–5·4)	<0·0001
Physician diagnosed eczema by 2 years	3·8 (1·9–7·8)	0·0002	1·1 (0·4–3·3)	0·9	2·0 (1·0–4·1)	0·047
Early wheezing phenotype						
Transient early	1·6 (0·7–3·5)	0·3	2·0 (0·8–4·8)	0·14	1·4 (0·7–2·9)	0·3
Late onset	5·4 (2·5–11)	<0·0001	4·6 (1·7–12)	0·003	7·4 (3·9–14·0)	<0·0001
Persistent	8·9 (4·0–20)	<0·0001	4·0 (1·2–14)	0·027	14·0 (6·8–28)	<0·0001
Alternaria skin-test positive at 6 years	2·0 (1·0–4·0)	0·067	0·6 (0·2–2·2)	0·4	3·6 (2·1–6·4)	<0·0001
CA-BHR at 6 years	2·4 (0·9–6·5)	0·083	6·9 (2·3–21·0)	0·0006	4·5 (1·9–10·0)	0·0006
Lowest V′maxFRC quartile at 6 years	1·1 (0·5–2·4)	0·8	2·8 (1·1–6·9)	0·029	2·1 (1·1–3·9)	0·021

Multinomial odds ratio (M-OR) estimated with multinomial logistic regression with all risk factors listed in the table included in the model with the no asthma group as the reference group. Models were additionally adjusted for ethnicity, sex, and current smoking at age 22 years. CA-BHR=bronchial hyperresponsiveness to cold air challenge at age 6 years. V′maxFRC=lowest quartile compared to upper three quartiles combined.

Table 5: **Multinomial odds ratio for asthma groups at age 22 years by different risk factors in early life**

first diagnosis between inactive and chronic asthma (32% *vs* 45% diagnosed at 2–6 years, 41% *vs* 35% diagnosed at 8–11 years, and 27% *vs* 21% diagnosed 13–16 years, respectively, p=0·2). However, there was a significant effect of age at diagnosis on the FEV_1/FVC ratio at age 22 years (figure). For both chronic and inactive asthma, age at diagnosis was significantly and linearly related to the FEV_1/FVC ratio (p=0·009) after adjusting for asthma status and sex.

Univariate and multinomial analyses for the association between early life risk factors and asthma at age 22 years are shown in tables 4 and 5, respectively. Newly diagnosed asthma was twice as likely in women as in men. Parental asthma and both late onset and persistent wheezing during the first 6 years of life were associated with inactive, newly diagnosed, and chronic asthma (tables 4 and 5 and the webfigure). By contrast, eczema by age 2 years and *A alternata* sensitisation at age 6 years were associated with inactive and chronic asthma but not with newly diagnosed asthma. Low V′maxFRC at age 6 years was associated with newly diagnosed and chronic asthma but not inactive asthma at age 22 years. There was a strong positive association between cold-air bronchial hyper-responsiveness and both newly diagnosed asthma (M-OR 6·9, 95% CI 2·3–21·0) and chronic asthma (4·5, 1·9–10·0). The population attributable risks of cold-air bronchial hyper-responsiveness for newly diagnosed and chronic asthma were 33% and 26%, respectively. Inactive asthma at age 22 years was not associated with cold-air bronchial hyper-responsiveness at age 6 years.

See Online for webfigure

Discussion

In over 70% of people with current asthma and 63% of those with newly diagnosed asthma at age 22 years, episodes of wheezing had happened in the first 3 years of life or were reported by parents at age 6 years (table 4). Cold-air bronchial hyper-responsiveness (but not sensitisation to *Alternaria*) at age 6 years, late-onset and persistent wheezing by 6 years, and female sex, were independent predictors of incident physician-diagnosed asthma at 22 years. Moreover, cold-air bronchial hyper-responsiveness and sensitisation to *Alternaria* at age 6 years, together with persistent and late-onset wheezing by that age, were independent predictors of chronic asthma. Early sensitisation to other allergens prevalent in other locations might show similar strong associations with adult asthma as seen with *Alternaria* in our study area. Male sex was a significant predictor of asthma remission. Our findings support our previous proposition that most forms of asthma have their origins in early life,[12] but we now extend that proposition to asthma diagnosed in early adult life.

Few studies have prospectively assessed the early-life risk factors for prevalent, incident, and remitted asthma in early adult life.[3] In the most comprehensive study, Strachan and co-workers[13] assessed the 1958 British cohort and reported a yearly incidence of asthma of 11·1 per 1000 person-years) among people age 17–33 years, which is much the same as the incidence of 12·6 per 1000 person-years between 16 and 22 years in our study. In Sweden, Larsson and colleagues[14] reported an incidence of 11·1 per 1000 person-years at age 16–19 years. In neither of the previous two studies, however, was prospectively obtained information from the first years of life available.

Both chronic and newly diagnosed asthma at age 22 were much more common (4·5 and 6·9 times more likely, respectively) in those with cold-air bronchial hyper-responsiveness at age 6 years than in those without (table 4), and this association was independent of current asthma symptoms by that age. These results suggest that asymptomatic changes in the regulation of airway tone are already present in preschool years and strongly predict the likelihood of having asthma in early adult life. Although we had previously shown that cold-air bronchial hyper-responsiveness at age 6 years is associated with allergic sensitisation at that age,[8] the association between this risk factor and incident physician-diagnosed asthma

at 22 years was independent of sensitisation to *Alternaria*.[11] However, people with newly diagnosed asthma were more likely to be sensitised to aeroallergens at 22 years than those with no asthma. These results strongly suggest that, much like chronic asthma, newly diagnosed asthma at 22 years is associated with the clinical expression of cold-air bronchial hyper-responsiveness already present in early childhood. However, and contrary to chronic asthma, newly diagnosed asthma is associated with late-onset sensitisation and is unrelated to early sensitisation to local aeroallergens.

Persistent wheezing in early childhood was a strong predictor of both chronic and incident asthma at 22 years. We had previously shown that transient early wheezing was unrelated to the risk of asthma symptoms at age 8–16 years, whereas persistent and late-onset wheezing were consistently associated with these symptoms in that age group.[1] We interpret these findings as indicating that children classified with persistent or late-onset wheezing in early life are predisposed to chronic symptoms that will either last throughout childhood or reappear more intensely in early adult life, especially in women.

Women were twice as likely as men to have asthma diagnosed at age 16–22 years (table 4). Moreover, more than 70% of participants with newly diagnosed asthma at age 22 were women. Conversely, men were more likely than women to have inactive asthma at age 22 years (table 4), suggesting higher rates of asthma remission in men age 16–22 years. These findings confirm and extend those recorded in several other longitudinal studies in this age group, which have suggested a gradual change in the prevalence of asthma between male and female individuals between the pubertal years and early adult life.[15–18]

As expected, mean FEV_1/FVC ratio was significantly lower at age 22 years in participants with both newly diagnosed and chronic asthma than in those with inactive asthma and no asthma (table 3). However, a positive response to bronchodilators was present only in people with chronic asthma, suggesting irreversible deficits in lung function in newly diagnosed asthma. Of particular interest was the fact that, in both inactive and chronic asthma, FEV_1/FVC ratio at age 22 years was strongly and linearly correlated with age at diagnosis assessed prospectively (figure). These findings support the notion that changes in airway structure and function are more likely when initiation of the airway inflammatory processes associated with childhood asthma happens in preschool years. However, chronic airway hyper-responsiveness in school years, even in the absence of symptoms, is associated with deficits in the normal increases in lung function that accompany child growth,[19] which might predispose to asthma in early adult life.

Active smoking was a strong predictor of asthma, current wheezing, and current shortness of breath with wheeze in early adult life. These findings are in agreement with those of other studies in this age group[20] and support the contention that deleterious effects on lung health can be detected soon after starting to smoke.

Our study has limitations that need to be taken into account when interpreting our findings. As with most long-term cohort studies, by age 22 we had lost track of over a third of participants and those remaining were better educated, less likely to belong to ethnic minority groups, and less exposed to parental smoking than those who withdrew from the study (table 2). Furthermore, almost half the participants at age 22 years had moved out of Tucson and could not be tested for lung function or allergy. Because of concerns about the ethics of doing airway challenges in very young children, we did not test for cold-air bronchial hyper-responsiveness at 6 years in children with current wheezing or those requiring active asthma treatment at that age; our results might, therefore, underestimate the association between this risk factor and chronic and incident asthma in early adult life. Finally, we relied on physician diagnosis reported by parental questionnaire to assess the presence of asthma at all ages. This epidemiological approach has been widely used to assess asthma incidence and prevalence both in longitudinal studies[21] and in national asthma surveys.[22,23] Although subject to diagnostic drift and bias, physician-diagnosed asthma is a strong indicator of need for health care use in people with asthma-like symptoms and thus allows differentiation of those with mild or misinterpreted wheezing episodes from those with symptoms needing physician attention. Indeed, almost two-thirds of all children without a diagnosis of asthma during follow-up had at least one report of wheezing at age 2–16 years. Our study should thus be interpreted as assessing risk factors for asthma symptoms significant enough to induce a diagnosis of asthma by a physician. Others have proposed use of objective markers, such as concomitant increased responses to salbutamol or methacholine to assess the presence of asthma in symptomatic patients.[24] We have previously shown, however, that each of these objective markers identifies different asthma phenotypes,[25] and thus their isolated use is likely to introduce analytical biases towards different forms of asthma that coexist during childhood and adolescence.

Our study confirms and extends to the first years of life the findings of two cohorts from New Zealand[26] and Australia,[27] which showed strong correlations between asthma symptoms, lung function, and bronchial responsiveness assessed during the school years and chronic asthma up to the fifth decade of life. We conclude that asthma that apparently develops in early adult life affects mainly women and is commonly the clinical expression of latent changes of airway responses that are present in the preschool years. From the point of view of public health, primary prevention of this form of asthma will only be possible when the genetic and environmental factors that determine these changes have been identified and their effects blocked or reversed.

Contributors

FDM designed the current study; DAS analysed the data under the direction of FDM; all authors interpreted the data; FDM and DAS wrote the report with input from the other authors.

Conflict of interest statement

We declare that we have no conflict of interest.

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