Respiratory Medicine 224 (2024) 107581

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Original Research

No remission in 60% of those with childhood-onset asthma - A population-based cohort followed from 8 to 28 years of age

Linnéa Almqvist *, Martin Andersson, Helena Backman, Eva Rönmark, Linnéa Hedman

Department of Public Health and Clinical Medicine, Section of Sustainable Health, The OLIN Unit, Umeå University, Umeå, Sweden

ARTICLE INFO

Keywords:
Asthma
Remission
Relapse
Epidemiology
Longitudinal
Risk factors

ABSTRACT

Background: Although remission occur, childhood-onset asthma may persist until adulthood. Since few longitudinal population-based studies have followed a cohort from childhood until adulthood, the knowledge on predictors of persistence of asthma is sparse.
Aim: To estimate persistence of asthma from 8 to 28 years and its associated factors.
Methods: Within the OLIN (Obstructive Lung Disease in Northern Sweden) studies, a cohort was recruited in 1996 (age 8y, n = 3430) and followed annually with questionnaires about asthma and risk factors until 19y. Clinical examinations included skin prick tests (at 8, 12 and 19y) and lung function tests (17 and 19y) whereof a subsample performed bronchial hyperreactivity test. We identified n = 248 with asthma at 8y whereof 170 (69%) participated in a follow-up at 28y (73% of possible to invite).
Results: Of the 170 participants at 28y, 105 (61.8%) had persistent asthma (women: 49/76, 64.5%; men: 56/94, 59.6%, p = 0.513). Factors collected at recruitment: allergic sensitization (OR7.8, 95%CI 3.0–20.2), severe respiratory infection (OR2.6, 95%CI 1.1–6.3) and higher asthma severity score (OR1.6, 95%CI 1.1–2.4) were associated with asthma at 28y after adjustment for sex, family history of asthma, breastfeeding <3 months and eczema. Replacing allergic sensitization with rhinoconjunctivitis in the model yielded OR3.4 (95%CI 1.5–8.0). Bronchial hyperreactivity at age 17y associated with asthma at 28y (OR9.0, 95%CI 1.7–47.0).
Conclusions: Among children with asthma onset by 8y, 62% still had asthma at age 28 years. Persistent asthma was associated with allergic sensitization, rhinoconjunctivitis, severe respiratory infection, a more severe asthma and bronchial hyperreactivity.

1. Introduction

Although asthma usually is considered a chronic disease, remission can occur. Remission of asthma with onset in adulthood is low [1], whereas asthma with onset in childhood is more likely to remit [2,3]. The reported asthma remission rates from childhood to young adulthood vary greatly, from 16 to 60% [4]. Explanations for the large variation may be differences in the ages of the study populations, the length of the observation period, and the definition of remission, as there is no gold standard. However, what is perceived as remission could also be a temporary period without symptoms [5] while the underlying pathology still remains [6]. Thus, with a longer follow-up those with periodic asthma symptoms may relapse [1,7].

Although asthma can occur without eczema, rhinitis or allergic sensitization, these atopic conditions often exist concomitantly, referred to as allergic multimorbidity. It has been shown that allergic multimorbidity in childhood is associated with persistence as well as relapse of asthma in adulthood [2,8,9]. Furthermore, in a long-term follow-up of a birth cohort, among those with asthma in remission airway obstruction in late adolescence was associated with relapse of asthma in young adulthood [7].

There are indeed early life events associated with childhood onset of asthma, for instance low birthweight, no or short time of breastfeeding, house dampness, smoking during pregnancy, exposure to parental smoking and severe respiratory infections [10–13]. Many of these factors have also been associated with the persistence of asthma until adulthood [6]. Since there are only a few prospective studies following a cohort from childhood until adulthood, the knowledge on persistence, remission and relapse of asthma and its associated factors are sparse.

The Obstructive Lung Disease in Northern Sweden (OLIN) studies have previously shown that the remission of asthma was 21% from 8 to 19 years of age and that having a less severe asthma and a negative skin prick test (SPT) was associated with remission in late adolescence [14].

* Corresponding author. The OLIN studies Norrbotten County Council, SE-971 89, Luleå, Sweden.
E-mail address: linnea.qvist@umu.se (L. Almqvist).

https://doi.org/10.1016/j.rmed.2024.107581
Received 17 November 2023; Received in revised form 14 February 2024; Accepted 25 February 2024
Available online 28 February 2024

Abbreviations

BHR	bronchial hyperreactivity
BMI	body mass index
CI	confidence interval
FEV_1	forced expiratory volume in 1 s
FVC	forced vital capacity
GLI	global lung function initiative
ISAAC	international study of asthma and allergies in childhood
LLN	lower limit of normal
OLIN	the obstructive lung disease in northern Sweden
OR	odds ratio
SPT	skin prick test

The aim of the current study was to estimate the persistence of asthma in an even longer perspective, up to 28 years of age, and its associated factors. We hypothesized that lasting remission of childhood asthma is not as common as previously assumed.

2. Material and method

2.1. Study design and sample

The OLIN studies recruited its first pediatric cohort in 1996; the study design and recruitment procedure has been described elsewhere [15,16]. In summary, the parents to all children attending first and second grade, aged 7–8 years (median age 8) from three municipalities in northern Sweden (Kiruna, Luleå and Piteå) were invited to complete a questionnaire about asthma, rhinitis and eczema. Of the invited, 97%, n = 3430, participated, of which 248 children with current asthma were identified either by self-reported physician-diagnosed asthma or diagnosed by a pediatrician in a validation study [14,17]. There were annual follow-ups by questionnaire until the age of 19 years and at age 28 years a follow-up survey by postal questionnaire was performed (Fig. 1). Of the n = 3245 still alive and possible to trace, n = 2291 participated, 71% of invited and 67% of the original cohort [18,19]. Of the 248 children with asthma at age 8 years, 234 were possible to invite and 170 participated and constitute our study sample.

The Regional Ethical Review Board in Umeå, Sweden, has approved the study (96–032; 99–408; 2014/365–31; 2015-379-32 M). At recruitment, the parents provided written consent, and as adults the participants provided consent themselves.

2.2. Questionnaire

The same questionnaire was used for all annual surveys between 8 and 19 years of age [14,20], including the International Study of Asthma and Allergies in Childhood (ISAAC) core questions about asthma, rhinitis and eczema [21]. Questions about physician-diagnosis and use of asthma medication, as well as potential risk factors such as parental smoking, family history of allergic diseases, environmental exposures, respiratory infections, birth weight and breastfeeding were added [20]. The question about physician diagnosis of asthma has been clinically validated showing a specificity of 99% and sensitivity 70% [17]. In 2015, at age 28 years, the OLIN questionnaire for adults was used [22], which included questions about physician-diagnosis of asthma, respiratory symptoms and use of asthma medication last 12 months [19].

2.3. Clinical examinations

2.3.1. Skin prick tests

The children in two of the municipalities were invited to skin prick tests (SPT) at age 8y, 12y and 19y. A standard panel of ten airborne allergens were used; birch, timothy, mugwort, cat, dog, horse, two mites (*Dermatophagoides Farinae* and *D. Pteronyssinus*) and two molds (*Cladosporium* and *Alternaria*) (Soluprick, ALK, Hørsholm, Denmark). A positive SPT reaction was defined as a mean wheal ≥3 mm after 15 min to any of the tested allergens.

2.3.2. Height and weight

Height and weight was measured prior to the lung function test. In 13 individuals, spirometry was not performed and for these, self-reported height and weight from the questionnaire was used for calculation of body mass index (BMI).

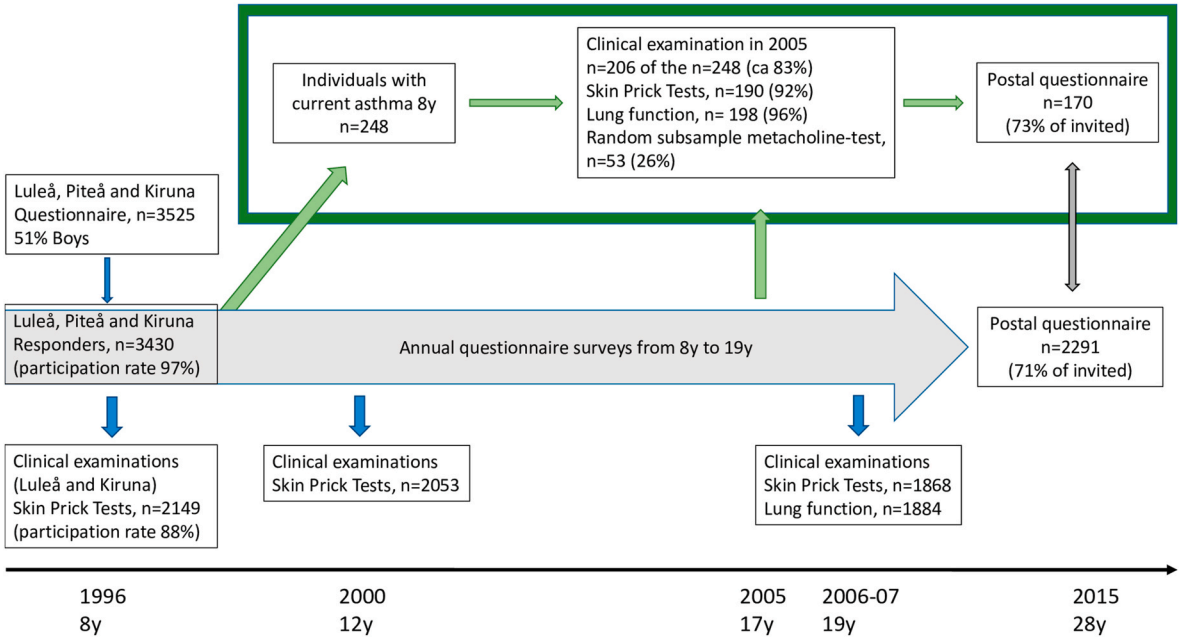

Fig. 1. Flow chart of the first OLIN pediatric cohort, green arrows/box illustrates the current study population. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2.3.3. Spirometry

Lung function tests at age 19 years were performed according to the previously accepted international guidelines [23] using a Spirare flow-volume spirometer (Diagnostica, Oslo, Norway). If a spirometry was not performed at 19y, the results from a previous lung function test at age 17 years were used (n = 50) (using a dry volume spirometer Vicatest 5, Mijnhardt, Odijk, the Netherlands). The Global Lung function Initiative (GLI) reference values for spirometry were used [24] for calculation of % predicted (pp) for Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 s (FEV_1) and for FEV_1/FVC < LLN (Lower Limit of Normal).

2.3.4. Bronchial hyperreactivity

Bronchial hyperreactivity (BHR) was measured by a Metacholine provocation test performed in a randomly selected subsample of 53 individuals at age 17 years [14]. BHR was defined by a 20% decrease in FEV_1 in accordance with a method described by Nieminen [25].

2.4. Definitions

Physician-diagnosed asthma: an affirmative answer to the question "Has your child/have you been diagnosed by a physician as having asthma?"
Asthma by 8 years: onset before age 8 years based on reported physician-diagnosis of asthma or diagnosed by a pediatrician in a validation study following the questionnaire survey [17].
Wheeze last 12 months*:* affirmative response to the question 'Have you/Has your child had wheeze in the last 12 months?'.
Asthma severity score: was based on an arbitrary score ranging from 0 to 5 and included wheeze last 12 months, daily use of asthma medication, ≥1 night per week with disturbed sleep, at least one episode of speech-limiting wheeze, and >12 episodes of wheezing. Each item should have occurred during the last 12 months and yielded one point each [26].

Asthma at 19 years was categorized as follows [14].

Remission 19y: neither wheeze nor use of asthma medications during the last 12 months as reported at age 19y and in the two preceding annual surveys (i.e. for ≥3 years).
Persistent asthma 19y: report of wheeze or use of asthma medication in the last 12 months in all questionnaires.
Periodic asthma 19y: neither remission nor persistent asthma.

Asthma at 28 years was categorized as follows.

Current asthma (persistent asthma 28y): wheeze or use of asthma medications during the last 12 months.
Current asthma (relapse 28y): Individuals with current asthma at 28y that were in remission at 19y.
Remission 28y: neither wheeze nor use of asthma medications during the last 12 months.
Allergic multimorbidity: Presence of asthma as well as either a positive SPT, rhinoconjunctivitis or eczema.
Allergic sensitization 8y: defined as a positive SPT at age 8y.
Allergic sensitization by 19y: any positive SPT at age 8, 12 or 19y.

Definitions of potential predictors of persistence and remission of asthma are presented in an online supplement table E1.

2.5. Statistical analyses

Statistical analyses were performed using SPSS, version 26.0 (IBM Corp, New York, USA). A p-value of <0.05 was considered statistically significant. Chi-square tests, or Fisher's exact test when appropriate, were used for comparisons of proportions. For comparison of means, *t*-test or ANOVA was used. Last observation carried forward was utilized for missing values on individual questions. Sex, family history of asthma and significant risk factors in unadjusted analyses were included in adjusted regression analyses. Logistic regression analysis was performed, with *'remission 28y'* as reference and '*current asthma'* at age 28 years as outcome and the results presented as odds ratios (OR) with 95% confidence intervals (95% CI). The adjusted analyses were performed with the covariates rhinojonjunctivitis and allergic sensitization entered one at the time in separate models. Finally, an adjusted analysis was performed where all risk factors were analyzed by backward stepwise logistic regression. In addition, stratified analyses by sex and allergic sensitization, respectively, were performed.

3. Results

3.1. Lost to follow-up in 2015

Of the 248 individuals with asthma by 8 years of age, six had migrated from Sweden, eight could not be traced and 64 of those possible to invite declined participation by 28 years of age. Of the 234 invited, 170 individuals (73%) participated in the follow-up survey at 28y, whereof n = 76 (44.7%) were women. Compared with the 170 participants, having smoking parents was more common among the 78 non-participants (57.4% vs. 37.7%, p = 0.008) (Online supplement table E2). However, there were no significant differences in sex distribution, family history of asthma, low birthweight, breastfeeding <3 months, any severe respiratory infection, asthma severity score or allergic multimorbidity by 8y.

3.2. Persistence, remission and relapse of asthma from 8 to 28 years of age

Among the 170 individuals, 105 (61.8%) had current asthma at age 28y while 65 (38.2%) were in remission. Fig. 2 illustrates changes in asthma status from 8y, until the follow-up at 19y and further to 28y. Of the 32 in remission by 19y (of which 73% were men), there were 24 (75.0%) individuals with lasting remission until 28y. Eight individuals (25.0%) of those in remission by 19y had relapsed and had current asthma at 28y. Those in remission at 28y included 10 individuals categorized as persistent asthma at 19y and 28 individuals with periodic asthma at 19y. Of the n = 68 with persistent asthma at age 19y, 14.7% were in remission at age 28y. Correspondingly, of the n = 64 with

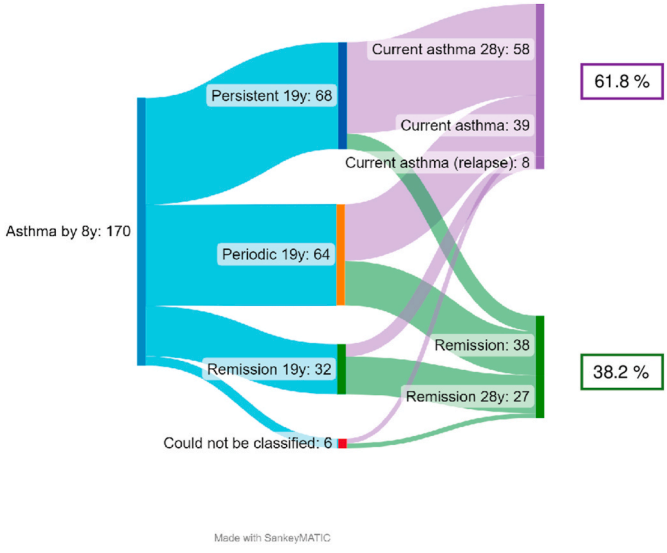

Fig. 2. Sankey diagram illustrating the persistence and remission of asthma up to 28 years among those with asthma onset by 8 years.

periodic asthma, 43.8% were in remission.

3.3. Characteristics of those with current asthma at 28 years

Severe respiratory infection in childhood was reported more frequently among those with current asthma at 28y than among those without (82.9% vs 69.2%, p = 0.038), while breastfeeding <3 months was more common among those in remission (50.0% vs 29.7%, p = 0.009) (Table 1). Having eczema, rhinoconjunctivitis or allergic sensitization at 8y were significantly more common among those with current asthma than among those in remission. A higher mean asthma severity score at 8y was associated with current asthma at 28y.

There were no differences in clinical characteristics at 19y regarding lung function measures, BMI, daily smoking, exposure to parental tobacco smoke or house dampness between those with and without current asthma at age 28y (Table 2). However, presence of bronchial hyperreactivity (BHR) at 17y was more common among those with current asthma at 28y than those without (76.9% vs 33.3%, p = 0.006), as was rhinoconjunctivitis at 19y and allergic sensitization by 19y.

3.4. Risk factors for current asthma at 28y

In an adjusted analysis (model A), current asthma was associated with asthma severity score (OR 1.5) and rhinoconjunctivitis at age 8y (OR 3.4) (Table 3). When allergic sensitization by 8y was included in the model instead of rhinoconjunctivitis (model B), current asthma was associated with severe respiratory infection (OR 2.6), asthma severity (OR 1.6) and allergic sensitization at 8y (OR 7.8) respectively. When all risk factors were analyzed by backward stepwise logistic regression (model C), severe respiratory infection, breastfeeding <3 months, asthma severity and allergic sensitization were significantly associated with current asthma. Breastfeeding <3 months was significantly negatively associated with current asthma in all models, with ORs of 0.41–0.46. When breastfeeding was excluded from the models, no major differences in the ORs and CIs of the other variables were seen.

In an adjusted analysis including sex, family history and rhinoconjunctivitis at 19y, BHR at age 17y remained associated with current asthma (OR 8.14, 95% CI 1.61–41.01). When adjusting for allergic sensitization at 19y but not rhinoconjunctivitis, only BHR remained (OR 8.98, 95% CI 1.72–47.00) significantly associated with current asthma at 28y.

Table 1
Childhood factors in association with current asthma or remission, respectively, at age 28 years among those with asthma at age 8 years, presented as n (%).

Childhood factors, age 8y	Asthma status at age 28y		p-value
	Current asthma	Remission[1]	
	n = 105 (%)	n = 65 (%)	
Boys	56 (53.3)	38 (58.5)	0.513
Family history of asthma	43 (41.0)	30 (46.2)	0.506
Birthweight <2500g	8 (8.0)	3 (4.7)	0.313
Breastfeeding <3 months	30 (29.7)	32 (50.0)	**0.009**
Severe respiratory infection	87 (82.9)	45 (69.2)	**0.038**
Smoking during pregnancy	22 (21.4)	19 (29.7)	0.224
Maternal smoking first 2y	30 (29.7)	21 (32.8)	0.674
Paternal smoking first 2y	24 (24.0)	16 (26.2)	0.751
Any parent smoking first 2y	37 (35.9)	26 (40.6)	0.542
Ever house dampness	28 (28.0)	14 (21.9)	0.381
Rural living	16 (15.2)	9 (13.8)	0.803
Ever eczema	68 (64.8)	31 (47.7)	**0.028**
Ever rhinitis	68 (64.8)	22 (33.8)	**<0.001**
Rhinoconjunctivitis	45 (42.9)	11 (16.9)	**<0.001**
Allergic sensitization[2]	50 (69.4)	12 (26.7)	**<0.001**
Asthma severity score[3], mean (SD)	1.58 (1.06)	1.05 (0.93)	**<0.001**

[1]Neither wheeze nor asthma medicine use last 12 months. [2]Among the n = 117 participating in SPT, skin prick test, at age 8y. [3]Asthma severity score with range 0–5. Higher scores indicate a more severe asthma. Bold font indicates p < 0.05.

Table 2
Clinical characteristics at age 19 years in association with current asthma or remission by 28 years, among those with asthma at recruitment at age 8 years. Presented as n (%) unless otherwise stated.

Characteristics at age 19y	Asthma status at age 28y		p-value
	Current asthma	Remission[1]	
	n = 105	n = 65	
Lung function[2]			
FEV_1 pp, mean (SD)	93.7 (11.2)	96.4 (10.4)	0.136
FVC pp, mean (SD)	97.3 (10.7)	96.9 (10.6)	0.828
FEV_1 pp < 80	11 (11.3)	4 (6.7)	0.249
FEV_1/FVC < LLN	13 (13.4)	3 (5.0)	0.074
Bronchial hyperreactivity[3]	20 (76.9)	5 (33.3)	**0.006**
Body Mass Index			
BMI, mean (SD)	23.8 (4.6)	23.1 (4.2)	0.341
BMI categories			
Underweight (BMI <18.5)	4 (4.1)	5 (8.1)	0.479
Normal weight (BMI 18.5–24.9)	64 (65.3)	40 (64.5)	
Overweight (BMI 25–29.9)	18 (18.4)	13 (21.0)	
Obese (BMI >30)	12 (12.2)	4 (6.5)	
Daily smoker[4]	13 (14.4)	7 (11.5)	0.597
Mother smoker[5]	22 (25.0)	16 (26.7)	0.820
Father smoker[6]	14 (16.3)	13 (22.8)	0.329
Current house dampness	5 (5.5)	2 (18.0)	0.804
Ever eczema	51 (48.6)	24 (36.9)	0.137
Ever rhinitis	41 (39.0)	17 (26.2)	0.085
Rhinoconjunctivitis	41 (39.0)	12 (18.5)	**0.005**
Allergic sensitization by 19y[7]	71 (80.7)	37 (62.7)	**0.016**

[1]Neither wheeze nor asthma medicine use last 12 months. [2]Among the n = 157 participating in spirometry. [3]Among the n = 53 participating in bronchial hyperreactivity test. [4]n = 19 missing. [5]n = 22 missing [6]n = 27 missing [7]Among the n = 147 participating in SPT, skin prick test, either at age 8y, 12y, or 19y. FEV_1=Forced Expiratory Volume in 1 s. FVC=Forced Vital Capacity. LLN = Lower Limit of Normal. BMI=Body Mass Index. Bold font indicates p < 0.05.

3.5. Current asthma at age 28 years stratified by sex and allergic sensitization, respectively

The proportion of current asthma was similar among women and men (n = 49/76 (64.5%) and n = 56/94 (59.6%), respectively, p = 0.513). Men and women had a similar risk factor pattern but the analyses were unpowered (Online supplement, table E3 and E4).

Among those with allergic sensitization by 19y, current asthma was associated with breastfeeding more than 3 months, severe respiratory infection, ever rhinitis, rhinoconjuctivitis and a higher mean asthma severity score at 8y (Table 4). Among those without allergic sensitization by 19y, current asthma at age 28y was associated with low birthweight.

4. Discussion

In this population-based, long-term follow-up of childhood asthma, 170 individuals were followed until 28 years of age, and although some were in remission as teenagers, almost two thirds still had current asthma in adulthood. Persistence of asthma from childhood to adulthood was associated with allergic sensitization and rhinconjunctivitis but also severe respiratory infection, breastfeeding >3 months, asthma

Table 3
The association between childhood factors and current asthma at 28 years, among the n = 170 with asthma onset by 8 years. Unadjusted analyses and adjusted analyses using logistic regression with remission at age 28 years as reference and current asthma as outcome and with the results presented as odds ratios (OR) with 95% confidence intervals (95%CI). Model A includes rhinoconjunctivitis, Model B includes allergic sensitization and in Model C all risk factors were analyzed by backwards stepwise logistic regression.

Childhood factors, age 8y	Outcome: current asthma at age 28y							
	Unadjusted		Adjusted Model A		Adjusted Model B[3]		Adjusted Model C	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Boys	0.81	(0.44–1.52)	0.84	(0.42–1.70)	0.79	(0.38–1.64)		
Family history of asthma	0.81	(0.43–1.51)	0.60	(0.29–1.21)	0.57	(0.27–1.20)		
Breastfeeding <3 months[1]	**0.42**	**(0.22–0.81)**	**0.41**	**(0.20–0.84)**	**0.45**	**(0.21–0.96)**	**0.46**	**(0.22–0.96)**
Severe respiratory infection	**2.15**	**(1.03–4.46)**	2.28	(0.99–5.25)	**2.60**	**(1.07–6.32)**	**2.59**	**(1.09–6.16)**
Ever eczema	**2.02**	**(1.07–3.79)**	1.11	(0.53–2.31)	1.21	(0.57–2.57)		
Rhinoconjunctivitis	**3.68**	**(1.73–7.83)**	**3.43**	**(1.48–7.96)**				
Allergic sensitization at age 8y	**2.53**	**(1.09–5.85)**	–		**7.78**	**(3.00–20.15)**	**7.24**	**(2.86–18.28)**
Asthma severity score[2]	**1.79**	**(1.24–2.57)**	**1.48**	**(1.00–2.18)**	**1.60**	**(1.08–2.38)**	**1.62**	**(1.10–2.38)**

[1]Reference: breastfeeding >3 months. [2]Asthma severity score with range 0–5. Higher scores indicate a more severe asthma. Bold font indicates $p < 0.05$. [3]Interaction term between allergic sensitization and asthma severity score: $p = 0.133$.

Table 4
Childhood factors in association with current asthma at age 28y, stratified by allergic sensitization, among the n = 147 with current asthma that participated in skin prick test (SPT). Presented as n (%) unless otherwise stated.

Childhood factors, age 8y	All negative SPT	All positive SPT	Asthma status at age 28y					
			Negative SPT			Positive SPT		p-value[2]
			Current asthma	Remission[1]		Current asthma	Remission[1]	
	n = 39	n = 108	n = 17	n = 22	p-value[2]	n = 71	n = 37	
Sex, men	20 (51.3)	61 (56.5)	7 (41.2)	13 (59.1)	0.267	39 (54.9)	22 (59.5)	0.652
Family history of asthma	13 (33.3)	52 (48.1)	4 (23.5)	9 (40.9)	0.213	33 (46.5)	19 (51.4)	0.631
Birthweight <2500g	6 (16.2)	3 (2.9)	5 (31.3)	1 (4.8)	**0.043**	1 (1.5)	2 (5.4)	0.288
Breastfeeding <3 months	23 (59.0)	28 (27.2)	8 (47.1)	15 (68.2)	0.184	14 (20.9)	14 (38.9)	**0.050**
Severe respiratory infection	34 (87.2)	78 (72.2)	16 (94.1)	18 (81.8)	0.255	56 (78.9)	22 (59.5)	**0.033**
Smoking during pregnancy	14 (35.9)	22 (21.0)	6 (35.3)	8 (36.4)	0.945	12 (17.4)	10 (27.8)	0.214
Maternal smoking first 2y	17 (43.6)	29 (28.2)	7 (41.2)	10 (45.5)	0.789	19 (28.4)	10 (27.8)	0.950
Paternal smoking first 2y	12 (34.2)	24 (23.1)	4 (26.7)	8 (40.0)	0.324	17 (24.6)	7 (20.0)	0.596
Any parent smoking first 2y	21 (53.8)	36 (34.3)	8 (47.1)	13 (59.1)	0.455	24 (34.8)	12 (33.3)	0.882
Ever house dampness	13 (33.3)	28 (27.5)	6 (35.3)	7 (31.8)	0.819	21 (31.8)	7 (19.4)	0.181
Ever eczema	16 (41.0)	69 (63.9)	9 (52.9)	7 (31.8)	0.184	49 (69.0)	20 (54.1)	0.125
Ever rhinitis	12 (30.8)	66 (61.1)	6 (35.3)	6 (27.3)	0.590	52 (73.2)	14 (37.8)	**<0.001**
Rhinoconjunctivitis	1 (2.6)	47 (43.5)	0	1 (4.5)	0.564	39 (54.9)	8 (21.6)	**<0.001**
Asthma severity score[3], mean (SD)	1.26 (1.0)	1.44 (1.1)	1.24 (0.9)	1.27 (1.1)	0.911	1.70 (1.1)	0.92 (0.8)	**<0.001**

[1]Neither wheeze nor asthma medicine use last 12 months. [2]Comparing current asthma and remission among individuals with a negative and positive SPT, skin prick test, respectively. [3]Asthma severity score with range 0–5. Higher scores indicate a more severe asthma. Bold font indicates $p < 0.05$.

severity at 8y years of age, and bronchial hyperreactivity in adolescence.

Through our prospective study design, including multiple measurements from childhood, adolescence and up to adulthood, we were able to make a detailed long-term prognosis of childhood onset asthma. Overall, both the majority of those in remission at 19 years of age and the majority of those with persistent asthma until 19 years of age had the same asthma status 10 years later. Nevertheless, almost one in four of those who had been in remission for at least three years at age 19 years, reported relapse, i. e symptoms of asthma or use of asthma medication at age 28 years. The remission rate from 19 to 28 years of age was higher among those defined as periodic asthma than those with persistent asthma at age 19 years, indicating having a less severe or more intermittent disease. Based on the same cohort, we have previously reported a remission rate of asthma from 8 to 19 years of 21% [13] but in this continued follow-up, only 14% were still in remission when the observation period was longer. Thus, when based on repeated measurements over time the proportion of remission was lower compared to studies with fewer measurement points [3,27]. Thereby, with longer follow-up time, our hypothesis seems to be confirmed, asthma with onset in childhood does not remit to the same extent as previously assumed.

Asthma is a heterogeneous disease that may coexist with eczema, rhinitis and allergic sensitization. Allergic multimorbidity is associated with asthma severity and not surprisingly, we found that having a more severe asthma in childhood was associated with persistence of asthma [8,9]. Furthermore, persistent asthma was associated with allergic conditions such as rhinitis, rhinoconjuctivitis and allergic sensitization in childhood. Also in retrospective studies among adults it has been shown that current asthma was associated with sensitization, particularly among those with childhood onset asthma [28]. In contrast to other studies [29,30] we found no associations with eczema in the adjusted models, nor did we find any differences between sexes though it has been proposed that eczema particularly increases the risk of childhood asthma among boys [30]. Studies in the same geographical area as the current study have shown that BHR in adults was associated with persistence of asthma [1] and we found that BHR in late adolescence was associated with current asthma at 28 years of age, in line with results from the Dunedin birth cohort from the beginning of the seventies [31]. Moreover, it has also been shown that individuals with several

manifestations of atopic disease had an increased risk of more severe BHR [32]. As we hypothesized, what appears to be remission may in fact only be a temporary period without symptoms, but if BHR is still present the individual may not reach a complete remission since normalization of the underlying pathology has not occurred [7,33].

In another publication based on the whole cohort of n = 3430 children, studying the incidence of asthma, we found that severe respiratory infection was associated with asthma onset by age 8 years [13]. In the present study, respiratory infection was also associated with persistence of asthma up to 28 years. Similarly, a Finnish study found an association between childhood viral wheeze and asthma up to 20 years of age [34]. On the other hand, it has been suggested that the strength of association between respiratory infections and asthma decreases by time and becomes less important with age [35], in contrast to our results. Moreover, the associations between respiratory infections and breastfeeding and the effect on asthma prognosis is difficult to disentangle. We found that breastfeeding <3 months was rather protective with regard to current asthma at 28 years, independent of any severe respiratory infection before 8 years of age. Among younger children, a Swedish study has shown that at least four months of breastfeeding can reduce the risk of asthma during the first years of life [10] while another study, based on our cohort, found an protective effect on non-atopic-asthma among children that had been breastfed less than 3 months [17]. In line with our study, a study from New Zeeland found that breastfeeding four weeks or longer was associated with asthma in adolescence and young adulthood [36]. Thus, among younger children breastfeeding seems to reduce the risk of asthma, while the association is less clear in a long-term perspective [36].

In contrast to other studies [6], we did not find an association between exposure to parental smoking or personal smoking habits and the persistence of asthma from childhood to adulthood. However, lost to follow-up analysis showed that non-response was higher among those with smoking parents. Another explanation could be that the associations differed between men and women and thereby cancelled each other out in the analyses among all: among men smoking during pregnancy and exposure to smoking during first years of life was more common among those in remission, but among women it was more common among those with persistent asthma. Moreover, the proportion of smokers has steadily decreased in Sweden and with stricter tobacco laws that were entered into force in the mid-1990s may thus have contributed to reduced tobacco smoke exposure for the individuals in our cohort.

The strengths of the current study is the prospective population-based study design and the long-term follow-up; annually from the age of 8–19 years and an additional follow-up at age 28 years. Thus, our study is highly generalizable for asthma in the general population, in contrast to studies in hospital settings where severe asthma is predominant. Furthermore, a validated and international questionnaire was used [15,21,22] and the asthma diagnosis was validated by pediatricians at 8y [17] as well as by bronchial hyperreactivity test. Thus, we maintain a high validity for the asthma diagnosis throughout the study period. However, current asthma at 28 years was based on postal questionnaire reports and not confirmed by clinical measurements. Even though there was a high participation rate among those with asthma onset by 8 years of age, some were lost to follow-up. However, as there were no differences in clinical characteristics at age 8y between those participating and not participating at age 28 years, the study does not seem to suffer from any major selection or attrition bias. Other limitations are that the sample size did not provide enough statistical power to allow for all subgroup analyses and that data on parental socioeconomic status was not collected.

In conclusion, in this prospective cohort study of individuals with asthma onset by 8 years of age, we found that allergic multimorbidity, asthma severity and severe respiratory infection in childhood as well as bronchial hyperreactivity in adolescence was associated with persistent asthma up to adulthood. Almost two-thirds of those with childhood-onset asthma still reported asthma in adulthood, and one-fourth of those who had been in remission for more than 3 years at age 19 had relapsed at age 28 years, indicating that remission from childhood onset asthma may be less common than previously assumed.

Data statement

Data is available from the authors upon reasonable request and after a confidentiality evaluation.

CRediT authorship contribution statement

Linnéa Almqvist: Writing – review & editing, Writing – original draft, Visualization, Formal analysis. **Martin Andersson:** Writing – review & editing, Supervision. **Helena Backman:** Writing – review & editing, Supervision, Data curation. **Eva Rönmark:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Linnéa Hedman:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation.

Declaration of competing interest

HB: Personal fees for presentation at scientific meeting outside the submitted work from AstraZeneca, Boehringer Ingelheim and GlaxoSmithKline. None of the other authors have any conflicts of interest.

Acknowledgements and funding

We want to acknowledge the late professor Bo Lundbäck, the founder of the OLIN-studies. Sigrid Sundberg, Aina Jonsson, Kerstin Kemi Björnström and Lena Gustafsson are acknowledged for data collection and Elsy Jönsson and Ola Bernhoff for data management. This work was supported by grants from the Swedish Heart-Lung foundation, the Swedish foundation for health care science and allergy research (Vårdal), the Swedish Asthma-Allergy foundation, VISARE NORR Fund: Northern county councils' Regional federation, a regional agreement between Umeå University and Västerbotten county council (ALF), and Norrbotten county council. Additional support was given by GlaxoSmithKline/Worldwide epidemiology and ALK, Denmark. None of the funders had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2024.107581.

References

[1] L. Almqvist, E. Rönmark, C. Stridsman, H. Backman, A. Lindberg, B. Lundbäck, L. Hedman, Remission of Adult Onset Asthma Is Rare – a 15 Year Follow-Up Study, ERJ Open Res., 2020, https://doi.org/10.1183/23120541.00620-2020, 00620–02020.

[2] J.A. Burgess, M.C. Matheson, L.C. Gurrin, G.B. Byrnes, K.S. Adams, C.L. Wharton, G.G. Giles, M.A. Jenkins, J.L. Hopper, M.J. Abramson, E.H. Walters, S. C. Dharmage, Factors influencing asthma remission: a longitudinal study from childhood to middle age, Thorax 66 (2011) 508–513, https://doi.org/10.1136/thx.2010.146845.

[3] B.E. Sekerel, E. Civelek, E. Karabulut, S. Yildirim, A. Tuncer, G. Adalioglu, Are risk factors of childhood asthma predicting disease persistence in early adulthood different in the developing world? Allergy 61 (2006) 869–877, https://doi.org/10.1111/j.1398-9995.2006.01082.x.

[4] R. De Marco, F. Locatelli, I. Cerveri, M. Bugiani, A. Marinoni, G. Giammanco, S. Accordini, G. Verlato, E. Zanolin, O. Buriani, L. Carrozzi, R. Dallari, F. Ginesu, A. Poli, P. Struzzo, R. Cavallini, C. Saletti, M. Cellini, M. Faustini, A. De Togni, A. Carolei, C. Montomoli, S. Villani, M. Comelli, M. Ponzio, M. Grassi, C. Rezzani,

L. Casali, M.C. Zoia, A. Corsico, S. Colato, G. Moscato, L. Perfetti, G. Viegi, F. Pistelli, F. Di Pede, P.L. Paggiaro, A. Santolicandro, P. Giovannetti, P. Pirina, S. Ostera, G.P. Pinna, A. Farre, S. Imparato, E. Turrini, M. Foglia, S. Pignato, A. Rotondo, A. Cuspilici, P. Piccioni, A. Carosso, W. Arossa, E. Caria, G. Castiglioni, E. Migliore, C. Romano, D. Fabbro, G. Ciccone, C. Magnani, P. Dalmasso, R. Bono, G. Gigli, A. Giraudo, M.C. Brussino, C. Bucca, G. Rolla, U. Orefice, M. Schneider, F. Chittaro, D. Peresson, M.E. Zanolin, L. Cazzoletti, L. Battisti, C. Pattaro, N. Dorigo, S. Cantarelli, D. Ciresola, V. Lo Cascio, M. Olivieri, M. Ferrari, C. Biasin, P. Lauriola, G. Danielli, D. Sesti, E. Ghigli, P. Natale, M. Grosa, A. Tacconi, P. Frontero, A. Salomoni, Incidence and remission of asthma: a retrospective study on the natural history of asthma in Italy, J. Allergy Clin. Immunol. 110 (2002) 228–235, https://doi.org/10.1067/mai.2002.125600.

[5] D. Thomas, V.M. McDonald, I.D. Pavord, P.G. Gibson, Asthma remission: what is it and how can it be achieved? Eur. Respir. J. 60 (2022) 2102583 https://doi.org/10.1183/13993003.02583-2021.

[6] O. Fuchs, T. Bahmer, K.F. Rabe, E. von Mutius, Asthma transition from childhood into adulthood, Lancet Respir. Med. 5 (2017) 224–234, https://doi.org/10.1016/S2213-2600(16)30187-4.

[7] D.R. Taylor, J.O. Cowan, J.M. Greene, A.R. Willan, M.R. Sears, Asthma in remission: can relapse in early adulthood be predicted at 18 years of age? Chest 127 (2005) 845–850, https://doi.org/10.1378/chest.127.3.845.

[8] P.E. Martin, M.C. Matheson, L. Gurrin, J.A. Burgess, N. Osborne, A.J. Lowe, S. Morrison, D. Mészáros, G.G. Giles, M.J. Abramson, E.H. Walters, K.J. Allen, S. C. Dharmage, Childhood eczema and rhinitis predict atopic but not nonatopic adult asthma: a prospective cohort study over 4 decades, J. Allergy Clin. Immunol. 127 (2011), https://doi.org/10.1016/j.jaci.2011.02.041.

[9] J.A. Burgess, E.H. Walters, G.B. Byrnes, M.C. Matheson, M.A. Jenkins, C. L. Wharton, D.P. Johns, M.J. Abramson, J.L. Hopper, S.C. Dharmage, Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: a longitudinal study, J. Allergy Clin. Immunol. 120 (2007) 863–869, https://doi.org/10.1016/j.jaci.2007.07.020.

[10] I. Kull, C. Almqvist, G. Lilja, G. ran Pershagen, M. Wickman, Breast-feeding reduces the risk of asthma during the first 4 years of life, J. Allergy Clin. Immunol. 114 (2004) 755–760, https://doi.org/10.1016/j.jaci.2004.07.036.

[11] K. Bønnelykke, N.H. Vissing, A. Sevelsted, S.L. Johnston, H. Bisgaard, Association between respiratory infections in early life and later asthma is independent of virus type, J. Allergy Clin. Immunol. 136 (2015) 81–86.e4, https://doi.org/10.1016/j.jaci.2015.02.024.

[12] F.D. Gilliland, K. Berhane, R. McConnell, W.J. Gauderman, H. Vora, E. B. Rappaport, E. Avol, J.M. Peters, Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function, Thorax 55 (2000) 271–276, https://doi.org/10.1136/thorax.55.4.271.

[13] L. Hedman, L. Almqvist, A. Bjerg, M. Andersson, H. Backman, M.S. Perzanowski, E. Rönmark, Early-life risk factors for development of asthma from 8 to 28 years of age: a prospective cohort study, ERJ Open Res 8 (2022) 74–2022, https://doi.org/10.1183/23120541.00074-2022.

[14] M. Andersson, L. Hedman, A. Bjerg, B. Forsberg, B. Lundbäck, E. Rönmark, Remission and persistence of asthma followed from 7 to 19 years of age, Pediatrics 132 (2013) 435, https://doi.org/10.1542/peds.2013-0741.

[15] E. Rönmark, B. Lundbäck, E. Jönsson, T. Platts-Mills, Asthma, type-1 allergy and related conditions in 7- and 8-year-old children in Northern Sweden: prevalence rates and risk factor pattern, Respir. Med. 92 (1998) 316–324, https://doi.org/10.1016/S0954-6111(98)90115-9.

[16] L. Hedman, A. Bjerg, M. Perzanowski, E. Rönmark, Good agreement between parental and self-completed questionnaires about allergic diseases and environmental factors in teenagers, J. Clin. Epidemiol. 63 (2010) 783–789, https://doi.org/10.1016/j.jclinepi.2009.08.017.

[17] E. Rönmark, E. Jönsson, T. Platts-Mills, B. Lundbäck, Different pattern of risk factors for atopic and nonatopic asthma among children - report from the obstructive lung disease in northern Sweden study, Allergy Eur. J. Allergy Clin. Immunol. 54 (1999) 926–935, https://doi.org/10.1034/j.1398-9995.1999.00044.x.

[18] S. Selberg, L. Hedman, S.A. Jansson, H. Backman, C. Stridsman, Asthma control and acute healthcare visits among young adults with asthma—a population-based study, J. Adv. Nurs. 75 (2019) 3525–3534, https://doi.org/10.1111/jan.14174.

[19] C. Schyllert, M. Andersson, H. Backman, A. Lindberg, E. Rönmark, L. Hedman, Childhood onset asthma is associated with lower educational level in young adults – a prospective cohort study, Respir. Med. 186 (2021), https://doi.org/10.1016/j.rmed.2021.106514.

[20] E. Rönmark, A. Bjerg, M. Perzanowski, T. Platts-Mills, B. Lundbäck, Major increase in allergic sensitization in schoolchildren from 1996 to 2006 in northern Sweden, J. Allergy Clin. Immunol. 124 (2009) 357, https://doi.org/10.1016/j.jaci.2009.05.011.

[21] M.I. Asher, U. Keil, H.R. Anderson, R. Beasley, J. Crane, F. Martinez, E.A. Mitchell, N. Pearce, B. Sibbald, A.W. Stewart, D. Strachan, S.K. Weiland, H.C. Williams, International Study of Asthma and Allergies in Childhood (ISAAC): Rationale and Methods, Eur. Respir. J., 1995, pp. 483–491, https://doi.org/10.1183/09031936.95.08030483.

[22] B. Lundbäck, L. Nyström, L. Rosenhall, N. Stjernberg, Obstructive lung disease in northern Sweden: respiratory symptoms assessed in a postal survey, Eur. Respir. J. 4 (1991) 257–266.

[23] M.R. Miller, J. Hankinson, V. Brusasco, F. Burgos, R. Casaburi, A. Coates, R. Crapo, P. Enright, C.P.M. van der Grinten, P. Gustafsson, R. Jensen, D.C. Johnson, N. MacIntyre, R. McKay, D. Navajas, O.F. Pedersen, R. Pellegrino, G. Viegi, J. Wanger, Standardisation of spirometry, Eur. Respir. J. 26 (2005) 319–338, https://doi.org/10.1183/09031936.05.00034805.

[24] P.H. Quanjer, S. Stanojevic, T.J. Cole, X. Baur, G.L. Hall, B.H. Culver, P.L. Enright, J.L. Hankinson, M.S.M. Ip, J. Zheng, J. Stocks, C. Schindler, Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations, Eur. Respir. J. 40 (2012) 1324–1343, https://doi.org/10.1183/09031936.00080312.

[25] M.M. Nieminen, Unimodal distribution of bronchial hyperresponsiveness to methacholine in asthmatic patients, Chest 102 (1992) 1537–1543, https://doi.org/10.1378/chest.102.5.1537.

[26] M. Andersson, A. Bjerg, B. Forsberg, B. Lundbäck, E. Rönmark, The clinical expression of asthma in schoolchildren has changed between 1996 and 2006, Pediatr, Allerg. Immunol. (Leipz.) 21 (2010) 859–866, https://doi.org/10.1111/j.1399-3038.2010.01055.x.

[27] M.R. Sears, J.M. Greene, A.R. Willan, E.M. Wiecek, D.R. Taylor, E.M. Flannery, J. O. Cowan, G.P. Herbison, P.A. Silva, R. Poulton, A longitudinal, population-based, cohort study of childhood asthma followed to adulthood, N. Engl. J. Med. 349 (2003) 1414–1422, https://doi.org/10.1056/NEJMoa022363.

[28] K. Warm, L. Hedman, A. Lindberg, J. Lötvall, B. Lundbäck, E. Rönmark, Allergic sensitization is age-dependently associated with rhinitis, but less so with asthma, J. Allergy Clin. Immunol. 136 (2015) 1559–1565.e2, https://doi.org/10.1016/j.jaci.2015.06.015.

[29] J.A. Burgess, A.J. Lowe, M.C. Matheson, G. Varigos, M.J. Abramson, S. C. Dharmage, Does eczema lead to asthma? J. Asthma 46 (2009) 429–436, https://doi.org/10.1080/02770900902846356.

[30] A.J. Lowe, J.B. Carlin, C.M. Bennett, C.S. Hosking, M.J. Abramson, D.J. Hill, S. C. Dharmage, Do boys do the atopic march while girls dawdle? J. Allergy Clin. Immunol. 121 (2008) 1190–1195, https://doi.org/10.1016/j.jaci.2008.01.034.

[31] M.R. Sears, J.M. Greene, A.R. Willan, E.M. Wiecek, D.R. Taylor, E.M. Flannery, J. O. Cowan, G.P. Herbison, P.A. Silva, R. Poulton, A longitudinal, population-based, cohort study of childhood asthma followed to adulthood, N. Engl. J. Med. 349 (2003) 1414–1422, https://doi.org/10.1056/nejmoa022363.

[32] D. Schramm, M. Reuter, L.B. Grabenhenrich, A. Schuster, C. Lex, C.P. Bauer, U. Hoffmann, J. Forster, F. Zepp, R.L. Bergmann, K.E. Bergmann, U. Wahn, T. Keil, S. Lau, What does lung function tell us about respiratory multimorbidity in childhood and early adulthood? Results from the MAS birth cohort study, Pediatr. Allergy Immunol. 29 (2018) 481–489, https://doi.org/10.1111/pai.12901.

[33] Y. Komatsu, K. Fujimoto, M. Yasuo, K. Urushihata, M. Hanaoka, T. Koizumi, K. Kubo, Airway hyper-responsiveness in young adults with asthma that remitted either during or before adolescence, Respirology 14 (2009) 217–223, https://doi.org/10.1111/j.1440-1843.2008.01413.x.

[34] K. Backman, H. Ollikainen, E. Piippo-Savolainen, K. Nuolivirta, M. Korppi, Asthma and lung function in adulthood after a viral wheezing episode in early childhood, Clin. Exp. Allergy 48 (2018) 138–146, https://doi.org/10.1111/cea.13062.

[35] S.A. Régnier, J. Huels, Association between respiratory syncytial virus hospitalizations in infants and respiratory sequelae: systematic review and meta-analysis, Pediatr. Infect. Dis. J. 32 (2013) 820–826, https://doi.org/10.1097/INF.0b013e31829061e8.

[36] M.R. Sears, J.M. Greene, A.R. Willan, D.R. Taylor, E.M. Flannery, J.O. Cowan, G. P. Herbison, R. Poulton, Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study, Lancet 360 (2002) 901–907, https://doi.org/10.1016/S0140-6736(02)11025-7.