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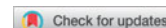
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Objective confirmation of asthma diagnosis improves medication adherence

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ABSTRACT

Objective: The impact of diagnostic work-up in asthma management on medication redemption and probably also drug adherence is largely unknown, but we hypothesized that a confirmed diagnosis of asthma in a hospital-based out-patient clinic increases the willingness to subsequent medication redemption in a real life setting. **Methods:** In a retrospective register-based study, 300 medical records of patients referred with possible asthma during one year were examined, of whom 171 had asthma (57%). One-year data on dispensed medicine was collected using the Danish Registry of Medicinal Product Statistics. Patients who had a positive asthma (e.g. bronchial challenge) were classified as verified asthma, whereas unverified asthma refers to doctor's diagnosis of asthma with negative or no diagnostic tests performed. **Results:** 111 (65%) had a verified diagnosis and patients with verified asthma were more frequently prescribed new therapy compared to those with unverified asthma (88.9% vs. 65.0%, respectively, $p < 0.001$). No difference was found in first time redemption of prescriptions (72% vs. 64%, respectively, $p = 0.3$), whereas the second (52% vs. 27%, $p = 0.001$) and third or more asthma redeemed prescriptions (37% vs. 17%, $p = 0.006$) showed increased redemption of prescription and probably adherence in the verified compared with the unverified patients with asthma. Furthermore, the use of inhaled corticosteroid (ICS) was calculated as Percent Days Covered (PDC), which was higher in the verified group compared with the non-verified asthma group (88% vs. 30%, $p = 0.004$). **Conclusion:** Objective verification of a diagnosis of asthma using asthma tests was associated with an improved redemption of prescription.

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Introduction

Studies have shown that patients with well-controlled asthma have fewer emergency visits and a reduced risk of hospitalization (1) emphasizing the importance of achieving asthma control through preventive medication.

Guidelines on the diagnosis and treatment of asthma have been developed to improve the quality of asthma care (2). Studies have shown that explicit guidelines, which are easy to follow, can improve clinical practice (3). It has been recommended that a diagnosis of asthma is based on a history of asthma-like symptoms, but should if possible be confirmed by an objective measure of variable airflow obstruction (4), (5). Unfortunately, physician adherence to treatment guidelines may be low, especially for preventive medications (6). This remains one common reason for failure of asthma management (7).

Adherence has been reported to be as low as 30–70% (2) in patients with asthma, for multiple reasons

including poor communication with the healthcare provider (8). Poor adherence to prescribed treatment regimens is a major contributor to lack of asthma control (9), (10). Adherence to asthma medication can be divided into patient's willingness to take the prescribed medication or patients forgetting to take the prescribed medication (11) and lastly, healthcare providers not following the treatment algorithms. Furthermore, it has been reported that specific patient groups do not redeem as many as 27% of prescriptions prescribed by the physicians directed by a guideline-based regimen (12). Low redemption of prescriptions and low adherence to prescribed medication might be a result of reduced understanding of why one has to buy and take very expensive anti-asthmatic medication. This lack of understanding could be due to lack of knowledge of the pathology of asthma and furthermore, lack of understanding of the asthma challenge test. We speculate that low adherence could be partly a result of

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Statement of contribution by each named author

Backer V: Examined patients' files, included data in the database, written the paper, finalized the statistical analysis

Stensen L: Examined patients' files, included data in the database, co-written the paper, merged the data with the register data

Sverrild A: Examined patients' files, included data in the database, co-written the paper

Wedge E: Co-written the paper

Porsbjerg C: Examined patients' files, included data in the database, co-written the paper

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a lack of disease awareness, including uncertainty about the diagnosis.

We therefore hypothesized that objective verification of an asthma diagnosis is associated with higher adherence to prescribed asthma medications. In the present study, we examined the extent of diagnostic assessment of asthma in a hospital-based specialist asthma clinic, and the relationship to patients' medications adherence, assessed using the Danish Registry of Medicinal Product Statistics, as a surrogate variable for treatment adherence.

Material and methods

Study design

The MAPOut I study was a retrospective observational register-based study including all patients referred with suspected asthma to the Respiratory Outpatient Clinic at Bispebjerg Hospital, Copenhagen, Denmark from January 1, 2010 to December 31, 2010 (Figure 1). Four respiratory specialists reviewed all medical records of these patients, to extract data concerning basic characteristics, such as asthma symptoms, lung function, and diagnostic tests. Furthermore, data on therapy prescribed pre-referral and after the consultation with a specialist were collected.

We considered an asthma diagnosis to be objectively verified if the patient had a positive asthma test; either a beta-2-agonist reversibility test, a bronchial challenge

test with methacholine or mannitol, a eucapnic voluntary hyperpnoea test (EVH), or 2-week peak flow diary.

Patients diagnosed with asthma by their general practitioner or respiratory specialist based on their symptoms were classified as unverified asthma if they had no objective asthma test performed, or negative results. We did not include registration, of which specialist who performed the diagnostic work out with the patients, as this was not the issue of the present paper, to pin point one doctor ahead of another. Data on prescribed asthma medication was collected from patient files and data on dispensed asthma medication was obtained from the Danish Registry of Medicinal Product Statistics. Patient adherence was evaluated by a number of filled prescriptions and PDC.

Methods

Diagnostic tests

A positive reversibility test was defined as an increase in FEV1 of at least 12% and 200 mL post beta-2-agonist (13). A positive methacholine test was defined as a decrease in FEV1 of 20% or more after inhaling ≤ 8 micromoles of methacholine ($PD_{20} < 8 \mu\text{mol}$) (14), and a positive mannitol test was defined as a decrease in FEV1 of 15% or more after inhalation of ≤ 635 mg of mannitol ($PD_{15} < 635$ mg) (15). For Peak Expiratory Flow (PEF), a positive test was defined as day-to-day variation of 20% or more. An EVH test was performed was defined as positive if the subject had a decrease in FEV1 of at least 10% on 2 consecutive measurements (16).

Assessment of patient adherence

Patient adherence to prescribed asthma medication was defined as a minimum of 2 redeemed prescriptions of controller medication prescribed by the outpatient clinic (17), (18).

Furthermore, we calculated PDC as a second method of assessing adherence (19), (20). PDC describes the percentage of days that patients had access to medication according to the amount of medication they had collected, assuming daily use was prescribed. This was calculated using defined daily doses (DDDs) for each redemption.

Registry data

All inhabitants in Denmark are registered via a civil personal registration identification number, which enables individual linkage of nationwide administrative registers. All prescriptions dispensed from Danish pharmacies since 1995 are collected in the Danish Registry of Medicinal Product Statistics. The registry contains information

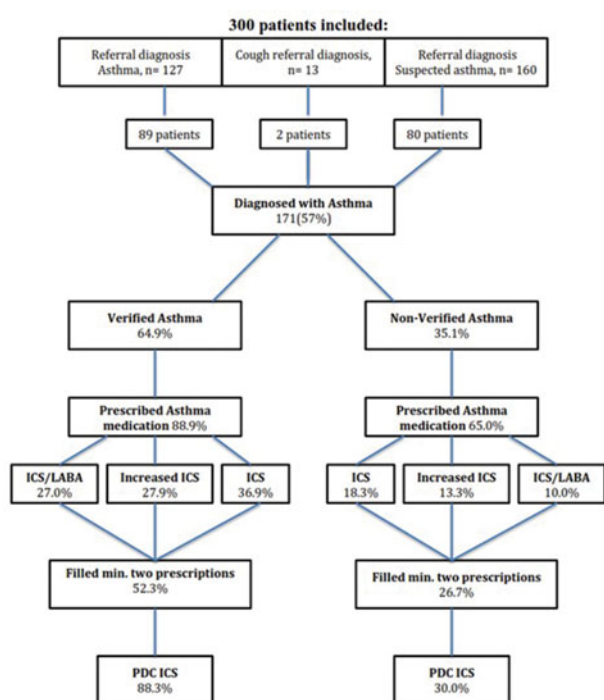


Figure 1. Flow-chart of the participating patients in a real life study.

on the physician issuing the prescription, the date of purchase, purchased amount of the drug in DDDs, anatomic therapeutic chemical (ATC) code, and the patient's identification number. All pharmacies in Denmark are required to register all prescriptions dispensed, which ensures complete registration of dispensed pharmacotherapy.

In this study we acquired data via the Danish Registry of Medicinal Product Statistics on dispensed medicine for each patient in the 12 months after they attended the outpatient clinic. We obtained data on medication with the ATC-code R corresponding to Respiratory medicine and the data was made available to us via Statistics Denmark.

Statistical analysis

Statistical analysis was carried out using SPSS (version 20.0). All data were considered normally distributed and was analyzed using parametric statistics. Continuous variables were reported as mean (SD). Unpaired *t*-tests were used for comparisons of continuous variables, and Chi-Square tests for categorical variables. Results with *P*-values below 0.05 were considered significant.

Ethics

The study was approved by the Danish National Health Board (Jr Nr 7-604-04-2/279/KWH), as well as the Danish Data Protection Agency and all data made available to us were cross-linked by CPR-number by Statistics Denmark and provided anonymized to us.

Results

Baseline variables

Three hundred patients were referred with possible asthma. A total of 167 (55.7%) were females, the average age (SD) was 35.5 (17) years, and average BMI 24.1 (4.4). The majority were never-smokers (69.7%), 13.3% were former smokers, and 10.3% were current smokers, whereas 6.7% had no smoking status documented in the files (Table 1). Of the initial 300 patients, 171 (57%) were diagnosed with asthma by the specialist and were included for further analysis. Of the remaining patients, 48 (16%) were still in diagnostic work-up after a year and were not considered as asthma patients, 40 (13.3%) were diagnosed with a pulmonary disease other than asthma, and 41 (13.7%) did not have a pulmonary disease. In total, one-third of those referred with possible asthma were deemed non-asthmatic by the specialist and were discharged (Figure 1). The majority (50.9%) of the 171 asthma patients were diagnosed at their first visit

Table 1. Patient characteristics.

	All cases included <i>n</i> = 300	Asthma cases <i>n</i> = 171	Verified asthma <i>n</i> = 111	Non-verified asthma <i>n</i> = 60
Female <i>n</i> (%)	167(55.7)	86(50.3)	56(50.5)	30(50.0)
Age years(SD)	35.5(17)	31.9(15.5)	30.4(15.9)	34.6(14.4)
BMI (SD)	24.1(4.4)	23.6(4.3)	23.2(3.8)	24.4(5.0)
FEV1%(SD)	89.8(20.6)	92.1(19.3)	93.4(18.4)	89.3(21.0)
FEV1/FVC % (SD)	78.2(11.6)	77.8(12.0)	78.6(12.3)	76.3(11.1)
Smoking status <i>n</i> (%)				
Non-smoker	209(69.7)	131(76.7)	93(83.8)	38(63.3)
Smoker	31(10.3)	9(5.3)	6(5.4)	3(5.0)
Former smoker	40(13.3)	22(12.9)	18(16.2)	4(6.7)

and 24.3% at the second visit, whereas 9.9% needed 4 or more consultation before the diagnosis of asthma was registered.

Objective verification of asthma

Spirometry was available in 163 (95.3%) of the patients diagnosed with asthma. Eight (4.7%) had PEF day-to-day measured over a period of 2 weeks, 103 (60.2%) performed a reversibility test, 108 (63.2%) performed a bronchial provocation test (BPT), and 30 (17.5%) performed no objective tests other than spirometry (Figure 2). The number of subjects with positive results for these tests is displayed in Table 2 and Figure 3.

Ninety-five (55.6%) of the patients had one positive objective test and 16 (9.4%) patients had 2 or more positive tests performed (Table 3). In total, 64.9% had a verified asthma diagnosis, leaving 35.1% (*n* = 60) with non-verified asthma due to either lack of asthma testing (*n* = 30, 17.5%) or lack of a positive result, i.e., negative test panel (*n* = 30, 17.5%) (Table 3).

Medication prior to referral

At the time of referral, 93 (54.4%) patients were using ICS inhalation therapy and there was no significant

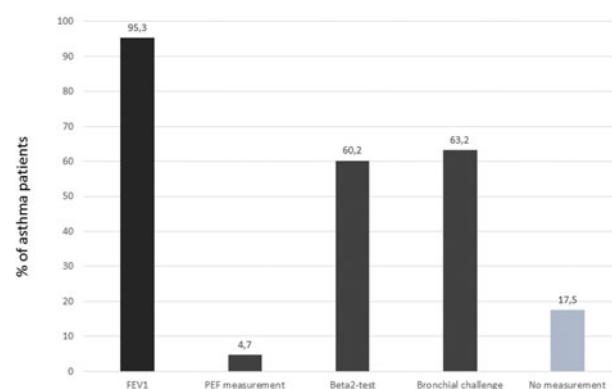
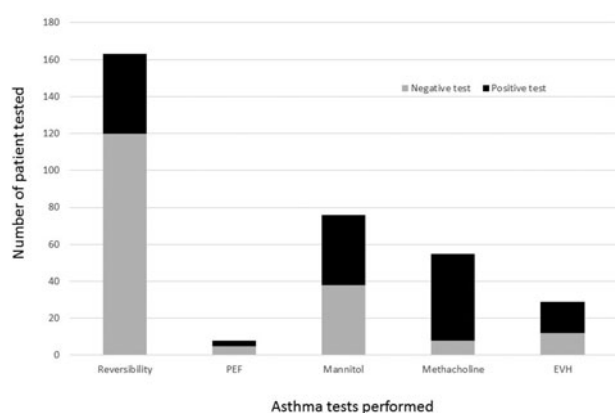


Figure 2. The distribution of the different bronchial challenge tests used in the evaluation of asthma patients.

Table 2. Objective tests performed.

	Asthma cases <i>n</i> = 171	Verified asthma <i>n</i> = 111	Non-verified asthma <i>n</i> = 60
Spirometry			
Yes <i>n</i> (%)	163(95.3)	108(97.3)	55(91.7)
Obstructive*	32(18.7)	19(17.1)	13(21.7)
Reversibility test			
Yes <i>n</i> (%)	103(60.2)	77(69.4)	26(43.3)
≥12% reversibility	37(21.6)	37(33.3)	0(0)
Peak Expiratory Flow			
Yes <i>n</i> (%)	8(4.7)	4(3.6)	4(6.7)
≥20% variability	2(1.2)	2(1.8)	0(0)
AHR			
Test performed <i>n</i> (%)	108(63.2)	88(79.3)	20(33.3)
Mannitol	76(44.4)	60(54.1)	16(26.7)
-Mannitol pos.	36(47.4)	36(60.0)	0(0)
Methacholine	55(32.2)	45(40.5)	10(16.7)
-Methacholine pos.	39(70.9)	39(86.7)	0(0)
EHV	29(17.0)	22(19.8)	7(11.7)
-EHV pos.	13(44.8)	13(59.1)	0(0)

Note. *Obstructive = FEV1/FVC < 0.7.

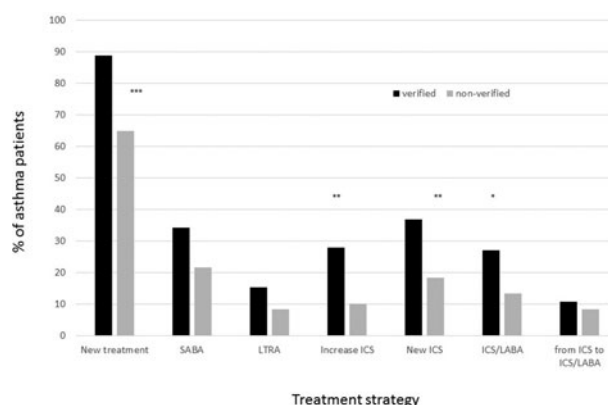
**Figure 3.** Number of asthma tests performed, both those with positive and negative results.

difference in the use of SABA, ICS, ICS/LABA, or Leukotriene-receptor antagonist (LTRA) between the entire population and the group with verified asthma.

After specialist assessment, 137 (80.1%) of subjects with asthma were prescribed at least one new asthma drug. A significantly greater proportion of patients with verified asthma were prescribed new therapy compared to those with non-verified asthma (88.9% vs. 65.0%, respectively, $p < 0.001$). Patients with verified asthma were also significantly more likely to be altered in asthma treatment compared to those with unverified asthma (Figure 4).

Table 3. Positive tests confirming the diagnose of asthma.

Number of tests	Asthma cases <i>n</i> = 171
No test performed <i>n</i> (%)	30(17.5)
0 positive tests <i>n</i> (%)	30(17.5)
1 positive test <i>n</i> (%)	95(55.6)
2 or more positive tests <i>n</i> (%)	16(9.4)
Subjects with a positive test	111(64.9)

**Figure 4.** Treatment selected after asthma tests has been performed. SABA: Short-acting beta2-agonist, LABA: long-acting beta2-agonist, LTRA: Leukotrien-antagonist, ICS: inhaled corticosteroids.

Adherence to asthma medication

When looking at all prescribed asthma medication, no significant difference was found in first time redemption of prescriptions between the verified and non-verified groups (72.4% vs. 64.1%, respectively, $p = 0.336$). Nor did we find a significant difference in first time prescription redemption between different types of inhalation therapy (SABA, ICS, and ICS/LABA).

However, 52.3% of patients with verified asthma redeemed at least the 2 prescriptions compared to 26.7% in the non-verified group ($p < 0.01$), and 36.9% vs. 16.7%, respectively filled at least 3 prescriptions ($p < 0.01$) (Table 4) – within a year of examination. To further assess adherence to use of ICS, we calculated PDC. Of the patients with ICS prescription redemption in 2010, PDC was 88.3% in the verified group and 30.0% in the non-verified asthma group (Figure 1, $p = 0.004$). For ICS/LABA combination therapy, the PDC was 35.7% in the verified group and 27.9% in the non-verified group ($p = 0.52$).

Discussion

In this study, we have shown that the diagnosis of asthma was verified objectively in two-thirds of patients with

Table 4. Distribution of all prescription filled among the 137 asthma cases who were prescribed new asthma medication in the outpatient clinic.

	Verified asthma <i>n</i> = 98	Non-verified asthma <i>n</i> = 39	<i>p</i> -value
No prescription filled <i>n</i> (%)	27(27.6)	14(35.9)	
Filled min. 1 prescription <i>n</i> (%)	71(72.4)	25(64.1)	0.336
Filled min. 2 prescriptions <i>n</i> (%)	48(52.3)	26(26.7)	0.001
Filled min. 3 prescriptions <i>n</i> (%)	41(36.9)	10(16.7)	0.006

possible asthma referred to a specialist setting. Furthermore, patients with verified asthma were subsequently prescribed more new asthma medication than patients with non-verified asthma, and this difference was significant for all medication types. Finally, patients with a verified diagnosis of asthma were significantly more adherent in filling prescriptions. In this study we were unable to evaluate whether redemption of a prescription was the same as taking the medication, i.e., being adherent to the anti-asthma medication, but we assume that, if patients are buying expensive anti-asthma medication for the third time during one year, they most likely are taking it.

The majority of asthma patients were diagnosed within the first 2 visits to the outpatient clinic, whereas 27% of those referred from primary care with suspected asthma, were classified as non-asthmatic after assessment of symptoms and objective tests. A study conducted in Canada in 2008 found a similar result with a 30% rate of incorrect asthma diagnosis (21). This emphasizes the need for validation, which is supported by the current guidelines (2), (22). However, the diagnosis of asthma was only verified with a positive objective test in 64.9% of cases, the remaining 17% had a negative asthma test panel and furthermore 17% had no test performed although all were classified as having asthma. It is known that the combination of asthma symptoms and low level of pulmonary function tests or positive challenge test are predictive of the risk of recurrent life-threatening exacerbations (23), (24). Underestimating asthma severity can lead to suboptimal treatment, by selecting a lower treatment step than sufficient to control the disease, furthermore it would lead to increased morbidity, sick leave from work or school, and decreased quality of life (25), (26). One of the findings in the present study was that an association between asthma tests and prescribing behavior of physicians was found. These findings suggest, that asthma patients with a verified diagnosis were more likely to be prescribed ICS with or without a second controller. In this study, no follow-up visits were included as standard, which might have changed the adherence in a positive direction as suggested by Visser R et al. and Ulrik CS et al. (27), (28). Furthermore, Allen-Ramey et al. stated that the number of patients managed by a physician tend to have an association with the prescription of ICS (29). In the present University clinic, the physicians have seen many asthma patients, and have a large experience, indicating a higher use of ICS, which also was the case in this study. However, based on our study we found that verifying an asthma diagnosis with objective tests importantly is associated with initiation of inhalation therapy and alteration of already prescribed ICS treatment. Overall, objective signs of reversible airway disease increase the possibility of individualized treatment, both concerning type

and dosage of asthma medication when the suspicion of asthma and severity of disease is confirmed.

In an earlier study by Ulrik CS et al. (28), it was discovered that patients tend to stop treatment when having no asthma symptoms, believing they are cured. This is a significant issue for patients' education, that asthma is a chronic disease which needs permanent treatment for a longer period. We found that patients with an objectively verified asthma diagnosis were significantly more adherent in redeeming prescriptions than those in the non-verified group. This might indicate that the patients during the asthma testing and the consultation with the respiratory specialist enable the pathology behind the disease. Furthermore, the non-verified group include both patients with a negative test panel and patients who had no asthma test performed. These patients most likely have no confirmation of having a disease other than a normal FEV1, and thereby no knowledge and education of why to use daily medication. These findings support that it is exceptionally unsatisfactory that the group of non-verified asthma patients included newly referred patients who had no asthma tests performed. Furthermore, as patients with verified asthma had a significantly higher PDC at 88.3%, indicating that this group of asthmatics had prophylactic medication available almost all the time, unlike the non-verified group who only had prophylactic medication available 30.0% of the time. This indicates that not only did the patients with non-verified asthma less frequently redeem prescription, the physicians also less frequently make ICS available. Perhaps the process of seeing a positive test or the effect of medication (when performing, for example, a reversibility test) proves the need for inhalation therapy from the patient perspective. If this is the case, it underlines the importance of the use of objective measurements when diagnosing asthma. Perhaps patients with a positive objective test were more likely to have severe asthma and therefore felt the effect of prophylactic medication more than patients with non-verified asthma, leading to more consistent filling of prescriptions.

Another important finding in our study is that 38.5% of the patients who were prescribed ICS therapy did not fill a single prescription. Whether these 38.5% did not use any medication or had medication from elsewhere is not known. Retrospective assessment gives no possibility of knowing whether patients are not redeeming the anti-asthma medication, as they already have asthma medication prescribed prior to referral to a specialist, which they would tend to use up before purchasing new medication. Secondly, most ICS inhalators and ICS/LABA inhalators last approximately 3–6 months, a box with 3 inhalers or puffers with 200 doses, which was included in the present analysis as adherence was defined as redemption of 2

or more prescriptions within the calendar year of 2010. This analysis therefore supports the importance of verifying the diagnosis of asthma, in management of asthma patients.

A critique might be that these patients had less severe asthma and therefore did not feel the need of inhalation therapy, although the physician did so. On the other hand, these patients were defined as asthma patients, and patients with cough only and negative test panel were excluded and their short use of ICS was not included in the present analysis. Indicating these patients with non-verified asthma must have had very recognizable asthma symptoms, and therefore needing no testing although needing new or increased anti-asthma prescribed medication. These patients probably have difficult-to-treat asthma or uncontrolled asthma (GINA step 2–5), although an asthma score was not available in the study. Increased adherence to ICS treatment is associated with lower risk of uncontrolled asthma with fewer exacerbations, lower rescue medication use, and lower health care utilization (30). We know from previous studies, that many factors influence patient adherence to medication: perceived necessity, safety concerns, asthma chronicity/medication effectiveness, advice from family/friends, motivation/routine, ease of use, and satisfaction with asthma management (31). Willingness to treatment is among the important factors, and this willingness might be based on education. A positive asthma test and a thorough consultation with an asthma specialist probably is needed, when paying a larger sum of money for the combination therapy (ICS/LABA), than ICS only or SABA only. To improve adherence it is important to identify any modifiable problematic beliefs and behaviors of individual patients (32) and this is difficult because it is time consuming.

One of the strengths of this study is that we collected data from real life, a complete population of patients referred for specialist management of asthma, over a 12-month period, which makes our findings more likely to be representative of patients in the daily clinical setting. Furthermore, data was collected from patient files hence we have almost complete data on objective measurements, prescribed medication, and changes in medication regimes. This combined with the full registry data from Danish RMPS gives us a good picture of the correlation between physician adherence (patient investigation according to guidelines) and patient adherence. With the unique Danish Civil Registration System and the National Prescription Database we had the opportunity to identify a large cohort of medication users and have access to specific objective information on dispensed medication, thereby avoiding patient recall bias.

An important limitation of this study is that the data from the Prescription Database only tells us if the patient has redeemed their prescriptions or not. One could argue that dispensed medication does not necessarily indicate actual use of medication. We could therefore have overestimated drug adherence and thereby overestimated the value of objective verification of asthma diagnosis. Furthermore, another limitation might be the cases where patients have recurrent exacerbations, the clinician may decide to administer pulmonary function tests when visiting the clinic and the patient may be motivated to use medicine because of the frequent exacerbations. Lastly, in real life studies the communication between the physician and patients is unknown, and we have to conclude that patients given the diagnose of asthma, handed a prescription, were told to take the specified anti-asthma drug.

Conclusion

The diagnosis of asthma was only verified objectively in 64.9% of cases in our outpatient clinic. Patients with a verified diagnosis were prescribed ICS treatment more often than patients with a non-verified diagnosis. But more importantly, asthma patients with an objectively verified diagnosis were more consistent in medication redemption.

Declaration of interest

None of the authors have any conflicts of interest.

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