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The level of specialist assessment of adult asthma is influenced by patient age

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Summary
Background: Late onset asthma is associated with more severe disease and higher morbidity than in younger asthma patients. This may in part relate to under recognition of asthma in older adults, but evidence on the impact of patient age on diagnostic assessment of asthma in a specialist setting is sparse.
Aim: To examine the impact of patient age on the type and proportion of diagnostic tests performed in patients undergoing specialist assessment for asthma.
Methods: Data from a clinical population consisting of all patients consecutively referred over a 12 months period to a specialist clinic for assessment of asthma were analysed.
Results: A total of 224 patients with asthma or suspected asthma were referred during the 12 month period; 86 adults aged <35 years, 95 aged 35–55 years and 43 aged >55 years. Symptom characteristics were similar, but adults >35 years had a lower lung function than younger adults, and were more frequently smokers. However, a regression analysis showed that older age was associated with a lower likelihood of diagnostic assessment with a reversibility test, a bronchial challenge test, or measurement of exhaled NO, independently of a known diagnosis of asthma, smoking habits and lung function at referral.
Conclusion: A lower level of diagnostic assessment was observed already after the age of 35 years, indicating a risk for under diagnosis of asthma at an earlier patient age than previously thought.

Abbreviations: FeNO, fraction of exhaled nitric oxide; SABA, short-acting beta-2-agonist; SPT, skin prick test; AHR, airway hyperresponsiveness; PRF, patient record form.

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Introduction

Diagnostic assessment of asthma is the starting point of asthma management: International Guidelines recommend that a diagnosis of asthma is based on symptom history combined with objective measures of variable airflow obstruction, e.g. reversibility to beta-2-agonist, peak flow variability or airway hyperresponsiveness [1,2]. The next step is to assess asthma control to determine the need for commencing treatment, and a baseline assessment from which the effect of treatment may be determined [1].

In patients with known asthma and insufficiently controlled asthma symptoms, obtaining objective disease evidence may furthermore be important, to differentiate asthma symptoms from non-specific symptoms that may relate to other factors such as poor fitness or hyperventilation. Finally, measurement of markers of the asthma phenotype, such as allergic sensitisation or eosinophilic airway inflammation, may aid in targeting treatment to the individual patient [3–5].

Under diagnosis of asthma, and under recognition of the severity of asthma, has significant adverse impact on the treatment of asthma: In a Danish population sample of 10,877 adults aged 18–44 years, only 50% of asthma cases had previously been diagnosed, and among the previously undiagnosed cases, 74% had persistent symptoms (>2/week) indicating a significant unmet need for treatment [6].

Older asthma patients have a higher morbidity than younger asthma patients, in terms of a lower lung function and more severe exacerbations [7–10]. This may in part relate to an under recognition of asthma by physicians as well as patients [11–14]: In a community sample of 4581 persons >65 years old from the Cardiovascular Health Study, only half of those with asthma like symptoms had a previous diagnosis of asthma [11]. Similarly, in a retrospective study of 98 individuals with asthma onset after the age of 65 years, only 43% had a spirometry performed in relation to having the diagnosis made [14].

However, there is limited evidence of whether specialists assess asthma in older adults differently to younger adults within the same clinical setting. Given that late onset asthma is generally reported to be associated with irreversible airflow obstruction [14,15], clinicians could be less likely to test older adults for reversibility or airway hyperresponsiveness. Furthermore, since that late onset asthma is more often non-atopic [16,17], it may be that the use of additional diagnostic tests to aid in a phenotypic characterisation of asthma, such as measurement of exhaled nitric oxide (FeNO) and skin prick testing for allergy is used less frequently in the older patients. Finally, it is unclear whether specialists have a different approach to adult asthma patients already earlier on, i.e. after the age of 35–40 years.

We hypothesized that in a specialist clinic, the level of diagnostic assessment of adult asthma is influenced by patient age. Hence, we compared the number and type of diagnostics tests performed in a clinical cohort of patients consecutively referred for assessment of asthma over a 12 month period, and compared young, middle aged and older adults.

Methods

A complete population of all patients consecutively referred to a specialist asthma clinic for either suspected or known asthma, over a 12 months period in 2010, were studied at the outpatient clinic at the Department of Respiratory Medicine at Bispebjerg University Hospital, Copenhagen, Denmark. A retrospective design was purposefully chosen to avoid observer bias, as the outcome of interest was the pattern of specialist assessment of older versus younger adults.

Data was obtained from patient record forms (PRF), including physician notes on asthma symptoms, including characterisation of symptoms, asthma medications used and diagnostic tests requested. The study was approved by the Danish National Health Board (Jr Nr 7-604-04-2/279/KWH), as this retrospective study did not require approval from the Ethics Committee.

The following was registered, regarding the level of diagnostic assessment:

Symptoms:

- *Symptoms assessed*: Did the physician *record* the following asthma symptoms at rest and during exercise: Shortness of breath, tightness of the chest, wheezing and cough?
- *Symptoms reported*: If recorded, did the patient *report* any of above asthma symptoms?

Diagnostic tests performed:

- Reversibility of FEV_1 to short-acting beta-2-agonist (SABA)?
- Bronchial challenge with either methacholine or mannitol?

Additional tests performed:

- Measurement of exhaled nitric oxide (FeNO)?
- Skin prick test (SPT) to a standard panel of inhalation allergens.

Description of the diagnostic methods

- Spirometry (Jaeger MasterSceen Pneumo spirometer, CareFusion, Yorba Linda, CA): best of two measurements of FEV_1, FVC and FEV_1/FVC ratio according to ERS recommendations [18]. Reversibility test 20 min after inhalation with terbutaline sulphate (1.5 mg).
- Exhaled NO (FeNO) (NIOX, Intra Medic, Denmark) average of 3 measurements (flow rate 50 ml) was measured according to the ATS/ERS guidelines [19].
- Mannitol provocation test (osmohale™ Mannitol, pharmaxis, UK): inhalation of ascending dosages 0, 5, 10, 20, 40, 80, 160, 160, 160 mg [20]. A positive test was defined as a 15% fall in FEV_1 or more and resulted in termination of test.
- Methacholine provocation test with the Yan method (Jaeger device, nebulised fluid: methacholine bromide): Inhalation of isotonic saline, thereafter five successively

increasing doses of methacholine ranging from 0.06 to 8 μmol were delivered, until a cumulated dose of 8 μmol or a 20% decrease in FEV_1 was reached [21]. Measurements of FEV_1 exactly 1 min after inhalation. A 20% fall in FEV_1 or more was defined as a positive result and terminated the test.

- A skin prick test to 10 aeroallergens (birch [Betula species], grass [Phleumpratense] mugwort, horse, dog, cat [Felis domesticus], house dust mite [Der p1 and Der f2], and fungi [Alternaria and Cladosporium species; ALK-Abello, Hoersholm, Denmark]) according to the EAACI recommendations [22]. Allergic sensitization was defined as a positive skin prick test response to at least 1 of these 10 aeroallergens.

Statistical analysis

Patients were divided into three groups, in order to evaluate how the pattern of diagnostic testing changed with increasing age: Young adults: age <35 years, middle aged adults: age 35–55 years, and older adults: age >55 years at the time of referral.

Patient characteristics were compared for the three age groups using chi-square tests for categorical variables and anova for continuous variables. Pair-wise comparisons were subsequently made with chi-square test and non-paired *t*-tests.

As the proportion of patients with known asthma at referral did not differ between the three age groups, data was analysed without a separation of patients with suspected and known asthma at referral. Known asthma was defined a patient reported previous doctors diagnosis of asthma.

The proportion of patients within the three age groups who had a diagnostic test was compared, using a Chi^2 test. Furthermore, a backward regression analysis was performed to determine whether the effect of patient age on the diagnostic tests performed was independent of other potential explanatory variables (smoking status, airflow obstruction (FEV_1 < 80%), known asthma at referral and symptoms of allergic rhinoconjuctivitis).

Data was analysed with SPSS version 20.0 (SPSS, Inc, Chicago, Ill).

Results

The characteristics of the 224 patients referred to the specialist clinic during 2010 are summarised in Table 1, for the three age groups (<35 years, 35–55 years and >55 years). The proportion of patients who, according to the referring physician, had known asthma at the time of referral was the same in the three age groups (44%, 40% and 42%, NS). The FEV_1% as well as the FEV_1/FVC% of predicted was lower in the two older age groups compared to the youngest group, and accordingly a significantly higher proportion of patients with reduced FEV_1 (FEV < 80% of predicted: 20%, 40% and 53% respectively).

In spite of the lower lung function, the use of regular anti-inflammatory medications was similar in the three groups, with 42% of young adults, 48% of adults aged 35–55 years, and 45% of adults >55 years using either ICS or an ICS + LABA (ns)(Table 1).

A previous smoking history was more common in the older age groups, with approximately half of adults >55 years being either current or previous smokers (Table 1).

The diagnosis recorded in the PRF by the specialist was compared for the three age groups: After the specialist assessment, older adults were less likely to receive a final diagnosis of asthma than younger adults (23% in adults >55 years vs 54% in adults aged 35–55 years and 59% in <3 year olds, $p < 0.001$).

Symptom assessment recorded in the PRF showed that symptoms at rest were assessed for a similar proportion of patients in the three age groups (Fig. 1). Furthermore, the symptoms reported were similar, except for cough and phlegm production, which were more frequently reported in adults aged 35–55 years vs adults <35 years (Cough: 47% vs 25%, $p < 0.05$. Phlegm production: 7.9% vs 18.4%,

Table 1 Patient characteristics in 224 patients referred for specialist assessment of asthma.

	<35 Years (n = 86)	35–55 Years (n = 95)	>55 Years (n = 43)	p
Age (years, median (min–max))	24 (15–34)	44 (35–54)	64 (55–82)	<0.001
Gender (female)	54.7%	55.8%	67.4%	0.34
BMI (mean (SD))	23.2 (3.6)	26.3 (4.5)	26.1 (4.2)	<0.001
Smoker	12.0%	14.9%	20.9%	0.69
Ex-smoker	6.2%	17.6%[b,*]	27.5%[b,*]	0.009
Known asthma at referal[a]	44.0%	40.4%	41.9%	0.89
ICS	19.7%	21.0%	14.9%	0.44
ICS + LABA	22.1%	27.3%	30.2%	0.64
FEV_1% (mean (SD))	92.3 (±16.6)	85.5 (±21.5)[b,*]	76.2 (±24.0)[b,**]	<0.001
FVC% (mean (SD))	98.1 (±17.1)	93.2 (±22.3)	83.8 (±18.5)[b,**]	0.003
FEV_1/FVC% (mean (SD))	0.80 (±0.11)	0.75 (±0.10)	0.71(±0.14)	0.001
FEV_1 < 80% of predicted (% (n))	19.7% (15)[b,*]	39.5% (32)	52.5% (21)[b,**]	0.001

*$p < 0.05$.
**$p < 0.001$.
[a] Previous diagnosis of asthma at the time of referal.
[b] Comparison with young age group (<35 years).

$p < 0.01$). Only one subject, aged >55 years, reported chronic mucus secretion (i.e. cough and phlegm for more than three months, two years in a row). Smokers had more cough than non-smokers (58.6% vs 34.8%, $p < 0.05$), but similar frequencies of other respiratory symptoms.

In comparison, symptoms during exercise were more frequently assessed in the youngest age group (shortness of breath, tightness of the chest and wheezing (Fig. 1(A)), and this group also reported more exercise related symptoms (Fig. 1(B))).

The degree of diagnostic assessment differed between the three age groups: Although patients >35 years more often had a reduced lung function, a similar number had a reversibility test performed (Table 2). Bronchial challenge testing was performed more often in the youngest age group, which was in keeping with the majority of this group having a normal lung function. On the other hand, 78% of 35–55 year olds, and 60% of the >55 year olds had a lung function that allowed for a bronchial challenge ($FEV_1 > 70\%$). Overall, the number of diagnostic tests was higher in the younger age group, with only few older adults having more than one test performed (Table 2).

In order to adjust for the confounding effect of the lower lung function and higher smoking history in older adults, a regression analysis was performed. This showed that older age was independently associated with a lower likelihood of having a reversibility test performed, or a bronchial challenge (Table 3). Similarly, older age was associated with a lower likelihood of having additional testing with measurement of FeNO, as well as skin prick testing performed (Table 3).

When comparing the test results for those patients in each age group, who did have a test performed, there was no significant difference in the degree of reversibility or in the proportion of subjects with a positive bronchial challenge test (Table 4). Furthermore, the level of FeNO as well as the proportion of patients with a positive skin prick test to aeroallergens, was similar in all three age groups, among those tested (Table 4). Despite the lower number of tests performed in the oldest age groups, the proportion of subjects with a positive objective test (reversibility or AHR) was the same in all three groups; (31%, 36% and 36%, ns).

According to the specialist evaluation, older adults were more frequently concluded to have COPD or a combination of COPD and asthma, than younger adults: (Age >55 years: Asthma: 30.2%, asthma/COPD: 14.0%, COPD: 16.3%. Age <55 years: Asthma 57.2%, asthma/COPD: 2.1%, COPD: 1.2%, $p < 0.001$).

Table 3 Backward regression analysis of predictors of diagnostic tests performed.

	OR	C.I.	p
Reversibility to SABA			
Age group[a]	0.62	0.41–0.95	0.03
Current smoker	0.92	0.84–0.99	0.04
FEV_1 < 80% of predicted	1.82	0.93–3.57	0.08
Known asthma at referal	0.77	0.57–1.03	0.08
Bronchial challenge[b]			
Age group[a]	0.62	0.40–0.95	0.03
Current smoker	0.93	0.85–1.01	0.08
FEV1<80% of predicted	0.37	0.19–0.73	0.004
Known asthma at referal	0.74	0.52–1.06	0.11
FeNO			
Age group[a]	0.59	0.38–0.90	0.01
Current smoker	0.90	0.83–0.98	0.02
Skin prick test performed[c]			
Age group[a]	0.65	0.42–1.02	0.06
Current smoker	0.92	0.84–0.99	0.04
FEV_1 < 80% of predicted	0.57	0.29–1.10	0.09
Symptoms of allergic rhinoconjuctivitis	0.93	0.85–1.01	0.08

[a] Age group: <35 years, 35–54 years, >55 years.
[b] Bronchial challenge with methacholine or mannitol.
[c] Panel of ten aeroallergens (grass, birch mugwort, cat,dog,-horse, derm P, derm F, cladosporium, alternaria).

Discussion

In this clinical population consisting of all patients referred consecutively over a 12 months period for assessment of asthma, we found that commonly objective diagnostic tests for asthma were applied less frequently in older adults, already from the age of 35 years, indicating a potential under diagnosis of asthma from early middle age.

Most studies have described older adults, typically aged over 55–60 years [12,23], and younger adults [24], and less is known about how the age group in between is typically assessed. Adult onset asthma is however common, and it has recently been found that in females, adult onset

Table 2 Diagnostic tests performed in young, middle aged and older adults referred for specialist assessment of asthma.

	<35 Years ($n = 86$)	35–55 Years ($n = 95$)	>55 Years ($n = 43$)	p
Reversibility test to SABA performed	54%[NS]	55%[NS]	37%[NS]	0.12
Bronchial challenge testing performed[a]	57%	40%*	28%*	0.004
Number of diagnostic tests performed (reversibility or bronchial challenge test):				
0	31%	29%	42%	
1	29%	47%	51%	
2	40%	24%	7%	0.001
FeNO measurement performed	70%	58%	48%*	0.04
Skin prick test performed	65.1%	52.1%[NS]	38.1%*	0.014

*$p < 0.05$. NS: non-significant, $p > 0.05$.
[a] Bronchial challenge with methacholine, mannitol or comparison with young age group (<35 years).

Table 4 Proportion of positive tests[a] in young, middle aged and older adults referred for specialist assessment of asthma.

	<35 Years	35–55 Years	>55 Years	*p*
Reversibility to SABA >12% (% (*n*/*n*))	18% (8/44)	28% (14/51)	37% (6/16)	0.28
ΔFEV_1 (%) (mean (SD))	8.4% (7.8)	10.5% (15.5)	10.1% (8.4)	0.68
Bronchial challenge test positive[b](% (*n*/*n*))	44% (19/41)	49% (20/37)	62% (9/13)	0.64
FeNO > 25 ppb (% (*n*/*n*))	21% (12/57)	30% (16/54)	21% (4/19)	0.54
FeNO (ppb) (mean (SD))	22 (24)	26 (26)	24 (29)	0.69
Skin prick test positive	46% (25/54)	40% (20/50)	38% (6/16)	0.73

[a] Among patients in whom the test was performed.
[b] Bronchial challenge with methacholine, mannitol.

asthma was the most common phenotype [25]. Similarly, we found that among those referred to the specialist clinic, there was a similar number of suspected new cases of asthma in all three age groups, indicating that there is an equal requirement for diagnostic assessment of potential asthma across all adult age groups.

Part of the observed differences in diagnostic testing may relate to a reduced lung function in a large proportion of the older adults, precluding a bronchial challenge test. However, the effect of patient age on whether a bronchial challenge was performed was independent of a reduction in lung function. Furthermore, most of the older patients in the present population had an $FEV_1 > 70\%$, and could have had a bronchial provocation test performed. This could suggest that clinicians have a biased approach to older patients with possible asthma, and that older patients are assumed more likely to have COPD rather than asthma, regardless of their smoking exposure.

At the same time, given the higher degree of airflow obstruction among older patients, it is surprising that a low proportion had a reversibility test performed. Interestingly, the degree of reversibility in those tested was similar in the three age groups, indicating a similar ability of the airways to dilate in spite of a lower FEV_1 in the older patients.

We found that a similar proportion of patients in the three age groups had at least one positive diagnostic test, which could suggest that further tests were not deemed necessary in the older age group. Our results also indicate that younger adults had milder disease, hence requiring more tests before the diagnosis could be confirmed. On the other hand, a total of 42% of the oldest age group did not have a reversibility test or a bronchial challenge, and hence a substantial proportion of the older patients were not tested for variable airflow obstruction.

Under diagnosis of asthma is common in older adults [11] and may relate to under perception by patients, who do not seek their GP [26,27], as well as to a lack of diagnostic testing by the physician. Param et al. found that within a community sample of 1362 individuals, only 21 out of 95 older adults with asthma received regular ICS treatment, despite significant symptoms and airflow obstruction [12].

Symptoms of asthma are often non-specific in that other conditions such as COPD and chronic bronchitis as well as heart failure may result in similar symptoms. Hence, confirming a suspicion of asthma with an objective diagnostic test is of particular importance in older adults [28]. The lower lung function in late onset asthma could lead to misclassification as COPD. This could lead to under treatment or erroneous treatment, such as the use of LABA monotherapy. As older adults have a more severe asthma, they furthermore represent a group of patient in whom a higher level of diagnostic awareness should be present. Specifically, asthma patients with airflow obstruction and asthma/COPD overlap syndrome have been shown to have a significantly better prognosis than COPD patients [29].

Symptom characteristics did however not differ significantly between the three age groups, apart from cough being more frequent in older adults. Furthermore, symptoms in relation to exercise were not recorded as often in older adults, suggesting a degree of under assessment of symptoms.

Older adults were also more often smokers or ex-smokers, which could also influence the pattern of diagnostic testing. However, the effect of age was not explained by the patient's smoking habits, as it was independent of the effect of smoking in the regression analysis.

Measurement of FeNO and SPT to aeroallergens may be used to characterise asthma, and predict effect of specific therapies such as ICS [4,5]. They were performed less often in older patients, which may relate to assumptions regarding the inflammatory phenotype in older asthma patients. The percentage of sputum eosinophils in older asthma patients is however similar to younger patients [30], and, eosinophilic airway inflammation is also a driver of airway hyperresponsiveness in asthma in older adults [31]. Assessing markers of eosinophilic airway inflammation is therefore equally relevant in the older asthma patient. We found that in those who were tested, the level of FeNO and the proportion of atopic individuals were similar in older and younger patients.

In conclusion, in a clinical population of adults referred for asthma assessment in a specialist setting, the level of diagnostic evaluation decreased already from the age of 35 years, with the lowest proportion of diagnostic testing in the oldest age group. This may have significant negative implications for the management of asthma in middle aged and older adults.

Contributor statement

C Porsbjerg has contributed to conception and design, analysis and interpretation of data; and to drafting the article and finalising the version to be published.

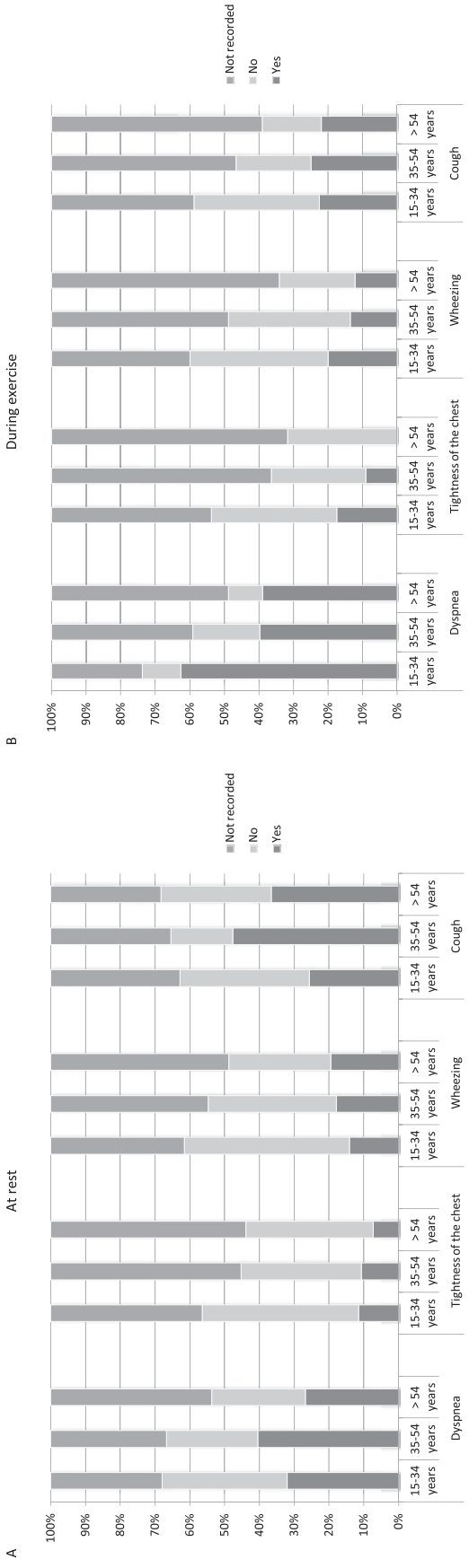

Figure 1 Respiratory symptoms* in young, middle aged and older adults referred for specialist assessment of asthma, at rest (A) and during exercise (B).

A Sverrild has contributed to conception and design, analysis and interpretation of data; and to revising it critically for important intellectual content; and on final approval of the version to be published.

L Stensen has contributed to conception and design, analysis and interpretation of data; and to revising it critically for important intellectual content; and on final approval of the version to be published.

V Backer has contributed to conception and design, analysis and interpretation of data; and to revising it critically for important intellectual content; and on final approval of the version to be published.

Data sharing statement

Additional data is available by e-mailing the corresponding author.

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