Global trends and challenges in the management of asthma

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WOOLCOCK
LEADERS IN BREATHING & SLEEP RESEARCH

CENTRE OF EXCELLENCE IN
SEVERE ASTHMA
Innovative solutions for severe asthma

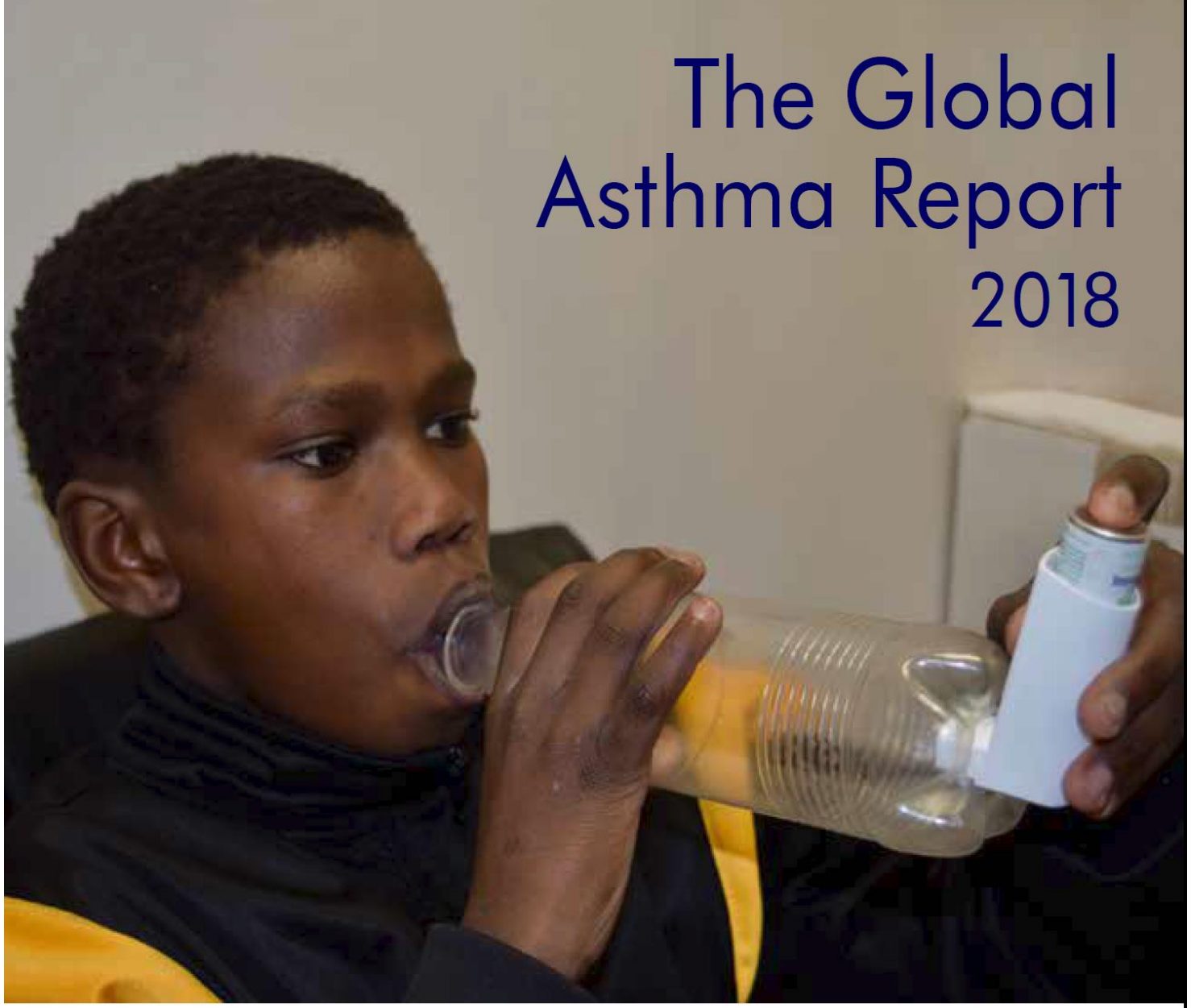
SCIENTIA
MANU ET MENTE
UNSW
SYDNEY

Disclosures

- My institutions receive funds for research from
  - GSK
  - AstraZeneca
- This trip is funded by Boehringer Ingelheim
- I have served on Advisory Boards for
  - Novartis
  - AstraZeneca
- I am President of the International Union Against Tuberculosis and Lung Disease (IUATLD, The Union)

What I will talk about

- Global burden of asthma
- Risk factors
- Access to medicines
- Multi-dimensional assessment and management
- A new paradigm for mild asthma
- Severe asthma
  - Macrolides
  - Biologicals
  - Severe asthma toolkit



Global Asthma Network

Innes Asher
Chair
Global Asthma Network

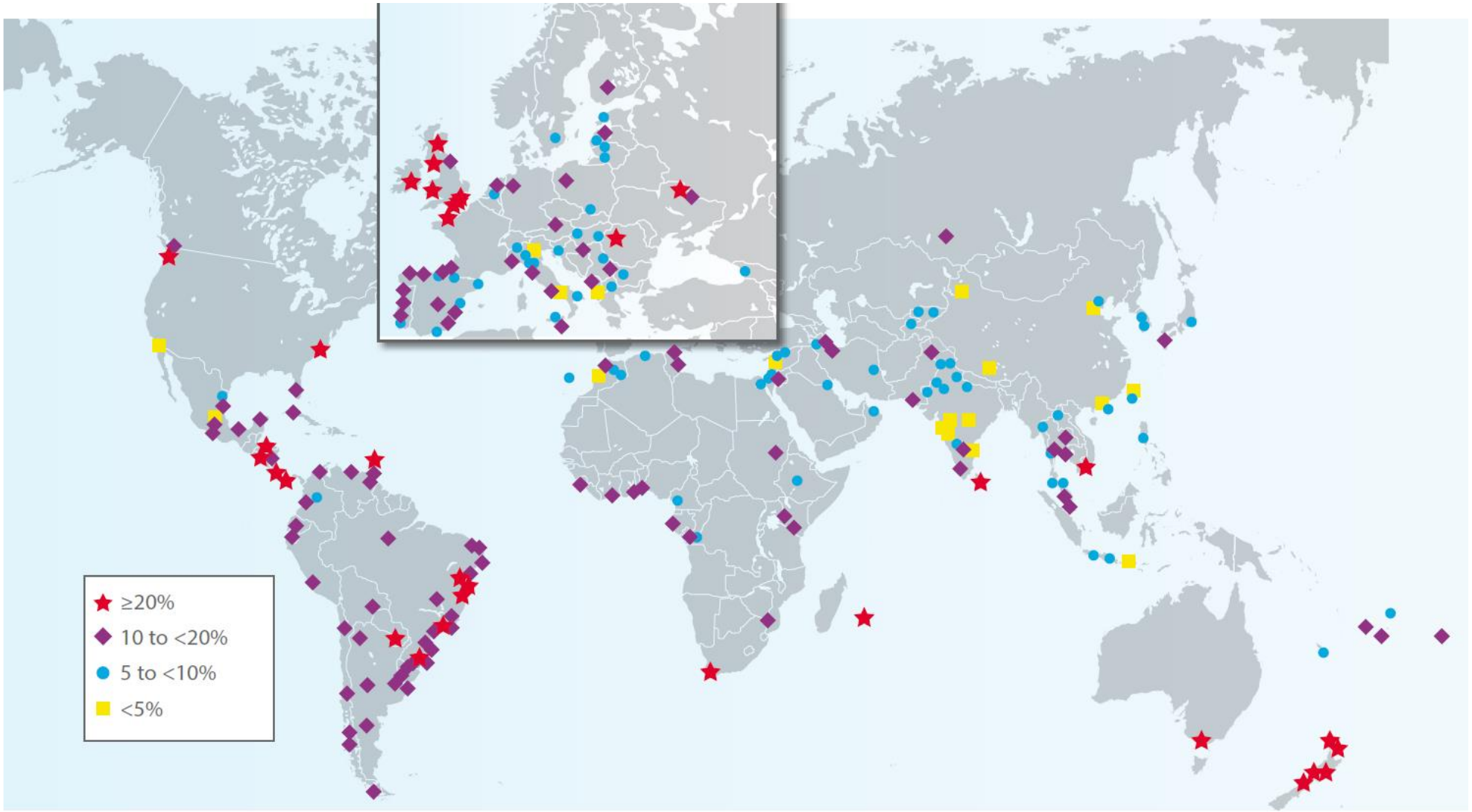
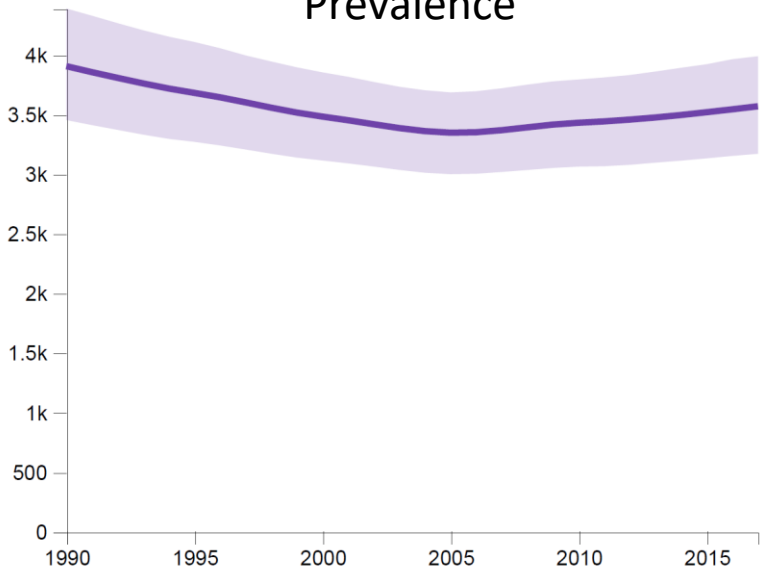


Figure 1: Prevalence of asthma symptoms among 13-14 year olds (ISAAC).

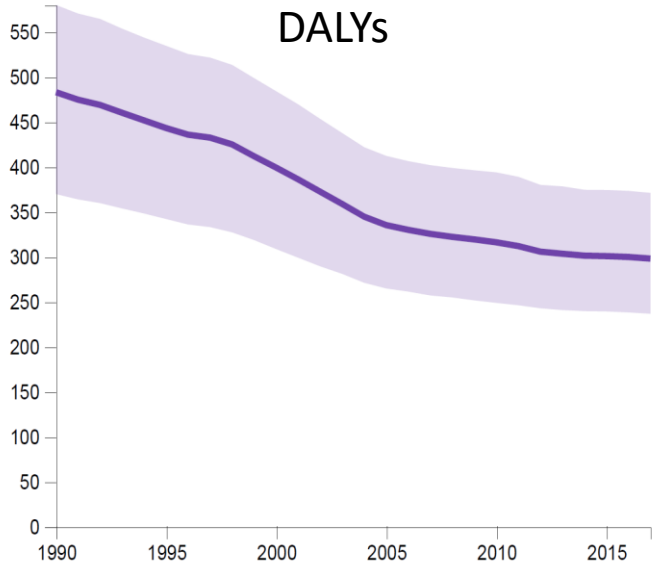
Source: Lai CKW, et al. Thorax 2009.

Global Burden of Asthma, 1990-2017

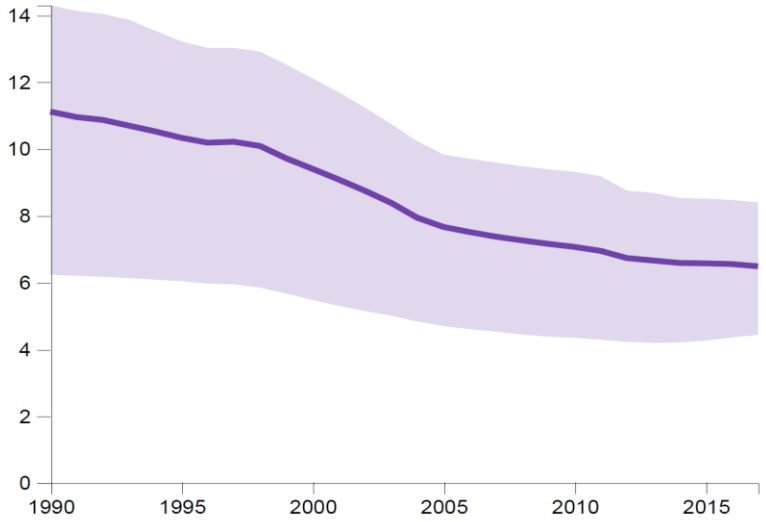
Prevalence



DALYs

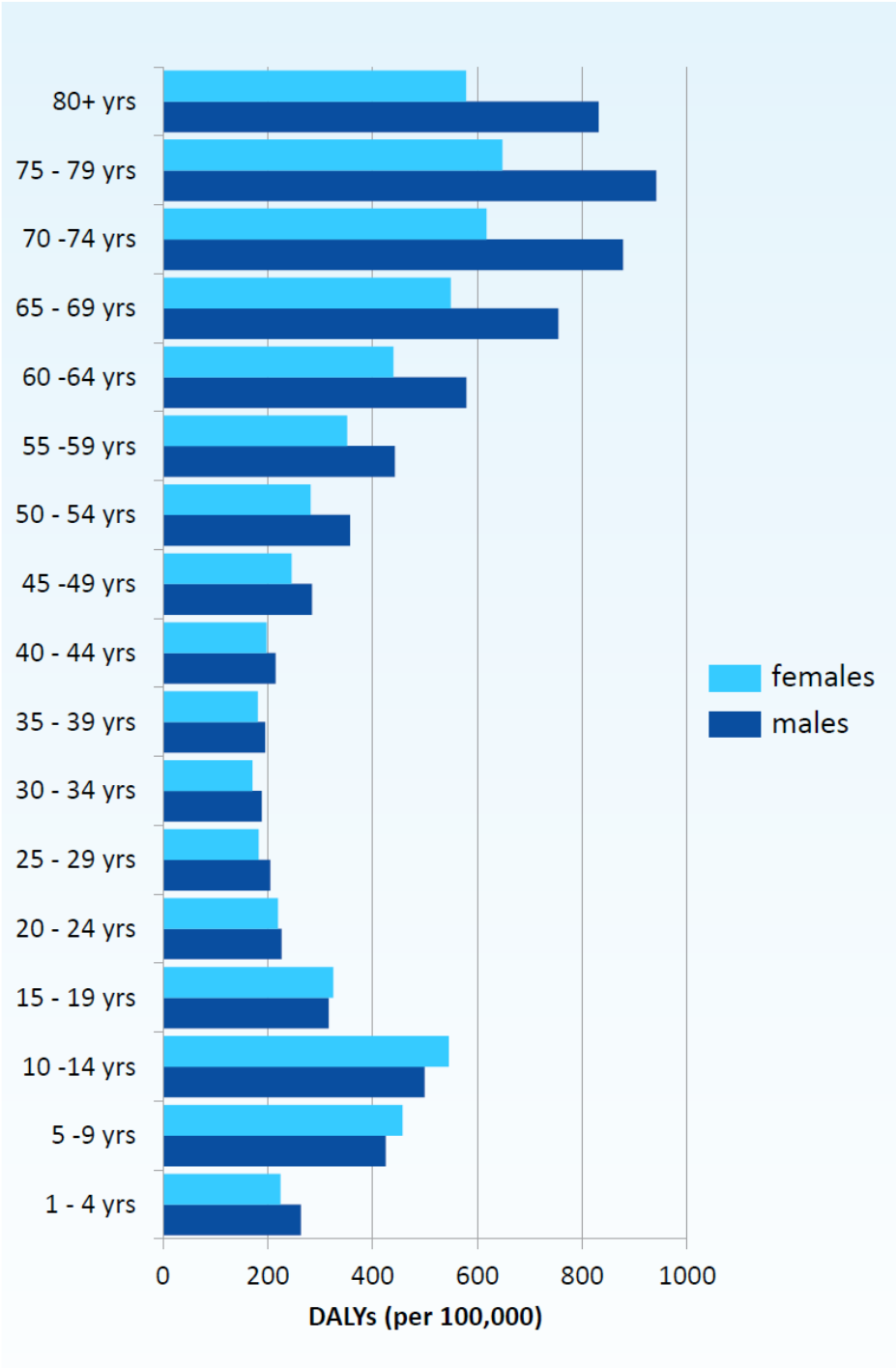


Deaths

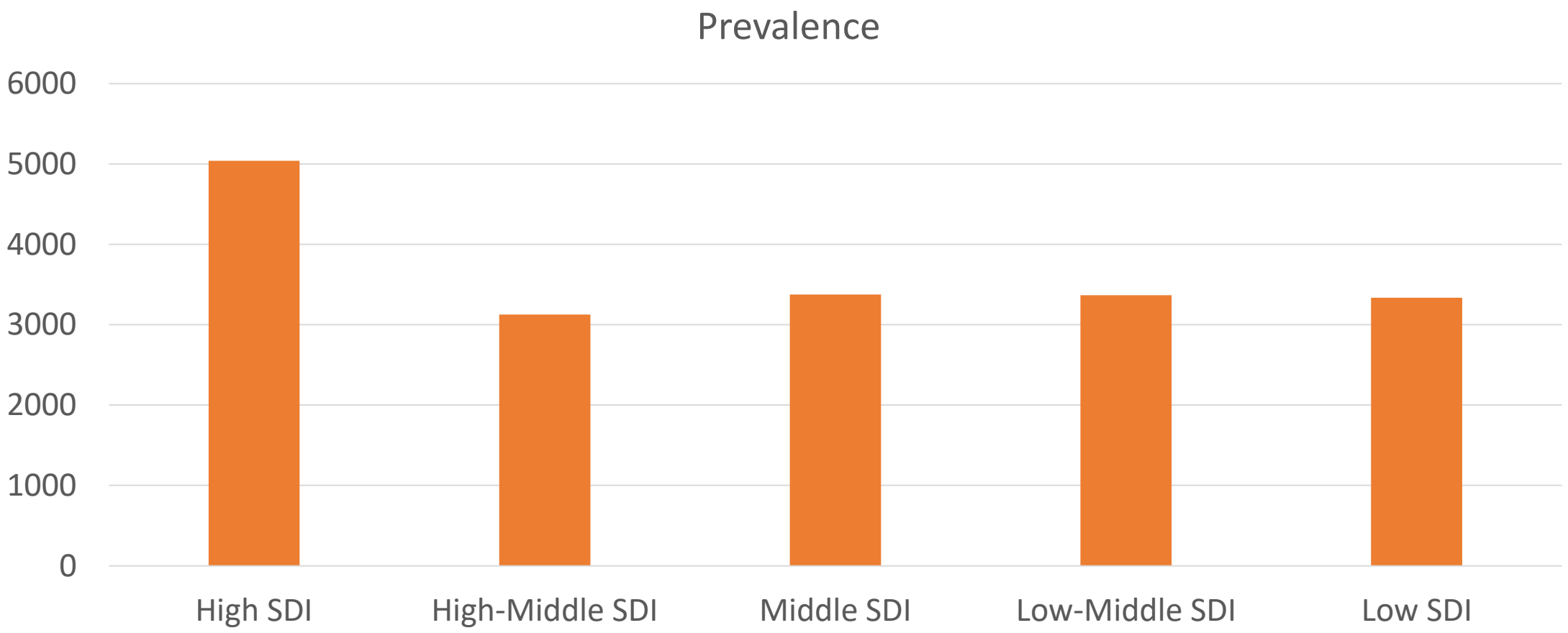


IHME Global Burden of Disease study

Burden of disease (DALYs) due to asthma by age and sex, 2010

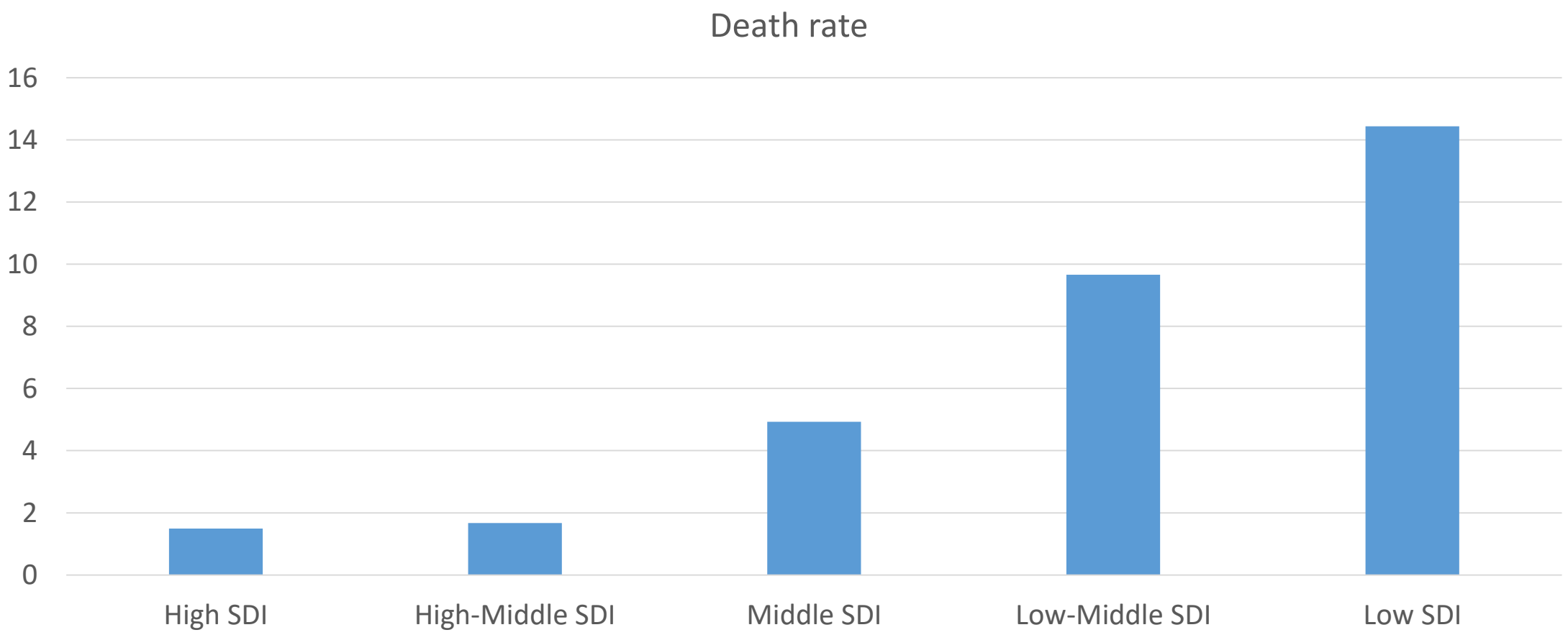


Prevalence of asthma by national development status, 2017



IHME Global Burden of Disease study

Deaths due to asthma by national development status

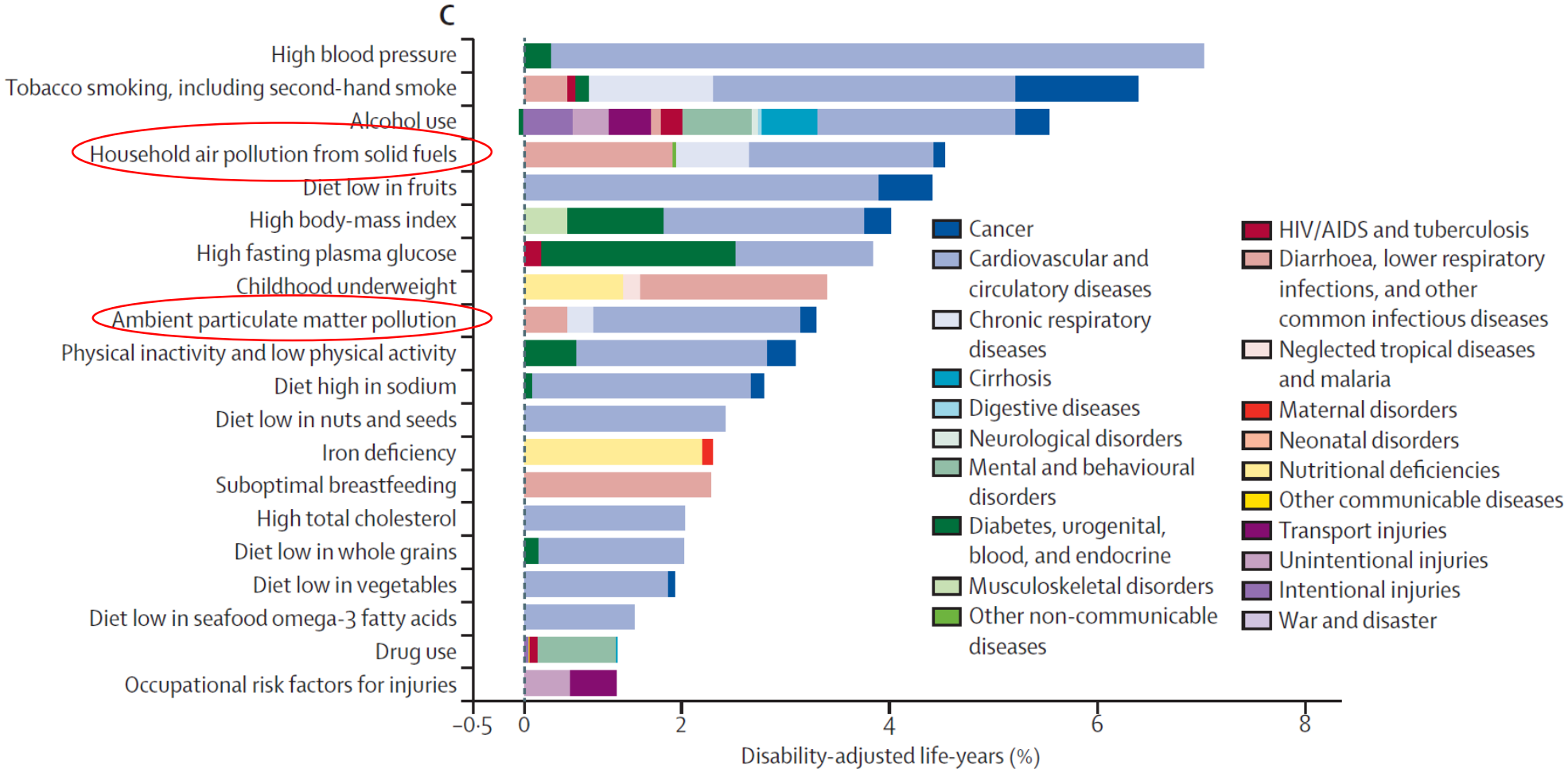


IHME Global Burden of Disease study

Case fatality rate

- Risk of death among people with asthma is much higher in lower-middle and lower SDI countries
- Why?
  - Lack of access to inhaled corticosteroids
  - Lack of access to acute care for exacerbations
  - More exposure to triggers and exacerbating factors

Major risk factors for global burden of disease



Lim SS, Vos T, Flaxman AD, Danaei G, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2012; 380:2224-60.

Issues on access to medicines for asthma

- Right medicine
- Available
- Prescribed / recommended
- Affordable
- Quality-assured
- Inhaler technique
- Adherence

Table 2 Comparative costs, in US dollars, for a year of treatment for a case of moderate persistent asthma in eight low and middle-income countries in 1998

Location	Monthly salary of a nurse	Cost of asthma treatment
Algeria	120	52
Vietnam	35	60
Syria	65	104
Guinea	100	128
Ivory Coast	200	132
Turkey	300	136
Mali	81	152
Burkina Faso	70	244

Ait-Khaled N, Auregan G, Bencharif N, Camara Mady L, Dagli E, Djankine K, et al. Affordability of inhaled corticosteroids as a potential barrier to treatment of asthma in some developing countries. Int J Tuberc Lung Dis. 2000;4:268-71.

Review

Asthma in older adults

Peter G Gibson, Vanessa M McDonald, Guy B Marks

Asthma in older people is common and is characterised by underdiagnosis and undertreatment. Ageing is associated with unique issues that modify expression, recognition, and treatment of the disease. In particular, asthma and chronic obstructive pulmonary disease (COPD) both overlap and converge in older people. This concurrence, together with absence of precise diagnostic methods, makes diagnosis complex. A multidimensional assessment that addresses airway problems, comorbidities, risk factors, and management skills will draw attention to key needs for intervention. Increased attention to the complications of asthma and obstructive airway disease in older people is needed, specifically to develop effective systems of care, appropriate clinical practice guidelines, and a research agenda that delivers improved health outcomes.

Lancet 2010; 376: 803–13

See Editorial page 744

School of Medicine and Public Health, Faculty of Health (Prof P G Gibson FRACP, V M McDonald B Nurs) and School of Nursing and Midwifery, Faculty of Health (V M McDonald) University of Newcastle, Callaghan, NSW

Multi-dimensional assessment of chronic airways disease

- Airway and respiratory components
  - Airflow obstruction
  - Airway inflammation
  - Airway infection / colonisation
  - Acute exacerbations / attacks
  - Oxygen desaturation
  - Exercise intolerance
- Comorbidity
- Self-management
- Risk factors

Gibson PG, McDonald VM, Marks GB. Asthma in older adults. Lancet. 2010;376(9743):803-13.

Multi-dimensional assessment of asthma

- Airway and respiratory components
- Comorbidity
  - Heart disease (including diastolic dysfunction)
  - Anxiety and depression
  - Obesity
  - Vocal cord dysfunction
  - Dysfunctional breathing
  - Anaemia
  - Sleep disordered breathing
  - Cataracts
  - GORD
  - Osteoporosis
- Self-management
- Risk factors

Gibson PG, McDonald VM, Marks GB. Asthma in older adults. Lancet. 2010;376(9743):803-13.

Multi-dimensional assessment of asthma

- Airway and respiratory components
- Comorbidity
- Self-management
  - Exacerbations
  - Device use
  - Adherence
  - Polypharmacy
- Risk factors

Gibson PG, McDonald VM, Marks GB. Asthma in older adults. Lancet. 2010;376(9743):803-13.

Multi-dimensional assessment of asthma

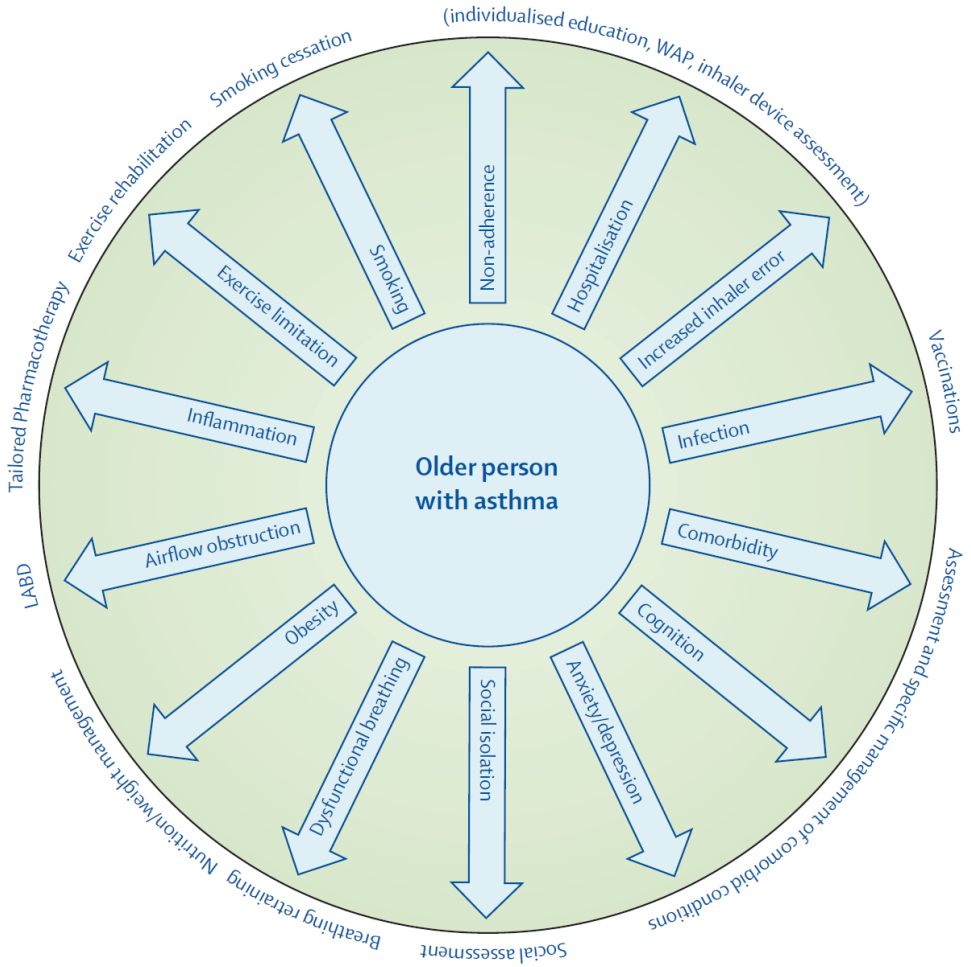
- Airway and respiratory components
- Comorbidity
- Self-management
- Risk factors
  - Smoking
  - Nutrition (over- and under-)
  - Physical inactivity
  - Workplace exposures
  - Domestic exposures

Gibson PG, McDonald VM, Marks GB. Asthma in older adults. Lancet. 2010;376(9743):803-13.

Multi-dimensional management of asthma

Gibson PG, McDonald VM, Marks GB. Asthma in older adults. Lancet. 2010;376(9743):803-13.

Multi-dimensional management of asthma



Gibson PG, McDonald VM, Marks GB. Asthma in older adults. Lancet. 2010;376(9743):803-13.

Multi-dimensional management of asthma

	Treatment
Pharmacotherapy	
Airflow obstruction	Long-acting bronchodilator
Airway inflammation	Corticosteroids; macrolides
Systemic inflammation	Statins (potentially)
Self management	
Inhaler technique inadequacy	Appropriate device selection, education, and reassessment
Non-adherence	Self management education; patient–clinician partnership
Exacerbations	Written action plan
Risk factor modification	
Smoking	Smoking cessation counselling and pharmacotherapy
Obesity	Diet modification and weight loss interventions
Physical inactivity	Pulmonary rehabilitation
Comorbidity	
See panel 2	Guideline based treatment is recommended for specific comorbidities

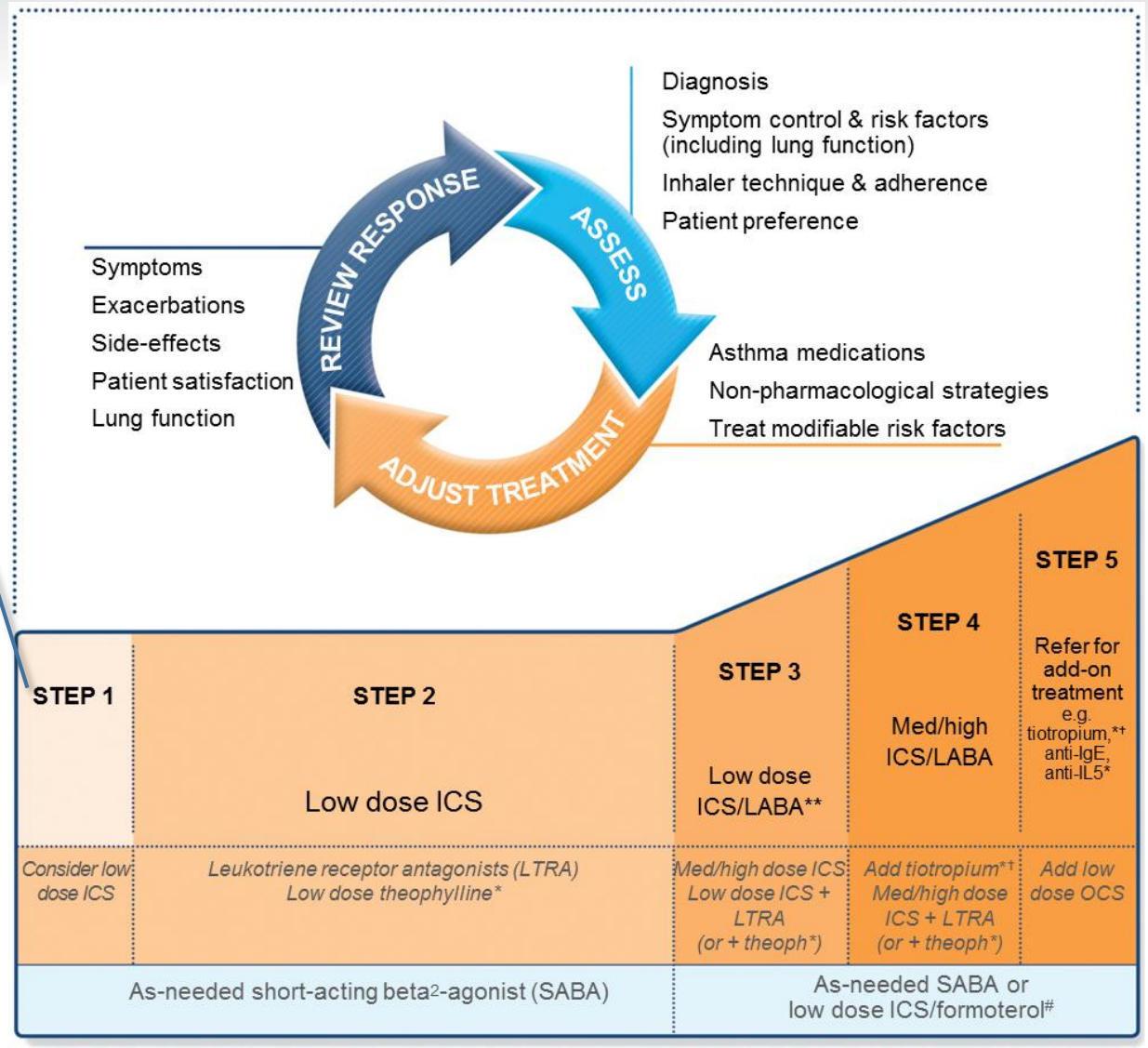
***Table* 3: Components of airway disease and targeted treatment**

Gibson PG, McDonald VM, Marks GB. Asthma in older adults. Lancet. 2010;376(9743):803-13.

GINA 2018 – main treatment figure

Step 1 treatment is for patients with symptoms <twice/month and no risk factors for exacerbations

Previously, no controller was recommended for Step 1, i.e. SABA-only treatment was 'preferred'



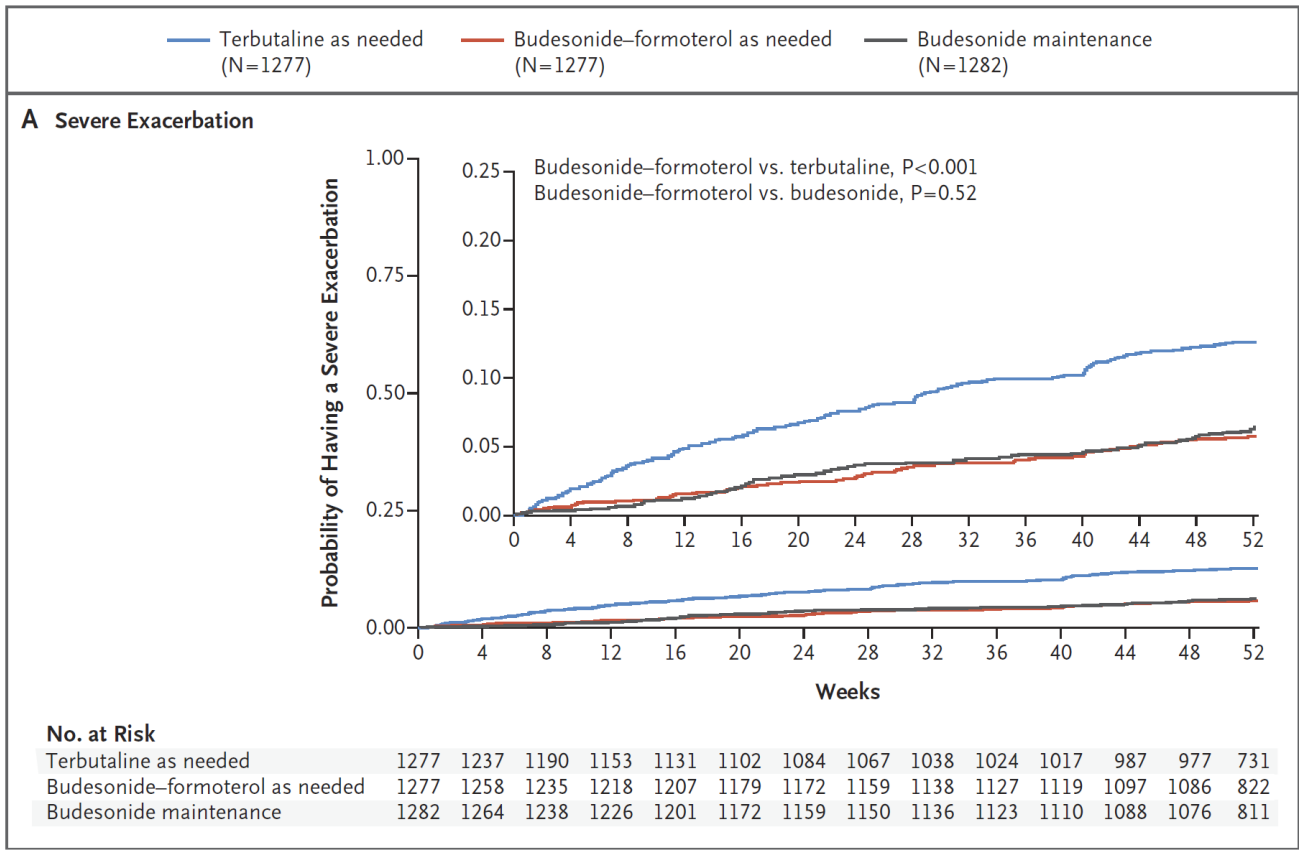
*Not for children <12 years

**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

#For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

SYGMA studies: formoterol-ICS as required for mild asthma



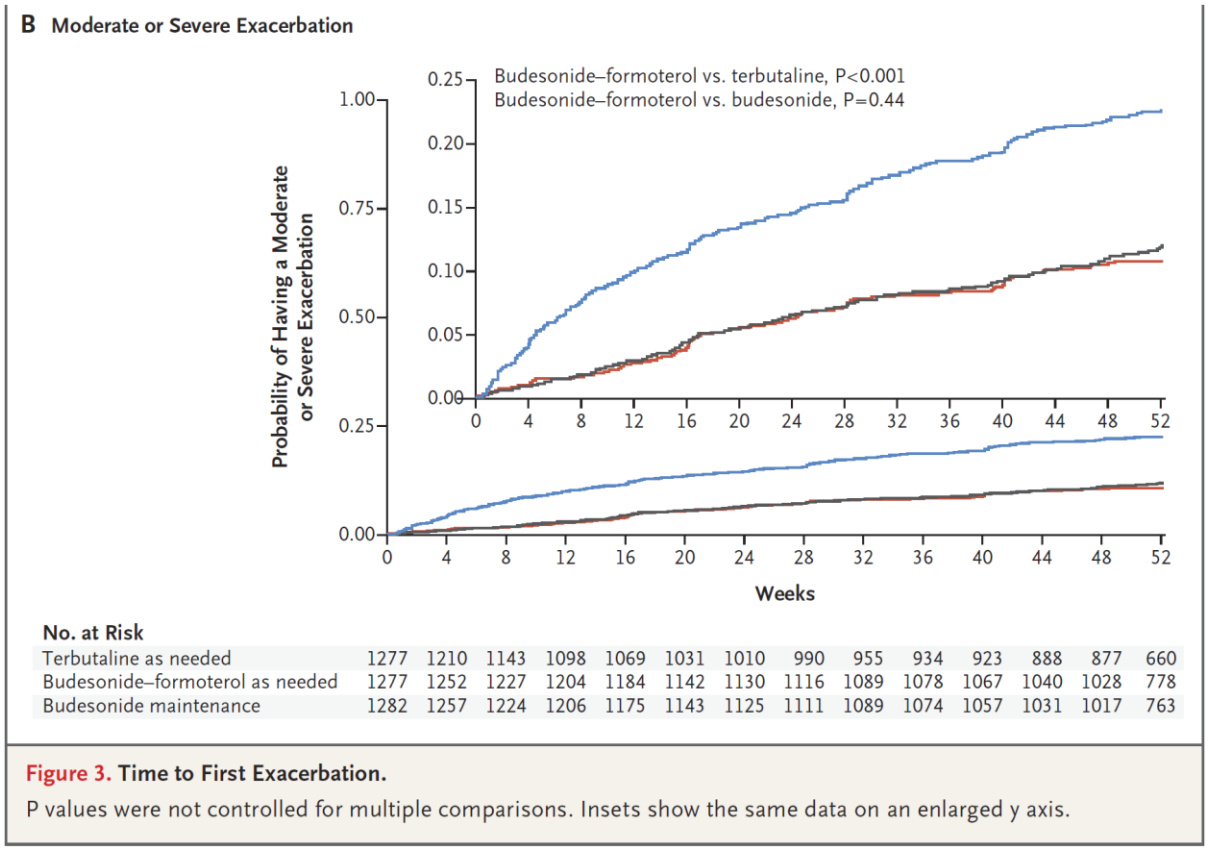


Figure 3. Time to First Exacerbation.

P values were not controlled for multiple comparisons. Insets show the same data on an enlarged y axis.

O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. N Engl J Med. 2018;378(20):1865-76.

Novel Start

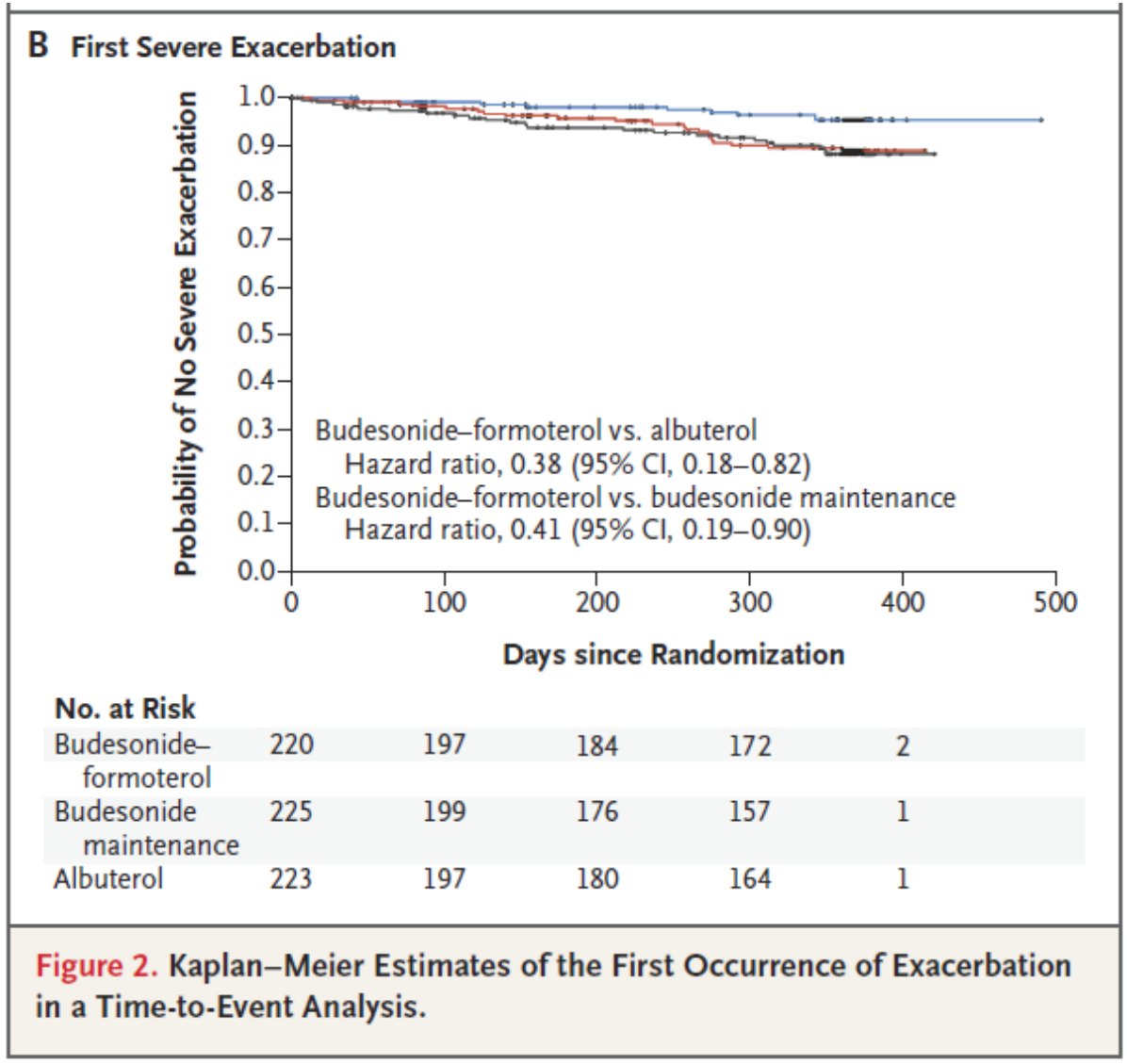


Figure 2. Kaplan–Meier Estimates of the First Occurrence of Exacerbation in a Time-to-Event Analysis.

Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al. Controlled Trial of Budesonide-Formoterol as Needed for Mild Asthma. N Engl J Med. 2019;380(21):2020-30.

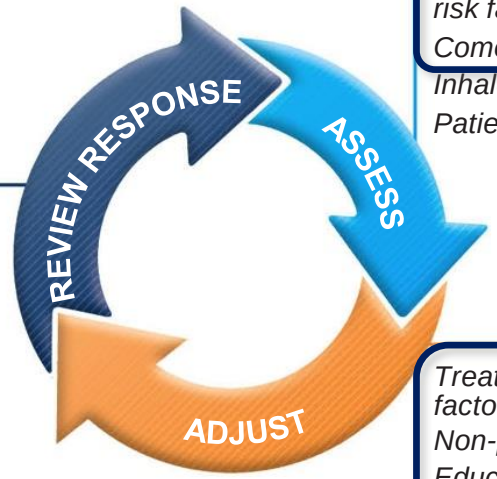
New paradigm for mild asthma

- For preventing exacerbations in patients with mild asthma formoterol-ICS combination, used as required for symptoms, is
  - as effective, or more effective, than regular ICS + SABA PRN, in preventing exacerbations
  - More effective than SABA PRN alone.

Box 3-5A

Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Patient goals

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

Asthma medication options:
Adjust treatment up and down for individual patient needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	As-needed low dose ICS-formoterol *	Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *	Low dose ICS-LABA	Medium dose ICS-LABA	High dose ICS-LABA Refer for phenotypic assessment ± add-on therapy, e.g.tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Other controller options	*Low dose ICS taken whenever SABA is taken †*	*Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †*	*Medium dose ICS, or low dose ICS+LTRA #*	*High dose ICS, add-on tiotropium, or add-on LTRA #*	*Add low dose OCS, but consider side-effects*
PREFERRED RELIEVER	As-needed low dose ICS-formoterol *		As-needed low dose ICS-formoterol for patients prescribed maintenance and reliever therapy ‡		
Other reliever option	*As-needed short-acting β_2 -agonist (SABA)*				

* Off-label; data only with budesonide-formoterol (bud-form)
† Off-label; separate or combination ICS and SABA inhalers

‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy
# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV$_1$ >70% predicted

Severe asthma

- Multi-dimensional assessment and management / treatable traits
- Macrolides
- Biologicals
- Severe asthma toolkit

Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial

Peter G Gibson, Ian A Yang, John W Upham, Paul N Reynolds, Sandra Hodge, Alan L James, Christine Jenkins, Matthew J Peters, Guy B Marks, Melissa Baraket, Heather Powell, Steven L Taylor, Lex E X Leong, Geraint B Rogers, Jodie L Simpson

Lancet. 2017;390:659-68.

AMAZES

P: Patients with symptomatic asthma on inhaled maintenance therapy

- Asthma symptoms and evidence of variable airflow obstruction
- Taking regular ICS + LABA
- ACQ6 ≥ 0.75

I: Low dose macrolide therapy

- Azithromycin 500mg three times per week for one year

C: No additional therapy

- Matching placebo

O: Exacerbations and QoL

- Exacerbations = increase in symptoms
  - Severe = requires hospitalisation or oral steroids
  - Moderate = requires any increase in treatment
- QoL = AQLQ score

AMAZES trial profile

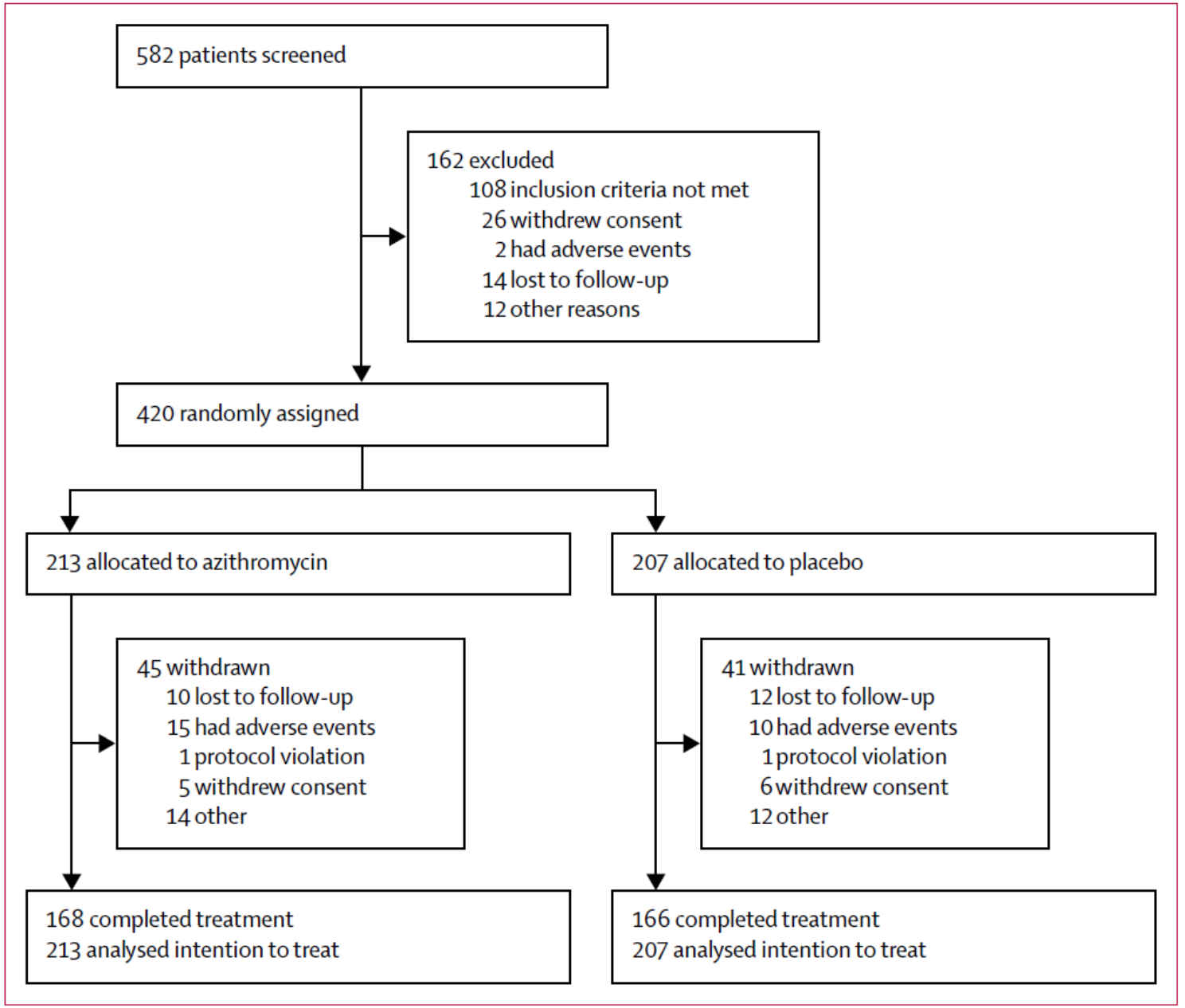


Figure 1: **Trial profile**

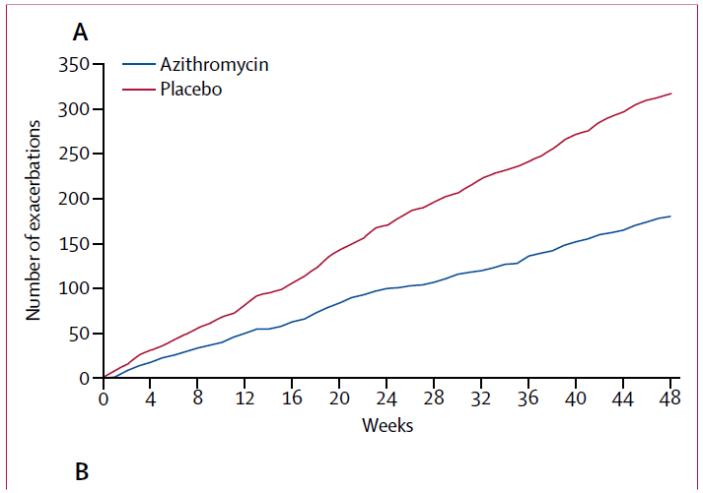
Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised double-blind placebo-controlled trial. Lancet. 2017;390:659-68.

AMAZES
Primary endpoints

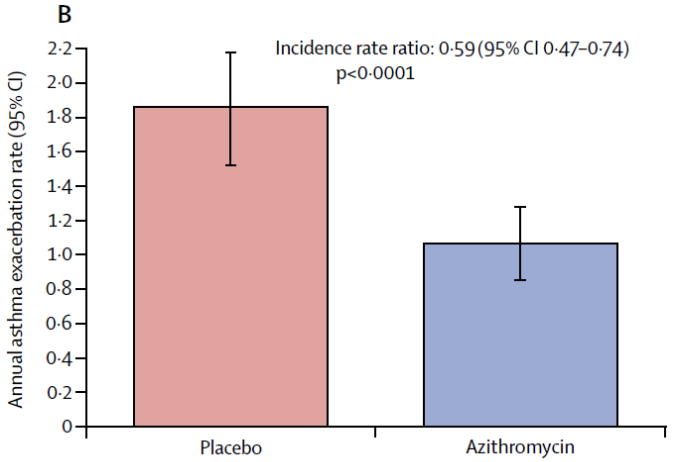
	Placebo	Azithromycin
Primary endpoints		
Asthma exacerbation rate		
Number of patients analysed	207	213
Rate estimate (95% CI)	1·86 (1·54 to 2·18)	1·07 (0·85 to 1·29)
Absolute difference estimate (95% CI)	..	−0·46 (−0·79 to −0·14)
Incidence rate ratio *vs* placebo (95% CI)*	..	0·59 (0·47 to 0·74), p<0·0001
Quality of life		
Number of patients analysed	204	209
AQLQ mean score end of treatment (mean, 95% CI)	5·55 (5·40 to 5·70)	5·73 (5·58 to 5·88)
AQLQ mean score end of treatment difference *vs* placebo (adjusted mean, 95% CI)†	..	0·36 (0·21 to 0·52), p=0·001‡

Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised double-blind placebo-controlled trial. Lancet. 2017;390:659-68.

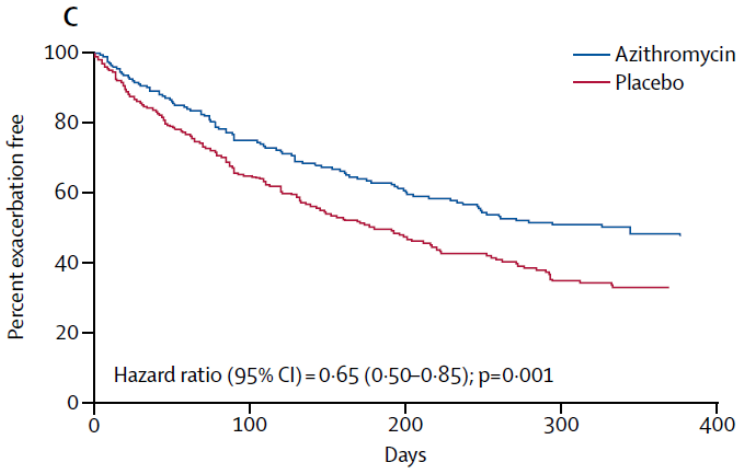
AMAZES
Moderate and severe exacerbations by treatment group allocation



Cumulative incidence



Incidence per person-year of follow-up



Exacerbation-free weeks

Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised double-blind placebo-controlled trial. Lancet. 2017;390:659-68.

AMAZES
Sub-group analysis for exacerbations

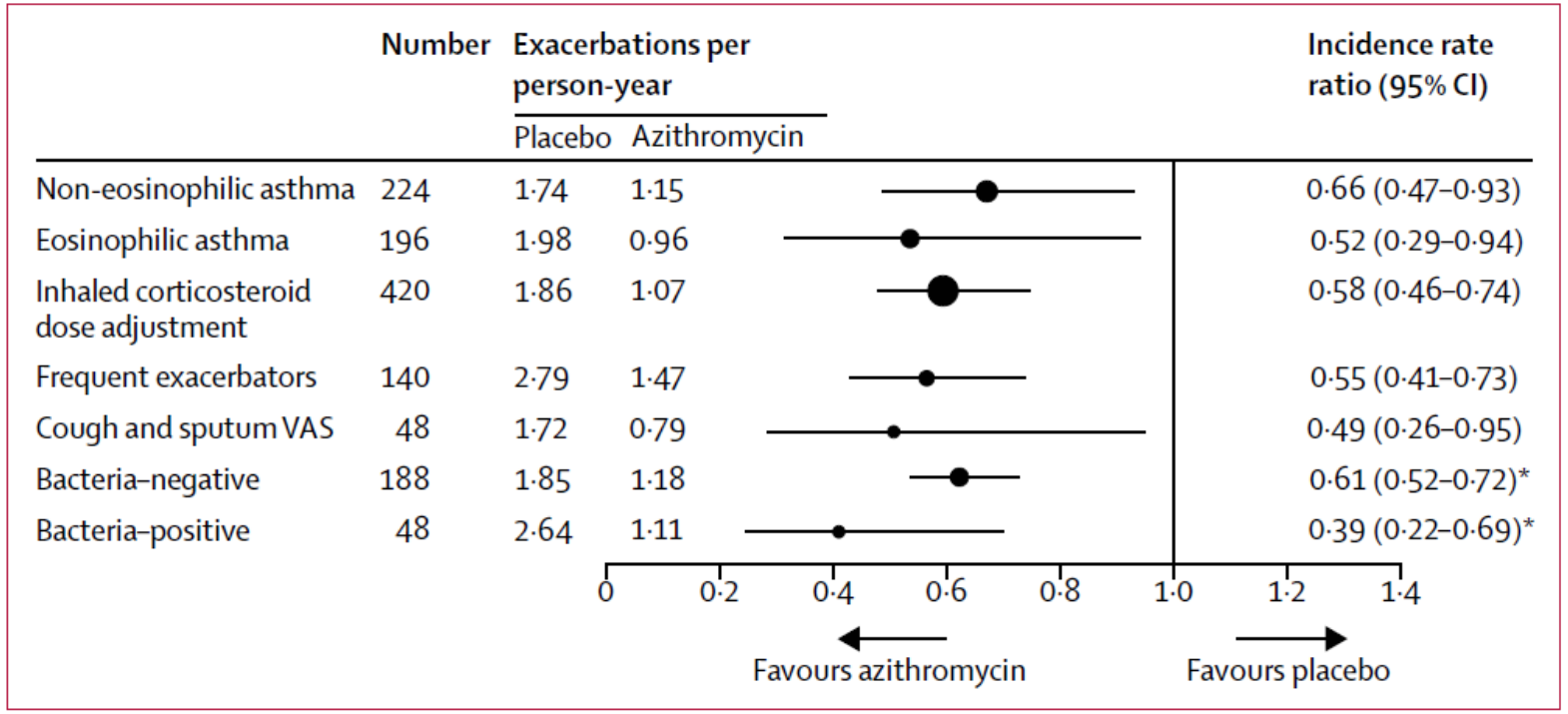


Figure 3: **Effect of add-on azithromycin treatment on asthma exacerbations according to prespecified subgroup analyses**

Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised double-blind placebo-controlled trial. Lancet. 2017;390:659-68.

AMAZES
Adverse events

	Placebo (n=207)	Azithromycin (n=213)
Serious adverse events		
Total number of events; number of people (%)	31; 26 (13%)	26; 16 (8%)
Cardiac	8; 6 (3%)	7; 5 (2%)
Gastrointestinal tract	5; 4 (2%)	5; 5 (2%)
Other health issue	10; 8 (4%)	9; 3 (1%)
Possible infectious serious adverse event	8; 8 (4%)	5; 3 (1%)
Number of events per person		
No events	180 (87%)	195 (92%)
One event	25 (12%)	14 (7%)
Two events	0	1 (<1%)
Three events	2 (1%)	2 (1%)
Four events	0	1 (<1%)
Antibiotic-treated respiratory tract infections (number of events; number of people [%])	115; 65 (31%)	57; 42 (20%)
Study withdrawal (treatment discontinuation due to adverse event)	10 (5%)	15 (7%)

Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised double-blind placebo-controlled trial. Lancet. 2017;390:659-68.

AMAZES Conclusions

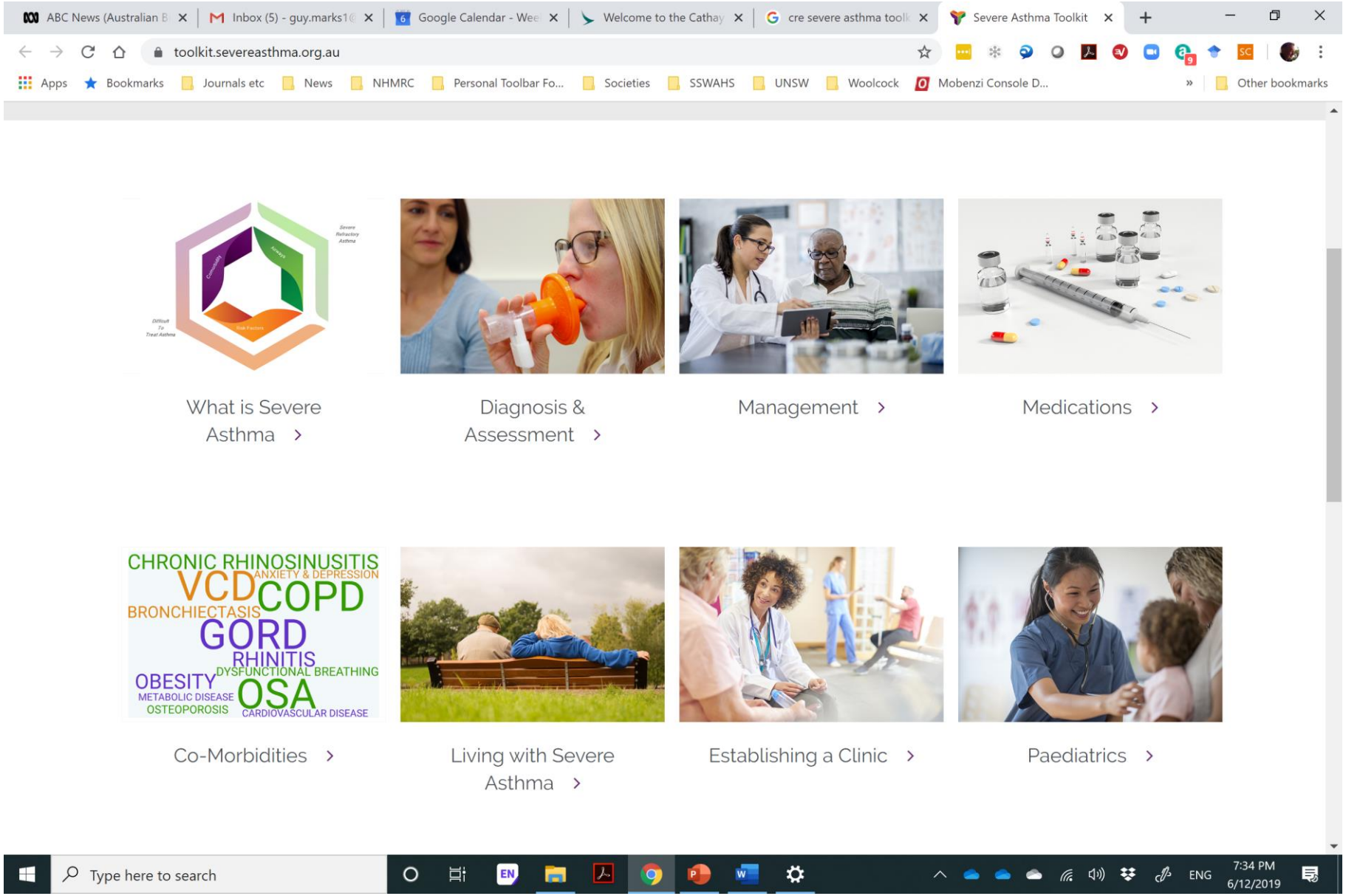
- In patients with asthma who remain symptomatic despite regular treatment with inhaled corticosteroids and long-acting bronchodilators
- Long-term treatment with azithromycin (500mg 3 times per week) is
  - Effective in reducing the incidence of moderate and severe exacerbations
  - Effective in improving QoL
  - Not associated with an excess of serious adverse events
- No predictors of benefit were identified

Biologicals

- For patients with uncontrolled disease despite regular inhaled therapy
- Atopic patients
  - Omalizumab (anti-IgE)
- Patients with airway eosinophilia
  - Mepolizumab (anti-IL5)
  - Benralizumab (anti-IL5 receptor)
- Most effective in
  - Reducing risk and incidence of exacerbations
  - Oral steroid sparing
- Predictors of treatment success not well established
  - Biomarkers (IgE, blood eosinophils, sputum eosinophils, FeNO, serum periostin) have a role but not as helpful as first hoped

Severe asthma toolkit

https://toolkit.severeasthma.org.au/



Finally:

- Asthma remains a major problem globally
  - There is substantial avoidable suffering and death
- Most of the progress we have made is NOT new drugs or new tests but new ways of thinking and doing:
  - ICS-formoterol as a first-line therapy for mild asthma
  - Treatable traits / multi-dimensional assessment
  - Macrolides for severe asthma
  - Severe asthma toolkit
- Still much to do
  - Access to medicines (distribution, cost, feasible devices)
  - Better predictors – biomarkers