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RESEARCH ARTICLE

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Defined daily dose definition in medication adherence assessment in asthma

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ABSTRACT

Adherence to inhaled corticosteroids (ICS) has been described as poor. In adherence studies, if the actual prescribed dosing is not available, generic defined daily doses (DDD) are applied instead when assessing adherence. We evaluated asthma patients' adherence in a large prospective follow-up survey. We also analysed whether World Health Organization (WHO) and Global Initiative for Asthma (GINA) reference doses give different results. The current study was cross-sectional and included respondents attending to HeSSup follow-up questionnaire in 2012. Altogether 1,141 of 12,854 adult participants answered positively to the question about having asthma. According to the Finnish Social Insurance Institutions' medication register, 686 of them had purchased ICS medication during 2011. DDDs for ICS by WHO as well as medium doses from GINA report were used as reference doses to evaluate adherence. To estimate adherence to ICS, the proportion of days covered (PDC) over one year was calculated for every patient. If the lower limit of GINA medium ICS dose was used as a reference, 65% of the patients were adherent (PDC ≥ 80%). Use of WHO's DDD as reference halved the proportion of adherent patients. Adherence was higher among those using a combination inhaler of corticosteroid and long-acting β_2-agonist compared to those using steroid only inhalers. Use of WHO's daily defined doses as reference values may lead to underestimation of adherence to inhaled corticosteroids. Thus, attention should be paid when choosing the reference doses for the evaluation of adherence to inhaled corticosteroids in asthma.

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Introduction

Asthma is one of the most common chronic diseases. The prevalence of physician-diagnosed asthma varies globally. Among adults in Finland, it is approximately 11% [1,2], and the incidence of adulthood increases by age [3,4]. Poor asthma control is associated with more exacerbations and has negative influence on various aspects of quality of life [5,6]. Improvement in asthma control reduces disability and leads to significant overall cost savings despite the rise in primary care visits and medical costs [7].

According to the Global Initiative for Asthma (GINA) report [8], long-term goal of asthma treatment for each patient is to be free of symptoms and capable of normal daily life activities. Asthma treatment is individually modified based on regular assessment of asthma control. Inhaled corticosteroid (ICS) is the basis of medical asthma treatment. If asthma control is insufficient, a stepwise add-on treatment protocol is recommended [8]. The next step is to add a long-acting β_2-agonist (LABA), which has been shown to be more effective than increasing the ICS dose [9].

Overall, adherence to anti-inflammatory asthma medication has been described to be poor [10]. Mean adherence to ICS has been reported to range from 22% to 63% [11]. However, in a 12-year follow-up study of patients with clinically confirmed adult-onset asthma, the mean adherence to ICS therapy was shown to be 69%, with the highest adherence being after the first year of treatment [12]. Poor adherence to ICS is associated with more exacerbations [10] and steeper decline in lung function [12,13]. In adherence studies, adherence varies depending on the study population as well as definition and measurements of adherence [10].

Several methods for measuring adherence are available. Patients' self-reported adherence is subject to bias [14]. Moreover, prescription fill data are not usually available to clinical practitioners and give no information of the actual use of these regimens [15,16]. In

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population-oriented research involving registry data, the optimal way would be to assess adherence by comparing the dispensed medication to the prescribed medication. However, often this is not possible because of a lack of relevant data, either on prescribed or dispensed medication. Proportion of days covered (PDC) is a way used to estimate the use of long-term medication based on electronic prescription data [17]. Adherence to medical treatment of chronic diseases is most often defined as PDC and the cut-off≥80% is considered for good adherence [15].

World Health Organization (WHO) recommends the Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) as a measurement unit to be used in drug utilization research [18]. DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. If the information of prescribed daily dose is not available, DDD may be used to estimate the treatment intensity for individual patients during a specific period [18]. WHO DDD for ICS-LABA combination products depends on the LABA component, which leads to differences in the amount of daily ICS dose defined as DDD in salmeterol/fluticasone inhalers as compared to inhalers containing fluticasone only [19].

DDD may vary between WHO and GINA recommendations. For example, the daily dose recommendation for fluticasone propionate is 0.6 mg in WHO recommendation, but in GINA recommendation the lower limit is 0.25 mg and the upper limit 0.5 mg.

In this study we evaluated asthma patients' adherence to medication. We also analyzed the adherence to ICS preparations among adult asthmatics according to different recommended daily treatment doses.

Material and methods

Study subjects

The study is based on the population of The Health and Social Support Study (HeSSup), which is a prospective follow-up survey on psychosocial health of Finnish working age population. The first postal questionnaire was sent in 1998 to a random sample of 64,797 working-aged individuals drawn from the Finnish Population Register. Follow-up questionnaires in 2003 and 2012 were sent to those responding to the first HeSSup survey. Detailed information of the HeSSup study has been published previously [20–22].

The concurrent joint Ethics Committee of the University of Turku and the Turku University Central Hospital considered a statement of approval not necessary for a normal cohort study. All participants signed an informed consent form containing information about the study and granted permission to allow subsequent studies with the same data set and a possibility to link with national health registries.

The questionnaire screens various self-reported factors and disturbances related to health. It includes a question about various medical conditions with the phrase: 'Has a doctor ever told you that you have or have had' followed by the name of disease or condition. Asthma is one of these diseases. The current study was cross-sectional and included 13,050 respondents attending to HeSSup follow-up questionnaire in 2012. Altogether 12,853 participants answered this question about asthma. Of them 1,141 reported on having asthma. The formation of our study population is presented in Figure 1.

Study design

In The Finnish Social Insurance Institution (SII) registers we identified respondents who had purchased at least one inhaler of inhaled corticosteroids alone (ATC code R03BA) or combined to long-acting β_2-agonists (ATC code R03AK) during 2011. Name and strength of the active substance, number of doses in the inhaler and number of inhalers purchased by each person during next 365 days after the first prescription claim in 2011 were recorded. SII registers also include information about the entitlement for special reimbursement of certain medications. Finnish asthma patients are entitled to get special reimbursement (i.e. 65% discount of asthma medicines) if the diagnostic criteria of asthma are fulfilled and they have been shown to need regular long-term control medication. The criteria for this were dependent on a positive reversibility test, airway hyperresponsiveness or peak flow variation.

Analysis

All ICS dispensed during 2011 in the SII register were collected. The total amount of both ICS alone as well as combined to long-acting β_2-agonists were calculated for each asthma patient. This has been done even in cases where the corticosteroid used might have changed during the year. To estimate adherence to ICS, the proportion of days covered (PDC) over one year was calculated for every patient. In the current study adherence refers to PDC and good adherence was considered when PDC was at least 80%. As a reference dosing for PDC calculation we used four different options. Firstly, the ATC/DDD system of WHO was used to define daily doses for the pure ICS products (later: WHO DDD) as well as for the ICS in the unit doses of combination inhalers (later: Modified WHO DDD) (Table 1). Secondly, as WHO DDDs are not

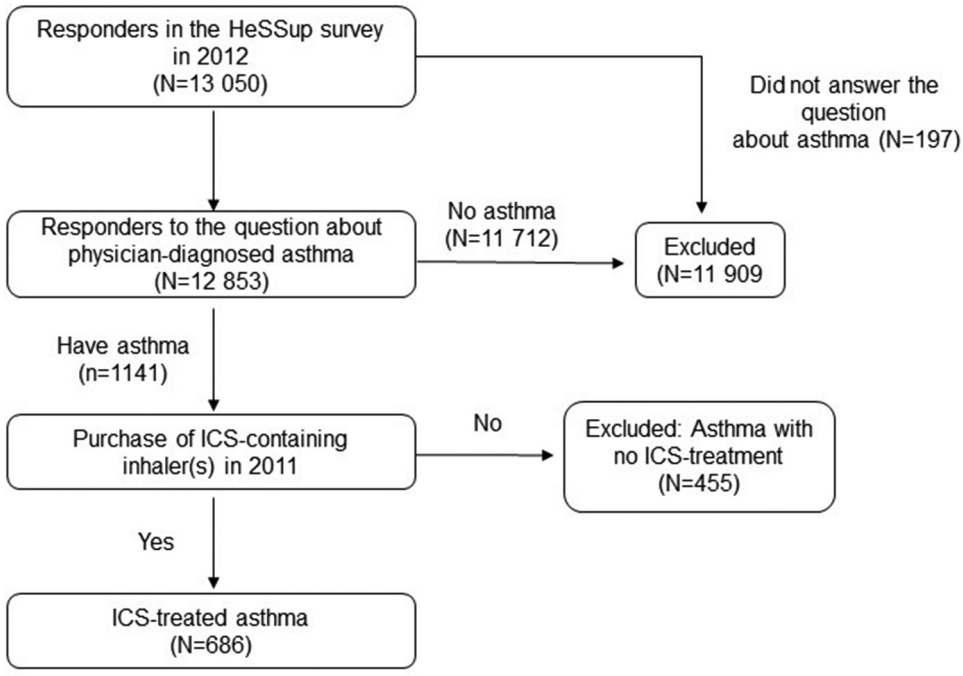

Figure 1. Flowchart of study population.

HeSSup = Health and Social Support Study, ICS = Inhaled corticosteroid

Table 1. Total daily doses for inhaled corticosteroid preparations according to WHO's defined daily dose (DDD) for inhaled corticosteroid (ICS) and long-acting β_2-agonist combination (ICS-LABA) preparations and recommended ranges of medium doses by Global Initiative for Asthma (GINA) -report.

	WHO DDD		GINA-report recommended daily medium dose	
Name	ICS (mg ICS)	ICS-LABA (mg ICS)	Lower limit (mg ICS)	Upper limit (mg ICS)
beclometasone				
dry powder inhaler	0.8	-	0.2*	0.4*
pressurized metered dose inhaler	0.8	-	0.4	0.8
budesonide	0.8	-	0.4	0.8
fluticasone propionate		-		
dry powder inhaler	0.6		0.25	0.5
pressurized metered dose inhaler	0.6		0.25	0.5
mometasone	0.4	-	0.2	0.2
siclesonide	0.16	-	0.16	0.32
salmeterol 50 mcg/ fluticasone 0.1 mg	0.6	2 UD** = 0.2 mg	0.25	0.5
salmeterol 50 mcg/ fluticasone 0.25 mg	0.6	2 UD = 0.5 mg	0.25	0.5
salmeterol 50 mcg/ fluticasone 0.5 mg	0.6	2 UD = 1.0 mg	0.25	0.5
salmeterol 25 mcg/ fluticasone 50 mcg	0.6	4 UD = 0.2 mg	0.25	0.5
salmeterol 25 mcg/ fluticasone 0.125 mg	0.6	4 UD = 0.5 mg	0.25	0.5
salmeterol 25 mcg/ fluticasone 0.25 mg	0.6	4 UD = 1.0 mg	0.25	0.5
formoterol 4.5 mcg/ budesonide 80 mcg	0.8	4 UD = 0.4 mg	0.4	0.8
formoterol 4.5 mcg/ budesonide 0.16 mg	0.8	4 UD = 0.8 mg	0.4	0.8
formoterol 9 mcg/ budesonide 0.32 mg	0.8	2 UD = 0.8 mg	0.4	0.8

*Value for beclomethasone dipropionate inhalation powder obtained from the Finnish Current Care Guideline [22] as it was not available from GINA-report [8].

**UD=Unit dose according to WHO's Guidelines for ATC classification and DDD assignment 2021 [17]. As the WHO DDDs for combination products are given in Unit doses, the dose of inhaled corticosteroid (mg) based on this definition is given.

indicated in the treatment guidelines, for comparison, we used daily doses based on moderate dose range of ICS recommended in GINA report [8] by using the lower and upper limit of medium doses. National current care guideline [22] was used for beclomethasone powder dose, because it was not available in GINA report. The different daily ICS doses for available inhalers are shown in Table 1.

Finally, the study population of ICS-treated asthmatics was divided into four categories: 1) PDC at least 80%, 2) PDC at least 50% but less than 80%, 3) PDC at least 25% but less than 50% and PDC less than 25% of the days of the 365-day period after the first purchase.

To analyse statistical significance between demographic features of groups crosstabulation with Pearson's chi-squared test was used. Alpha level of 0.05 was selected to indicate statistical significance. IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY: IBM Corp) was used for statistical analysis.

Results

Study population

Altogether 1,141 (8.9%) of all respondents answered that they have been told by a physician to have or have had asthma, 69.7% of them were females. According to the SII's medication register 686 (60.1%) of them had purchased≥1 inhaler of ICS or ICS-LABA combination during 2011 and thus formed our study group. Of the 686 responders who did purchase at least one inhaler, 524 (76.4%) were entitled to special reimbursement of their asthma medication. Demographic features of the study group are presented in Supplementary Table S1.

Adherence to inhaled corticosteroids among ICS users

When WHO DDD for ICS, modified WHO DDD or the upper dose of GINA medium dose range were used as reference to calculate PDC, 29.1%–30.6% of the patients were adherent to ICS therapy (Table 2). This suggests that WHO DDD, modified WHO DDD and upper range limit of GINA medium dose give similar results, which is also seen in the division of the patients between different levels of adherence (<25%, 25–<50%, 50–<80% and ≥ 80%; Figure 2). In contrast, when the lower dose level of GINA medium dose range was used, 64.9% of patients were adherent to ICS therapy (Figure 2). More detailed results are presented in Supplementary Table S2.

If a lower cut point for adherence (≥50% PDC reflecting moderate to good adherence) is used, the correspondent proportions were 48.1% for WHO DDD, 50.7% for modified WHO DDD and 50.3% for GINA medium dose (Table 2). This again suggests that WHO DDD, modified WHO DDD and upper range limit of GINA medium dose give similar results. By using those, the data show that every second patient has poor (<50%) adherence. In contrast, by using the lower range limit of GINA medium ICS recommendation, only 22.7% are poorly (<50%) adherent (Figure 2).

Of all asthma patients, 7.3% reported that they had not bought their medicines during the last year because of high prices. There was no difference between genders. However, in the youngest age group financial reasons were reported to be the cause of not purchasing medication more often than in older age groups.

Adherence to ICS among patients using ICS only or ICS-LABA combination

Adherence to ICS may be affected by the type of ICS preparation, i.e. whether it is ICS inhaler only or an ICS-LABA combination. To evaluate this and to see whether the difference between the results by using different reference values is due to use of ICS only or ICS-LABA combination, adherence was evaluated separately in those groups. During the following 365

Table 2. Adherence to inhaled corticosteroids. Proportion of days covered by inhaled corticosteroids during one year as number of patients ($N = 686$) in different daily dose calculation method groups.

Proportion of days covered by ICS	WHO DDD/ICS		WHO DDD/MOD		GINA* medium dose lower limit		GINA* medium dose upper limit	
	n	%	n	%	n	%	n	%
<25	163	23.8	170	24.8	45	6.5	154	22.4
25 — 50	193	28.1	168	24.5	111	16.2	187	27.3
50 — 80	130	19.0	133	19.4	85	12.4	135	19.7
≥80	200	29,1	215	31.3	445	64.9	210	30.6
Tot	686	100.0	686	100.0	686	100.0	686	100.0

*Recommended treatment dose for beclomethasone dipropionate inhalation powder obtained from the Finnish Current Care Guideline [22] as it was not available from GINA-report [8].

WHO DDD/ICS: The defined daily dose for pure corticosteroid regimen is used both for ICS and combination products.

WHO DDD/MOD: For those using only ICS, the defined daily dose for ICS is used. For those using ICS+LABA, the unit dose -based defined daily doses is used. For the total population both these groups are combined when presenting data.

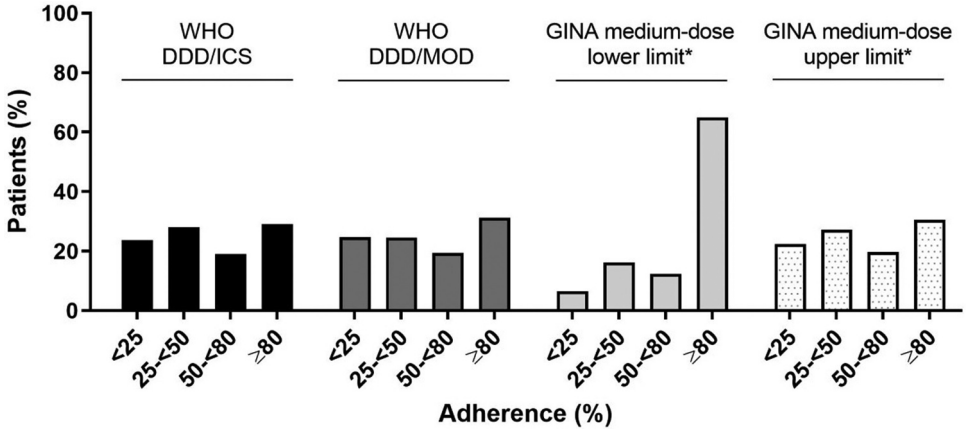

Figure 2. Adherence to inhaled corticosteroids in patients having purchased at least one inhaler containing ICS.

Adherence is given as proportion of days covered (%) by inhaled corticosteroids during one year as proportion of patients (N = 686) in different daily dose calculation method groups. WHO DDD/ICS: The defined daily dose for pure corticosteroid regimen is used both for ICS alone and combination products. WHO DDD/MOD: For those using only ICS, the defined daily dose for ICS is used. For those using ICS-LABA, the unit dose-based defined daily doses are used. For the total study subgroup both these groups are combined when presenting data.

*recommended treatment dose for beclomethasone dipropionate inhalation powder obtained from the Finnish Current Care Guideline[21] as it was not available from the GINA-report [8]

days after the first prescription claim, 322 patients purchased only ICS inhalers (subgroup A) and 364 purchased ICS-LABA-combination inhalers (subgroup B, out of which 78 patients also purchased ICS inhalers).

Firstly, by using any of the definitions for the reference dose values, the adherence was higher among those using ICS-LABA combination (Figure 3b) compared to those using ICS only (Figure 3a).

The lower level of GINA ICS medium dose recommendation gave the highest adherence rates in the subgroups A and B (Figure 3). Altogether 75.0% of the patients using combination products had ≥80% of the days of the year covered if this treatment dose was used as defined daily dose. Of the ICS only users, the same number was 53.4%, respectively (Figure 3). No differences were found in gender or age between those using only ICS compared to ICS-LABA users. However, those using only ICS inhalers had higher level of education (Supplementary Table S3).

Adherence among patients having special reimbursement for asthma medication

We calculated the proportion of days covered by ICS in the 524 patients who were entitled to special reimbursement on asthma medication (meaning 65% discount off the price) as well as in the 162 patients without this entitlement. Using the lower limit of medium dose in GINA report as a reference value, 73.3% of those entitled to special reimbursement had ≥80% proportion of days covered compared to 37.7% of the patients without special reimbursement. As seen in the whole study group, the adherence to ICS treatment was higher among patients using combination products than among those using only ICS also in these patients. More detailed information is provided in Supplementary Tables 4 and 5.

Discussion

In this randomly selected adult population with asthma, we assessed long-term adherence to ICS by using PDC with different reference daily dose values. When using WHO DDD for ICS, modified WHO DDD or the upper limit of GINA medium-dose, one third of the patients were adherent to ICS treatment (PDC ≥ 80%). However, if adherence was computed by lower limit of GINA medium-dose, 65% of the patients were adherent to ICS therapy (PDC ≥ 80%). When using any of the definitions for the reference dose values, the adherence was higher among those using ICS-LABA combination compared to those using only ICS. Moreover, patients with special reimbursement on asthma medicines had higher adherence to ICS (73%) compared to those with basic rate of reimbursement (38%).

In this study, 8.9% of randomly selected adult population reported that they have been told by a doctor that they have or have had asthma. This is slightly lower than recent reports of asthma prevalence in Finland [1,2]. This may be since response rate in the

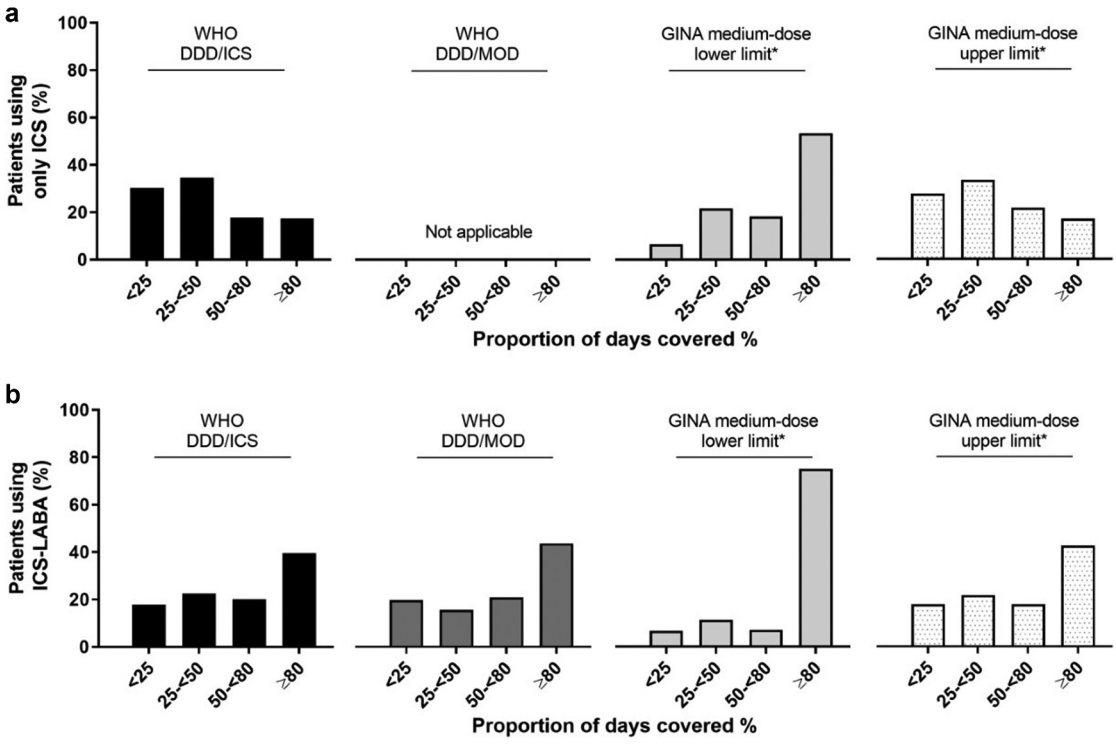

Figure 3. Adherence to inhaled corticosteroid treatment between different subgroups measured as proportion of days covered during one year and based on different ways to define daily doses.

Subgroup a: Patients using only ICS products (n = 322). Subgroup b: ICS-LABA product users (n = 364) WHO DDD/ICS: The defined daily dose for pure corticosteroid regimen is used both for ICS and combination products. WHO DDD/MOD: For those using only ICS, the defined daily dose for ICS is used. For those using ICS-LABA, the unit dose-based defined daily doses are used. For the total study subgroup both these groups are combined when presenting data.

*recommended treatment dose for beclomethasone dipropionate inhalation powder obtained from the Finnish Current Care Guideline [21] as it was not available from GINA-report [8]

study population was highest in the youngest age group [21] but asthma prevalence increases by age [3,4].

In our study, combination treatment was more commonly used than ICS alone, which is similar to the findings in some other European countries [23–25]. There is evidence that patients' adherence to ICS-LABA combination inhaler treatment is higher than adherence to ICS alone [26]. In our study this same finding was supported by the clearly higher number of patients having proportion of days covered at least 80% among the combination users regardless of the way defined daily dose was estimated. We do not know whether our finding is because doctors prescribed these inhalers more often, because patients adhere to combination inhalers better or if they have more severe disease, or possibly all these reasons. It is also possible, that the medication is started with a combination or LABA is added to treatment later, but then the medication is continued on this level without trying to decrease it. This may differ from the guidelines' step-down approach if asthma control is good [8,27]. One reason for this might be that the follow-up visits do not take place as often as recommended [28] and the prescriptions are renewed without properly assessing the situation. However, the more severe disease with combination inhaler treatment hardly has influenced our findings regarding WHO and GINA recommendations.

When measuring adherence in a large number of patients, an optimal way would be to assess adherence by comparing the dispensed medication to the prescribed medication. However, often relevant data, either on prescribed or dispensed medication is not available. In fact, several recent studies have used either prescribed or dispensed medication data but not both [29–32], and the availability of data may depend on the country where the study is done. In Scandinavia, the large nationwide registers allow combination of patient data by using unique person identification code [33] and often include data on dispensed asthma medication. However, as most often the data on exact prescribed doses and dosing changes are not available, a reference value, for example DDD is needed for comparison to calculate adherence. In fact, this has been used in several recent

Scandinavian studies [34–36]. Only some recent studies from Scandinavia have used other values to relate the redemption data, either GINA doses [33] or actual prescribed doses [12,13]. Thus, it is important that the value used to compare dispensed medication data is clinically relevant over a wide range of countries and healthcare systems.

Our results demonstrate the possible risks of using defined daily doses instead of actual prescription information. Most asthma patients have a mild or moderate disease [37], but WHO's defined daily doses are based on the starting dose in moderate to severe asthma and for combination (ICS-LABA) products on the maintenance dose in severe asthma [18]. This may lead to underestimation of medication adherence. WHO DDD values for ICS are usually equal or nearly equal to the upper limit for medium dose range in GINA [8]. Discrepancies between fixed defined daily dose database and prescribed daily dose have been shown to be relevant for other drugs as well [38]. The unit doses per day for combination products are based on the dose of long-acting β_2-agonist leading to varying ICS DDDs on salmeterol-fluticasone combination inhalers. Adding to that, WHO DDDs for fluticasone cannot be exactly met by most of the inhalers on the market. This means that using those DDDs can lead to either over- or underestimation of the drug usage. Moreover, according to a recent Nordic study updated GINA recommendations provide a reliable view of asthma medicine use [39].

We also found that 7.3% of the asthmatic respondents said that they had not bought medication because of high prices. This is also a relevant finding because medication cost is one of the various reasons affecting each patient's adherence to medical treatment [40] and combination products are more expensive than ICS alone. Adherence was higher among those having special reimbursement and this was especially seen among those using combination inhalers. This may have a connection to the price of medication but also to the severity of the disease. We may assume, that among the 162 patients without special reimbursement, there are patients who have a very mild disease, or they may be using ICS medication for some other reasons than properly diagnosed asthma.

The strength of this study is that the original population is a random sample of Finnish working aged adults representing the population as it is including smokers and patients with comorbidities. Another strength is that the medication information is derived from a national record, which covers the whole population. Adding to that, all dispensed ICS were obtained from SII records covering every patient's purchased medicines in Finland. We can thus conclude that the findings in our study can be considered highly reliable. Although the diagnosis was self-reported, we were able to assure that 76.4% of our asthma group had definite diagnosis, because they were entitled for the special reimbursement. The criteria for special reimbursement are the same as the objective lung function diagnostic criteria for asthma. In addition, the patient must have used a control medication for at least six months.

There are some limitations to be addressed. Firstly, even though the dispensation data include all dispensed medicines from any Finnish pharmacy, the dispensation does not guarantee whether the purchased inhalers were used by the patients. Secondly, we excluded those people 455 (approximately 40%) who reported having or having had asthma, but who didn't purchase any inhaled corticosteroids during the previous year of the survey. Other studies have shown that approximately 30–35% of adult patients within the community diagnosed with asthma do not have current asthma [41] which is somewhat less than our finding. This means that we may have excluded some patients with mild disease but also patients who were non-adherent to ICS. Thirdly, dispensation data did not include details on prescription such as dosage or dose instructions (e.g. in case the medication was meant to be used only during respiratory infections or the pollen season). Therefore, different methods to evaluate the defined daily doses were used in this study.

It is also possible that patients with good adherence to medication have responded more actively to the follow-up surveys of the HeSSup study. Moreover, the response rates in the survey were 40% in 1998, 75% in 2003 and 57% in 2012. However, according to the non-response analysis in 1998 respondents and non-respondents were comparable with respect to the most important demographic variables including gender and age distribution [21]. In addition, the differences in physical health between participants and the general population were minor both in 1998 and 2003 [21,22].

Nowadays in Finland, pharmacy refill record of every patient is available for the doctor through the national electronic prescription system. Both public and private health care as well as pharmacies are combined into the same database, and all have access to the data. This offers a better possibility to evaluate adherence to treatment for both doctors and future researchers.

We conclude that using DDDs in asthma medication adherence studies is vulnerable to misinterpretation because the average disease severity in population may conflict with the severity assumed in the given

DDDs. In this respect our results are new and thus give relevant information for physicians treating asthma patients. Adding to that, the use of combination preparations is considerably common, and patient adherence is higher to combination products than ICS only products. There is a need for further studies on the prescription patterns of doctors who treat asthma to thoroughly understand these phenomena.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

[1] Honkamäki J, Hisinger-Mölkänen H, Ilmarinen P, et al. Age- and gender-specific incidence of new asthma diagnosis from childhood to late adulthood. Respir med. 2019;154:56–62.
[2] Hisinger-Mölkänen H, Pallasaho P, Haahtela T, et al. The increase of asthma prevalence has levelled off and symptoms decreased in adults during 20 years from 1996 to 2016 in Helsinki, Finland. Respir med. 2019;15:121–126.
[3] Pelkonen M, Notkola I-L, Laatikainen T, et al. 30-year trends in asthma and the trends in relation to hospitalization and mortality. Respir med. 2018;142:29–35.
[4] Kankaanranta H, Tuomisto L, Ilmarinen P. Age-specific incidence of new asthma diagnoses in Finland. J Allergy Clin Immunol Pract. 2017;5:189–191.e3.
[5] Ilmarinen P, Juboori H, Tuomisto L, et al. Effect of asthma control on general health-related quality of life in patients diagnosed with adult-onset asthma. Sci Rep. 2019;9:16107.
[6] Stanescu S, Kirby S, Thomas M, et al. A systematic review of psychological, physical health factors, and quality of life in adult asthma. NPJ Prim Care Respir Med. 2019;29:37.
[7] Haahtela T, Herse F, Karjalainen J, et al. The Finnish experience to save asthma costs by improving care in 1987-2013. J Allergy Clin Immunol. 2017;139:408–414.
[8] Global Initiative for Asthma. Global strategy for asthma management and prevention, 2020. Available from www.ginasthma.org.
[9] Kankaanranta H, Lahdensuo A, Moilanen E, et al. Add-on therapy options in asthma not adequately controlled by inhaled corticosteroids: a comprehensive review. Respir Res. 2004;5:17.
[10] Engelkes M, Janssens H, De Jongste J, et al. Medication adherence and the risk of severe asthma exacerbations: a systematic review. Eur Respir J. 2015;45:396–407.
[11] Bårnes C, Ulrik C. Asthma and adherence to inhaled corticosteroids: current status and future perspectives. Respir Care. 2015;60:455–468.
[12] Vähätalo I, Ilmarinen P, Tuomisto L, et al. 12-Year adherence to inhaled corticosteroids in adult-onset asthma. ERJ Open Res. 2020;6:00324–02019.
[13] Vähätalo I, Kankaanranta H, Tuomisto L, et al. Long-term adherence to inhaled corticosteroids and asthma control in adult-onset asthma. ERJ Open Res. 2021;7:00715–2020.
[14] Jensen FF, Håkansson KE, Nielsen BO, et al. Self-reported vs. objectively assessed adherence to inhaled corticosteroids in asthma. Asthma Res Pract. 2021;7:7.
[15] Hansen R, Kim M, Song L, et al. Adherence: comparison of methods to assess medication adherence and classify nonadherence. Ann Pharmacother. 2009;43:413–422.
[16] Lehmann A, Aslani P, Ahmed R, et al. Assessing medication adherence: options to consider. Int J Clin Pharm. 2014;36:55–69.
[17] Raebel M, Schmittdiel J, Karter A, et al. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. Med care. 2013;51:S11–21.
[18] WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2021. Oslo, Norway: Norwegian Institute of Public Health; 2020.
[19] WHO Collaborating Centre for Drug Statistics Methodology. List of DDDs combined products.Date last updated: may 2, 2022. Date last accessed: June 19, 2022. https://www.Whocc.no/ddd/list-of-ddds-combined-products
[20] Varinen A, Kosunen E, Mattila K, et al. The association between bullying victimization in childhood and fibromyalgia. Data from the nationwide Finnish health and social support (HeSsup) study based on a sample of 64,797 individuals. J Psychosom Res. 2019;117:48–53.
[21] Korkeila K, Suominen S, Ahvenainen J, et al. Non-response and related factors in a nation-wide health survey. Eur J Epidemiol. 2001;17:991–999.
[22] Suominen S, Koskenvuo K, Sillanmäki L, et al. Non-response in a nationwide follow-up postal survey in Finland: a register-based mortality analysis of respondents and non-respondents of the health and social support (HeSsup) study. BMJ Open. 2012;2:e000657.
[23] Sweeney J, Patterson C, Plant G, et al. Inappropriate prescribing of combination inhalers in Northern Ireland: retrospective cross-sectional cohort study of prescribing practice in primary care. Prim Care Respir Med. 2014;23:74–78.
[24] Geraets I, Schermer T, Kocks J, et al. Primary care cohort study in the sequence of diagnosing chronic respiratory diseases and prescribing inhaled corticosteroids. Prim Care Respir Med. 2018;28:37.
[25] Baldacci S, Simoni M, Maio S, et al. Prescriptive adherence to GINA guidelines and asthma control: an Italian cross-sectional study in general practice. Respir med. 2019;146:10–17.
[26] Foden J, Hand C. Does use of a corticosteroid/long--acting beta-agonist combination inhaler increase adherence to inhaled corticosteroids? Prim Care Respir J. 2008;17:246–247.
[27] Working group set up by the Finnish medical society duodecim, Finnish respiratory society, Finnish

paediatric society and Finnish society of clinical physiology. Asthma. current care guidelines. Helsinki: The Finnish Medical Society Duodecim; 2012.
[28] Takala J, Ilmarinen P, Tuomisto L, et al. Planned primary health care asthma contacts during 12-year follow-up after Finnish national asthma programme: focus on spirometry. NPJ Prim Care Respir Med. 2020;30:1–8.
[29] Papi A, Ryan D, Soriano JB, et al. Relationship of inhaled corticosteroid adherence to asthma exacerbations in patients with moderate-to-severe asthma. J Allergy Clin Immunol Pract. 1018;6:1989–1998.
[30] Engelkes M, Janssens HM, de Jongste JC, et al. Prescription patterns, adherence and characteristics of non-adherence in children with asthma in primary care. Pediatr All Immunol. 2016;27:201–208.
[31] Sadatsafavi M, FitzGerald M, Marra C, et al. Costs and health outcomes associated with primary vs secondary care after and asthma-related hospitalization. A population-based study. Chest. 2013;144:428–435.
[32] Wu AC, Li L, Fung V, et al. Use of leukotriene receptor antagonists are associated with a similar risk of asthma exacerbations as inhaled corticosteroids. J Allergy Clin Immunol. 2014;2:607–613.
[33] Janson C, Bjermer L, Lehtimäki L, et al. Eosinophilic airway diseases: basic science, clinical manifestations and future challenges. Eur Clin Respir J. 2022;9:2040707.
[34] Björnsdottir US, Sigurdardottir ST, Jonsson JS, et al. Impact of changes to reimbursement of fixed combinations of inhaled corticosteroids and long-acting β_2-agonists in obstructive lung diseases: a population-based, observational study. Int J Clin Pract. 2014;68:812–819.
[35] Dahlen E, Bergström A, Ödling M, et al. Non-adherence and sub-optimal treatment with asthma medications in young adults: a population-based cohort study. J Asthma. 2022;58:1661–1669.
[36] Davidsen JR, Sondergaard J, Hallas J, et al. Increased use of inhaled corticosteroids among young Danish adult asthmatics: an observational study. Respir med. 2010;104:1817–1824.
[37] Kauppi P, Peura S, Salimäki J, et al. Reduced severity and improved control of self-reported asthma in Finland during 2001-2010. Asia Pac Allergy. 2015;5:32–39.
[38] Abrantes C, Tonin F, Reis-Pardal J, et al. Implications of a defined daily dose fixed database for drug utilization research studies: the case of statins in Portugal. Br J Clin Pharmacol. 2021;87:3542–3549.
[39] Lehtimäki L, Arvidsson M, Erdemli B, et al. Regional variation in intensity of inhaled asthma medication and oral corticosteroid use in Denmark, Finland, and Sweden. Eur Clin Respir J. 2022;9:1.
[40] Mäkelä M, Backer V, Hedegaard M, et al. Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD. Respir med. 2013;107:1481–1490.
[41] Aaron S, Boulet L, Reddel H, et al. Underdiagnosis and overdiagnosis of asthma. Am J Respir Crit Care Med. 2018;198:1012–1020.