Does adherence to inhaled corticosteroids predict asthma-related outcomes over time? A cohort study

Alexandra L. Dima, PhD[1], Eric van Ganse, PhD [1,2,3], Gertraud Stadler, PhD [4,5], Marijn de Bruin, PhD [5,6], and the ASTRO-LAB group*

1 Health Services Performance Research EA 7425 HESPER, University Claude Bernard Lyon 1, Lyon, France 2 Respiratory Medicine, Croix-Rousse University Hospital, Lyon, France 3 PELyon, Pharmacoepidemiology, Lyon, France 4 Institute of Applied Health Sciences, University of Aberdeen, Scotland, UK 5 Columbia University, USA 6 Radboud University Medical Center, Radboud Institute for Health Sciences, IQ Healthcare, the Netherlands

Corresponding author:

Alexandra Dima, Université Claude Bernard Lyon 1, 8 avenue Rockefeller, 69373 Lyon 8, France; email: alexandra.dima@univ-lyon1.fr

*Members of the ASTRO-LAB group were: Marijn de Bruin, Alexandra L. Dima (ASCoR, University of Amsterdam, The Netherlands); Eric Van Ganse, Laurent Laforest, Sandrine Herbage, Manon Belhassen, Marine Ginoux, Flore Jacoud, Maeva Nolin (University Claude Bernard Lyon 1, France); Stéphane Schück, Nathalie Texier, Sandy Leproust, Hélène Le Cloarec (Kappa Santé, France); Richard Hubbard (University of Nottingham, England); Alison Bourke, Mary Thompson, Delphine Vial, David Ansell (Cegedim Strategic Data, England); Javier Olaiz, Ana Valcarcel Orti (Lyon Ingénierie Projets, France); and Montse Ferrer, Olatz Garin, Gimena Hernandez (IMIM - Hospital del Mar Medical Research Institute, Spain).

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ICS adherence and asthma-related outcomes over time

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Abstract

Inhaled corticosteroids (ICS) adherence is important for asthma management. Current evidence on the impact of ICS adherence on outcomes is mostly based on correlational analyses of between-person data. Although it is widely acknowledged that asthma outcomes fluctuate over time, evidence on predictors of within-person change is scarce. We aimed to quantify these fluctuations and the longitudinal relationships between ICS adherence and outcomes at both between- and within-person levels.

A prospective cohort of persistent asthma patients in France and the United Kingdom (N = 847, age 6–40 years) provided 3756 reports over up to 2 years via computer-assisted telephone interviews and text messages on ICS adherence, asthma control, reliever medication use, and exacerbations. We examined adherence–outcome relations via longitudinal models, controlling for confounders, including severity.

Considerable within-person variability was found for exacerbations (91%), asthma control (59%), and reliever use (52%); 431 (11.5%) reports signalled exacerbations and 2046 (54.5%) poor control. At between-person level, patients with higher average adherence were more likely to report asthma control (OR=1.25 95%CI[1.06–1.47]) but not asthma exacerbations (OR=0.99 [0.87–1.12] or lower reliever use (b=-.0004 [-0.089–0.088]). At within-person level, higher-than-usual adherence was associated with higher concomitant reliever use (b=0.092 [0.053–0.131]) and lower subsequent reliever use (b=-0.047 [-0.005– -0.088]); it was unrelated to asthma control (OR=0.93 [0.84–1.02]) or exacerbations (OR=1.04 [0.94–1.16]).

Patients maintaining high ICS adherence over time have better asthma control. Temporarily increasing ICS adherence tends to be simultaneous to higher reliever use and reduces reliever use later on. Causes of within-person variation in outcomes require more investigation.

Take home message:

Cohort study in routine care finds large variability in asthma outcomes over time. Patients with higher mean ICS adherence report better asthma control. ICS adherence and reliever use tend to increase at the same time and reduce use of relievers later on.

Plain language summary:

Taking inhaled corticosteroids as prescribed is important for managing asthma. For people who suffer from asthma, symptoms vary over time. We wanted to know whether differences between people in how they use their inhalers are related to how they experience symptoms, and also whether their symptoms change when they use their inhalers differently than usual. We found that people who keep taking their inhaled corticosteroids inhalers regularly as prescribed experience less symptoms in the long term. At times when they increase the use of their inhaled corticosteroids they also tend to use their reliever inhalers more, which does not have a large impact on symptoms or exacerbations but tends to result in less reliever use later on.

Keywords: asthma; adherence to medications; inhaled corticosteroids; asthma control; asthma exacerbations; routine care

INTRODUCTION

Inhaled corticosteroids (ICS) are a pillar of asthma management (1–3). Clinical guidelines recommend assessing and improving ICS adherence (1), yet current interventions achieve limited benefits (4). For interventions to be effective, they would need to rely on understanding adherence variations in routine care and their effects on outcomes both between persons (do patients who maintain on average higher adherence have better outcomes?) and within persons over time (do patients have better outcomes *when* they improve their adherence compared to their average level?). To date, research evidence has focused on the between-person level, mostly with cross-sectional designs, which have provided inconsistent results (5,6). As asthma is a variable condition, patients may experience substantial changes in symptoms and medication intake across time (7,8), therefore studying adherence as a dynamic time-varying process is more appropriate (9). As cross-sectional studies are known to provide limited insight into causal links, a longitudinal examination of ICS adherence and its relationships with asthma-related outcomes would establish to what degree adherence is important both between and within persons over time.

Within a European Commission-funded prospective cohort study in asthma (ASTRO-LAB) conducted in the United Kingdom (UK) and France (10), we investigated ICS adherence variations between and within persons and their relationships with three outcomes commonly used in asthma research: asthma control, reliever use, and asthma exacerbations. Asthma control and exacerbations are considered key endpoints of asthma management and capture distinct types of variation in clinical manifestations of asthma in response to treatment (11). Reliever use, while often used to indicate loss of control or moderate exacerbations (11,12), is also a self-management behaviour influenced by clinical factors as well as psychological factors (13,14), which varies across time and may impact on asthma control and exacerbations (15). We therefore also investigated between- and within-person variations of reliever use and their links with asthma control and exacerbations. We examined three research questions separately for each outcome. First, how was the variation in the asthma-related outcome distributed at between- and within-person levels (RQ1)? Second, were between-person differences in ICS adherence (and reliever use, if applicable) associated with the outcome (RQ2)? Third, were within-person current or prior

fluctuations in ICS adherence and reliever use associated with variations in outcomes (i.e. at the same time or at the next measurement) (RQ3).

METHODS

Study design and participants

The ASTRO-LAB study protocol, including sample size determination and regulatory approvals, was described elsewhere (10). Briefly, we enrolled French and British patients with persistent asthma, meeting the following criteria: 6-40 years old, ≥6 months of prescribed use of controller inhalers during a 12-month baseline period (ICS or long-acting beta-agonists [LABA] in monotherapy, or ICS and LABA in distinct inhalers or fixed-dose combinations); no chronic oral corticosteroids (OCS) use (≥15 consecutive days 3 months before enrollment); no omalizumab use during the baseline period; no concomitant respiratory disease; and no asthma exacerbations 2 months before enrollment.

Included participants were followed for 12-24 months via computer-assisted telephone interviews ('regular interviews') every 4 months, and monthly text messages. Adults and teenagers (12-40 years) and parents of children (6-11 years) reported on asthma control, adherence to controller medication, reliever use, and exacerbation occurrence. Monthly text messages inquired about new exacerbations since last contact, and positive answers triggered additional 'post-exacerbation interviews' (see Figure 1 for an overview). Primary care records, i.e. study-specific electronic records completed by participating general practitioners in France and THIN data (16) in the UK, were used to extract socio-demographic information (gender, age, country, primary care practice identifier) and compute asthma severity markers at baseline. For this analysis, we selected patients and reports with ICS inhalers prescribed for regular use, as detailed below.

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Measures

Asthma exacerbations

Exacerbations were defined as: OCS courses of ≥2 days, unscheduled primary care, or hospital contacts (emergency room visits and/or overnight hospitalizations), or death due to asthma. Interviewers described asthma exacerbations to patients as 'asthma attacks' ('situations when asthma gets worse, for example when someone becomes too breathless to speak, and reliever/normal inhalers do not help enough'), assessed self-reported occurrence, identified dates of any exacerbations and ensured they were not previously recorded.

Asthma control

Asthma control was measured via the 5-item Asthma Control Questionnaire symptoms-only (ACQ; (17)) for adults and teenagers. ACQ-5 assesses presence and intensity of night symptoms, morning symptoms, activity limitations, shortness of breath, and weezing during the past week; mean scores <0.75 were coded as 'well-controlled asthma' (18). As the ACQ-5 is not available for children, we adapted for parent report the Royal College of Physicians three questions (RCP3Q; (19), which evaluate night symptoms, day symptoms (cough, weeze, chest tightness, breathlessness) and activity limitations over the past month; sum scores equal to 0 were considered 'well-controlled asthma' (20).

Reliever use

To facilitate recall during the interview conversations, we developed and pilot-tested two questions on reliever use (short-acting beta agonists and anticholinergics). We asked how often relievers were used over the past 4 weeks ('every day', 'almost every day', 'once or twice every week' and 'less than once a week'), then more details on the number of inhalations and times which were used to estimate the daily average number of inhalations (Supplementary Online Material 1; SOM1); values were winsorised (range 0 – 6) for model convergence.

ICS adherence

We developed and validated the Medication Intake Survey - Asthma (MIS-A), a new instrument for telephone interviews, which assesses adherence separately for each controller inhaler based on self-reported prescription start date, daily dosage recommendations, and 6 questions on controller use over increasing time periods (1 day to 4 months); percentages of medication used versus prescribed are

calculated first for each question and subsequently as composite scores (21). In the present analysis, we used 1-week composite scores based on: (Q1) inhalations used the day before; (Q2) days on which no inhalations were used in the past 7 days; (Q3) days on which all prescribed inhalations were used in the past 7 days. We computed scores for each inhaler and then averaged across inhalers for reports when patients used >1 ICS.

For asthma control, reliever use and ICS adherence, reporting was required for the period immediately prior to the interview (regular reports in regular interviews) or before the exacerbation (pre-exacerbation reports, in regular or post-exacerbation interviews).

Patient characteristics

Asthma severity at baseline was: 1) the number of OCs courses prescribed 12 months before the first interview, from primary care records, and 2) the ICS daily dose prescribed self-reported at first interview (beclometasone equivalent doses (22)). Type of ICS-based treatment was grouped into 3 categories: ICS in fixed dose combination with LABA (FDC; reference group), single ICS inhaler ('ICS only') and a third category ('ICS plus') for reports of ≥1 ICS (single or FDC) and a LABA (in a separate inhaler) and/or leukotriene antagonists (LTRA). Gender, country (UK or France), and age at enrollment coded in three categories -adults (18-40, reference group), teenagers (12-17) and children (6-11)- were extracted from primary care records.

Analysis

Data were analysed using R (23). We identified variables that predicted missing interviews (22.28% planned regular interviews were skipped and 33.52% of SMS texts did not receive a reply), and included them as predictors in the main models. Missing data in recorded reports were rare due to compulsory completion rules, and replaced by mode, median, or closest value (SOM2). To isolate the effects of the implementation stage of ICS adherence (24), i.e. the extent to which patients take the doses prescribed while on treatment, we censored the follow-up of patients (i.e. we kept only their previous reports in the dataset) when they had a report with no daily ICS prescribed (no ICS prescribed at all, ICS ended

recently without any other ongoing/started ICS, ICS prescribed as needed, or only daily LABA prescribed) or in which they reported being prescribed other asthma controllers (e.g., tiotropium).

Continuous time-varying predictors (adherence and reliever use) were decomposed into three variables to distinguish between-person effects and simultaneous and sequential within-person effects. **Average adherence/use** was calculated as the mean score for each patient across all reports (one score per patient) and used for examining whether differences in adherence/use between patients predict outcomes. **Current fluctuation** was the difference between patient's average adherence/use and the score in a given report (multiple scores per patient) and helped examine whether changes in adherence/use within patients are associated with concomitant changes in outcome (i.e. measured in the same report). **Prior fluctuation** was computed as lagged variable, i.e. the difference between patient' average and the score in their previous report (25), usually 4 months earlier (thus, also multiple scores per patient); similar to 'current fluctuation', this variable aimed to examine whether changes in adherence/use predict outcomes measured in the subsequent report.

Descriptive statistics were calculated for patient characteristics, adherence and outcomes, and bivariate relations between adherence variables were examined between and within-person. We followed established procedures for hierarchical longitudinal modelling (25). Two-level longitudinal mixed models (LMM; reports within patients) were built separately for asthma control and exacerbation occurrence (logistic models), and reliever use (linear models). We conducted visual data exploration fitting non-parametric lowess functions (see SOM2), which supported the appropriateness of linear modelling. First, unconditional means models were built to assess the proportion of variance at different levels via Variance Partition Coefficients (VPC) for logistic models, or intra-class correlation coefficients (ICC) for linear models (RQ1). A cut-off of .05 indicated substantial variance (26). Practice was initially modeled as third level, and excluded for not meeting this criterion. Several variance-covariance structures of residuals (compound symmetry, first-order autoregressive, general correlation matrix) were compared for the linear models and the best fitting selected; logistic models specified unstructured covariance. Next, unconditional growth models were tested, with time modelled as days since the first interview per patient (random and fixed); models were compared and selected based on fit and parsimony. Conditional growth

models added covariates (including reliever use for asthma control and exacerbation models) and adherence predictors (personal average, current effect, lagged effect). Residuals of the full models were examined for normality.

Exploratory analyses were also performed to examine possible moderators of adherence-outcomes relationships: age, type of ICS, country, and severity. Sensitivity analyses were performed with 1-month adherence scores (SOM3).

RESULTS

Sample characteristics

Of 4647 reports from 934 patients collected between May 2013 and January 2016, 3756 reports (847 patients) were included (see flowchart in Figure 2). There were 1-13 reports per patient (median = 4, inter-quartile range(IQR) = 4); resulting in mean (SD) follow-up time of 406 (249) days, and maximum 758 days. Patients were predominantly French (80.4%), with good gender and age representation (47.6% female; 56.6% adults). Of 3756 CATI reports, 1929 (51.4%) were about FDC, 785 (20.9%) about ICS in single inhalers, and 1042 (27.7%) were prescribed LABA and/or LTRA in addition to ICS. Exacerbations were reported by 246 patients in 433 (11.5%) reports. Median 1-week adherence was 85.71% (IQR = 50%). Patients indicated ICS adherence above 80% in 55.88% reports. Uncontrolled asthma was reported by 683 patients in 2046 (54.5%) reports. Median reliever use was 0.18 inhalations per day (range 0 to 6). Sample characteristics are reported in Table 1.

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Longitudinal associations between ICS adherence and asthma outcomes

Table 2 presents results for the composite 1-week adherence score (similar results with 1-month scores available in SOM3). Most variation in outcomes was present at within-person level; the proportion of variation between-person was 41% for asthma control, 9% for exacerbations, and 48% for reliever use.

Asthma control. Patients with higher average ICS adherence were more likely to report controlled asthma (OR 1.25 [95% CI, 1.06-1.47] per 1 SD=26%). At within-person level, current and prior fluctuations in ICS adherence had no significant association with asthma control (OR 0.93 [95% CI, 0.84-1.02] and 1.05 [95% CI, 0.95-1.15]). Controlled asthma was also more likely in patients who on average used less relievers (OR 0.30 [95% CI, 0.24-0.37] per 1 SD=1.23 times/day). Current increases in reliever use were associated with decreased likelihood of controlled asthma (OR 0.50 [95% CI, 0.43-0.58] per 1 SD=1 time/day); prior fluctuations had no effects on asthma control (OR 1.04 [95% CI, 0.94-1.16]). Of note, when reliever use variables were excluded from the model (see SOM3), current fluctuations in ICS adherence were weakly associated with asthma control; since ICS adherence and reliever use were associated and both reacted to changes in symptoms, this suggests that common variance in asthma control was explained here by fluctuations in reliever use.Well-controlled asthma was less likely for children compared to adults, for patients in the UK compared to France, for patients taking ICS with add-on medication compared to FDC, and for patients with higher dose of ICS at baseline. In exploratory analyses, we identified age as a moderator for the effect of average ICS adherence on asthma control, which was weaker for children and adolescents (see SOM3). Asthma control increased during the study.

Exacerbations. Average ICS adherence scores and prior or simultaneous fluctuations were not associated with exacerbation occurrence (OR 0.99 [95% CI, 0.87-1.12], OR 1.04 [95% CI, 0.94-1.16] and 0.99 [95% CI, 0.89-1.11]). Patients with higher average reliever use were more likely to report an exacerbation (OR 1.46 [95% CI, 1.30-1.63] per 1 SD=1.23 times/day); current and prior fluctuations in reliever use were unrelated to exacerbations (OR 1.08 [95% CI, 0.98-1.19] and 1.00 [95% CI, 0.91-1.10]). Exacerbations were more likely to occur earlier in the study, in children, women, in France, for patients taking add-on medication, and with higher asthma severity.

Reliever use. Average ICS adherence scores were unrelated to reliever use (b=-0.0004, [95% CI, -0.089-0.088]). When patients increased their ICS adherence (current fluctuation) they also reported higher reliever use simultaneously (b=0.092, [95% CI, 0.053-0.131] per 1 SD=20%), and lower reliever use in the next interview (prior fluctuation; b=-0.047, [95% CI, -0.005- -0.088] per 1 SD=20%). Reliever use was higher for British patients, and those with higher asthma severity.

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DISCUSSION

This study presents evidence on the long-term role of ICS adherence in asthma routine care, based on detailed patient-reported data collected by trained interviewers via computer-assisted telephone interviews from participants aged 6 to 40 years in two European countries. Hierarchical longitudinal models disentangled effects of both average (between-person) levels and within-person fluctuations of ICS adherence on asthma control, exacerbations, and reliever use. The role of reliever use was also examined using the same approach.

Regarding Research Question 1, we found considerable variation in asthma outcomes and reliever use due to within-person fluctuations (91% of the chances of reporting exacerbations; 59% of asthma control; 52% of reliever use) rather than between-person differences. These fluctuations can only be explained by factors changing within patients over time and not by stable differences between patients. This indicates that commonly-used between-person designs are not suited to explaining the full variation in asthma outcomes, and highlights the need to also focus on within-person variation. Previous findings from the Astrolab cohort (21) indicate substantial within-person variability in ICS adherence scores as well (41-71%). We recommend using hierarchical modeling more broadly in respiratory research, especially given that longitudinal data are increasingly collected in routine care via digital technologies (27). These results also highlight the importance for clinical practice to assess not only average levels of medication use and outcomes across time, but also how these change between consultations. Moreover, interventions

would need to identify and target personal and context factors that changed during or before this period and possibly caused changes in the patient's behaviours and health status.

Separating effects of long-term average levels from temporary fluctuations in medication use allowed us to answer two related but distinct questions regarding ICS adherence and reliever use. Regarding Research Question 2, we found that between-person differences in ICS adherence were associated with better asthma control (patients *who* were on average 26% more adherent to ICS were 25% more likely to report controlled asthma), but not exacerbations or reliever use. These results can be interpreted following the Asthma Care logic Model (ACM; (28): ICS adherence is temporally more proximal to asthma control than exacerbations, and patient behaviours during symptom aggravation, including reliever use, may have independent contributions to exacerbation occurrence and severity.

Regarding Research Question 3 focusing on within-person fluctuations in ICS adherence and reliever use both prior and concurrent to a given report, we found that *at times when* patients increased their ICS temporarily they tended to increase simultaneously their reliever use, and to report less reliever use *following these times* (with an increase of 20% in ICS adherence corresponding to using relievers 1 time more than usual in 11 days in the same period and using them 1 time in 21 days less than average in the next report). Temporary fluctuations in ICS adherence were unrelated to asthma control or exacerbations. Prior studies have mostly reported a protective effect of ICS adherence on outcomes, yet some found either positive or no associations (5,6). Increasing ICS adherence in response to worsening symptoms has been proposed as an explanation for these paradoxical results (29,30). Our findings are consistent with this possibility, and start building a more nuanced picture of the dynamic interplay between asthma medication use and health status, which is undetectable with a between-person design. Importantly, they concur with recent calls for reconsidering the role of relievers (short-acting beta agonists) in asthma management following concerns of preferential use in place of controller inhalers, which may mask underlying inflammation by providing only symptom relief; in contrast, improving ICS adherence (in response to symptom aggravation or proactively as part of a self-management plan) reduces inflammation and therefore future need for symptom relief (31).

Several findings on other predictors of asthma outcomes are important to highlight. Men reported less exacerbations, consistent with recent findings on large medical records data in the UK (32). There were less exacerbations and more reliever use reported in the UK, possibly explained by better implementation of self-management support in primary care (33), which includes increasing controller and reliever use as a first step before OCs use (1). Patients who had at least one ICS prescribed (single or FDC) and a LABA and/or LTRA reported less control and more exacerbations compared to FDC, consistent with clinical recommendations for stepwise asthma treatment (1). All associations with the two severity markers were in the expected direction, except a nonsignificant effect of number of OC courses during the baseline year on asthma control. The alignment of these results with previous research supports the validity of the main findings.

Our findings need to be interpreted in light of several limitations. First, given the prospective cohort design, we were only able to examine the role of average levels of adherence and fluctuations from average in usual care. Our results therefore do not exclude the possibility that a systematic effort to raise average levels of adherence long term may well have a positive effect on asthma outcomes. Second, we found that, as the study progressed, patients reported better outcomes, partly driven by selective attrition of participants with worse asthma control (see missing value analyses in SOM2); moreover, differences in proxy versus self-report and asthma control measures may have contributed to more reports of uncontrolled asthma and exacerbations in children. Controlling for time (days since first interview) and age in our models adjusted for these sources of bias. Third, we grouped treatment regimens based on commonly-used categories and did not consider possible variations in pharmacokinetic and pharmacodynamic profiles of ICS formulations (34), and interactions with LABA in FDC (35); we encourage replications of this approach on specific medications. Fourth, adherence was measured by self-report. The interview questions were carefully worded to improve recall and reduce social desirability, and they were previously validated against objective measures (21). Nevertheless, there are limitations related to the use of self-reports over 4-month time intervals when studying continuous processes. In the not-too-distant future, similar studies could be conducted with user-friendly electronic monitors for both adherence and outcomes (e.g., asthma control). Finally, a 4-month lag between measurements was most feasible given the study context, yet it can only capture medium-term variation. Clinical outcomes have

been shown to improve within weeks from starting ICS, and return to baseline levels within weeks after treatment cessation or reduction (36–38). Variation in medication use for different time intervals, lags and data sources need to be further studied, as the feasibility of data collection will increase with the development of digital technologies.

This study demonstrated a novel approach to examining ICS adherence in asthma routine care. By separating between- and within-person variation, we captured a potentially protective role of ICS adherence for asthma control long term, and an interplay between ICS and reliever use short term, which deserves further investigation. These findings suggest three recommendations for clinicians aiming to help patients improve their asthma management. First, clinicians should expect that medication use and health status fluctuate over time, and routinely assess these in a factual, non-judgmental manner, for example using the questions in Table 3 (adapted from Astrolab interviews). Second, they should clarify how patients use both controllers and relievers in relation to symptoms and agree on asthma action plans. And third, they should support patients to work towards high average levels of adherence to the agreed ICS daily dosage for long-term control.

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References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, Updated 2017. Auckland, New Zealand: Global Asthma Network; 2017.

2. British Thoracic Society Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma. Thorax. 2008 May 1;63(Supplement 4):iv1–121.

3. National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma—full report 2007 [Internet]. 2007. Available from: Available from: www.nhlbi.nih.gov/files/docs/guidelines/asthgdln.pdf.

4. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, et al. Interventions for enhancing medication adherence. In: Cochrane Database of Systematic Reviews [Internet]. John Wiley & Sons, Ltd; 2014 [cited 2015 Jan 11]. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000011.pub4/abstract

5. Engelkes M, Janssens HM, Jongste JC de, Sturkenboom MCJM, Verhamme KMC. Medication adherence and the risk of severe asthma exacerbations: a systematic review. Eur Respir J. 2015 Feb 1;45(2):396–407.

6. Bårnes CB, Ulrik CS. Asthma and Adherence to Inhaled Corticosteroids: Current Status and Future Perspectives. Respir Care. 2015 Mar 1;60(3):455–68.

7. Johnson KM, FitzGerald JM, Tavakoli H, Chen W, Sadatsafavi M. Stability of Asthma Symptom Control in a Longitudinal Study of Mild-Moderate Asthmatics. J Allergy Clin Immunol Pract. 2017 Nov 1;5(6):1663-1670.e5.

8. Souverein PC, Koster ES, Colice G, van Ganse E, Chisholm A, Price D, et al. Inhaled Corticosteroid Adherence Patterns in a Longitudinal Asthma Cohort. J Allergy Clin Immunol Pract [Internet]. [cited 2016 Nov 9]; Available from: http://www.sciencedirect.com/science/article/pii/S2213219816304238

9. Vrijens B, Dima AL, Van Ganse E, van Boven JFM, Eakin MN, Foster JM, et al. What We Mean When We Talk About Adherence in Respiratory Medicine. J Allergy Clin Immunol Pract. 2016 Sep;4(5):802–12.

10. Van Ganse E, Texier N, Dima AL, Laforest L, Ferrer M, Hernandez G, et al. Assessment of the safety of long-acting β2-agonists in routine asthma care: the ASTRO-LAB protocol. Npj Prim Care Respir Med. 2015 Jun 18;25:15040.

11. Reddel HK, Taylor DR, Bateman ED, Boulet L-P, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009 Jul 1;180(1):59–99.

12. Fuhlbrigge A, Peden D, Apter AJ, Boushey HA, Camargo CA, Gern J, et al. Asthma outcomes: Exacerbations. J Allergy Clin Immunol. 2012 Mar 1;129(3, Supplement):S34–48.

13. Gerald JK, Carr TF, Wei CY, Holbrook JT, Gerald LB. Albuterol Overuse: A Marker of Psychological Distress? J Allergy Clin Immunol Pract. 2015 Nov 1;3(6):957–62.

14. Reddel HK, Ampon RD, Sawyer SM, Peters MJ. Risks associated with managing asthma without a preventer: urgent healthcare, poor asthma control and over-the-counter reliever use in a cross-sectional population survey. BMJ Open. 2017 Sep 1;7(9):e016688.

15. Stanford RH, Shah MB, D'Souza AO, Dhamane AD, Schatz M. Short-acting β-agonist use and its ability to predict future asthma-related outcomes. Ann Allergy Asthma Immunol. 2012 Dec 1;109(6):403–7.

16. Blak B, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. J Innov Health Inform. 2011;19(4):251–5.

17. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999 Oct 1;14(4):902–7.

18. Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med. 2006 Apr 1;100(4):616–21.

19. Pinnock H, Burton C, Campbell S, Gruffydd-Jones K, Hannon K, Hoskins G, et al. Clinical implications of the Royal College of Physicians three questions in routine asthma care: a real-life validation study. Prim Care Respir J J Gen Pract Airw Group. 2012 Sep;21(3):288–94.

20. Thomas M, Gruffydd-Jones K, Stonham C, Ward S, Macfarlane TV. Assessing asthma control in routine clinical practice: use of the Royal College of Physicians "3 questions." Prim Care Respir J J Gen Pract Airw Group. 2009 Jun;18(2):83–8.

21. Dima AL, van Ganse E, Laforest L, Texier N, de Bruin M, The Astro-Lab Group null. Measuring medication adherence in asthma: Development of a novel self-report tool. Psychol Health. 2017 Feb 20;1–20.

22. British Thoracic Society Scottish Intercollegiate Guidelines Network, Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma [Internet]. SIGN BTS; 2012 [cited 2018 Apr 19]. Available from: https://www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2012/

23. R Core Team. R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria; 2013. Available from: http://www.R-project.org

24. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012;73(5):691–705.

25. Singer JD, Willett JB. Applied longitudinal data analysis: Modeling change and event occurrence. New York: Oxford University Press; 2003.

26. Heck RH, Thomas SL, Tabata LN. Multilevel and Longitudinal Modeling with IBM SPSS. Routledge; 2013. 462 p.

27. Blakey JD, Bender BG, Dima AL, Weinman J, Safioti G, Costello RW. Digital Technologies and Adherence in Respiratory Diseases: The Road Ahead. Eur Respir J. 2018 Jan 1;1801147.

28. Dima AL, de Bruin M, van Ganse E. Mapping the Asthma Care Process: Implications for Research and Practice. J Allergy Clin Immunol Pract [Internet]. [cited 2016 Jun 10]; Available from: http://www.sciencedirect.com/science/article/pii/S2213219816301301

29. Williams LK, Peterson EL, Wells K, Ahmedani BK, Kumar R, Burchard EG, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. J Allergy Clin Immunol. 2011 Dec;128(6):1185-1191.e2.

30. Colice G, Martin RJ, Israel E, Roche N, Barnes N, Burden A, et al. Asthma outcomes and costs of therapy with extrafine beclomethasone and fluticasone. J Allergy Clin Immunol. 2013 Jul 1;132(1):45-54.e10.

31. Martin MJ, Harrison TW. Is it time to move away from short-acting beta-agonists in asthma management? Eur Respir J. 2019 Apr 1;53(4):1802223.

32. Blakey JD, Price DB, Pizzichini E, Popov TA, Dimitrov BD, Postma DS, et al. Identifying Risk of Future Asthma Attacks Using UK Medical Record Data: A Respiratory Effectiveness Group Initiative. J Allergy Clin Immunol Pract. 2017 Jul 1;5(4):1015-1024.e8.

33. de Bruin M, Dima AL, Texier N, van Ganse E. Explaining the Amount and Consistency of Medical Care and Self-Management Support in Asthma: A Survey of Primary Care Providers in France and the United Kingdom. J Allergy Clin Immunol Pract [Internet]. 2018 May 9 [cited 2018 Jun 17]; Available from: http://www.sciencedirect.com/science/article/pii/S2213219818303167

34. Derendorf H, Nave R, Drollmann A, Cerasoli F, Wurst W. Relevance of pharmacokinetics and pharmacodynamics of inhaled corticosteroids to asthma. Eur Respir J. 2006 Nov 1;28(5):1042–50.

35. Barnes PJ. Scientific rationale for using a single inhaler for asthma control. Eur Respir J. 2007 Mar 1;29(3):587–95.

36. Vathenen AS, Knox AJ, Wisniewski A, Tattersfield AE. Time Course of Change in Bronchial Reactivity with an Inhaled Corticosteroid in Asthma. Am Rev Respir Dis. 1991 Jun 1;143(6):1317–21.

37. Sovijärvi ARA, Haahtela T, Ekroos HJ, Lindqvist A, Saarinen A, Poussa T, et al. Sustained reduction in bronchial hyperresponsiveness with inhaled fluticasone propionate within three days in mild asthma: time course after onset and cessation of treatment. Thorax. 2003 Jun 1;58(6):500–4.

38. Juniper EF, Kline PA, Vanzieleghem MA, Hargreave FE. Reduction of budesonide after a year of increased use: A randomized controlled trial to evaluate whether improvements in airway responsiveness and clinical asthma are maintained. J Allergy Clin Immunol. 1991 Feb 1;87(2):483–9.

1 **Table 1. Sample characteristics - descriptive statistics**

Characteristic	Statistic
Patient level (N=847)	
Country (% French)	681 (80.4)
Gender (% women)	403 (47.6)
Age (% adults)	479 (56.6)
(% children)	206 (24.3)
(% teenagers)	162 (19.1)
Baseline severity (number of OC courses; median[range])	0.00 [0.00, 7.00]
Baseline severity (number of ICS and LABA canisters; median[range])	12.00 [2.00, 60.00]
Baseline severity (ICS daily dose at first interview; median[range])	500.00 [100.00, 10000.00]
Report level (n=3756)	
Treatment type (% FDC)	1929 (51.4)
(% ICS single inhaler)	785 (20.9)
(% ICS plus LABA/LTRA)	1042(27.7)
Asthma control (% uncontrolled)	2046 (54.5)
Exacerbations (% occurrence)	433 (11.5)
Time - days since first CATI (mean(SD))	261.19 (220.16)
Reliever use (median[range])	0.18 [0.00, 6.00]
1-month adherence – composite (median[range])	85.71 [0.00, 100.00]
1-week adherence - composite (median[range])	85.71 [0.00, 100.00]
1-day taking adherence (median[range])	100.00 [0.00, 1250.00]
1-week therapeutic coverage (median[range])	100.00 [0.00, 100.00]
1-week correct dosing (median[range])	85.71 [0.00, 100.00]
1-month therapeutic coverage (median[range])	92.86 [0.00, 100.00]

4-month drug holidays (median[range])	100.00 [0.00, 100.00]

Note: Abbreviations: OC, oral corticosteroids; ICS, inhaled corticosteroids; LABA, long-acting beta agonists; LTRA, leukotriene antagonists; FDC, fixed dose combination; SD, standard deviation.

Table 2. Multilevel models of asthma control, AE (logistic) and reliever use (linear)

	Dependent variable:		
	Asthma control (OR[CI])	Exacerbation occurrence (OR[CI])	Reliever use (b(SE))
Intercept	0.78[@] [0.59 – 1.04]	0.15[***] [0.12 - 0.19]	0.819[***] (0.079)
Time (days since first CATI) [a]	1.31[***] [1.16 - 1.48]	0.58[***] [0.5 - 0.67]	-0.109[***] (0.027)
Gender (male)	1.24 [0.89 - 1.71]	0.70[**] [0.54 - 0.90]	-0.017 (0.091)
Age (child)	0.45[***] [0.30 - 0.68]	1.68[**] [1.23 - 2.29]	-0.074 (0.112)
Age (teenager)	0.81 [0.52 - 1.25]	0.98 [0.68 - 1.43]	-0.180 (0.120)
Country (UK)	0.87 [0.52 - 1.44]	0.56[*] [0.35 - 0.90]	0.441[***] (0.136)
Treatment type (ICS only[#])	1.26 [0.85 – 1.86]	0.85 [0.60 - 1.21]	0.021 (0.102)
Treatment type (ICS plus[#])	0.71[*] [0.51 – 0.99]	1.54[**] [1.18 – 2.02]	0.038 (0.086)
Baseline severity (number of OC courses) [a]	1.15[@] [0.98 - 1.34]	1.27[***] [1.14 - 1.41]	0.117[**] (0.045)
Baseline severity (ICS daily dose at first interview) [a]	0.61[***] [0.50 - 0.74]	1.17[**] [1.05 - 1.31]	0.109[*] (0.046)
1-week ICS adherence			
Average adherence [a,b]	1.25[**] [1.06 - 1.47]	0.99 [0.87 - 1.12]	-0.0004 (0.045)
Current fluctuation [a]	0.93 [0.84 - 1.02]	1.04 [0.94 - 1.16]	0.092[***] (0.020)
Prior fluctuation [a]	1.05 [0.95 - 1.15]	0.99[0.89 - 1.11]	-0.047[*] (0.021)
Reliever use			
Average use [a,b]	0.30[***] [0.24 - 0.37]	1.46[***] [1.30 - 1.63]	
Current fluctuation [a]	0.50[***] [0.43 - 0.58]	1.08 [0.98 - 1.19]	
Prior fluctuation [a]	1.04 [0.94 - 1.16]	1.00 [0.91 - 1.10]	
VPC (logistic); ICC(linear)	0.4075	0.0891	0.4765
Observations	2,909	2,909	2,909
Log Likelihood	-1,618.598	-1,104.696	-4,793.214
AIC	3,271.195	2,243.392	9,622.429
BIC	3,372.780	2,344.977	9,729.989

Notes: [@] p<.1; [*] p<.05; [**] p<.01; [***] p<.001; [a] variable standardized before inclusion into regression model to facilitate interpretation and model convergence (z-scores); [,b] Average denotes individual mean across the follow-up period; [#] Reference group = ICS with LABA in fixed dose combination, ICS only = single ICS inhaler, and ICS plus = at least one ICS and a LABA in separate inhaler and/or LTRA; Abbreviations: OR, odds ratio; CI, confidence intervals; b, b coefficient; SE, standard error; UK, United Kingdom; ICS, inhaled corticosteroids; OC, oral corticosteroids; LABA, long-acting beta agonists; LTRA, leukotriene antagonists; VPC, Variance Partition Coefficient; ICC, Intra-class correlation; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table 3. Example questions for assessing asthma control, ICS adherence and reliever use

Variable	Question examples In the last month,
Asthma control (RCP3Q; 19)	- Have you had difficulty sleeping because of your asthma symptoms (including cough)? - Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)? - Has your asthma interfered with your usual activities (e.g. housework, work, school, etc.) Never/rarely/every week/ every day (answers 'rarely' or more for at least one question indicate uncontrolled asthma)
ICS adherence	- On how many days did you not use your ICS inhaler at all, for example because you forgot or did not want to use it? (number of days x 100 / 28 = % ICS adherence)
Reliever use	- How often have you usually taken [your reliever inhaler]? Every day/ almost every day/ once or twice every week / less than once a week - How many puffs how many times per day/week, on average? (average times per day = average times per week/ 4)

Captions

Figure 1. Example illustration of study timeline and data collection schedule – hypothetical example for a participant with 7 regular computer-assisted telephone interviews and two interviews after asthma exacerbations were identified by text messages (SMSs) at month 2 (M2) and 21 (M21). Primary care records were used at baseline to extract patient socio-demographic and medical history variables.

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Figure 1 provided in separate file

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Figure 2. Flowchart for the selection of interview reports and patients meeting analysis criteria (Note: reports were censored, therefore part of the patients with excluded reports remained in the sample; abbreviation: LABA, long-acting beta agonists).

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Figure 2 provided in separate file

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