EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

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Please cite this article as: Dima AL, van Ganse E, Stadler G, *et al*. Does adherence to inhaled corticosteroids predict asthma-related outcomes over time? A cohort study. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.00901-2019).

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

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Funding: The research leading to these results has received funding from the European Community 7th Framework (FP7/2007-2013) under grant agreement n°282593, and H2020 programme (MSCA-IF) under GA n°706028 for AD during manuscript preparation.

Running Title**:**

ICS adherence and asthma-related outcomes over time

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.

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, 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.

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 non-significant 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.

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.

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.

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.

_____

Figure 1 provided in separate file

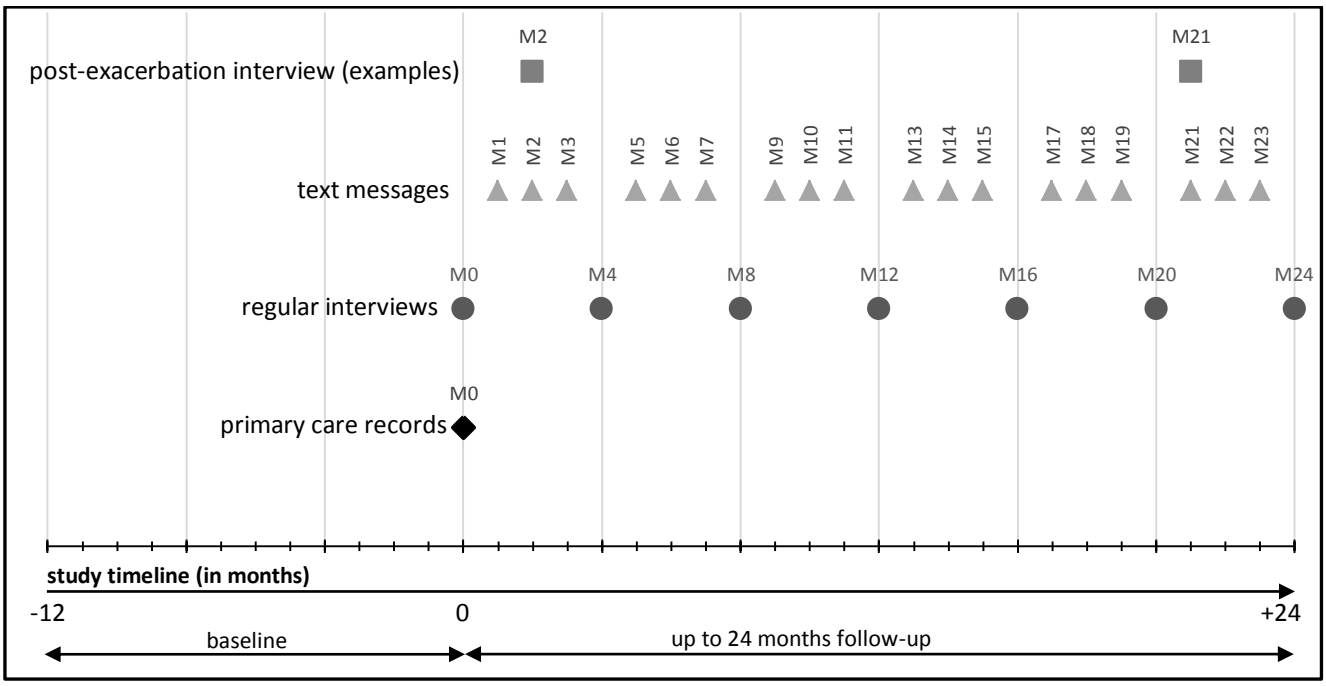
_____

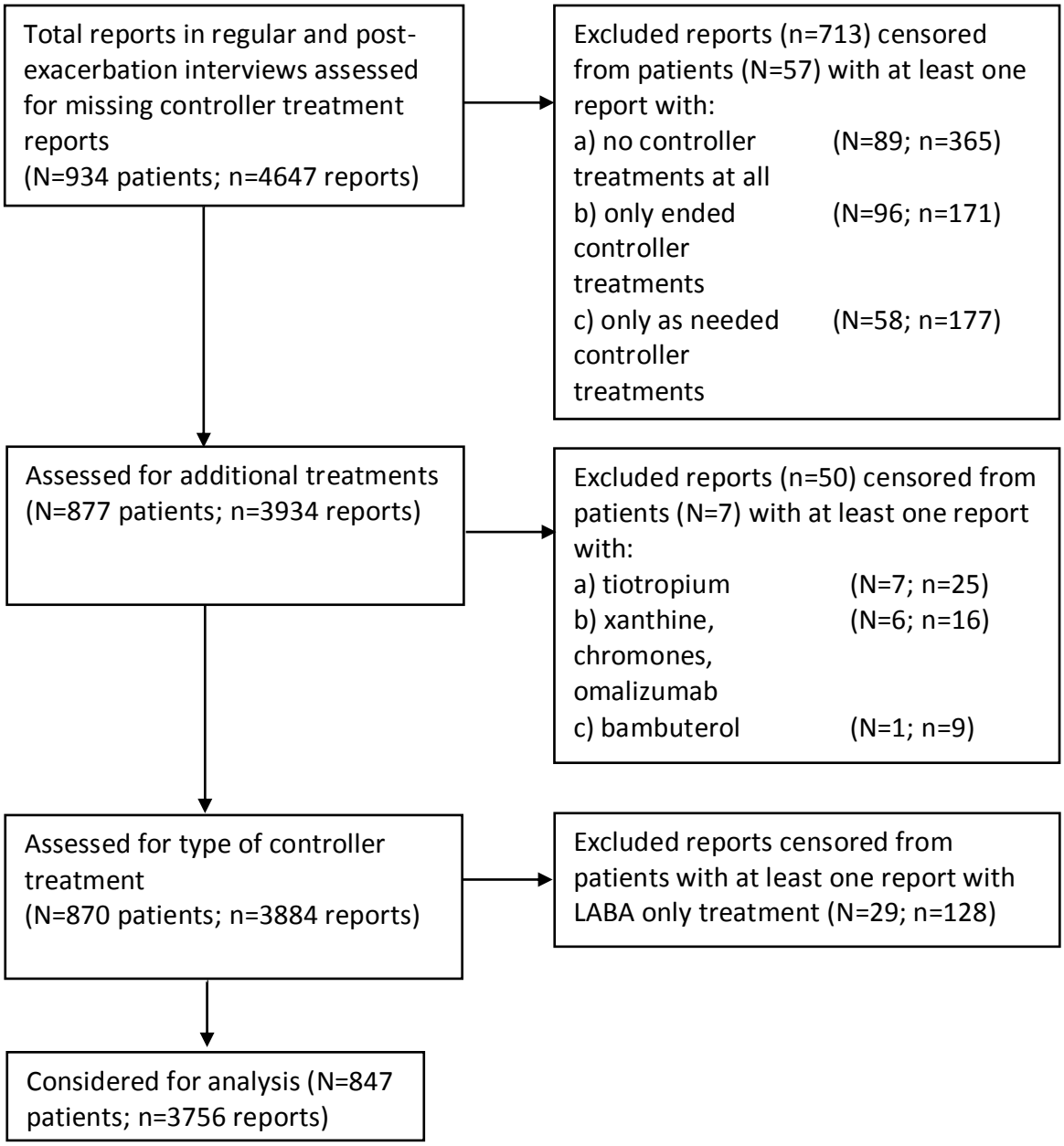
Figure 2. Flowchart for the selection of interview reports and patients meeting analysis criteria (Note: reports were censored, therefore part of the patients with excluded reports remained in the sample; abbreviation: LABA, long-acting beta agonists).

_____

Figure 2 provided in separate file

_____


M2
M21
post-exacerbation interview (examples)
M1
M2
M3
M5
M6
M7
M9
M10
M11
M13
M14
M15
M17
M18
M19
M21
M22
M23
text messages
M0
M4
M8
M12
M16
M20
M24
regular interviews
M0
primary care records
study timeline (in months)
-12
0
+24
baseline
up to 24 months follow-up


Total reports in regular and post-exacerbation interviews assessed for missing controller treatment reports
(N=934 patients; n=4647 reports)
Excluded reports (n=713) censored from patients (N=57) with at least one report with:
a) no controller treatments at all (N=89; n=365)
b) only ended controller treatments (N=96; n=171)
c) only as needed controller treatments (N=58; n=177)
Assessed for additional treatments
(N=877 patients; n=3934 reports)
Excluded reports (n=50) censored from patients (N=7) with at least one report with:
a) tiotropium (N=7; n=25)
b) xanthine, chromones, omalizumab (N=6; n=16)
c) bambuterol (N=1; n=9)
Assessed for type of controller treatment
(N=870 patients; n=3884 reports)
Excluded reports censored from patients with at least one report with LABA only treatment (N=29; n=128)
Considered for analysis (N=847 patients; n=3756 reports)

Supplementary Online Material 1.

Questions on reliever use in the English adult script for Astrolab computer-assisted telephone interviews (CATIs)

Topic	Question	Answer format
Prescription	What is the name of the treatment?	list of available medications (drug class, quantity, dosage per inhalation in µg)
	When did you start [medication name]?	more than 4 months ago/ during the last 4 months
	If during the last 4 months: When exactly?	If yes: ⌊_⌊_⌋ weeks/days ago
	For treatments ended in previous CATIs: When did the doctor add/interrupt it?	⌊_⌊_⌋ weeks/days ago
	For [medication name], how many puffs, how many times per day did the doctor recommend you to take?	⌊_⌊_⌋ times/ I don't know for each time: ⌊_⌊_⌋ inhalations nth time
Reliever use	How often have you usually taken [medication name] in the last 4 weeks [if exacerbation, add: before this happened]? Variable name: `CPRTB_adhr_frq_use`	Every day Almost every day Once or twice every week Less than once a week

	[if every day/almost every day] How many puffs how many times per day, on average? Variable name: CPRTB_adhr_everyday_n_puff; CPRTB_adhr_everyday_n_time	⌊_⌊_⌋ inhalations ⌊_⌋ times per day/ I don't know (DK)
	[if once or twice every week] How many puffs how many times per week, on average? Variable name: CPRTB_adhr_everyweek_n_puff; CPRTB_adhr_everyweek_n_time	⌊_⌊_⌋ inhalations ⌊_⌋ times per week/ I don't know (DK)
	[if less than once a week] How many puffs how many times in the last 4 weeks? Variable name: CPRTB_adhr_less_n_puff; CPRTB_adhr_less_n_time	⌊_⌊_⌋ inhalations ⌊_⌋ times per month/ I don't know (DK)

Mean daily use of relievers in the last 4 weeks before interview/exacerbation was computed for each treatment reported.

Extreme values for times per day and inhalations per time every day or almost every day (less than 10 values higher than 10 for either variable in regular and exacerbation reports) were capped to 10. To compute missing data for reliever treatment use, the following rules were applied:

- DKs for the general question (e.g. n=7 for regular CATIs) were replaced by "less than once a week" (most frequent value)

- DKs for the mean daily inhalations score were replaced with the median value for the respective response option to the general question (e.g. DKs for treatments used “Every day” were replaced with the median value for the values in the “Every day” category, etc.)

Number of times and number of puffs per time were combined as follows:

- if every day use was reported, daily use was number of times per day x number of puffs per time
- if almost every day use was reported, daily use was number of times per day x number of puffs per

time x 5 days a week x 4 weeks divided by 28 days

- if once or twice every week was reported, daily use was number of times per week x number of puffs per time x 4 weeks divided by 28 days
- if less than once a week was reported, daily use was number of times x number of puffs per time divided by 28 days

The following R code was used to perform this calculation:

```
s <- !is.na(CATItrBvld$CPRTB_adhr_frq_use) & CATItrBvld$CPRTB_adhr_frq_use == "Every day"
CATItrBvld$CPRTB_rel_use4w[s] <-
CATItrBvld$CPRTB_adhr_everyday_n_puff[s]*CATItrBvld$CPRTB_adhr_everyday_n_time[s]
s <-  !is.na(CATItrBvld$CPRTB_adhr_frq_use) & CATItrBvld$CPRTB_adhr_frq_use == "Almost every day"
CATItrBvld$CPRTB_rel_use4w[s] <-
CATItrBvld$CPRTB_adhr_everyday_n_puff[s]*CATItrBvld$CPRTB_adhr_everyday_n_time[s]*5*4/28
s <-  !is.na(CATItrBvld$CPRTB_adhr_frq_use) & CATItrBvld$CPRTB_adhr_frq_use =="Once or twice every week"
```

```
CATItrBvld$CPRTB_rel_use4w[s] <-
CATItrBvld$CPRTB_adhr_everyweek_n_puff[s]*CATItrBvld$CPRTB_adhr_everyweek_n_time[s]*4/28
s <-  !is.na(CATItrBvld$CPRTB_adhr_frq_use) & CATItrBvld$CPRTB_adhr_frq_use =="Less than once a week"
CATItrBvld$CPRTB_rel_use4w[s] <- CATItrBvld$CPRTB_adhr_less_n_puff[s]*CATItrBvld$CPRTB_adhr_less_n_time[s]/28
```

Astrolab cohort - Longitudinal models ICS adherence and outcomes

Preparatory Analysis Report

This report was generated on August 22, 2019 with R version 3.5.3 (2019-03-11).

Contents

Part I
Summary

This script prepared the data for longitudinal analyses on the Astrolab database (final January 2016 extraction) to investigate the role of ICS adherence in asthma control, occurence of exacerbations, and use of reliever inhalers. This document shows the data preparation and descriptive plots, and the missing data analysis. Prior scripts performed consistency checks and prepared data from multiple sources for merging at report level in the present dataset. These are available upon request, together with .Rnw versions, and will be accessible via zenodo.org following data safety checks and anonymization.

Outcome variables were computed and described at interview level. Longitudinal plots of adherence, drug exposure, asthma control, exacerbations and reliever use were displayed. Differences in adherence scores between treatments were examined at interview level and for interviews with concomitant inhalers reported. Bivariate correlations between adherence and asthma outcomes at interview level were performed.

For missing data analyses, regular CATIs were first analysed separately to examine how many of the planned CATIs were recorded per participant and whether missingness was influenced by patient-level variables (proportion of CATIs recorded versus planned at patient level, patients with at least one CATI missing versus none, and recorded versus missing at CATI level). SMS planned and received, and post-exacerbation (AE) CATIs, were examined next, to identify the proportion of SMSs answered from the number planned, and the extent to which the SMS answered confirming an exacerbation were followed-up by a CATI record of this exacerbation. Missing values in the recorded CATIs were checked and missing data patterns examined.

Part II
Results

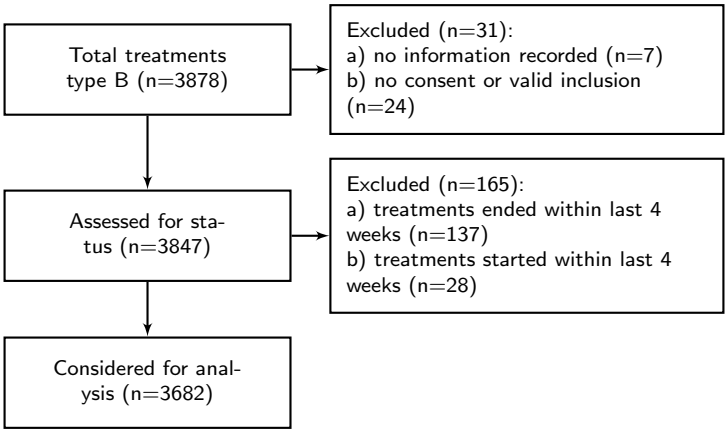
1 Descriptives asthma outcomes and use of other medication per interview

1.1 Reliever use

Reliever (SABA or anticholinergic) use in the last 4 weeks: How often have you usually taken ... in the last 4 weeks? every day OR almost every day - how many puffs how many times per day, on average; once or twice every week - how many puffs how many times per week, on average; less than once a week - how many puffs how many times in the last 4 weeks, on average

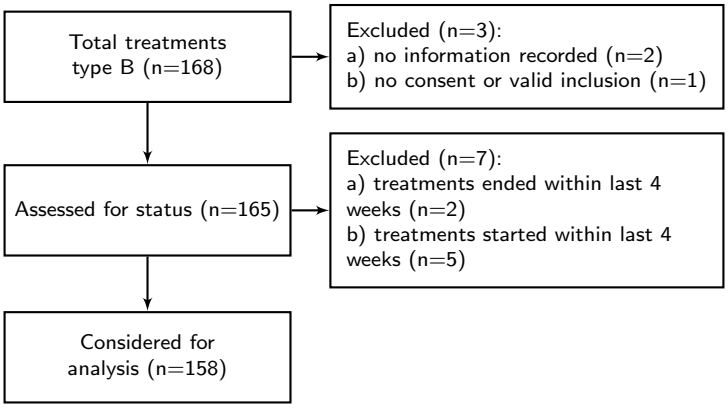
For the current analysis, all treatments that ended in the last 4 months before a regular CATI were excluded.

Figure 1: Flowchart of reliever treatment reports in regular CATIs



Selection of reliever treatments in regular CATIs considered for analysis: in Figure 1.

Figure 2: Flowchart of reliever treatment reports in SAE CATIs



Selection of reliever treatments in SAE CATIs considered for analysis: in Figure 2.

Number of reliever treatments reported in regular CATIs: 3682, from 857 patients.

Number of reliever treatments reported before SAE in regular CATIs: 376, from 213 patients.

Number of reliever treatments reported before SAE in SAE CATIs: 158, from 122 patients.

Mean daily use of relievers was computed separately for SABAs and anticholinergics. Number of times and number of puffs per time were combined as follows:

- if every day use was reported, daily use was number of times per day x number of puffs per time
- if almost every day use was reported, daily use was number of times per day x number of puffs per time x 5 days a week x 4 weeks divided by 28 days
- if once or twice every week was reported, daily use was number of times per week x number of puffs per time x 4 weeks divided by 28 days

- if less than once a week was reported, daily use was number of times x number of puffs per time divided by 28 days

Extreme values for times per day and inhalations per time every day or almost every day (less than 10 values higher than 10 for either variable in regular and SAE CATIs) were capped to 10. To compute missing data for reliever treatment use, the following rules were applied:

- DKs for the general question (e.g. n=7 for regular CATIs) were replaced by "less than once a week" (most frequent value)
- DKs for the mean daily inhalations score were replaced with the median value for the respective response option to the general question (e.g. DKs for treatments used "Every day" were replaced with the median value for the values in the 'Every day" category, etc.)

Note: all treatment labels were available in the correspondence table.

Use was computed separately for SABA treatments with or without anticholinergics (n= 3629 in regular CATI and 155 in SAE CATIs) and anticholinergic treatments (n=40 in regular CATIs and 2 in SAE CATI).

```
   1    2    3
3443   90    2

  1   2   3
327  17   1

  1   2
139   8
```

The great majority of interviews report only one reliever, but a few report 2 or even 3 per interview (numbers before regular CATIs, before SAE in regular CATIs, and before SAE in SAE CATIs). Daily reliever use per interview was transferred to the interview table by adding the values of daily use for all individual treatments type B reported in each interview. If values were missing for one treatment, the total reliever use value was considered as missing.

1.2 Other controller use

Use of other controllers in the last 4 months: What is the name of the treatment? II.1.2 CATI M0 : When did you start? II.1.2 if less than 4 months ago, When exactly? II.1.2 When did the doctor interrupt it?

No treatments were recorded as ended (the question for ended treatments has all values NA; it seems to not have been included in the CATI script for this treatment group). Thus, we can only know which interviews reported such treatments OR had prior interviews reporting them (if treatments were ended before, treatments will show up as ongoing). Treatments in regular CATIs were: SINGULAIR 10MG COMPRIME; in SAE CATIs, they were: SINGULAIR (dosage non connu du patient). Note: all treatment labels were available in the correspondence table.

Number of other controller treatments reported in regular CATIs: 884, from 244 patients. Of these, 872 were LTRA, and only 8 xanthine, cromones or xolair.

Number of other controller treatments reported before SAE in regular CATIs: 138, from 81 patients.

Number of other controller treatments reported before SAE in SAE CATIs: 55, from 46 patients. Of these, 54 were LTRA, and only 1 xanthine, cromones or xolair.

Of these, only 9 treatments were reported as started within 4 months in regular CATIs, and 0 in SAE CATIs. Note: start information for some treatments in regular CATIs doesn't correspond with the exact start question, which reports 22 treatments started in the last 4 months.

LTRA treatments were transferred to the CATI table as dichotomous variable. If the interview included at least one LTRA treatment, it was coded as reporting LTRA. The number of interviews reporting LTRA treatments were: 872 of 4106 regular CATIs, 131 before SAE in regular CATIs (of 378 CATIs), and 48 of 163 SAE CATIs.

1.3 Asthma control

Asthma control was computed for all regular CATIs for adults and children separately, based on ACQ and RCP3Q items.

Values	Frequency	Percent	Valid Percent	Cum Percent
0	642.00	20.88	21.18	21.18
0.2	240.00	7.80	7.92	29.10
0.4	351.00	11.41	11.58	40.68
0.6	297.00	9.66	9.80	50.48
0.8	223.00	7.25	7.36	57.84
1	221.00	7.19	7.29	65.13
1.2	197.00	6.41	6.50	71.63
1.4	165.00	5.37	5.44	77.07
1.6	141.00	4.59	4.65	81.72
1.8	121.00	3.93	3.99	85.71
2	85.00	2.76	2.80	88.52
2.2	88.00	2.86	2.90	91.42
2.4	52.00	1.69	1.72	93.14
2.6	51.00	1.66	1.68	94.82
2.8	33.00	1.07	1.09	95.91
3	36.00	1.17	1.19	97.10
3.2	24.00	0.78	0.79	97.89
3.4	24.00	0.78	0.79	98.68
3.6	14.00	0.46	0.46	99.14
3.8	8.00	0.26	0.26	99.41
4	10.00	0.33	0.33	99.74
4.2	2.00	0.07	0.07	99.80
4.4	1.00	0.03	0.03	99.84
4.6	2.00	0.07	0.07	99.90
4.8	2.00	0.07	0.07	99.97
5	1.00	0.03	0.03	100.00
NA's	44.00	1.43		
Total	3075.00	100.00	100.00	

Table 1: Asthma control regular CATIs all - adults

Asthma control for adults all CATIs: in Table 1, Table 2, and Table 3, and Figure 3.

Asthma control for children all regular CATIs: in Table 4, Table 5, Table 6, and Figure 4.

Dichotomous control was computed for adults and children in a single variable, based on a threshold of 0.75 for adults and 0 for children. There were 2076 (50.56%) reports of uncontrolled asthma before regular CATI, 232 (67.05%) reports of uncontrolled asthma before SAE in regular CATIs, and 118 (72.39%) reports of uncontrolled asthma before SAE in SAE CATIs.

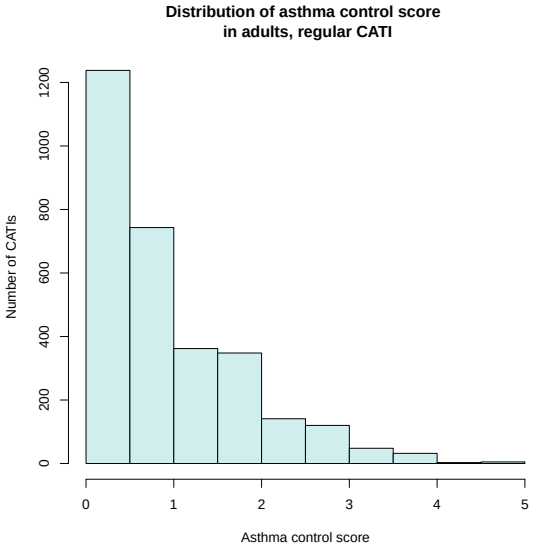


Figure 3: Histogram asthma control at regular CATIs - adults

Values	Frequency	Percent	Valid Percent	Cum Percent
0	33.00	13.41	14.60	14.60
0.2	6.00	2.44	2.65	17.26
0.4	11.00	4.47	4.87	22.12
0.6	7.00	2.85	3.10	25.22
0.8	9.00	3.66	3.98	29.20
1	16.00	6.50	7.08	36.28
1.2	18.00	7.32	7.96	44.25
1.4	9.00	3.66	3.98	48.23
1.6	4.00	1.63	1.77	50.00
1.8	9.00	3.66	3.98	53.98
2	10.00	4.07	4.42	58.41
2.2	15.00	6.10	6.64	65.04
2.4	12.00	4.88	5.31	70.35
2.6	11.00	4.47	4.87	75.22
2.8	9.00	3.66	3.98	79.20
3	9.00	3.66	3.98	83.19
3.2	8.00	3.25	3.54	86.73
3.4	4.00	1.63	1.77	88.50
3.6	5.00	2.03	2.21	90.71
3.8	7.00	2.85	3.10	93.81
4	4.00	1.63	1.77	95.58
4.2	1.00	0.41	0.44	96.02
4.4	3.00	1.22	1.33	97.35
4.6	2.00	0.81	0.88	98.23
4.8	2.00	0.81	0.88	99.12
5	1.00	0.41	0.44	99.56
5.8	1.00	0.41	0.44	100.00
NA's	20.00	8.13		
Total	246.00	100.00	100.00	

Table 2: Asthma control before SAE in regular CATIs all - adults

Values	Frequency	Percent	Valid Percent	Cum Percent
0	12.00	10.34	10.62	10.62
0.2	5.00	4.31	4.42	15.04
0.4	3.00	2.59	2.65	17.70
0.6	6.00	5.17	5.31	23.01
0.8	4.00	3.45	3.54	26.55
1	6.00	5.17	5.31	31.86
1.2	5.00	4.31	4.42	36.28
1.4	9.00	7.76	7.96	44.25
1.6	3.00	2.59	2.65	46.90
1.8	6.00	5.17	5.31	52.21
2	8.00	6.90	7.08	59.29
2.2	8.00	6.90	7.08	66.37
2.4	3.00	2.59	2.65	69.03
2.6	2.00	1.72	1.77	70.80
2.8	6.00	5.17	5.31	76.11
3	4.00	3.45	3.54	79.65
3.2	4.00	3.45	3.54	83.19
3.4	3.00	2.59	2.65	85.84
3.6	4.00	3.45	3.54	89.38
3.8	3.00	2.59	2.65	92.04
4	4.00	3.45	3.54	95.58
4.2	1.00	0.86	0.88	96.46
4.4	1.00	0.86	0.88	97.35
5.4	3.00	2.59	2.65	100.00
NA's	3.00	2.59		
Total	116.00	100.00	100.00	

Table 3: Asthma control before SAE in SAE CATIs all - adults

Values	Frequency	Percent	Valid Percent	Cum Percent
0	474.00	45.97	46.38	46.38
1	163.00	15.81	15.95	62.33
2	148.00	14.35	14.48	76.81
3	101.00	9.80	9.88	86.69
4	54.00	5.24	5.28	91.98
5	40.00	3.88	3.91	95.89
6	23.00	2.23	2.25	98.14
7	9.00	0.87	0.88	99.02
8	2.00	0.19	0.20	99.22
9	8.00	0.78	0.78	100.00
NA's	9.00	0.87		
Total	1031.00	100.00	100.00	

Table 4: Asthma control regular CATIs all - children

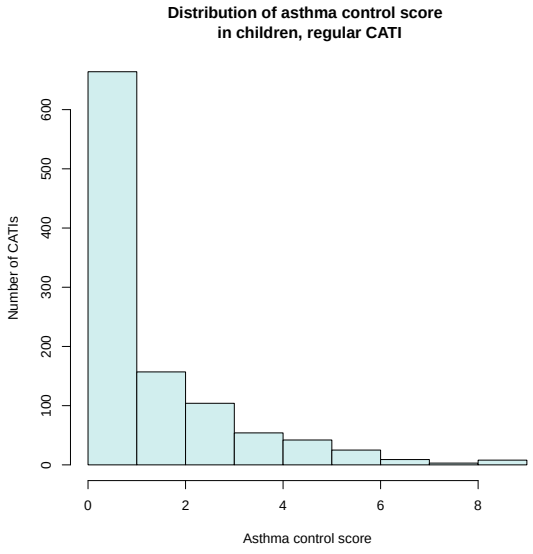


Figure 4: Histogram asthma control at regular CATIs - children

Values	Frequency	Percent	Valid Percent	Cum Percent
0	55.00	41.67	46.61	46.61
1	16.00	12.12	13.56	60.17
2	20.00	15.15	16.95	77.12
3	12.00	9.09	10.17	87.29
4	4.00	3.03	3.39	90.68
5	3.00	2.27	2.54	93.22
6	4.00	3.03	3.39	96.61
7	3.00	2.27	2.54	99.15
8	1.00	0.76	0.85	100.00
NA's	14.00	10.61		
Total	132.00	100.00	100.00	

Table 5: Asthma control before SAE in regular CATIs all - children

Values	Frequency	Percent	Cum Percent
0	19.00	40.43	40.43
1	6.00	12.77	53.19
2	4.00	8.51	61.70
3	6.00	12.77	74.47
4	3.00	6.38	80.85
5	2.00	4.26	85.11
6	4.00	8.51	93.62
7	1.00	2.13	95.74
8	1.00	2.13	97.87
9	1.00	2.13	100.00
Total	47.00	100.00	

Table 6: Asthma control before SAE in regular CATIs all - children

1.4 Asthma exacerbations

Occurrence of exacerbations (asthma attacks) was investigated for the 2 months prior to M0 CATIs, and 4 months prior to all other regular CATIs, as well as in SAE CATIs triggered by an SMS report of SAE. the interviewer asked about the type of SAE (GP call or visit or out-of-hours or walk-in centre; ambulance or hospital visit; course of OCS); number of events; when these happened (number of weeks before the interview). For the last event, the interviewer asked the name of the OCS treatment taken (and start and end of OCS course, and quantity per day), other actions taken (GP call or visit, out-of-hours or walk-in centre visit, NHS helpline, ambulance, A&E, hospital admission); perceived causes; and medication adherence before the event.

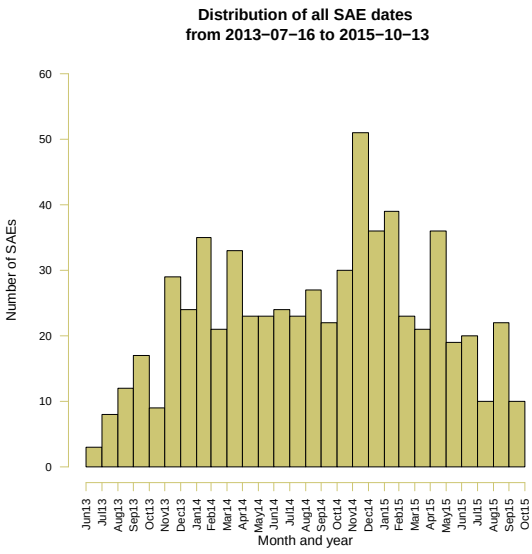


Figure 5: Dates for all SAEs reported

The analysis and selection of valid exacerbations reported in CATIs was performed separately, therefore will not be examined here. Dates of SAE as reported in regular and SAE CATIs are shown in Figure 5.

2 Longitudinal plots adherence and asthma outcomes

2.1 Adherence and drug exposure (regular CATIs)

Longitudinal summary statistics are presented below:
Number of patients with at least 1 value of 4-month global adherence score before regular CATIs less than 100 percent: 726.
Number of patients with only 100 percent adherence reported during 4 months before regular CATIs: 208.
Number of patients with at least 1 value <80 percent during 4 months before regular CATIs: 593.
Number of patients with no value below 80 percent during 4 months before regular CATIs: 341.
Number of patients with all values above 80 but not all 100 during 4 months before regular CATIs: 133.

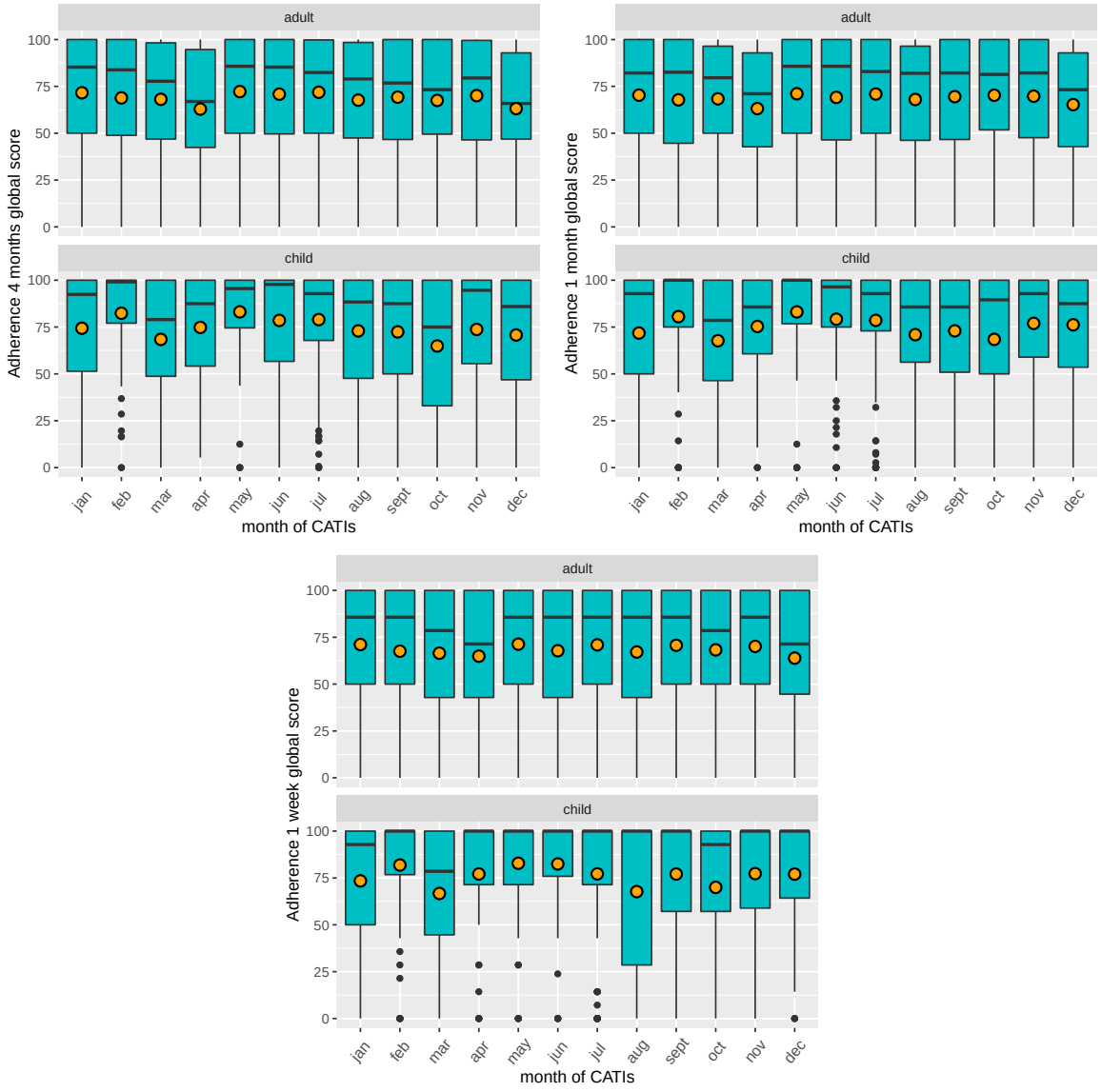


Figure 6: Distribution of adherence global scores in regular CATIs per calendaristic month

2.2 Asthma control

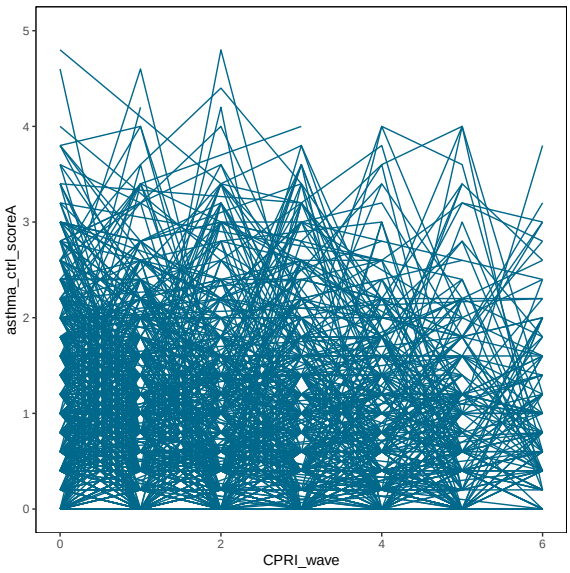


Figure 7: Plot control in regular CATIs (adults)

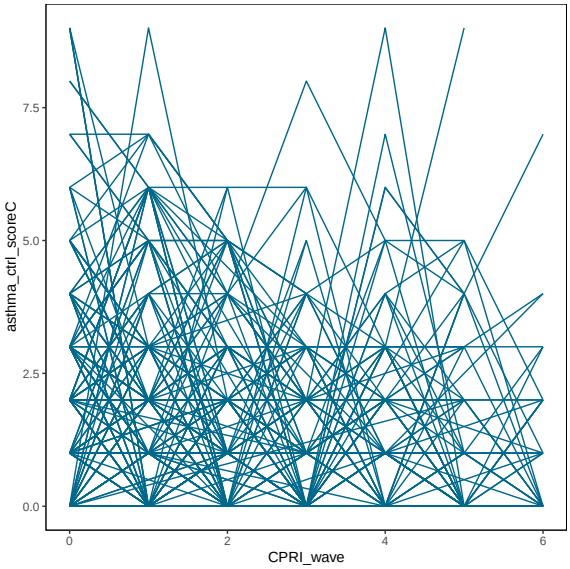


Figure 8: Plot control in regular CATIs (children)

Changes in asthma control in regular CATIs: in Figure 7 (adults) and 8 (children)

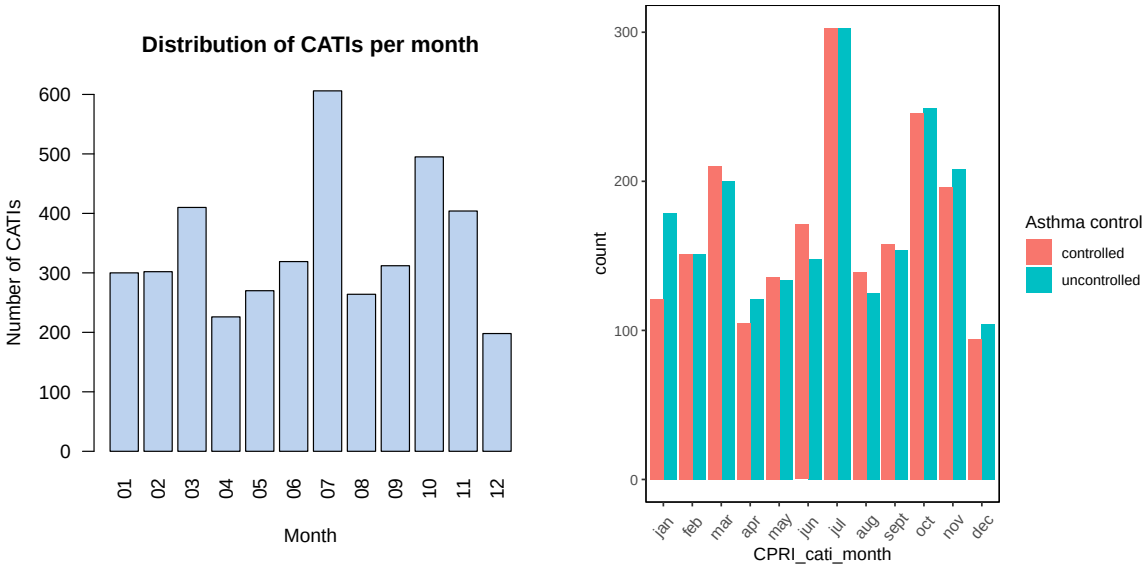


Figure 9: Controlled versus uncontrolled asthma reported in regular CATIs - per calendar month

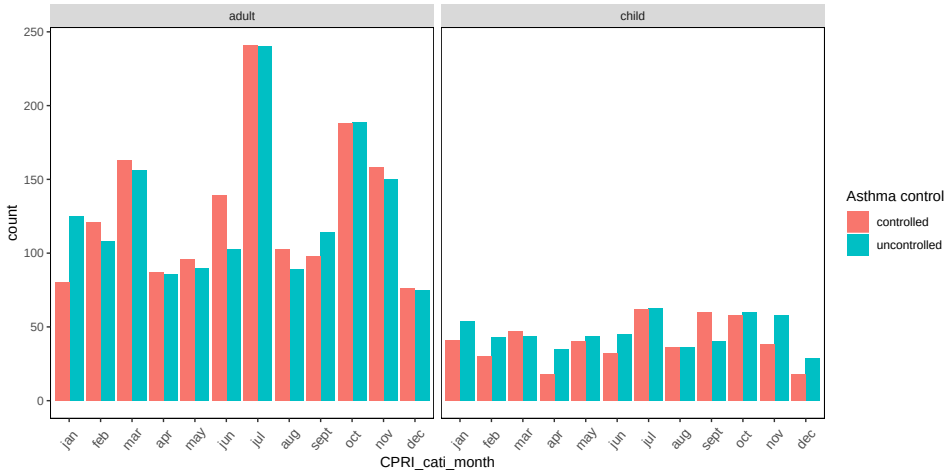


Figure 10: Controlled versus uncontrolled asthma reported in regular CATIs - per calendar month and age

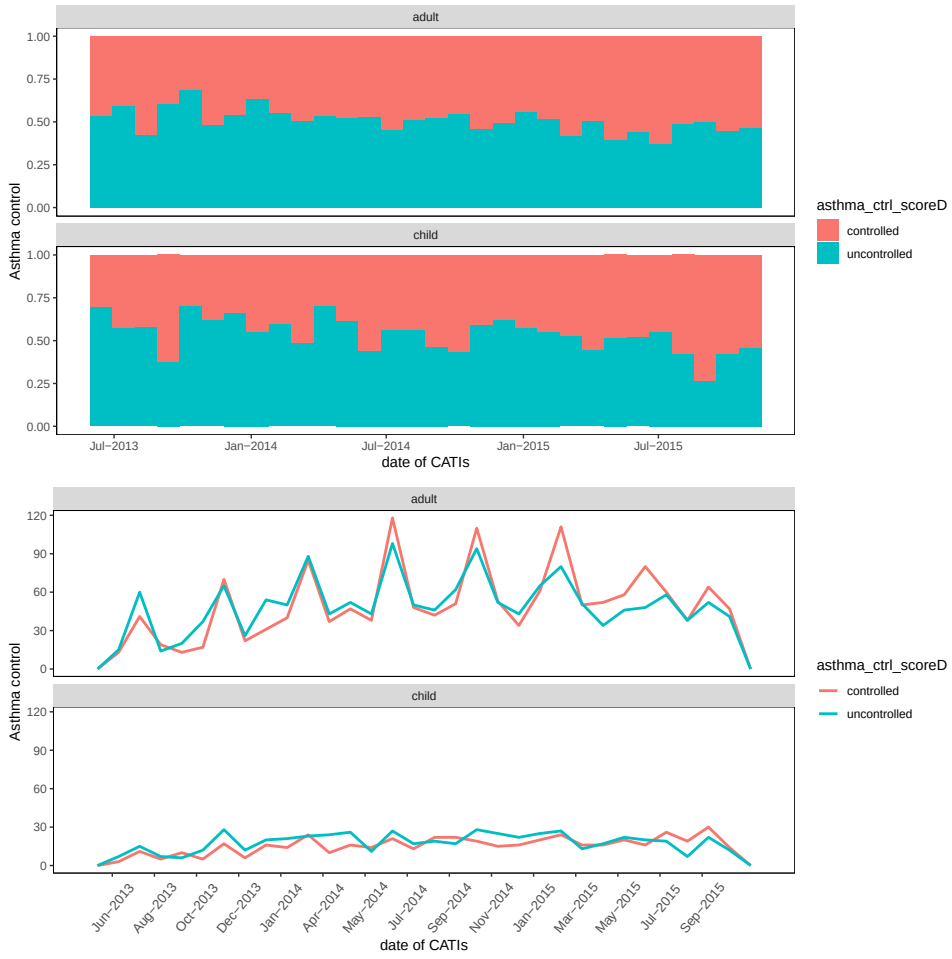


Figure 11: Controlled versus uncontrolled asthma reported in regular CATIs - as proportions and as frequency lines

2.3 Exacerbations

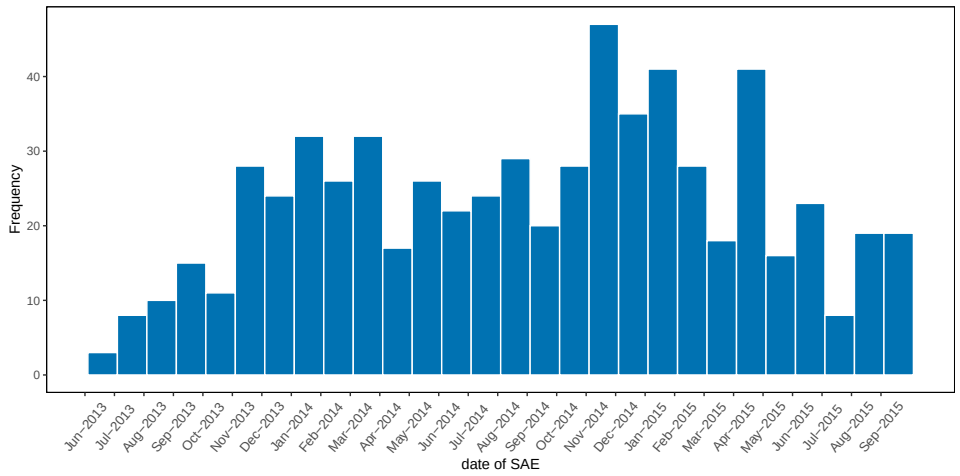


Figure 12: Frequency of exacerbations during the follow-up months

SAE frequency was examined per time interval. The frequencies of SAEx reported per each month of the follow-up period are reported in Figure 12.

2.4 Reliever use (regular CATIs)

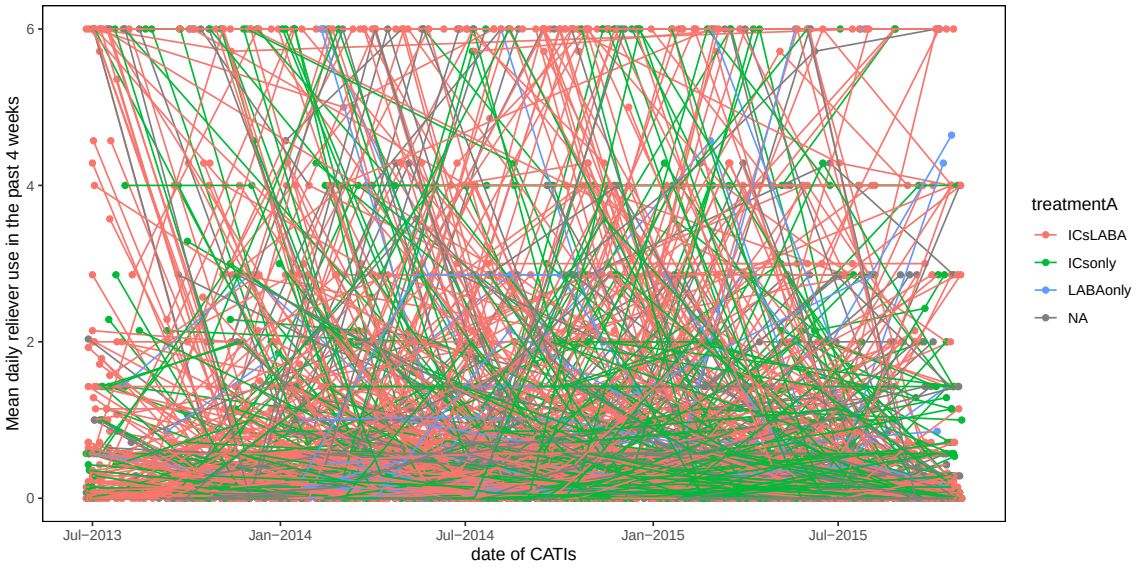


Figure 13: Mean daily reliever use before regular CATIs during the follow-up months

Variation in mean daily reliever use in regular CATIs during the follow-up are reported in Figure 13.

3 Missing data analyses

3.1 Regular CATIs

The following rules we used to estimate number of planned CATI in the UK and France:

- if UK, either 7 CATIs (first enrollment process) or maximum 4 CATIs depending on time lag between date of M0 CATI and date 7 days before last CATI in the follow-up (as planning CATIs has probably stopped 1 week before last CATI recorded, i.e. mid-October last planned, end October last recorded);
- if FR, maximum 7 CATIs depending on time lag M0 CATI - 7 days before last CATI.

In total, based on these rules, 5283 CATIs were planned, of which 1177 CATIs did not take place (22.28%). Of these, several CATIs were not performed due to withdrawal of patient from the study (39 patients withdrew at various moments during their follow up, for various reasons recorded in the D5.2. Data analysis report).

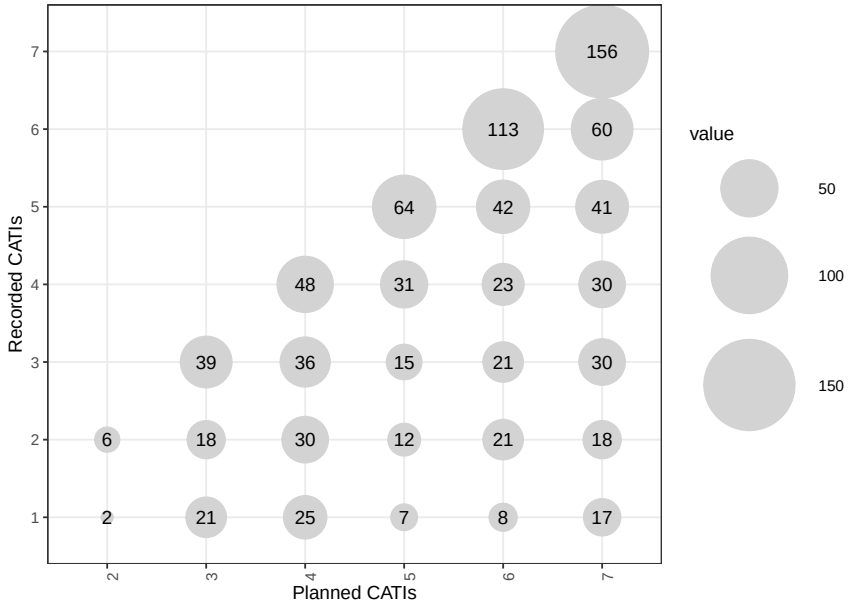


Figure 14: Comparison planned versus recorded regular CATI

Figures 14 and 15 show the number CATIs planned versus recorded per patient, and the percentage of planned vs recorded CATIs per patient. For the large majority of patients, all CATIs planned were recorded.

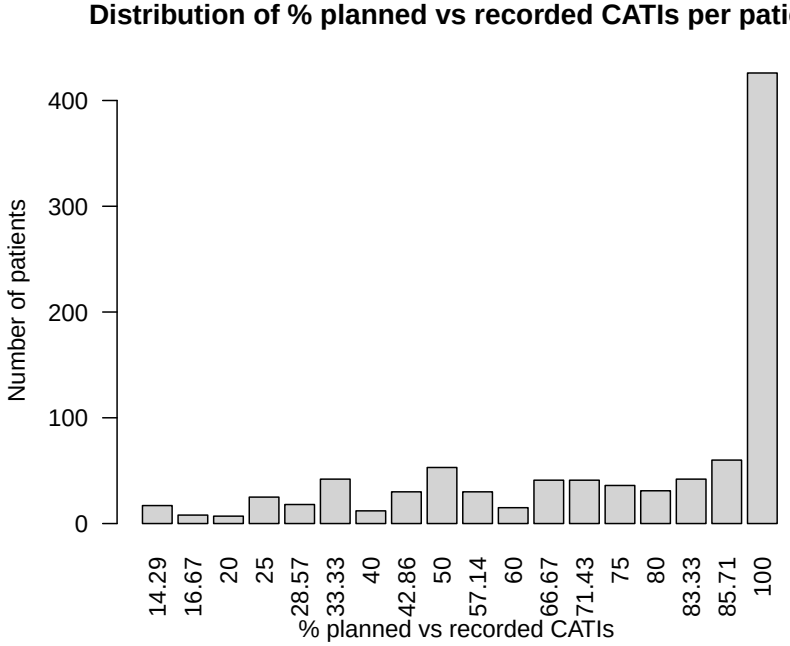


Figure 15: Percentage of planned vs recorded CATIs per patient

Models predicting binary variable 'all planned CATIs recorded (1) vs less than planned CATIs recorded (0)" from patient baseline characteristics are shown in Table 7. Patients in the UK were less likely to have all planned CATIs recorded (which was due to the difficulties recruiting in the UK). Uncontrolled asthma and more use of relievers at baseline were also linked to lower likelihood of having all CATIs recorded during the follow-up.

Models predicting percentage of planned vs recorded from patient baseline characteristics are shown in Table 8. Patients in the UK had a lower percentage of CATIs recorded. Those in the LABA+ICs group also has less recorded CATIs (more recruitment efforts were done later in the study to recruit in this group, which resulted in the study needing to stop before all planned CATIs could be performed). Uncontrolled asthma, more use of relievers, and LTRA use at baseline were also linked to lower percentages of CATIs recorded during the follow-up. Patients who had at least an exacerbation during the follow-up had a higher percentage on CATIs recorded from the total planned.

Models predicting recorded versus missing CATIs (0-missing; 1-recorded) from patient baseline characteristics are shown in Table 9. CATIs were more likely to be missing later in the study, in UK patients, in the LABA+ICs group, and for patients with higher reliever use and uncontrolled asthma at baseline, and with no AE during the study.

Table 7: Results logistic regression model percentage planned vs recorded

	Dependent variable:
	PlRecNY
Intercept	0.273
	(0.357)
Country(UK)	-0.838^{***}
	(0.213)
Gender(male)	0.114
	(0.147)
Age (from 6yo)	-0.004
	(0.009)
Report(parent)	0.208
	(0.235)
Treatment group (ICs)	-0.153
	(0.202)
Treatment group (LABAs)	1.101
	(0.614)
Treatment group (LABAs+ICs)	-0.383
	(0.395)
Baseline severity(no. OC courses)	-0.051
	(0.082)
Baseline severity(no. canisters ICs and LABA)	-0.003
	(0.010)
Baseline severity(ICs daily dose M0)	-0.00002
	(0.0001)
Adherence baseline(1-month score)	0.002
	(0.002)
LABA use	0.071
	(0.427)
LTRA use	-0.199
	(0.177)
Reliever use	-0.112^{**}
	(0.043)
AE occurrence	0.341^{*}
	(0.163)
Asthma control (uncontrolled)	-0.488^{**}
	(0.155)
Observations	868
Log Likelihood	-562.265
Akaike Inf. Crit.	1,158.529
Note:	*p<0.05; **p<0.01; ***p<0.001

Table 8: Results linear regression model percentage planned vs recorded

	Dependent variable:
	PercPlRec
Intercept	82.510^{***}
	(4.259)
Country(UK)	-13.403^{***}
	(2.413)
Gender(male)	2.362
	(1.756)
Age (from 6yo)	0.043
	(0.109)
Report(parent)	3.760
	(2.798)
Treatment group (ICs)	-0.684
	(2.412)
Treatment group (LABAs)	4.948
	(6.731)
Treatment group (LABAs+ICs)	-12.871^{**}
	(4.446)
Baseline severity(no. OC courses)	-0.690
	(0.961)
Baseline severity(no. canisters ICs and LABA)	-0.089
	(0.117)
Baseline severity(ICs daily dose M0)	-0.00004
	(0.001)
Adherence baseline(1-month score)	-0.001
	(0.027)
LABA use	5.671
	(4.758)
LTRA use	-4.174^{*}
	(2.096)
Reliever use	-1.160^{*}
	(0.498)
AE occurrence	7.630^{***}
	(1.944)
Asthma control(uncontrolled)	-5.767^{**}
	(1.861)
Observations	868
R^2	0.123
Adjusted R^2	0.107
Note:	*p<0.05; **p<0.01; ***p<0.001

Table 9: Results logistic 2-level regression model recorded vs not recorded

	Dependent variable:
	CATImiss
Intercept	4.431^{***}
	(0.338)
CATI number	-0.576^{***}
	(0.030)
Gender(male)	0.208
	(0.161)
Age (from 6yo) (z)	-0.018
	(0.109)
Report(parent)	0.295
	(0.260)
Country(UK)	-1.859^{***}
	(0.228)
Treatment group (ICs)	-0.088
	(0.221)
Treatment group (LABAs)	0.937
	(0.669)
Treatment group (LABAs+ICs)	-0.911^{*}
	(0.402)
Baseline severity(no. OC courses) (z)	-0.073
	(0.079)
Baseline severity(no. canisters ICs and LABA) (z)	-0.043
	(0.089)
Baseline severity(ICs daily dose M0) (z)	-0.013
	(0.088)
Adherence baseline(1-month score) (z)	0.060
	(0.081)
LABA use	0.240
	(0.430)
LTRA use	-0.333
	(0.192)
Reliever use	-0.093^{*}
	(0.044)
AE occurrence	0.776^{***}
	(0.183)
Asthma control(uncontrolled)	-0.648^{***}
	(0.174)
Observations	4,906
Log Likelihood	$-2,064.755$
Akaike Inf. Crit.	4,167.510
Bayesian Inf. Crit.	4,290.976
Note:	*p<0.05; **p<0.01; ***p<0.001

3.2 AEx CATIs

In total, excluding the reminder messages (and M0 messages, which represented a first message for testing connection), 12864 SMS were sent, of which 4313 SMS did not receive a reply (33.53%). Answer rates during follow-up are presented in the D5.3 Data analysis report and range from 74.0 to 58.5%. The text message was the following: "Bonjour, ASTRO-LAB SMS. Des nouveaux comprimes pour votre asthme ? Consultation imprevue ? Hospitalisation ? Repondez O ou N au [numero]. Merci!" or "Message from the ASTRO-LAB study: Any new tablet for your asthma? Unexpected visit to your GP or hospital because of asthma? PLEASE TEXT BACK yes OR no."

A recorded AE CATI (CATIall CATItype value 2) following an SMS report of exacerbation was considered if the date of a CATI ("CATI_date") was within less or equal to 30 days of answer ("SPFR_reception_date") to a positively answered SMS (SPFR_sae value "Yes"). If more such CATIs were available the closest CATI was considered. The date was recorded in a separate variable.

It is important to note that not all exacerbation confirmations were 'real' AE. The AE CATIs included qualifying questions and the interview did not continue if this was not confirmed (some additional records were present in the initial AE database, but only qualified deduplicated AE were considered in this clean dataset). Therefore, a 'missCATI' does not always represent a missing AE. Of the 272 positive SMS replies indicating an exacerbation and not followed by an early regular CATI, 162 (59.56%)led to a AE interview within 30 days. An earlier regular CATI was planned following 101 positive responses.

Models predicting answered (1) versus missing (0) SMS replies from patient baseline characteristics are shown in Table 10. SMSs were more likely to receive a reply earlier in the study, from UK patients, those with higher adherence and lower reliever use at baseline, and with at least an AE during the study.

Note: predicting models of missing AE CATI is not possible since the call was intended to verify if an exacerbation occurred. Thus, it is possible that the missing call would have not lead to a AE recording. However, percentages of AE recorded in this sample are similar to those recorded in other studies, which suggest an acceptable accuracy for this measurement (and probably a negligible percentage of missing AE).

Table 10: Results logistic 2-level regression model replied vs not replied SMS

	Dependent variable:
	MissNY
Intercept	2.146^{***}
	(0.338)
SMS number	-0.082^{***}
	(0.006)
Gender(male)	-0.317
	(0.180)
Age (from 6yo) (z)	0.222
	(0.122)
Report(parent)	0.063
	(0.289)
Country(UK)	1.334^{***}
	(0.264)
Treatment group (ICs)	-0.032
	(0.246)
Treatment group (LABAs)	0.219
	(0.689)
Treatment group (LABAs+ICs)	-0.313
	(0.461)
Baseline severity(no. OC courses) (z)	-0.163
	(0.089)
Baseline severity(no. canisters ICs and LABA) (z)	0.038
	(0.102)
Baseline severity(ICs daily dose M0) (z)	-0.131
	(0.098)
Adherence baseline(1-month score) (z)	0.210^{*}
	(0.090)
LABA use	0.219
	(0.493)
LTRA use	0.283
	(0.216)
Reliever use	-0.181^{***}
	(0.051)
AE occurrence	0.841^{***}
	(0.200)
Asthma control(uncontrolled)	-0.261
	(0.193)
Observations	11,992
Log Likelihood	$-5,443.946$
Akaike Inf. Crit.	10,925.890
Bayesian Inf. Crit.	11,066.340
Note:	*p<0.05; **p<0.01; ***p<0.001

3.3 Examination of missing data within recorded CATIs

An examination of missing data showed that there were 3244 complete reports in the selected sample (4647 reports). There were no missing data on socio-demographic and treatment variables, and AE occurrence, LABA and LTRA use (due to how they were computed). The pre-SAE reports had missings by design for 4-month adherence items (overuse and drug holidays) and score (questions were not asked for pre-SAE intervals). Around 500 reports had no adherence scores but only health outcomes data available, and only 3 with no data at all. For the moment, they will not be imputed. Imputation would need to be performed for the selected dataset, since most missings in the complete dataset are justified (e.g. medication not used, taken as needed, pre-AE information not recorded for more than one AE in a regular interview; missing values have already been imputed in earlier data preparation stages for adherence composite scores if at least one raw score was present), based on the following rules:

- last week score (if valid but missing): Q2, Q3, Q4, Q1
- last month score (if valid but missing): Q4, 1-week score, Q2, Q3, Q1
- last 4-month score(if valid but missing): 1-month score, Q4, 1 week score, Q2, Q3, Q1

Number cases	asthma control	reliever use	treatment type	adh1w	puffsYvsP	adh1m	daysOKadhvs7	days0adhvs7	days0adhvs28	adh4m	overusePerc4m	stopPerc4m	Number missings
3244	1	1	1	1	1	1	1	1	1	1	1	1	0
9	1	1	1	1	1	1	1	1	1	1	1	0	1
6	1	1	1	1	1	1	1	1	1	1	0	1	1
71	1	1	1	1	1	1	1	1	1	1	0	0	2
11	1	1	1	1	1	1	1	1	1	0	1	0	2
524	1	1	1	1	1	1	1	1	1	0	0	0	3
45	1	1	1	1	1	1	1	1	0	1	1	1	1
3	1	1	1	1	1	1	1	1	0	1	1	0	2
4	1	1	1	1	1	1	1	1	0	1	0	0	3
22	1	1	1	1	1	1	1	1	0	0	0	0	4
33	1	1	1	1	1	1	1	0	1	1	1	1	1
2	1	1	1	1	1	1	1	0	1	0	1	0	3
1	1	1	1	1	1	1	1	0	0	1	1	1	2
10	1	1	1	1	1	1	0	1	1	1	1	1	1
3	1	1	1	1	1	1	0	1	1	0	0	0	4
1	1	1	1	1	1	1	0	1	0	1	1	0	3
1	1	1	1	1	1	1	0	1	0	0	0	0	5
9	1	1	1	1	1	1	0	0	1	1	1	1	2
2	1	1	1	1	1	1	0	0	1	0	1	0	4
5	1	1	1	1	1	1	0	0	1	0	0	0	5
5	1	1	1	1	1	1	0	0	0	1	1	1	3
3	1	1	1	1	1	1	0	0	0	0	0	0	6
39	1	1	1	1	1	0	1	1	0	0	0	0	5
1	1	1	1	1	1	0	0	1	1	0	1	0	4
4	1	1	1	1	1	0	0	1	0	0	0	0	6
1	1	1	1	1	1	0	0	0	0	0	0	0	7
5	1	1	1	1	0	1	1	1	1	1	1	1	1
1	1	1	1	1	0	1	1	1	1	1	1	0	2
4	1	1	1	1	0	1	1	1	1	0	0	0	4
1	1	1	1	1	0	1	1	1	0	0	0	0	5
1	1	1	1	1	0	1	0	1	1	1	1	1	2
1	1	1	1	1	0	1	0	1	1	0	0	0	5
1	1	1	1	1	0	1	0	0	1	1	1	1	3
2	1	1	1	1	0	1	0	0	1	0	0	0	6
1	1	1	1	1	0	0	0	1	0	0	0	0	7
2	1	1	1	0	1	0	0	1	1	0	1	1	4
1	1	1	1	0	0	0	1	1	1	0	1	1	4
1	1	1	1	0	0	0	0	1	1	0	1	1	5
21	1	1	1	0	0	0	0	0	0	0	0	0	9
511	1	1	0	0	0	0	0	0	0	0	0	0	10
2	1	0	1	1	1	1	1	1	1	0	0	0	4
1	1	0	1	1	1	1	0	0	0	0	0	0	7
29	0	0	1	0	0	0	0	0	0	0	0	0	11
3	0	0	0	0	0	0	0	0	0	0	0	0	12
	32	35	514	568	583	614	619	629	696	1198	1259	1283	8030

Table 11: Missing value patterns

Astrolab cohort - Longitudinal models ICS adherence and outcomes

Analysis Report - Hierarchical Longitudinal Models

This report was generated on August 23, 2019 with R version 3.5.3 (2019-03-11).

Contents

Part I
Summary

This report focuses on longitudinal analyses on the Astrolab database (January 2016 extraction) to investigate the role of adherence to daily inhalers in asthma control, occurrence of exacerbations, and use of reliever inhalers. A subsample of regular and AE CATIs using ICS-based controllers is selected to investigate the impact of adherence on asthma outcomes, controlling for patient and treatment characteristics. The questions answered are;

- 1) does adherence matter at between-subject level? Prior studies suggest it does, hence we hypothesize that higher average levels of adherence at patient level are related to more control, lower chances of exacerbation and less use of inhalers.
- 2) does adherence matter at within-subject level? No studies have investigated this level in asthma, and for such intervals. We hypothesize that it does matter - higher adherence earlier, leads to better outcomes at the next CATI; higher adherence is associated with worse outcomes in the same CATI.
- 3) do adherence patterns matter? This question is exploratory, we do not have an a priori hypothesis on which question is more associated with outcomes, and we would like to explore differences in predictive validity between drug holidays and 1-week or 1-month adherence.
- 4) does adherence-outcome relationships depend on the type of ICS? (ICS-only, fixed dose combination, or ICS + other medication such as long-acting beta-agonists or leucotriene receptor antagonists). No a priori hypotheses.
- 5) does adherence-outcome relationships depend on asthma severity? (ICS daily dose at baseline). No apriori hypotheses. Sensitivity analyses are performed with severity at baseline excluded (only 2 database-derived severity variables included) to check the possibility of overcontrolling for severity in the main models.
- 6) does adherence-outcome relationships depend on age? (children - adolescents (12-18) - adults). No a priori hypotheses.

Part II
Results

1 Sample selection and variable preparation

Regular and pre-AE adherence reports were merged into a single dataset, with 4106 reports before regular CATIs, 378 reports before AEs in regular CATIs, and 163 reports before AE in AE CATIs.

The following variable transformations were performed:

- Reliever use was winsorized (capped at 95 percentile, i.e. 6 inhalations per day) to reduce skewness and facilitate model convergence.
- All continuous time-varying variables were person-centered by calculating person means and deviations from the person mean for each patient (Singer and Willett, 2003)
- Lead and lag variables, representing the value of the variable in the previous and subsequent CATI, respectively, were calculated for all time-varying variables.

- Treatment type was coded in 3 categories: ICS-only (if one or more ICS-only inhalers were prescribed), ICsLABA (if any combination of ICS and LABA inhalers was prescribed, fixed combination), and ICS-plus (if LABA or-and LTRA were prescribed in addition to ICS-only or ICsLABA inhalers). It is important to note that most prescriptions were either for fixed combination ICS-LABA or for ICS-only inhalers, yet there were several reports of ICS-only and FDCs, ICS and LABA in separate inhalers (no statistical difference in adherence reported), and also LABA in monotherapy (as reported in more detail below). In the selected sample for final analyses, no treatment switches between ICS-only and ICS-LABA were reported (LABA-only patients were censored at first occurrence of LABA-only treatment, as described below)

- Age was categorised as adults (18-40), teenagers (12-17) and children (6-11).

- Continous variables with skewed distributions (adherence, reliever use, time, severity markers) were standardized to facilitate model convergence. Thus, the intercept would refer to the average values (the value of the DV in an adult patient of average adherence, reliever use, in the middle of the follow-up period, with average asthma severity), and betas would refer to changes in the DV with every standard deviation from the average value.

To perform longitudinal models predicting asthma control based on adherence scores, a selection of patients was necessary. The following secondary exclusion criteria are possible (per interview or per patient):

- had no treatments with adherence reported in an interview (270 CATIs for 89 patients); interviews that do not report adherence for any treatment (excluding ended, as needed, prescription not remembered) are coded at the moment as missing values, therefore they are automatically excluded from the computation. If they need to be included, they would need to be imputed as 0 adherence. DECISION: censor CATIs from patients that do not report any prescribed inhaler at all in at least a CATI (not ended and not as needed) - all CATIs after the first such CATI. REASON: patients that are not under treatment for the whole follow-up interval cannot be assessed on adherence (the precondition of having a treatment with known recommendations is necessary). Imputation of non-adherence based on GP prescription data and or dispensing data is of limited use (incomplete prescription data and partial matching with dispensing data in France) and the question remains on whether the problem is about adherence or about a precondition for adherence not being met (e.g. not knowing what they are prescribed).

- had ended treatments (additional treatment might have interferred with asthma control) (373 interviews, 249 patients); DECISION: if other treatments are ongoing, keep CATI; if no other treatments are ongoing (patient reports having no prescriptions anymore for daily use), censor CATIs from patient - all CATIs after the first such CATI. REASON: if a patient stopped a treatment it is unlikely to have an impact on control if there are ongoing treatment (maybe switch to similar treatment); if patients are recommended to stop daily treatment, they most likely do not have persistent asthma.

- had as needed treatments (exposure to treatment and its influence on control is unknown) (167 interviews, 86 patients); DECISION: if treatment is ICS-based (single or combination inhaler), censor CATIs from patient - all CATIs after the first such CATI; if LABA, consider the ICS-based adherence values. REASON: A fixed daily recommendation is the basis for asthma management (guidelines), and necessary for computing adherence. If an ICS-based treatment is recommended 'as needed', the relationship adherence - outcomes cannot be studied in this case.

- had treatments added more recently than 1 month (lack of stable prescribed treatment may confuse the relation adherence - control) (90 interviews with at least one treatment added within the last week, from 61 patients); DECISION: keep CATI and rely on default missing data procedures (listwise deletion in analyses where those variables are missing). REASON: they are one or two CATIs per patient, and they are likely valid reports so they can be used for the applicable intervals without reduction of sample size. The impact of a recently added treatment can be assessed by adding this information as a dichotomous variable in some models, but it is unlikely to impact models (small number of CATIs affected)

- had treatments with missing recommendations (some of them inferred from other data, such as use and adherence, but may indicate that something went wrong in the CATI so less reliable data was produced (applies only to regular interviews, no missing in pre-AE reports): 37 interviews, from 28 patients). DECISION: keep CATI and compute remaining missings. REASON: only one or two CATIs per patient, reasons for missingness are likely unrelated to adherence - outcomes relationship, few CATIs concerned

- had also treatments that were not relievers or LTRA; i.e.:

  - 54 CATIs with anticholinergics (18 patients);
  - 31 CATIs with Spiriva (9 patients);
  - 15 CATIs with xanthine, cromones or xolair (7 patients);
  - 6 CATIs with Oxeol (1 patient);

  DECISION: keep patients with xanthine-chromones, combine anticholinergics (Bronchodual and Atrovent) with SABA, and exclude all others; REASON: prescription of these treatments may suggest patient profiles different from the target group

- had multiple treatments reported in the same interview; (adherence is computed as mean of scores for ICS-based treatments, and therefore does not indicate use of a specific medication).

  - 46 CATIs with more than 1 inhaler of which at least 1 is FDC for 24 patients;
  - 47 CATIs with FDC and ICS for 28 patients;
  - 231 CATIs with more than 1 inhaler of which at least 1 is ICS for 77 patients;

  DECISION: keep patients with at least one ICS-based treatment; REASON: the analysis can focus on understanding the role of adherence to ICS-based treatments irrespective of whether they are in a single inhaler or in several inhalers. A separate dichotomous variable codes whether a treatment plan includes only ICS inhalers (one or more) or one or more FDC in combination with ICS inhalers or not. CATIs with more ICS-based inhalers are fewer and therefore not likely to influence the results (and not feasible to test their separate influence).

- had LABA only (127 CATIs for 33 patients); DECISION: censor at the first CATI with LABA-only; REASON: this group is different than the rest of the sample from the point of view of asthma management, and not large enough to examine separately

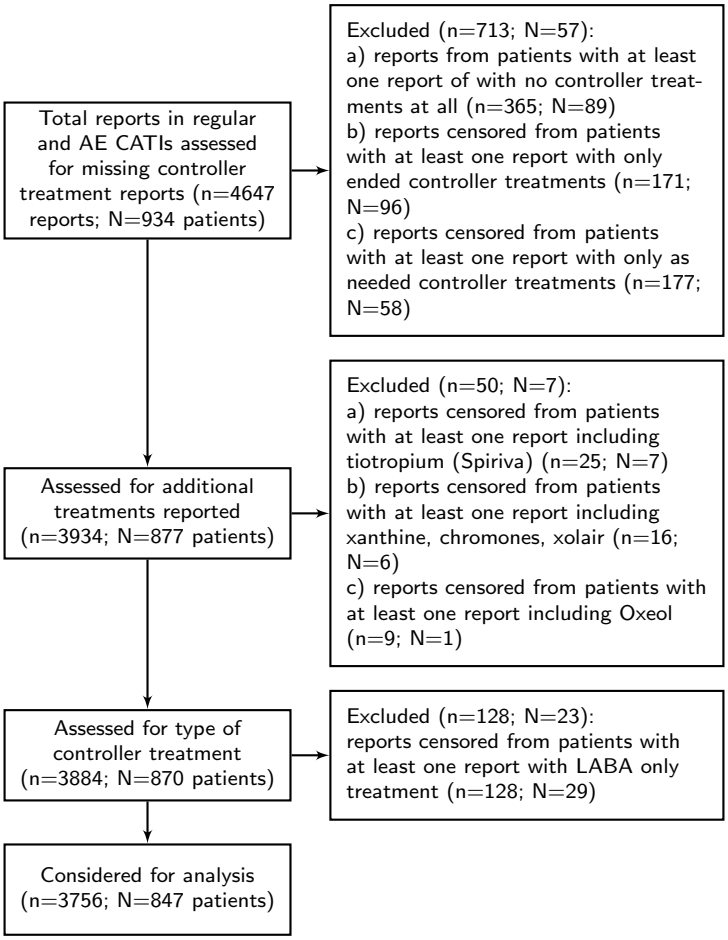
- patients with only 1 or 2 CATIs, as these do not contribute to estimating within-person variation: 162 patients. DECISION: patients with only one CATI are automatically excluded from the model when lagged variables are considered (default is listwise exclusion, and lagged variables will be missing); no patients were excluded from the analyses at this point REASON: impact of proportion of singletons on model estimation is little researched, but is likely diminished by the high number of level 2 units (patients). Lagged models need however at least 2 data points, otherwise either all predictors or all outcomes are missing. However, in the simultaneous models the additional patients would bring more precision to the between-patient effects.

Note: of all 934 patients, only 151 patients never experienced an exacerbation and consistently reported control during the whole follow-up period, and 55 of these reported no use of relievers for the whole period. These may need to be excluded in an additional sensitivity analysis, as they may show mild asthma and do not have any variation in outcomes.

An examination of missing data showed that there were 3244 complete reports in the selected sample. There were no missing data on socio-demographic and treatment variables, and AE occurrence, LABA and LTRA use (due to how they were computed). The pre-AE reports had missings by design for 4-month adherence items (overuse and drug holidays) and score (questions were not asked for pre-AE intervals). Around 500 reports had no adherence scores but only health outcomes data available, and only 3 with no data at all. Variables puffsYvsP, days0adhvs7, daysOKadhvs7, days0adhvs28, adh1m, adh1w, SABAuse, and

asthma control scores which were missing in any of the remaining CATIs (between 27 for asthma control and 143 for days0adhvs28) were replaced with the non-missing value closest in time from that particular CATI from the same patient, or with the median or mode of the total sample. Variables adh4m, overusePerc4m, and stopPerc4m were replaced only in regular CATIs.

Figure 1: Flowchart of CATI selection for longitudinal analyses



This subsample included 681 (80.4%) French patients, 403 (47.58%) women, of mean (SD) age 21.77 (10.77); 479 adults, 162 adolescents, and 206 children. They were recruited by 232 French GPs and 80 UK practices.

The mean (sd) follow-up time (days from the first to the last CATI recorded for each patient) was 406 (249); maximum follow-up time was 758. There were 108 participants with a single report. There were a maximum of 13 reports per patient; median(IQR) 4 (13) reports per patient.

Median (IQR) 1-week adherence 85.71 (50), and 1-month adherence was 85.71 (50), when considering all reports, including regular and pre-AE. Median (IQR) drug-holiday adherence was 100 (6.25).

Percentage 1-week adherence $< 60\%$: 33.07

Percentage 1-week adherence 60-80%: 11.05

Percentage 1-week adherence $>80\%$: 55.88

Percentage 1-week adherence 100%: 42.41

question	answer	count (%)
n		847
Country (%)	FR	681 (80.4)
	UK	166 (19.6)
Gender (%)	Female	403 (47.6)
	Male	444 (52.4)
Age (%)	adult	479 (56.6)
	kid	206 (24.3)
	teen	162 (19.1)
Baseline severity(no. OC courses) (median[range])		0.00 [0.00, 7.00]
Baseline severity(no. canisters ICs and LABA) (median[range])		12.00 [2.00, 60.00]
Baseline severity(ICs daily dose M0)(median[range])		500.00 [100.00, 10000.00]

Table 1: Sample characteristics (patient level)

question	answer	count (%)
n		3756
Treatment type (%)	ICsLABA	1929 (51.4)
	ICsonly	785 (20.9)
	ICsplus	1042 (27.7)
Asthma control (%)	controlled	1710 (45.5)
	uncontrolled	2046 (54.5)
Exacerbation occurrence (%)	no	3323 (88.5)
	yes	433 (11.5)
Days since 1st 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]

Table 2: Sample characteristics (report level)

Between and within-person correlations adherence - outcomes - control variables are shown in Table 3.

To examine linearity, scatterplots with LOWESS lines between SABA use and 1-month adherence at baseline (mean and fluctuation; Figure 2 and Figure 3). No marked non-linear trends were noticeable.

2 Impact of adherence on asthma outcomes - all sample

Models to identify predictors of asthma-related health outcomes at patient-level and CATI-level were performed using the following predictors, in addition to the patient ID, practice ID, and the time variable (number of days since patient's first CATI):

- country: UK vs France - to examine between-country differences in health status
- gender - to examine differences in health status between males and females
- age (children, adolescents, comparison with adults) - to examine differences between these 3 categories of respondents (parents report for children)
- treatment reported: ICS in FDC, ICS in single inhaler and ICS with add-on medication (LABA, LTRA) - to examine differences in health status depending on the type of ICS-based controller treatment (Note: these may not correspond with treatment allocation, i.e. FDC, ICs, LABA, LABA with ICs, which was decided based on prescribed treatment 1 year before assessment of eligibility and is not relevant for the current treatment)
- baseline severity markers available for both countries: number prescribed OC 12 months before inclusion, and daily IC dose prescribed at M0 - to examine the possible effect of severity on health status

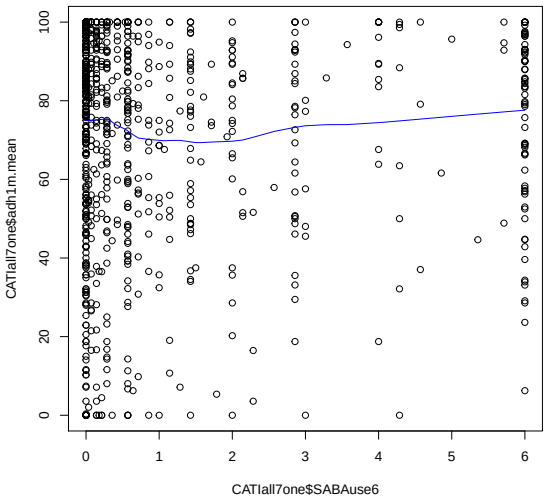


Figure 2: Scatterplot and LOWESS line: reliever use vs 1-month adherence mean at baseline

- adherence to ICS-based controller: a day before (puffsYvsP), days with no use in the last week (days0adhvs7), days with adherent use in the last week (daysOKadhvs7), days with no use in the last month (days0adhvs28), drug holidays in the last 4 months (stopPerc4m), global score 1 month (adh1m), global score 1 week (adh1w) - to examine influence of adherence on health status controlling for the other relevant predictors
- reliever use (for asthma control and asthma exacerbations models) - to control for the effect of increased use of relievers (in particular short-acting beta-agonists) in perception of recent symptoms and early management of worsening symptoms to avoid exacerbation (as per asthma action plans)

The following asthma-related outcomes were considered as dependent:

- asthma control (dichotomous for both kids and adults)
- AE occurrence (report on time interval before CATI vs before AE)
- mean daily reliever use in the last 4 weeks

The following modeling steps were followed to test related hypotheses regarding influences on health status

- Model 1: unconditional means
- Model 2: unconditional growth
- Model 3: conditional growth model with sociodemographics and treatment variables - severity markers, treatment type
- Model 4: model with added adherence scores (average, variation in the same CATI, prior variation)
- Model 5: model with added adherence scores and reliever use scores, for AC and AR models

Models were performed for each outcome separately.

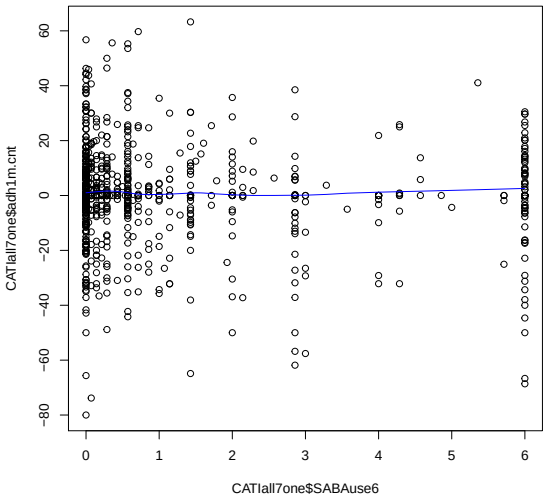


Figure 3: Scatterplot and LOWESS line: reliever use vs 1-month adherence deviation at baseline

	Q1:1-day	Q2	Q3	Q4	1m score	1w score	drughols	AC	SAE	reliever use	ICSonly	ICSplus	gender	age	noOCs	nocan	ddM0
between groups																	
Q2:1-week no use	0.67																
Q3:1-week ok use	0.73	0.74															
Q4:4-week no use	0.64	0.91	0.69														
1-month score	0.75	0.81	0.93	0.85													
1-week score	0.78	0.87	0.96	0.81	0.95												
drug holidays	0.63	0.76	0.59	0.81	0.72	0.7											
asthma control no/yes	0.03	0.08	0.11	0.1	0.11	0.1	0.03										
SAE no/yes	0.06	0	-0.02	0	0	0.01	0.01	-0.26									
reliever use	0	-0.07	-0.03	-0.08	-0.04	-0.04	-0.06	-0.46	0.26								
ICSonly	-0.11	-0.13	-0.05	-0.14	-0.08	-0.08	-0.11	0.06	-0.09	0.02							
ICSplus	0.09	0.13	0.11	0.12	0.11	0.12	0.1	-0.14	0.19	0.03	-0.34						
gender	0.08	0.04	0.1	0.02	0.09	0.09	0.02	0.06	-0.09	0	0.04	-0.01					
age	0.03	0.09	0.01	0.08	0.03	0.03	0.08	0.07	-0.06	0	-0.17	0	-0.23				
noOCs	0.04	0.05	0.05	0.06	0.06	0.05	0.03	-0.03	0.29	0.12	-0.07	0.06	-0.06	-0.08			
nocan	0.1	0.1	0.03	0.11	0.05	0.05	0.06	0.02	0.06	0	-0.45	0.09	-0.05	0.16	0.11		
ddM0	-0.11	-0.01	-0.11	-0.03	-0.11	-0.09	-0.03	-0.17	0.18	0.11	-0.24	0.05	-0.18	0.28	0.07	0.25	
days since CATI1	0.02	0	0.02	0.03	0.04	0.02	-0.01	0.13	0.05	0	-0.09	-0.02	0.03	0.01	0	0.14	0.05
within groups																	
Q2:1-week no use1	0.44																
Q3:1-week ok use1	0.47	0.61															
Q4:4-week no use1	0.35	0.66	0.45														
1-month score1	0.45	0.54	0.8	0.74													
1-week score1	0.52	0.77	0.92	0.56	0.81												
drug holidays1	0.24	0.34	0.25	0.45	0.37	0.3											
asthma control no/yes1	-0.08	-0.05	-0.02	-0.04	-0.02	-0.04	-0.05										
SAE no/yes1	0.06	0	0.01	0.02	0.03	0.03	-0.02	-0.02									
reliever use1	0.06	0.05	0.04	0.04	0.05	0.06	0	-0.21	0.06								
ICSonly1	-0.04	-0.02	-0.03	-0.03	-0.03	-0.04	-0.01	-0.04	-0.01	0.05							
ICSplus1	0.01	0.03	0.02	0.02	0.02	0.03	0	0.01	0	0	-0.15						
gender1																	
age1																	
noOCs1																	
nocan1																	
ddM01																	
days since CATI11	-0.02	-0.04	-0.02	-0.03	-0.02	-0.03	-0.09	0.12	0	-0.15	0.02	0.01					

Table 3: Between and within groups correlations

2.1 Asthma control

Table 4: Results basic models asthma control

	Dependent variable:			
	Asthma control			
	Un.Means	Un.Growth	No Growth	Socio-dem.
Intercept	-0.346^{***}	-0.307^{***}	-0.415^{***}	-0.120
	(0.079)	(0.080)	(0.085)	(0.141)
Days since 1st CATI (z)		0.341^{***}		0.332^{***}
		(0.044)		(0.046)
Gender(male)				0.234
				(0.163)
Age(kid)				-0.612^{**}
				(0.203)
Age(teen)				-0.094
				(0.214)
Country(UK)				-0.461^{*}
				(0.225)
Treatment(ICS only)				0.112
				(0.185)
Treatment(ICS+addon)				-0.393^{*}
				(0.163)
Baseline severity(no. OC courses) (z)				0.042
				(0.079)
Baseline severity(ICs daily dose M0) (z)				-0.472^{***}
				(0.091)
VPC	0.4969	0.5019	0.5066	0.4773
Observations	3,756	3,756	3,756	3,756
Log Likelihood	$-2,270.822$	$-2,242.075$	$-2,269.063$	$-2,219.374$
Akaike Inf. Crit.	4,545.643	4,494.149	4,546.126	4,460.747
Bayesian Inf. Crit.	4,558.106	4,525.305	4,571.050	4,529.290
Note:				@ p<.1; * p<.05; ** p<.01; *** p<.001

Models of asthma control suggested the following results:

- Model 1: the variance in asthma control scores was present at 2 levels (within- and between-patients) but not between practices.
- Model 2: there was a significant increase in asthma control overall, and variation between patients was found in control changes over time; effect sizes were small.
- Model 3: kids were more likely to report uncontrolled asthma; no differences were found in gender and country. Patients with add-on medications were less likely to be controlled. The recommended daily dose of ICS at baseline (first CATI) was significantly associated with control (higher baseline ICS daily dose predicted lower likelihood of control)
- Model 4: average adherence was higher in patients reporting controlled asthma; when patients reported increased 1-week adherence they were more likely to report uncontrolled asthma
- Model 5: the effects of average adherence remained when reliever use variables were included in the model. The effect of 1-week adherence variations reduced below significance levels. Patients with lower average levels of reliever use were more likely to report controlled asthma, and this probability increased when they reported decreasing their reliever use.

Table 5: Results selected asthma control models - composite adherence scores

	Dependent variable:			
	Asthma control			
	1-month	1-month (rel use)	1-week	1-week (rel use)
Intercept	−0.052	−0.245@	−0.058	−0.249@
	(0.149)	(0.146)	(0.149)	(0.146)
Days since 1st CATI (z)	0.302***	0.269***	0.306***	0.272***
	(0.059)	(0.061)	(0.059)	(0.061)
Gender(male)	0.198	0.211	0.199	0.211
	(0.173)	(0.166)	(0.173)	(0.167)
Age(kid)	−0.751***	−0.791***	−0.751***	−0.789***
	(0.215)	(0.207)	(0.215)	(0.208)
Age(teen)	−0.068	−0.216	−0.067	−0.215
	(0.231)	(0.222)	(0.232)	(0.223)
Country(UK)	−0.545*	−0.154	−0.532*	−0.140
	(0.258)	(0.258)	(0.258)	(0.258)
Treatment(ICS only)	0.221	0.235	0.217	0.227
	(0.202)	(0.199)	(0.203)	(0.199)
Treatment(ICS+addon)	−0.353*	−0.344*	−0.352*	−0.345*
	(0.175)	(0.172)	(0.176)	(0.173)
Baseline severity(no. OC courses) (z)	0.032	0.132	0.036	0.136@
	(0.083)	(0.082)	(0.083)	(0.082)
Baseline severity(ICs daily dose M0) (z)	−0.573***	−0.483***	−0.581***	−0.490***
	(0.102)	(0.099)	(0.103)	(0.099)
Mean reliever use (z)		−1.206***		−1.206***
		(0.109)		(0.109)
Variation reliever use (z)		−0.691***		−0.686***
		(0.076)		(0.076)
Prior variation reliever use (z)		0.042		0.043
		(0.052)		(0.052)
Mean 1-month adherence (z)	0.260**	0.242**		
	(0.085)	(0.082)		
Variation 1-month adherence (z)	−0.079@	−0.018		
	(0.046)	(0.048)		
Prior variation 1-month adherence (z)	0.064	0.032		
	(0.048)	(0.050)		
Mean 1-week adherence (z)			0.234**	0.222**
			(0.086)	(0.083)
Variation 1-week adherence (z)			−0.116*	−0.077
			(0.046)	(0.048)
Prior variation 1-week adherence (z)			0.077	0.045
			(0.048)	(0.050)
VPC	0.4512	0.407	0.4521	0.4075
Observations	2,909	2,909	2,909	2,909
Log Likelihood	−1,745.038	−1,619.386	−1,743.707	−1,618.598
Akaike Inf. Crit.	3,518.076	3,272.773	3,515.414	3,271.195
Bayesian Inf. Crit.	3,601.734	3,374.357	3,599.072	3,372.780
Note:				@ p<.1; * p<.05; ** p<.01; *** p<.001

predictors	AC - 1m adh	AC - 1w adh
(Intercept)	0.95 [0.71 - 1.27]	0.94 [0.7 - 1.26]
daysown1stCATISc	1.35 [1.2 - 1.52]	1.36 [1.21 - 1.53]
patient_genderMale	1.22 [0.87 - 1.71]	1.22 [0.87 - 1.71]
patient_age3kid	0.47 [0.31 - 0.72]	0.47 [0.31 - 0.72]
patient_age3teen	0.93 [0.59 - 1.47]	0.94 [0.59 - 1.47]
patient_languageUK	0.58 [0.35 - 0.96]	0.59 [0.35 - 0.97]
treatmentBICsonly	1.25 [0.84 - 1.85]	1.24 [0.83 - 1.85]
treatmentBICsplus	0.7 [0.5 - 0.99]	0.7 [0.5 - 0.99]
av_sc_n_ocSc	1.03 [0.88 - 1.21]	1.04 [0.88 - 1.22]
av_sc_ic_daily_dose_M0Sc	0.56 [0.46 - 0.69]	0.56 [0.46 - 0.68]
adh1m.cntLDSc	1.07 [0.97 - 1.17]	
adh1m.meanSc	1.3 [1.1 - 1.53]	
adh1m.cntSc	0.92 [0.84 - 1.01]	
adh1w.cntLDSc		1.08 [0.98 - 1.19]
adh1w.meanSc		1.26 [1.07 - 1.49]
adh1w.cntSc		0.89 [0.81 - 0.98]

Table 6: ORs - Asthma control models adherence predictors

predictors	AC - 1m adh	AC - 1w adh
(Intercept)	0.78 [0.59 - 1.04]	0.78 [0.59 - 1.04]
daysown1stCATISc	1.31 [1.16 - 1.48]	1.31 [1.16 - 1.48]
patient_genderMale	1.23 [0.89 - 1.71]	1.24 [0.89 - 1.71]
patient_age3kid	0.45 [0.3 - 0.68]	0.45 [0.3 - 0.68]
patient_age3teen	0.81 [0.52 - 1.25]	0.81 [0.52 - 1.25]
patient_languageUK	0.86 [0.52 - 1.42]	0.87 [0.52 - 1.44]
treatmentBICsonly	1.26 [0.86 - 1.87]	1.26 [0.85 - 1.86]
treatmentBICsplus	0.71 [0.51 - 0.99]	0.71 [0.51 - 0.99]
av_sc_n_ocSc	1.14 [0.97 - 1.34]	1.15 [0.98 - 1.34]
av_sc_ic_daily_dose_M0Sc	0.62 [0.51 - 0.75]	0.61 [0.5 - 0.74]
SABAuse6.meanSc	0.3 [0.24 - 0.37]	0.3 [0.24 - 0.37]
SABAuse6.cntSc	0.5 [0.43 - 0.58]	0.5 [0.43 - 0.58]
SABAuse6.cntLDSc	1.04 [0.94 - 1.15]	1.04 [0.94 - 1.16]
adh1m.meanSc	1.27 [1.08 - 1.5]	
adh1m.cntSc	0.98 [0.89 - 1.08]	
adh1m.cntLDSc	1.03 [0.94 - 1.14]	
adh1w.meanSc		1.25 [1.06 - 1.47]
adh1w.cntSc		0.93 [0.84 - 1.02]
adh1w.cntLDSc		1.05 [0.95 - 1.15]

Table 7: ORs - Asthma control models adherence and reliever use predictors

predictors	AC - 1m adh	AC - 1w adh
(Intercept)	0.78 [0.59 - 1.04]	0.78 [0.59 - 1.04]
daysown1stCATISc	1.31 [1.16 - 1.48]	1.31 [1.16 - 1.48]
patient_genderMale	1.23 [0.89 - 1.71]	1.24 [0.89 - 1.71]
patient_age3kid	0.45 [0.3 - 0.68]	0.45 [0.3 - 0.68]
patient_age3teen	0.81 [0.52 - 1.25]	0.81 [0.52 - 1.25]
patient_languageUK	0.86 [0.52 - 1.42]	0.87 [0.52 - 1.44]
treatmentBICsonly	1.26 [0.86 - 1.87]	1.26 [0.85 - 1.86]
treatmentBICsplus	0.71 [0.51 - 0.99]	0.71 [0.51 - 0.99]
av_sc_n_ocSc	1.14 [0.97 - 1.34]	1.15 [0.98 - 1.34]
av_sc_ic_daily_dose_M0Sc	0.62 [0.51 - 0.75]	0.61 [0.5 - 0.74]
SABAuse6.meanSc	0.3 [0.24 - 0.37]	0.3 [0.24 - 0.37]
SABAuse6.cntSc	0.5 [0.43 - 0.58]	0.5 [0.43 - 0.58]
SABAuse6.cntLDSc	1.04 [0.94 - 1.15]	1.04 [0.94 - 1.16]
adh1m.meanSc	1.27 [1.08 - 1.5]	
adh1m.cntSc	0.98 [0.89 - 1.08]	
adh1m.cntLDSc	1.03 [0.94 - 1.14]	
adh1w.meanSc		1.25 [1.06 - 1.47]
adh1w.cntSc		0.93 [0.84 - 1.02]
adh1w.cntLDSc		1.05 [0.95 - 1.15]

Table 8: ORs - Asthma control models drug holidays and 1-week adherence

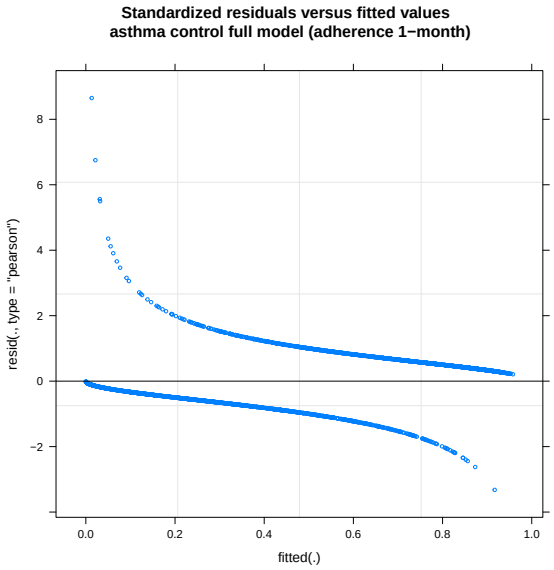


Figure 4: Residuals plot asthma control model (1-month adherence predictors)

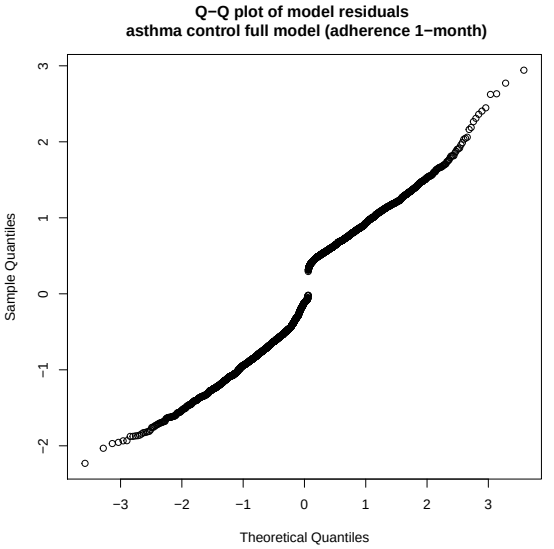


Figure 5: QQplot residuals asthma control model (1-month adherence predictors)

2.2 AE occurrence

predictors	AE - 1m adh	AE - 1w adh
(Intercept)	0.14 [0.11 - 0.18]	0.14 [0.11 - 0.19]
daysown1stCATISc	0.57 [0.49 - 0.65]	0.57 [0.49 - 0.65]
patient_genderMale	0.7 [0.53 - 0.92]	0.7 [0.53 - 0.92]
patient_age3kid	1.67 [1.21 - 2.3]	1.67 [1.21 - 2.3]
patient_age3teen	0.94 [0.64 - 1.37]	0.94 [0.64 - 1.37]
patient_languageUK	0.75 [0.48 - 1.17]	0.75 [0.47 - 1.17]
treatmentBICsonly	0.84 [0.59 - 1.21]	0.84 [0.59 - 1.21]
treatmentBICsplus	1.6 [1.21 - 2.11]	1.6 [1.21 - 2.11]
av_sc_n_ocSc	1.32 [1.18 - 1.48]	1.32 [1.18 - 1.48]
av_sc_ic_daily_dose_M0Sc	1.22 [1.09 - 1.37]	1.22 [1.09 - 1.37]
adh1m.cntLDSc	0.96 [0.86 - 1.07]	
adh1m.meanSc	0.99 [0.86 - 1.12]	
adh1m.cntSc	1.07 [0.96 - 1.19]	
adh1w.cntLDSc		0.98 [0.88 - 1.1]
adh1w.meanSc		0.99 [0.86 - 1.13]
adh1w.cntSc		1.06 [0.95 - 1.18]

Table 9: ORs - Exacerbations with adherence predictors

predictors	AE - 1m adh	AE - 1w adh
(Intercept)	0.14 [0.11 - 0.19]	0.14 [0.11 - 0.19]
daysown1stCATISc	0.57 [0.49 - 0.65]	0.56 [0.49 - 0.65]
patient_genderMale	0.7 [0.54 - 0.92]	0.7 [0.53 - 0.92]
patient_age3kid	1.66 [1.2 - 2.28]	1.64 [1.19 - 2.27]
patient_age3teen	0.93 [0.63 - 1.36]	0.94 [0.64 - 1.37]
patient_languageUK	0.75 [0.48 - 1.19]	0.75 [0.48 - 1.18]
treatmentBICsonly	0.83 [0.58 - 1.19]	0.84 [0.59 - 1.21]
treatmentBICsplus	1.6 [1.22 - 2.11]	1.59 [1.21 - 2.1]
av_sc_n_ocSc	1.32 [1.19 - 1.48]	1.33 [1.19 - 1.48]
av_sc_ic_daily_dose_M0Sc	1.22 [1.09 - 1.37]	1.22 [1.09 - 1.37]
drghols.meanSc	0.95 [0.83 - 1.08]	0.91 [0.75 - 1.11]
drghols.cntSc	1.01 [0.9 - 1.14]	0.99 [0.87 - 1.12]
drghols.cntLDSc	0.93 [0.84 - 1.04]	0.93 [0.83 - 1.05]
adh1w.cntLDSc		1.01 [0.9 - 1.13]
adh1w.meanSc		1.06 [0.86 - 1.3]
adh1w.cntSc		1.07 [0.95 - 1.2]

Table 10: ORs - Exacerbations with adherence predictors - drug holidays and 1-week adherence

Models of severe asthma exacerbations suggested the following results:

- Model 1: the variance in AE occurrence was present at 2 levels (within- and between-patients) but not between practices.
- Model 2: there was no significant time trend in AE occurrence overall, and no variation between patients was found in AE occurrence changes over time.
- Model 3: no differences in AE occurrence were found depending on country; males were less likely to report AE, and parents were more likely to report AEs than adults and teens. Patients with add-on medications were more likely to report AE. Two of 3 baseline severity markers, recommended daily dose of ICS at baseline (first CATI) and number of OCs canisters in baseline year, were significantly associated with AE occurrence
- Model 4: adherence levels did not influence AE occurrence;
- Model 5: Patients with higher average reliever use were more likely to report AE

Table 11: Results basic models SAE occurrence

	Dependent variable:			
	SAE occurrence			
	Un.Means	Un.Growth	No Growth	Socio-dem.
Intercept	-2.477^{***}	-2.474^{***}	-2.468^{***}	-2.396^{***}
	(0.100)	(0.101)	(0.100)	(0.135)
Days since 1st CATI (z)		−0.058		0.017
		(0.087)		(0.056)
Gender(male)				-0.338^{*}
				(0.136)
Age(kid)				0.492^{**}
				(0.162)
Age(teen)				−0.113
				(0.191)
Country(UK)				−0.295
				(0.222)
Treatment(ICS only)				−0.175
				(0.180)
Treatment(ICS+addon)				0.434^{**}
				(0.138)
Baseline severity(no. OC courses) (z)				0.281^{***}
				(0.055)
Baseline severity(ICs daily dose M0) (z)				0.208^{***}
				(0.059)
VPC	0.2138	0.2127	0.2114	0.1461
Observations	3,756	3,756	3,756	3,756
Log Likelihood	−1,312.889	−1,311.747	−1,311.973	−1,272.719
Akaike Inf. Crit.	2,629.778	2,633.494	2,631.946	2,567.439
Bayesian Inf. Crit.	2,642.240	2,664.650	2,656.871	2,635.981
Note:				@ p<.1; * p<.05; ** p<.01; *** p<.001

Table 12: Results selected SAE occurrence models - composite adherence scores

	Dependent variable:			
	SAE occurrence			
	1-month	1-month (rel use)	1-week	1-week (rel use)
Intercept	-1.953^{***}	-1.898^{***}	-1.950^{***}	-1.896^{***}
	(0.135)	(0.131)	(0.134)	(0.130)
Days since 1st CATI (z)	-0.568^{***}	-0.550^{***}	-0.569^{***}	-0.551^{***}
	(0.073)	(0.074)	(0.073)	(0.074)
Gender(male)	-0.358^{**}	-0.364^{**}	-0.358^{**}	-0.363^{**}
	(0.138)	(0.133)	(0.138)	(0.133)
Age(kid)	0.512^{**}	0.519^{**}	0.512^{**}	0.520^{**}
	(0.164)	(0.158)	(0.164)	(0.158)
Age(teen)	-0.067	-0.014	-0.067	-0.016
	(0.195)	(0.190)	(0.195)	(0.190)
Country(UK)	-0.292	-0.574^{*}	-0.294	-0.573^{*}
	(0.231)	(0.236)	(0.231)	(0.236)
Treatment(ICS only)	-0.173	-0.159	-0.171	-0.160
	(0.184)	(0.179)	(0.184)	(0.180)
Treatment(ICS+addon)	0.470^{***}	0.434^{**}	0.469^{***}	0.434^{**}
	(0.141)	(0.137)	(0.141)	(0.137)
Baseline severity(no. OC courses) (z)	0.280^{***}	0.238^{***}	0.279^{***}	0.238^{***}
	(0.057)	(0.054)	(0.056)	(0.054)
Baseline severity(ICs daily dose M0) (z)	0.201^{***}	0.157^{**}	0.201^{***}	0.157^{**}
	(0.060)	(0.058)	(0.060)	(0.058)
Mean reliever use (z)		0.376^{***}		0.377^{***}
		(0.057)		(0.057)
Variation reliever use (z)		0.076		0.078
		(0.049)		(0.049)
Prior variation reliever use (z)		0.003		0.0001
		(0.050)		(0.049)
Mean 1-month adherence (z)	-0.015	-0.011		
	(0.067)	(0.066)		
Variation 1-month adherence (z)	0.066	0.051		
	(0.055)	(0.055)		
Prior variation 1-month adherence (z)	-0.039	-0.027		
	(0.056)	(0.056)		
Mean 1-week adherence (z)			-0.013	-0.014
			(0.068)	(0.066)
Variation 1-week adherence (z)			0.059	0.043
			(0.055)	(0.055)
Prior variation 1-week adherence (z)			-0.019	-0.009
			(0.056)	(0.056)
VPC	0.1254	0.0897	0.1247	0.0891
Observations	2,909	2,909	2,909	2,909
Log Likelihood	$-1,126.566$	$-1,104.467$	$-1,126.929$	$-1,104.696$
Akaike Inf. Crit.	2,281.131	2,242.935	2,281.859	2,243.392
Bayesian Inf. Crit.	2,364.789	2,344.519	2,365.517	2,344.977
Note:				@ p<.1; * p<.05; ** p<.01; *** p<.001

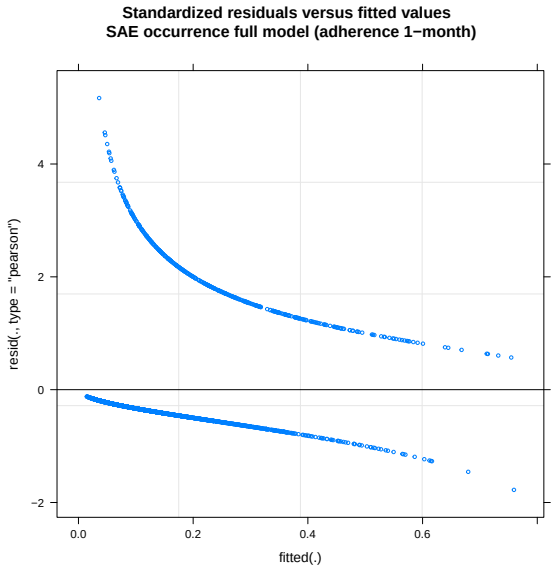


Figure 6: Residuals plot AE occurrence model (1-month adherence predictors)

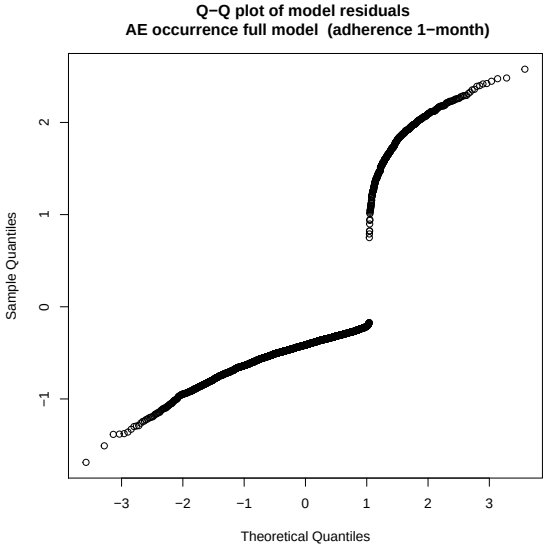


Figure 7: QQplot residuals AE occurrence model (1-month adherence predictors)

2.3 Reliever use

Table 13: Results basic models reliever use

	Dependent variable:			
	Reliever 4-week mean daily dose			
	Un.Means	Un.Growth	No Growth	Socio-dem.
Intercept	0.911^{***}	0.879^{***}	0.820^{***}	0.861^{***}
	(0.044)	(0.043)	(0.042)	(0.075)
Days since 1st CATI (z)		-0.170^{***}		-0.158^{***}
		(0.022)		(0.022)
Gender(male)				0.032
				(0.087)
Age(kid)				−0.146
				(0.108)
Age(teen)				-0.252^{*}
				(0.114)
Country(UK)				0.422^{***}
				(0.123)
Treatment(ICS only)				0.054
				(0.096)
Treatment(ICS+addon)				0.057
				(0.082)
Baseline severity(no. OC courses) (z)				0.156^{***}
				(0.043)
Baseline severity(ICs daily dose M0) (z)				0.134^{**}
				(0.045)
Variance components				
Level 1 residual	1.4159	1.3096	1.3144	1.306
Level 2 intercept	1.1255	1.1179	1.1195	1.0551
Level 2 slope		0.0397	0.064	0.0368
Level 2 slope-int corr		-0.88	-0.747	-0.833
Level 2 ICC	0.4428	0.4605	0.46	0.4469
Observations	3,756	3,756	3,756	3,756
Log Likelihood	−6,470.811	−6,412.906	−6,441.737	−6,393.333
Akaike Inf. Crit.	12,949.620	12,839.810	12,895.470	12,816.670
Bayesian Inf. Crit.	12,974.550	12,883.430	12,932.860	12,910.130
Note:				@ p<.1; * p<.05; ** p<.01; *** p<.001

Models of 4-week mean daily reliever use suggested the following:

- Model 1: the variance in reliever use was present within- and between-patients, but not between practices
- Model 2: there was a small but significant decrease in reliever use overall, and variation between patients was found in reliever use slopes over time
- Model 3: there were no significant differences in reliever use based on gender; reliever use was significantly higher in the UK than in France; teens reported less reliever use than adults; higher baseline severity (number of OC canisters in baseline period and recommended ICS daily dose at baseline) was associated with higher reliever use; there were no differences in reliever use depending on type of ICS inhalers
- Model 4: Average adherence levels were not related to reliever use levels; when patients increased their ICs adherence they reported higher reliever use levels.

Table 14: Results selected reliever use models - composite adherence scores

	Dependent variable:			
	Reliever 4-week mean daily dose			
	1-month (sim)	1-month (before)	1-week (sim)	1-week (before)
Intercept	0.866***	0.814***	0.866***	0.819***
	(0.075)	(0.079)	(0.076)	(0.079)
Days since 1st CATI (z)	−0.156***	−0.105***	−0.156***	−0.109***
	(0.022)	(0.027)	(0.022)	(0.027)
Gender(male)	0.023	−0.016	0.025	−0.017
	(0.087)	(0.091)	(0.087)	(0.091)
Age(kid)	−0.150	−0.074	−0.151	−0.074
	(0.108)	(0.112)	(0.108)	(0.112)
Age(teen)	−0.239*	−0.179	−0.240*	−0.180
	(0.114)	(0.120)	(0.115)	(0.120)
Country(UK)	0.408**	0.445**	0.411***	0.441**
	(0.124)	(0.136)	(0.124)	(0.136)
Treatment(ICS only)	0.071	0.026	0.066	0.021
	(0.096)	(0.102)	(0.096)	(0.102)
Treatment(ICS+addon)	0.050	0.039	0.050	0.038
	(0.082)	(0.086)	(0.082)	(0.086)
Baseline severity(no. OC courses) (z)	0.155***	0.119**	0.155***	0.117**
	(0.044)	(0.045)	(0.043)	(0.045)
Baseline severity(ICs daily dose M0) (z)	0.135**	0.108*	0.134**	0.109*
	(0.045)	(0.046)	(0.045)	(0.046)
Mean 1-month adherence (z)	0.025	−0.012		
	(0.041)	(0.044)		
Variation 1-month adherence (z)	0.092***	0.116***		
	(0.018)	(0.020)		
Prior variation 1-month adherence (z)		−0.035@		
		(0.021)		
Mean 1-week adherence (z)			0.024	−0.0004
			(0.041)	(0.045)
Variation 1-week adherence (z)			0.079***	0.092***
			(0.018)	(0.020)
Prior variation 1-week adherence (z)				−0.047*
				(0.021)
Variance components				
Level 1 residual	1.2972	1.1382	1.2997	1.1467
Level 2 intercept	1.0544	1.05	1.0548	1.0439
Level 2 slope	0.0403	0.0396	0.039	0.0372
Level 2 slope-int corr	-0.824	-0.73	-0.829	-0.73
Level 2 ICC	0.4484	0.4799	0.448	0.4765
Observations	3,756	2,909	3,756	2,909
Log Likelihood	−6,380.531	−4,788.158	−6,383.900	−4,793.214
Akaike Inf. Crit.	12,795.060	9,612.317	12,801.800	9,622.429
Bayesian Inf. Crit.	12,900.990	9,719.877	12,907.730	9,729.989

Note: @ p<.1; * p<.05; ** p<.01; *** p<.001

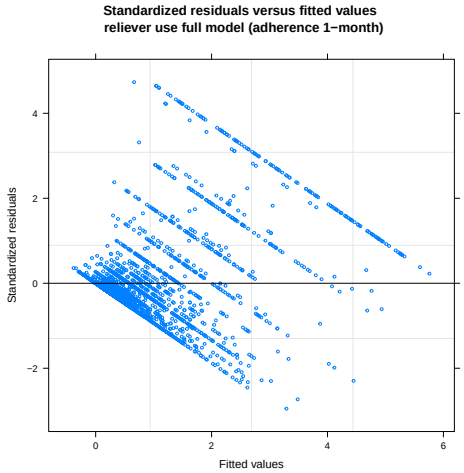


Figure 8: Residuals plot reliever model (1-month adherence predictors)

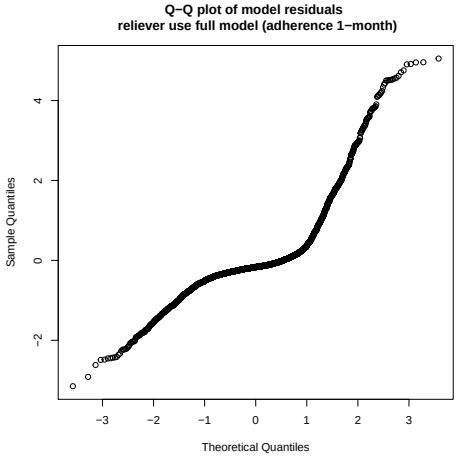


Figure 9: QQplot residuals reliever model (1-month adherence predictors)

3 Moderation analyses

3.1 Medication type

These models examine the possible interactions between ICS adherence and medication type. The comparison group is fixed-dose combinations, with which we compare ICS-only inhalers and ICS plus additional medication. The relationship between average adherence levels and exacerbations is weaker in the ICS-only group and (less so) in ICS-addon group. For reliever use, the effect of current variation in adherence is stronger in the ICS-addon group.

3.2 Asthma severity

These models examine the possible interactions between ICS adherence and asthma severity measured as ICS daily dose reported by the patient in the first CATI. No consistent interaction effect was found for any of the three outcomes. Excluding this marker of asthma severity from the models alltogether does not influence results.

3.3 Age

These models examine the possible interactions between ICS adherence and age. The comparison group is adults, with which we compare children and teenagers. The relationship between average adherence levels and asthma control is weaker in both kids and teens. No effects on exacerbations and reliever use is noted.

3.3.1 Age - separated models for adults and teenagers/children

These models examine the same hypotheses separately for adults and young people. Children and teenagers were considered the same group for sample size reasons, and because a moderation effect between average adherence levels and asthma control was noted above in both kids and teens. Indeed, the effect of average adherence levels on asthma control is non-significant in young people, which may be due to lower power and less precision in measuring adherence in these participants. Although these results need to be treated with caution due to low sample sizes, they suggest it might be useful for future studies to focus on comparing the longitudinal dynamics of medication use and asthma outcomes between specific age groups.

Table 15: Results selected models asthma control and asthma exacerbations - medication moderation

	Dependent variable:			
	Asthma control		AE occurrence	
	AC 1-month adh	AC 1-week adh	AE 1-month adh	AE 1-week adh
Intercept	−0.049	−0.060	−1.962***	−1.956***
	(0.149)	(0.150)	(0.135)	(0.134)
Days since 1st CATI (z)	0.301***	0.308***	−0.575***	−0.574***
	(0.059)	(0.059)	(0.073)	(0.073)
Gender(male)	0.200	0.199	−0.353*	−0.346*
	(0.173)	(0.174)	(0.138)	(0.138)
Age(kid)	−0.764***	−0.759***	0.499**	0.494**
	(0.215)	(0.216)	(0.164)	(0.164)
Age(teen)	−0.069	−0.063	−0.061	−0.067
	(0.231)	(0.232)	(0.195)	(0.195)
Country(UK)	−0.531*	−0.522*	−0.275	−0.278
	(0.258)	(0.259)	(0.231)	(0.231)
Treatment(ICS only)	0.217	0.220	−0.234	−0.223
	(0.204)	(0.205)	(0.191)	(0.190)
Treatment(ICS+addon)	−0.320@	−0.307@	0.494***	0.495***
	(0.178)	(0.178)	(0.142)	(0.141)
Baseline severity(no. OC courses) (z)	0.031	0.032	0.286***	0.282***
	(0.083)	(0.083)	(0.056)	(0.056)
Baseline severity(ICs daily dose M0) (z)	−0.574***	−0.581***	0.213***	0.212***
	(0.103)	(0.103)	(0.060)	(0.059)
Mean 1-month adherence (z)	0.341**		0.177@	
	(0.114)		(0.098)	
Variation 1-month adherence (z)	−0.099		0.113	
	(0.065)		(0.081)	
Prior variation 1-month adherence (z)	−0.017		−0.095	
	(0.067)		(0.082)	
Mean 1-mo adherence * ICSonly group	−0.074		−0.466**	
	(0.184)		(0.170)	
Mean 1-mo adherence * ICSaddon group	−0.244		−0.288@	
	(0.185)		(0.149)	
Variation 1-mo adherence * ICSonly group	−0.017		0.026	
	(0.117)		(0.152)	
Variation 1-mo adherence * ICSaddon group	0.097		−0.161	
	(0.113)		(0.125)	
Prior variation 1-mo adherence * ICSonly group	0.164		−0.005	
	(0.118)		(0.152)	
Prior variation 1-mo adherence * ICSaddon group	0.147		0.185	
	(0.118)		(0.128)	
Mean 1-week adherence (z)		0.320**		0.181@
		(0.116)		(0.100)
Variation 1-week adherence (z)		−0.185**		0.109
		(0.065)		(0.080)
Prior variation 1-week adherence (z)		0.030		−0.030
		(0.067)		(0.081)
Mean 1-we adherence * ICSonly group		−0.082		−0.418*
		(0.185)		(0.169)
Mean 1-we adherence * ICSaddon group		−0.256		−0.310*
		(0.188)		(0.151)
Variation 1-we adherence * ICSonly group		0.122		−0.045
		(0.118)		(0.150)
Variation 1-we adherence * ICSaddon group		0.173		−0.133
		(0.114)		(0.126)
Prior variation 1-we adherence * ICSonly group		0.206@		−0.120
		(0.122)		(0.155)
Prior variation 1-we adherence * ICSaddon group		−0.006		0.093
		(0.117)		(0.127)
VPC	0.4514	0.4537	0.121	0.1189
Observations	2,909	2,909	2,909	2,909
Log Likelihood	−1,742.314	−1,739.970	−1,119.986	−1,121.630
Akaike Inf. Crit.	3,524.629	3,519.939	2,279.972	2,283.259
Bayesian Inf. Crit.	3,644.140	3,639.450	2,399.484	2,402.771
Note:				@ p<.1; * p<.05; ** p<.01; *** p<.001

Table 16: Results selected reliever use models - medication moderation

	Dependent variable:	
	Reliever 4-week mean daily dose	
	1-month	1-week
Intercept	0.819^{***}	0.823^{***}
	(0.079)	(0.079)
Days since 1st CATI (z)	-0.106^{***}	-0.109^{***}
	(0.027)	(0.027)
Gender(male)	−0.020	−0.022
	(0.091)	(0.091)
Age(kid)	−0.081	−0.077
	(0.112)	(0.113)
Age(teen)	−0.180	−0.184
	(0.120)	(0.121)
Country(UK)	0.445^{**}	0.443^{**}
	(0.136)	(0.136)
Treatment(ICS only)	0.047	0.038
	(0.103)	(0.103)
Treatment(ICS+addon)	0.057	0.055
	(0.087)	(0.087)
Baseline severity(no. OC courses) (z)	0.117^{**}	0.115^{*}
	(0.045)	(0.045)
Baseline severity(ICs daily dose M0) (z)	0.104^{*}	0.107^{*}
	(0.046)	(0.046)
Mean 1-month adherence (z)	−0.032	
	(0.058)	
Variation 1-month adherence (z)	0.071^{**}	
	(0.027)	
Prior variation 1-month adherence (z)	-0.072^{*}	
	(0.029)	
Mean 1-mo adherence * ICSonly group	$0.163^{@}$	
	(0.094)	
Mean 1-mo adherence * ICSaddon group	−0.082	
	(0.090)	
Variation 1-mo adherence * ICSonly group	0.054	
	(0.050)	
Variation 1-mo adherence * ICSaddon group	0.124^{**}	
	(0.048)	
Prior variation 1-mo adherence * ICSonly group	0.058	
	(0.051)	
Prior variation 1-mo adherence * ICSaddon group	0.081	
	(0.051)	
Mean 1-week adherence (z)		−0.019
		(0.059)
Variation 1-week adherence (z)		0.056^{*}
		(0.027)
Prior variation 1-week adherence (z)		-0.075^{**}
		(0.029)
Mean 1-we adherence * ICSonly group		0.137
		(0.094)
Mean 1-we adherence * ICSaddon group		−0.069
		(0.091)
Variation 1-we adherence * ICSonly group		0.031
		(0.051)
Variation 1-we adherence * ICSaddon group		0.112^{*}
		(0.048)
Prior variation 1-we adherence * ICSonly group		0.030
		(0.053)
Prior variation 1-we adherence * ICSaddon group		0.082
		(0.050)
Variance components		
Level 1 residual	1.1283	1.1353
Level 2 intercept	1.0512	1.0452
Level 2 slope	0.0392	0.0393
Level 2 slope-int corr	-0.707	-0.681
Level 2 ICC	0.4823	0.4793
Observations	2,909	2,909
Log Likelihood	−4,781.229	−4,787.948
Akaike Inf. Crit.	9,610.459	9,623.896
Bayesian Inf. Crit.	9,753.872	9,767.309
Note:	@ p<.1; * p<.05; ** p<.01; *** p<.001	

Table 17: Results selected models asthma control and asthma exacerbations - severity moderation

	Dependent variable:			
	Asthma control		AE occurrence	
	AC 1-month adh	AC 1-week adh	AE 1-month adh	AE 1-week adh
Intercept	−0.055	−0.059	−1.954***	−1.954***
	(0.149)	(0.150)	(0.135)	(0.135)
Days since 1st CATI (z)	0.302***	0.307***	−0.569***	−0.568***
	(0.059)	(0.059)	(0.073)	(0.073)
Gender(male)	0.199	0.201	−0.361**	−0.358**
	(0.173)	(0.173)	(0.138)	(0.139)
Age(kid)	−0.761***	−0.754***	0.535**	0.533**
	(0.216)	(0.216)	(0.166)	(0.166)
Age(teen)	−0.072	−0.071	−0.049	−0.054
	(0.231)	(0.232)	(0.195)	(0.196)
Country(UK)	−0.548*	−0.531*	−0.281	−0.283
	(0.258)	(0.259)	(0.231)	(0.231)
Treatment(ICS only)	0.221	0.205	−0.188	−0.194
	(0.203)	(0.204)	(0.185)	(0.186)
Treatment(ICS+addon)	−0.351*	−0.356*	0.459**	0.453**
	(0.175)	(0.176)	(0.142)	(0.142)
Baseline severity(no. OC courses) (z)	0.031	0.036	0.281***	0.280***
	(0.083)	(0.083)	(0.057)	(0.057)
Baseline severity(ICs daily dose M0) (z)	−0.589***	−0.598***	0.205***	0.191**
	(0.103)	(0.102)	(0.061)	(0.065)
Mean 1-month adherence (z)	0.257**		−0.019	
	(0.085)		(0.067)	
Variation 1-month adherence (z)	−0.083@		0.057	
	(0.046)		(0.056)	
Prior variation 1-month adherence (z)	0.062		−0.038	
	(0.048)		(0.057)	
Mean 1-mo adherence * ICs daily dose M0	−0.034		0.066	
	(0.100)		(0.066)	
Variation 1-mo adherence * ICs daily dose M0	0.076		0.045	
	(0.051)		(0.043)	
Prior variation 1-mo adherence * ICs daily dose M0	0.071		−0.017	
	(0.053)		(0.043)	
Mean 1-week adherence (z)		0.235**		−0.015
		(0.087)		(0.068)
Variation 1-week adherence (z)		−0.115*		0.049
		(0.047)		(0.055)
Prior variation 1-week adherence (z)		0.076		−0.014
		(0.048)		(0.057)
Mean 1-we adherence * ICs daily dose M0		0.004		0.079
		(0.104)		(0.069)
Variation 1-we adherence * ICs daily dose M0		0.133*		0.073
		(0.053)		(0.049)
Prior variation 1-we adherence * ICs daily dose M0		0.027		−0.038
		(0.053)		(0.047)
VPC	0.451	0.4534	0.1253	0.1261
Observations	2,909	2,909	2,909	2,909
Log Likelihood	−1,742.933	−1,740.455	−1,125.429	−1,124.632
Akaike Inf. Crit.	3,519.866	3,514.910	2,284.857	2,283.264
Bayesian Inf. Crit.	3,621.450	3,616.494	2,386.442	2,384.848
Note:				@ p<.1; * p<.05; ** p<.01; *** p<.001

Table 18: Results selected reliever use models - severity moderation

	Dependent variable:	
	Reliever 4-week mean daily dose	
	1-month	1-week
Intercept	0.816^{***}	0.818^{***}
	(0.079)	(0.079)
Days since 1st CATI (z)	-0.106^{***}	-0.109^{***}
	(0.027)	(0.027)
Gender(male)	−0.019	−0.018
	(0.091)	(0.091)
Age(kid)	−0.059	−0.058
	(0.113)	(0.112)
Age(teen)	−0.172	−0.172
	(0.120)	(0.120)
Country(UK)	0.454^{***}	0.449^{***}
	(0.136)	(0.135)
Treatment(ICS only)	0.018	0.012
	(0.102)	(0.103)
Treatment(ICS+addon)	0.035	0.033
	(0.086)	(0.086)
Baseline severity(no. OC courses) (z)	0.119^{**}	0.116^{**}
	(0.045)	(0.045)
Baseline severity(ICs daily dose M0) (z)	0.111^{*}	0.112^{*}
	(0.047)	(0.047)
Mean 1-month adherence (z)	−0.008	
	(0.045)	
Variation 1-month adherence (z)	0.117^{***}	
	(0.020)	
Prior variation 1-month adherence (z)	$-0.034^{@}$	
	(0.021)	
Mean 1-mo adherence * ICs daily dose M0	0.070	
	(0.050)	
Variation 1-mo adherence * ICs daily dose M0	−0.017	
	(0.018)	
Prior variation 1-mo adherence * ICs daily dose M0	−0.006	
	(0.019)	
Mean 1-week adherence (z)		0.005
		(0.045)
Variation 1-week adherence (z)		0.092^{***}
		(0.020)
Prior variation 1-week adherence (z)		-0.046^{*}
		(0.021)
Mean 1-we adherence * ICs daily dose M0		0.068
		(0.051)
Variation 1-we adherence * ICs daily dose M0		−0.0003
		(0.017)
Prior variation 1-we adherence * ICs daily dose M0		−0.018
		(0.020)
Variance components		
Level 1 residual	1.1394	1.1449
Level 2 intercept	1.0429	1.0337
Level 2 slope	0.0388	0.0398
Level 2 slope-int corr	-0.726	-0.694
Level 2 ICC	0.4779	0.4745
Observations	2,909	2,909
Log Likelihood	−4,786.681	−4,792.019
Akaike Inf. Crit.	9,615.362	9,626.038
Bayesian Inf. Crit.	9,740.849	9,751.524
Note:	@ p<.1; * p<.05; ** p<.01; *** p<.001	

Table 19: Results selected models asthma control and asthma exacerbations - age moderation

	Dependent variable:			
	Asthma control		AE occurrence	
	AC 1-month adh	AC 1-week adh	AE 1-month adh	AE 1-week adh
Intercept	−0.041	−0.051	−1.958***	−1.954***
	(0.149)	(0.149)	(0.135)	(0.135)
Days since 1st CATI (z)	0.302***	0.305***	−0.566***	−0.566***
	(0.059)	(0.059)	(0.073)	(0.073)
Gender(male)	0.193	0.197	−0.353*	−0.350*
	(0.172)	(0.173)	(0.138)	(0.139)
Age(kid)	−0.713***	−0.713**	0.507**	0.514**
	(0.216)	(0.217)	(0.165)	(0.165)
Age(teen)	−0.161	−0.175	−0.037	−0.051
	(0.235)	(0.237)	(0.196)	(0.199)
Country(UK)	−0.522*	−0.507*	−0.294	−0.294
	(0.258)	(0.258)	(0.231)	(0.231)
Treatment(ICS only)	0.201	0.194	−0.170	−0.177
	(0.202)	(0.203)	(0.184)	(0.184)
Treatment(ICS+addon)	−0.366*	−0.365*	0.478***	0.474***
	(0.175)	(0.176)	(0.141)	(0.141)
Baseline severity(no. OC courses) (z)	0.042	0.042	0.277***	0.277***
	(0.083)	(0.083)	(0.056)	(0.056)
Baseline severity(ICs daily dose M0) (z)	−0.594***	−0.603***	0.206***	0.209***
	(0.103)	(0.103)	(0.060)	(0.060)
Mean 1-month adherence (z)	0.463***		−0.083	
	(0.112)		(0.087)	
Variation 1-month adherence (z)	−0.071		0.079	
	(0.066)		(0.078)	
Prior variation 1-month adherence (z)	0.114@		−0.030	
	(0.068)		(0.079)	
Mean 1-mo adherence * kids	−0.458*		0.123	
	(0.210)		(0.160)	
Mean 1-mo adherence * teens	−0.501*		0.229	
	(0.212)		(0.184)	
Variation 1-mo adherence * kids	−0.026		−0.064	
	(0.104)		(0.121)	
Variation 1-mo adherence * teens	0.011		0.071	
	(0.129)		(0.168)	
Prior variation 1-mo adherence * kids	−0.097		−0.033	
	(0.107)		(0.123)	
Prior variation 1-mo adherence * teens	−0.103		0.022	
	(0.133)		(0.169)	
Mean 1-week adherence (z)		0.438***		−0.083
		(0.113)		(0.088)
Variation 1-week adherence (z)		−0.095		0.055
		(0.064)		(0.076)
Prior variation 1-week adherence (z)		0.129@		−0.016
		(0.067)		(0.078)
Mean 1-we adherence * kids		−0.435*		0.090
		(0.213)		(0.162)
Mean 1-we adherence * teens		−0.517*		0.278
		(0.213)		(0.185)
Variation 1-we adherence * kids		−0.049		−0.092
		(0.104)		(0.119)
Variation 1-we adherence * teens		−0.006		0.309@
		(0.135)		(0.176)
Prior variation 1-we adherence * kids		−0.083		0.022
		(0.107)		(0.123)
Prior variation 1-we adherence * teens		−0.148		−0.100
		(0.137)		(0.179)
VPC	0.4495	0.451	0.1233	0.1232
Observations	2,909	2,909	2,909	2,909
Log Likelihood	−1,740.430	−1,738.949	−1,125.315	−1,123.131
Akaike Inf. Crit.	3,520.859	3,517.897	2,290.630	2,286.262
Bayesian Inf. Crit.	3,640.370	3,637.409	2,410.141	2,405.773
Note:				@ p<.1; * p<.05; ** p<.01; *** p<.001

Table 20: Results selected reliever use models - age moderation

	Dependent variable:	
	Reliever 4-week mean daily dose	
	1-month	1-week
Intercept	0.813^{***}	0.818^{***}
	(0.079)	(0.079)
Days since 1st CATI (z)	-0.106^{***}	-0.110^{***}
	(0.027)	(0.027)
Gender(male)	−0.015	−0.017
	(0.091)	(0.091)
Age(kid)	−0.078	−0.083
	(0.113)	(0.114)
Age(teen)	−0.174	−0.170
	(0.122)	(0.123)
Country(UK)	0.441^{**}	0.435^{**}
	(0.136)	(0.136)
Treatment(ICS only)	0.028	0.026
	(0.102)	(0.103)
Treatment(ICS+addon)	0.041	0.041
	(0.086)	(0.086)
Baseline severity(no. OC courses) (z)	0.117^{**}	0.116^{*}
	(0.045)	(0.045)
Baseline severity(ICs daily dose M0) (z)	0.109^{*}	0.111^{*}
	(0.046)	(0.046)
Mean 1-month adherence (z)	−0.032	
	(0.058)	
Variation 1-month adherence (z)	0.132^{***}	
	(0.028)	
Prior variation 1-month adherence (z)	−0.034	
	(0.029)	
Mean 1-mo adherence * kids	0.043	
	(0.112)	
Mean 1-mo adherence * teens	0.053	
	(0.111)	
Variation 1-mo adherence * kids	−0.017	
	(0.045)	
Variation 1-mo adherence * teens	−0.060	
	(0.055)	
Prior variation 1-mo adherence * kids	0.006	
	(0.046)	
Prior variation 1-mo adherence * teensp	−0.013	
	(0.057)	
Mean 1-week adherence (z)		−0.033
		(0.059)
Variation 1-week adherence (z)		0.105^{***}
		(0.027)
Prior variation 1-week adherence (z)		−0.045
		(0.028)
Mean 1-we adherence * kids		0.081
		(0.114)
Mean 1-we adherence * teens		0.076
		(0.111)
Variation 1-we adherence * kids		−0.016
		(0.045)
Variation 1-we adherence * teens		−0.053
		(0.056)
Prior variation 1-we adherence * kids		0.002
		(0.047)
Prior variation 1-we adherence * teens		−0.013
		(0.059)
Variance components		
Level 1 residual	1.1387	1.1462
Level 2 intercept	1.049	1.0433
Level 2 slope	0.0392	0.0364
Level 2 slope-int corr	-0.731	-0.732
Level 2 ICC	0.4795	0.4765
Observations	2,909	2,909
Log Likelihood	−4,787.377	−4,792.363
Akaike Inf. Crit.	9,622.753	9,632.726
Bayesian Inf. Crit.	9,766.167	9,776.139
Note:	@ p<.1; * p<.05; ** p<.01; *** p<.001	

Table 21: Results selected models asthma control and asthma exacerbations - adults

	Dependent variable:			
	Asthma control		AE occurrence	
	AC 1-month adh	AC 1-week adh	AE 1-month adh	AE 1-week adh
Intercept	−0.252	−0.261	−1.844***	−1.840***
	(0.165)	(0.165)	(0.154)	(0.153)
Days since 1st CATI (z)	0.200*	0.205*	−0.617***	−0.619***
	(0.080)	(0.080)	(0.100)	(0.100)
Gender(male)	0.456*	0.460*	−0.690***	−0.690***
	(0.211)	(0.211)	(0.183)	(0.183)
Country(UK)	0.332	0.348	−0.606*	−0.608*
	(0.341)	(0.340)	(0.307)	(0.307)
Treatment(ICS only)	−0.045	−0.053	0.423@	0.421@
	(0.278)	(0.279)	(0.241)	(0.241)
Treatment(ICS+addon)	−0.553*	−0.547*	0.428*	0.427*
	(0.222)	(0.222)	(0.181)	(0.181)
Baseline severity(no. OC courses) (z)	0.133	0.131	0.227**	0.227**
	(0.108)	(0.108)	(0.071)	(0.071)
Baseline severity(ICs daily dose M0) (z)	−0.488***	−0.496***	0.214**	0.215**
	(0.112)	(0.112)	(0.069)	(0.069)
Mean reliever use (z)	−1.203***	−1.203***	0.278***	0.278***
	(0.134)	(0.134)	(0.075)	(0.074)
Variation reliever use (z)	−0.589***	−0.581***	0.132*	0.135*
	(0.097)	(0.097)	(0.067)	(0.067)
Prior variation reliever use (z)	0.064	0.066	−0.005	−0.006
	(0.072)	(0.072)	(0.069)	(0.069)
Mean 1-month adherence (z)	0.413***		−0.021	
	(0.107)		(0.084)	
Variation 1-month adherence (z)	−0.016		0.049	
	(0.068)		(0.078)	
Prior variation 1-month adherence (z)	0.079		−0.025	
	(0.070)		(0.079)	
Mean 1-week adherence (z)		0.386***		−0.022
		(0.108)		(0.085)
Variation 1-week adherence (z)		−0.058		0.027
		(0.066)		(0.077)
Prior variation 1-week adherence (z)		0.096		−0.014
		(0.069)		(0.078)
VPC	0.3806	0.3811	0.0725	0.0713
Observations	1,691	1,691	1,691	1,691
Log Likelihood	−928.394	−928.676	−624.968	−625.154
Akaike Inf. Crit.	1,886.788	1,887.352	1,279.935	1,280.308
Bayesian Inf. Crit.	1,968.284	1,968.848	1,361.431	1,361.804
Note:				@ p<.1; * p<.05; ** p<.01; *** p<.001

Table 22: Results selected reliever use models - adults

	Dependent variable:	
	Reliever 4-week mean daily dose	
	1-month	1-week
Intercept	0.715^{***}	0.720^{***}
	(0.094)	(0.094)
Days since 1st CATI (z)	-0.098^{**}	-0.100^{**}
	(0.036)	(0.036)
Gender(male)	0.150	0.151
	(0.121)	(0.121)
Country(UK)	0.502^{**}	0.500^{**}
	(0.188)	(0.188)
Treatment(ICS only)	−0.078	−0.086
	(0.153)	(0.153)
Treatment(ICS+addon)	0.156	0.151
	(0.117)	(0.117)
Baseline severity(no. OC courses) (z)	0.153^{*}	0.153^{*}
	(0.064)	(0.064)
Baseline severity(ICs daily dose M0) (z)	0.148^{*}	0.150^{*}
	(0.059)	(0.059)
Mean reliever use (z)	−0.053	
	(0.060)	
Variation reliever use (z)	0.131^{***}	
	(0.027)	
Prior variation reliever use (z)	−0.033	
	(0.029)	
Mean 1-month adherence (z)		−0.057
		(0.061)
Variation 1-month adherence (z)		0.105^{***}
		(0.027)
Prior variation 1-month adherence (z)		−0.044
		(0.028)
Variance components		
Level 1 residual	1.1046	1.1116
Level 2 intercept	1.1389	1.135
Level 2 slope	0.0502	0.0465
Level 2 slope-int corr	-0.68	-0.687
Level 2 ICC	0.5077	0.5052
Observations	1,691	1,691
Log Likelihood	−2,783.061	−2,785.915
Akaike Inf. Crit.	5,598.123	5,603.830
Bayesian Inf. Crit.	5,685.052	5,690.759
Note:	@ p<.1; * p<.05; ** p<.01; *** p<.001	

Table 23: Results selected models asthma control and asthma exacerbations - children and teenagers

	Dependent variable:			
	Asthma control		AE occurrence	
	AC 1-month adh	AC 1-week adh	AE 1-month adh	AE 1-week adh
Intercept	-0.586^{*}	-0.590^{*}	-1.923^{***}	-1.924^{***}
	(0.275)	(0.276)	(0.241)	(0.241)
Days since 1st CATI (z)	0.369^{***}	0.366^{***}	-0.499^{***}	-0.499^{***}
	(0.097)	(0.097)	(0.110)	(0.110)
Gender(male)	-0.224	-0.218	0.160	0.160
	(0.277)	(0.278)	(0.218)	(0.219)
Country(UK)	-0.583	-0.581	-0.738^{*}	-0.733^{*}
	(0.402)	(0.402)	(0.373)	(0.373)
Treatment(ICS only)	0.438	0.435	-0.612^{*}	-0.611^{*}
	(0.289)	(0.289)	(0.265)	(0.265)
Treatment(ICS+addon)	-0.064	-0.066	0.479^{*}	0.479^{*}
	(0.276)	(0.277)	(0.213)	(0.213)
Baseline severity(no. OC courses) (z)	0.157	0.155	0.223^{**}	0.226^{**}
	(0.125)	(0.125)	(0.084)	(0.084)
Baseline severity(ICs daily dose M0) (z)	$-0.326^{@}$	$-0.330^{@}$	0.006	0.001
	(0.188)	(0.187)	(0.123)	(0.123)
Mean reliever use (z)	-1.240^{***}	-1.236^{***}	0.557^{***}	0.557^{***}
	(0.186)	(0.186)	(0.092)	(0.092)
Variation reliever use (z)	-0.820^{***}	-0.817^{***}	0.018	0.019
	(0.122)	(0.122)	(0.075)	(0.075)
Prior variation reliever use (z)	0.015	0.011	0.015	0.014
	(0.076)	(0.076)	(0.072)	(0.072)
Mean 1-month adherence (z)	-0.025		0.067	
	(0.128)		(0.103)	
Variation 1-month adherence (z)	-0.016		0.042	
	(0.069)		(0.080)	
Prior variation 1-month adherence (z)	-0.018		-0.029	
	(0.071)		(0.081)	
Mean 1-week adherence (z)		-0.029		0.054
		(0.127)		(0.103)
Variation 1-week adherence (z)		-0.100		0.046
		(0.072)		(0.081)
Prior variation 1-week adherence (z)		-0.012		-0.010
		(0.073)		(0.082)
VPC	0.431	0.4324	0.0856	0.0858
Observations	1,218	1,218	1,218	1,218
Log Likelihood	-680.448	-679.518	-467.719	-467.835
Akaike Inf. Crit.	1,390.897	1,389.036	965.438	965.670
Bayesian Inf. Crit.	1,467.471	1,465.610	1,042.012	1,042.244
Note:				@ p<.1; * p<.05; ** p<.01; *** p<.001

Table 24: Results selected reliever use models - children and teenagers

	Dependent variable:	
	Reliever 4-week mean daily dose	
	1-month	1-week
Intercept	0.847^{***}	0.858^{***}
	(0.135)	(0.135)
Days since 1st CATI (z)	-0.118^{**}	-0.125^{**}
	(0.042)	(0.042)
Gender(male)	−0.199	−0.206
	(0.140)	(0.140)
Country(UK)	$0.379^{@}$	$0.368^{@}$
	(0.195)	(0.194)
Treatment(ICS only)	0.068	0.067
	(0.137)	(0.137)
Treatment(ICS+addon)	−0.130	−0.128
	(0.127)	(0.127)
Baseline severity(no. OC courses) (z)	0.100	0.098
	(0.063)	(0.063)
Baseline severity(ICs daily dose M0) (z)	0.019	0.023
	(0.078)	(0.077)
Mean 1-month adherence (z)	0.039	
	(0.065)	
Variation 1-month adherence (z)	0.099^{***}	
	(0.028)	
Prior variation 1-month adherence (z)	−0.036	
	(0.030)	
Mean 1-week adherence (z)		0.072
		(0.065)
Variation 1-week adherence (z)		0.077^{**}
		(0.029)
Prior variation 1-week adherence (z)		−0.049
		(0.031)
Variance components		
Level 1 residual	1.1756	1.1871
Level 2 intercept	0.8934	0.8799
Level 2 slope	0.023	0.0195
Level 2 slope-int corr	-0.794	-0.795
Level 2 ICC	0.4318	0.4257
Observations	1,218	1,218
Log Likelihood	−1,998.281	−2,000.110
Akaike Inf. Crit.	4,028.562	4,032.219
Bayesian Inf. Crit.	4,110.242	4,113.898
Note:	@ p<.1; * p<.05; ** p<.01; *** p<.001	