



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

Alexandra L. Dima^{1,2}, Eric van Ganse^{1,3,4}, Gertraud Stadler^{5,6} and Marijn de Bruin^{5,7}, the ASTRO-LAB group⁸

Affiliations: ¹Health Services Performance Research EA 7425 HESPER, University Claude Bernard Lyon 1, Lyon, France. ²Dept of Communication Science, ASCoR, University of Amsterdam, Amsterdam, The Netherlands. ³Respiratory Medicine, Croix-Rousse University Hospital, Lyon, France. ⁴PELyon, Pharmacoepidemiology, Lyon, France. ⁵Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK. ⁶Dept of Psychology, Columbia University, New York, NY, USA. ⁷Radboud University Medical Center, Radboud Institute for Health Sciences, IQ Healthcare, The Netherlands. ⁸A list of members of the ASTRO-LAB group can be found in the acknowledgements section.

Correspondence: Alexandra L. Dima, Université Claude Bernard Lyon 1, 8 avenue Rockefeller, 69373 Lyon 8, France. E-mail: alexandra.dima@univ-lyon1.fr

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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. <http://bit.ly/2kK1bbv>

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

A prospective cohort of persistent asthma patients in France and the UK (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 relationships *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, 95% CI 0.87–1.12) or lower reliever use (b –0.0004, 95% CI –0.089–0.088). At within-person level, higher-than-usual adherence was associated with higher concomitant reliever use (b 0.092, 95% CI 0.053–0.131) and lower subsequent reliever use (b –0.047, 95% CI –0.005– –0.088); it was unrelated to asthma control (OR 0.93, 95% CI 0.84–1.02) or exacerbations (OR 1.04, 95% CI 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.

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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 in studies 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 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 end-points 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 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]. Therefore, we 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 (research question 1)? Second, were between-person differences in ICS adherence (and reliever use, if applicable) associated with the outcome (research question 2)? 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) (research question 3)?

Methods

Study design and participants

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

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 (aged 12–40 years) and parents of children (aged 6–11 years) reported on asthma control, adherence to controller medication, reliever use and exacerbation occurrence. Monthly text messages enquired 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 The Health Improvement Network data [16] in the UK were used to extract sociodemographic information (sex, 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 hospitalisations), 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 five-item Asthma Control Questionnaire symptoms-only (ACQ [17]) for adults and teenagers. ACQ-5 assesses presence and intensity of night symptoms, morning symptoms,

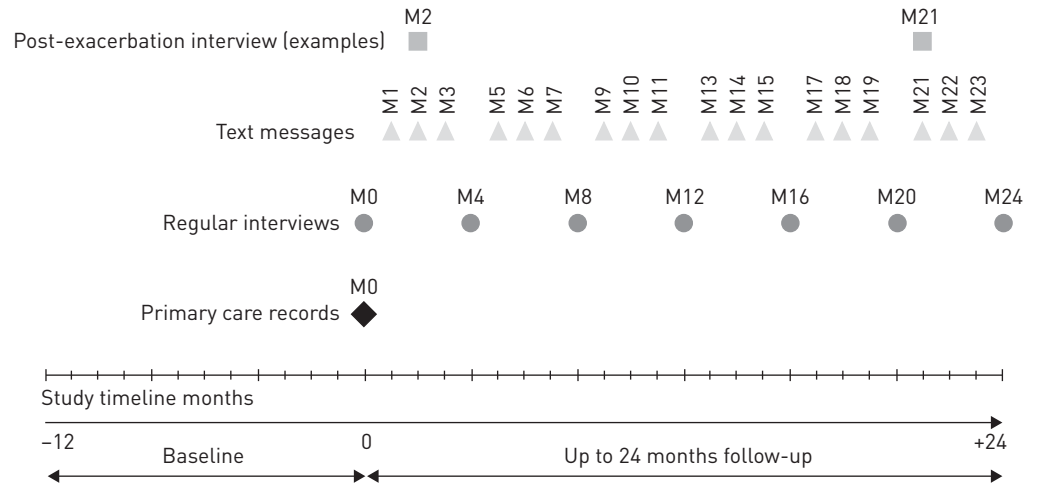


FIGURE 1 Example illustration of study timeline and data collection schedule: hypothetical example for a participant with seven regular computer-assisted telephone interviews and two interviews after asthma exacerbations were identified by text messages at month 2 [M2] and 21 [M21]. Primary care records were used at baseline to extract patient sociodemographic and medical history variables.

activity limitations, shortness of breath and wheezing 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 [19], which evaluates night symptoms, day symptoms (cough, wheeze, 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 β-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 material 1); values were winsorised (range 0–6) for model convergence.

ICS adherence

We developed and validated the Medication Intake Survey – Asthma, 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 six 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; and (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 more than one 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) ICS daily dose prescribed self-reported at first interview (beclomethasone-equivalent doses [2]). Type of ICS-based treatment was grouped into three 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 at least one ICS (single or FDC) and a LABA (in a separate inhaler) and/or leukotriene antagonists (LTRA). Sex, country (UK or France) and age at enrolment coded in three categories (adults aged 18–40 years (reference group), teenagers [12–17] and children [6–11]) were extracted from primary care records.

Analysis

Data were analysed using R [22]. We identified variables that predicted missing interviews (22.28% of planned regular interviews were skipped and 33.52% of 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 (supplementary material 2). To isolate the effects of the implementation stage of ICS adherence [23], *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's average and the score in their previous report [24], usually 4 months earlier (thus, 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 [24]. Two-level longitudinal mixed models (within-patient reports) were built separately for asthma control and exacerbation occurrence (logistic models), and reliever use (linear models). We conducted visual data exploration fitting nonparametric loss functions (supplementary material 2), 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 for logistic models or intraclass correlation coefficients for linear models (research question 1). A cut-off of 0.05 indicated substantial variance [25]. Practice was initially modelled 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.

In addition, exploratory analyses were performed to examine possible moderators of adherence-outcome relationships: age, type of ICS and severity. Sensitivity analyses were performed with 1-month adherence scores (supplementary material 3).

Results

Sample characteristics

Out of 4647 reports from 934 patients collected between May 2013 and January 2016, 3756 reports (847 patients) were included (figure 2). There were between one and 13 reports per patient (median, interquartile range (IQR) 4, 4), resulting in mean \pm SD follow-up time of 406 \pm 249 days and maximum 758 days. Patients were predominantly French (80.4%), with good sex and age representation (47.6% female; 56.6% adults). Out of 3756 computer-assisted telephone interview 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 (IQR) 1-week adherence was 85.71% (50%). Patients indicated ICS adherence >80% in 55.88% of reports. Uncontrolled asthma was reported by 683 patients in 2046 (54.5%) reports. Median (range) reliever use was 0.18 (0–6) inhalations per day. 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 supplementary material 3). 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.

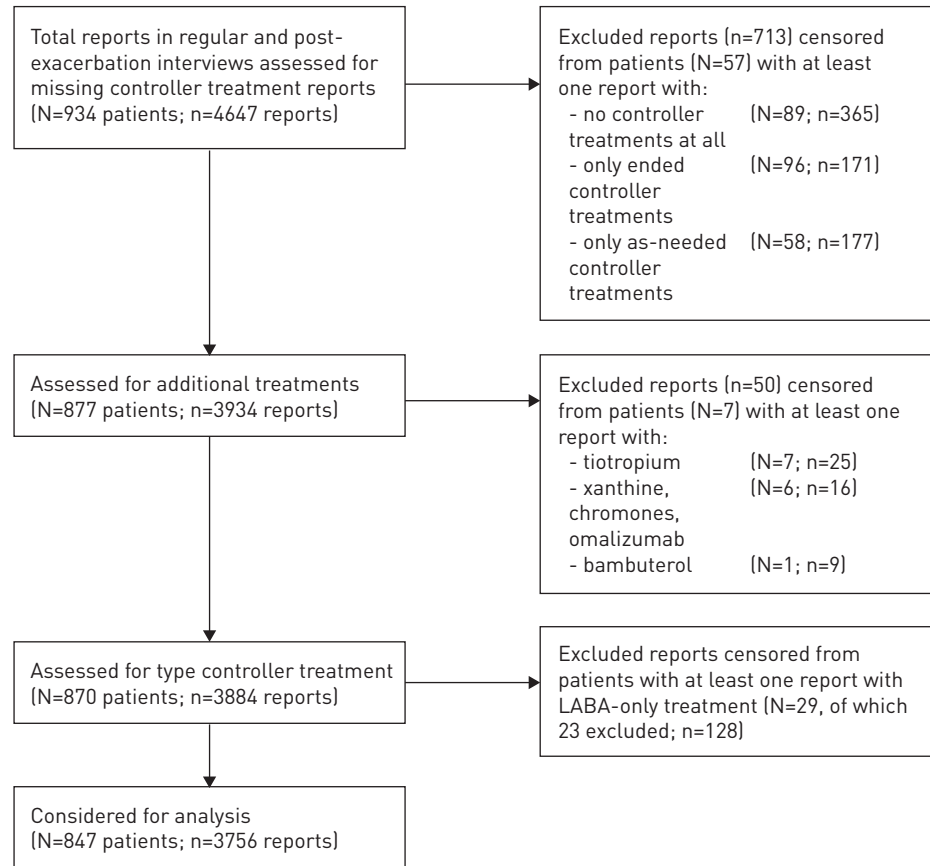


FIGURE 2 Flowchart for the selection of interview reports and patients meeting analysis criteria. Reports were censored, therefore some of the patients with excluded reports remained in the sample. LABA: long-acting β -agonist.

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 (0.93, 0.84–1.02 and 1.05, 0.95–1.15, respectively). In addition, controlled asthma was more likely in patients who on average used relievers less (0.30, 0.24–0.37 per 1 SD=1.23 times per day). Current increases in reliever use were associated with decreased likelihood of controlled asthma (0.50, 0.43–0.58 per 1 SD=1 time per day); prior fluctuations had no effects on asthma control (1.04, 0.94–1.16). Of note, when reliever use variables were excluded from the model (supplementary material 3), 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 doses 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 nonsignificant for children and adolescents (supplementary material 3). 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; 1.04, 0.94–1.16; and 0.99, 0.89–1.11, respectively). Patients with higher average reliever use were more likely to report an exacerbation (1.46, 1.30–1.63 per 1 SD=1.23 times per day); current and prior fluctuations in reliever use were unrelated to exacerbations (1.08, 0.98–1.19 and 1.00, 0.91–1.10, respectively). 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.

TABLE 1 Sample characteristics: descriptive statistics

Patient level	
Subjects	847
Country: France	681 (80.4)
Sex: female	403 (47.6)
Age	
Adults	479 (56.6)
Children	206 (24.3)
Teenagers	162 (19.1)
Baseline severity	
Number of OCS courses	0.00 (0.00–7.00)
Number of ICS and LABA canisters	12.00 (2.00–60.00)
ICS daily dose at first interview µg	500.00 (100.00–10000.00)
Report level	
Subjects	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	261.19±220.16
Reliever use	0.18 (0.00–6.00)
1-month adherence: composite	85.71 (0.00–100.00)
1-week adherence: composite	85.71 (0.00–100.00)
1-day taking adherence	100.00 (0.00–1250.00)
1-week therapeutic coverage	100.00 (0.00–100.00)
1-week correct dosing	85.71 (0.00–100.00)
1-month therapeutic coverage	92.86 (0.00–100.00)
4-month drug holidays	100.00 (0.00–100.00)

Data are presented as n, n (%), median [range] or mean±sd. OCS: oral corticosteroid; ICS: inhaled corticosteroid; LABA: long-acting β-agonist; FDC: fixed-dose combination; LTRA: leukotriene antagonist; CATI: computer-aided telephone interview.

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 (0.092 , 0.053 – 0.131 per 1 SD=20%) and lower reliever use in the next interview (prior fluctuation; -0.047 , -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 6–40 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 ASTRO-LAB cohort [21] indicate substantial within-person variability in ICS adherence scores as well (41–71%). We recommend using hierarchical modelling more broadly in respiratory research, especially given that longitudinal data are increasingly collected in routine care *via* digital technologies [26]. In addition, these results 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,

TABLE 2 Multilevel models of asthma control, asthma exacerbation (logistic) and reliever use (linear)

	Dependent variable		
	Asthma control	Exacerbation occurrence	Reliever use
Intercept	0.78 [§] (0.59–1.04)	0.15*** (0.12–0.19)	0.819±0.079***
Time (days since first CATI)[#]	1.31*** (1.16–1.48)	0.58*** (0.5–0.67)	–0.109±0.027***
Sex (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 OCS courses)[#]	1.15 [§] (0.98–1.34)	1.27*** (1.14–1.41)	0.117±0.045**
Baseline severity (ICS daily dose at first interview)[#]	0.61*** (0.50–0.74)	1.17** (1.05–1.31)	0.109±0.046*
1-week ICS adherence			
Average adherence ^{#,*}	1.25** (1.06–1.47)	0.99 (0.87–1.12)	–0.0004±0.045
Current fluctuation [#]	0.93 (0.84–1.02)	1.04 (0.94–1.16)	0.092±0.020***
Prior fluctuation [#]	1.05 (0.95–1.15)	0.99(0.89–1.11)	–0.047±0.021*
Reliever use			
Average use ^{#,*}	0.30*** (0.24–0.37)	1.46*** (1.30–1.63)	
Current fluctuation [#]	0.50*** (0.43–0.58)	1.08 (0.98–1.19)	
Prior fluctuation [#]	1.04 (0.94–1.16)	1.00 (0.91–1.10)	
VPC (logistic); ICC (linear)	0.4075	0.0891	0.4765
Observations	2909	2909	2909
Log likelihood	–1618.598	–1104.696	–4793.214
AIC	3271.195	2243.392	9622.429
BIC	3372.780	2344.977	9729.989

Data are presented as OR (95% CI) or b±se, unless otherwise stated. CATI: computer-assisted telephone interview; ICS: inhaled corticosteroids; OCS: oral corticosteroids; VPC: variance partition coefficient; ICC: intraclass correlation; AIC: Akaike information criterion; BIC: bayesian information criterion. [#]: variable standardised before inclusion into regression model to facilitate interpretation and model convergence (z-scores); [¶]: reference group: ICS with long-acting β-agonist (LABA) in fixed-dose combination, ICS only: single ICS inhaler, ICS plus: at least one ICS and a LABA in separate inhaler and/or leukotriene antagonist; *: average denotes individual mean across the follow-up period. [§]: p<0.1; *: p<0.05; **: p<0.01; ***: p<0.001.

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 process Model [27] (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 one time more than usual in 11 days in the same period and using them once 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 [28, 29]. 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 β-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 [30].

Several findings on other predictors of asthma outcomes are important to highlight. Males reported fewer exacerbations, consistent with recent findings on large medical records data in the UK [31]. There were fewer exacerbations and more reliever use reported in the UK, possibly explained by better implementation of self-management support in primary care [32], 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 OCS 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. Therefore, our results 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 (missing value analyses in supplementary material 2); 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 [33], and interactions with LABA in FDC [34]; 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 [35–37]. 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 in the long term, and an interplay between ICS and reliever use in the 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

TABLE 3 Example questions for assessing asthma control, inhaled corticosteroid (ICS) adherence and reliever use

Variable	Question examples	Responses
Asthma control (RCP3Q) [19]	In the past month:	
	Have you had difficulty sleeping because of your asthma symptoms (including cough)?	Never/rarely/every week/every day (answers “rarely” or more for at least one question indicate uncontrolled asthma)
	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.)		
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×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

RCP3Q: Royal College of Physicians three questions.

use and health status fluctuate over time, and routinely assess these in a factual, nonjudgmental manner, for example using the questions in table 3 (adapted from ASTRO-LAB interviews). Second, they should clarify how patients use both controllers and relievers in relation to symptoms and agree on asthma action plans. Third, they should support patients to work towards high average levels of adherence to the agreed ICS daily dosage for long-term control.

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

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