

Asthma Medication Ratio Phenotypes in Elderly Women



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What is already known about this topic? The low controller-to-total asthma medication ratio, estimated from drug claims data, was associated with a higher risk of poor asthma control in children and adults. No study addressed specifically the clinical significance of this ratio in elderly individuals.

What does this article add to our knowledge? Both the magnitude and the long-term fluctuations of the controller-to-total asthma medication ratio are able to identify groups of elderly individuals with asthma at an increased risk of poor asthma control.

How does this study impact current management guidelines? We generalized and extended previous studies on the clinical relevance of the controller-to-total asthma medication ratio. Drug claims data provide the opportunity to target poorly controlled asthma, and to implement tailored and timely prevention.

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Abbreviations used

ACO- Asthma-COPD overlap
 AQLQ- Asthma Quality of Life Questionnaire
 ATC- Anatomical Therapeutic Chemical
 BMI- Body mass index
 CI- Confidence interval
 COPD- Chronic obstructive pulmonary disease
 E3N- Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale
 GINA- Global Initiative for Asthma
 ICS- Inhaled corticosteroids
 LABA- Long-acting β_2 -agonists
 LCA- Latent class analysis
 LTRA- Leukotriene receptor antagonists
 MGEN- Mutuelle Générale de l'Education Nationale
 OR- Odds ratio

BACKGROUND: With population aging, further asthma research is needed in the elderly.

OBJECTIVE: We assessed the relevance of the controller-to-total asthma medication ratio and its fluctuations over time to identify participants with a subsequent risk of poor asthma-related outcomes among well-characterized elderly women.

METHODS: We studied 4,328 women with ever asthma (69.6 ± 6.1 years) from the Asthma-E3N study (Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale), which combined drug claims data since 2004 with prospective individual characteristics. The levels of the yearly controller-to-total asthma medication ratio from 2004 to 2011 were included in latent class analysis to identify groups of women characterized by specific long-term fluctuations of the ratio. Multiple regression models estimated the subsequent risk of uncontrolled asthma, asthma attacks, asthma exacerbations, and poor asthma-related quality of life associated with the level and the fluctuations of the ratio.

RESULTS: A short-term (12 months) ratio below 0.5 was associated with a higher risk of subsequent uncontrolled asthma, asthma attacks, asthma exacerbations (odds ratio [95% confidence interval (CI)] = 2.13 [1.41; 3.23], 1.51 [1.01; 2.26], and 2.18 [1.37; 3.44], respectively), and a lower total asthma quality of life questionnaire score (β [95% CI] = -0.49 [-0.68 ; -0.29]). The analysis of the long-term fluctuations of the ratio identified 5 profiles ("Never regular treatment," 53.2%; "Persistent high ratio," 21.8%; "Increasing ratio," 4.4%; "Initiating treatment," 8.8%; "Treatment discontinuation," 11.8%). The subsequent risk of poor asthma-related outcomes was significantly higher in profiles characterized by no or interrupted asthma maintenance therapy over time, compared with the "Persistent high ratio" group.

CONCLUSIONS: The level and the long-term fluctuations of the controller-to-total asthma medication ratio predict poor asthma-related outcomes in elderly women. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:897-906)

Key words: Asthma; Elderly people; Asthma phenotypes; Asthma medications; Drug claims data

According to the World Health Organization, "aging well" is a global priority.¹ The worldwide burden of aging represents a public health challenge to adapt the quality of care of chronic

diseases, such as asthma. Asthma in the elderly is a heterogeneous disease as prevalent as in the youngest population (5% to 10%) and affecting more often women.²⁻⁵ Asthma in the elderly is marked by poor control, higher rate of mortality, health care use and medical costs related to asthma and multimorbidity, and poorer health-related quality of life than asthma in younger adults.^{2,4} Its management is hampered by multiple factors including misdiagnosis, underdiagnosis, undertreatment, comorbidities such as chronic obstructive pulmonary disease (COPD), and potentially lower drug response.²⁻⁷ Current guidelines for asthma therapeutic management do not consider asthma in the elderly as a specific condition. In addition, older adults are usually not included in randomized controlled trials, limiting the extrapolation of the results to this age group.^{5,8,9}

The global burden of asthma needs ongoing monitoring aiming at identifying patients at high risk of adverse events. Claims data provide the unique opportunity to prospectively follow large populations and identify such patients.¹⁰ Asthma medication ratios calculated from drug administrative data have been developed to assess the asthma quality of care.¹¹⁻¹⁶ These ratios, mainly studied in the US population, have been shown to have a good predictive ability to detect adults with poor asthma-related outcomes in the short term. However, such quality-of-care markers might behave differently in other countries with a different health care system, or in an older population. Moreover, besides the level of this ratio estimated over a specific time window, its long-term fluctuations have never been addressed. It is unknown to what extent these fluctuations over several years could identify specific asthma trajectories related to the subsequent risk of poor asthma-related outcomes.

We prospectively investigated the controller-to-total asthma medication ratio in a unique population-based cohort of elderly women. Our specific aims were: (1) to characterize the controller-to-total asthma medication ratio in elderly women and to identify its determinants; (2) to prospectively assess the relationship of the short-term (12 months) ratio with the subsequent risk of poor asthma-related outcomes; and (3) to prospectively investigate the relationship of distinct profiles of the long-term fluctuations of the ratio with asthma-related outcomes.

METHODS

Population

Analyses were performed among participants with ever asthma from the Asthma-E3N study (Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale). The Asthma-E3N study (2011-2012) is a nested case-control study on asthma within the E3N study, a prospective study of major chronic diseases among female members of a French national health insurance plan covering mostly teachers, aged 40 to 65 years at inclusion in 1990.^{17,18} All women who reported having ever had asthma (defined by a positive answer to the question "Have you ever had an asthma attack?" as recommended by the American Thoracic Society Epidemiology Standardization Project¹⁹) at least once between 1992 and 2008 ($n = 7,100$) and confirmed in the Asthma-E3N questionnaire were included in the analyses.^{17,18,20} In addition to detailed questionnaires, dispensings for nonhospital medications were comprehensively collected from the Mutuelle Générale de l'Education Nationale (MGEN) database for each woman from 2004 onwards.

The study protocol was approved by the French Institutional Ethics Committee and written informed consent was obtained for all participants. Ethical approval was granted to use the MGEN database.

Level and long-term fluctuations of the controller-to-total asthma medication ratio

Asthma medications were identified by Anatomical Therapeutic Chemical (ATC) codes from the exhaustive MGEN drug database.²¹ As recently proposed, the controller-to-total asthma medication ratio was defined over 12 months as the ratio of the number of dispensed inhaled corticosteroids (ICS, alone and combined) and leukotriene receptor antagonists (LTRA) to the number of dispensed R03 medications (drugs for obstructive airway diseases according to the ATC classification).¹⁵ As in previously published studies, the ratio was calculated among women regularly exposed to asthma maintenance therapy (≥ 4 dispensings of ICS or LTRA) over 12-month periods; we considered a 0.5-threshold to define low (<0.5) and high ratios (≥ 0.5).¹¹⁻¹⁶ The ratio was calculated in the 12 months that preceded each outcome to assess the relationship of the short-term ratio with the subsequent risk of poor asthma-related outcomes (from month -13 to month -1 for asthma control and the health-related quality of life, and from month -24 to month -12 for asthma attacks and exacerbations, which were reported over the preceding year) (see [Figure E1](#) in this article's Online Repository at www.jaci-inpractice.org).

Level of asthma therapy

The level of asthma therapy was determined over the 12 months that preceded the asthma-related outcomes, according to the Global Initiative for Asthma (GINA) 2016 guidelines (see this article's Online Repository at www.jaci-inpractice.org).

Asthma-related outcomes assessed at the Asthma-E3N questionnaire

The asthma control level was assessed over the previous month by the standardized and validated Asthma Control Test.²² It covers 5 domains (symptom frequency, rescue therapy utilization, sleep interference, activity limitation, and self-rating of control) and varies from 5 to 25 (ie, higher score meaning better asthma control). A 19-threshold was used to define controlled versus uncontrolled asthma.²² The health-related quality of life was assessed by the standardized and validated Asthma Quality of Life Questionnaire (AQLQ), consisting of 32 questions on a 7-point scale (from 7 = not impaired at all to 1 = severely impaired) relating to the preceding 2 weeks, and covering 4 domains (symptoms, activity limitation, emotional function, and susceptibility to environmental exposure).²³ The overall AQLQ score was computed as the mean of all questions and was compared with the smallest difference considered as clinically and socially relevant (0.5).²³ Asthma attack was assessed by a positive answer to, "Have you had an asthma attack over the previous 12 months?" Asthma exacerbation was defined as the report of an asthma attack lasting at least 2 days during the same period. Severe exacerbation was defined with self-reported emergency health care use for asthma (emergency department visit or hospital admission), oral corticosteroid courses during at least 3 days, or modification of asthma maintenance therapy.²⁴

Characteristics

Sociodemographic characteristics included age, body mass index (BMI), educational level ($<$ high school diploma; high school to

2-level university; 3-/4-level university; ≥ 5 -level university), and active smoking (never, ex-, and current smoker). Asthma characteristics included age at asthma onset (<16 , 16-40, and ≥ 40 years old), a 3-class asthma symptom score according to GINA recommendations assessed over the 3 months that preceded the Asthma-E3N questionnaire, and parental history of asthma (none, father, mother, and both). Chronic comorbidities strongly associated with asthma (ever eczema, ever rhinitis, and COPD) were also included. COPD was defined from the Asthma-E3N self-questionnaire by a positive answer to the question, "Did a doctor ever tell you that you had one of these COPD forms: chronic bronchitis, emphysema, COPD (unspecified form)?"²⁵ Women who reported COPD were considered as having asthma-COPD overlap (ACO). Medical follow-up (frequency of medical consultations and physician specialization) was assessed in the 12 months that preceded the Asthma-E3N questionnaire.

Selection bias

A previous study showed that the women not invited to participate to the Asthma-E3N study (women who did not answer the asthma question in the previous E3N questionnaires) did not show marked differences from the Asthma-E3N participants.²⁰

Statistical analysis

The controller-to-total asthma medication ratio was described among elderly women with ever asthma using a 0.5-threshold. Potential determinants of the controller-to-total asthma medication ratio were selected from the literature, and we hypothesized that older age, higher BMI, lower educational level, and smoking were associated with a low ratio.⁸ Linear and logistic regressions adjusted for age, active smoking, ever rhinitis, and BMI were used to assess the predictive ability of the short-term ratio for the subsequent risk of poor asthma-related outcomes. To keep the whole population in the analyses, we performed multiple imputation (see this article's Online Repository at www.jaci-inpractice.org).²⁶

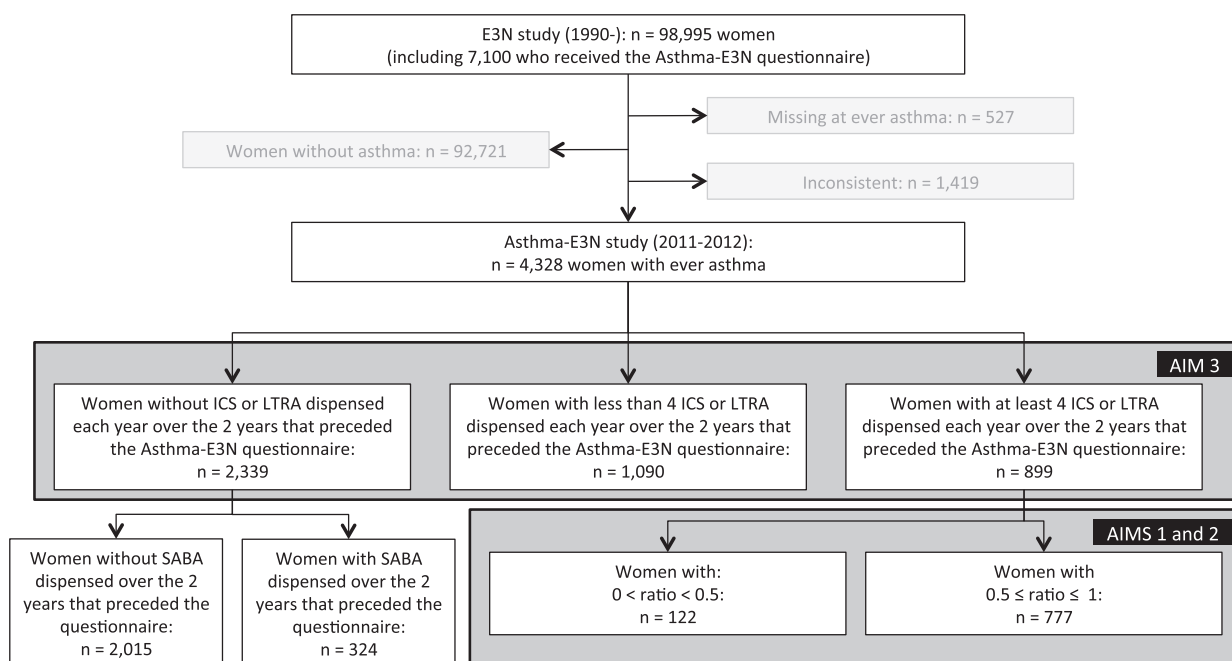
As previously used to define trajectories of wheezing phenotypes and specific IgE response, we applied latent class analysis (LCA),²⁷ a data-driven approach to identify groups of women characterized by the 8-year fluctuations of the ratio (see this article's Online Repository at www.jaci-inpractice.org).^{28,29} The impact of the longitudinal profiles of the ratio derived from the LCA on the subsequent risk of uncontrolled asthma, asthma attacks, and exacerbations was estimated by logistic regressions weighted by the posterior probability of belonging to the cluster to account for the uncertainty in the cluster membership. The LCA was performed using the SAS 9.4 statistical software (SAS Institute, Cary, NC) with the SAS LCA procedure.³⁰

A sensitivity analysis considering a 0.75-threshold of the ratio (according to the ratio distribution in the population) was performed to prospectively assess the relationship of the short-term ratio with the subsequent risk of poor asthma-related outcomes. We also conducted 2 stratified analyses according to: (1) the level of asthma therapy, and (2) the COPD status.

RESULTS

Study population

Among the 6,724 women who completed the Asthma-E3N questionnaire (response rate: 94.7%), 4,328 reported to have ever had asthma ([Figure 1](#)). They were 69.6 ± 6.1 years old, mostly with high educational level, and never or ex-smokers ([Table I](#)). Two-thirds had late-onset asthma (≥ 40 years old)



E3N, Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Éducation Nationale; ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonists; SABA, short-acting β_2 -agonists.

FIGURE 1. Study population flowchart and study aims. “Inconsistent” defined women who did not report to have ever asthma in the Asthma-E3N questionnaire. AIM 1, to characterize the level of the controller-to-total asthma medication ratio in elderly women and identify its determinants ($n = 899$); AIM 2, to prospectively assess the relationship of the short-term (12 months) ratio with the subsequent risk of poor asthma-related outcomes; and AIM 3, to prospectively investigate the relationship of distinct profiles of the long-term fluctuations of the ratio with asthma-related outcomes ($n = 4,328$).

and 21.2% reported at least 3 symptoms in the previous 3 months. COPD and ever rhinitis were reported by 22.7% and 72.1%, respectively.

Among women regularly exposed to asthma maintenance therapy ($n = 899$) during the study period, 13.6% had a low controller-to-total asthma medication ratio (<0.5). The intra-class correlation coefficient of the ratio (95% confidence interval [CI]) estimated for the 2 consecutive years (month -24 to -12 and month -13 to -1) was 0.93 [0.92; 0.93]. As compared with women with a high ratio (≥ 0.5), women with a low ratio were older, more often obese and ex- or current smokers, and had more often asthma symptoms and COPD (Table I). No association was found between ratio level and educational level, allergic and atopic status, age at asthma onset, parental history of asthma, and medical follow-up. Analyses adjusted for age showed similar results (data not shown). As expected, women with a low ratio had a lower asthma maintenance therapy level (22.2% vs 5.1%, $P < .001$) and they more often used asthma reliever medications than those with a high ratio (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

Level of the controller-to-total asthma medication ratio: association with asthma-related outcomes and relevance in ACO

A low ratio was associated with a higher risk of subsequent uncontrolled asthma (49.5% vs 29.8%, $P < .001$), asthma attacks (47.4% vs 37.5%, $P = .04$), asthma exacerbations (33.3% vs

19.2%, $P = .001$), and a lower total AQLQ score (5.1 ± 1.2 vs 5.7 ± 1.0 ; adjusted β [95% CI] = -0.49 [-0.68 ; -0.29], $P < .001$), as compared with a high ratio (Figure 2, A). Women with a low ratio had an increased risk of severe asthma exacerbations (31.7% vs 17.9%; adjusted odds ratio [OR] [95% CI] = 2.08 [1.31 ; 3.31], $P = .001$). Results were similar in women with ACO except for asthma control for which no association was observed (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Associations were not modified when considering a ratio threshold of 0.75 (see Tables E3 and E4 in this article's Online Repository at www.jaci-inpractice.org).

The patterns of associations between the ratio level and the asthma-related outcomes did not differ according to the level of asthma maintenance therapy (P interaction $>.41$), although most of the associations did not reach the level of statistical significance in the low asthma maintenance therapy group because of limited statistical power (Figure 2, B and C).

Long-term fluctuations of the controller-to-total asthma medication ratio and asthma-related outcomes

Among the 4,328 women with ever asthma, the LCA identified 5 groups of women characterized by their fluctuations of the ratio over the 2004-2011 period: (A) never regularly asthma maintenance therapy (<4 dispensings of ICS or LTRA during a year) (labeled “Never regular treatment”; $n = 2,302$; 53.2%), (B) persistent ratio ≥ 0.5 (labeled “Persistent high ratio”; $n = 943$; 21.8%), (C) increased ratio from <0.5 to ≥ 0.5 (labeled

TABLE I. Characteristics of the study population according to asthma controller medication exposure over the 2 years that preceded the Asthma-E3N questionnaire*

Asthma ECR questionnaire								
	Whole population (n = 4,328)	Women unexposed (n = 2,339)	Women irregularly exposed (n = 1,090)	Women regularly exposed				
Variable				Whole group (n = 899)	Ratio <0.5 (n = 122)	Ratio ≥0.5 (n = 777)	P value†	P value‡
Sociodemographic characteristics								
Age (y), mean ± SD	69.6 ± 6.1	69.2 ± 5.9	69.4 ± 6.0	71.0 ± 6.3	72.2 ± 6.4	70.9 ± 6.2	<.001	.02
BMI (kg/m ²), n (%)								
BMI < 20	431 (10.9)	253 (11.9)	100 (10.1)	78 (9.5)	11 (9.8)	67 (9.4)	.02	.04
20 ≤ BMI < 25	2,082 (52.9)	1,159 (54.4)	492 (49.9)	431 (52.6)	56 (50.0)	375 (53.0)		
25 ≤ BMI < 30	1,035 (26.3)	526 (24.7)	283 (28.7)	226 (27.6)	25 (22.3)	201 (28.4)		
BMI ≥ 30	389 (9.9)	193 (9.0)	111 (11.3)	85 (10.3)	20 (17.9)	65 (9.2)		
Education level, n (%)								
<High school diploma	449 (10.8)	251 (11.1)	109 (10.3)	89 (10.4)	14 (11.8)	75 (10.2)	<.001	.79
High school to 2-level university	2,050 (49.2)	1,033 (45.8)	553 (52.6)	464 (54.2)	67 (56.3)	397 (53.9)		
3-/4-level university	840 (20.2)	487 (21.6)	204 (19.4)	149 (17.4)	20 (16.8)	129 (17.5)		
≥5-level university	826 (19.8)	486 (21.5)	186 (17.7)	154 (18.0)	18 (15.1)	136 (18.4)		
Smoking, n (%)								
Never smoker	2,152 (50.1)	1,106 (47.6)	557 (51.8)	489 (54.6)	53 (43.8)	436 (56.3)	.005	.03
Ex-smoker	1,975 (46.0)	1,118 (48.2)	482 (44.8)	375 (41.9)	62 (51.2)	313 (40.5)		
Current smoker	166 (3.9)	98 (4.2)	37 (3.4)	31 (3.5)	6 (5.0)	25 (3.2)		
Comorbidities								
COPD, n (%)	863 (22.7)	269 (13.0)	266 (28.0)	328 (41.6)	63 (57.8)	265 (39.0)	<.001	<.001
Ever rhinitis, n (%)	2,978 (72.1)	1,556 (69.8)	797 (76.3)	625 (72.9)	82 (68.9)	543 (73.6)	<.001	.29
Ever eczema, n (%)	1,432 (34.4)	805 (35.8)	356 (33.9)	271 (31.4)	36 (30.8)	235 (31.5)	.06	.87
Asthma								
Age at asthma onset (y), n (%)								
Age < 16	1,225 (30.9)	776 (36.4)	251 (25.4)	198 (23.5)	33 (28.9)	165 (22.7)	<.001	.13
16 ≤ age < 40	1,282 (32.4)	717 (33.7)	318 (32.1)	247 (29.3)	37 (32.5)	210 (28.8)		
Age ≥ 40	1,455 (36.7)	637 (29.9)	421 (42.5)	397 (47.2)	44 (38.6)	353 (48.5)		
Asthma symptoms, n (%)								
0	1,248 (37.5)	893 (47.5)	210 (26.6)	145 (21.9)	14 (16.9)	131 (22.7)	<.001	.04
1	891 (26.7)	582 (31.0)	168 (21.3)	141 (21.3)	13 (15.6)	128 (22.1)		
2	488 (14.6)	189 (10.1)	157 (19.8)	142 (21.5)	15 (18.1)	127 (22.0)		
≥3	705 (21.2)	217 (11.4)	255 (32.3)	233 (35.3)	41 (49.4)	192 (33.2)		
Parental asthma, n (%)								
None	3,071 (76.2)	1,714 (78.1)	748 (74.2)	609 (73.5)	80 (72.8)	529 (73.6)	.02	.53
Father	454 (11.3)	239 (10.9)	108 (10.7)	107 (12.9)	11 (10.0)	96 (13.3)		
Mother	437 (10.8)	208 (9.5)	131 (13.0)	98 (11.8)	16 (14.5)	82 (11.4)		
Both	69 (1.7)	33 (1.5)	21 (2.1)	15 (1.8)	3 (2.7)	12 (1.7)		
Medical follow-up during the last 12 mo, n (%)	1,306 (33.1)	269 (12.3)	467 (48.5)	570 (72.2)	75 (73.5)	495 (72.0)	<.001	.76
Regular monitoring for asthma	733 (18.3)	96 (4.3)	190 (19.4)	447 (55.0)	70 (60.3)	377 (54.2)	<.001	.22
General practitioner	1,188 (30.9)	304 (13.8)	437 (46.3)	447 (64.4)	67 (69.1)	380 (63.6)	<.001	.30
Consultant	826 (21.7)	158 (7.3)	258 (28.3)	410 (56.3)	63 (64.3)	347 (55.1)	<.001	.09

BMI, Body mass index; COPD, chronic obstructive pulmonary disease; E3N, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; SD, standard deviation.

*Women regularly exposed had at least 4 dispensings of inhaled corticosteroids or leukotriene receptor antagonists each year during the 2-year period.

†P value comparing the 3 groups of asthma maintenance therapy exposition (unexposed, irregularly, and regularly exposed).

‡P value comparing the 2 groups of the controller-to-total asthma medication ratio among women regularly exposed (ratio < 0.5 and ratio ≥ 0.5).

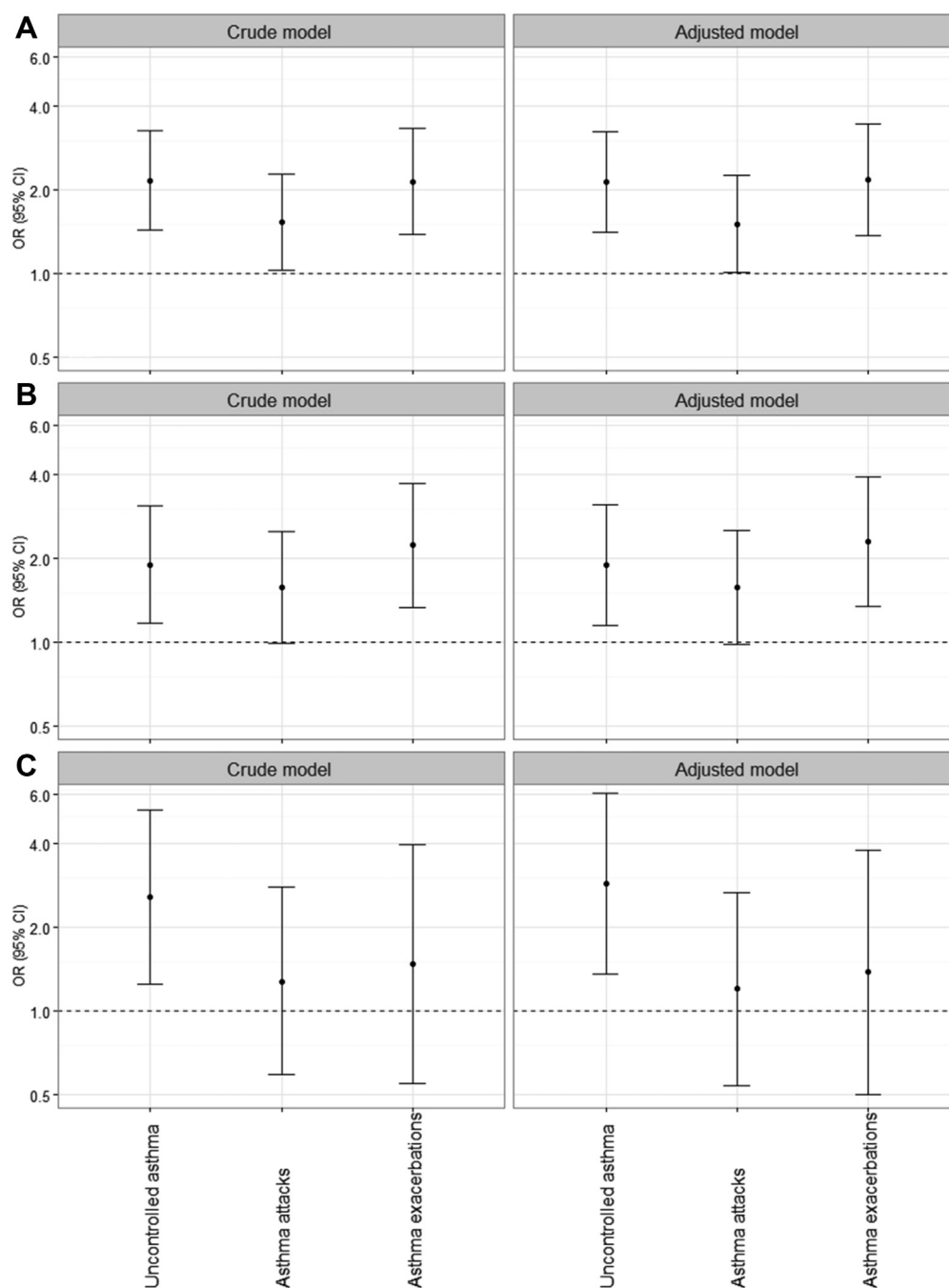


FIGURE 2. Predictive ability of the controller-to-total asthma medication ratio below 0.5 (odds ratio with 95% CI) for poor asthma-related outcomes (uncontrolled asthma, asthma attacks, and asthma exacerbations) among women regularly exposed to asthma maintenance therapy over the previous 12 months ($n = 899$): **A**, whole population; **B**, women with a high asthma maintenance therapy level (steps 4 and 5 according to the GINA classification; $n = 555$ over the 2 years that preceded the Asthma-E3N questionnaire); and **C**, women with a low asthma maintenance therapy level (steps 1 to 3 according to the GINA classification; $n = 344$ over the 2 years that preceded the Asthma-E3N questionnaire). Adjusted models included age, active smoking, ever rhinitis, and body mass index. *CI*, Confidence interval; *E3N*, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Éducation Nationale; *GINA*, Global Initiative for Asthma; *OR*, odds ratio.

“Increasing ratio”; $n = 190$; 4.4%), (D) initiation of asthma maintenance therapy with a ratio ≥ 0.5 (labeled “Initiating treatment”; $n = 381$; 8.8%), and (E) cessation of asthma maintenance therapy during the period (labeled “Treatment discontinuation”;

$n = 512$; 11.8%) (Figure 3). The mean ($\pm$ standard deviation) of the maximum posterior probabilities of belonging to the assigned cluster was high (0.93 ± 0.13) and above 0.80 for each cluster, indicating a clear delineation of the clusters.

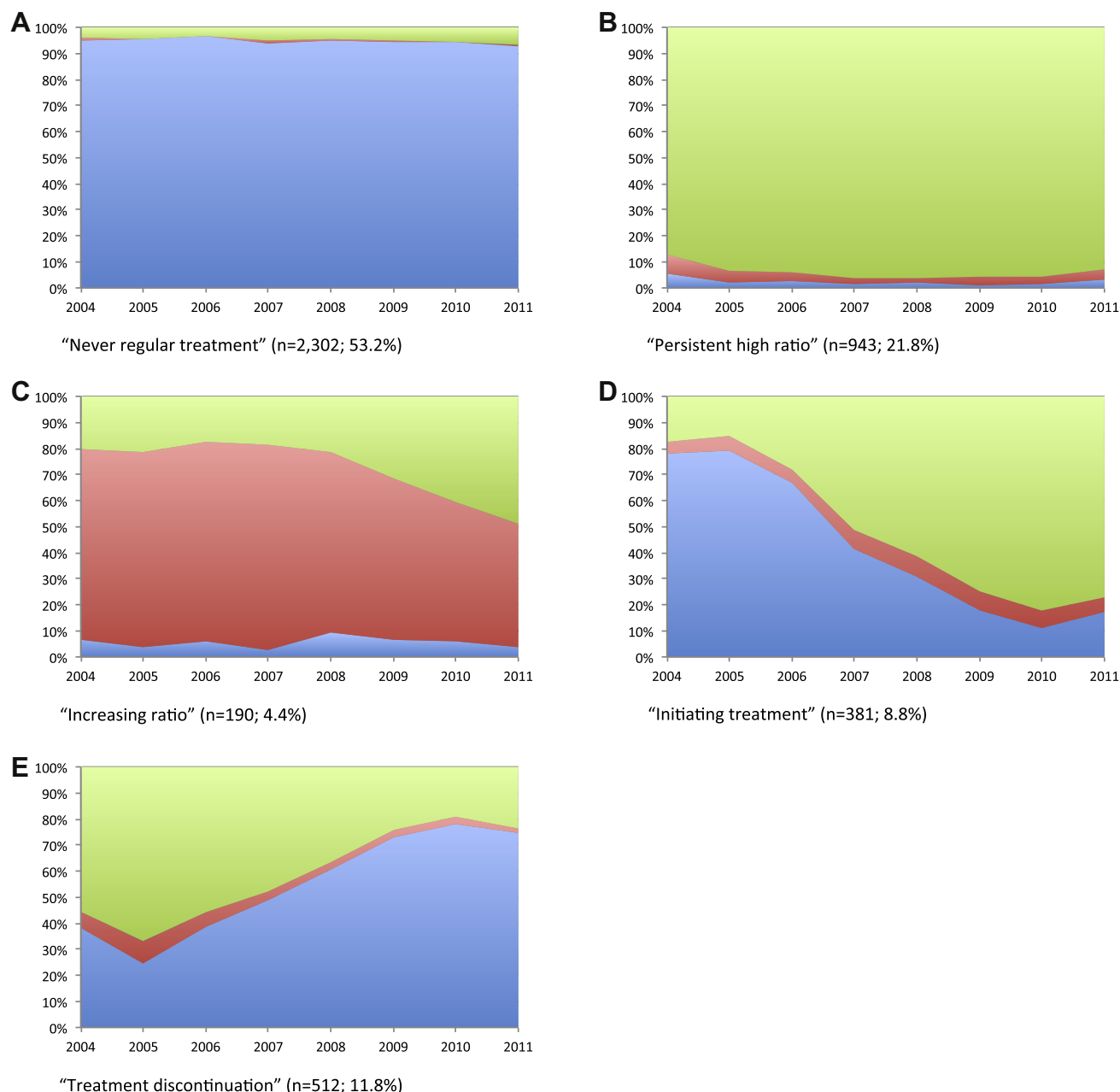


FIGURE 3. Description of the fluctuations of the controller-to-total asthma medication ratio over an 8-year period, defined by latent class analysis among women with ever asthma from the Asthma-E3N study ($n = 4,328$): **A**, never regularly asthma maintenance therapy (labeled "Never regular treatment"); **B**, persistent controller-to-total asthma medication ratio ≥ 0.5 (labeled "Persistent high ratio"); **C**, increased controller-to-total asthma medication ratio from < 0.5 to ≥ 0.5 (labeled "Increasing ratio"); **D**, initiation of asthma maintenance therapy with a controller-to-total asthma medication ratio ≥ 0.5 (labeled "Initiating treatment"); and **E**, cessation of asthma maintenance therapy during the period (labeled "Treatment discontinuation"). *Green* represents a ratio ≥ 0.5 (ie, an adequate asthma quality of care), *red* a ratio < 0.5 (ie, an inadequate asthma quality of care), and *blue* an irregular asthma maintenance therapy (ie, < 4 dispensings of ICS or LTRA over a 12-month period). The vertical axis represents the proportion of women in each category. *E3N*, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Éducation Nationale; *ICS*, inhaled corticosteroids; *LTRA*, leukotriene receptor antagonists.

Women belonging to the "Persistent high ratio" cluster were less often ever smokers than those in the other clusters (see Table E5 in this article's Online Repository at www.jaci-inpractice.org). As compared with women from the "Persistent high ratio" cluster, women from the "Never regular treatment" and "Treatment discontinuation" clusters had a

younger age, higher educational level, and reported less often COPD and medical follow-up. As compared with the reference group ("Persistent high ratio"), women belonging to the "Increasing ratio," "Initiating treatment," and "Treatment discontinuation" clusters had a higher BMI and those belonging to the "Never regular treatment" cluster had less

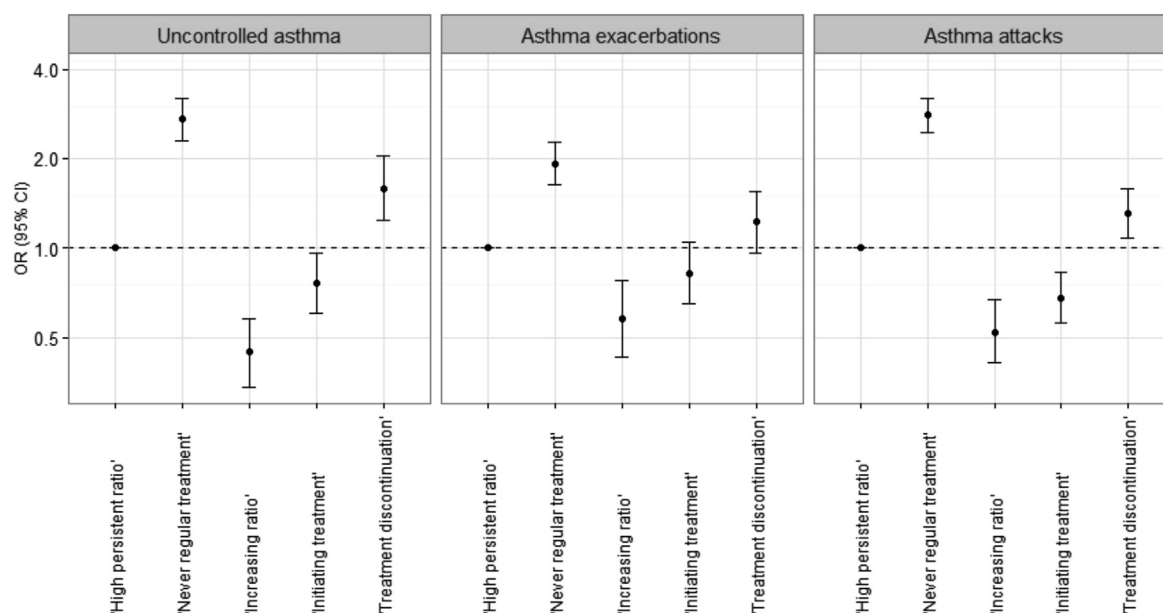


FIGURE 4. Associations (*odds ratio* with 95% CI) between the clusters of the controller-to-total medication ratio fluctuations obtained by latent class analysis and poor asthma-related outcomes (uncontrolled asthma, asthma attacks, and asthma exacerbations) among women with ever asthma from the Asthma-E3N study ($n = 4,328$). Logistic regressions were weighted by the posterior probability of belonging to the cluster. *CI*, Confidence interval; *E3N*, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Éducation Nationale; *OR*, odds ratio.

asthma symptoms, less rhinitis, and a younger age at asthma onset.

The trajectories of the ratio over time were associated with a different risk of poor-asthma-related outcomes. Women belonging to the “Never regular treatment” and “Treatment discontinuation” clusters had an increased risk of subsequent uncontrolled asthma and asthma attacks or exacerbations, as compared with those belonging to the reference group (Figure 4). The “Increasing ratio” and “Initiating treatment” clusters were associated with a lower risk of each poor asthma-related outcome, as compared with the “Persistent high ratio” cluster, although women belonging to these 3 clusters had a high short-term ratio. Among women with a low short-term ratio, the risk of poor asthma-related outcomes increased in the “Treatment discontinuation” cluster, as compared with the “Never regular treatment” cluster (OR [95% CI] = 1.60 [1.25; 2.04] and 1.31 [1.04; 1.59] for uncontrolled asthma and asthma attacks, respectively).

DISCUSSION

This is the first study showing that a low level of the controller-to-total asthma medication ratio increases the subsequent risk of poor asthma-related outcomes in elderly women. By investigating a new feature of this ratio, its long-term fluctuations, we identified specific asthma trajectories at an increased risk of poor asthma-related outcomes.

A novelty of our analysis relies on the focus in the elderly population which is growing worldwide.⁵ A major strength of our study relies on the design of the Asthma-E3N study, combining personal and phenotypic characteristics collected by questionnaire complemented by an independent 8-year

comprehensive drug database. The asthma-related outcomes were measured once at the end of the longitudinal follow-up, and not throughout the study period. We therefore could not investigate the impact of the asthma quality-of-care markers in the evolution of the outcomes. The study design allowed including all participants with ever asthma independently of the asthma treatment status, thus limiting the selection bias. The Asthma-E3N study allows a comprehensive assessment of different domains of asthma-related outcomes derived from standardized and validated questionnaires. We acknowledge that several months might separate some asthma-related outcomes from the measurement period of the ratio. Nevertheless, this should not affect our results, as there was a very low within participant variability of the ratio within the 2-year period. We acknowledge that our study has some limitations. The Asthma-E3N study included only women, thus limiting the external validity regarding men. Nevertheless, our findings are highly relevant from the public health viewpoint because asthma in elderly women is more prevalent and severe than in men.³ Ever asthma was defined by a positive answer to the question “Have you ever had an asthma attack?”, a question widely used in epidemiological studies.¹⁹ As previously shown in the E3N population, the repeated answer to this question over time improved the assessment of ever asthma, limiting potential misdiagnosis.²⁰ Moreover, the associations between the ratio and asthma-related outcomes were estimated in women regularly exposed to asthma maintenance therapy (≥ 4 dispensings of ICS or LTRA in the past 12 months), for which the diagnosis of asthma is very likely. To define ACO, COPD was assessed by questionnaire, as the protocol did not include lung function measurements.^{2,3,5,7} However, the self-report of COPD was validated in a previous study among health professionals.²⁵

The controller-to-total asthma medication ratio included LTRA in the numerator, as suggested in a recent study.¹⁵ Considering LTRA in the ratio are relevant in the elderly because it has been suggested that LTRA improve asthma control in this population.^{2,31} The 2-class ratio we used is easily applicable in practice and displays similar performance to a weighted ratio.³² Our findings show that both 0.5- and 0.75-thresholds for the ratio level performed similarly when studied in relation with asthma-related outcomes in elderly women. Our study combined with previous studies supports the 0.5-threshold of this unweighted ratio.^{14,15,32}

To our knowledge, this is the first time that the personal, medical, and socioeconomic characteristics associated with the level of the controller-to-total asthma medication ratio were investigated among elderly women. No differences regarding educational level or medical follow-up were observed between the low and high ratio groups probably because of the limited interindividual variability of the socioeconomic status in our population, mostly composed of teachers. The investigation of a link between the ratio and asthma-related comorbidities was focused on rhinitis, eczema, and COPD, which are strongly associated with asthma. We acknowledge that all nonasthma medications and asthma-related comorbidities, which might act as confounders in the studied associations, were not considered in the analyses. Further studies with a comprehensive approach are needed to provide a global view of multimorbidity in the elderly with asthma.

Our findings extend those from previous studies by showing that the controller-to-total asthma medication ratio, using administrative data as quality-of-care marker, is also relevant in elderly people.¹¹⁻¹⁶ The low prevalence of reported emergency department visit/hospitalization for asthma over the 12 months that preceded the Asthma-E3N questionnaire reported in this study (2.8%) did not enable us to properly address the association between the ratio and this outcome in our population.^{11,12,14,15} Nevertheless, analyses considering severe exacerbations showed similar patterns of association as those observed for any exacerbations. The statistical power of the stratified analyses was limited and prevented any firm conclusion. However, our findings suggest that the controller-to-total asthma medication ratio could be a clinically relevant marker in asthma across the whole age range and whatever the asthma severity, although less so in ACO, a specific phenotype.

To the best of our knowledge, this is the first study characterizing the long-term fluctuations of the controller-to-total asthma medication ratio and showing that some specific longitudinal profiles were associated with the subsequent risk of poor asthma-related outcomes. Asthma follows a dynamic process with changes in the disease symptoms over time.^{33,34} Compared with most chronic diseases, asthma does not always get worse with time and little is known about long-term fluctuations.³⁴ Previous studies showed that short-term fluctuations of airway function among individuals with asthma were associated with a higher risk of subsequent poor asthma-related outcomes.^{33,35} Recently, using a similar data-driven approach on administrative-linked health records, 3 trajectories of childhood asthma phenotypes were distinguished and differentially associated with environmental exposure.³⁶ In the present study, we identified 5 long-term trajectories of the ratio over 8 years. We assumed that women belonging to the “High persistent ratio”

had an optimal asthma quality of care over time (reference group), although we could not exclude that some of these women were overtreated. The risk of subsequent poor asthma-related outcomes differed between the clusters, a higher risk being observed in women with no or interrupted asthma maintenance therapy over time. A large part of our population had no regular asthma maintenance therapy over time, although 1 in 2 of these women had asthma symptoms over the previous 12 months. It suggests that undertreatment might explain the increased risk of poor asthma-related outcomes observed in the “Never regular treatment” cluster. The reduced perception of symptoms, undertreatment, and nonadherence are major factors, which hamper an optimal asthma quality of care, particularly in the elderly, leading to treatment cessation, and thus to adverse asthma events.^{5,37} On the contrary, the 2 other clusters (“Initiating treatment” and “Increasing ratio”) showed a lower subsequent risk of poor asthma-related outcomes than the reference group. This may be explained by an improvement of asthma therapeutic management over time and a lower severity of the disease among women belonging to these clusters, as compared with women belonging to the “High persistent ratio” cluster.

Our findings highlight the importance of characterizing the variability in asthma quality of care over time, as it provides complementary information to the short-term ratio level in predicting adverse asthma events. Indeed, among women with a similar short-term ratio level, the long-term fluctuations of the ratio were associated with a different risk of poor asthma prognosis. These findings are highly relevant in the context of the unmet needs in asthma management and suggest a new approach to analyze asthma treatments in the context of drug administrative database surveillance.

In conclusion, our findings that identified markers from drug claims data able to target elderly people at an increased risk of poor asthma control are particularly relevant in the context of the policies on aging, where health and care services are undergoing changes to adapt systems to the growing demands caused by expansion of chronic diseases and aging. The information obtained from this study will be valuable in the frame of the AIRWAYS ICPs (Integrative care pathways for airway diseases) initiative approved by the European Innovation Partnership on Active and Healthy Ageing, aimed at launching a collaboration to develop practical multisectoral care pathways to reduce chronic respiratory disease burden, mortality, and multimorbidity.³⁸ In the context of pharmacoepidemiological surveillance by drug administrative databases, we provided valuable insights into new ways to improve asthma quality of care.

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ONLINE REPOSITORY METHODS

Level of asthma therapy

The level of asthma therapy was determined over the 12 months that preceded the asthma-related outcomes, according to the Global Initiative for Asthma (GINA) 2016 guidelines: (1) step 1, regular use of inhaled corticosteroids (ICS) or leukotriene receptor antagonists (LTRA) over the 12 months (≥ 4 dispensings during the period) but not enough to be defined as mean daily asthma maintenance therapy; (2) step 2, low mean daily dose of ICS or LTRA or xanthines alone; (3) step 3, either (a) low mean daily dose of ICS associated with long-acting β_2 -agonists (LABA) or LTRA or theophylline or (b) medium/high mean daily dose of ICS; (4) step 4, medium/high mean daily dose of ICS associated with LABA or high mean daily dose of ICS associated with LTRA or theophylline; (5) step 5, add-on treatment (eg, omalizumab).^{E1} Oral corticosteroids were not included in our classification because of their use for many other conditions than asthma, particularly in the elderly. The GINA treatment steps were gathered into 2 levels (steps 1, 2, and 3 vs steps 4 and 5).

Statistical analysis

Multiple imputation. To keep the whole population in the analyses, we performed multiple imputation. Given the rather low proportion of missing data in the analysis (10.3%) and the rejection of the missing completely at random assumption ($P < .001$), we assumed a missing at random pattern of missing data. We thus performed 20 imputations using the PROC MI SAS procedure.^{E2}

Latent class analysis. Latent class analysis is a cluster-based model, used here to identify subgroups of women sharing a similar history in their asthma medication therapies. It estimates 2 sets of parameters: (1) the conditional probabilities, which represent the probabilities of belonging to a class given a specific pattern of the ratio, and (2) the posterior probabilities of cluster membership for each woman given their history of the controller-to-total asthma medication ratio (derived from the conditional probabilities), which allowed accounting for the uncertainty in the cluster membership. The number of profiles was determined using both the Akaike information criterion and the Bayesian information criterion.^{E3}

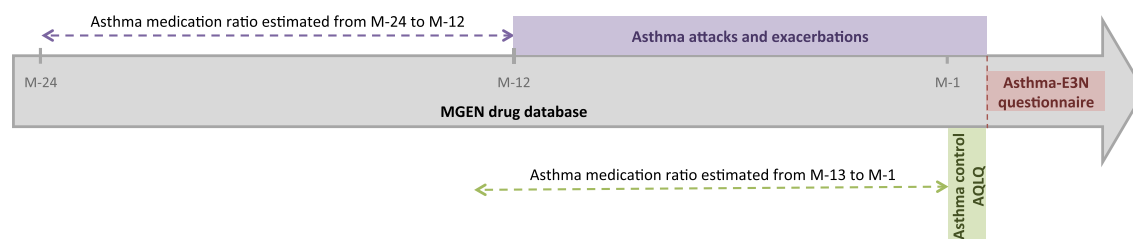


FIGURE E1. Study design for the definition of the level of the controller-to-total asthma medication ratio. The level of the controller-to-total asthma medication ratio was estimated from the MGEN drug database in the 12 months that preceded each asthma-related outcome (from month –13 to month –1 for asthma control and the health-related quality of life, and from month –24 to month –12 for asthma attacks and exacerbations, which were reported over the preceding year). *AQLQ*, Asthma quality of life questionnaire; *E3N*, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; *M*, month; *MGEN*, Mutuelle Générale de l'Education Nationale.

TABLE E1. Description of asthma medication treatments among the study population according to asthma controller medication exposure over the 2 years that preceded the Asthma-E3N questionnaire*

Mean number of dispensed units per 1-y period (mean $\pm$ SD)	Whole population (n = 4,328)	Women unexposed (n = 2,339)	Women irregularly exposed (n = 1,090)	Women regularly exposed			P value†	P value‡
				Whole group (n = 899)	Ratio < 0.5 (n = 122)	Ratio $\geq$ 0.5 (n = 777)		
Controller medications								
Inhaled corticosteroids (any type)	2.05 $\pm$ 3.51	0	1.69 $\pm$ 1.37	7.83 $\pm$ 3.56	8.21 $\pm$ 3.36	7.77 $\pm$ 3.59	<.001	.20
Inhaled corticosteroids (alone)	0.62 $\pm$ 1.89	0	0.66 $\pm$ 1.00	2.17 $\pm$ 3.55	5.16 $\pm$ 4.20	1.69 $\pm$ 3.19	<.001	<.001
Inhaled corticosteroids (ICS-LABA fixed combination)	1.44 $\pm$ 3.00	0	1.03 $\pm$ 1.33	5.66 $\pm$ 4.21	3.05 $\pm$ 4.11	6.08 $\pm$ 4.07	<.001	<.001
Leukotriene receptor antagonists	0.72 $\pm$ 2.62	0	0.22 $\pm$ 0.77	3.18 $\pm$ 4.95	0.86 $\pm$ 2.70	3.55 $\pm$ 5.13	<.001	<.001
Long-acting β_2 -agonists (other than ICS-LABA fixed combination)	0.39 $\pm$ 1.79	0.04 $\pm$ 0.50	0.42 $\pm$ 1.74	1.27 $\pm$ 3.17	5.28 $\pm$ 4.90	0.64 $\pm$ 2.22	<.001	<.001
Cromones	0.001 $\pm$ 0.023	0	0.002 $\pm$ 0.034	0.002 $\pm$ 0.033	0	0.003 $\pm$ 0.036	.005	.43
Xanthines	0.07 $\pm$ 0.93	0.01 $\pm$ 0.39	0.07 $\pm$ 0.97	0.24 $\pm$ 1.61	1.32 $\pm$ 3.72	0.07 $\pm$ 0.80	<.001	<.001
Omalizumab	0.01 $\pm$ 0.40	0	0	0.06 $\pm$ 0.88	0.18 $\pm$ 1.43	0.05 $\pm$ 0.76	<.001	.12
Long-acting muscarinic antagonists	0.20 $\pm$ 1.29	0.03 $\pm$ 0.44	0.15 $\pm$ 0.88	0.73 $\pm$ 2.50	3.12 $\pm$ 4.72	0.36 $\pm$ 1.64	<.001	<.001
Reliever medications								
Short-acting β_2 -agonists	0.58 $\pm$ 1.40	0.14 $\pm$ 0.51	0.77 $\pm$ 1.38	1.52 $\pm$ 2.24	2.89 $\pm$ 3.46	1.31 $\pm$ 1.90	<.001	<.001
Short-acting muscarinic antagonists	0.05 $\pm$ 0.51	0.004 $\pm$ 0.066	0.05 $\pm$ 0.45	0.17 $\pm$ 0.99	0.70 $\pm$ 2.22	0.08 $\pm$ 0.57	<.001	<.001

E3N, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonists; SD, standard deviation.

*Women regularly exposed had at least 4 dispensings of inhaled corticosteroids or leukotriene receptor antagonists each year during the 2-year period.

†P value comparing the 3 groups of asthma maintenance therapy exposition (unexposed, irregularly, and regularly exposed).

‡P value comparing the 2 groups of controller-to-total asthma medication ratio among women regularly exposed (ratio < 0.5 and ratio $\geq$ 0.5).

TABLE E2. Stratified analysis on chronic obstructive pulmonary disease (COPD) for the predictive ability of the controller-to-total asthma medication ratio below 0.5 (*odds ratio* or **beta* with 95% CI) for poor asthma-related outcomes (uncontrolled asthma, asthma attacks and exacerbations, and poor asthma-related quality of life) in women with asthma maintenance therapy over the 12 months that preceded each asthma-related outcome; models were adjusted for age, active smoking, ever rhinitis, and body mass index

Outcome	Women with COPD (n = 328)		Women without COPD (n = 460)	
	OR [95% CI]	P value	OR [95% CI]	P value
Uncontrolled asthma				
Ratio <0.5 vs ratio $\geq$ 0.5	1.32 [0.74; 2.35]	.34	3.83 [1.93; 7.63]	<.001
Asthma exacerbations				
Ratio <0.5 vs ratio $\geq$ 0.5	2.01 [1.08; 3.76]	.03	2.30 [1.11; 4.80]	.03
Asthma attacks				
Ratio <0.5 vs ratio $\geq$ 0.5	1.61 [0.90; 2.85]	.11	1.64 [0.87; 3.07]	.12
Poor asthma-related quality of life*				
Ratio <0.5 vs ratio $\geq$ 0.5	−0.37 [−0.66; −0.07]	.01	−0.55 [−0.86; −0.25]	<.001

CI, Confidence interval; OR, odds ratio.

Asthma-related quality of life was defined using the Asthma Quality of Life questionnaire.

TABLE E3. Description of the asthma-related outcomes according to a 0.75-threshold of the controller-to-total asthma medication ratio (n = 899)

Outcome	Whole population	0 ≤ ratio < 0.75	0.75 ≤ ratio ≤ 1	P value
Asthma control				
Controlled, n (%)	477 (67.6)	136 (52.9)	341 (76.0)	<.001
Uncontrolled, n (%)	229 (32.4)	121 (47.1)	108 (24.0)	
Asthma symptoms				
At least 1 asthma attack, n (%)	336 (38.8)	132 (42.7)	204 (36.6)	.08
At least 1 asthma exacerbation, n (%)	164 (21.1)	78 (28.6)	86 (17.0)	.0002
Asthma-related quality of life				
Symptoms, mean ± SD	5.6 ± 1.1	5.3 ± 1.2	5.8 ± 1.1	<.001
Activity limitation, mean ± SD	5.5 ± 1.1	5.2 ± 1.2	5.7 ± 1.0	<.001
Emotional function, mean ± SD	5.7 ± 1.2	5.4 ± 1.3	5.9 ± 1.1	<.001
Environmental exposure, mean ± SD	5.7 ± 1.2	5.4 ± 1.3	5.9 ± 1.2	<.001
Overall score, mean ± SD	5.6 ± 1.0	5.3 ± 1.1	5.8 ± 1.0	<.001

SD, Standard deviation.

Descriptive analysis was performed using non-imputed data. Asthma control was defined using the Asthma Control Test. Asthma-related quality of life was defined using the Asthma Quality of Life Questionnaire.

TABLE E4. Predictive ability of the controller-to-total asthma medication ratio below 0.75 (*odds ratio* or **beta* with 95% CI) for poor asthma-related outcomes (uncontrolled asthma, asthma attacks and exacerbations, and poor asthma-related quality of life) in women with asthma maintenance therapy over the 12 months that preceded each asthma-related outcome (n = 899); adjusted models included age, active smoking, ever rhinitis, and body mass index

Outcome	Crude model		Adjusted model	
	OR [95% CI]	P value	OR [95% CI]	P value
Uncontrolled asthma				
Ratio <0.75 vs ratio ≥0.75	2.85 [2.09; 3.90]	<.001	2.79 [2.03; 3.84]	<.001
Asthma exacerbations				
Ratio <0.75 vs ratio ≥0.75	1.98 [1.42; 2.76]	<.001	2.08 [1.48; 2.92]	<.001
Asthma attacks				
Ratio <0.75 vs ratio ≥0.75	1.28 [0.97; 1.70]	.08	1.31 [0.98; 1.74]	.07
Asthma-related quality of life*				
Ratio <0.75 vs ratio ≥0.75	−0.50 [−0.65; −0.36]	<.001	−0.48 [−0.61; −0.34]	<.001

CI, Confidence interval; OR, odds ratio.

Asthma-related quality of life was defined using the Asthma Quality of Life Questionnaire.

TABLE E5. Characteristics of the 5 trajectories of the controller-to-total asthma medication ratio identified by latent class analysis over an 8-year period among women with ever asthma from the Asthma-E3N study

Variable	Whole population (n = 4,328)	Never regular treatment (n = 2,302)	Persistent high ratio (n = 943)	Increasing ratio (n = 190)	Initiating treatment (n = 381)	Treatment discontinuation (n = 512)	P value
Sociodemographic characteristics							
Age (y), mean $\pm$ SD	69.6 $\pm$ 6.1	69.2 $\pm$ 5.9	70.6 $\pm$ 6.2	71.4 $\pm$ 6.4	69.9 $\pm$ 6.2	69.0 $\pm$ 6.0	<.001
BMI (kg/m ²), n (%)							
BMI < 20	431 (10.9)	246 (11.7)	89 (10.3)	18 (10.3)	30 (8.7)	48 (10.5)	<.001
20 $\leq$ BMI < 25	2,082 (52.9)	1,168 (55.6)	466 (54.1)	85 (48.6)	158 (45.5)	205 (45.1)	
25 $\leq$ BMI < 30	1,035 (26.3)	518 (24.7)	226 (26.3)	49 (28.0)	108 (31.1)	134 (29.5)	
BMI $\geq$ 30	389 (9.9)	167 (8.0)	80 (9.3)	23 (13.1)	51 (14.7)	68 (14.9)	
Education level, n (%)							
<High school diploma	449 (10.8)	245 (11.0)	79 (8.8)	17 (9.1)	43 (11.6)	65 (13.2)	<.001
High school to 2-level university	2,050 (49.2)	1,038 (46.8)	484 (53.8)	105 (56.2)	215 (58.3)	208 (42.4)	
3-/4-level university	840 (20.2)	479 (21.6)	169 (18.8)	35 (18.7)	53 (14.4)	104 (21.2)	
$\geq$ 5-level university	826 (19.8)	457 (20.6)	167 (18.6)	30 (16.0)	58 (15.7)	114 (23.2)	
Smoking, n (%)							
Never smoker	2,152 (50.1)	1,076 (47.0)	536 (57.3)	95 (50.8)	191 (50.4)	254 (50.3)	<.001
Ex-smoker	1,975 (46.0)	1,113 (48.7)	371 (39.7)	81 (43.3)	175 (46.2)	235 (46.5)	
Current smoker	166 (3.9)	98 (4.3)	28 (3.0)	11 (5.9)	13 (3.4)	16 (3.2)	
Comorbidities							
COPD, n (%)	863 (22.7)	263 (12.9)	320 (38.2)	79 (47.0)	103 (32.3)	98 (22.1)	<.001
Ever rhinitis, n (%)	2,978 (72.1)	1,536 (69.9)	667 (74.4)	139 (76.0)	271 (74.5)	365 (74.8)	.02
Ever eczema, n (%)	1,432 (34.4)	797 (36.0)	285 (31.6)	52 (28.7)	131 (35.3)	167 (34.1)	.08
Asthma							
Age at asthma onset (y), n (%)							
Age < 16	1,225 (30.9)	783 (37.4)	192 (21.8)	53 (29.9)	77 (22.4)	120 (25.7)	<.001
16 $\leq$ age < 40	1,282 (32.4)	724 (34.6)	263 (29.8)	66 (37.3)	99 (28.8)	130 (27.9)	
Age $\geq$ 40	1,455 (36.7)	587 (28.0)	426 (48.4)	58 (32.8)	168 (48.8)	216 (46.4)	
Asthma symptoms, n (%)							
0	1,248 (37.5)	880 (48.2)	166 (23.8)	18 (12.5)	50 (19.1)	134 (33.4)	<.001
1	891 (26.7)	548 (30.0)	150 (21.5)	26 (18.1)	58 (22.1)	109 (27.1)	
2	488 (14.6)	186 (10.2)	150 (21.5)	27 (18.7)	63 (24.1)	62 (15.4)	
$\geq$ 3	705 (21.2)	212 (11.6)	232 (33.2)	73 (50.7)	91 (34.7)	97 (24.1)	
Parental asthma, n (%)							
None	3,071 (76.2)	1,676 (78.0)	636 (72.9)	127 (74.7)	272 (75.3)	360 (75.2)	.09
Father	454 (11.3)	235 (11.0)	108 (12.4)	18 (10.6)	43 (11.9)	50 (10.4)	
Mother	437 (10.8)	205 (9.5)	116 (13.3)	20 (11.8)	36 (10.0)	60 (12.5)	
Both	69 (1.7)	33 (1.5)	12 (1.4)	5 (2.9)	10 (2.8)	9 (1.9)	
Medical follow-up during the last 12 mo, n (%)	1,306 (33.1)	282 (13.2)	561 (67.4)	119 (73.0)	194 (57.6)	150 (31.9)	<.001
Regular monitoring for asthma	733 (18.3)	88 (4.1)	415 (48.7)	96 (55.8)	86 (25.6)	48 (10.0)	<.001
General practitioner	1,188 (30.9)	318 (14.7)	439 (59.7)	110 (69.2)	172 (53.9)	149 (31.9)	<.001
Consultant	826 (21.7)	166 (7.8)	379 (49.5)	82 (54.0)	116 (37.4)	83 (18.2)	<.001

BMI, Body mass index; COPD, chronic obstructive pulmonary disease; E3N, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; SD, standard deviation.

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