ORIGINAL ARTICLE
ASTHMA

Pharmacological treatment of asthma in a cohort of adults during a 20-year period: results from the European Community Respiratory Health Survey I, II and III

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ABSTRACT Asthma often remains uncontrolled, despite the fact that the pharmacological treatment has undergone large changes. We studied changes in the treatment of asthma over a 20-year period and identified factors associated with the regular use of inhaled corticosteroid (ICS) treatment.

Changes in the use of medication were determined in 4617 randomly selected subjects, while changes in adults with persistent asthma were analysed in 369 participants. The study compares data from three surveys in 24 centres in 11 countries.

The use of ICSs increased from 1.7% to 5.9% in the general population and the regular use of ICSs increased from 19% to 34% among persistent asthmatic subjects. The proportion of asthmatic subjects reporting asthma attacks in the last 12 months decreased, while the proportion that had seen a doctor in the last 12 months remained unchanged (42%). Subjects with asthma who had experienced attacks or had seen a doctor were more likely to use ICSs on a regular basis.

Although ICS use has increased, only one-third of subjects with persistent asthma take ICSs on a regular basis. Less than half had seen a doctor during the last year. This indicates that underuse of ICSs and lack of regular healthcare contacts remains a problem in the management of asthma.

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Despite increased ICS use, only 34% of subjects with persistent asthma take ICSs on a regular basis; <50% have seen a doctor in the last year. Underuse of ICSs and lack of regular healthcare contacts remains a problem in asthma. http://ow.ly/GUZ630mZkVN

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Introduction

The pharmacological treatment of asthma has undergone large changes during the last two decades with new treatment options such as long-acting β_2-agonists (LABAs), leukotriene antagonist (LTRAs), fixed combinations of inhaled corticosteroids (ICSs) and LABAs (ICS+LABA), long-acting muscarinic receptor antagonists (LAMAs), anti-IgE, and anti-interleukin (IL)-5 therapies. International guidelines have been available since the 1990s and are continuously updated with regular use of ICSs as the cornerstone of first-line treatment of asthma [1]. Despite this there are reports showing that asthma remains uncontrolled in a large proportion of patients [2–4], still has a large effect on quality of life [5, 6], influences patients' sleep [7, 8] and causes a large economic burden for society [9, 10].

The European Community Respiratory Health Survey (ECRHS) is a unique study where participants from the general population in a large number of countries have been surveyed 3 times over a 20-year period [11, 12]. At the first ECRHS survey (ECRHS I), large differences were found regarding the prevalence of asthma therapy, with an 8-fold difference in the use of ICSs among countries [13]. In the second survey (ECRHS II) there was an increase in the use of ICSs, but despite this only 17% of participants with asthma were using ICSs on a daily basis [14]. Analyses from the first two time-points showed that females with asthma were more likely and smokers with asthma less likely to use ICSs than males and nonsmokers, respectively [14, 15]. A surprisingly low use of ICSs on a daily basis in asthmatic subjects has also been found in other studies [4, 16]. Change in medication is influenced by longitudinal change in the prevalence of asthma and asthma symptoms. Longitudinal studies of asthma and asthma symptoms in adults have shown diverging results, with an increase in self-reported asthma and asthma symptoms with age in an English and a Canadian study [17, 18], and a decrease in the prevalence of asthma symptoms in a German study [19]. There are, however, very few studies of longitudinal change in the pharmacological treatment of asthma and such studies are needed in order to optimise the therapeutic management of asthma at the population level.

The third survey of the ECRHS (ECRHS III) was completed between 2011 and 2014. An analysis of data from a short postal questionnaire showed an increase in the use of asthma medication [20]. The aim of the present study was to undertake a more detailed investigation of changes in the pharmacological treatment of asthma over a 20-year period and to investigate factors associated with the regular use of ICSs.

Methods

Population

The designs of ECRHS I and II have been described in detail [21, 22]. In ECRHS I, each participant was sent a brief questionnaire (stage 1) and from those who responded, a random population-based sample

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was selected to undergo a more detailed clinical examination. In addition, a "symptomatic sample", reporting been woken by an attack of shortness of breath, asthma attacks or using asthma medication in stage 1, was also invited to the same clinical examination. This examination included spirometry, allergy testing and a structured interview. In ECRHS II, subjects who had participated in the clinical phase of ECRHS I were invited to participate in the follow-up. The clinical phase of ECRHS I and II was performed during 1991–1994 and 1998–2002, respectively. ECRHS III is the second follow-up and was performed from February 2011 to January 2014 [23]. The numbers of participants in the various parts of ECRHS I–III are presented in figure 1.

Only participants from the random sample were included when describing change in the prevalence of use of medication and geographical difference in the general population. The participants who had originally been selected as part of the random or the symptomatic sample were included when analysing medication in subjects with persistent asthma.

Centres and countries

This investigation included 24 centres from 11 countries: Iceland (Reykjavik), Norway (Bergen), Sweden (Gothenburg, Umeå and Uppsala), Estonia (Tartu), Germany (Erfurt and Hamburg), UK (Ipswich and Norwich), Belgium (Antwerp), France (Bordeaux, Grenoble, Montpellier and Paris), Spain (Albacete, Barcelona, Galdakao, Huelva and Oviedo), Italy (Pavia, Torino and Verona) and Australia (Melbourne).

Questionnaire

The subjects underwent a structured interview asking for detailed information on respiratory symptoms, asthma and asthma therapy. Pictures, samples or lists of different asthma medications were shown to facilitate a correct answer to the therapy questions.

Definition of asthma-related variables

Physician-diagnosed asthma: a positive answer to the questions "Have you ever had asthma?" and "Was this confirmed by a doctor?".

Asthma-related symptoms in the last 12 months: reported having had wheeze, nocturnal chest tightness or attacks of breathlessness following activity, at rest or at night during the last 12 months.

Current asthma: having physician-diagnosed asthma and having had at least one of the following criteria: asthma-related symptoms, attacks of asthma in the last 12 months or reported current use of any medicines for asthma.

Persistent asthma: having current asthma at all three surveys.

The participants were also asked whether they had asthma attacks within the last 12 months and if "yes", the number of attacks.

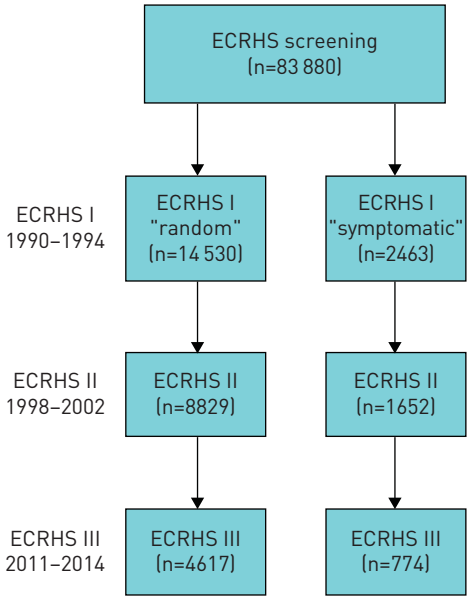

FIGURE 1 Selection of population. ECRHS: European Community Respiratory Health Survey.

Medications for asthma

Participants were considered to be taking medication for asthma if they reported having used any of the following drugs for their breathing in the 12 months preceding each survey: 1) inhaled asthma medications (short-acting β_2-agonists (SABAs), LABAs, short-acting muscarinic receptor antagonists, LAMAs and ICSs), 2) oral asthma medications (β_2-agonists, theophylline, LTRAs and oral corticosteroids (OCSs)) and 3) injections for the treatment of allergy (including omalizumab). Patients who used fixed combinations of ICS+LABA were considered to be using both drugs. Patients that reported having used ICSs "continuously" in the last 3 months before each survey were defined as regular users of ICSs.

Healthcare utilisation

The participants were asked whether they had spent a night in hospital and whether they had been seen by a doctor because of breathing problems in the 12 months preceding each survey.

Smoking, chronic obstructive pulmonary disease, educational level and body mass index

Current smoker was defined by answering yes to the two questions "Have you ever smoked for as long as a year?" and "Do you now smoke, as of 1 month ago?". In ECRHS III the participants were asked whether a doctor ever told them that they have chronic obstructive pulmonary disease (COPD). Information on educational level was collected in ECRHS I and a low education level was defined as having completed full-time education before the age of 16 years [14]. Body mass index (BMI) was calculated from height and weight recorded in all three surveys.

Ethics approval

Local ethics committees at each centre approved the study protocols. All participants provided written informed consent.

Statistics

All statistical analyses were conducted using Stata version 14 (StataCorp, College Station, TX, USA). Absolute net changes in medication, asthma attacks and healthcare utilisation between the surveys were estimated using population-averaged, generalised estimating equations for a binomial outcome with identity link, with participants identified as the clustering factor and the number of the survey as an independent variable. Results were expressed as net percentage change between surveys. The Wald test was used to examine differences in change of prevalence by survey. Estimated changes in treatments by country were examined for heterogeneity and combined using random effects meta-analyses.

The Chi-squared test was used when comparing the prevalence of medication between countries in cross-sectional analyses. Spearman's correlation test was used when analysing the ecological association between the prevalence of current asthma and the prevalence of the use of medication for asthma.

We assessed the influence of several personal and asthma characteristics on the regular use of ICS treatment among subjects with persistent asthma. The associations were estimated using mixed effects logistic regressions with the participant as the clustering unit to account for the repeated measurements. The factors assessed were chosen based on previous experience [14], and included age, sex, BMI, smoking, educational level, doctor visits, hospitalisations, asthma attacks, survey and country. Only variables with a p-value <0.1 in the unadjusted analyses were included in the final model.

Results

Use of medications for asthma in the random population sample

The random sample included 4617 subjects (52.1% female) that were seen at all three surveys. The mean±SD age at ECRHS I was 34.4±7.1 years and the mean follow-up was 20.1 years. Those who participated in all three surveys were less likely to be smokers (32.7% *versus* 39.8%), were slightly older (mean±SD age 34.4±7.1 *versus* 33.2±7.2 years; p<0.0001) and had used SABAs more often (4.8% *versus* 3.6%; p=0.003) at ECRHS I than those that only participated in the first survey. No significant difference was found in sex and BMI distribution or use of ICSs between those that participated in all three surveys and those that only participated in the first survey (data not shown).

The prevalence of use of medication for asthma had almost doubled from 5.2% to 9.9% between ECRHS I and III (table 1). A significant increase was found for all inhaled compounds as well as LTRAs and OCSs, while a significant decrease was found for theophylline. Changes in the use of ICSs between ECRHS I and III by country are presented in figure 2. A significant increase was found in most countries. There was significant heterogeneity between countries.

In the random sample, 43 (0.9%) participants reported that they had a diagnosis of COPD. Excluding these subjects had only a marginal effect on the prevalence of use of pharmacological treatment. As an

TABLE 1 Use of medication during the last 12 months in the random sample[#]

	ECRHS I	ECRHS II	ECRHS III	Change in prevalence
Inhaled SABAs	3.6	5.7	6.2	2.7 (2.0–3.4)
Inhaled LABAs[¶]		1.2	4.2	3.0 (2.4–3.6)
ICSs[¶]	1.7	4.0	5.9	4.2 (3.5–4.9)
ICS+LABA		0.9	3.8	2.9 (2.4–3.5)
Inhaled anticholinergics	0.2	0.2	0.5	0.3 (0.07–5.1)
Theophylline	0.7	0.2	0.1	−0.6 (−0.9–−0.4)
Oral β_2-agonists	0.4	0.3	0	−0.4[+]
LTRAs		0.2	0.6	0.4 (0.2–0.7)
OCSs	0.6	1.1	1.0	0.4 (0.1–0.8)
Any medication for asthma	5.2	8.0	9.9	4.8 (3.9–5.6)

Data are presented as %, and change between European Community Respiratory Health Survey (ECRHS) I and III in % (95% CI), or in case of absence of information from ECRHS I, change between ECRHS II and ECRHS III in % (95% CI). SABA: short-acting β_2-agonist; LABA: long-acting β_2-agonist; ICS: inhaled corticosteroid; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroid. [#]: n=4617; [¶]: as a single inhaler or in combination; [+]: not possible to calculate 95% confidence interval.

example, the prevalence of use of ICSs decreased from 5.9% to 5.5% and the corresponding values for SABAs were from 6.2% to 5.9%.

The highest prevalence of current asthma and medication use for asthma in ECRHS III was found in Australia and the lowest in Belgium (table 2). There were statistically significant differences between the countries in the use of SABAs and LABAs, but not in the use of ICSs. There was a strong statistical ecological association between the prevalence of current asthma and the prevalence of use of any medication for asthma, whereas no significant association was found between the prevalence of asthma and the prevalence of ICS use (figure 3).

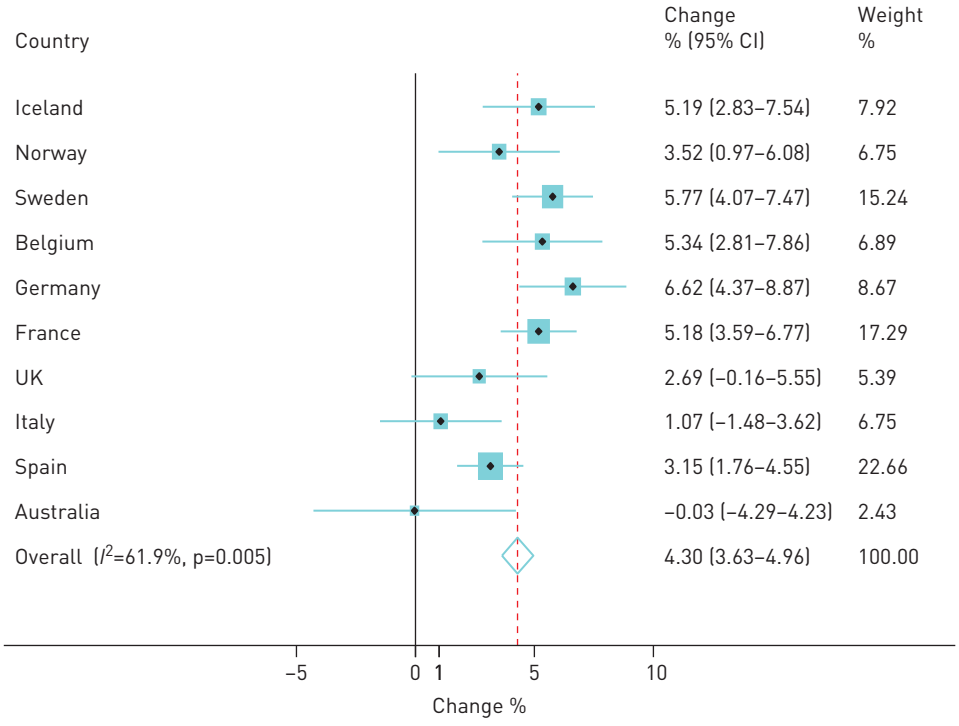

FIGURE 2 Change in the use of inhaled corticosteroids (as a single inhaler or in combination; any use in the last 12 months) in the random sample between European Community Respiratory Health Survey (ECRHS) I and III analysed by country and combined in a meta-analysis. Analysis was not possible for Estonia due to the limited number of participants. The area of each square is proportional to the reciprocal of the variance of the estimate for the country. The combined random effects estimate is shown by the dashed line; the width of the diamond is the 95% confidence interval.

TABLE 2 Prevalence of current asthma and use of medication for asthma in the random sample at European Community Respiratory Health Survey III per participating country

	Subjects	Current asthma	SABA	LABA#	ICS#	Any medication
Iceland	347	12.4	8.4	5.7	5.4	11.2
Norway	330	12.2	8.0	5.9	5.9	12.1
Sweden	717	9.8	7.8	4.0	6.7	10.7
Estonia	105	7.6	2.9	4.8	7.6	8.6
Belgium	286	3.5	1.5	3.6	4.9	5.6
Germany	377	11.4	3.6	4.4	8.0	8.8
France	889	12.3	7.1	4.7	6.8	12.5
UK	249	13.3	12.4	2.0	3.6	12.8
Italy	226	9.7	4.0	0	4.0	6.6
Spain	872	7.9	3.7	3.6	4.6	6.7
Australia	219	16.9	10.7	8.0	8.5	15.5
p-value		<0.0001	<0.0001	0.003	0.13	<0.0001

Data are presented as n, unless otherwise stated. SABA: short-acting β_2-agonist; LABA: long-acting β_2-agonist; ICS: inhaled corticosteroid. #: as single inhalers or in combination.

Treatment in subjects with persistent asthma

The number of participants with current asthma in the combined random and symptomatic sample (n=5391) was 516 (9.6%) in ECRHS I, 720 (13.4%) in ECRHS II and 856 (15.9%) in ECRHS III. Of these, 369 had persistent asthma. Approximately three out of four subjects with persistent asthma reported having used medication for asthma in the last 12 months in all three surveys, but there was a significant increase in the use of LABAs, ICSs and LTRAs, and a decreased use of SABAs and theophylline (table 3).

Of the participants with persistent asthma, 17 (4.6%) had physician-diagnosed COPD. Excluding these participants had only a minor effect on the prevalence of pharmacological treatment. The prevalence of ICS use in ECRHS III decreased from 49.1% to 48.5% and the corresponding values for SABAs were from 58.0% to 57.4%.

The proportion of adults with asthma who reported regular use of ICSs increased (table 3). This increase was from 21.5% to 41.8% when excluding asthmatic subjects without self-reported asthma attacks. Changes in regular use of ICSs between ECRHS I and III by country are presented in figure 4. No significant heterogeneity between countries was found.

Asthma attacks decreased throughout the study, whereas hospitalisations and the proportion of participants who reported having seen at doctor for their breathing problem in the last 12 months remained stable (table 3).

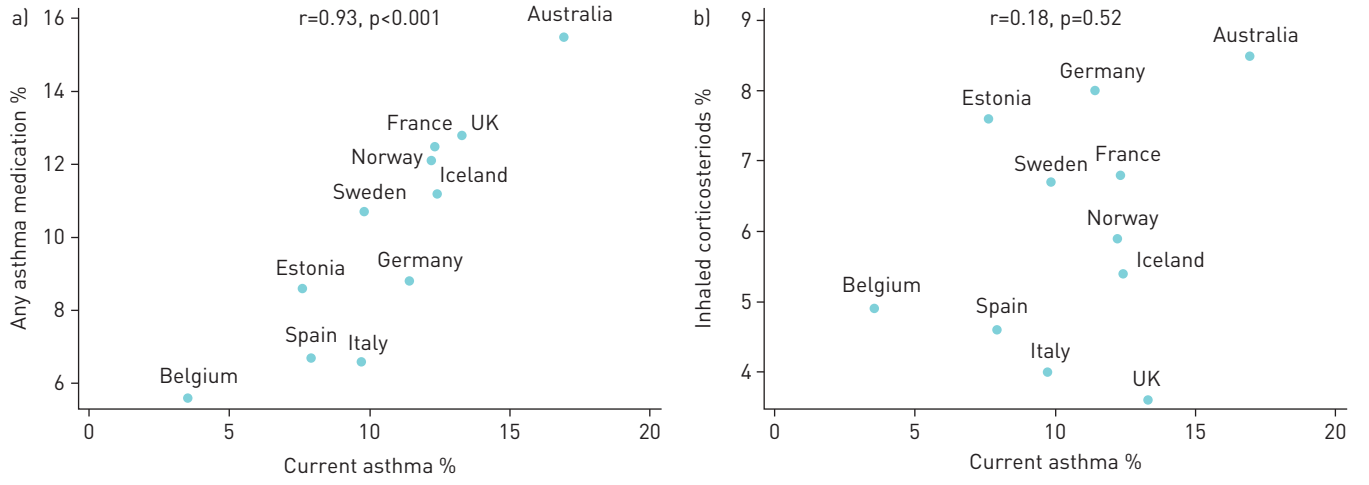

FIGURE 3 Ecological analysis of the association between prevalence of current asthma and the use of mediation for asthma in each country: a) any asthma medication and b) inhaled corticosteroids.

TABLE 3 Use of medication, asthma attacks and healthcare utilisation during the last 12 months in subjects with persistent asthma[#]

	ECRHS I	ECRHS II	ECRHS III	Change in prevalence
Inhaled SABA	68.6	67.5	58.0	−10.1 (−15.5–−4.7)
Inhaled LABAs[¶]		14.8	40.4	25.3 (19.5–31.1)
ICSs[¶]	31.4	46.2	49.1	17.2 (11.6–22.9)
ICSs used daily in the last 3 months	18.8	26.3	32.8	13.5 (8.6–18.3)
ICS+LABA		12.7	36.4	23.5 (17.9–29.0)
Inhaled anticholinergics	2.6	2.3	3.7	1.0 (−1.5–3.4)
Theophylline	13.0	2.9	0.3	−12.5 (−15.9–9.1)
Oral β_2-agonists	7.5	1.7	0	−7.5[+]
LTRAs		3.3	7.1	3.7 (0.07–6.7)
OCSs	8.8	9.1	6.7	−1.6 (−5.1–1.9)
Any medication for asthma	72.9	76.9	73.9	1.2 (3.2–5.7)
Hospitalisations	2.2	1.5	1.2	−1.1 (−3.0–0.8)
At least one asthma attack in the last 12 months	68.8	51.0	40.9	−27.9 (−33.7–−22.1)
Three or more asthma attacks in the last 12 months	46.5	35.8	25.8	−20.8 (−26.5–−15.0)
Doctor visit for breathing problems in the last 12 months	41.7	34.3	42.3	0.6 (−5.7–6.9)

Data are presented as % or % (95% CI). ECRHS: European Community Respiratory Health Survey; SABA: short-acting β_2-agonist; LABA: long-acting β_2-agonist; ICS: inhaled corticosteroid; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroid. [#]: n=369; [¶]: as a single inhaler or in combination; [+]: not possible to calculate 95% confidence interval.

Variables associated with the regular use of ICSs

Using ICSs on a regular basis in the participants with persistent asthma was related to having had asthma attacks and having been seen by a doctor in the last 12 months (table 4). There was also an association of borderline statistical significance between higher age and regular use of ICSs (p=0.06).

Discussion

The main finding in the present analysis was an increase in the use of medication for asthma (*e.g.* ICSs and LABAs) in the general population during the 20-year follow-up period. Among those with persistent

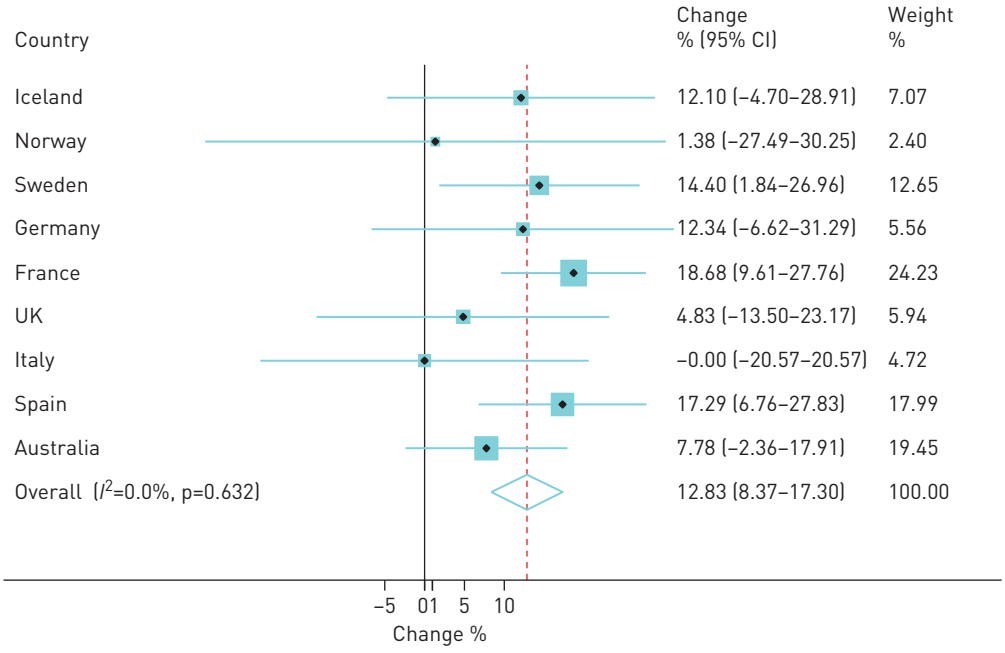

FIGURE 4 Change in the regular use of inhaled corticosteroids (as a single inhaler or in combination; any use in the last 12 months) in participants with persistent asthma analysed by country and combined in a meta-analysis. Analysis was not possible for Estonia due to the limited number of participants. The area of each square is proportional to the reciprocal of the variance of the estimate for the country. The combined random effects estimate is shown by the dashed line; the width of the diamond is the 95% confidence interval.

TABLE 4 Predictors of regular use of inhaled corticosteroids in participants with persistent asthma[#]

	Crude OR (95% CI)	Adjusted OR (95% CI)[¶]
Female	2.16 (1.09–4.28)	1.61 (0.81–3.13)
Age at baseline (per 10 year)	1.59 (0.97–2.61)	1.61 (0.98–2.64)
BMI (per 5 units)	1.69 (1.20–2.38)	1.23 (0.87–1.75)
Current smoking	0.38 (0.17–0.85)	0.89 (0.38–2.09)
Low educational level	1.61 (0.51–5.04)	Not included
Asthma attack in the last 12 months	2.09 (1.23–3.55)	2.56 (1.37–4.79)
Doctor visit in the last 12 months	4.27 (2.51–7.27)	3.58 (1.96–6.55)
Hospitalisation in the last 12 months	9.76 (0.63–150)	Not included

BMI: body mass index. [#]: n=369; [¶]: adjusted for the variables in the table, survey and country.

asthma there has been a reduction in asthma attacks, suggesting an improvement of asthma control. However, two-thirds of adults with persistent asthma did not take ICSs regularly, 40% reported having at least one asthma attack and less than half had seen a doctor because of their breathing problem in the last year.

In the present study a third of the participants with persistent asthma were using ICSs on a regular basis at the second follow-up. This is almost a doubling proportion compared with the first survey in 1991–1994 [13], but still a surprisingly low figure given that the regular use of ICSs is recommended in all adults with asthma except in those with infrequent asthma symptoms [1, 24]. An increased use of ICSs over time is in accordance with data from a large Canadian registry study [25], but our findings also reflect those of the 1999 AIRE (Asthma insights and reality in Europe) study which reported low ICS use in asthma [4]. A low usage of ICSs on a daily basis was also reported in the REALISE (Recognise asthma and link to symptoms and experience) study, where over half of the participants on preventer therapy reported using this less than daily [16]. AIRE and REALISE also showed a high prevalence of uncontrolled asthma, a finding that has been replicated in several other studies [2, 3]. A positive aspect is that we found a decrease in reported asthma attacks, which suggests an improvement in asthma control; even in the present study 40% of those with persistent asthma reported having had at least one asthma attack in the last year. This result is in accordance with a recent report from a Canadian study [26], but in contrast with some previous studies reporting that the level of asthma control is not improving over time [2, 27, 28]. One reason for this is that this is a cohort study, and we are therefore looking at both temporal and age-related changes.

Several new types of drugs have been introduced during the follow-up time of the ECRHS. LABAs are now used by two-thirds of those using ICSs in ECRHS III. The addition of LABAs to ICSs has been shown to decrease exacerbations and improve symptom control in asthmatic subjects that are not well controlled with ICSs alone [29]. However, there are also data indicating that the ICS+LABA combination is used in some patients that could be controlled with ICSs alone [30]. Treatment with LTRAs has also been shown to improve asthma control when added to ICSs in patients with uncontrolled asthma [31]. LTRAs are included in international guidelines as an alternative to LABAs [1]. Despite this we found that LTRAs had been used in less than one out of 10 of the adults with asthma in ECRHS III. The use of theophylline and oral β_2-agonists has almost disappeared during this 20-year study period. Anticholinergics were used only by a small number of patients, which is expected as tiotropium was introduced in asthma guidelines in 2015 [32]. None of the participants reported using omalizumab or anti-IL-5 treatment.

At the first ECRHS survey large differences were found regarding the prevalence of use of ICSs among countries [13]. This difference is much lower now and, in fact, no longer statistically significant. This change might be related to the fact that the Global Initiative for Asthma (GINA) guidelines [1] as well as national guidelines [33] have been implemented in most countries. As in our previous analyses of ECRHS, we found the highest prevalence of current asthma and use of medication for asthma was in Australia [13]. There was a strong correlation between the prevalence of asthma and the prevalence of use of any medication for asthma in the ECRHS countries. This was, however, not the case for the prevalence of ICS use, indicating that factors other than asthma prevalence may play a role in how much ICS is used in a country. These factors may include national guidelines, different views on the risk of ICS-related side-effects and differences how the healthcare system is organised in the different countries.

Having seen a doctor for breathing problems increased the likelihood of regular ICS use. However, in the present study only ~40% of the adults with asthma had seen a doctor in the last year for breathing

problems. These results are in accordance with those from a recent study that also showed that most asthmatic subjects in Sweden lacked regular healthcare contacts [34]. The results of the present study suggest that having regular follow-ups in patients with asthma may be a way of improving treatment in asthma. This is probably related to increased adherence, as regular healthcare consultations was the strongest predictor for increased adherence between ECRHS I and II in a previous analysis [35]. An alternative way of interpreting our results is that patients with more frequent symptoms tend to use asthma drugs more frequently and require more frequent doctor visits. This interpretation is supported by the fact that the other factor that was related to regular ICS use was having had asthma attacks, which is what is to be expected as ICSs are often used to decrease the risk of further asthma attacks. In analyses of ECRHS I and II we have previously reported that current smokers with asthma were less likely to be using asthma medications [15], and to have started using ICSs between the first and second survey [14]. This was also found in the unadjusted analysis in the present study, but the association was not significant after adjusting for other variables such as doctor visits and asthma attacks. In the same way, we found that females were more likely to use ICSs than males in the unadjusted analyses [14, 15], but this association also became nonsignificant in the adjusted model. In the present analysis there was a borderline significant association between regular use of ICSs and higher age. This finding is in accordance with some previous studies showing a higher adherence to use of ICSs in older patients [36, 37].

The present study is unique in that we were able to follow a large population sample for 20 years. The methodology used in the three surveys was identical and this, together with the large sample size, is a major strength of the study. A weakness is that we lost a relatively large proportion of those investigated in the first survey. The nonparticipants were somewhat younger, and more likely to be smokers and to use SABAs. Another weakness is that we fully rely on self-reported data. The number of participants from each country was small and therefore the geographical variation shown in the study may not necessarily give an accurate picture of the geographical pattern in asthma treatment. As the participants are selected from the general population, most participants with asthma will have mild asthma and the study therefore gives little information on treatment with severe asthma. In the study we used self-reported asthma attacks as a proxy for asthma control. The reason for this is that the GINA definition of asthma control [1] was not available at the first survey.

In conclusion, this longitudinal survey shows that the therapeutic management of asthma has changed over time, with an increase in the use of ICSs and ICS+LABA combinations. There was also a decrease in reported asthma attacks. Despite this, only one-third of subjects with asthma were regularly using ICSs, 40% reported having at least one asthma attack and less than half had seen a doctor in the last 12 months. This indicates that underuse of ICSs and lack of regular healthcare remains a problem in the management of asthma.

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