ORIGINAL ARTICLE

Clinical and functional differences between early-onset and late-onset adult asthma: a population-based Tasmanian Longitudinal Health Study

Daniel J Tan,[1,2] E Haydn Walters,[1,2] Jennifer L Perret,[1] John A Burgess,[1] David P Johns,[3] Adrian J Lowe,[1,4] Caroline J Lodge,[1] Panteha Hayati Rezvan,[5] Julie A Simpson,[5] Stephen Morrison,[6] Bruce R Thompson,[7] Paul S Thomas,[8] Iain Feather,[9] Graham G Giles,[1,10] John L Hopper,[1] Michael J Abramson,[11] Melanie C Matheson,[1] Shyamali C Dharmage[1,4]

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2015-208183).

For numbered affiliations see end of article.

Correspondence to
Dr Shyamali C Dharmage, Level 3, 207 Bouverie Street, Parkville VIC 3052, Australia; s.dharmage@unimelb.edu.au

MCM and SCD contributed equally.

Received 11 December 2015
Accepted 18 May 2016
Published Online First 14 June 2016

ABSTRACT

Background Differences between early-onset and late-onset adult asthma have not been comprehensively described using prospective data.

Aims To characterise the differences between early-onset and late-onset asthma in a longitudinal cohort study.

Methods The Tasmanian Longitudinal Health Study (TAHS) is a population-based cohort. Respiratory histories and spirometry were first performed in 1968 when participants were aged 7 (n=8583). The cohort was traced and resurveyed from 2002 to 2005 (n=5729 responses) and a sample, enriched for asthma and bronchitis participated in a clinical study when aged 44 (n=1389).

Results Of the entire TAHS cohort, 7.7% (95% CI 6.6% to 9.0%) had early-onset and 7.8% (95% CI 6.4% to 9.4%) late-onset asthma. Atopy and family history were more common in early-onset asthma while female gender, current smoking and low socioeconomic status were more common in late-onset asthma. The impact on lung function of early-onset asthma was significantly greater than for late-onset asthma (mean difference prebronchodilator (BD) FEV_1/FVC −2.8% predicted (−5.3 to −0.3); post-BD FEV_1FVC −2.6% predicted (−5.0 to −0.1)). However, asthma severity and asthma score did not significantly differ between groups. An interaction between asthma and smoking was identified and found to be associated with greater fixed airflow obstruction in adults with late-onset asthma. This interaction was not evident in adults with early-onset disease.

Conclusions Early-onset and late-onset adult asthma are equally prevalent in the middle-aged population. Major phenotypic differences occur with asthma age-of-onset; while both share similar clinical manifestations, the impact on adult lung function of early-onset asthma is greater than for late-onset asthma.

Key messages

What is the key question?

- What are the differences between early-onset and late-onset asthma in middle age?

What is the bottom line?

- Early-onset adult asthma is associated with greater prebronchodilator and postbronchodilator airflow obstruction, nocturnal asthma symptoms and hospitalisation in the preceding year.

Why read on?

- This study, the world's longest-running population-based study of respiratory disease, uses data collected prospectively over four decades to more accurately describe the characteristics of early-onset and late-onset asthma in middle-age.

INTRODUCTION

Asthma is a major global health problem and contributes substantially to the worldwide burden of disease.[1] While incidence and prevalence are highest in children, asthma is also common among adults. Prevalence estimates of adult asthma prevalence have varied considerably between countries, ranging from 2.8% to 15.7% in young adults[2] and up to 10% in older adults aged over 65 years.[3] However, the condition is frequently underdiagnosed in older age-groups and these numbers may underestimate the true prevalence of adult disease.[4]

Asthma also presents diagnostic challenges in middle-aged and older adults. There is considerable clinical and physiological overlap between asthma and COPD, and the distinction between the two can often be unclear.[5 6] 'Asthma' is commonly described as an umbrella-term for a number of overlapping clinical subgroups and in adults, multiple phenotypes such as the 'asthma-COPD overlap' syndrome have been proposed.[7] This current taxonomy of asthma and airways disease is widely debated and thought to be of limited relevance to clinical practice.[8] Given the rising worldwide prevalence of asthma and global trend to

To cite: Tan DJ, Walters EH, Perret JL, *et al*. *Thorax* 2016;**71**:981–987.

greater life expectancy, a new approach to asthma diagnosis and management tailored to specific, well-defined phenotypes is required.

While numerous classifications have been proposed, few adult phenotypes have been described in detail and further studies are required to disentangle asthma heterogeneity in middle-age. To date, phenotypes based on asthma severity and inflammatory subtype have been emphasised and studied in some detail. Recent statistically based studies have emphasised age at asthma onset as a core discriminatory variable of adult clusters,[9 10] although relatively few studies have characterised the differences between early-onset and late-onset disease.

Previous cross-sectional studies comparing early-onset and late-onset asthma in adults have had methodological limitations, including potential for recall bias and non-standardisation of comparison groups.[11] These studies also demonstrated notable inconsistency in lung function and clinical outcomes. There are currently no prospective studies that have comprehensively compared such age-based subgroups.

We aimed to compare the characteristics of early-onset and late-onset current adult asthma within a longitudinal cohort study, using prospectively collected data since childhood and age-standardised comparison groups. We hypothesised that major differences exist between early-onset and late-onset adult asthma, and that early-onset asthma has a greater impact on lung function and clinical outcomes.

METHODS

Tasmanian Longitudinal Health Study

Methods of the baseline study and subsequent follow-ups have been published elsewhere.[12 13] These have been summarised in figure 1. Briefly, the Tasmanian Longitudinal Health Study (TAHS) is a whole-population cohort of children born in 1961 and being schooled in Tasmania, Australia in 1968 (n=8583). Participants were largely of a European, Anglo-Celtic background. Questionnaire data and spirometry were first collected in 1968 when participants were aged 7 and a large follow-up survey was distributed in 1974 (age 13). Smaller studies occurred at ages 21 and 32. In the most recent comprehensive follow-up from 2002 to 2005 (age 44), the original cohort was traced and resurveyed (n=5729 responses) (see online supplementary methods E1). Of the respondents, a sample was invited to participate in a further clinical study (n=2373). Their selection was based on participation in previous follow-up studies, and enriched for individuals with a history of asthma or bronchitis. A total of 1389 (58.5%) attended the laboratory.

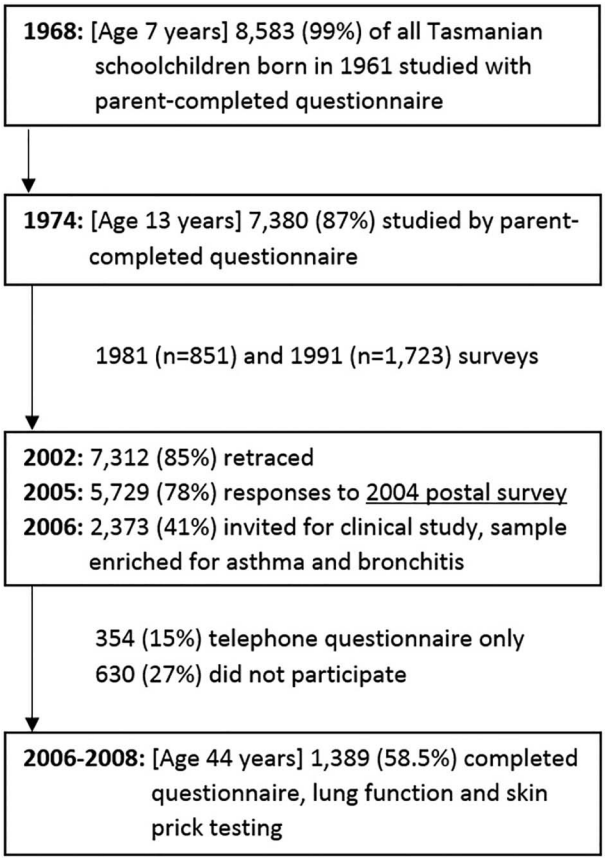

Figure 1 Tasmanian Longitudinal Health Study (TAHS) design.

Data collection

Lung function testing was performed according to the joint American Thoracic Society and European Respiratory Society guidelines.[14] Predicted values of prebronchodilator and post-bronchodilator (BD) spirometry were derived from reference equations developed by Hankinson and colleagues.[15] Skin prick testing for eight common aeroallergens was also performed (EBOS Groups, Australia): *Dermatophagoides pteronyssinus*, cat pelt, *Cladosporioides*, *Alternaria tenuis*, *Penicillium* mix, *Aspergillus fumigatus*, perennial rye grass and eight mixed grasses.

Definitions

Current asthma at age 44 was defined as asthma-related symptoms and/or healthcare usage in the last 12 months, and was categorised as early-onset (asthma or 'wheezy breathing' in the 1968 and/or 1974 surveys) or late-onset (no asthma or wheezy breathing in both the 1968 and 1974 surveys). Age 13 was thus used to delineate the two age-of-onset subgroups. Participants who did not meet the criteria for current asthma, but responded affirmatively to asthma 'ever' in any of the 1968, 1974 or 2004 surveys were categorised as having remitted asthma. Atopy was defined as a positive skin prick test (weal size ≥3 mm larger than the negative control) to one or more allergens.

Asthma severity was based on the Australian National Asthma Council classification of asthma (see online supplementary methods E2): asymptomatic, intermittent, mild persistent, moderate persistent and severe persistent asthma. Grades of severity were separated by frequency of symptoms and flare-ups occurring within the preceding year. Asthma symptom scores were developed from survey responses to questions modelled on those used in the European Community Respiratory Health Survey (ECRHS) continuous asthma score framework, ranging from 0 to 8 (see online supplementary methods E3).

Statistical analysis

Population prevalence was estimated using known sampling fractions derived from the 1968, 1974 and 2004 postal surveys.

Basic characteristics of early-onset and late-onset adult asthma were compared using univariate models. Continuous variables were analysed using linear regression. Dichotomous variables were analysed using log-binomial models; where the log-binomial models failed to converge, Poisson regression with robust error variance was used. Lung function and clinical characteristics were compared using multivariate models while adjusting for potential confounding factors and sampling weights.

Covariates in the multivariable models were identified in the literature or from previous TAHS analyses as potential

confounding factors, independently associated with both exposure and outcome. Smoking status, social class and family history of obstructive lung disease were included as a priori confounding factors. Parental smoking and childhood lung infection were added only if their inclusion produced a change-in-estimate of 10% or greater. Sampling weights were derived by calculating the inverse probability of selection for the 2006 clinical study. A single model was fitted to each of pre-BD FEV_1 (pre-BD lung function), post-BD FEV_1 (post-BD lung function) and asthma score (clinical outcomes) and then applied to the remaining parameters in that category.

Interactions between the effects of asthma and smoking on adult lung function in both age-based groups were also assessed. All multivariable analyses used complete-case analysis (CCA) for dealing with missing data. Results from CCA were compared with those derived from multiple imputation (MI) (see online supplementary methods E4). All analyses were conducted using STATA V.13.1 (Stata Corporation 2013, College Station, Texas, USA).

RESULTS

Of the 1389 who participated in the laboratory study, 1308 had sufficient data to be categorised as early-onset (n=191), late-onset (n=127), remitted (n=582) or never asthma (n=408). The characteristics of these 1308 participants are summarised in table 1.

Reweighted population prevalence

At age 44 years, 7.7% (95% CI 6.6% to 9.0%) and 7.8% (95% CI 6.4% to 9.4%) of the whole TAHS cohort were estimated to have early-onset and late-onset asthma, respectively. Therefore, of active asthma at this age, approximately one-half started in childhood and one-half were of later onset. Of the cohort, 28.2% (95% CI 25.7% to 30.1%) had remitted asthma and consequently, approximately 43.6% had experienced asthma at some point in their lives.

Early-onset versus late-onset adult asthma

Early-onset adult asthma was more strongly associated with atopy and family history of asthma, whereas late-onset adult asthma was more strongly associated with female gender, current smoking and low socioeconomic class. Both groups had similar high Body Mass Index (BMI) (p=0.99), and there was no significant difference in lifetime history of rhinitis (p=0.54) or eczema (p=0.25), current inhaled corticosteroid (ICS) therapy (p=0.53) or current ICS+long-acting β_2-receptor agonist use (p=0.12).

When adjusting only for age, sex and height, there were no significant differences in lung function between the two groups, but when other potential confounders were included in multivariate models, lung function was found to be consistently lower in adults with early-onset disease (table 2). This was true for both pre-BD and post-BD spirometry. The key variable responsible for this change-in-estimate was smoking status. Further adjusting for childhood lung function did not attenuate the mean difference in lung function between the two groups. BD reversibility was not significantly different between the two groups (p=0.30).

There were no significant differences in asthma severity or asthma score between early-onset and late-onset phenotypes (table 3). Of the individual asthma symptoms, the nocturnal symptoms of 'waking due to an attack of shortness of breath in the last year' and 'waking with chest tightness in the last year'

Table 1 Characteristics of the study groups

	Early-onset (n=191) Mean (SD)	Late-onset (n=127) Mean (SD)	Remitted (n=582) Mean (SD)	Never asthma (n=408) Mean (SD)	Early-onset vs late-onset MD (95% CI)
BMI, kg/m^2	29.1 (6.6)	29.1 (6.9)	28.9 (6.5)	27.2 (5.6)	−0.01 (−1.52 to 1.50)
	N (%)	**N (%)**	**N (%)**	**N (%)**	**RR (95% CI)**
Female	95 (50)	90 (71)	266 (46)	198 (49)	**0.70 (0.59 to 0.84)†**
Smoking status					
Never	93 (49)	49 (39)	226 (39)	181 (44)	–
Former	56 (29)	34 (27)	185 (32)	120 (29)	0.87 (0.50 to 1.50)
Pack-years, median [IQR]	6.8 [1.2–11.9]	8.4 [2.2–25.5]	6.3 [2.0–16.3]	7.9 [2.0–14.4]	
Current	41 (22)	44 (35)	170 (29)	107 (26)	**0.49 (0.28 to 0.85)***
Pack-years, median [IQR]	22.9 [17.6–29.0]	24 [10.2–32.0]	20.3 [9.6–28.8]	21 [12.0–28.0]	
Social class					
1 (highest)	57 (30)	29 (23)	173 (30)	112 (28)	–
2	16 (8)	14 (11)	67 (12)	54 (13)	0.58 (0.25 to 1.35)
3	42 (22)	13 (10)	125 (22)	83 (20)	1.64 (0.76 to 3.54)
4	34 (18)	31 (25)	103 (18)	71 (18)	0.56 (0.29 to 1.08)
5	40 (21)	39 (31)	111 (19)	85 (21)	**0.52 (0.28 to 0.98)***
FH asthma	132 (71)	59 (49)	311 (56)	151 (38)	**1.45 (1.18 to 1.78)†**
Atopic	153 (80)	75 (59)	329 (57)	173 (42)	**1.36 (1.15 to 1.59)†**
Rhinitis (ever)	158 (83)	108 (86)	364 (63)	180 (44)	0.97 (0.88 to 1.07)
Eczema (ever)	119 (63)	70 (56)	262 (45)	124 (31)	1.11 (0.92 to 1.35)
ICS (current)	19 (10)	10 (8)	–	–	1.26 (0.61 to 2.63)
ICS+LABA (current)	37 (19)	16 (14)	–	–	1.54 (0.89 to 2.64)

*p<0.05; †p<0.001.
BMI, body mass index; FH, family history; ICS, inhaled corticosteroid; LABA, long-acting β_2-receptor agonist; MD, mean difference; RR, risk ratio.
The bolded text identifies results reaching statistical significance (p<0.05).

Table 2 Difference in lung function between early-onset and late-onset adult asthma

	Early-onset (n=191) Mean (SD)	Late-onset (n=127) Mean (SD)	Unadjusted mean difference MD (95% CI)	Adjusted mean difference† MD (95% CI)
Pre-BD (% predicted)				
FEV_1	87.2 (16.5)	90.1 (15.2)	−2.8 (−6.4 to 0.8)	−2.7 (−6.3 to 0.9)
FVC	95.0 (13.3)	96.1 (12.8)	−1.1 (−4.1 to 1.9)	0.1 (−3.0 to 3.2)
FEV_1/FVC	91.1 (10.9)	92.7 (9.6)	−1.6 (−3.9 to 0.8)	**−2.8 (−5.3 to −0.3)***
$FEF_{25–75}$	73.6 (29.9)	77.1 (27.7)	−3.5 (−10.1 to 3.0)	−7.0 (−14.5 to 0.5)
Post-BD (% predicted)				
FEV_1	91.6 (15.0)	94.5 (14.2)	−3.0 (−6.3 to 0.4)	−2.4 (−5.8 to 0.9)
FVC	96.8 (12.6)	97.8 (12.1)	−1.1 (−3.9 to 1.8)	0.3 (−2.9 to 3.4)
FEV_1/FVC	94.2 (10.7)	95.8 (9.2)	−1.6 (−3.9 to 0.7)	**−2.6 (−5.0 to 0.1)***
$FEF_{25–75}$	83.2 (31.0)	89.0 (29.8)	−5.8 (−12.7 to 1.1)	**−8.7 (−16.6 to 0.7)***
Reversibility, %Δ	6.0 (7.7)	5.5 (6.4)	0.4 (−1.2 to 2.1)	0.9 (−0.8 to 2.5)

*p<0.05.
†Adjusted for smoking status, social class, family history of obstructive lung, childhood lung infections.
BD, bronchodilator; FEF, forced expiratory flow; MD, mean difference.
The bolded text identifies results reaching statistical significance (p<0.05).

were more common in adults with early-onset asthma. Hospitalisation for asthma in the last year was also higher in the early-onset group. These findings were unchanged by adding current ICS use to the multivariable models.

Asthma–smoking interaction and post-BD lung function

We observed a two-way interaction between the effects of late-onset asthma and active smoking on post-BD FEV_1/FVC (table 4). Late-onset asthmatics who were active smokers (≥1 pack-year smoking history) had reductions in post-BD FEV_1/FVC that were significantly greater than the individual effects of late-onset asthma and smoking combined (p value for interaction=0.01). The reduction in post-BD FEV_1/FVC due to this interaction was 5.0% predicted units. This was equivalent to an absolute FEV_1/FVC loss of 3.9% in males and 4.1% in females. This interaction was not evident in adults with early-onset disease (p value for interaction=0.34) (table 5). Adjusting for a continuous measurement of pack-year smoking history did not significantly alter the results.

Remitted asthma

Adults with remitted asthma had similar lung function to the control group, with only mild evidence of airflow limitation. The effect size was considerably smaller than for early-onset or late-onset current asthma (see online supplementary results E1).

MI for handling missing data

The proportion of missing data in the confounding variables ranged from 2% for social class to 3% for smoking status. Results from the MI analysis (see online supplementary results E2–E5) were similar to the CCA with only slight differences observed for the estimated association with nocturnal asthma

Table 3 Difference in clinical outcomes between early-onset and late-onset adult asthma

	Early-onset (n=191) Median [IQR]	Late-onset (n=127) Median [IQR]	Unadjusted estimates RD (95% CI)	Adjusted estimates† RD (95% CI)
Asthma score‡	4 [2–6]	4 [3–5]	−0.1 (−0.5 to 0.4)	0.9 (−0.0 to 1.8)
	N (%)	**N (%)**	**RR (95% CI)**	**RR (95% CI)**
Wheeze with dyspnoea (last year)‡	109 (57)	78 (61)	0.93 (0.78 to 1.12)	1.12 (0.88 to 1.43)
Woken up with chest tightness (last year)‡	98 (51)	56 (44)	1.16 (0.92 to 1.48)	**1.39 (1.01 to 1.90)***
Woken by shortness of breath (last year)‡	65 (34)	36 (28)	1.20 (0.85 to 1.69)	**1.53 (1.02 to 2.30)***
Dyspnoea (after exercise)‡	57 (30)	52 (41)	0.73 (0.54 to 0.99)	0.88 (0.61 to 1.27)
Dyspnoea (at rest)	17 (9)	15 (12)	0.75 (0.39 to 1.45)	1.07 (0.51 to 2.21)
Asthma severity‡				
Asymptomatic	36 (22)	20 (20)	–	–
Intermittent	48 (30)	21 (21)	1.27 (0.60 to 2.69)	1.82 (0.69 to 4.78)
Mild, persistent	31 (19)	26 (26)	0.66 (0.31 to 1.41)	0.98 (0.38 to 2.53)
Moderate, persistent	31 (19)	20 (20)	0.86 (0.39 to 1.89)	1.28 (0.44 to 3.68)
Severe, persistent	16 (10)	13 (13)	0.68 (0.27 to 1.70)	1.01 (0.34 to 2.95)
Asthma hospitalisation (last year)	4 (2)	0 (0)	–	–

*p<0.05.
†Adjusted for gender, age, smoking status, social class, family history of obstructive lung disease, childhood lung infections.
‡Analysis performed using Poisson regression with robust error variance.
RD, rate difference; RR, risk ratio.
The bolded text identifies results reaching statistical significance (p<0.05).

Table 4 Interaction between late-onset asthma and smoking on post-BD FEV_1/FVC (% predicted)

	Smoking (≥1 pack-year)	Post-BD FEV_1/FVC	$p_{[Interaction]}$
Control (never asthma)	No	Reference	
	Yes	−1.94 (−3.34 to −0.54)*	
Late-onset	No	−0.65 (−0.34 to 2.04)	**0.01**
	Yes	−7.61 (−10.26 to −4.97)†	

Adjusted for smoking status, social class, family history of obstructive lung disease, childhood lung infection.
*p<0.01; †p<0.001.
BD, bronchodilator.
The bolded text identifies results reaching statistical significance (p<0.05).

symptoms. Before and after imputation, the associations between early-onset asthma and 'waking due to chest tightness in the last year' were risk ratio (RR) 1.39 (95% CI 1.01 to 1.90) and RR 1.25 (95% CI 0.94 to 1.66), respectively.

DISCUSSION

Asthma is a common condition, with over 15% of this middle-aged sample having current asthma as defined in our study. Of these, approximately half were early-onset persisting into adulthood, and half were late-onset.

Key features associated with early-onset adult asthma were atopy and family history of asthma, whereas late-onset adult asthma was more related to female gender, current smoking and low socioeconomic status. The impact on lung function of early-onset asthma was considerably greater than for late-onset asthma, although asthma severity and overall asthma symptom score were not significantly different between the two groups. In contrast, nocturnal symptoms and hospital admissions in the preceding year were both more common in adults with early-onset disease.

Our results reaffirm that age-at-onset is an important distinguishing factor of adult asthma phenotypes. While clinically, adults with early-onset and late-onset asthma have similar overall disease severity and symptom frequency, key differences in their sociodemographic characteristics suggest the two phenotypes may have differing aetiological factors and detailed pathophysiologies.

Reweighted population prevalence

While the prevalence of 'current' and 'ever asthma' identified in our study was high compared with international standards, these findings were not entirely unexpected. Australia is known to have one of the highest rates of asthma worldwide, with estimates of current asthma prevalence from the ECRHS (Australia) and a Melbourne-based study being comparable to the TAHS (11.9% and 17.4%, respectively).[16 17] The prospective nature of our study also meant that prevalence estimates of remitted asthma were likely to be higher, but more accurate, than previous cross-sectional studies. In support of this, we have previously demonstrated that up to 34% of young adults do not recall having asthma in early childhood, whereas only 3% incorrectly recall having childhood asthma where they did not.[18] On the other hand, our definition of asthma also included wheezy breathing, which may not always be representative of asthma, particularly in younger age-groups.

Table 5 Interaction between early-onset asthma and smoking on post-BD FEV_1/FVC (% predicted)

	Smoking (≥1 pack-year)	Post-BD FEV_1/FVC	$p_{[Interaction]}$
Control (never asthma)	No	Reference	
	Yes	−1.96 (−3.36 to −0.57)*	
Early-onset	No	−5.16 (−6.97 to −3.35)†	0.34
	Yes	−8.83 (−11.78 to −5.89)†	

Adjusted for smoking status, social class, family history of obstructive lung disease, childhood lung infection.
*p<0.01; †p<0.001.
BD, bronchodilator.

Basic characteristics and aetiology

Familial factors appear to play a greater role in early-onset adult asthma, which commonly manifests as atopic asthma in childhood that persists into adulthood.[19] The relationship between early-onset persistent asthma and family history has been previous reported, and genome-wide association studies have further linked specific genetic variants with increased susceptibility to asthma onset in childhood.[20 21] More recently, the GABRIEL consortium has demonstrated that while early-onset and late-onset asthma share a number of genetic susceptibilities, there are distinct differences in susceptibilities between the two groups. Of the genetic variants common to both, the effects were reported to be generally more pronounced for childhood-onset asthma.[22] To date, such studies have been cross-sectional.

In contrast, late-onset adult asthma likely differs biologically.[20] There is emerging evidence supporting the role of female reproductive history in the pathogenesis of adult-onset asthma, particularly in relation to contraception and hormonal replacement therapy.[23 24] Asthma incidence in females also varies in concordance with the timing of the major lifetime biological patterns in hormonal changes, most notably during puberty and menopause.[25 26] Smoking is another well-documented risk factor for new-onset asthma, despite some inconsistency in the epidemiological data.[27] Our findings support the hypothesis that late-onset asthma may be related to female hormones and current smoking. The link between low socioeconomic status and late-onset asthma may be reflective of the greater number of smokers in this group, but could also be partially attributed to factors relating to lifestyle, house-hold dampness and fungal exposure, as well as reduced access to healthcare.[28]

Biomarkers

While not included in this paper, we have previously reported the cytokine profiles of current early-onset and late-onset asthma at age 44 years.[29] The analysis demonstrated that of the cytokines IL-4, 5, 6, 8, 10 and TNF-α, IL-4 was significantly lower in adults with late-onset compared with early-onset asthma. IL-4 is well recognised as a mediator of allergic inflammation, with critical roles in the Th2 cell development and response.[30] This finding is consistent with our current analysis and supports the concept that early-onset and late-onset asthma have differences in their underlying pathophysiology. Notably, IL-5, recognised for its association with eosinophilic asthma was not different between the two groups.

Lung function

Previous reports on the lung function difference between early-onset and late-onset asthma in adults have been largely inconsistent.[31–33] Our analysis showed that at age 44, the cumulative impact of early-onset asthma is considerably greater than

for late-onset disease. Measures of lung function spanning both large and small airways (FEV_1/FVC, $FEF_{25–75}$) were lower in adults with early-onset asthma. This was consistent for spirometry measured before and after inhaled BD. As there was no difference in FVC between the two groups, this airflow obstruction relates to a disproportionate decrease in FEV_1. Additionally, while late-onset asthma has been associated with reduced BD reversibility,[32 34] we found no significant difference in this measurement between the two groups.

Of note, our analysis could not account for duration of disease as this was intrinsically related to age of asthma onset, the defining characteristic of our two groups. The extent to which lower lung function at age 44 years is due to deficits established in childhood (and reduced maximally attained lung function in young adulthood) or due to greater lung function decline over time is a point of great interest. Unfortunately, lung function measurement was performed on only a very small number of participants during follow-ups occurring between the ages 13 and 44 years. Because of this lack of lung function data, regrettably we are unable to determine our participants' lifetime maximally attained lung function and hence impact of early-onset and late-onset asthma on lung function decline. Longitudinal follow-up of these subgroups, as is currently underway in TAHS, will provide insight into their impact on lung function decline in older adulthood.

Asthma–smoking interaction

Asthma–smoking interactions have been explored in some detail, and may be one potential mechanism underlying the overlap between asthma and COPD. To date, few studies have assessed these interactions in relation to age-of-onset phenotypes.[35] A previous TAHS analysis reported asthma–smoking interactions in both early-onset and late-onset asthma.[36] The study, however, used an age cut-off of 20 years to delineate the two groups. In conjunction with these findings, our study suggests that while smoking is an important risk factor for fixed airflow obstruction in normal individuals, in adults with asthma and particularly those with onset after age 13 years, the risk is far greater. This interaction might explain why some studies have reported greater fixed airflow obstruction in asthmatics with late-onset asthma.[37] Finally, our interaction analysis showed that fixed airflow obstruction in late-onset asthmatics was largely attributable to the effects of smoking (both independently and via asthma–smoking interaction), whereas early-onset asthma was in itself a strong independent risk factor that was worsened by smoking.

Strengths and limitations

There are several strengths that distinguish our study from the previous literature. First, the Tasmanian Longitudinal Cohort Study is a whole-population-based cohort, this allowed us to accurately estimate the prevalence of current asthma in a middle-aged sample. Second, data on asthma age-at-onset was prospectively collected, hence participants were more reliably categorised as being early-onset or late-onset. Previous cross-sectional studies have relied solely on retrospective data collected in adulthood, which is subject to recall bias and has been shown to result in differential misclassification.[18 38 39] Finally, our subjects were age-standardised by nature of their original recruitment, and an extensive dataset allow us to account for the effects of potential confounding in the statistical analysis.

It should be noted that our study used only a single age-of-onset cut-off. Age 13 years was selected to be most consistent with previous literature,[11] and it also represents the age at which prevalence of asthma changes from being higher in males, to being higher in females. It is likely that these subgroups could be further refined, not only by age cut-off, but also in combination with other important variables, such as atopy and inflammatory subtype. New statistical methods of determining asthma phenotypes based on multiple variables appear promising.[9 10] Cluster-based approaches incorporating objective clinical data, such as age-at-onset, with genetic and biological markers may facilitate the development of clinically relevant, treatment-specific phenotypes.

CONCLUSION

This study used prospectively collected data to determine the phenotype prevalence of early-onset and late-onset current asthma in a large population-based cohort. Key differences separating the two phenotypes include their relative association with familial compared with environmental factors. Clinically, both groups appear to have similar disease severity despite different durations of disease. In contrast, early-onset asthma was associated with significantly greater pre-BD and post-BD airflow obstruction, higher frequency of nocturnal symptoms and hospitalisation for asthma in the preceding year. Overall, this study reaffirms that age at onset is an important determinant of different asthma phenotypes in adults.

Author affiliations
[1]Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia
[2]NHMRC Centre of Research Excellence for Chronic Respiratory Disease, School of Medicine, University of Tasmania, Hobart, Tasmania, Australia
[3]Menzies Research Institute, Hobart, Tasmania, Australia
[4]Murdoch Children Research Institute, Melbourne, Victoria, Australia
[5]Biostatistics Unit, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia
[6]Department of Medicine, University of Queensland, Brisbane, Queensland, Australia
[7]Department of Allergy Immunology and Respiratory Medicine, Alfred Hospital, Melbourne, Victoria, Australia
[8]Department of Medicine, University of New South Wales, Sydney, New South Wales, Australia
[9]Gold Coast Hospital, Southport, Queensland, Australia
[10]Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne, Victoria, Australia
[11]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia

Acknowledgements We wish to acknowledge the participants and previous investigators of the Tasmanian Longitudinal Health Study (TAHS). We thank Mark Jenkins, Centre for Epidemiology and Biostatistics, University of Melbourne, Australia, who is a TAHS investigator but not a coauthor of this manuscript, for his assistance in obtaining funds and data collection. We also acknowledge all the respiratory scientists who collected data in the lung function laboratories of Tasmania, Victoria, Queensland and New South Wales; the research interviewers and data entry operators and the organisational roles of Ms Cathryn Wharton and Dr Desiree Mészáros. The Archives Office of Tasmania provided data from the 1968 and 1974 TAHS questionnaires and copies of the school medical records.

Contributors Study concept and design: SCD, EHW, MJA, DPJ, GGG and JLH. Acquisition of data: SCD, EHW, MJA, MCM, PST, IF, SM, DPJ and JAB. Analysis and interpretation of data: DJT, SCD, JLP, JAB, JAS, PHR and EHW. Drafting of the manuscript: DJT, JLP, SCD and EHW. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: DJT, JLP, JAB, PHR and SCD. Obtained funding: SCD, EHW, SM, MJA, DPJ and JLH. Administrative, technical and material support: SCD. Study supervision: SCD, EHW, JLP and JAB.

Funding Supported by the National Health and Medical Research Council of Australia grant 299901; Clifford Craig Medical Research Trust of Tasmania; Victorian, Queensland and Tasmanian Asthma Foundations and the Australian Lung Foundation.

Competing interests None declared.

Ethics approval The study was approved by the Human Ethics Review Committees at The Universities of Melbourne, Tasmania and New South Wales, the Alfred Hospital, and Royal Brisbane and Women's Hospital Health Service District. Written informed consent was obtained from all participants.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Bateman ED, Hurd SS, Barnes PJ, *et al*. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31:143–78.
2 Basagaña X, Sunyer J, Kogevinas M, *et al*. Socioeconomic status and asthma prevalence in young adults: the European Community Respiratory Health Survey. *Am J Epidemiol* 2004;160:178–88.
3 Gibson PG, McDonald VM, Marks GB. Asthma in older adults. *Lancet* 2010;376:803–13.
4 Enright PL, McClelland RL, Newman AB, *et al*. Underdiagnosis and undertreatment of asthma in the elderly. Cardiovascular Health Study Research Group. *Chest* 1999;116:603–13.
5 Beasley R, Weatherall M, Travers J, *et al*. Time to define the disorders of the syndrome of COPD. *Lancet* 2009;374:670–2.
6 Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? *Thorax* 2009;64:728–35.
7 Soler-Cataluña JJ, Cosío B, Izquierdo JL, *et al*. Consensus document on the overlap phenotype COPD-asthma in COPD. *Arch Bronconeumol* 2012;48:331–7.
8 Postma DS, Rabe KF. The asthma-COPD overlap syndrome. *N Engl J Med* 2015;373:1241–9.
9 Haldar P, Pavord ID, Shaw DE, *et al*. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218–24.
10 Moore WC, Meyers DA, Wenzel SE, *et al*. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;181:315–23.
11 Tan DJ, Walters EH, Perret JL, *et al*. Age-of-asthma onset as a determinant of different asthma phenotypes in adults: a systematic review and meta-analysis of the literature. *Expert Rev Respir Med* 2015;9:109–23.
12 Gibson HB, Silverstone H, Gandevia B, *et al*. Respiratory disorders in seven-year-old children in Tasmania. Aims, methods and administration of the survey. *Med J Aust* 1969;2:201–5.
13 Giles GG, Lickiss N, Gibson HB, *et al*. Respiratory symptoms in Tasmanian adolescents: a follow up of the 1961 birth cohort. *Aust N Z J Med* 1984;14:631–7.
14 Miller MR, Hankinson J, Brusasco V, *et al*. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
15 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179–87.
16 Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996;9:687–95.
17 Abramson M, Kutin J, Czarny D, *et al*. The prevalence of asthma and respiratory symptoms among young adults: is it increasing in Australia? *J Asthma* 1996;33:189–96.
18 Burgess JA, Walters EH, Byrnes GB, *et al*. Who remembers whether they had asthma as children? *J Asthma* 2006;43:727–30.
19 London SJ, James Gauderman W, Avol E, *et al*. Family history and the risk of early-onset persistent, early-onset transient, and late-onset asthma. *Epidemiology* 2001;12:577–83.
20 Bouzigon E, Corda E, Aschard H, *et al*. Effect of 17q21 variants and smoking exposure in early-onset asthma. *N Engl J Med* 2008;359:1985–94.
21 Moffatt MF, Kabesch M, Liang L, *et al*. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature* 2007;448:470–3.
22 Moffatt MF, Gut IG, Demenais F, *et al*. A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med* 2010;363:1211–21.
23 Jenkins MA, Dharmage SC, Flander LB, *et al*. Parity and decreased use of oral contraceptives as predictors of asthma in young women. *Clin Exp Allergy* 2006;36:609–13.
24 Romieu I, Fabre A, Fournier A, *et al*. Postmenopausal hormone therapy and asthma onset in the E3N cohort. *Thorax* 2010;65:292–7.
25 Almqvist C, Worm M, Leynaert B, working group of GALENWPG. Impact of gender on asthma in childhood and adolescence: a GA2LEN review. *Allergy* 2008;63:47–57.
26 Real FG, Svanes C, Omenaas ER, *et al*. Lung function, respiratory symptoms, and the menopausal transition. *J Allergy Clin Immunol* 2008;121:72–80.e3.
27 Polosa R, Thomson NC. Smoking and asthma: dangerous liaisons. *Eur Respir J* 2013;41:716–26.
28 Matheson MC, Abramson MJ, Dharmage SC, *et al*. Changes in indoor allergen and fungal levels predict changes in asthma activity among young adults. *Clin Exp Allergy* 2005;35:907–13.
29 Kandane-Rathnayake RK, Tang ML, Simpson JA, *et al*. Adult serum cytokine concentrations and the persistence of asthma. *Int Arch Allergy Immunol* 2013;161:342–50.
30 Steinke JW, Borish L. Th2 cytokines and asthma. Interleukin-4: its role in the pathogenesis of asthma, and targeting it for asthma treatment with interleukin-4 receptor antagonists. *Respir Res* 2001;2:66–70.
31 Holguin F, Comhair SA, Hazen SL, *et al*. An association between L-arginine/asymmetric dimethyl arginine balance, obesity, and the age of asthma onset phenotype. *Am J Respir Crit Care Med* 2013;187:153–9.
32 Hsu JY, King SL, Kuo BI, *et al*. Age of onset and the characteristics of asthma. *Respirology* 2004;9:369–72.
33 Ségala C, Priol G, Soussan D, *et al*. Asthma in adults: comparison of adult-onset asthma with childhood-onset asthma relapsing in adulthood. *Allergy* 2000;55:634–40.
34 Rossall M, Cadden P, Kolsum U, *et al*. A comparison of the clinical and induced sputum characteristics of early- and late-onset asthma. *Lung* 2012;190:459–62.
35 Perret JL, Walters EH, Abramson MJ, *et al*. The Independent and combined effects of lifetime smoke exposures and asthma as they relate to COPD. *Expert Rev Respir Med* 2014;8:503–14.
36 Perret JL, Dharmage SC, Matheson MC, *et al*. The interplay between the effects of lifetime asthma, smoking, and atopy on fixed airflow obstruction in middle age. *Am J Respir Crit Care Med* 2013;187:42–8.
37 Miranda C, Busacker A, Balzar S, *et al*. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol* 2004;113:101–8.
38 Brogger J, Eagan T, Eide GE, *et al*. Bias in retrospective studies of trends in asthma incidence. *Eur Respir J* 2004;23:281–6.
39 Strachan DP, Griffiths JM, Johnston ID, *et al*. Ventilatory function in British adults after asthma or wheezing illness at ages 0–35. *Am J Respir Crit Care Med* 1996;154(Pt 1):1629–35.