

Stability of Asthma Symptom Control in a Longitudinal Study of Mild-Moderate Asthmatics



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What is already known about this topic? The level of asthma symptom control can change within an individual over time because of intrinsic factors, such as change in asthma activity, or extrinsic factors, such as treatment.

What does this article add to our knowledge? This article examines the degree of stability of asthma symptom control within individuals and the variation in stability across individuals. The stability of symptom control has not previously been investigated as an independent clinical trait.

How does this study impact current management guidelines? This study may help practitioners identify patients who are likely to experience instability in symptom control based on their previous history of control; these patients may require closer monitoring.

BACKGROUND: Achieving and maintaining symptom control is a primary goal of asthma management. Although factors associated with the likelihood of achieving symptom control have been studied, there are unanswered questions on the stability of symptom control, that is, the tendency of individuals to remain at a given symptom control level over time.

OBJECTIVE: The objective of this study was to evaluate the stability of symptom control using a longitudinal cohort of mild-moderate asthmatics.

METHODS: Participants reported symptom control using the Global Initiative for Asthma criteria at 5 assessments during the 1-year follow-up period. We described variability in the stability of symptom control between individuals, and used a random-effects logistic regression model to evaluate the impact of a suite of factors on the stability of symptom control.

RESULTS: A total of 429 individuals (67% female, mean age 51.6) contributed 2141 study visits. Individuals varied from completely stable in symptom control (18% remained at the same control level in all 5 visits) to completely unstable (12%

changed the control level between all subsequent visits). Only 4% of between-individual variation in the stability of symptom control was explained by the included exposures, and a secondary analysis indicated that the history of symptom control stability was the best predictor of current stability.

CONCLUSIONS: The tendency to remain at a given control level varies significantly among patients with asthma. Only a small fraction of this variability is explained by observable characteristics. In the absence of predictors, a previous history of symptom control stability is the best indicator of future stability and should be considered when monitoring symptom control. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:1663-70)

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Asthma is an inflammatory disease of the airways that affects more than 300 million people worldwide.¹ It is associated with variable airflow obstruction that results in respiratory symptoms such as wheezing, coughing, breathlessness, and chest tightness.² These symptoms are typically intermittent and reversible but often vary in their intensity over time.²

A major target of asthma management is to achieve and maintain asthma control. The Global Initiative for Asthma (GINA) defines asthma control as the degree to which the manifestations of asthma are reduced or removed by treatment.² The GINA divides asthma control into 2 components: symptom control and the future risk of adverse outcomes such as exacerbations or lung function decline.² Asthma symptoms can be controlled in most cases with pharmacological interventions and by reducing exposure to triggers. However, despite the availability of treatments, asthma remains uncontrolled in a substantial fraction of the population.³ Patients with uncontrolled asthma tend to have higher medical costs,⁴ greater productivity loss,⁵ and decreased quality of life.⁶

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Abbreviations used*CI*-Confidence interval*FEV₁*-Forced expiratory volume in 1 second*FVC*-Forced vital capacity*GINA*-Global initiative for asthma*MPR*-Medication possession ratio*OR*-Odds ratio*PEF*-Peak expiratory flow*R*²-Coefficient of determination*SCQ*-Self-administered Comorbidity Questionnaire

Previous studies have examined factors associated with the likelihood of achieving symptom control.⁷⁻¹⁰ However, the concept of “stability” in symptom control has received less attention. The stability of a disease marker is fundamentally different from the nominal value of that marker, and different factors are expected to affect each construct. For example, variations in blood pressure and heart rate are well-recognized clinical characteristics with associated predictors and prognostic implications independent of their nominal values.^{11,12}

To the best of our knowledge, the stability of asthma symptom control as a clinical characteristic has not yet been studied. Here, we define stability as the likelihood of a change in symptom control over time. We consider symptom control as stable in a period of time when the level of symptom control remains constant within that period, and unstable when the level of symptom control changes. Documenting heterogeneity and identifying factors associated with the stability of symptom control is of pathophysiological and clinical importance. High variability in symptom control could reflect differences in asthma treatments and environmental exposures, or it could be an innate feature of asthma. Identifying factors that affect the stability of symptom control may therefore improve our understanding of the disease mechanisms. It can also help identify subgroups of patients that might need closer monitoring of their symptom control over time.

The purpose of this study was to document between-individual variability in the stability of symptom control (objective 1) and to determine whether sociodemographic factors and clinical characteristics explain variation in the stability of control status (objective 2). We hypothesized that the stability of control varies between individuals, and that there are clinical, demographic, and environmental factors that are associated with the stability of symptom control.

METHODS**Study design and sample**

We used data from the Economic Burden of Asthma study, a prospective, longitudinal cohort study (University of British Columbia Human Ethics #H10-01542) of patients with asthma. The details of this study have been described elsewhere.^{13,14} Study inclusion criteria are explained in [Text E1](#), available in this article's Online Repository at www.jaci-inpractice.org. A total of 618 individuals were recruited and followed for 12 months with visits scheduled at 3-month intervals, resulting in 5 visits for individuals who completed the study (data from additional medical visits outside of the study visits were not included in this analysis). We considered all participants who were not hospitalized or admitted to the intensive care unit for an asthma-related event during or in the year before the start of the study as having mild-moderate asthma. Severe

asthma cases were excluded because there were very few of them in the original sample and also because we believe different mechanisms might affect the stability of symptom control in these individuals. The subsample for this analysis included adult (≥ 19 years) participants with mild-moderate asthma, having observations of control status from at least 2 consecutive visits, and having complete information for all studied exposures with the exception of income on those visits. Missing observations of income were included in the subsample as a separate category.

Outcome and exposure variables

Outcome: stability of symptom control. The GINA criteria were used to classify participants as uncontrolled, partially controlled, or controlled at each visit based on whether they had experienced daytime asthma symptoms more than twice per week, limited activity, nocturnal symptoms, or the need for rescue treatment more than once per week during the previous 4 weeks.² GINA-defined symptom control is shown to be well correlated with patient-reported outcomes.⁶

The observation unit for this analysis was the change of symptom control status between consecutive visits (1: change [unstable transition], 0: no change [stable transition]). This resulted in a maximum of 4 observations of the stability of symptom control for participants with complete follow-up. Our sample included 4 individuals with 3 observations of stability (4 visits); these participants were included in all analyses unless otherwise noted. The definition of stability was agnostic to the direction of change in control status to enable inference on stability independent of the likelihood of improvement in the level of control (as opposed to previous studies of symptom control^{9,15}). Therefore, observations of stable asthma control included individuals who maintained uncontrolled, partially controlled, or controlled asthma between consecutive visits. In the main analysis, the definition of stability was also agnostic to the magnitude of change (eg, transition from controlled to uncontrolled and from controlled to partially controlled were both coded as unstable [value of 1]). However, stability was redefined as a 3-level ordinal variable in a sensitivity analysis to capture the magnitude of change (a value of 2 represented a change from uncontrolled to controlled, or vice versa).

Exposure variables. We evaluated the association between the stability of symptom control and multiple variables representing the sociodemographic status of participants and their clinical characteristics. At baseline, participants reported their age, sex, ethnicity, education, annual household income, and when they were first diagnosed with asthma. We also recorded their smoking status and history (measured in pack-years), the duration of time they worked in a “dusty job,” and the number of allergens that triggered their asthma symptoms. We used the meteorological seasons to categorize the date of each of the visit transitions as winter, spring, summer, or fall (according to the date of the later visit). Participants reported the number of months and the number of days per week they took medications for their asthma during the 3 months before each follow-up visit (questionnaire in [Figure E1](#), available in this article's Online Repository at www.jaci-inpractice.org). These data were converted to the medication possession ratio (MPR), which indicates the proportion of total days in which controller medications were available to the participant.¹⁶ A list of the medications used to assess MPR is included in [Table E1](#) (available in this article's Online Repository at www.jaci-inpractice.org). Treatment intensity was classified as low if MPR was less than 80% and high if MPR was

greater than or equal to 80%.¹⁶ MPR entered the model as a continuous variable in a sensitivity analysis. Also, participants used the Self-administered Comorbidity Questionnaire (SCQ)¹⁷ at the final visit to report their comorbidity status over the 12-month study period. Each participant received a score between 1 and 36 with a higher score indicating a higher level of comorbidity. Spirometry was administered at the baseline and final visits; in this analysis, we considered percent of predicted forced expiratory volume in 1 second (% predicted FEV₁),¹⁸ forced vital capacity (FVC), and peak expiratory flow (PEF) measured without a bronchodilator response. For each participant, we interpolated spirometry measures for visit transitions 1, 2, and 3 assuming a linear change between the baseline and final visits and using the measure from the later of the 2 consecutive visits comprising a transition. FEV₁ reversibility was also included in the analysis and was measured as the percentage change in FEV₁ before versus 15 minutes after administration of 200 µg of salbutamol.

Statistical analysis

All analyses were performed in R version 3.1.3.¹⁹ We considered 2-tailed *P* values of less than .05 as statistically significant. We calculated descriptive statistics and compared the distribution of the exposures across visit transitions in which symptom control was stable or unstable using chi-squared tests of independence for categorical variables and 1-way analysis of variance for continuous variables.

We evaluated variability among participants in the stability of symptom control (objective 1) by calculating the proportion of individuals with a given number of stable transitions (control status being the same between consecutive visits) during the follow-up period. Individuals could have the same control status across all visits, or they could have experienced a change in control status once, twice, 3, or 4 times.

We identified factors that affect the stability of symptom control (objective 2) using a random-effects logistic regression model with stability as the dependent variable, and the previously mentioned exposures as the independent variables. The sociodemographic characteristics of participants and environmental factors were time invariant variables, whereas season, MPR, and lung function were time dependent. A variable indicating the visit transition number was also included to capture temporal trends. Our model produced estimates of the odds ratio (OR) for each exposure that represented its independent association with the likelihood of a change in symptom control between consecutive visits. An OR greater than 1 indicated that the variable was associated with lower stability in symptom control (higher likelihood of change). The regression intercept was modeled as a random-effects term, which allowed us to estimate each participant's tendency towards instability of symptom control that exceeds the effect of the included exposures. These random intercepts were converted to individual-specific ORs that represented the innate tendency of individuals to be unstable in control status (compared with an "average" individual) independent of the effects of the included exposures.

We estimated the overall ability of the included exposures to explain variability in the stability of symptom control by calculating the marginal and conditional coefficient of determination (*R*²) for our model.²⁰ The conditional *R*² is interpreted as the total variance explained by both the exposures and random effects in our model, relative to the total variation in the stability of symptom control. The marginal *R*² is the percentage of the total variation that is explained by the exposures only.²⁰ A large difference between the conditional

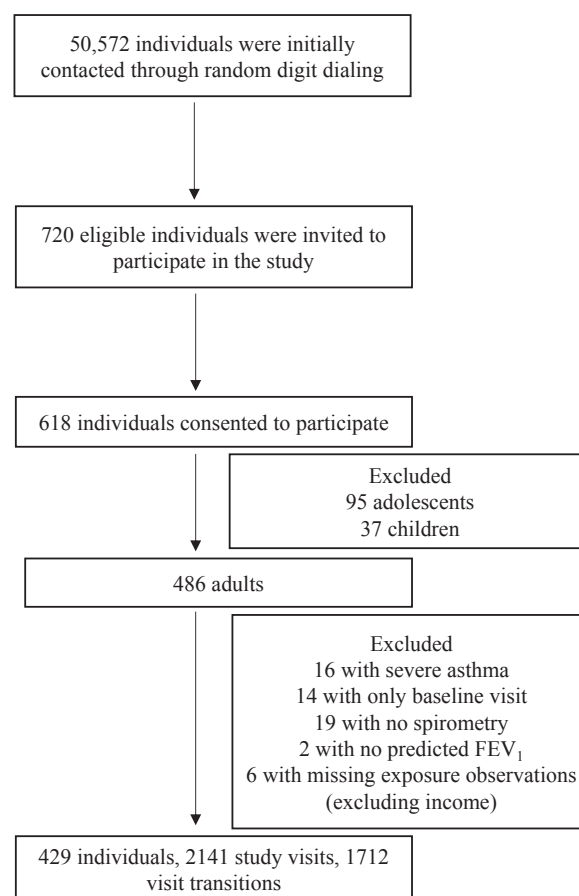


FIGURE 1. Cohort selection procedure. FEV₁, Forced expiratory volume in 1 s.

and marginal *R*² would suggest that intrinsic differences between individuals influence stability more than the factors represented by the exposures.

In a secondary analysis, we evaluated the predictive importance of a previous history of symptom control stability by comparing predictive power (quantified by the c-statistics²¹—the degree of concordance between predicted and observed transitions) between a null model with no exposures, the full model described above with all exposures, and a third model with symptom control stability in the previous visit transition included as an additional independent variable. The third model used a subset of the data with only visit transitions 2 to 4, as there was no observation of stability in the previous transition for the first visit transition.

RESULTS

Sample characteristics

The cohort selection procedure is shown in Figure 1. The final sample included 429 individuals contributing 2141 visits and 1712 visit transitions. The sample was 67% female and the average age at study entry was 51.6 years (standard deviation [SD] = 14.5). Sample characteristics are shown in Table I.

The proportion of participants with controlled, partially controlled, and uncontrolled asthma across all 2141 visits was 29%, 40%, and 31%, respectively. Participants were slightly more likely to remain at the same control level between

TABLE I. Characteristics of study participants at baseline and during follow-up visits

	Baseline (N = 429)	P value			
Age, mean (SD)	51.62 (14.52)				
Gender, % female (vs male)	67%				
Ethnicity					
Caucasian	82%				
Asian*	11%				
Other	7%				
Symptom control					
Uncontrolled	34%				
Partially controlled	40%				
Controlled	26%				
Annual household income >\$60,000 (vs <\$60,000)†	62%				
Postsecondary education and above (vs below)	89%				
Age at asthma diagnosis, mean (SD)	27.18 (19.13)				
Overall SCQ comorbidity scores, mean (SD)‡,§	3.13 (3.41)				
Number of pack-years, mean (SD)	0.81 (2.13)				
Number of years working in a dusty job, mean (SD)	3.91 (8.31)				
Number of allergens causing asthma symptoms, mean (SD)	8.89 (4.99)				
FEV ₁ reversibility, mean (SD)‡	8.76% (9.61)				
	Visit transition				
	1	2	3	4	
Percent predicted FEV ₁ , mean (SD)	85.99 (18.29)	85.53 (18.15)	85.08 (18.20)	84.55 (18.44)	.69
FVC, mean (SD)	3.63 (1.09)	3.62 (1.08)	3.61 (1.08)	3.59 (1.08)	.95
PEF, mean (SD)	6.88 (2.00)	6.88 (1.98)	6.88 (2.01)	6.88 (2.08)	.99
FEV ₁ /FVC	0.72 (0.1)	0.72 (0.1)	0.72 (0.1)	0.72 (0.1)	.92
Visit season¶					
Winter	13%	27%	38%	22%	<.01
Spring	23%	14%	28%	36%	
Summer	39%	21%	13%	28%	
Fall	25%	38%	21%	15%	
Medication possession ratio (MPR)					
MPR < 80%	56%	56%	55%	56%	.99
MPR ≥ 80%	44%	44%	45%	44%	
Stability of symptom control					
Stable	51%	52%	54%	56%	.40
Unstable	49%	48%	46%	44%	

FEV₁, Forced expiratory volume in 1 s; FVC, forced vital capacity; SCQ, Self-administered Comorbidity Questionnaire; SD, standard deviation.

*Included Arab/West Asian, Chinese, Japanese, Korean, South Asian, and South East Asian.

†Four percent of participants did not report their income.

‡Measured at the final visit.

§The SCQ has been validated against the Charlson Comorbidity Index and includes 13 common comorbid chronic conditions that are assigned a maximum of 3 points each.¹⁷ However, lung disease was removed from the SCQ given the inclusion criteria of the present study, resulting in a maximum score of 36.

||All variables were measured or interpolated at the later of the 2 consecutive visits that comprise a transition.

¶Study visits were separated by approximately 3 mo and therefore tended to take place in different seasons.

consecutive visits (53%, *n* = 913 transitions) than to change levels (47%, *n* = 799 transitions). The likelihood of maintaining the same level of control versus changing control categories stayed relatively constant across the 4 visit transitions (*P* = .40).

Figure 2 presents the distribution of individuals according to the number of stable/unstable visit transitions. Eighteen percent (*n* = 78) of participants retained the same control status over the entire study period (within this subgroup, 47%, 28%, and 25% remained in the uncontrolled, partially controlled, and controlled categories across all visits, respectively). In contrast, symptom control status changed in all 4 visit transitions in 12% (*n* = 50) of participants. The rest of the sample fell in between, with the

highest proportion belonging to individuals in whom half of transitions were stable.

Figure 3 shows the tendency of individuals to maintain stable or unstable symptom control. It depicts the average proportion of stable visit transitions as a function of the distance of the transition from a previous stable transition. If a transition was stable, the immediate next transition was more likely to be stable (67%, SD = 1.6). This was also the case for the second immediate (60%, SD = 0.5), and third immediate (64%) transitions. Likewise, a transition immediately after an unstable transition was most likely to be unstable (59%, SD = 2.2), although the second immediate transition was equally likely to be stable (50%,

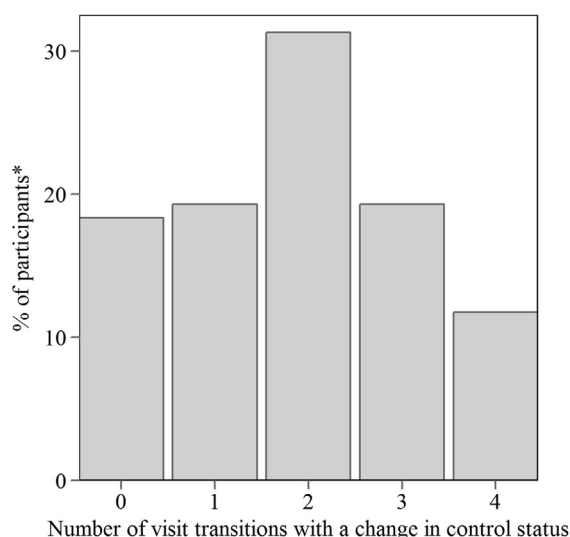


FIGURE 2. Cumulated number of visit transitions with a change in symptom control. *Four participants were excluded because less than 4 visit transitions were observed, N = 425.

SD = 1.0). These results indicate that the stability of symptom control tended to cluster within individuals. Had the stability of symptom control been a completely random phenomenon, it would not be affected by the previous history of stable versus unstable transitions.

Univariate associations

The distribution of MPR, visit season, comorbidity, and lung function between observations of stable and unstable symptom control in visit transitions is given in Table II. Higher MPR was related to stable symptom control ($P < .01$), but visit season ($P = .91$) and percent predicted FEV₁ ($P = .34$) were not. Comorbidity ($P < .01$), FEV₁ reversibility ($P = .04$), FVC ($P = .04$), and PEF ($P = .03$) were also associated with the stability of symptom control.

Adjusted analysis

The results from the random-effects logistic regression are provided in Table III. Females were more likely to have unstable symptom control than males (OR 1.98, 95% confidence interval [CI] 1.18-3.33, $P = .01$). A higher comorbidity level (OR 0.94 for a 1 unit increase in the SCQ score, 95% CI 0.90-0.99, $P = .01$) and increased length of time from baseline (OR 0.90 for visit transition number, 95% CI 0.82-0.99, $P = .03$) were negatively related to the likelihood of having unstable symptom control. None of the remaining exposures were significantly correlated with the stability of symptom control.

Sensitivity analyses

With the exception of FEV₁ reversibility becoming significant (OR 0.98, 95% CI 0.96-1.00, $P = .04$), we observed similar results in the alternative analysis in which stability was defined as a 3-level ordinal variable (to account for the magnitude of change in symptom control; Table E2, available in this article's Online Repository at www.jaci-inpractice.org). Increasing treatment intensity was negatively associated with unstable symptom control when MPR entered the model as a continuous variable (OR 9.98

for a 10% increase in MPR, 95% CI 9.97-10.00, $P = .04$; Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

Explained and unexplained variation in symptom control stability

The model explained a moderate amount of variation in the stability of symptom control. The marginal and conditional R^2 were 4% and 24%, respectively, indicating that intrinsic differences between individuals account for greater variation in stability than differences in the included exposures. Figure 4 presents the histogram of the individual-specific ORs, which represent the innate tendency of individuals to have unstable symptom control over and beyond the effects of the included exposures. Individuals at the 97.5th percentile were 7.70 times more likely to experience a change in control status between consecutive visits than individuals at the 2.5th percentile, after controlling for observed characteristics.

Importance of symptom control history

The main model had a c-statistic of 0.59, which is only marginally better than the null model with no exposures ($c = 0.5$), indicating that the exposures were not strongly predictive of symptom control stability. In contrast, the model with all of the previously mentioned exposures as independent variables plus symptom control stability in the previous transition had a c-statistic of 0.68. In other words, the inclusion of the history of symptom control stability improved the model performance as much as the inclusion of all exposure variables combined (increase in c-statistics of 0.09).

DISCUSSION

The objectives of this study were to describe between-individual variation (heterogeneity) in the stability of symptom control and assess the impact of sociodemographic factors and clinical characteristics on this stability. Symptom control remained stable throughout the 1-year follow-up period in only 18% of participants. We observed substantial variation between individuals in the number of consecutive visits in which symptom control status changed (unstable transitions). Only 4% of this variation was explained by the included sociodemographic and clinical characteristics.

Sex, comorbidity burden, and time since recruitment to the study were the only factors that were associated with the stability of symptom control. There were also trends towards positive associations between MPR, FEV₁ reversibility, and stability of symptom control; these associations became statistically significant in sensitivity analyses. Regarding comorbidity, the average SCQ score was higher in individuals with uncontrolled asthma (4.1) than in the rest of the sample (2.7). One explanation is that individuals with a high burden of comorbidity might not prioritize good asthma management and therefore tend to remain uncontrolled. Alternatively, it might be the case that some comorbid conditions (eg, anxiety, sinusitis) might directly deteriorate symptom control. In contrast, females were more likely to experience unstable symptom control and uncontrolled asthma (36% of visits with uncontrolled asthma, $n = 513$), compared with males (22% of visits, $n = 155$). This is in line with previous studies that have demonstrated a greater tendency to maintain well-controlled asthma.¹⁵ The negative association between time since recruitment to the study and the likelihood of changing

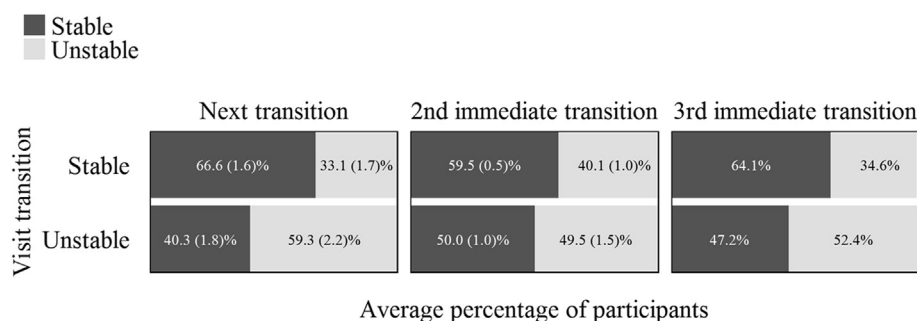


FIGURE 3. Average probability (and standard deviation) of transitioning between stable and unstable symptom control across 4 visit transitions. The third immediate transition describes the stability of control in visit transitions 1 and 4; therefore averages and standard deviations are not reported because there was only 1 observation per category. A stable transition occurred when a participant had the same level of symptom control between consecutive visits.

TABLE II. Number and proportion of stable and unstable visit transitions in each level of MPR and visit season, and mean and standard deviation of comorbidity and lung function in both levels of stability of symptom control

	Stability of symptom control		P value
	Stable (n = 913)	Unstable (n = 799)	
MPR			
MPR < 80%	481, 52.7%	477, 59.7%	<.01
MPR ≥ 80%	432, 47.3%	322, 40.3%	
Visit season			
Winter	225, 24.6%	203, 25.4%	.91
Spring	226, 24.8%	203, 25.4%	
Summer	228, 25.0%	200, 25.0%	
Fall	234, 25.6%	193, 24.2%	
Comorbidity, mean (SD)	3.4 (3.6)	2.7 (3.2)	<.01
Lung function			
FEV ₁ reversibility, mean (SD)	9.2% (10.3)	8.3% (8.7)	.04
Percent predicted FEV ₁ , mean (SD)	84.9 (19.3)	85.7 (17.0)	.34
FVC, mean (SD)	3.6 (1.1)	3.7 (1.1)	.04
PEF, mean (SD)	6.8 (2.0)	7.0 (2.0)	.03

FEV₁, Forced expiratory volume in 1 s; FVC, forced vital capacity; MPR, medication possession ratio; PEF, peak expiratory flow; SD, standard deviation.

All variables were measured or interpolated at the later of the 2 consecutive visits that comprise a transition, with the exception of comorbidity and FEV₁ reversibility, which were only assessed at the final visit.

control levels may be a manifestation of the regression to the mean phenomenon. In this context, it might be the case that symptomatic patients were more willing to enroll in this prospective study than patients whose asthma was well controlled, but the distribution of symptom control stabilized as the follow-up period progressed. Indeed, the proportion of participants with uncontrolled asthma was higher at the baseline visit (34%) than at the second visit (28%). This trend could also be explained by improved treatment adherence, as the proportion of participants with high treatment intensity increased by 12% during that same period, which resulted in relatively high treatment adherence overall (44% of participants with MPR ≥ 80%). Any possible association between MPR and the stability of symptom control could be due to the effect of controller medications in increasing the likelihood of achieving and retaining symptom control over time. Our results point towards the possibility that this effect results in stable symptom control only if adherence to controller medications is high (≥80%). There was also some indication that increasing variability of airflow obstruction is associated with

greater stability, which may reflect easier-to-control asthma in these participants. Aside from these factors, the sociodemographic and clinical characteristics of participants did not strongly influence their likelihood of experiencing instability in control status.

To our knowledge, this is the first study that examines the stability of symptom control as an independent clinical trait. The stability of symptom control was most influenced by differences between individuals that were not captured by the included exposures. These unobserved characteristics of participants explained 6 times more variation in the stability of control than the exposures included in our model. This unexplained variation could be related to factors that we did not measure. For example, the GINA definition of control status and our measurement of treatment intensity were self-reported and therefore subject to many factors that are difficult to quantify (eg, psychological factors that influence memory and recall). On the other hand, variation in the stability of symptom control might be an innate characteristic of the disease itself. The unmeasured differences

TABLE III. Effects of the independent variables on the stability of symptom control

	OR	95% CI	P value
Medication possession ratio (MPR)			.14
MPR < 80%	Reference		
MPR ≥ 80%	0.81	0.62-1.07	
Comorbidity	0.94	0.90-0.99	.01*
Visit season			.61
Fall	Reference		
Winter	1.21	0.89-1.64	
Spring	1.19	0.88-1.61	
Summer	1.11	0.82-1.49	
Visit	0.90	0.82-0.99	.03*
Age	1.00	0.99-1.02	.62
Sex			.01*
Male	Reference		
Female	1.98	1.18-3.33	
Ethnicity			.83
Asian	Reference		
Caucasian	0.95	0.59-1.52	
Other	1.14	0.58-2.26	
Annual household income			.66
<\$60,000	Reference		
>\$60,000	1.14	0.82-1.59	
Missing data	0.95	0.47-1.94	
Education			.27
Below postsecondary	Reference		
Postsecondary or higher	1.30	0.81-2.07	
Age at asthma diagnosis	1.00	0.99-1.01	.79
Number of allergens causing asthma symptoms	0.98	0.95-1.01	.18
Number of pack-years	0.96	0.90-1.03	.23
Number of years working in a dusty job	1.01	0.99-1.03	.27
FEV ₁ reversibility	0.98	0.96-1.00	.06
FVC	1.22	0.93-1.61	.16
PEF	1.07	0.95-1.20	.25
Percent predicted FEV ₁	0.99	0.98-1.00	.06

CI, Confidence interval; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; OR, odds ratio; PEF, peak expiratory flow.

An OR greater than 1 indicates that the variable was positively associated with the likelihood of changing control status between consecutive visits (unstable transition).

*P < .05.

between individuals are best captured in participants' previous history of symptom control stability, which was the best predictor of current stability in secondary analyses.

This study has several strengths. We estimated asthma symptom control, comorbidity, and treatment intensity using internationally accepted methods.^{2,16,17} Attrition rate was very low during the study, which provided a full year of longitudinal data for 99% of participants. In addition, our use of a random-effects regression model enabled us to account for and quantify the level of between-individual variation in the stability of symptom control. However, this study also has several limitations. The sample size might not have been large enough to detect associations between some of the exposures and the stability of symptom control. We were also not able to rule out the impact of factors that were not included in our model, for

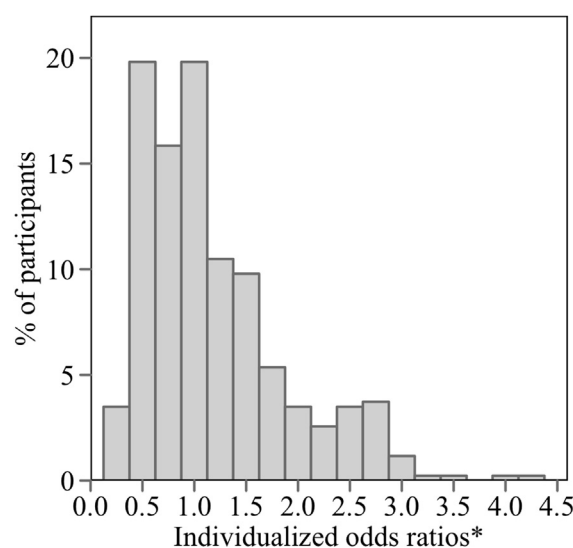


FIGURE 4. Individual-specific odds ratios of instability in control status in visit transitions. *The individualized odds ratios represent the tendency of individuals to have unstable symptom control that exceeds the effect of the included exposures.

instance, environmental triggers such as temperature, humidity, and air pollution. Spirometric variables were only measured in the first and last visits, and their values in the interim visits were imputed using linear interpolation. A more granular measurement of these variables might reveal a stronger association between lung function and stability of asthma symptom control. Similarly, medication intake was based on self-report; more accurate estimation may increase the association between pharmacotherapy and stability of symptom control. Lastly, the GINA control categories have not been extensively validated, and there is some uncertainty as to whether the differences between categories are clinically significant.

In summary, we observed substantial between-individual variation in the stability of symptom control that was not well explained by the clinical or sociodemographic characteristics of participants or by the environmental factors that we measured. Our results suggest that stability is an innate feature in mild-moderate asthma. From a research perspective, further studies are required to identify factors that predict the degree of stability of symptom control. From a clinical perspective, our study suggests that certain individuals are at high risk of instability in asthma symptom control, and that these individuals are more easily identified based on their history of change in symptom control than observable sociodemographic or clinical characteristics. Patients who have previously experienced instability may not be able to maintain good symptom control, and these individuals should be monitored closely by physicians and be characterized in more detail by future researchers.

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JMF and MS conceived, designed, and with WC, conducted the Economic Burden of Asthma study. KMJ and MS

formulated the current study idea and designed the study. KMJ performed all data analyses and wrote the first draft of the manuscript. HT and WC helped with data analysis. All authors critically commented on the manuscript and approved the final version. MS is the guarantor of the manuscript.

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ONLINE REPOSITORY

TEXT E1: DETAILED EXPLANATION OF THE STUDY INCLUSION CRITERIA

Individuals 1 to 85 years old with a self-reported physician diagnosis of asthma were detected through random digit dialing of land lines and cell phones in the Vancouver and Central Okanagan census subdivisions of the province of British Columbia, Canada. In 2011, these subdivisions had

populations of 603,502 and 179,830, respectively.^{E1} Individuals were eligible for recruitment to the study if they had at least 1 asthma-related encounter with the health care system in the past 5 years, had no other lung or airway diseases, reported a smoking history of less than 10 pack-years, were not pregnant or planning to become pregnant in the next 12 months, and intended to stay in the study area for at least 12 months.

SECTION 7: ASTHMA MEDICATIONS							
Now I am going to ask you about medicines that you may be taking to help with your breathing. I want to know about medicines that you take on a regular basis and medicines that you may take only for the relief of symptoms. I would like you to tell me each medicine that you take, what form do you take it in, and how often you take it each month							
1. During the past 12 months, have you taken any medications for your breathing (including medications for nasal congestion and asthma exacerbation such as prednisone and antibiotics)? ☐ 1. Yes ☐ 2. No							
If participant does not take any medications to help their breathing, skip to Question 5.1.							
Medication							
Name (not entered)							
Medication	_____	_____	_____	_____	_____	_____	_____
Code (consult the medication name and code list for number)							
Formulation (check one. If more than two formulations for one drug enter them as separate columns)	Pills ☐ 1 Inhaler ☐ 2 Nebulizer ☐ 3 Liquid ☐ 4 Suppository ☐ 5 Injection ☐ 6 Other ☐ 7	Pills ☐ 1 Inhaler ☐ 2 Nebulizer ☐ 3 Liquid ☐ 4 Suppository ☐ 5 Injection ☐ 6 Other ☐ 7	Pills ☐ 1 Inhaler ☐ 2 Nebulizer ☐ 3 Liquid ☐ 4 Suppository ☐ 5 Injection ☐ 6 Other ☐ 7	Pills ☐ 1 Inhaler ☐ 2 Nebulizer ☐ 3 Liquid ☐ 4 Suppository ☐ 5 Injection ☐ 6 Other ☐ 7	Pills ☐ 1 Inhaler ☐ 2 Nebulizer ☐ 3 Liquid ☐ 4 Suppository ☐ 5 Injection ☐ 6 Other ☐ 7	Pills ☐ 1 Inhaler ☐ 2 Nebulizer ☐ 3 Liquid ☐ 4 Suppository ☐ 5 Injection ☐ 6 Other ☐ 7	Pills ☐ 1 Inhaler ☐ 2 Nebulizer ☐ 3 Liquid ☐ 4 Suppository ☐ 5 Injection ☐ 6 Other ☐ 7
Is the Medicine taken on most days, or just when you have symptoms, or both?	Most Days ☐ 1 Symptoms ☐ 2 Both ☐ 3	Most Days ☐ 1 Symptoms ☐ 2 Both ☐ 3	Most Days ☐ 1 Symptoms ☐ 2 Both ☐ 3	Most Days ☐ 1 Symptoms ☐ 2 Both ☐ 3	Most Days ☐ 1 Symptoms ☐ 2 Both ☐ 3	Most Days ☐ 1 Symptoms ☐ 2 Both ☐ 3	Most Days ☐ 1 Symptoms ☐ 2 Both ☐ 3
When you are taking the medication, how many days a week do you take it?	Days	days	days	days	days	days	Days
When you are taking the medication, how many months during the past 12 months have you taken it?	0-3 ☐ 1 4-6 ☐ 2 7-9 ☐ 3 10-12 ☐ 4	0-3 ☐ 1 4-6 ☐ 2 7-9 ☐ 3 10-12 ☐ 4	0-3 ☐ 1 4-6 ☐ 2 7-9 ☐ 3 10-12 ☐ 4	0-3 ☐ 1 4-6 ☐ 2 7-9 ☐ 3 10-12 ☐ 4	0-3 ☐ 1 4-6 ☐ 2 7-9 ☐ 3 10-12 ☐ 4	0-3 ☐ 1 4-6 ☐ 2 7-9 ☐ 3 10-12 ☐ 4	0-3 ☐ 1 4-6 ☐ 2 7-9 ☐ 3 10-12 ☐ 4

FIGURE E1. Questionnaire used to assess the medication possession ratio at the baseline visit. The recall period was 1 year at the baseline visit and 3 months for the follow-up visits.

TABLE E1. List of asthma medications used in assessment of the medication possession ratio

Medication categories	Active ingredient(s)	DIN
Inhaled corticosteroid (ICS)	Beclomethasone	2242030, 2242029, 374407, 828521, 828548, 872334, 893633,
	Budesonide	897353, 1949993, 1950002, 2079976, 2213710, 2213729, 2215039,
	Fluticasone	2215047, 2215055, 2216531
Long-acting β -agonists (LABA)	Salmeterol	2211742, 2214261, 2231129, 2136139, 2136147
	Formoterol	2230898, 2237224, 2237225
ICS and LABA in combination (ICS+LABA)	Budesonide, formoterol	2245385, 2245386
	Fluticasone, salmeterol	2240835, 2245126, 2245127, 2240836, 2240837
Leukotriene receptor antagonists	Montelukast	2247997, 2238217, 2243602, 2238216
	Zafirlukast	2236606
Anti-immunoglobulin E monoclonal antibody	Omalizumab	2260565
Inhaled mast cell stabilizers	Cromoglicic acid (cromolyn)	2231431, 2231671, 2046113, 534609, 555649, 261238, 638641,
		2049082, 2219468
Theophylline	Choline theophyllinate	346071, 405310, 441724, 441732, 451282, 458708, 458716, 476366,
		476390, 476412, 503436, 511692, 536709, 565377, 589942,
		589950, 792934
	Theophylline	156701, 261203, 460982, 460990, 461008, 466409, 488070, 532223,
		556742, 575151, 599905, 627410, 631698, 631701, 692689,
		692697, 692700, 722065, 1926586, 1926594, 1926608, 1926616,
		1926640, 1966219, 1966227, 1966235, 1966243, 1966251,
		1966278, 1966286, 2014165, 2014181, 2230085, 2230086, 2230087
	Aminophylline	14923, 178497, 497193, 497193, 497207, 582654, 582662, 868450,
		2014270, 2014289
Other corticosteroids	Cortisone	280437, 16241, 16446, 16438
	Triamcinolone	2194090, 15016, 15024, 2194082
	Prednisone	610623, 598194, 550957, 312770, 252417, 210188, 868426, 868434,
		868442, 21695, 232378, 607517, 508586, 156876, 271373, 271381
	Prednisolone	21679, 2230619, 2152541, 2245532
	Methylprednisolone	1934325, 1934333, 1934341, 30759, 30767, 36129, 30988, 2245406,
		2245400, 2245408, 2245407, 2241229, 2231893, 2231894,
		2231895, 2232750, 2232748, 2063727, 2063697, 2063719,
		2063700, 36137, 2230210, 2230211, 30678, 30651, 30643
	Betamethasone	2237835, 36366, 2063190, 176834, 28096, 28185
	Hydrocortisone	888222, 888230, 888206, 888214, 30910, 30929, 872520, 872539,
		878618, 878626, 30635, 30600, 30619, 30627
	Dexamethasone	2261081, 2250055, 213624, 16462, 354309, 716715, 874582,
		1977547, 664227, 2204274, 2204266, 295094, 285471, 489158,
		2239534, 732893, 732885, 2260301, 2237044, 2260298, 2237046,
		2237045, 1946897, 1964976, 1964968, 1964070, 2279363, 783900,
		751863, 2311267, 2240687, 2240685, 2240684
Other xanthines	Theophylline, combination	545090, 476374, 334510, 356123, 792942, 721301, 317225, 828718,
		640093, 828726, 828742, 307548

DIN, Drug identification number.

TABLE E2. Random-effects ordinal regression with 3 levels of symptom control stability (0 [stable transition], 1 [unstable transition], or 2 [very unstable transition])

	Estimate	SE	OR	95% CI	P value
Medication possession ratio (MPR)					.22
MPR < 80%	Reference				
MPR ≥ 80%	−0.17	0.14	0.84	0.64-1.11	
Comorbidity	−0.07	0.03	0.93	0.89-0.98	.01*
Visit season					.50
Fall	Reference				
Winter	0.18	0.15	1.20	0.90-1.60	
Spring	0.21	0.15	1.23	0.92-1.65	
Summer	0.10	0.15	1.10	0.83-1.47	
Visit	−0.09	0.05	0.91	0.83-1.00	.05
Age	< 0.01	0.01	1.00	0.99-1.02	.51
Sex					.01*
Male	Reference				
Female	0.75	0.27	2.12	1.24-3.62	
Ethnicity					.86
Asian	Reference				
Caucasian	−0.09	0.25	0.91	0.56-1.48	
Other	0.06	0.36	1.06	0.53-2.14	
Annual household income					.47
<\$60,000	Reference				
>\$60,000	0.20	0.17	1.22	0.87-1.71	
Missing data	−0.06	0.38	0.94	0.45-1.97	
Education					.33
Below postsecondary	Reference				
Postsecondary or higher	0.24	0.25	1.27	0.78-2.06	
Age at asthma diagnosis	<0.01	0.01	1.00	0.99-1.01	.79
Number of allergens causing asthma symptoms	−0.03	0.02	0.97	0.94-1.01	.12
Number of pack-years	−0.04	0.04	0.96	0.89-1.03	.21
Number of years working in a dusty job	0.02	0.01	1.02	1.00-1.03	.10
FEV ₁ reversibility	−0.02	0.01	0.98	0.96-1.00	.04*
FVC	0.20	0.15	1.22	0.92-1.62	.17
PEF	0.06	0.06	1.06	0.94-1.19	.36
Percent predicted FEV ₁	−0.01	0.01	0.99	0.98-1.00	.11

CI, Confidence interval; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; OR, odds ratio; PEF, peak expiratory flow; SE, standard error.

*P < .05.

TABLE E3. Random-effects logistic regression (0 [stable transition], 1 [unstable transition]) with MPR entered in the model as a continuous variable

	Estimate	SE	OR	95% CI	P value
MPR [†]	−0.02	0.01	9.98	9.97-10.00	.04*
Comorbidity	−0.06	0.02	0.94	0.90-0.99	.02*
Visit season					.56
Fall	Reference				
Winter	0.20	0.15	1.22	0.90-1.65	
Spring	0.19	0.16	1.21	0.88-1.61	
Summer	0.11	0.15	1.12	0.83-1.51	
Visit	−0.11	0.05	0.90	0.81-0.99	.03*
Age	<0.01	0.01	1.00	0.99-1.02	.54
Sex					.01*
Male	Reference				
Female	0.69	0.26	1.99	1.18-3.33	
Ethnicity					.84
Asian	Reference				
Caucasian	−0.06	0.24	0.94	0.59-1.51	
Other	0.13	0.35	1.13	0.57-2.24	
Annual household income					.70
<\$60,000	Reference				
>\$60,000	0.13	0.17	1.14	0.82-1.59	
Missing data	−0.06	0.36	0.95	0.46-1.93	
Education					.26
Below postsecondary	Reference				
Postsecondary or higher	0.27	0.24	1.31	0.82-2.09	
Age at asthma diagnosis	<0.01	< 0.01	1.00	0.99-1.01	.89
Number of allergens causing asthma symptoms	−0.02	0.02	0.98	0.95-1.01	.26
Number of pack-years	−0.04	0.03	0.96	0.89-1.02	.20
Number of years working in a dusty job	0.01	0.01	1.01	0.99-1.03	.25
FEV ₁ reversibility	−0.02	0.01	0.98	0.96-1.00	.05
FVC	0.20	0.14	1.22	0.92-1.60	.16
PEF	0.07	0.06	1.07	0.96-1.21	.23
Percent predicted FEV ₁	−0.01	0.01	0.99	0.98-1.00	.05

CI, Confidence interval; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; MPR, medication possession ratio; OR, odds ratio; PEF, peak expiratory flow; SE, standard error.

**P* < .05.

[†]Effect size is reported per 10% increase in MPR.

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