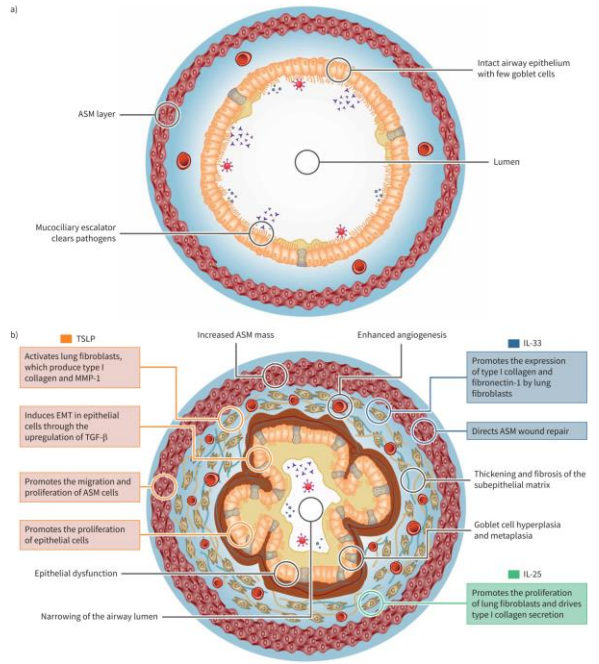
Mild and Manageable
: When Less Is Truly Less

가톨릭대학교
최준영

What is “mild” asthma?

ATS/ERS Task Force

- Severity assessment is based on the difficulty of treating the patient's asthma (retrospective).
- This is indicated by the **level of treatment needed** to manage sympt oms and exacerbations.



Severity of Asthma	Definition
Severe asthma	Uncontrolled despite high-dose ICS-LABA or requires high-dose ICS-LABA
Moderate asthma	Well managed with Step 3 or Step 4 treatment
Mild asthma	Controlled with low-intensity treatment, like low-dose ICS-formoterol or low-dose ICS with as-needed SABA.

Different Meanings of “Mild” and “Severe” Asthma

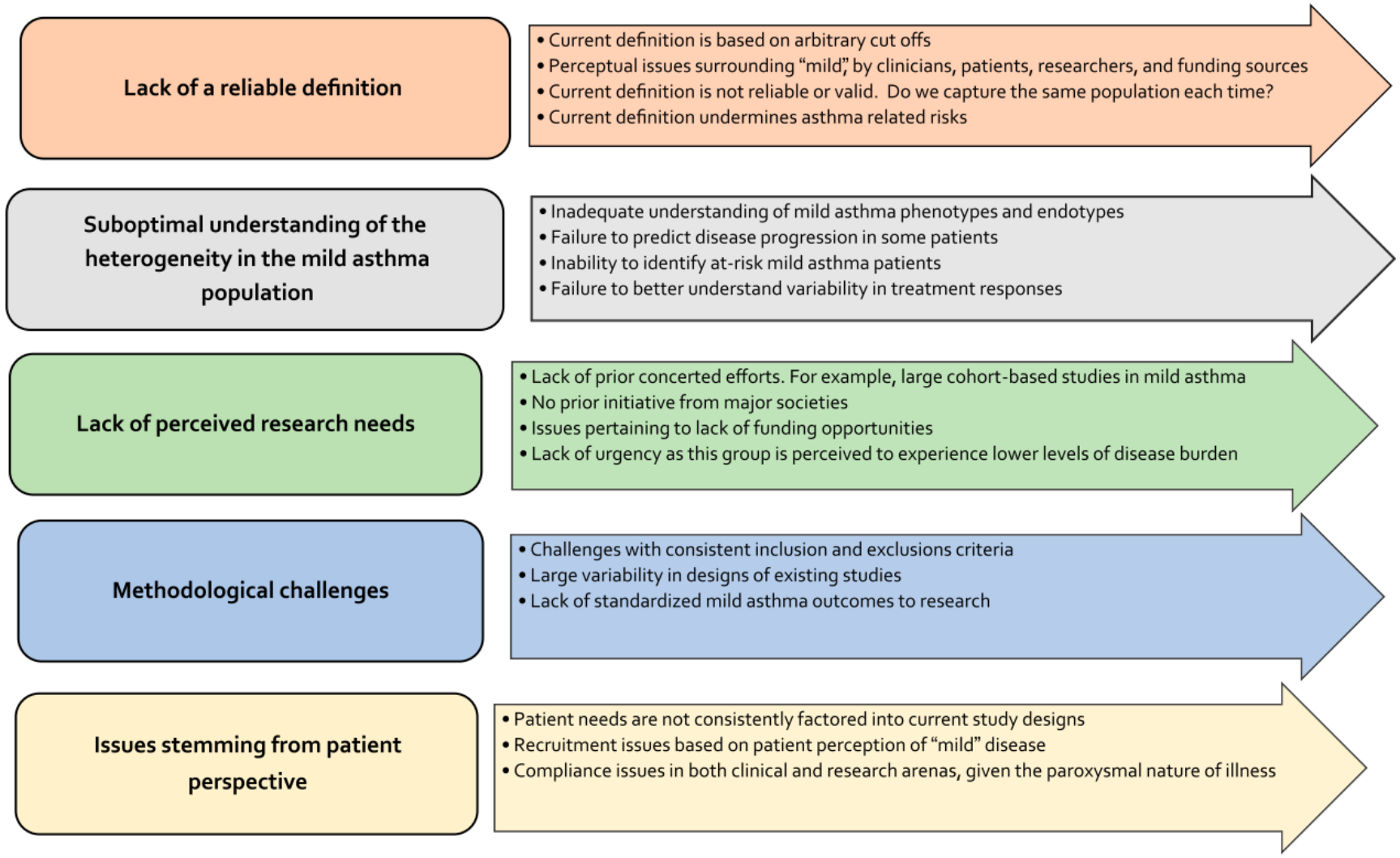
- **In clinical practice**, “mild” and “severe” are often based on symptoms or exacerbation frequency, not treatment. A patient may be labeled “severe” due to frequent symptoms, even with treatment.

- **In trials and guidelines**, asthma severity is often classified based on the prescribed treatment step (e.g., GINA), assuming treatment matches disease severity. This can lead to *under- or over-treatment.*

- **Biologic therapy trials** often enroll patients with uncontrolled asthma despite ICS-LABA, but contributing factors like poor inhaler technique or comorbidities are often overlooked. These patients might be *“difficult-to-treat,” not truly “severe.”*

- **Older guidelines** classify severity by symptoms and SABA use before ICS is started, distinguishing “intermittent” vs. “mild persistent” asthma. However, this classification was arbitrary and led to SABA-only treatment, which is now known to be unsafe.

Current challenges in research on mild asthma.



Mohan et al. Blue. 2023

Counterargument 1:

“Mild asthma can still lead to severe outcomes.”

Mild asthmatic can have a bad attack

Contents lists available at ScienceDirect

Respiratory Medicine

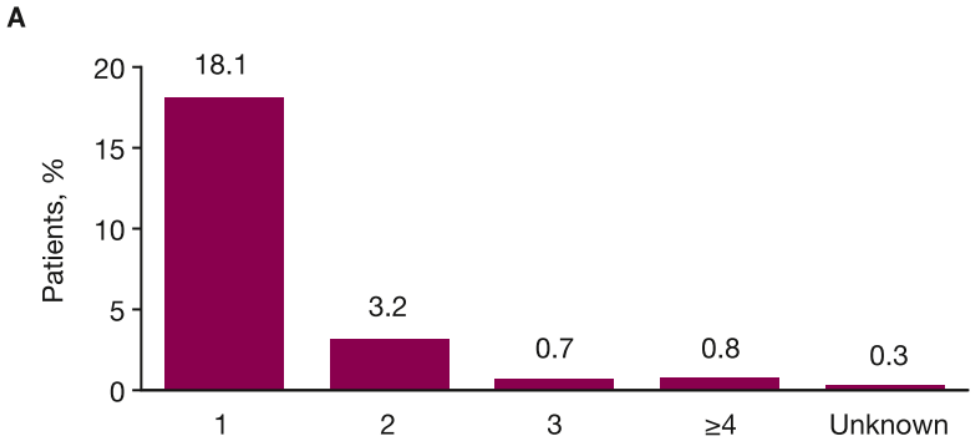
journal homepage: www.elsevier.com/locate/rmed

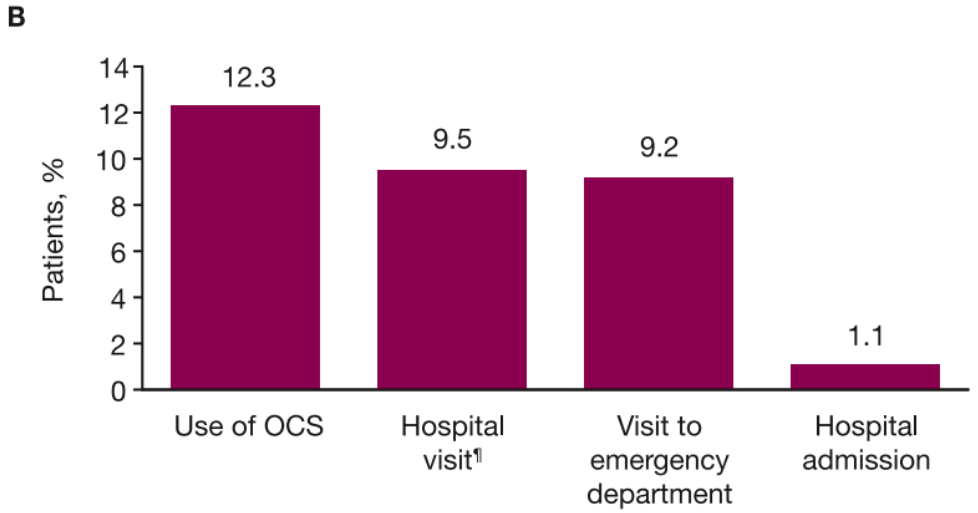
Original Research

The burden of mild asthma: Clinical burden and healthcare resource utilisation in the NOVELTY study

Sarowar Muhammad Golam [a], Christer Janson [b], Richard Beasley [c], J Mark FitzGerald [d], Tim Harrison [e], Bradley Chipps [f], Rod Hughes [g,*], Hana Müllerová [h], José María Olaguibel [i], Eleni Rapsomaniki [j], Helen K. Reddel [k], Mohsen Sadatsafavi [l], for the NOVELTY study investigators

Physician-reported exacerbations (previous 12 months)[b]	
Exacerbations	
Patients with data, n	1997
Mean (SD)	0.3 (0.8)
Patients with ≥1 exacerbation, n (%)	455 (22.8)
Severe exacerbations[c]	
Patients with data, n	1997
Mean (SD)	0.2 (0.6)
Patients with ≥1 severe exacerbation, n (%)	329 (16.5)
Exacerbations requiring OCS	
Patients with data, n	1997
Mean (SD)	0.2 (0.5)
Patients with ≥1 exacerbation requiring OCS, n (%)	246 (12.3)



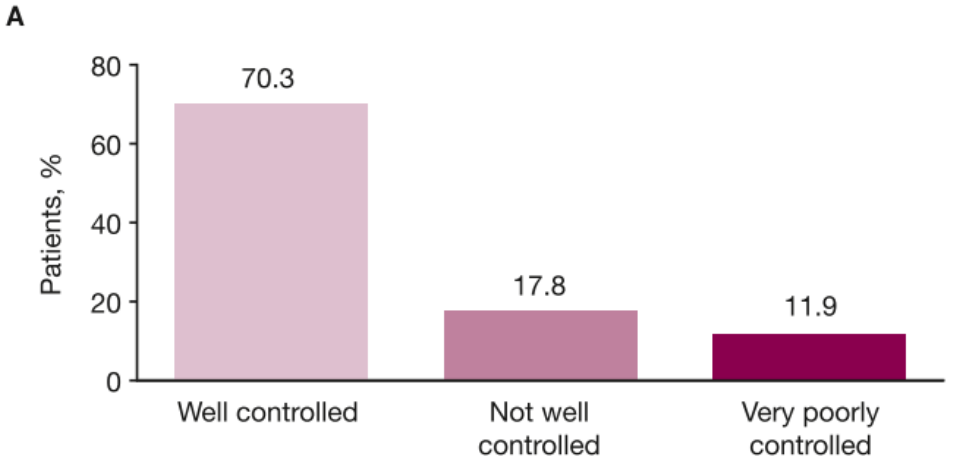


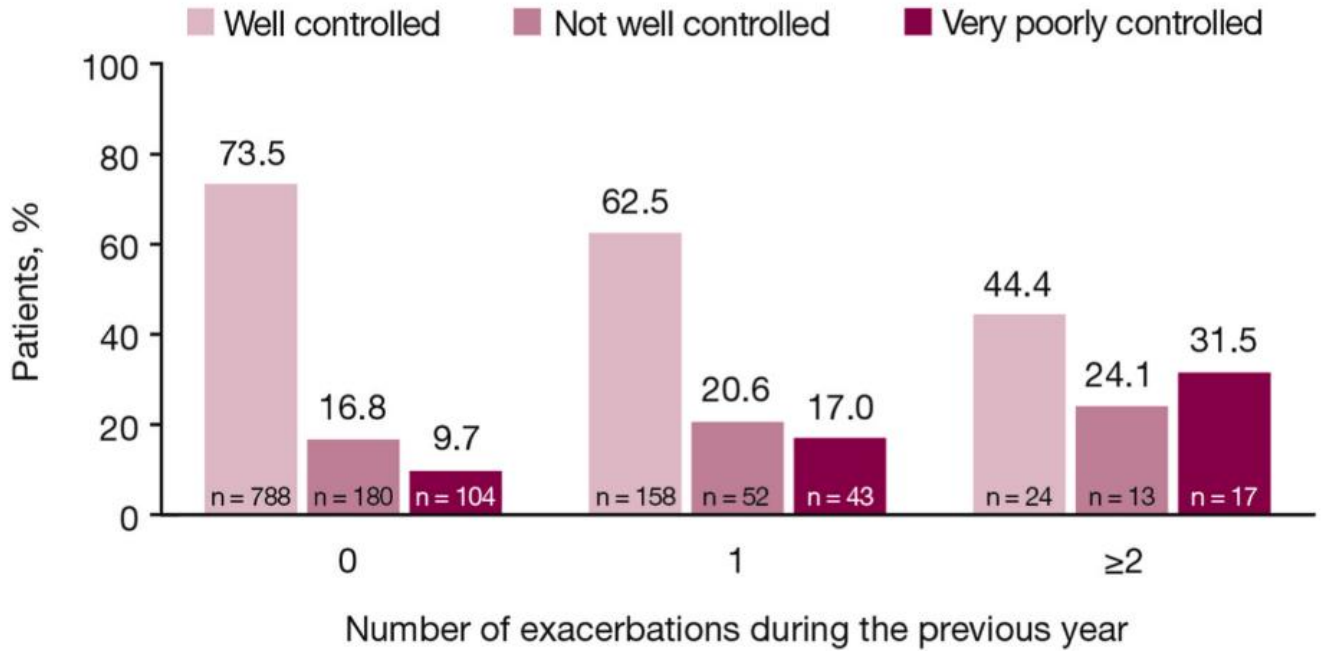
Golam et al. Respir Med 2022.

Are they all truly “mild asthma?”

Table 1
Baseline characteristics of patients with physician-assessed mild asthma.

Characteristic	Physician-assessed mild asthma (N = 2004)
Patient demographics	
Age (years), mean (SD)	50.1 (17.6)
Female, n (%)	1279 (63.8)
Smoking history, n (%)	
Patients with data, n	2001
Current smoker	174 (8.7)
Former smoker	565 (28.2)
Never smoker	1262 (63.1)
GINA 2017 treatment step[a], n (%)	
Steps 1 & 2 (SABA alone/low-dose ICS)	636 (31.7)
Step 3 (low-dose ICS + LABA)	783 (39.1)
Step 4 (medium-/high-dose ICS + LABA)	533 (26.6)
Step 5 (medium-/high-dose ICS + LABA with LAMA, biologic or maintenance OCS)	52 (2.6)





Golam et al. Respir Med 2022.

Baseline characteristics of patients with mild asthma on GINA 2017 treatment steps 1+2.

Physician-reported exacerbations (previous 12 months)*	
Exacerbations	
Mean (SD)	0.2 (0.6)
Patients with ≥1 exacerbation, n (%)	113 (17.8)
Severe exacerbations	
Mean (SD)	0.1 (0.4)
Patients with ≥1 severe exacerbation, n (%)	77 (12.1)
Exacerbations requiring OCS	
Mean (SD)	0.1 (0.4)
Patients with ≥1 exacerbation requiring OCS, n (%)	57 (9.0)

Golam et al. Respir Med 2022.

Large proportion of mild asthma does not follow guideline-directed therapy

Zerr et al. Allergy, Asthma & Clinical Immunology (2024) 20:27
https://doi.org/10.1186/s13223-024-00888-6

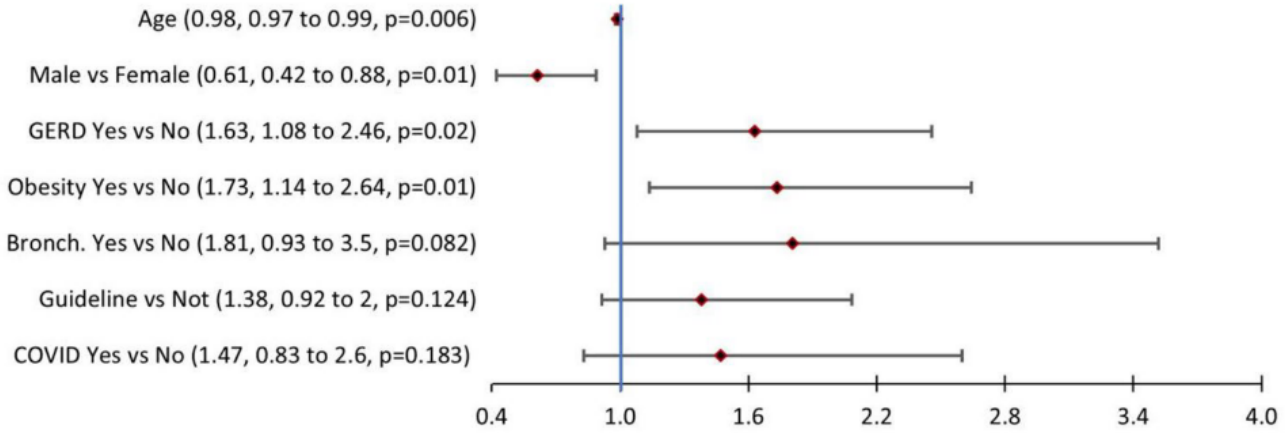
Allergy, Asthma & Clinical Immunology

RESEARCH Open Access

Evaluation of adherence to guideline-directed therapy and risk factors for exacerbation in mild asthma: a retrospective chart review

Beth A. Zerr[1*], Jacklyn M. Kruse[2*] and Jon J. Glover[3*]

- Guideline-directed therapy (-) : 284 (26%)
- Guideline-directed therapy (+) : 823 (74%)
  - ➢ (Diff:48.7%; 95% CI:45.1-52.3%, p < 0.001)



Factors associated with at least one asthma exacerbation

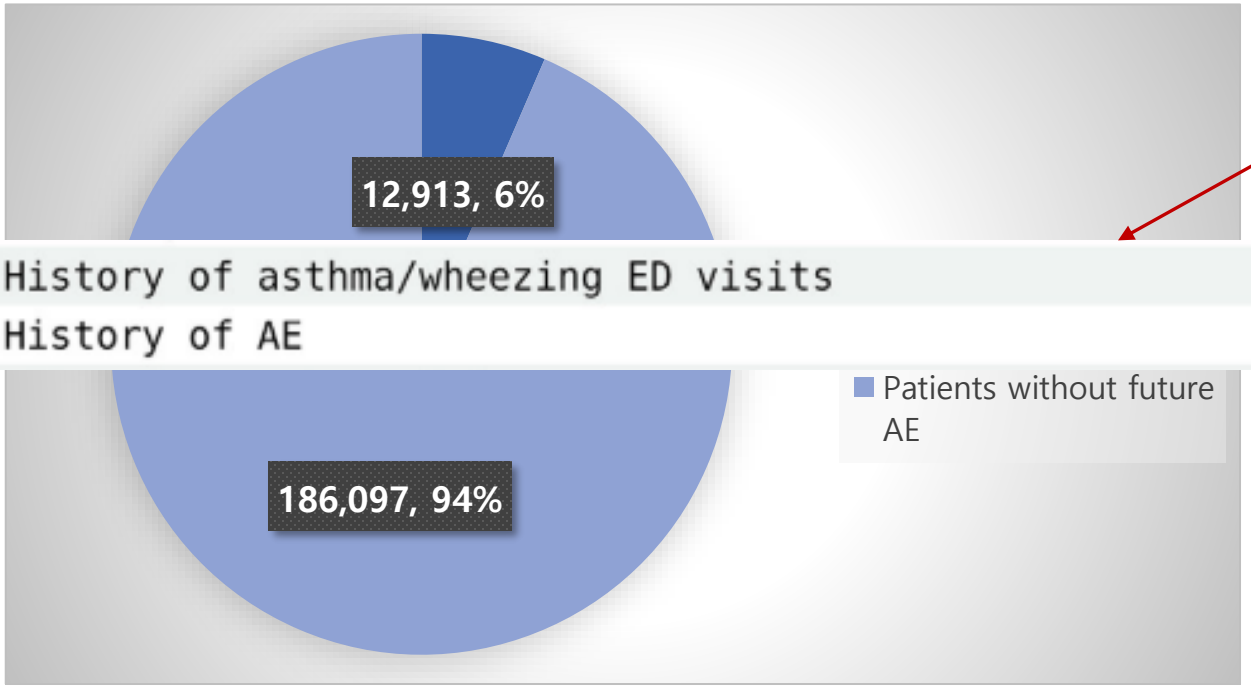
Zerr et al. JACI 2024

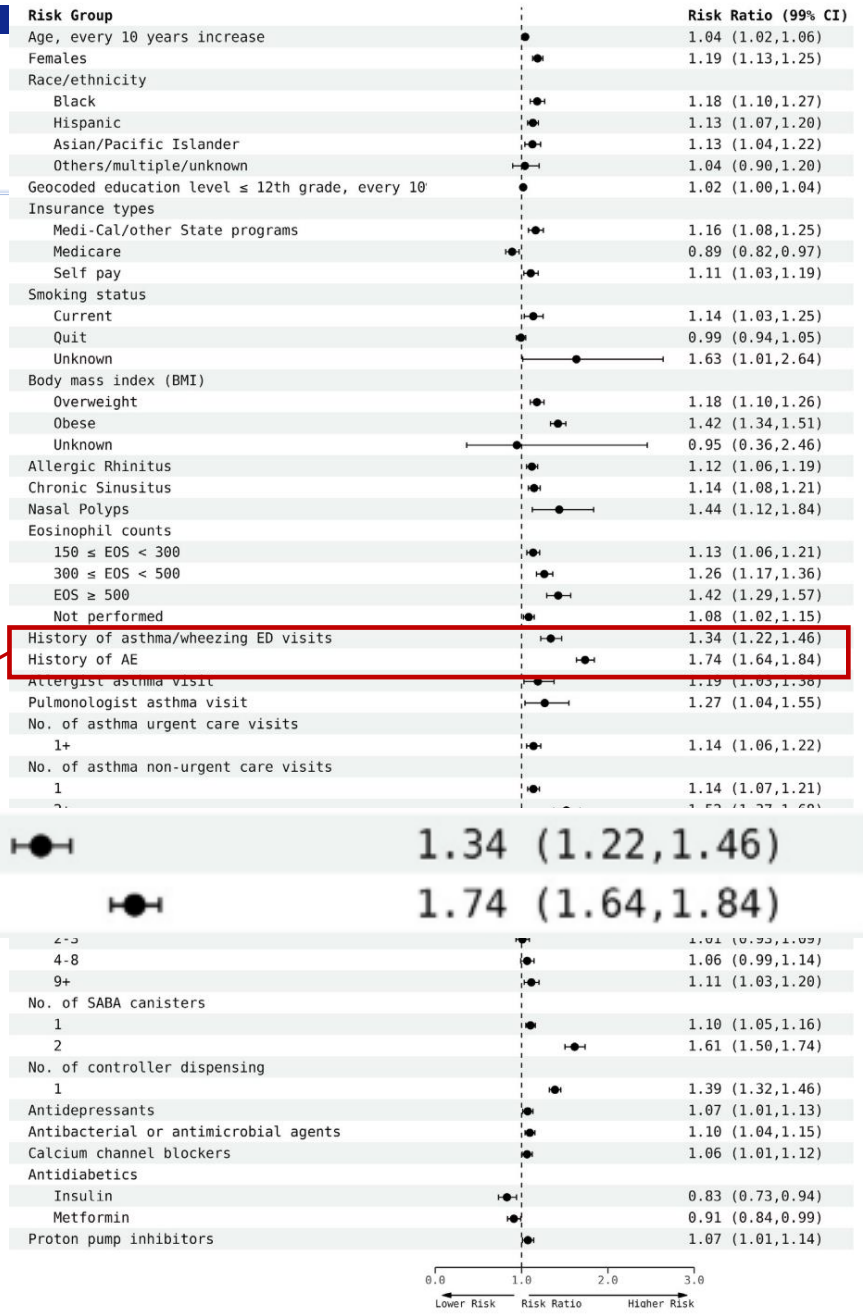
Past reflects the future exacerbation

Original Article

Risk Factors for Acute Asthma Exacerbations in Adults With Mild Asthma

Wansu Chen, PhD, MS[a], Eric J. Puttock, PhD[a], Michael Schatz, MD[b,c], William Crawford, MD[d], William M. Vollmer, PhD[e], Fagen Xie, PhD[a], Stanley Xu, PhD[a], Eva Lustigova, MPH[a], and Robert S. Zeiger, MD, PhD[b,c] *Pasadena, San Diego, and Harbor City, Calif; and Portland, Ore*





History of asthma/wheezing ED visits 1.34 (1.22,1.46)
History of AE 1.74 (1.64,1.84)

Chen et al. J Allergy Clin Immunol Pract. 2024

Past reflects the future exacerbation

ERJ OPEN RESEARCH
ORIGINAL RESEARCH ARTICLE
R. LOWDEN AND S. TURNER

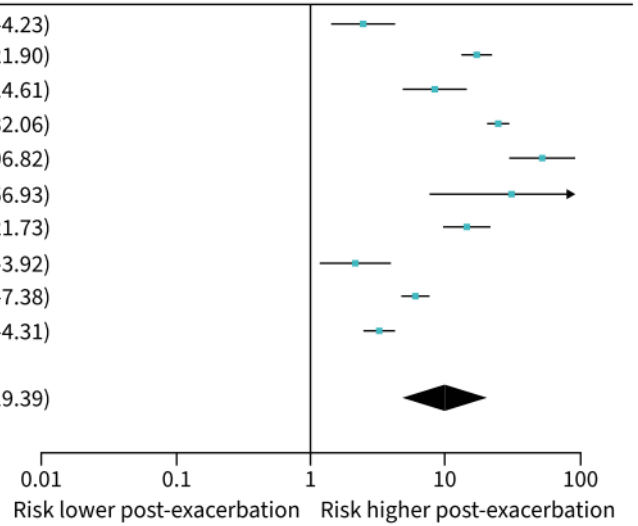
Past asthma exacerbation in children predicting future exacerbation: a systematic review

Rachel Lowden [1] and Steve Turner [1,2]

[1]Child Health, University of Aberdeen, Aberdeen, UK. [2]Paediatric Dept, NHS Grampian, Aberdeen, UK.

Study or subgroup	Previous exacerbation Events	Total	No previous exacerbation Events	Total	Weight	OR M-H, random, 95% CI
Covar, 2008	51	80	85	205	10.1%	2.48 (1.46–4.23)
Engelkes, 2016	129	415	352	13888	10.6%	17.34 (13.74–21.90)
Engelkes, 2020 (AUH)	20	103	282	10627	10.1%	8.84 (5.35–14.61)
Engelkes, 2020 (CPRD)	161	740	898	86805	10.7%	26.60(22.07–32.06)
Engelkes, 2020 (IPCI)	20	82	97	17027	10.1%	56.30 (32.74–96.82)
Engelkes, 2020 (PEDIANET)	2	15	29	6417	6.9%	33.89 (7.32–156.93)
Engelkes, 2020 (SIDIAP)	37	234	258	20838	10.4%	14.98 (10.33–21.73)
Quezada, 2016	91	218	19	77	9.9%	2.19 (1.22–3.92)
Turner, 2018	240	638	285	3138	10.6%	6.04 (4.94–7.38)
Wu, 2011	154	320	159	716	10.5%	3.25 (2.45–4.31)
Total (95% CI)		2845		159738	100.0%	9.87 (5.02–19.39)
Total events	905		2464			

Heterogeneity: Tau^2=1.11; Chi^2=377.23, df=9 (p<0.00001); I^2=98%
Test for overall effect: z=6.64 (p<0.00001)



Lowden et al. ERJ Open Res. 2022

Risk stratification with exacerbation risk may be needed

AIRQ® (Asthma Impairment and Risk Questionnaire)

PRECISION

For use by health care providers with their patients 12 years and older who have been diagnosed with asthma. AIRQ® is intended to be part of an asthma clinic visit.

Please answer all of the questions below.

In the past 2 weeks, has coughing, wheezing, shortness of breath, or chest tightness:

1. Bothered you during the day on **more than 4 days**? Yes / No
2. Woke you up from sleep **more than 1 time**? Yes / No
3. Limited the activities you want to do **every day**? Yes / No
4. Caused you to use your rescue inhaler or nebulizer **every day**? Yes / No

Primatene® MIST (Amphastar Pharmaceuticals) or Epinephrine | ProAir® HFA (Teva Respiratory, LLC) or Albuterol sulfate | ProAir RespiClick® (Teva Respiratory, LLC) or Albuterol sulfate | Proventil® HFA (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.) or Albuterol sulfate | Ventolin® HFA (GlaxoSmithKline) or Albuterol sulfate | Xopenex HFA® (Sunovion Pharmaceuticals Inc.) or Levalbuterol tartrate | Albuterol sulfate or Xopenex® (Sunovion Pharmaceuticals Inc.) or Levalbuterol HCl

Please see all prescribing information for all products.

In the past 2 weeks:

5. Did you have to limit your social activities (such as visiting with friends/relatives or playing with pets/children) because of your asthma? Yes / No
6. Did coughing, wheezing, shortness of breath, or chest tightness limit your ability to exercise? Yes / No
7. Did you feel that it was difficult to control your asthma? Yes / No

In the past 12 months, has coughing, wheezing, shortness of breath, or chest tightness:

8. Caused you to take steroid pills or shots, such as prednisone or Medrol®*? Yes / No
9. Caused you to go to the emergency room or have unplanned visits to a health care provider? Yes / No
10. Caused you to stay in the hospital overnight? Yes / No

Total YES Answers ☐

What Does My AIRQ® Score Mean?

The AIRQ® is meant to help your health care providers talk with you about your asthma control. The AIRQ® does not diagnose asthma. Whatever your AIRQ® score (total **YES** answers), it is important for your health care team to discuss the number and answers to each of the questions with you. All patients with asthma, even those who may be well-controlled, can have an asthma attack. As asthma control worsens, the chance of an asthma attack increases.[1] Only your medical provider can decide how best to assess and treat your asthma.

*Medrol® (Pfizer, Inc.) or methylprednisolone

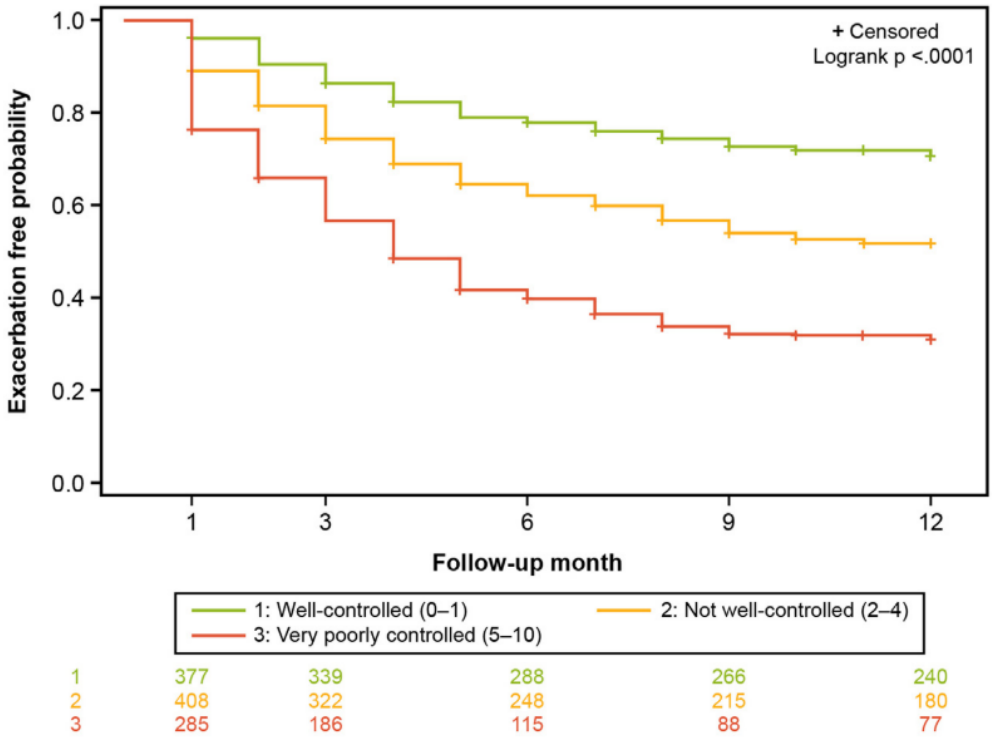
The trademarks depicted above are the property of their respective owners.

[1]Global Strategy for Asthma Management and Prevention: ©2021 Global Initiative for Asthma

Original Article

The Asthma Impairment and Risk Questionnaire (AIRQ) Control Level Predicts Future Risk of Asthma Exacerbations

David A. Beuther, MD, PhD[a], Kevin R. Murphy, MD[b], Robert S. Zeiger, MD, PhD[c], Robert A. Wise, MD[d], William McCann, MD, MBA[e], Joan Reibman, MD[f], Maureen George, PhD, RN[g], Ileen Gilbert, MD[h], James M. Eudicone, MS, MBA[h], Hitesh N. Gandhi, MBBS, MHA, MAS[h], Melissa Ross, PhD[i], Karin S. Coyne, PhD, MPH[i], and Bradley Chipps, MD[j] *Denver, Colo; Boys Town, Neb; Pasadena and Sacramento, Calif; Baltimore and Bethesda, Md; Asheville, NC; New York, NY; Wilmington, Del*



Beuther et al. J Allergy Clin Immunol Pract. 2022.

Risk stratification with exacerbation risk may be needed

Symptom control will be assessed using GINA recommendations.

In the past 4 weeks, has the patient had:		**Level of asthma symptom control**		
		Well controlled	Partly controlled	Uncontrolled
Daytime symptoms more than twice/week?	Yes / No	None	1-2	3-4
Any night time waking due to asthma?	Yes / No			
SABA reliever needed more than twice/week?	Yes / No			
Any activity limitation due to asthma?	Yes / No			

Patient A = Low symptoms, low exacerbation Patient B = Low symptoms, high exacerbation Patient C = High symptoms, low exacerbation Patient D = High symptoms, high exacerbation		**Exacerbations**	
		Low (≤1 per year)	High (> 1 per year)
Control	Well controlled (0 points)	A	B
	Partly controlled or uncontrolled (1-4 points)	C	D

A: Ideal patient to be classified as mild, low symptoms and low risk.
B: May be classified as mild if exacerbation risk is underestimated. Should be treated with ICS to reduce exacerbation burden.
C: May be classified as mild if control improves after 6 months of therapy.
D: High symptom burden (poor control) and high exacerbation frequency, should not be considered mild asthma.

Mohan A et al. Respir Med 2023

Risk prediction for mild asthma is needed

BOX 1 **Factors associated with higher risk of adverse outcomes in mild–moderate asthma.**

Factor	Outcome	References
Previous or ongoing higher treatment requirements for control	Increased exacerbations	38
Co-diagnosis of COPD	Increased exacerbations, Poorer quality of life	40
Low eosinophil count	Sub-optimal response to ICS	28,38
Current smoker	Poor response to ICS, Greater exacerbation risk, Greater risk of lung function decline	9,40,58
Female	Increased exacerbations, Premenstrual exacerbations, Post-menopausal persistence	15,40
Obese (BMI >30)	Greater risk of persistence	37,58
Comorbidities especially allergic rhinitis, reflux, depression or atopy	Worse symptom control	32
Socioeconomic disadvantage	More frequent exacerbations, Avoidable but frequent courses of systemic steroids	15,40
Older age (adults)	Under-recognized disease severity, under-treatment, worse airflow limitation, poor reversibility	
Inappropriate use of rescue medication – • >2 puffs of SABA per week in the absence of ICS use in the first year of asthma diagnosis • 9 or more canisters of SABA with under 100 mcg of ICS daily	Progression of disease to higher treatment requirements More frequent exacerbations	9
Under-treatment with anti-inflammatory medications	More persistent symptoms, airflow limitation and more frequent exacerbations	23,52,53,65
Recurrent early life wheezing Abnormal lung function early in life	More persistent airflow limitation	9,31,58
Occupational exposures	Worse asthma control and more persistent disease	11
Psychosocial factors, anxiety and depression	Worse asthma control	37,42

Mohan et al. Respir Med. 2023;216:107326.

Risk prediction for mild asthma is needed

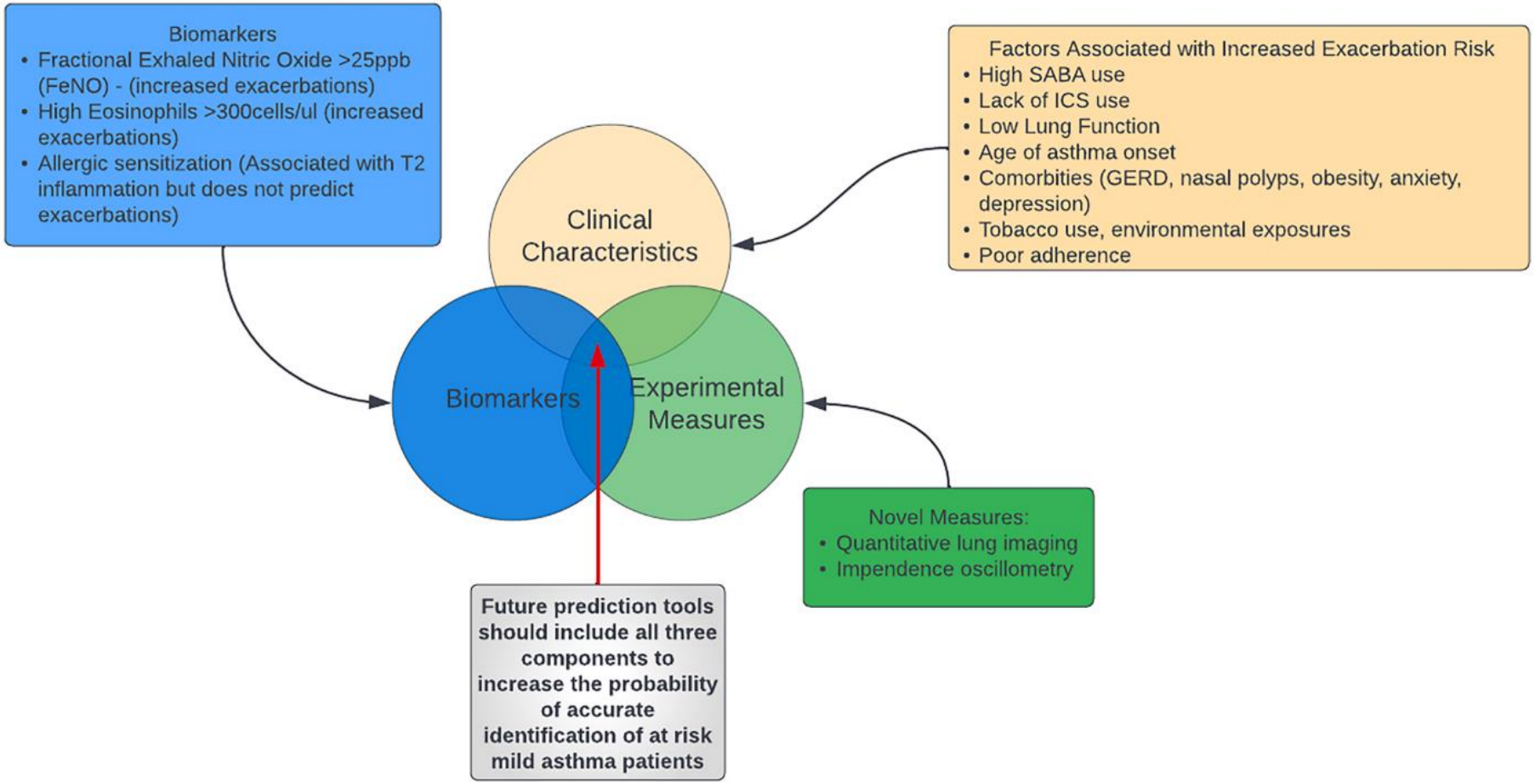


Fig. 3. Model for future risk prediction tool in mild asthma.

Mohan et al. Respir Med. 2023;216:107326.

Counterargument 2:

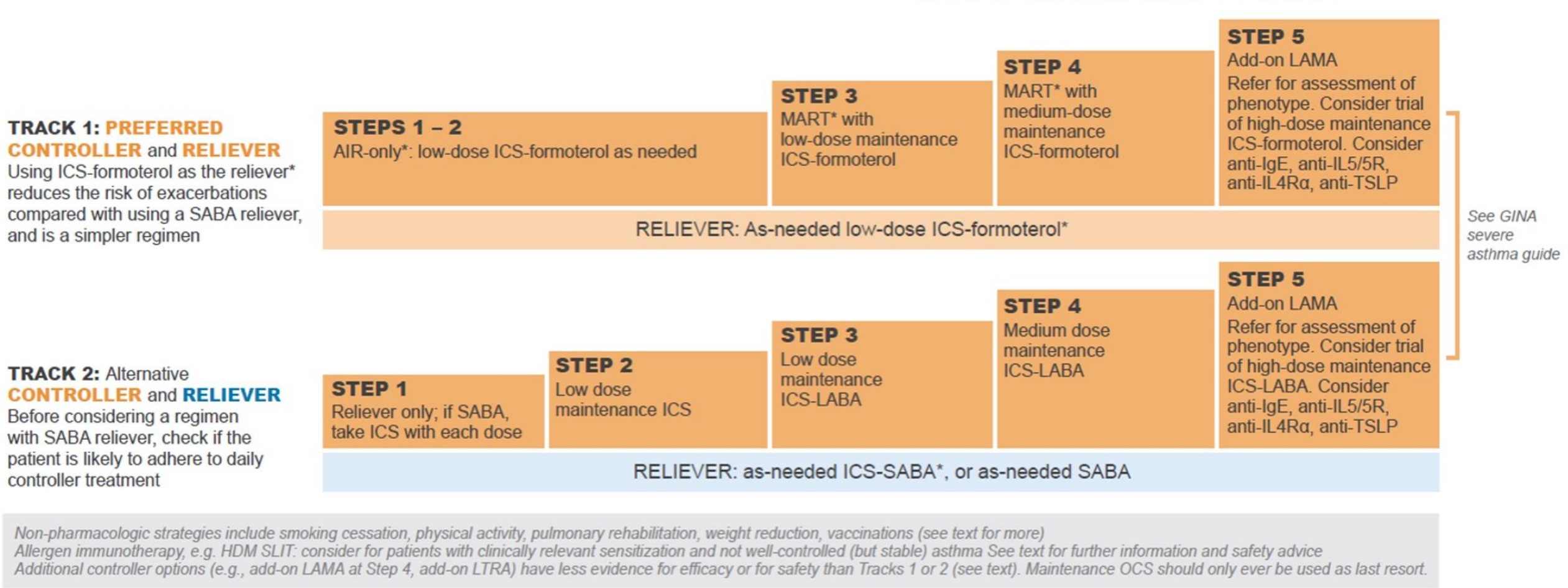
“Calling it ‘mild’ leads to underestimation and under-treatment.”

Mild ≠ Safe if untreated

- “Mild asthma” is a retrospective label, so it cannot be used to decide which treatment patients should receive.

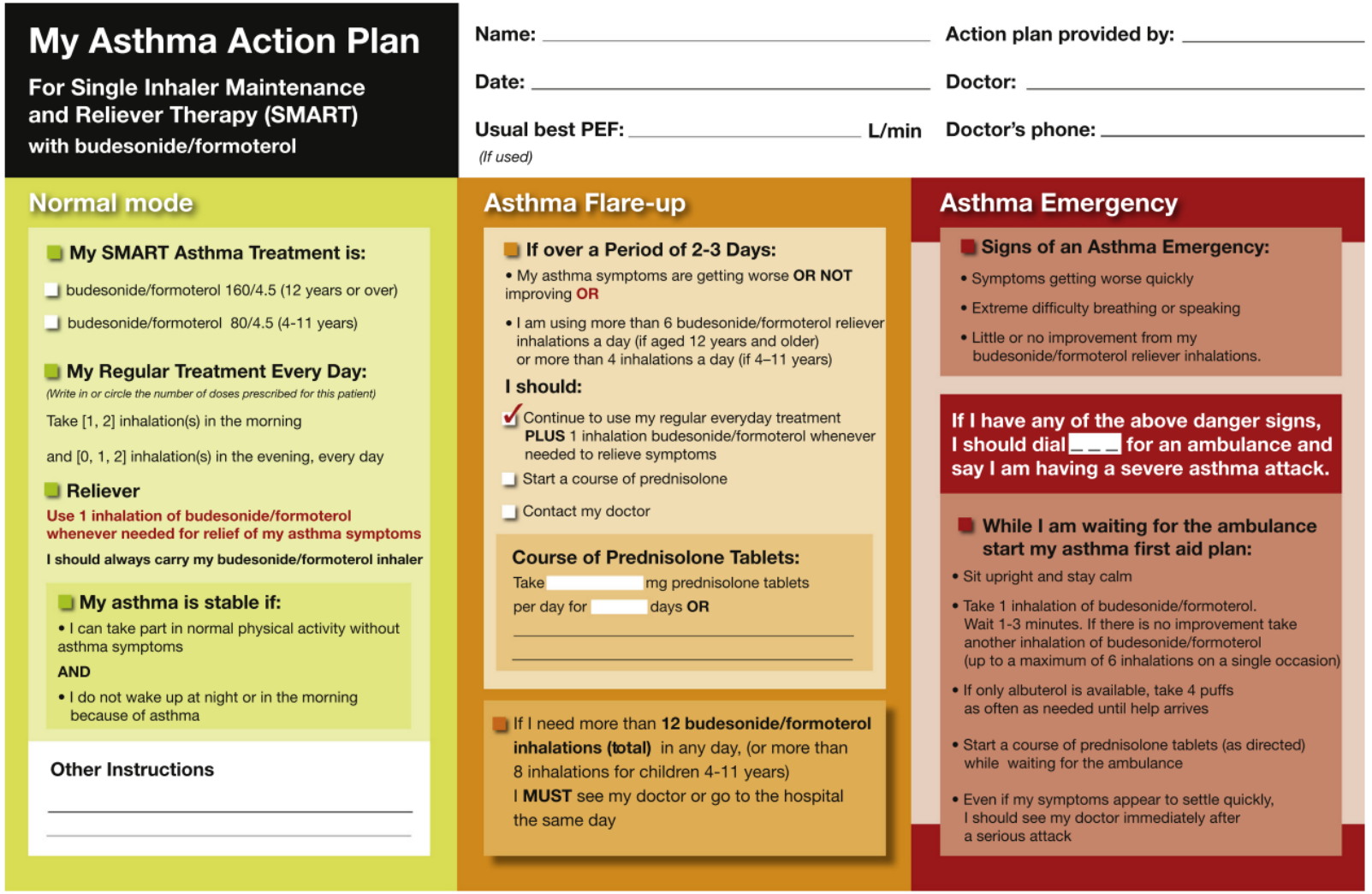
- Always emphasize the need for and benefit from ICS-containing treatment in patients with asthma, regardless of their symptom frequency or severity.

Mild ≠ Safe if untreated



GINA 2025, Reddel et al. JACI in practice 2022

Action plan may be adjusted to manage patients with mild asthma



My Asthma Action Plan

For Single Inhaler Maintenance and Reliever Therapy (SMART) with budesonide/formoterol

Name: _____ Action plan provided by: _____

Date: _____ Doctor: _____

Usual best PEF: _____ L/min (If used) Doctor's phone: _____

Normal mode

My SMART Asthma Treatment is:

- ☐ budesonide/formoterol 160/4.5 (12 years or over)
- ☐ budesonide/formoterol 80/4.5 (4-11 years)

My Regular Treatment Every Day:

(Write in or circle the number of doses prescribed for this patient)

Take [1, 2] inhalation(s) in the morning

and [0, 1, 2] inhalation(s) in the evening, every day

Reliever

Use 1 inhalation of budesonide/formoterol whenever needed for relief of my asthma symptoms

I should always carry my budesonide/formoterol inhaler

My asthma is stable if:

- I can take part in normal physical activity without asthma symptoms

AND

- I do not wake up at night or in the morning because of asthma

Other Instructions

_____

_____

Asthma Flare-up

If over a Period of 2-3 Days:

- My asthma symptoms are getting worse **OR NOT** improving **OR**
- I am using more than 6 budesonide/formoterol reliever inhalations a day (if aged 12 years and older) or more than 4 inhalations a day (if 4–11 years)

I should:

- ☑ Continue to use my regular everyday treatment **PLUS** 1 inhalation budesonide/formoterol whenever needed to relieve symptoms
- ☐ Start a course of prednisolone
- ☐ Contact my doctor

Course of Prednisolone Tablets:

Take _____ mg prednisolone tablets per day for _____ days **OR**

_____

_____

If I need more than **12 budesonide/formoterol inhalations (total)** in any day, (or more than 8 inhalations for children 4-11 years) I **MUST** see my doctor or go to the hospital the same day

Asthma Emergency

Signs of an Asthma Emergency:

- Symptoms getting worse quickly
- Extreme difficulty breathing or speaking
- Little or no improvement from my budesonide/formoterol reliever inhalations.

If I have any of the above danger signs, I should dial _ _ _ for an ambulance and say I am having a severe asthma attack.

While I am waiting for the ambulance start my asthma first aid plan:

- Sit upright and stay calm
- Take 1 inhalation of budesonide/formoterol. Wait 1-3 minutes. If there is no improvement take another inhalation of budesonide/formoterol (up to a maximum of 6 inhalations on a single occasion)
- If only albuterol is available, take 4 puffs as often as needed until help arrives
- Start a course of prednisolone tablets (as directed) while waiting for the ambulance
- Even if my symptoms appear to settle quickly, I should see my doctor immediately after a serious attack

Modified from Australian action plan with permission from National Asthma Council Australia and AstraZeneca Australia

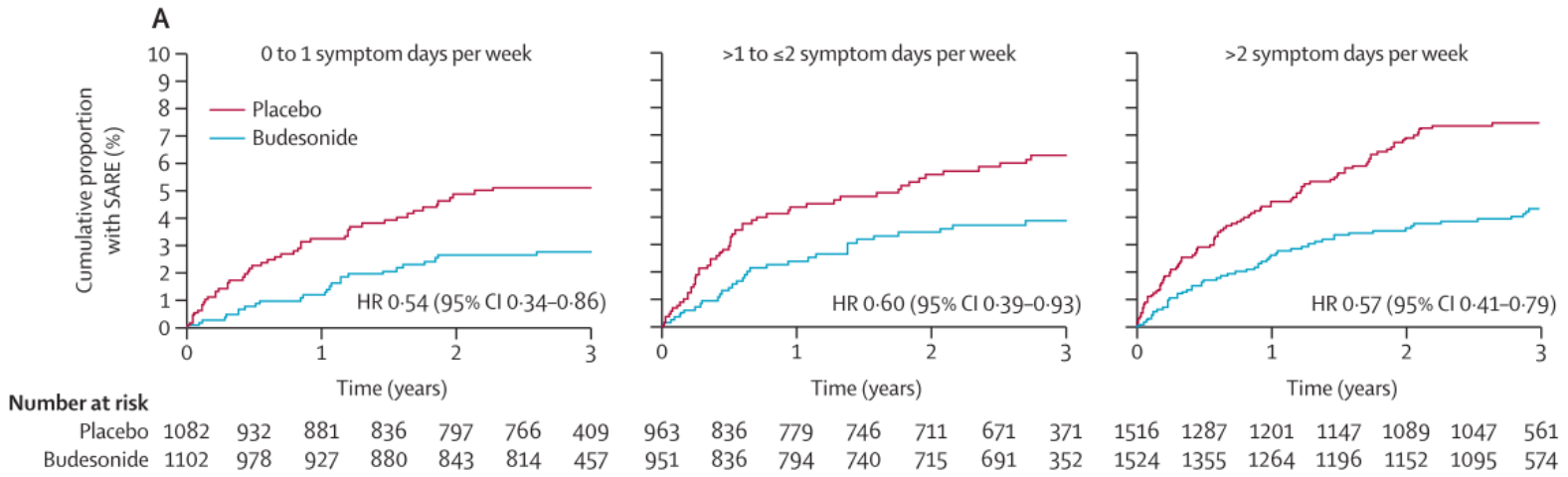
GINA 2025, Reddel et al. JACI in practice 2022

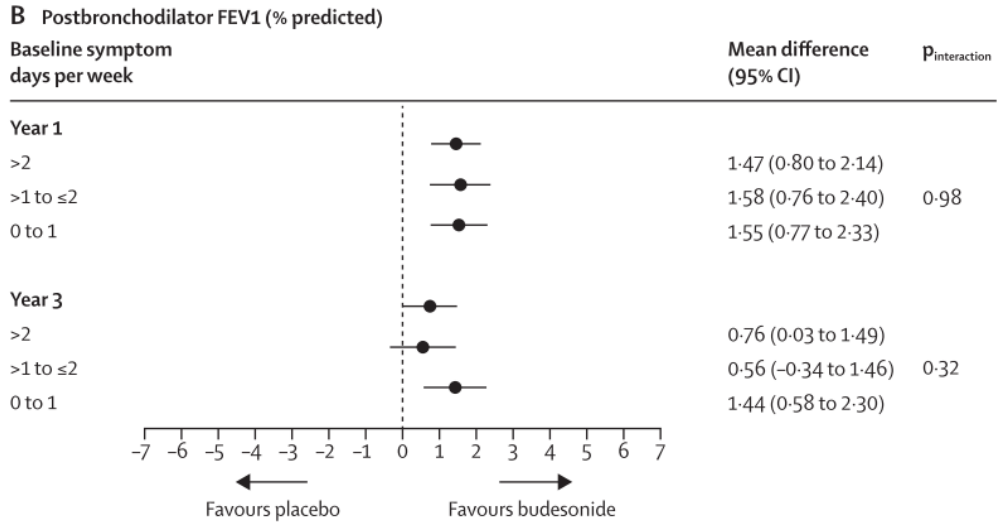
Appropriate use of ICS reduces exacerbation risk and increases lung function

Articles

Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study

Helen K Reddel, William W Busse, Søren Pedersen, Wan C Tan, Yu-Zhi Chen, Carin Jorup, Dan Lythgoe, Paul M O'Byrne





Reddel et al. Lancet. 2017

Appropriate use of ICS reduces exacerbation risk

Evidence synthesis

Combination fixed-dose β agonist and steroid inhaler as required for adults or children with mild asthma: a Cochrane systematic review

Iain Crossingham,[1] Sally Turner,[1] Sanjay Ramakrishnan ,[2,3] Anastasia Fries,[2] Matthew Gowell,[4] Farhat Yasmin,[5] Rebekah Richardson,[1] Philip Webb,[1] Emily O'Boyle,[4] Timothy Stopford Christopher Hinks [2]

Table 1 Summary of findings 1. As-required FABA/ICS inhalers compared with as-required FABA inhalers for mild asthma

As-required FABA/ICS inhalers compared with as-required FABA inhalers for mild asthma

Patient or population: Mild asthma
Setting: Community
Intervention: As-required FABA/ICS inhalers
Comparison: As-required FABA inhalers

Outcomes	Anticipated absolute effects[$] (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	Risk with as-required FABA inhalers	Risk with as-required FABA/ICS inhalers			
Asthma exacerbation requiring systemic steroid follow-up: 52 weeks	109 per 1000	52 per 1000 (40 to 68)	OR 0.45, 95% CI 0.34 to 0.60	2997 (2 RCTs)	⨁⨁⨁⨁ HIGH*†
Hospital admission, ED and urgent care visits follow-up: 52 weeks	34 per 1000	12 per 1000 (7 to 21)	OR 0.35, 95% CI 0.20 to 0.60	2997 (2 RCTs)	⨁⨁⊖⊖ LOW†‡

Crossingham et al. BMJ Evid Based Med. 2022.

Underlying pathology is developing in mild asthma?

Contents lists available at ScienceDirect

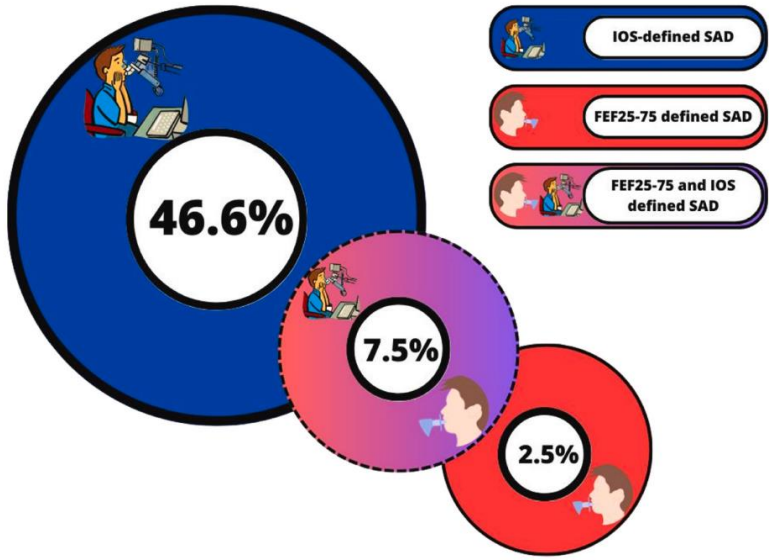
Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Original Research

Impulse oscillometry defined small airway dysfunction in asthmatic patients with normal spirometry: Prevalence, clinical associations, and impact on asthma control

Marcello Cottini [a], Benedetta Bondi [b,*], Diego Bagnasco [b], Fulvio Braido [b], Giovanni Passalacqua [b], Anita Licini [a], Carlo Lombardi [c], Alvise Berti [d], Pasquale Comberiati [e], Massimo Landi [f], Enrico Heffler [g,h], Giovanni Paoletti [g,h]



Spirometric, oscillometric and prevalence of SAD in the 321 patients according to GINA steps.

Variable	All patients (N = 321)	Step 2 (N = 84)	Step 3 (N = 174)	Step 4–5 (N = 63)	P Value
SAD (%)	182 (56.7%)	47 (56%)	93 (53.4%)	42 (66.7%)	0.190
Spirometry Data					
FEV1%, median (25%-75% IQR)	101 (80–145)	101 (80–126)	101 (81–142)	102 (80–145)	0.821
FEV1/FVC%, mean ± SD	79.9 (±5.80)	81.3 (±6.10)	79.5 (±5.30)	79.3 (±6.48)	**0.049**
FEF25-75, mean ± SD	91.8 (±24.8)	93.6 (±23.3)	90.1 (±23.8)	94.5 (±29.0)	0.378
Oscillometry Data					
R5-R20, median (25%-75% IQR)	0.09 (0.00–0.54)	0.09 (0.00–0.27)	0.08 (0.00–0.54)	0.11 (0.00–0.40)	**0.050**
X5, median (25%-75% IQR)	−0.13 (-0.48/-0.01)	−0.13 (-0.26/-0.05)	−0.13 (-0.44/-0.05)	−0.15 (-0.48/-0.01)	**0.021**
Fres, median (25%-75% IQR)	18.1 (0.43–42.0)	16.9 (0.89–26.2)	18.1 (0.43–33.1)	19.4 (0.63–42.0)	**0.017**
	N = 320		N = 173		
AX, median (25%-75% IQR)	0.77 (0.0–16.8)	0.66 (0.12–2.31)	0.71 (0.00–16.8)	1.12 (0.05–5.20)	**0.011**

Cottini et al. Respir Med. 2023;218:107391.

SAD is present mostly in partially controlled/uncontrolled → step-up required

Table 4

Prevalence of SAD and oscillometric parameters as a function of disease control classes according to GINA guidelines. *The values of the IOS and the ICS dosage were represented as median (25%- 75% IQR) because they were not normally distributed. Comparisons were analyzed with nonparametric methods, with the one-way ANOVA Krusall-Wallis test for independent samples (3-tailed), where appropriate. Significant P values (<0.05) are represented in bold.*

Variable	All patients (N = 321)	W (N = 147)	P (N = 129)	U (N = 45)	P Value
SAD n,%	182 (56.7%)	44 (29.9%)	93 (72.1%)	45 (100%)	**<.0001**
ICS Dosage (μg)	550	500	640	1000	**<.0001**
median (25%-75% IQR)	(100–5000)	(100–4000)	(100–2000)	(100–5000)	
Oscillometry Data					
R5-R20	0.09	0.05	0.11	0.16	
median (25%-75% IQR)	(0.00–0.54)	(0.00–0.23)	(0.00–0.51)	(0.08–0.54)	**<.0001**
X5	−0.13	−0.11	−0.15	−0.18	
median (25%-75% IQR)	(-0.48/-0.01)	(-0.31/-0.01)	(-0.48/-0.05)	(-0.44/-0.07)	**<.0001**
Fres	18.1	14.2	21.1	23.3	
median (25%-75% IQR)	(0.43–42.0)	(0.43–30.6)	(0.89–42.0)	(15.0–39.6)	<.0001
AX	0.77	0.43	1.13	1.54	
median (25%-75% IQR)	(0.0–16.8)	(0.05–16.8)	(0.00–4.23)	(0.6–6.65)	**<.0001**

W well controlled **P** partially controlled **U** uncontrolled

The univariate and multivariate analysis with the cross-sectional relationships between clinical and spirometric parameters and the presence of SAD. *The univariable analysis was performed with a binomial logistic regression. In*

Variable	Univariable analysis		Multivariable analysis	
	OR (95%CI)	P value	OR (95%CI)	P-value
Gender (females) n (%)	0.47 (0.30–0.74)	**0.001**		
Age	1.03 (1.01–1.04)	**<.0001**		
Asthma duration (years)	1.00 (0.98–1.02)	0.731		
Atopy	0.59 (0.37–0.95)	**0.028**		
Asthma exacerbations	5.77 (3.17–10.5)	**<.0001**	3.06 (1.34–6.97)	**0.008**
Emergency room visit	8.46	**0.004**		
GINA control classes (W–P + U) W as reference	8.97 (5.40–14.9)	**<.0001**	0.22 (0.06–0.84)	**0.026**
FeNO	1.02 (1.00–1.03)	**0.003**		
Eosinophils	1.00 (1.00–1.00)	**0.003**		
Step GINA 2 as reference				
Step 2-3	0.90 (0.54–1.53)	0.705		
Step 2–4+5	1.57 (0.80–3.10)	0.190		
Extra-fine therapy	0.20 (0.12–0.33)	**<.0001**		
ICS dosage	1.00 (1.00–1.00)	**<.0001**		
ICS/LABA	1.04 (0.63–1.72)	0.873		
Antileukotriene use	1.56 (0.78–3.09)	0.208		
LAMA	6.15 (1.38–27.37)	**0.017**		
BMI	1.17 (1.10–1.24)	**<.0001**	1.14 (1.05–1.23)	**0.002**
Night awakenings due to asthma	8.00 (4.28–14.93)	**<.0001**	6.88 (2.13–22.23)	**0.002**
EIA symptoms	20.72 (10.81–39.71)	**<.0001**	33.5 (9.51–117.8)	**<.0001**
Smoking	3.47 (1.94–6.22)	**<.0001**		
Spirometry Data				
FEV1%	0.96 (0.94–0.98)	**<.0001**		
FEV1/FVC%	0.98 (0.94–1.02)	0.256		
FEF25-75%	0.99 (0.98–1.00)	**0.01**		

Cottini et al. Respir Med. 2023;218:107391.

Low adherence of inhaler in the real-world

Original Article

Assessment of Adherence and Asthma Medication Ratio for a Once-Daily and Twice-Daily Inhaled Corticosteroid/Long-Acting β-Agonist for Asthma

- A retrospective cohort study of commercial and Medicare Advantage
- Patients initiating FF/VI or BUD/F for asthma.

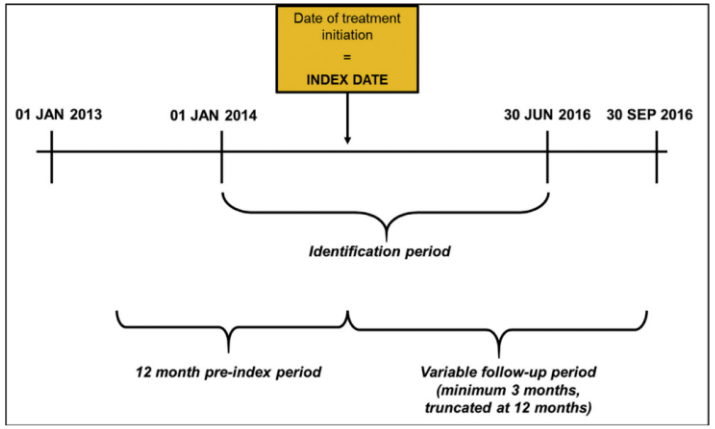
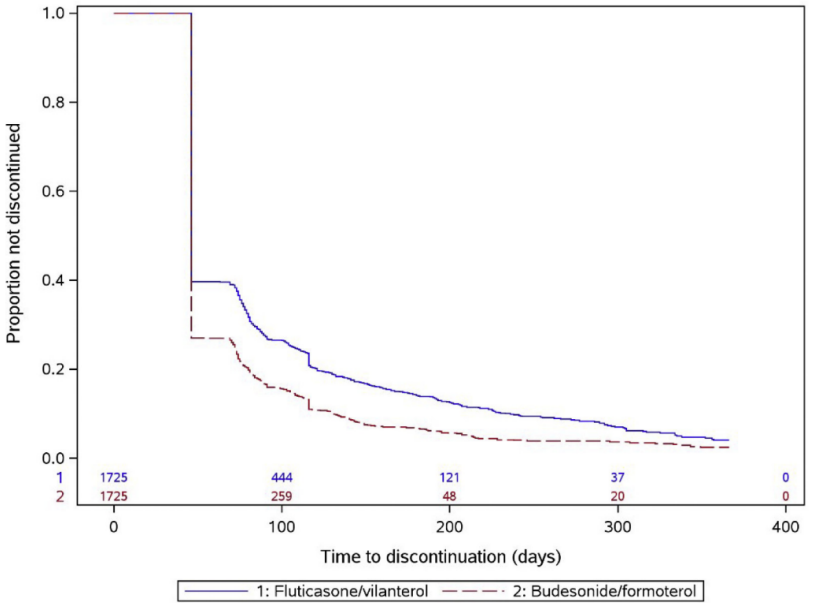


TABLE II. Means and percent that achieved each threshold for FF/VI vs BUD/F

Endpoint	FF/VI 100/25 µg (n = 1725)	BUD/F 160/4.5 µg (n = 1725)	*P* value
PDC, mean ± SD	0.43 ± 0.30	0.36 ± 0.27	<.001
≥0.5, %	38.3	26.6	<.001
≥0.8, %	17.5	10.2	<.001
Treatment discontinuation (within 12 mo), %	88.4	93.2	<.001
AMR, mean ± SD	0.63 ± 0.40	0.57 ± 0.42	<.001
≥0.5, %	68.6	62.3	<.001



Stanford et al. J Allergy Clin Immunol Pract. 2019

Factors associated with poor adherence

Patients with asthma who do not fill their inhaled corticosteroids: A study of primary nonadherence

L. Keoki Williams, MD, MPH,[a,b,c] Christine L. Joseph, PhD,[c] Edward L. Peterson, PhD,[c] Karen Wells, BS,[c] Mingqun Wang, MS,[b] Vimal K. Chowdhry, PhD,[b] Matthew Walsh, BBA,[d] Janis Campbell, RN,[b] Cynthia S. Rand, PhD,[e] Andrea J. Apter, MD, MSc,[f] David E. Lanfear, MD, MS,[a,b] Kaan Tunceli, PhD,[b] and Manel Pladevall, MD, MS[b] *Detroit, Mich, Baltimore, Md, and Philadelphia, Pa*

TABLE IV. Forward stepwise regression results for factors associated with primary nonadherence to ICSs among patients with asthma, stratified by race-ethnicity*

Risk factor	Likelihood of primary nonadherence, OR (95% CI)		
	All patients (n = 254)	African American patients (n = 87)	White patients (n = 159)
Age per year increase	0.97 (0.95-0.99)‖	—	—
Female	1.90 (1.01-3.55)‡	—	—
African American race-ethnicity†	2.00 (1.10-3.64)‡	—	—
No. outpatient visits in preceding year	—	0.87 (0.79-0.95)§	—
No. short-acting β-agonist fills in preceding year	0.83 (0.74-0.93)§	—	0.72 (0.59-0.88)§
No. oral corticosteroid fills in preceding year	—	0.35 (0.17-0.76)§	—

*The comparison group is patients with asthma who were adherent to their prescribed ICS (ie, adherence >80%).
†Comparison group is white patients.
‡*P* value < .05.
§*P* value < .01.
‖*P* value < .001.

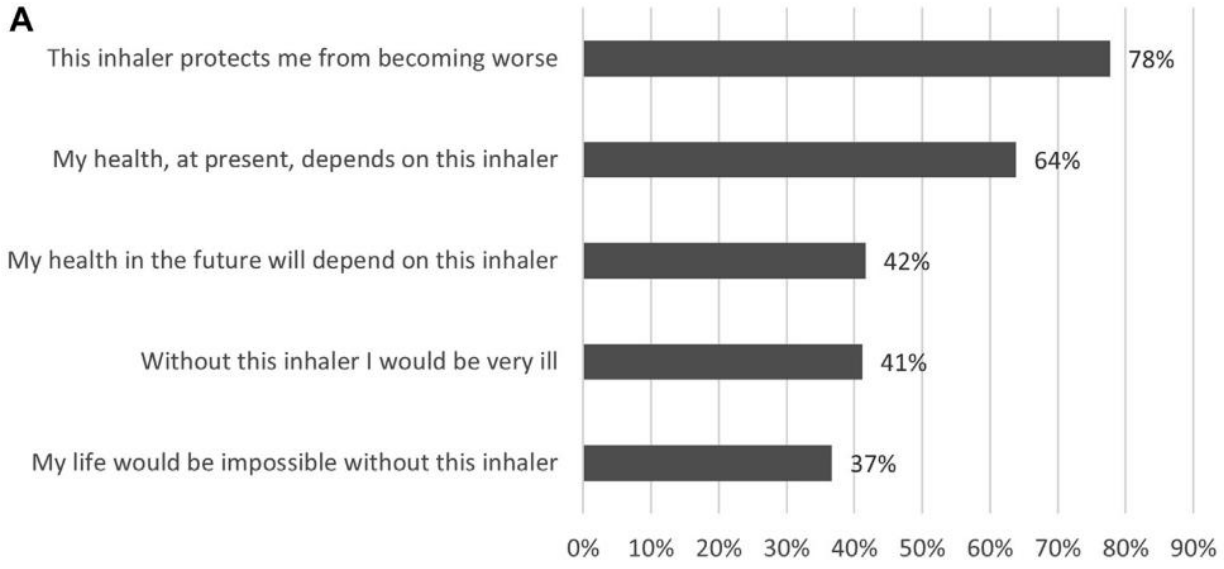
Williams et al. J Allergy Clin Immunol. 2007

How to enhance adherence to inhalers?

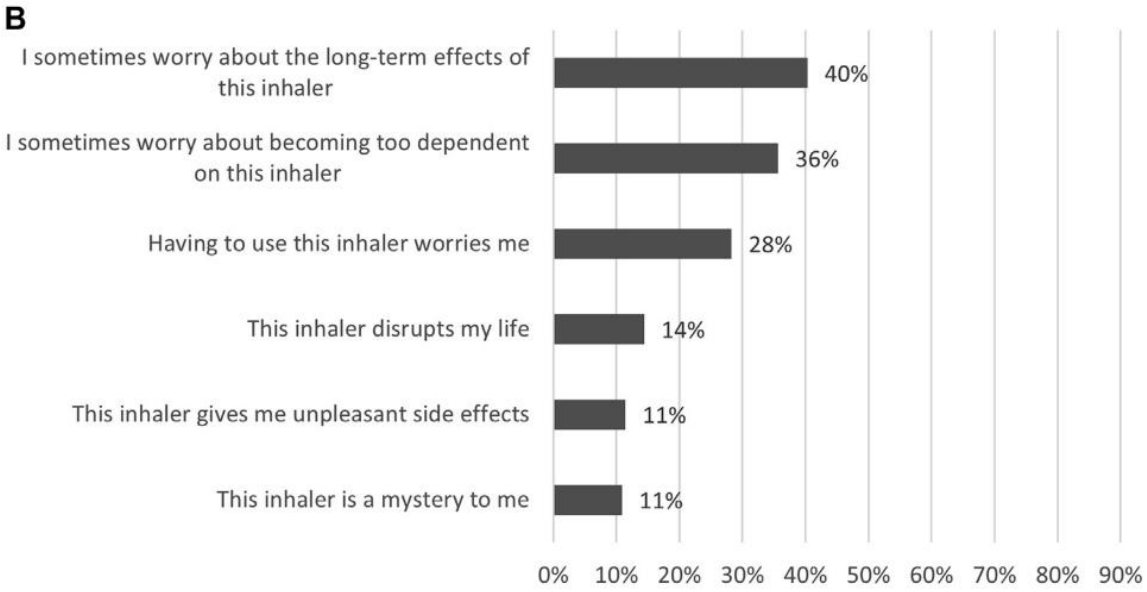
Medication beliefs, adherence, and outcomes in people with asthma: The importance of treatment beliefs in understanding inhaled corticosteroid nonadherence—a retrospective analysis of a real-world data set

Amy Hai Yan Chan, PhD,[a,b,c*] Caroline Brigitte Katzer, PhD,[a,b,d*] James Pike, MPhil,[e] Mark Small, BSc,[e] and Rob Horne, PhD[a,b,d]
London and Bollington, United Kingdom; and Auckland, New Zealand

Necessity

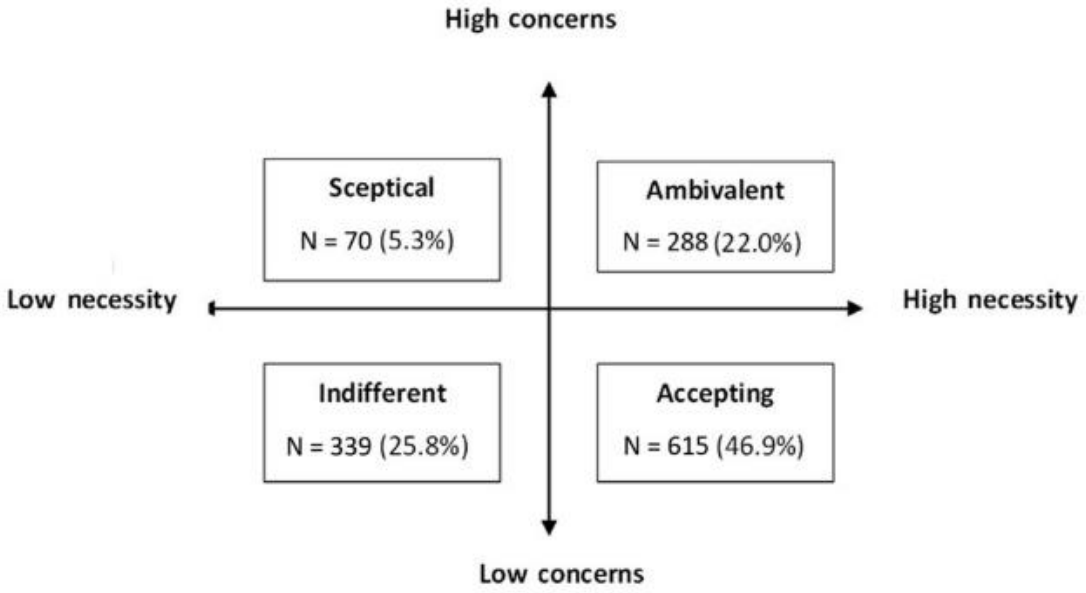


Concern



Chan et al. J Allergy Clin Immunol Glob. 2023.

Of course, EDUCATION is the most important.



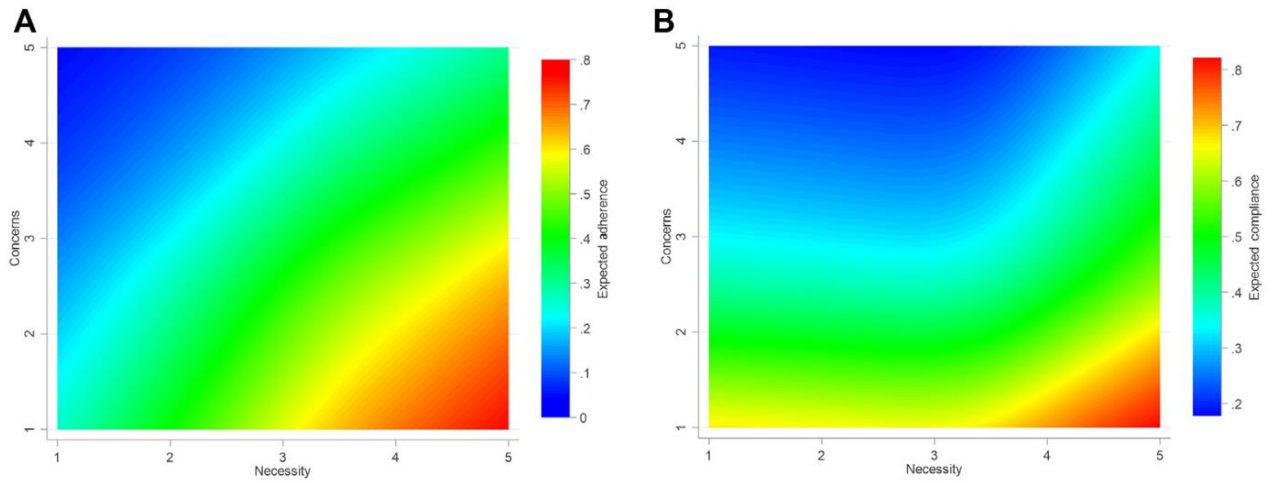
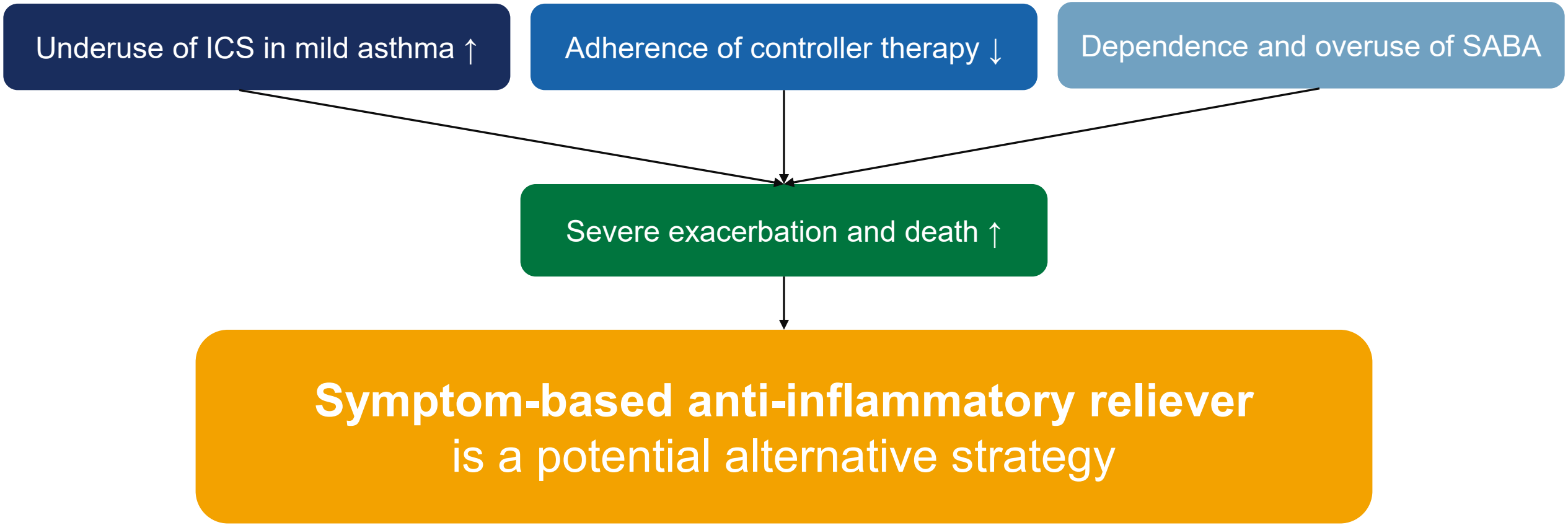


FIG 4. Contour regression plot of logistic regression of (**A**) patient-reported adherence (Necessity $P < .001$; Concerns $P = .002$) and (**B**) physician-reported adherence (Necessity $P = .021$; Concerns $P < .001$) vs Necessity and Concern scores. *Note:* Patient- and physician-reported adherence were dichotomized: Every day vs Not every day and Fully adherent vs Not fully adherent, respectively. Higher probabilities of high adherence are represented by the warmer colors (yellow/orange/red in order of increasing probability).

Chan et al. J Allergy Clin Immunol Glob. 2023.

Switching tracks may help



Will as-needed ICS-formoterol always better than maintenance ICS-LABA in inhaler adherences?

Switching tracks may help

SYGMA1

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 17, 2018 VOL. 378 NO. 20

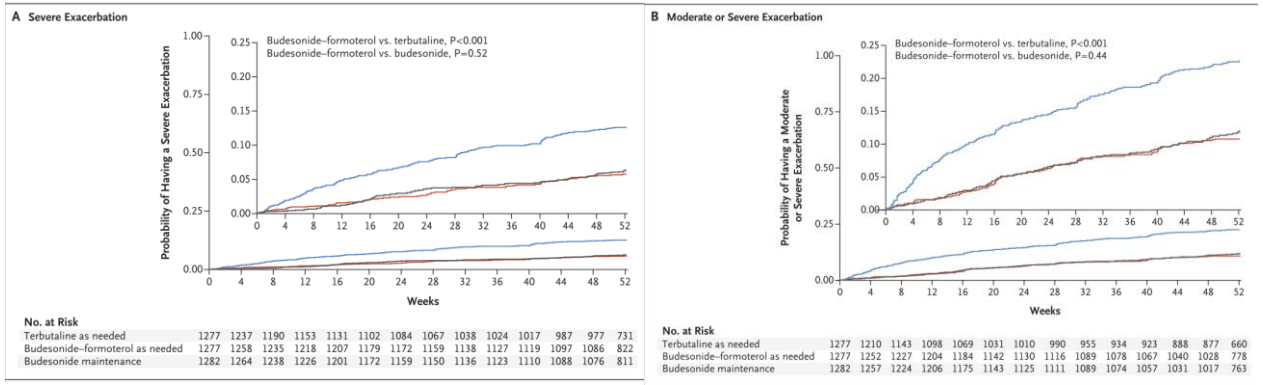
Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma

Paul M. O'Byrne, M.B., J. Mark FitzGerald, M.D., Eric D. Bateman, M.D., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D., Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D., Stefan Ivanov, M.D., Ph.D., and Helen K. Reddel, M.B., B.S., Ph.D.

Variable	Terbutaline as Needed (N=1277)	Budesonide–Formoterol as Needed (N=1277)	Budesonide Maintenance Therapy (N=1282)
All severe exacerbations			
Patients with ≥1 exacerbation — no. (%)	152 (11.9)	71 (5.6)	78 (6.1)
Total no. of exacerbations	188	77	89
Annualized exacerbation rate	0.20	0.07	0.09
Comparison between as-needed budesonide–formoterol and other regimen			
Rate ratio	0.36	—	0.83
95% CI	0.27–0.49	—	0.59–1.16
P value	<0.001	—	0.28
All moderate or severe exacerbations			
Patients with ≥1 exacerbation — no. (%)	274 (21.5)	131 (10.3)	143 (11.2)
Total no. of exacerbations	372	164	170
Annualized exacerbation rate	0.36	0.14	0.15
Comparison between as-needed budesonide–formoterol and other regimen			
Rate ratio	0.40	—	0.95
95% CI	0.32–0.49	—	0.74–1.21
P value	<0.001	—	0.66

Adherence did not differ significantly across the trial groups:

- Terbutaline group: 79.0±23.3%
- Budesonide-formoterol group: 79.1±23.0%
- Budesonide maintenance group: 78.9±22.4%



O'Byrne et al. N Engl J Med 2018.

Switching tracks may help

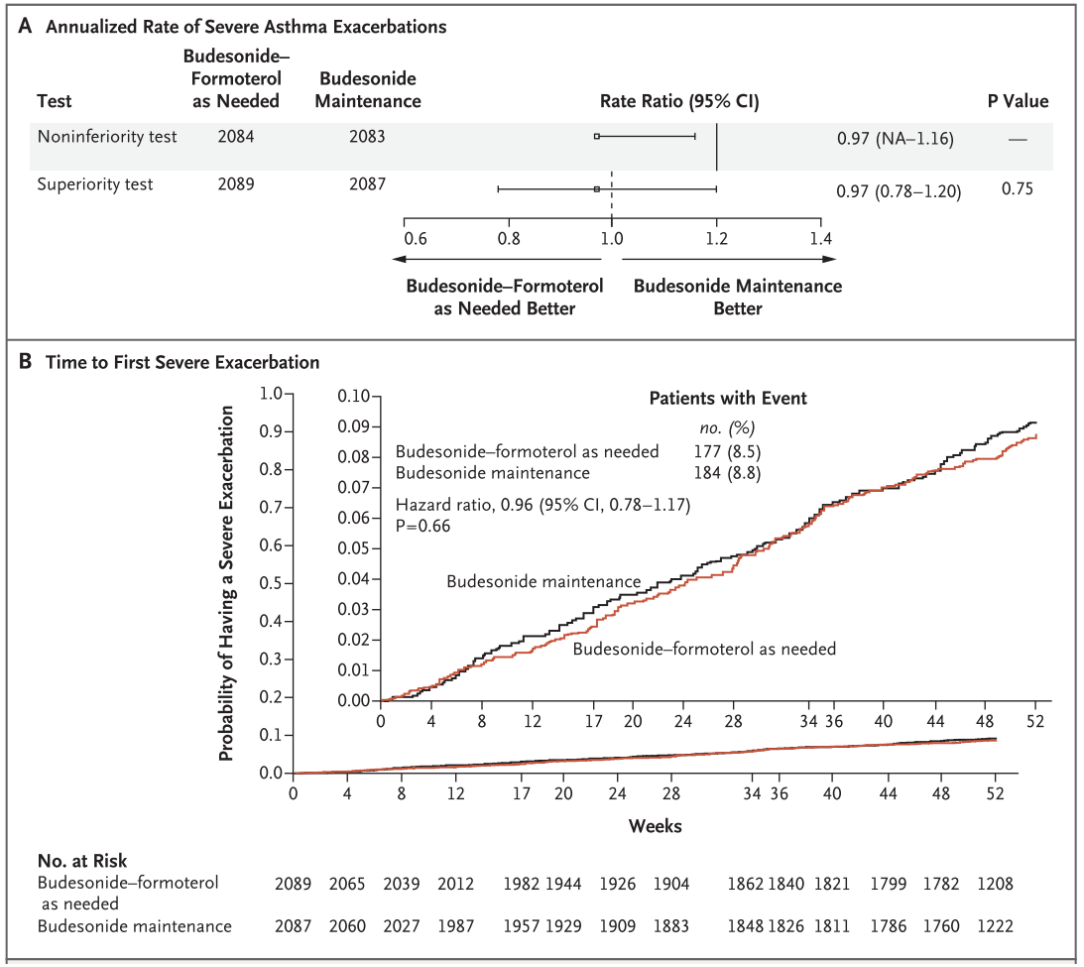
SYGMA2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

As-Needed Budesonide–Formoterol versus Maintenance Budesonide in Mild Asthma

Eric D. Bateman, M.D., Helen K. Reddel, M.B., B.S., Ph.D., Paul M. O'Byrne, M.B., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D., Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D., Agnieszka Siwek-Posluszna, M.D., and J. Mark FitzGerald, M.D.



Adherence did not differ significantly across the trial groups:

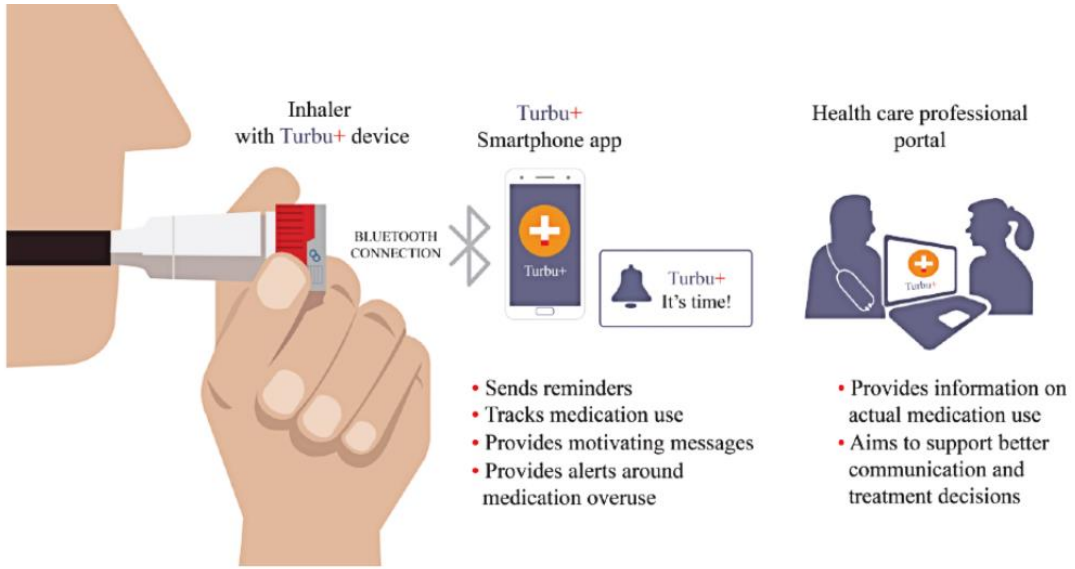
- Budesonide-formoterol group: 64.0±30.0%
- Budesonide maintenance group: 62.8±29.4%

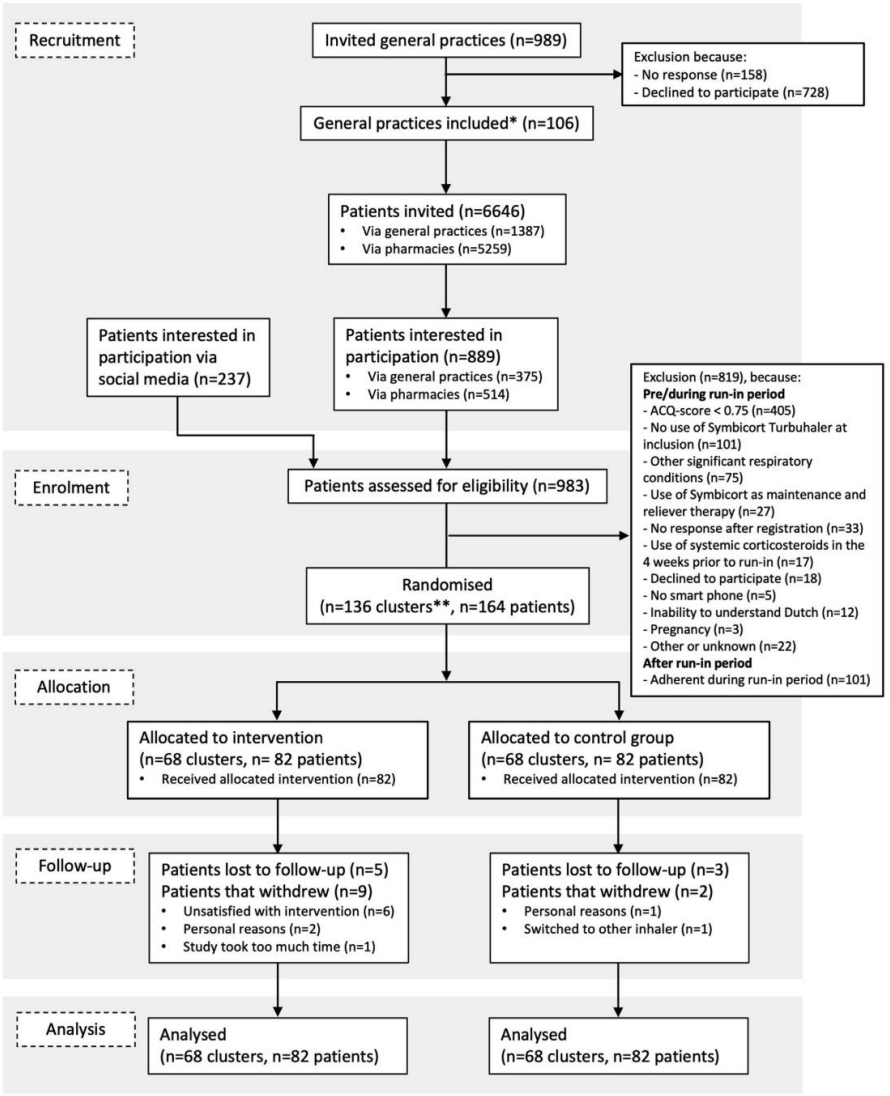
Bateman et al. N Engl J Med. 2018;378(20):1877-87.

Digital devices

Original Article

Long-Term Effectiveness of a Digital Inhaler on Medication Adherence and Clinical Outcomes in Adult Asthma Patients in Primary Care: The Cluster Randomized Controlled ACCEPTANCE Trial



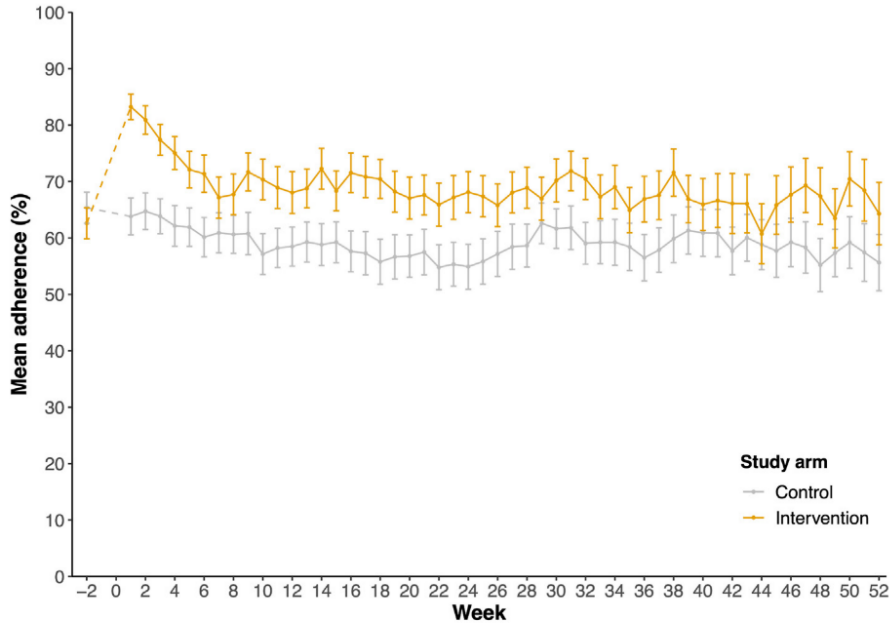


van de Hei SJ et al. J Allergy Clin Immunol Pract 2025.

Digital devices

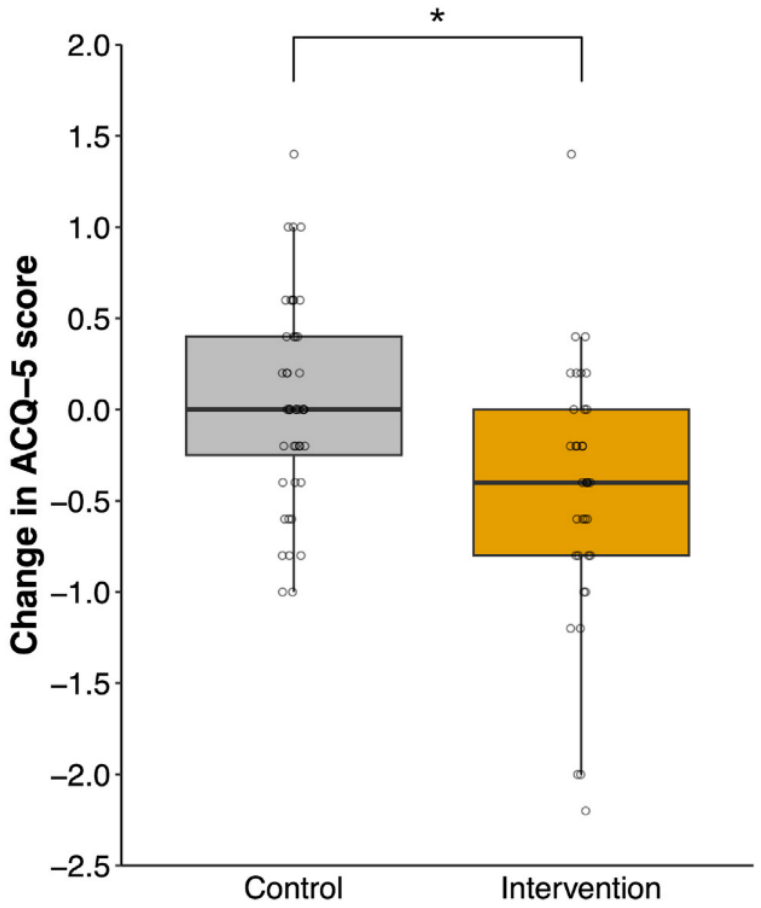
Original Article

Long-Term Effectiveness of a Digital Inhaler on Medication Adherence and Clinical Outcomes in Adult Asthma Patients in Primary Care: The Cluster Randomized Controlled ACCEPTANCE Trial



Participants in analysis	Control	-	-	81	79	77	75	71	71	64	72	71	71	70	73	66	60	71	68	65	62	61	53	55	56	54	51	50	22
	Intervention	-	-	81	78	78	76	75	74	67	72	69	71	70	69	61	64	67	64	61	54	53	43	45	43	42	40	38	24
Participants in study	Control	82	82	82	80	80	79	78	77	77	77	77	77	77	77	77	76	75	73	68	65	63	63	61	59	57	56	52	48
	Intervention	82	82	81	79	78	77	75	74	73	73	72	72	72	72	72	69	68	67	62	60	54	53	50	50	46	45	43	34
Cumulative withdrawals/LTFU	Control	0	0	0	2	2	3	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	Intervention	0	0	1	3	4	5	7	8	9	9	10	10	10	10	10	11	9	8	9	9	9	10	10	10	11	10	10	9

FIGURE 2. Mean medication adherence by study group and week. *LTFU*, Lost to follow-up.



*: Odds Ratio 3.000 (95% Confidence Interval: 1.133-8.345)

van de Hei SJ et al. J Allergy Clin Immunol Pract 2025.

Trying best to bringing up the adherences

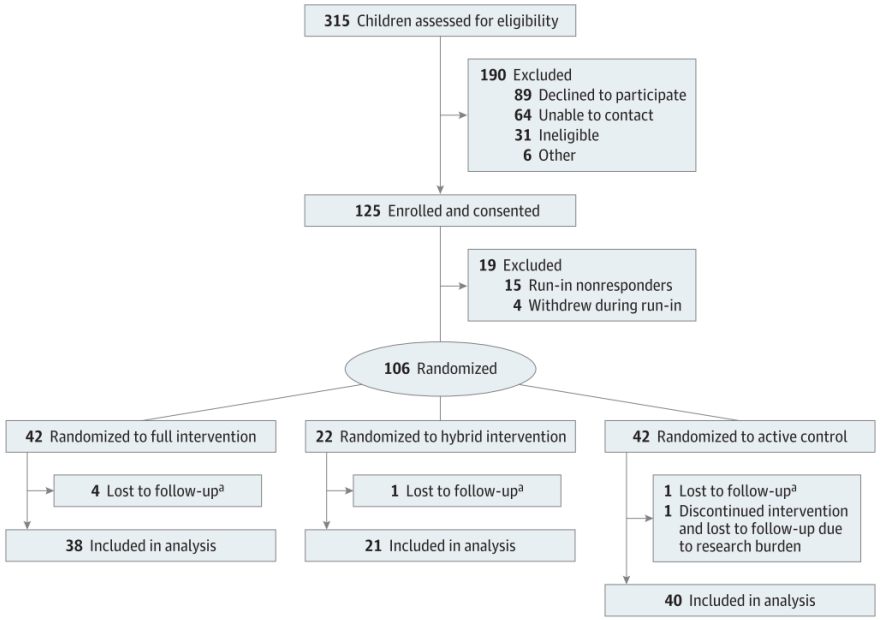
Research

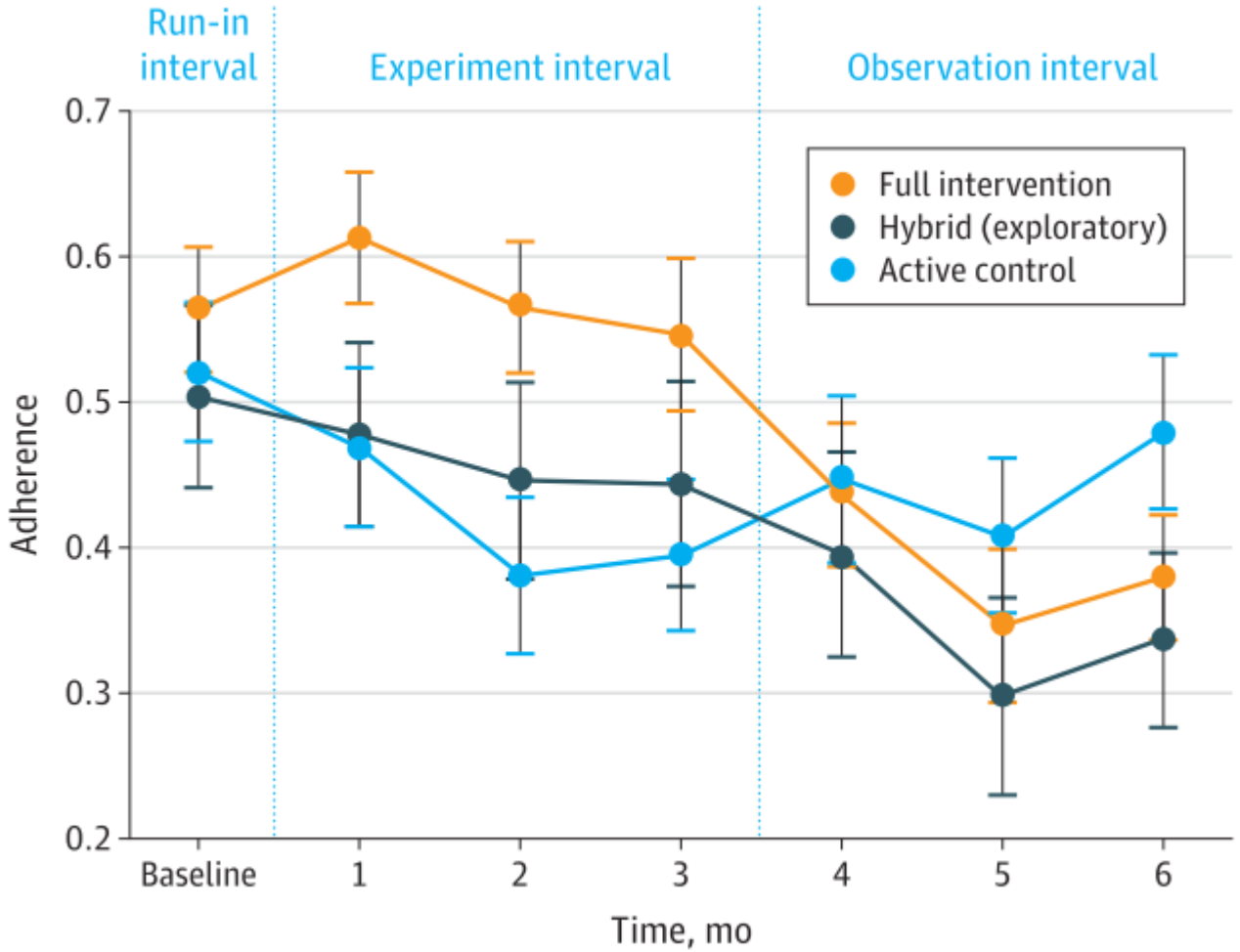
JAMA Pediatrics | Original Investigation

Tailored Adherence Incentives for Childhood Asthma Medications
A Randomized Clinical Trial

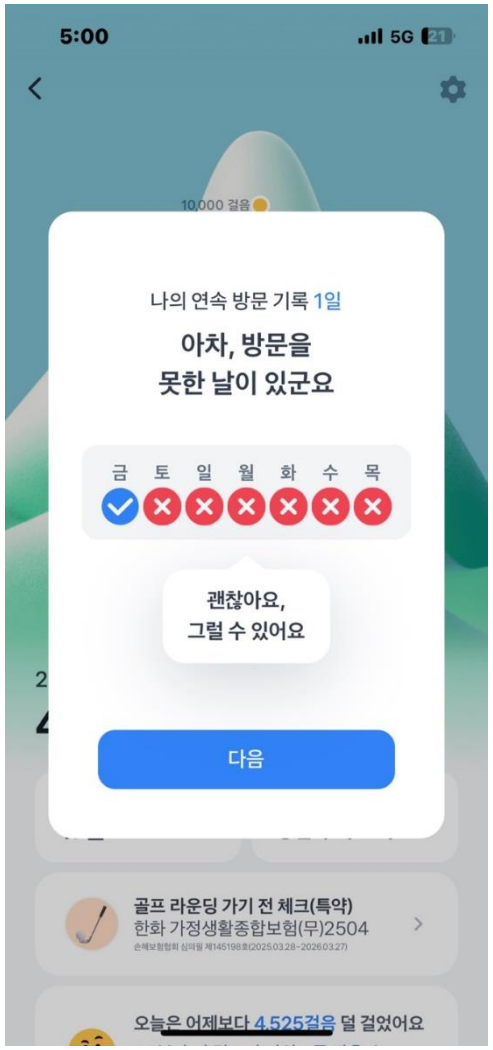
Chén C. Kenyon, MD, MSHP; William O. Quarshie, MS; Rui Xiao, PhD; Mishaal Yazdani, BS; Carina M. Flaherty, BA; G. Chandler Floyd, BA; Victoria A. Miller, PhD; Tyra C. Bryant-Stephens, MD; Joseph J. Zorc, MD, MSCE; Chris Feudtner, MD, PhD, MPH

Figure 1. CONSORT Diagram of Participant Flow for the Tailored Adherence Incentives for Childhood Asthma Medications Trial





JAMA Pediatr. 2025;179(5):500-7.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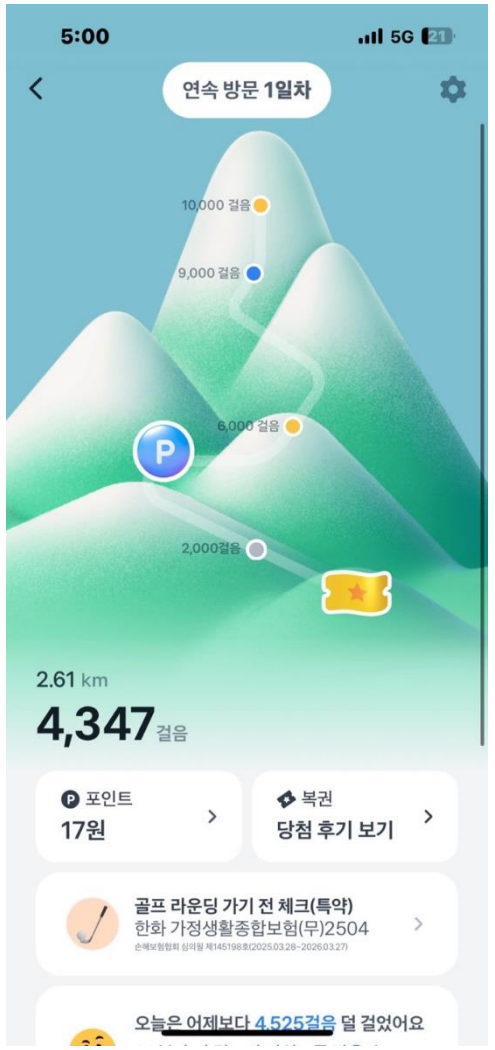
금 토 일 월 화 수 목
괜찮아요,
그럴 수 있어요
다음
골프 라운딩 가기 전 체크(특약)
한화 가정생활종합보험(무)2504
오늘은 어제보다 4,525걸음 덜 걸었어요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복권
당첨 후기 보기
골프 라운딩 가기 전 체크(특약)
한화 가정생활종합보험(무)2504
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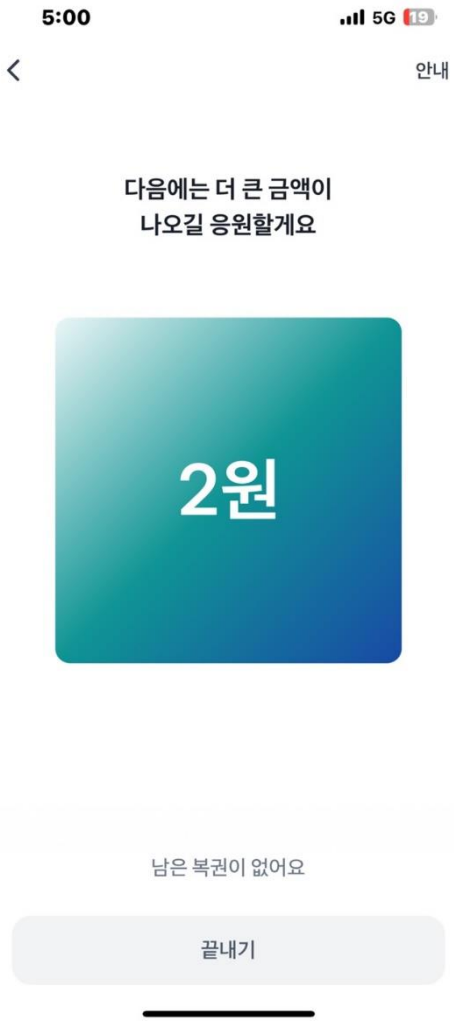
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안내
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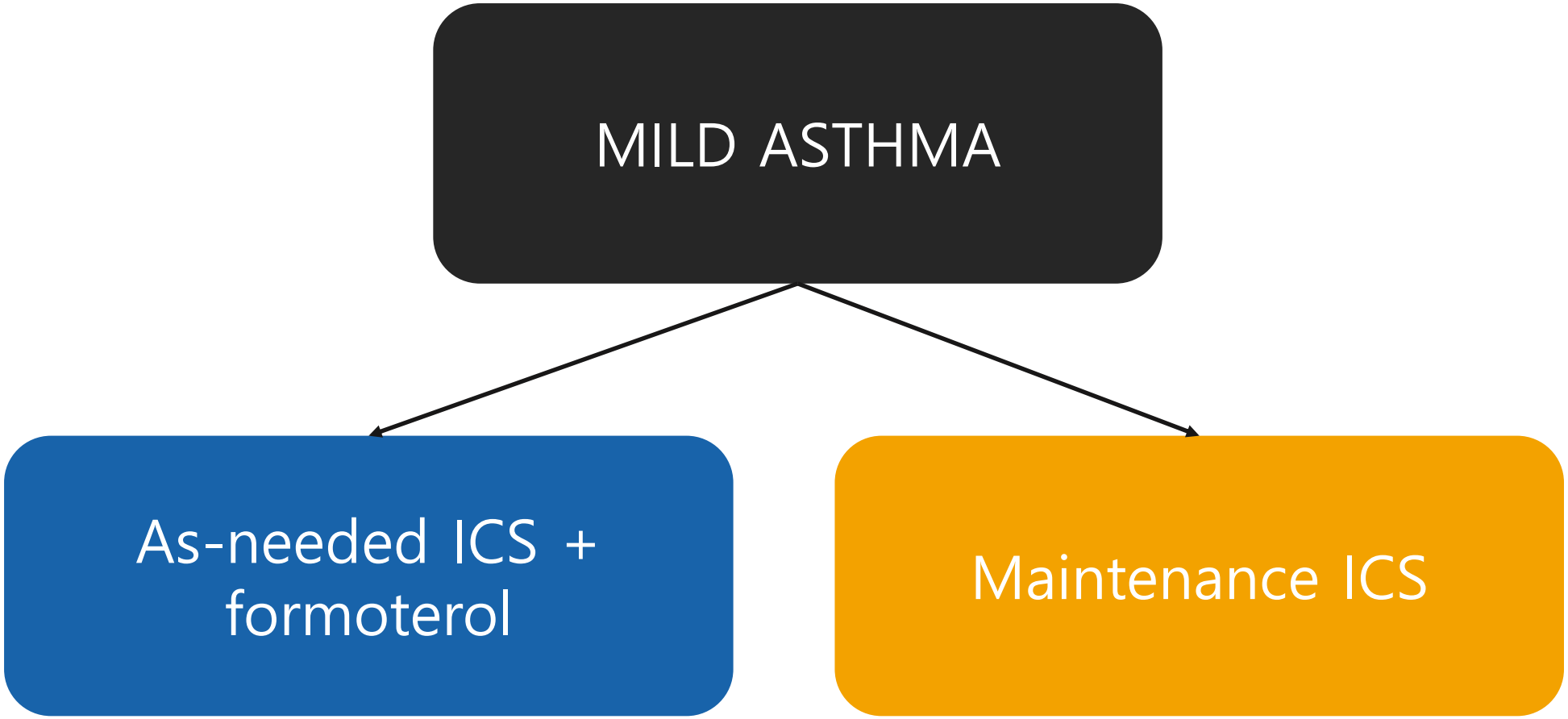
나오길 응원할게요
2원
남은 복권이 없어요
끝내기

If guidelines are followed, a mild asthmatic will not be left unattended



Counterargument 3:

“Mild asthma may be ‘mild’ now, but it can progress to severe asthma over time.”

Long-term trajectories of mild asthma

Original Article

Long-Term Trajectories of Mild Asthma in Adulthood and Risk Factors of Progression

Wenjia Chen, PhD[a], J. Mark FitzGerald, MD[b,c], Larry D. Lynd, PhD[a,d], Don D. Sin, MD[c,e], and Mohsen Sadatsafavi, MD, PhD[a,c] *Vancouver, BC, Canada*

TABLE I. Characteristics of the study sample in the index year

Characteristic	Patients with mild asthma (N = 70,829)
Age (y), mean ± SD	30.5 ± 9.7
Sex, n (%)	
Female	43,891 (62)
Male	26,938 (38)
Socioeconomic status, n (%)	
Low	29,993 (42)
Middle	14,430 (20)
High	26,406 (37)
Comorbidity, n (%)	
None (CCI score = 0)	62,342 (88)
Mild (CCI score = 1)	7,266 (10)
Moderate (CCI score = 2)	873 (1)
High (CCI score ≥ 3)	348 (0.5)
Allergic rhinitis, n (%)	9,398 (13)
Inappropriate SABA use,* n (%)	
No	42,186 (59)
Yes	8,399 (12)
No ICS or SABA use	20,244 (29)
ICS vs ICS + LABA use, n (%)	
ICS	24,522 (35)
ICS + LABA	8,253 (12)
Both	906 (1)
No ICS use	37,148 (52)
ICS-adjusted daily dose,† mean ± SD	82.9 ± 115.4
No. of other controllers/wk,‡ mean ± SD	0.0 ± 0.0
No. of SABA doses/wk,§ mean ± SD	2.3 ± 2.4
Moderate-to-severe exacerbations,‖ mean ± SD	0.1 ± 0.3
No. of nonasthma hospitalizations, mean ± SD	1.2 ± 4.6
No. of nonasthma physician visits, mean ± SD	12.8 ± 13.9
No. of nonasthma medications, mean ± SD	71.3 ± 256.4

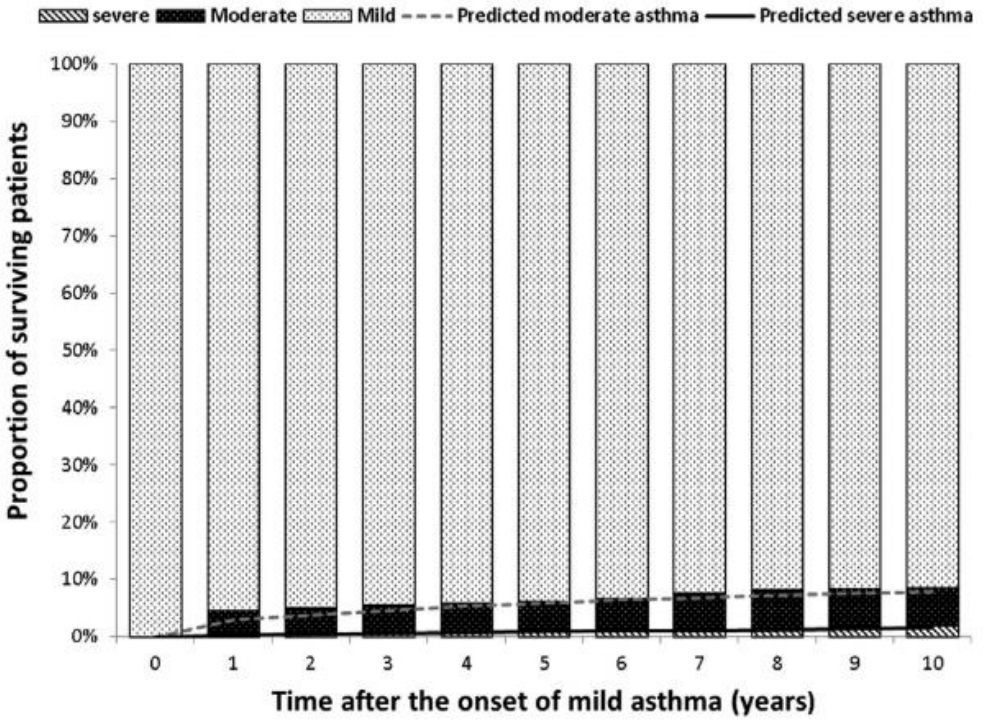


FIGURE 1. Proportions of surviving patients with incident asthma at different severity states over time. The dead state was not shown in the graph because of its very small contribution (only 0.1% had died over 10 years).

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Effect of SABA use, onset age, comorbidities on trajectory of mild asthma

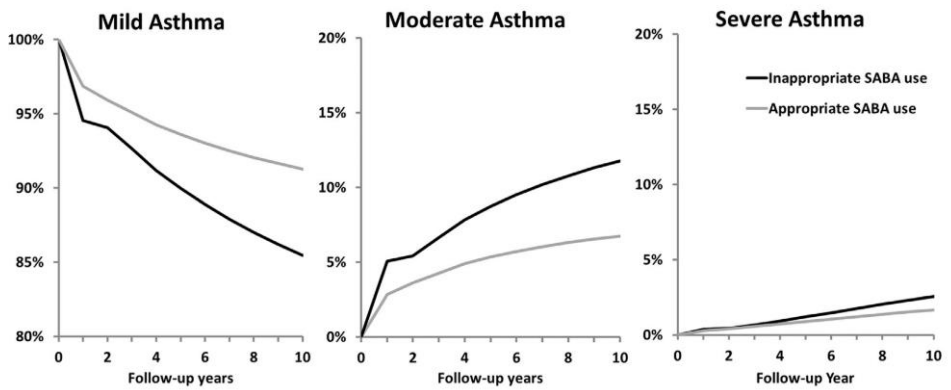


FIGURE 2. The influences of rescue medication use in the index year on the long-term trajectory of patients with incident mild asthma. Y-axis denotes the population-averaged probability of being in a specified severity state, with scales range between 80% and 100% for mild asthma and between 0% and 20% for moderate and severe asthma, respectively. Probability of being dead is not displayed. X-axis denotes the follow-up years since incident year of mild asthma.

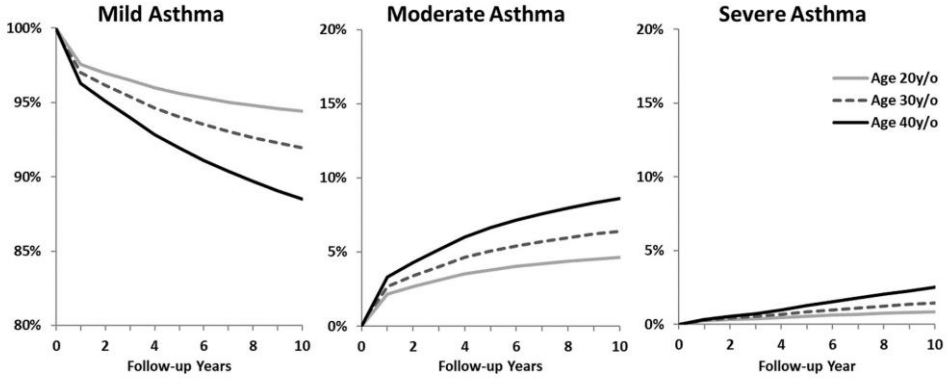


FIGURE 3. The influence of baseline age on long-term trajectory of patients with incident mild asthma. Y-axis denotes the population-averaged probability of being in a specified severity state, with scales range between 80% and 100% for mild asthma and between 0% and 20% for moderate and severe asthma, respectively. Probability of being dead is not displayed. X-axis denotes the follow-up years since incident year of mild asthma. *y/o*, Years of age.

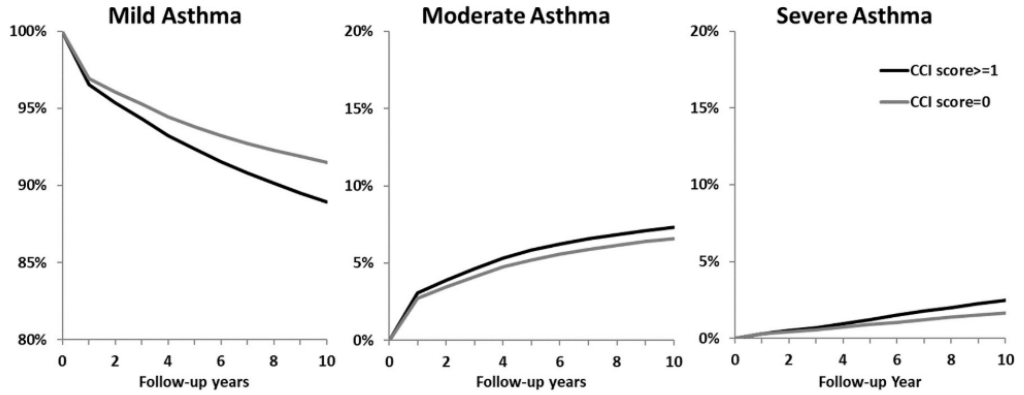


FIGURE 4. The influence of baseline comorbidity status on long-term trajectory of patients with incident mild asthma. Comorbidity was represented by the CCI (excluding asthma) scores: none (CCI score = 0), comorbidity (CCI score ≥ 1). Y-axis denotes the population-averaged probability of being in a specified severity state, with scales range between 80% and 100% for mild asthma and between 0% and 20% for moderate and severe asthma, respectively. Probability of being dead is not displayed. X-axis denotes the follow-up years since incident year of mild asthma.

Chen W et al. J Allergy Clin Immunol Pract. 2018

Traditional concept of asthma remission

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Longitudinal, Population-Based, Cohort Study of Childhood Asthma Followed to Adulthood

Malcolm R. Sears, M.B., Justina M. Greene, Andrew R. Willan, Ph.D., Elizabeth M. Wiecek, M.D., D. Robin Taylor, M.D., Erin M. Flannery, Jan O. Cowan, G. Peter Herbison, M.Sc., Phil A. Silva, Ph.D., and Richie Poulton, Ph.D.

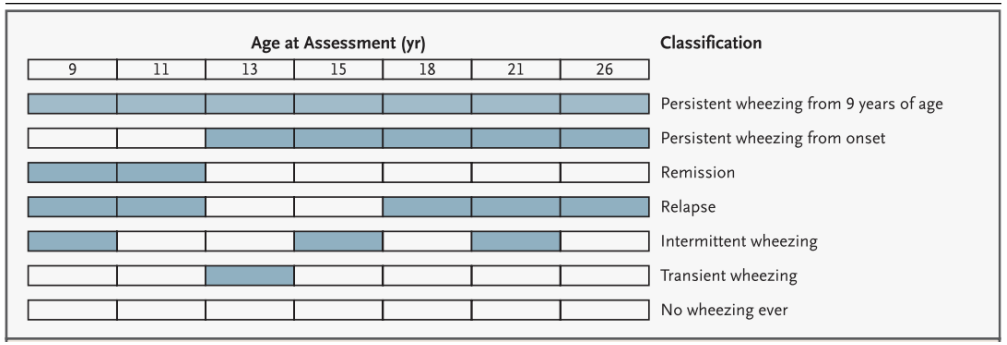


Table 2. Outcomes at Age 26 Years among 613 Study Members Who Provided Respiratory Data at Every Assessment, According to Sex.

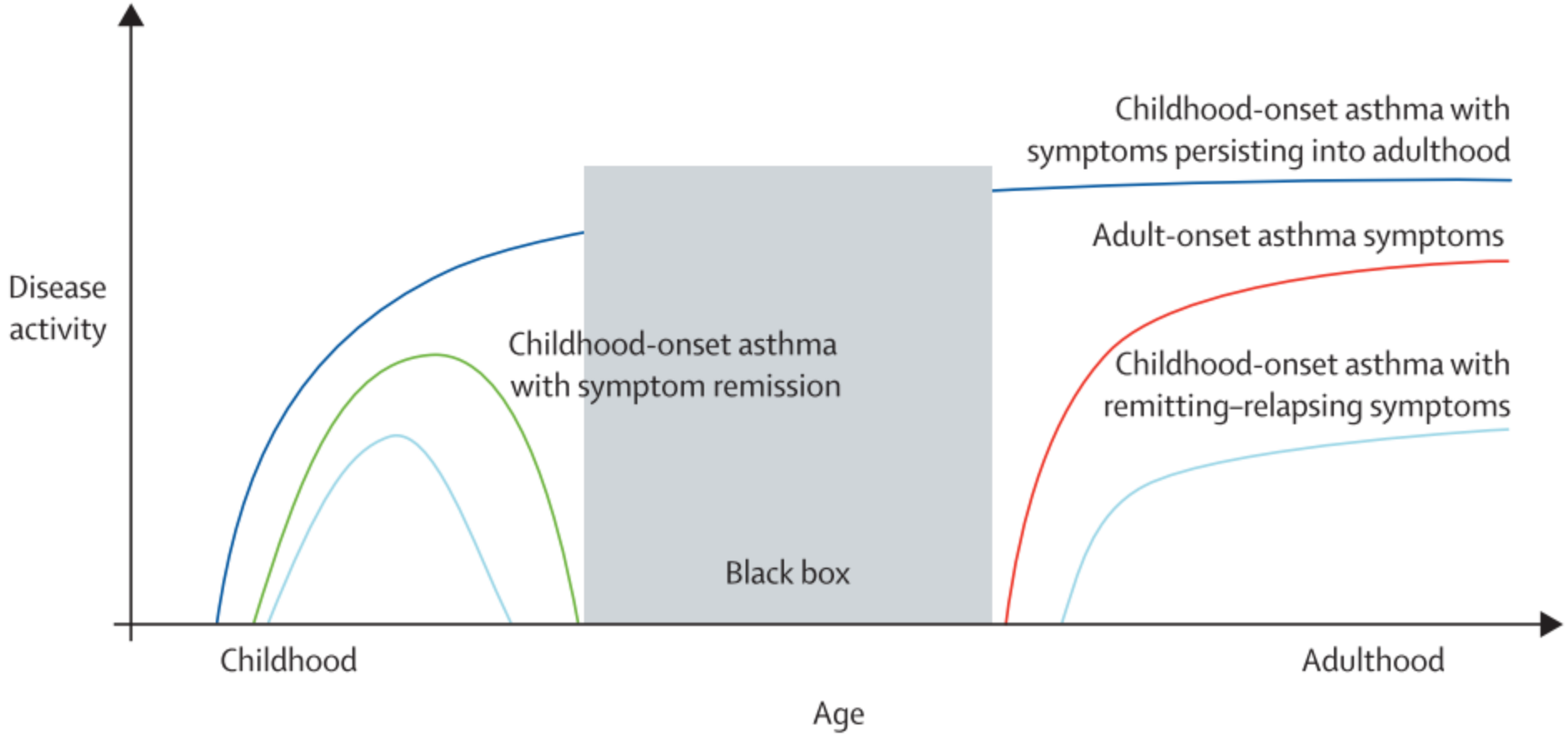
Outcome	Male Study Members (N=317)	Female Study Members (N=296)	Total (N=613)
	% (no. of study members)		
Persistent wheezing (from onset to 26 yr)	12.6 (40)	16.6 (49)	14.5 (89)
Relapse (wheezing stopped then recurred)	12.9 (41)	11.8 (35)	12.4 (76)
In remission (free of wheezing at 26 yr)	15.5 (49)	14.5 (43)	15.0 (92)
Intermittent wheezing	9.5 (30)	9.5 (28)	9.5 (58)
Transient wheezing (reported at only one assessment)	19.9 (63)	22.6 (67)	21.2 (130)
Wheezing never reported	29.7 (94)	25.0 (74)	27.4 (168)

Table 4. Odds Ratios for Factors Predicting Persistence of Wheezing from Onset to the Age of 26 Years or Relapse, by the Age of 26 Years.*

Multivariate (significant factors only)				
PC_{20} ≤8 mg/ml or BDR >10% at any assessment from 9 –21 yr	3.00 (1.71–5.26)	<0.001	3.03 (1.65–5.55)	<0.001
Positive skin test for house-dust-mite allergen at 13 yr	2.41 (1.42–4.09)	0.001	2.18 (1.18–4.00)	0.01
Female sex	1.71 (1.04–2.82)	0.03	—	—
Smoking at 21 yr	1.84 (1.13–3.00)	0.01	—	—
Age at onset of wheezing†	—	—	0.89 (0.85–0.94)	<0.001

Sears et al. N Engl J Med. 2003

Traditional concept of asthma remission



Fuchs et al. Lancet Respir Med. 2017;5(3):224-34.

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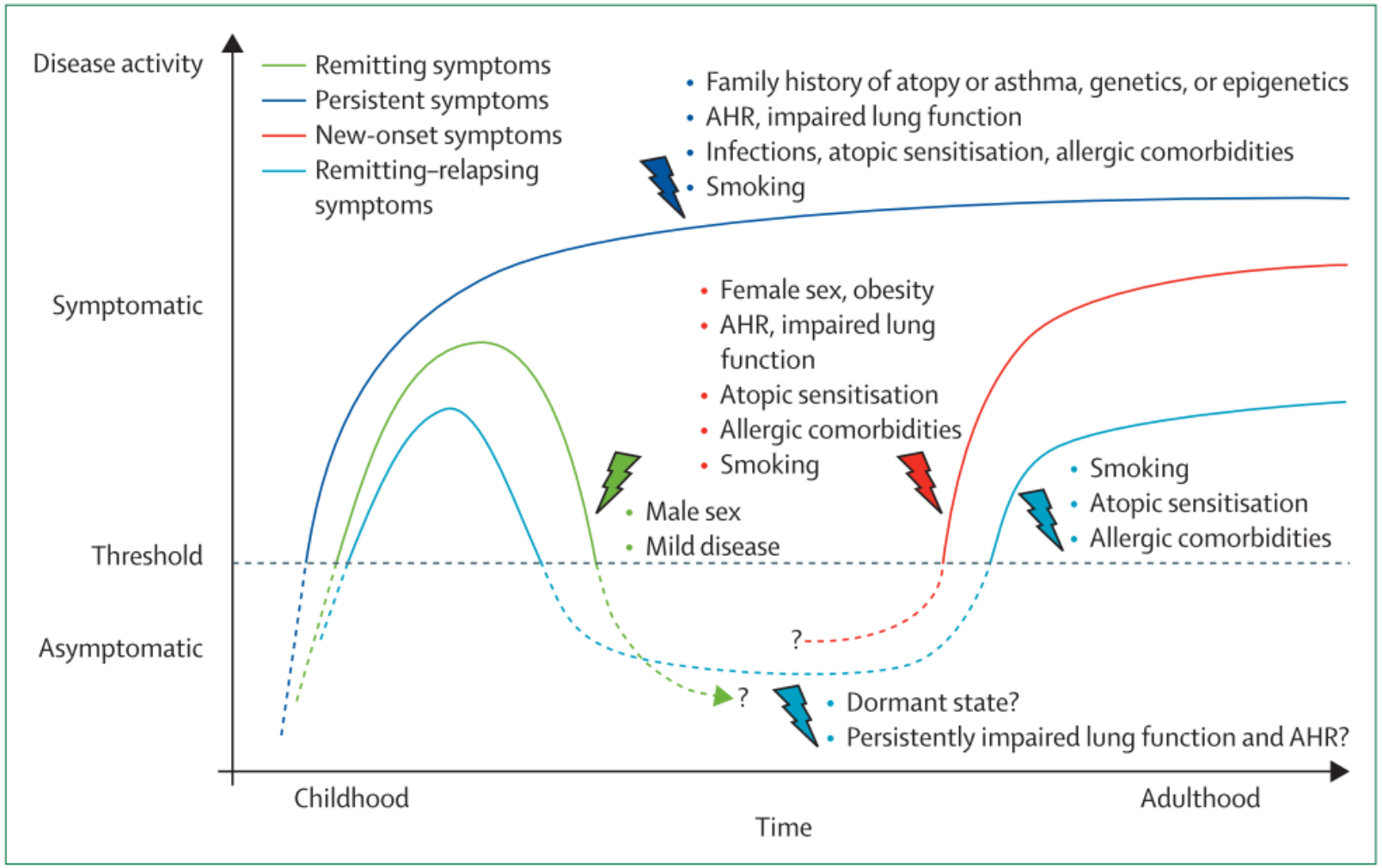

Fuchs et al. Lancet Respir Med. 2017;5(3):224-34.

Conclusion

1. Worse outcomes can be predicted, and risk prediction may be crucial (e.g., exacerbation history, medication adherence).

2. “Mild” ≠ ”Safe”. Enhancing adherence through patient education may be the most important factor.

3. Most patients with mild asthma remain stable in the long term, and some may even achieve spontaneous remission.


Mild is real — if we take it seriously.