



Lung function impairment increases with age of diagnosis in adult onset asthma[☆]



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KEYWORDS

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Summary

Background: Asthma-onset in older individuals has been associated with an accelerated decline in lung function, but direct comparisons with younger adults have not been reported. **Methods:** In a random population sample comprising 4983 individuals from the Copenhagen City Heart Study without asthma at baseline, we compared young (<35 years), middle-aged (35–64 years) and older (>64 years) adults with newly diagnosed asthma during a 10-year follow-up.

Results: The proportion of cases with newly diagnosed asthma during follow-up was similar across age groups (Older adults: 7% (84/1168), middle-aged adults: 7% (223/3147), and young adults: 6% (42/668) ($p = \text{ns}$)). In all three age groups, lung function was reduced at baseline in subjects who were subsequently diagnosed with asthma, but most pronounced in those >35 years. (Mean FEV₁%: Young 90.2% (± 13.9), middle-aged 80.8% (± 20.8), and older adults 80.8% (± 24.2), $p < 0.001$). Furthermore, incident asthma was associated with an accelerated decline in lung function in older adults (young adults 11.0 mL/year, middle-aged adults 18.2 mL/year, and older adults 30.8 mL/year). These differences were independent of FEV₁ at baseline and smoking status, and were not explained by undiagnosed asthma in older adults, as the frequency of respiratory symptoms, including wheeze, was similar in all three age groups at baseline.

Abbreviations: FEV₁, Forced expiratory volume in 1 s; FVC, Forced Vital Capacity; CMH, Chronic mucus hypersecretion.

[☆] The Copenhagen City Heart Study was performed at Rigshospitalet, National University Hospital of Denmark, and Bispebjerg University Hospital, Copenhagen, Denmark.

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Conclusions: Asthma was diagnosed as frequently in older as in younger adults. Preexisting symptoms were equally common, but lung function was more reduced pre-diagnosis, and declined more rapidly in older adults. This emphasizes the need for a high level of therapeutic attention in patients with asthma diagnosed late in life.

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Introduction

Asthma starts in childhood and young adulthood in the majority of cases, but asthma in older individuals is equally common, with prevalence rates reported to be around 6–10% [1,2]. Furthermore, given that asthma is a chronic disease with a low remission rate, the epidemic of asthma among younger individuals during the past decades, the proportion of asthmatics among the older adults is expected to increase.

Asthma seems to be more difficult to control in the elderly and older patients with asthma have a higher morbidity and mortality compared to younger asthmatics [3–5]. A central question is whether asthma is more severe in older individuals, or whether the increased morbidity relates to a combination of long-standing asthma, delayed diagnosis and under treatment, higher prevalence of comorbidities such as bronchiectasis, general deconditioning, and life-time exposures to potential noxious factors such as smoking and infections [4,6,7].

Asthma appears to have more detrimental effects on the airways of older adults. Older individuals with asthma are more likely to have fixed airflow obstruction at the time of diagnosis, as well as a subsequent accelerated loss of lung function [1,8–10]. Moreover, co-existing obstructive airways diseases increase with age, and possibly up to 30% of adults >60 years with airflow obstruction have been estimated to have the asthma and COPD overlap syndrome (ACOS), i.e. a mixture of variable and reversible airflow obstruction and fixed airflow limitation [11–13].

Non-reversible airflow obstruction in older adults with incident asthma could relate to a pre-existing decrement, or to an accelerated decline in lung function [2,9,12]. However, there is limited evidence from representative, unselected populations, comparing lung function in older adults versus young adults with newly diagnosed asthma. Hence at this point, it is unclear to which degree older adults have a higher loss of lung function compared to young adults with new onset asthma.

Under-recognition of the possibility of asthma, and misinterpretation of respiratory symptoms in older adults may result in delayed diagnosis, which may lead to development of non-reversible airflow obstruction [6,15]. The majority of older adults with incident asthma experience respiratory symptoms years before being diagnosed with asthma [6,16,17], which suggests a diagnostic delay [6,15]. A recent study indicates that even in a specialist setting, the level of diagnostic assessment is lower in older adults referred on a suspicion of asthma [18]:

Irreversible airflow obstruction has evident negative impacts on quality of life and exercise capacity, but has

furthermore been shown to increase mortality in older adults with asthma [19–21]. It is therefore important to recognise the increased risk of lung function reduction in older adults with asthma [1,22,23].

The Copenhagen City Heart Study (CCHS) is a large random sample of the adult general population of Copenhagen, Denmark, followed prospectively over four decades. In the present analysis of data from CCHS, we wished to examine the relationship between age at the time of an asthma diagnosis in adulthood, and lung function impairment, by comparing young, middle-aged and older adults with newly diagnosed asthma during a 10-year follow-up period. We hypothesized that asthma diagnosed late in adulthood is associated with a higher likelihood of pre-existing lung function impairment, as well as an accelerated decline in lung function.

Methods

All individuals participated in the Copenhagen City Heart Study (CCHS), an ongoing epidemiological study of the inhabitants of the inner city of Copenhagen, Denmark [24]. Details on study design, selection procedure, description of the non-responders together with the complete examination program have been presented elsewhere [24].

In the present analysis, we used data from the 3rd and 4th examination of The Copenhagen City Heart Study: The 3rd examination was performed from 1991 to 1994, and a total of 10,135 participants were examined. The 4th examination was performed in 2001–2003, and a total of 6,237 participants were examined. Only subjects ($n = 4,983$), who participated in both examinations, and who did not self-report asthma at the 3rd examination were included in the present analysis.

In the present paper, the third and fourth examinations are termed “Baseline examination” and “Follow-up examination” respectively. The local ethics committee approved the study protocol, and informed consent was obtained from all participants (KF100.2039/91).

The diagnosis of asthma was defined by an affirmative response to the question: ‘Do you have asthma?’ This definition is in keeping with the convention of most epidemiological studies by relying on the subjects’ perception of whether or not they have the disease [25,26].

In both examinations Forced Expiratory Volume at 1 s (FEV₁) and Forced Vital Capacity (FVC) were measured with the same dry wedge spirometer (Vitalograph, Maidenhed, UK), which was calibrated weekly with a 1-L syringe. At least two measurements of FEV₁ and FVC differing by less than 5% had to be produced and the best FEV₁ was used in the analyses. The use of bronchodilators prior to

lung function testing was not standardized. Data on FEV₁ are reported in absolute values and as a percentage of the predicted value where predicted values are based on analyses of age-height and gender matched never smokers in the third examination of The Copenhagen City Heart Study [24]. A self-administered questionnaire concerning symptoms, somatic diseases, social status, smoking and drinking habits, and medications was completed and checked by one of the staff at both examinations. Participants were characterized as smokers if they were continuous smokers of cigarettes, cigars, or pipe.

Statistical analysis

In order to describe the relationship between age at asthma onset and lung function, data was analysed in three groups, according to age at the baseline examination: A group aged 20–35 years (young adults), a group aged 35–64 years (middle aged), and a group aged >64 years (older adults). The characteristics of these three groups were compared, using either the χ^2 -test, Fishers exact test, ANOVA or t-test when appropriate. The annual decline in FEV₁ was calculated from the exact number of days between the spirometry at baseline and at follow-up, and expressed as the mL/year (Δ FEV₁). In order to determine the relative effect of age at onset on FEV₁-decline in incident asthma, we performed a multivariable linear regression analysis with Δ FEV₁ as the dependent variable and age at baseline and asthma status at follow-up, as the two variables of main interest and smoking status and FEV₁% pred at baseline examination as confounders. Data was analysed with the SPSS software, Version 12.0 (SPSS Inc. Chicago, IL, USA).

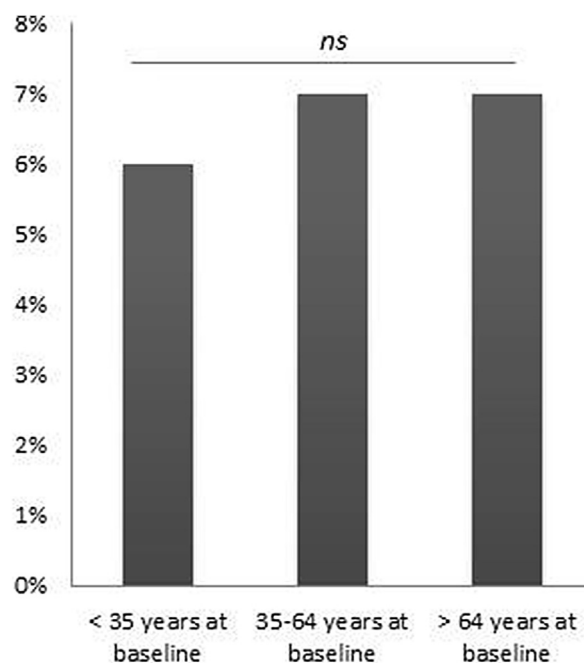
Results

A total of 4983 individuals, comprising 668 young adults (age 20–34 years), 3147 middle-aged adults (age 35–64 years), and 1168 older adults (age over 64 years) fulfilled the inclusion criteria as they reported not having asthma at the survey in 1991. Table 1 summarises participant

characteristics according to their self-reported asthma status at follow-up in 2001.

At the 10-year follow-up survey, a similar number of new cases were reported among young adults ($n = 42$, 6%), middle-aged adults (223 (7%)), and older adults (84 (7%)) (*non-significant (ns)*) (Fig. 1).

Overall, subjects with newly diagnosed asthma during follow-up, had significantly lower FEV₁% pred at baseline, compared with non-asthmatic individuals (Table 1). Furthermore, middle-aged and older adults with newly



*Comparison of all three age groups (All groups and pairwise comparisons): $p > 0.05$

Figure 1 Proportion with newly diagnosed asthma during a 10-year follow-up, according to age at baseline*.

Table 1 Characteristics of 4983 participants without asthma at enrolment, divided according to asthma status at the 10-year follow-up examination.

	Age <35 years (n = 668)		Age 35–64 years (n = 3147)		Age >64 years (n = 1168)	
	Never asthma (n = 626)	Incident asthma ^a (n = 42)	Never asthma (n = 2924)	Incident asthma ^a (n = 223)	Never asthma (n = 1084)	Incident asthma ^a (n = 84)
Sex (%female)	53%	55%	58%	69%	66%	59%
BMI (mean (SD))	22.9 (2.9)	23.1 (3.0)	25.5 (4.0)	26.1 (5.0)	26.2 (4.0)	25.7 (4.2)
Smoking:						
Current smoker (PY)	40%	40%	37%	36%	32%	45%*
FEV ₁ (L)	8.8 (6.9)	7.1 (4.3) [#]	27.1 (24.2)	27.7 (24.3) [#]	28.2 (24.1)	29.2 (24.5) [#]
(Mean, SD)	4.02 (0.87)	3.61 (0.81)	3.14 (0.83)	2.48 (0.91)*	2.23 (0.62)	1.94 (0.74)*
FEV ₁ (%)	98.0 (12.5)	90.2 (13.9)** [#]	97.0 (15.8)	80.8 (20.8)** [#]	96.9 (18.9)	80.8 (24.2)** [#]
FEV ₁ /FVC	0.84 (0.06)	0.81 (0.10)**	0.80 (0.07)	0.74 (0.11)**	0.77 (0.07)	0.70 (0.11)**

Within age group comparison of 'never asthma' vs incident asthma': * $p < 0.05$, ** $p < 0.001$.

Comparison of younger (<35 years) vs older group (35–64 years or > 64 years) with incident asthma during follow-up: [#] $p < 0.05$.

^a Incident asthma is defined as a self-reported diagnosis of asthma during 10-year follow-up.

diagnosed asthma had a lower FEV₁% at baseline than young adults (Table 1). Similarly, airflow obstruction (reduced FEV₁/FVC) was evident at baseline in both young and older subjects who developed asthma during observation period, but most pronounced in the older age group (Table 1, $p = 0.004$).

Among young and middle-aged adults, there was no difference in the proportion of smokers between those who did not develop asthma during follow-up and those who did (Table 1). In the older group, the prevalence of smoking at baseline was higher among subjects who developed asthma during follow-up (45% vs. 32%, $p = 0.042$), but the total number of tobacco pack-years in this group was similar to subjects who did not develop asthma (29.2 vs 28.2 pack years, NS).

In all three age groups, newly diagnosed asthma during follow-up was associated with an accelerated decline in lung function compared to never-asthmatics. Hence older adults aged >64 years had an excess decline in lung function of 30.8 mL/pr year, compared to age-matched never-asthmatics (Table 2). This was significantly more than in middle-aged adults in whom FEV₁ declined by 18.2 more than never-asthmatics (49.8 mL/year versus 38.5 mL/year) and young adults (11.0 mL/year: 42.6 mL/year versus 30.8 mL/year) (Table 2). Smoking and older age at the time of diagnosis had additional effect on FEV₁ decline. Accordingly, based on the results of the regression analysis, it can be calculated that individuals aged >64 years who smoked at baseline, and had asthma diagnosed during follow-up, had an annual decline in lung function of 80 mL/year, compared to 43 mL/year in an age-matched non-smoking individual without asthma (Table 2).

In accordance with the lower FEV₁ at baseline and the excess decline in lung function, a large proportion of older adults had a reduced FEV₁ (<80% of predicted) at follow-up; 62% among adults aged >64 years at baseline, and 58% in adults aged 35–64 years, compared to 39% among young adults ($p = 0.002$, Fig. 2).

Table 2 Regression analysis of factors associated with decline in FEV₁ in 4983 adults, who were non-asthmatic at the baseline survey in 1991, during a 10-year follow-up.

FEV ₁ (mL/year)	B	C.I	P-value
Intercept	−30.8	−36.5 to −25.1	<0.001
Age at baseline ^b			
35–64 years	−7.7	−9.1 to −6.3	<0.001
>64 years	−11.8	−13.1 to −10.2	<0.001
Incident asthma ^a			
Age <35 years	−11.0	−19.2 to −4.3	0.043
Age 35–64 years	−18.2	−23.3 to −13.1	0.001
Age >64 years	−30.8	−40.6 to −22.0	0.01
Smoker at baseline	−7.0	−11.0 to −4.0	0.008
FEV ₁ % of predicted at baseline	18.2	16.9–19.4	<0.001

^a Incident asthma is defined as a self-reported diagnosis of asthma during 10-year follow-up.

^b Age group <35 years is reference.

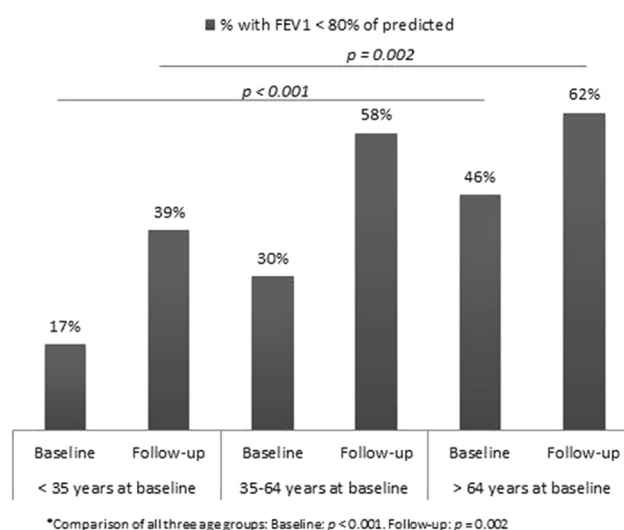


Figure 2 Proportion with FEV₁ < 80% of predicted in subjects with newly diagnosed asthma during 10-year follow-up according to age group.

In order to estimate whether undiagnosed asthma could be the cause of the relatively higher loss of FEV₁ in older individuals with incident asthma, self-reported respiratory symptoms at baseline were compared between the three age groups (Fig. 3). This showed that a similar proportion reported dyspnoea and wheeze at baseline, as well as cough and chronic mucus hypersecretion (CMH), indicating that unrecognised asthma in the oldest group was not likely to explain the accelerated decline in lung function in this group.

Discussion

In the present longitudinal study of newly diagnosed asthma in a random population sample of adult community residents, asthma was diagnosed as often in older adults as

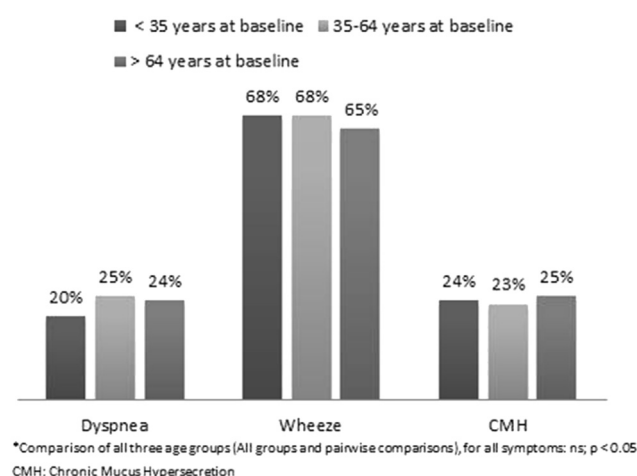


Figure 3 Self-reported respiratory symptoms at the baseline survey in young, middle aged and older adults with newly diagnosed asthma during 10-year follow-up*.

younger adults. Older adults with newly diagnosed asthma were more likely to have pre-existing lung function impairment, and experienced an accelerated decline in FEV₁, compared with middle-aged and younger adults. Pre-existing symptoms were common in all three age groups suggesting significant delays in the diagnosis of asthma, which may have caused the reduction in lung function at the time of diagnosis. However, older adults with incident asthma were not more likely to have pre-existing symptoms, and hence their relatively lower FEV₁ did not appear to be explained by more cases of unrecognized asthma.

Our findings emphasize the need for a high level of diagnostic attention in older adults with symptoms suggestive of asthma, as a large proportion have a significantly reduced lung function when diagnosed, which increases the risk of misdiagnosis of asthma as COPD. The present study is, to our knowledge, the first to directly compare lung function in older versus middle aged and younger adults with newly diagnosed asthma, before and after the time of diagnosis.

A limitation of the study is that asthma was defined as a self-reported diagnosis of asthma, rather than an objective verification of the diagnosis, i.e. by a reversibility test. This could potentially overestimate the loss of lung function, as we cannot determine whether the reduction in lung function was at least partly reversible. Conversely, some cases of self-reported asthma may also represent other lung diseases, in particular COPD, especially in the older group. At the time of the data collection, COPD as a diagnosis was less well recognized in the Danish general population. Hence, some patients with COPD may have been told by their physician that they have asthma, in order to explain their condition in familiar terms. An important caveat is therefore that at least to some degree lung function impairment in the older group may reflect COPD misdiagnosed as asthma. At the same time, it is important to recognize that the diagnosis of asthma is particularly problematic in older adults, who are more likely to have co-existing COPD [11]: In adults older than 60 years, more than 30% of those with obstructive airways disease have been reported to have an overlap between asthma, COPD, emphysema or chronic bronchitis [27]. The present findings illustrate this challenge: A significant proportion of older adults who were diagnosed with asthma had preexisting lung function impairment, and may potentially have developed asthma on the background of chronic airflow obstruction, or more likely, COPD on the background of pre-existing, unrecognized asthma. At present, the prognostic impact of these respective scenarios is largely unknown, although compared to COPD patients, patients with asthma-COPD overlap syndrome were recently reported to experience less decline in exercise capacity over a 4 year follow-up [28].

The impairment of lung function in older adults with incident asthma was not explained only by differences in smoking exposure; although the cumulative exposure to cigarette smoke was higher in older than in younger adults, there was no difference in the tobacco consumption between the individuals with incident asthma and those who did not report asthma within the respective age groups. Furthermore, in the regression analysis, the association between incident asthma and the decline in lung function

was independent of smoking. Accordingly, COPD misclassified as asthma seems unlikely to be the main contributor to the reduction in lung function in the older group.

The stable incidence of asthma throughout adulthood, from young to older adults, is similar to what was reported in a large 11-yr follow-up from Ontario, where the incidence of asthma remained constant after the age of 29 years [29]. This underlines that new onset asthma is as common in older adults as in young adults, although it is more frequently under recognized [2,18]. Hence, the reduction in lung function in older asthma patients could reflect long-standing, unrecognized and hence untreated, asthma [6,9]: This is supported by findings reported from the Tucson study, where 63% of older adults who developed asthma after the age of 60 years, reported asthma-like symptoms years before being diagnosed with asthma [1]. However, in a later report from the same study, a similar proportion among young adults reported wheezing or shortness of breath (69%), prior to a diagnosis of asthma [30]. In the present study, the frequency of self-reported respiratory symptoms, such as dyspnoea and wheezing, was relatively high at baseline, indicating a potential degree of under diagnosis. Nevertheless, we found no difference in symptoms reported by older compared to younger adults, indicating that untreated asthma is unlikely to explain their higher loss of lung function in the older age group. A caveat is however that we do not have information available on the duration of symptoms, hence we cannot rule out that the older age group comprised more cases of long-standing, unrecognized asthma.

The relationship between older age at onset of asthma and lung function has previously been described in a number of studies [17,31–33]. In the Tucson Epidemiologic Study of Airways Obstructive Diseases, in which a reduction in lung function was reported in older adults (aged >64 years) with late onset asthma, prior to the time of diagnosis (mean FEV₁ of 83% pred ($\pm 19\%$) versus 96% ($\pm 19\%$) in non-asthmatics [1]. In that study, older individuals with incident asthma experienced an excess decline of lung function of 19 mL/year, compared to never-asthmatics. In a separate publication from the Tucson Study, it was reported that young adults who developed asthma between 20 and 39 years of age did not have a reduced lung function prior to the time of diagnosis, but the subsequent decline in lung function was not reported [30].

We have demonstrated that the loss of FEV₁ related to asthma onset after the age of 64 years is approximately 20 mL/yr higher than in young adults who are diagnosed with asthma, indicating that asthma onset in older adults is associated with an excessive loss of lung function that is twice as high as in younger adults.

The implications of airflow limitation are potentially serious: The risk of misdiagnosis of asthma as COPD may result in under-treatment of airway inflammation. Hence, the recent joint project of GINA and GOLD on the diagnosis of diseases of chronic airflow limitation describing the Asthma-COPD overlap syndrome (ACOS) emphasize that patients with obstructive airflow limitations who present features suggestive of asthma should be treated with inhaled corticosteroids (ICS) [12]. Furthermore, it has been repeatedly shown that airflow limitation in asthma is

associated with doubled risk of mortality, with respiratory failure as the most common cause of death [19,21]. An observational study based on the present cohort indicates that ICS treatment may reduce the annual loss of lung function by app. 18 mL/year [34] and accordingly, early detection and initiation of treatment with ICS is important.

In conclusion, older adults who were diagnosed with asthma had a lower lung function prior to the diagnosis and a higher loss of lung function compared to younger adults with incident asthma. Hence, older adults with incident asthma are at risk of being misdiagnosed as COPD, and furthermore seem susceptible to develop more pronounced structural alterations of the airways, which emphasize the need for a high level of diagnostic and therapeutic attention in this patient group.

Author contributions

Celeste Porsbjerg is primary author and prepared the manuscript. Celeste Porsbjerg is guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

Peter Lange contributed to the preparation of the manuscript.

Charlotte Ulrik performed the statistical analyses and contributed to the preparation of the manuscript.

Conflicts of interest

Celeste Porsbjerg has no conflicts to declare relating to this manuscript.

Peter Lange has no conflicts to declare relating to this manuscript.

Charlotte Suppli Ulrik has no conflicts to declare relating to this manuscript.

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