Developing And Implementing an Asthma Program to Optimize Outcomes

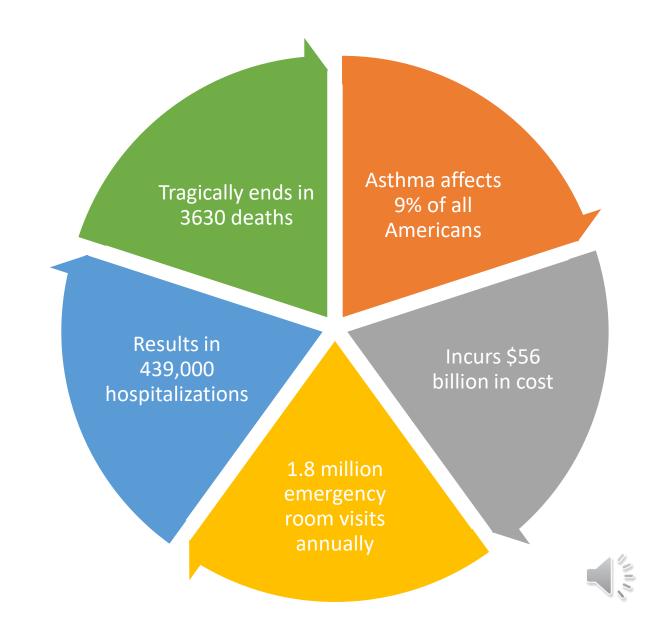
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Learning Objectives

- Describe the magnitude of asthma in the United States
- Define the goals of asthma management
- Review different strategies to optimize asthma outcomes
- Describe methodology to assess improvement in asthma outcomes

The Magnitude of Asthma



The Hidden Cost of Asthma

Report commissioned by Asthma Australia in partnership with the National Asthma Council Australia as part of consultations to develop the National Asthma Strategy 2016–2020



burden of disease \$24.7bn

72T./ DII

this includes the effect of disability and premature death



healthcare \$1.2bn

costs to the health system, including medication, hospital and out-of-hospital costs



productivity

\$1.1bn

in productivity losses including lost wages for people with asthma time off

2.1

ore days off ork for peopl th asthma



carers

\$72.9m

in lost wages for carers support

\$289.4m

for carers of people with asthma



45%

have poorly controlled asthma



Sources: The Hidden Cost of Ashbrox - Details Access Economics, November 2015

*Reddel H. Slawyer'S et al. (2015) 'Asthma control in Australia: a cross-sectional web-based survey in a nationally representative population." Medical Journal Australia: 202 (9), p483-497

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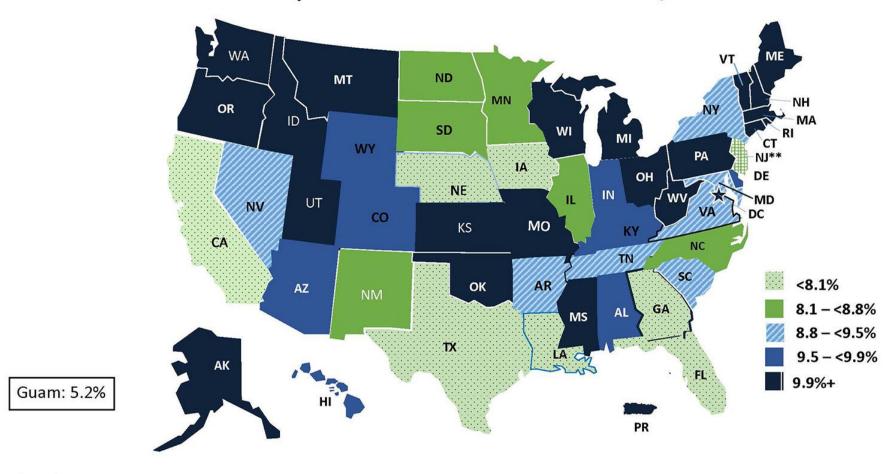








Adult* Self-Reported Current Asthma Prevalence, BRFSS 2019



^{*}Aged 18+ years



^{**}New Jersey did not meet the minimum requirements for inclusion in the annual aggregate data set for 2019 Legend: percentiles of the overall current asthma prevalence estimates from year 2011 data: 0%, 20%, 40%, 60%, 80%, 100%

Magnitude of Asthma

- As is true for many chronic diseases, a small fraction of asthma patients with severe disease, high vulnerabilities, or great barriers to care consume most health care costs and resources.
- The top 20% of patients consume 80% of costs, and the top 1% consume 25%.
- Often these patients are also refractory to conventional asthma interventions.
- Almost all private health plans provide, and most major employers purchase, care
 management services that implement tailored care plans with early interventions for
 high-risk patients to avoid high costs and health status degradation.



Asthma severity

- Intermittent
- Mild persistent
- Moderate persistent
- Severe persistent

Asthma control

- Well controlled
- Not well controlled
- Poorly controlled

Comorbidities

- Allergic rhinitis
- Eczema
- Food allergies
- Obesity
- SDB
- BPD

Atopic sensitization

- Serum IgE
- Skin prick testing/RAST
- Eosinophils
- FeNO

Pulmonary function test

- Spirometry
- Lung volumes
- Exercise testing

Severe persistent asthma, poorly controlled, non-allergic, with obesity, and low lung volumes

Mild persistent asthma, not well controlled non-allergic, with BPD

Patient-specific asthma definition

Mild persistent asthma, poorly controlled with

allergic sensitization to dog, and normal lung function

Intermittent asthma, well controlled, with eqsinophilia and EIB Moderate persistent asthma, not well controlled with sensitization to many indoor allergens, and reduced FEV

Severe persistent asthma, well controlled, with food allergies, and normal lung function



THE ASTHMA ICEBERG

Breathlessness

Recurrent Cough

Recurrent Wheeze

Nocturnal Cough

Persistent Cough

Exercise/Activity Induced Cough

Airways Inflammation

Airways very sensitive to asthma triggers e.g. pollen, dust mites



Adults & adolescents 12+ years

STEP 1

: As-needed

low dose

ICS-formoterol*

SABA is takent

Low dose ICS

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



Personalized asthma management:

Assess, Adjust, Review response

Symptoms Exacerbations Side-effects Lung function Patient satisfaction

REVIEW STANDASTAND ADJUS⁷

S

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

STEP 3

Low dose

ICS-LABA

STEP 5

High dose ICS-LABA

Refer for phenotypic assessment ± add-on therapy. e.g.tiotropium, anti-lgE, anti-IL5/5R. anti-IL4R

Add low dose OCS, but consider side-effects

Asthma medication options:

Adjust treatment up and down for individual patient needs

PREFERRED CONTROLLER

to prevent exacerbations and control symptoms

> Other controller options ! taken whenever

PREFERRED

RELIEVER

Other reliever option

STEP 2

Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol*

Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA takent

As-needed low dose ICS-formoterol*

As-needed low dose ICS-formoterol‡

As-needed short-acting β_2 -agonist (SABA)

Medium dose

ICS, or low dose ICS+LTRA#

High dose ICS, add-on tiotropium, or add-on LTRA#

STEP 4

ICS-LABA

Medium dose



Goals of Asthma Management

- The main goals of asthma management are to optimize control of asthma symptoms and reduce the risk of asthma exacerbations while minimizing medication adverse effects.
- It is expected that a person with well-controlled asthma should be able to participate in work, school, play, and sports without limitation due to breathing.
- Have uninterrupted sleep
- The four essential components of asthma management are patient education, minimizing exposure to asthma triggers, monitoring for changes in symptoms or lung function, and pharmacologic therapy.



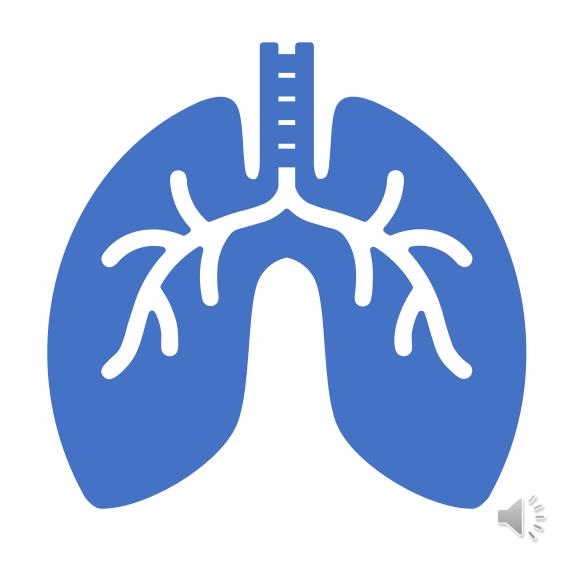
Goals of Asthma Management

- The four essential components of asthma management are:
 - patient education
 - minimizing exposure to asthma triggers
 - monitoring for changes in symptoms or lung function
 - and pharmacologic therapy for daily symptom control



Goals of Asthma Management

- No asthma symptoms during the day or night.
- No limits in activities or play.
- No missed school or work.
- Fewer attacks or flares.
- No emergency room or hospital visits for asthma.
- Decreased need for quick relief medicine.



Symptoms

Shortness of breath, chest tightness, wheeze, cough, difficulty breathing, nocturnal awakenings, daytime fatigue, acute attacks

Impact

Motivation, physical activity, social life, employment, relationships/intimacy, travel, mental health



Burden

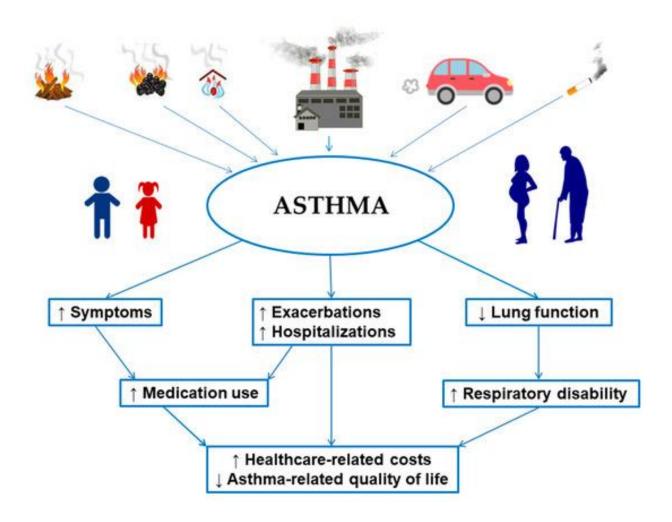
Emotional, financial, functional, medication



Treatment

Pharmacological interventions, nonpharmacological interventions, multidimensional assessment



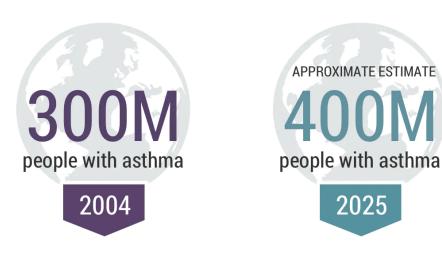




Global Asthma at a Glance



The Prevalence of Asthma Is Increasing



Source: Masoli M, Fabian D, Holt S, Beasley R; Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee Report. Allergy. 2004;59:469-478.

Rising Morbidity of Asthma

WORLD HEALTH ORGANIZATION ESTIMATES

430K deaths from asthma 2015 610K
deaths from asthma

Source: Global health estimates, World Health Organization, July 2013.

Patient Noncompliance or Adherence Failure

UP TO

of patients cannot use their inhaler correctly

AROUND

50%

of adults and children do not take their controller medications as prescribed



Source: Global Initiative for Asthma

How Do We Define Asthma Goals Not Being Obtained?

- Increased exacerbations
- Increased missed workdays or school absenteeism
- Increased ED visits
- Increased hospitalizations
- Lack of medication adherence



Six Step Method to Successful Asthma Management

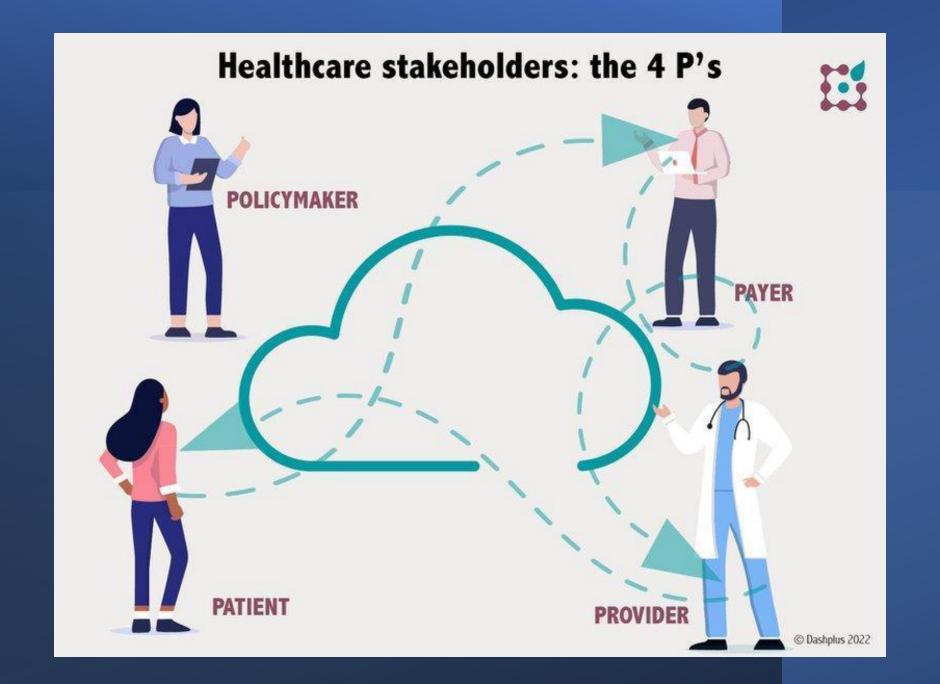
- Step 1: Make Your Medical Visits More Productive.
- Step 2: Create an Asthma Management Plan.
- Step 3: Assess and Monitor Your Control.
- Step 4: Understand Your Medication.
- Step 5: Reduce Asthma Triggers.
- Step 6: Learn Asthma Self-Management Skills.



Who Are The P's Healthcare Stakeholders?

- The 4 P's. the four types of stakeholders in the healthcare (eco)system:
 - patients,
 - providers,
 - payors
 - policymakers.
- They all have a different role in the healthcare value chain, which means that different interests and/or visions will also play a role.







Screening and identification of patients at risk of developing asthma/exacerbations

Role of

pharmacists

in asthma

managemen

Recommending an individualized treatment based upon disease severity, phenotype and control

Educating patients about disease, management strategies, and inhaler technique

Creating awareness among patients regarding triggers for asthma exacerbations and providing strategies to identify and avoid them

Encouraging medication adherence through patient counseling

Referring patients to specialists for further medical care



For this patient, which is the right class of medication?

Consider exacerbation risk reduction, symptom control, adverse effects

If different reliever and controller inhalers are needed, consider questions below for both

÷

For these medications, which inhalers are currently available to the patient?

Consider local availability, access, number of inhalers and cost to patient (higher cost → non-adherence → more exacerbations)

Which of these inhalers can the patient use correctly after training?

Test technique often: faulty technique → more symptoms, more urgent health care, and greater environmental burden OPTIMAL INHALER SELECTION

Safest and best for the patient and for the planet Which of these inhalers has the lowest environmental impact?

Consider manufacturing, propellant (for pMDIs), and potential for recycling

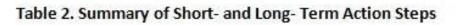
Follow-up: Is the patient satisfied with the medication(s) and inhaler(s)?

> Consider all of above steps



Potential Countermeasures

- An effective approach is needed to find high-risk patients and implement appropriate interventions to improve outcomes and to reduce costs and resource use.
- Care management is a cooperative process to assess, plan, coordinate, implement, evaluate, and monitor services and options to fulfill a patient's health and service needs.
- It includes a care manager who regularly calls the patient, arranges for health and related services, and helps make medical appointments.
- Asthma exacerbations account for 63% of annual total asthma cost Using care management properly can reduce asthma exacerbations, cut hospital admissions and emergency room visits by up to 40%.
- Trim cost by up to 15% and enhance patient treatment adherence, quality of life, and satisfaction by 30% to 60%.
- Owing to resource constraints, usually only 1% to 3% of asthma patients are enrolled in care management.



RECOMMENDATION CATEGORY	INITIAL STEPS	LONG-TERM STEPS
Define non-traditional asthma services for high risk patients	 Standardize definition of high risk patient Identify gaps in existing evidence Fund comparative effectiveness research to identify highest impact non-traditional asthma components 	 Align benefit design with highest value services for high risk patients
Use payment reform to support integration, system transformation, and service coverage	Define population outcome measures Offer small add-on payments to practices to support the costs of a shared social worker Identify best practices used by successful community asthma programs that have aligned medical, public health, and social services	Implement sustainable APM funding mechanisms Establish management structures, which share resources and accountability across health care and social services silos
Improve information sharing and coordination for asthma	Establish mechanism to collect and update contact information of local stakeholders and service providers Increase provider awareness of available services by working with specialty societies, state medical associations, and hospitals to disseminate information Establish task force with community stakeholders (schools, local health departments, housing) to identify regulations which could be improved	Build information exchange clearinghouse Identify gaps in community asthma programs and offer technical assistance to address them



What Asthma Patient Can Benefit From This?

- Ideally, the asthmatic patient enrolled should be those at the highest risk.
- Predictive modeling is the best method to find high-risk patients.
 - It uses a model for predicting individual patient cost or health outcome to automatically find high-risk patients
- Cost reflects use and efficiency of care and indirectly reflects outcomes such as hospitalization and emergency room visit.
- For patients predicted to have the highest costs or worst outcomes,
 - care managers examine patient records,
 - consider various factors such as social ones,
 - and make the ultimate allocation and intervention decisions.
- **Correct identification** of high-risk patients is key to effective care management, but current identification methods have limitations.





Data and Surveillance

Monitor trends, track progress, provide information for action. Disseminate data to improve health outcomes.



Environmental Approaches

Promote health, support and reinforce healthful behaviors in schools, childcare, worksites, and communities. Create awareness of asthma triggers and environmental factors that affect those living with asthma.



Health Care System Interventions

Improve the effective delivery and use of clinical and other preventive services in order to prevent disease, detect diseases early, and reduce or eliminate risk factors and mitigate or manage asthma complications.



Community Programs Linked to Clinical Services

Connecting clinical services to community programs and resources that help people prevent and manage their asthma.



Charter to Improve Patient Care in Severe Asthma

Developed to raise awareness and understanding of the impact of severe asthma, to empower patients and to create opportunities for improved care



I deserve timely, straightforward referral when my severe asthma cannot be managed in primary care

Referral to a specialist is needed if oral corticosteroids (OCS) use is > 3 months; >2 rounds OCS in past year, any hospitalisation for asthma or impaired lung function



2

I deserve a timely, formal diagnosis of my severe asthma by an expert team

By a specialist multidisciplinary team (MDT), following assessment and management of treatable factors



3

I deserve support to understand my type of severe asthma

Understanding of patient-specific processes causing disease (phenotype) to support a targeted therapy approach



4

I deserve care that reduces the impact of severe asthma on my daily life and improves my overall quality of care

Recognition of persistent symptoms and shared patient-clinician decision-making to minimise the effects of asthma



5

I deserve not to be reliant on oral corticosteroids

Limit the use and adverse effects of long-term OCS treatment





I deserve to access consistent quality care, regardless of where I live or where I choose to access it

Care models to support efficient service delivery and provide access to care regardless of geographic location







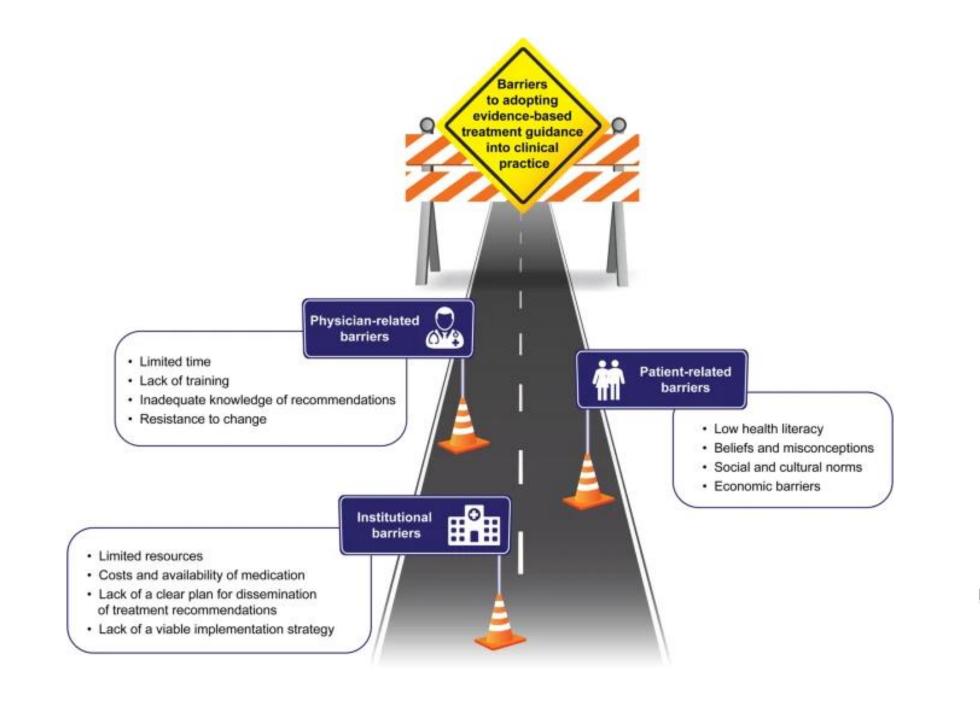
Barriers to Success

- Current predictive models for individual patient costs and health outcomes exhibit poor accuracy causing misclassification and need improvement.
- When projecting individual patient cost, the R2 accuracy measure of models reported in the literature is less than 20% and the average error is typically comparable to the average cost.
- When projecting individual patient health outcome, the area under the receiver operating characteristic curve accuracy measure is usually much smaller than 0.8
- Those large errors make enrollment miss more than half of patients a care management program can help most.
- Studies showed that the top 10% risk group identified by a predictive model missed more than 60% of the top 10% and about 50% of the top 1% of patients who had the largest costs.
- If 10% more of the top 1% patients who had the largest costs and enroll them, could save up to \$210 million in asthma care each year and also improve asthmatic outcomes.

Are The Social Needs of Asthma Patient Being Met?

- Persistent asthma severity status was associated with several unmet social needs
 - including housing quality and stability,
 - lack of money for food,
 - transportation,
 - healthcare costs.

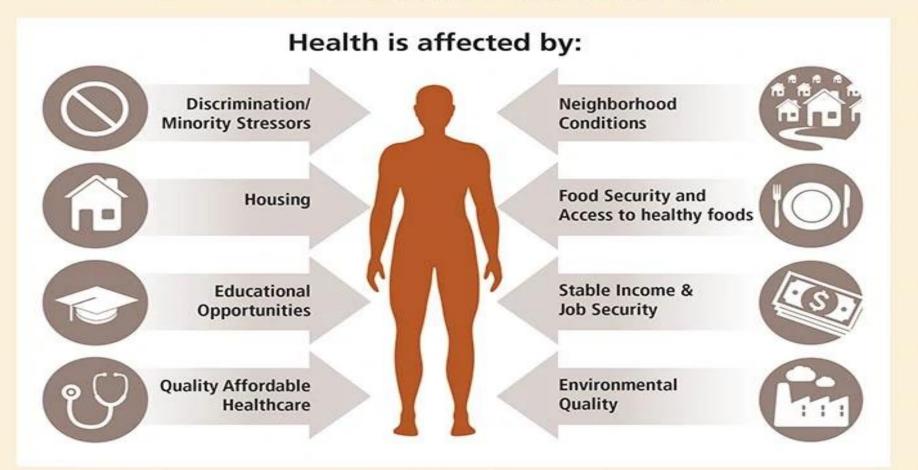






The Path to Achieving Health Equity

What social and economic factors must be addressed on the continued path to achieving Health Equity?





ASTHMA AND ALLERGY DISPARITIES: AT A GLANCE

Compared to white Americans:



Black Americans are nearly **1.5 times** more likely to have asthma¹



Puerto Rican Americans are nearly **2 times** more likely to have asthma¹



Black Americans are **5 times** more likely to visit the emergency department due to asthma²



Americans are **3 times** more likely to die from asthma³



When sex is factored in, BLACK WOMEN

have the highest rates of death due to asthma³

Compared to white children:

Black children are more likely to die from foodinduced anaphylaxis⁴



Black children are
1.5 times
more likely to have skin allergies⁵

Black children are
7% more likely
to have food allergies¹

- ¹ CDC, National Center for Health Statistics, National Health Interview Survey (2018)
- ² CDC, National Center for Health Statistics, National Ambulatory Medical Care Survey (2017)
- ³ CDC, National Center for Health Statistics, National Vital Statistics System: Mortality (2018)
- ⁴ Jerschow, E., Lin, R. Y., Scaperotti, M. M., & McGinn, A. P. (2014). Fatal anaphylaxis in the United States 1999–2010: temporal patterns and demographic associations. *The Journal of Allergy and Clinical Immunology*, 134(6), 1318–1328.e7. https://doi.org/10.1016/j.jaci.2014.08.018
- ⁵ Bilaver, L. A., et al. (2021). Prevalence and Correlates of Food Allergy Among Medicaid-Enrolled United States Children. *Academic Pediatrics*, 21(1), 84–92. https://doi.org/10.1016/j.acap.2020.03.005









ASTHMA: TAKE ACTION, TAKE CONTROL

asthma.chestnet.org

Asthma crosses all racial, ethnic and socioeconomic groups. It is more common among African-American, Hispanic and Native American populations, particularly those living in poor urban areas.

RATE OF ASTHMA-RELATED ER VISITS AND **DEATHS COMPARED WITH CAUCASIANS**

African-American children:

African-American

adults:

2.8X HIGHER

4.5X

Hispanic children: HIGHER

ER VISITS DEATHS

2X HIGHER

7X

HIGHER

3X

HIGHER

Adults with an annual income of

MORE LIKELY

to have asthma



People with asthma who earn

<\$50,000 per year are

twice as likely to have an asthma flare

Adults who didn't finish high school are **MORE**

LIKELY to have asthma



ADULTS WHO CANNOT AFFORD THEIR ASTHMA MEDICATION:

1 in 4 African-Americans 1 in 5 Hispanics

30% 20%



Puerto Ricans is

FACTORS THAT CAN LEAD TO ASTHMA DISPARITIES



 ACCESS TO CARE – Limited or lack of transportation can result in patients missing or rescheduling doctor appointments and forgoing or delaying medication use.



• INCOME - Poverty can affect access to healthcare and health insurance, forcing low-income patients to skimp on medical care, including preventive



• ENVIRONMENTAL ALLERGENS AND IRRITANTS - People with asthma who live in urban areas with substandard housing are exposed to more asthma triggers, including mold, dust mites, cockroaches and mice, cigarette smoke and vehicular exhaust from nearby highways.



• EDUCATION INEQUALITY - A lack of knowledge and understanding of the disease can lead to problems such as using asthma inhalers incorrectly or not following through on treatment.



LANGUAGE AND CULTURAL DIFFERENCES - People with asthma who speak Spanish as a primary language may struggle to get appropriate health services.

TALK WITH YOUR LEGISLATORS ABOUT POLICIES THAT IMPACT COMMUNITIES EXPERIENCING A GREATER BURDEN OF ASTHMA.

Sources: Centers for Disease Control and Prevention, Office of Minority Health and Health Equity; National Institutes of Health; American Academy of Allergy, Asthma & Immunology



Asthma Resources

- Allergy & Asthma Network Mothers of Asthmatics.
- American Academy of Allergy Asthma & Immunology.
- The Asthma and Allergy Foundation of America.
- The America Lung Association



Education on asthma self-management X-tinguishing smoking and exposure to secondhand smoke Home

visits for trigger reduction and asthma self-management education

Achievement of guidelines-based medical management

Linkages and coordination of care across settings

Environmental

policies or best practices to reduce asthma triggers from indoor, outdoor and occupational sources

Structural racism | Poverty | Public policy Access to care | Insurance coverage Provider implicit/explicit bias Provider-patient communication/trust Provider-patient physical safety | Noise pollution Physical safety | Noise pollution Physical safety | Poverty Physical safety | Poverty

OSA-related comorbidies
(asthma, obesity)
Sleep behaviors
Sleep environment
Parenting practices
Household chaos
Internalized racism
Health literacy
Income

Society

Public advocacy for policy change
Later school start times to increase sleep duration
Elimination of daylight savings time
Tax incentives for wellness programs
Sleep education initiatives
Employment policy to promote healthy work hours

Healthcare System

Sleep education

Resources to improve access (transportation, social services)
Provider training in bias and cross-cultural communitication

Neighborhood

Increase community resources (community centers, greenspace)
Public safety

Targeted provision of services to high-risk groups

Child/Family

Optimization of individual health Group-based interventions for weight loss Family education on sleep hygiene Web-based social support



How Do You Know Your Asthma Community Plan is Working?

- The Wisconsin Department of Health Services' Asthma Program provides leadership and coordination for asthma care and service-delivery statewide.
- While serving nearly 6 million state residents, activities focus on disproportionately affected populations including children, low-income, and racial and ethnic minorities.
- The Wisconsin Asthma Program is distinguished by its strong partnerships with community organizations and innovative projects including the Asthma-Safe Homes Program, the result of a successful collaboration with Medicaid to provide sustainable asthma funding.
- This program builds upon a pilot home-visiting program and demonstrated a successful return-on investment of \$2.34 for every \$1 spent, as well as a 45% reduction in asthma-related emergency department visits and an 88% reduction in asthma hospitalizations.
- The Wisconsin Asthma Program has led the nation in infrastructure development with its successful statewide asthma coalition. In partnership with the Children's Health Alliance of Wisconsin, the Wisconsin Asthma Coalition develops the state's asthma plan and brings together strategic partners including environmental experts, healthcare providers, schools, state and local government, and members of tribal communities.
- Through the development, implementation, and evaluation of the asthma plan activities, the Wisconsin Asthma Program successfully delivers high quality asthma care by building strong community ties, integrating health care services, and tailoring environmental interventions.

The Asthma-Safe Homes Program

- Identify and fix asthma triggers in your home.
- Learn how to better control your asthma or a family member's asthma.
- Live your best life.
- \$ave money by:
 - Using less asthma medication.
 - Making fewer trips to the emergency room or urgent care clinic.
 - Avoiding overnight stays in the hospital.
 - Missing fewer days of school and work.
 - Covering costs for home assessment and repair services for eligible clients.
 - Accessing free products to reduce home asthma triggers.
 - Accessing free professional services to create a healthier home.



Asthma Safe Home Project

- Component One: in-home asthma education and asthma products. An asthma educator provides asthma self-management education to clients during two to six home visits.
 - Topics include:
- Asthma self-management education on asthma symptoms, triggers, medication use, and asthma action plans.
- Home walkthrough to identify asthma triggers and ways to address them.
- Referral for limited home repairs if major asthma triggers are identified.
- Up to \$1,000 worth of free asthma-friendly products that can help reduce asthma triggers in the home. Products may include dust mite covers for pillows and mattresses, asthma-friendly cleaning kits, vacuums with HEPA filters, home air cleaners, air conditioners, and more.

Asthma Safe Home Plan

- Component Two: environmental home repair services. A trained asthma home assessor will conduct an in-depth review of your home and recommend repairs worth up to \$5,000.
 - Steps in the home repair process include:
- Getting a referral from the asthma educator to access eligible home repair services.
- Scheduling a time for a trained home assessor to investigate sources of asthma triggers and recommend ways to reduce them, such as mold cleanup, carpet removal, pest control, leaking plumbing or roof repairs, and drafty window and door sealing.
- Getting approval from property owners for recommended repairs and cleanup before home repairs begin. The Asthma-Safe Homes Program and partners can help get property owner approvals.
- Scheduling free home repair work with certified contractors worth up to \$5,000 per home.



Metrics to Asthma Success

- Asthma Attacks in the Past 12 Months by Year
- Asthma Attacks in the Past 12 Months by Age
- Asthma Attacks in the Past 12 Months by Gender
- Asthma Attacks in the Past 12 Months by Race and Ethnicity
- Asthma Attacks in the Past 12 Months by Poverty Level
- Asthma Attacks in the Past 12 Months by Area

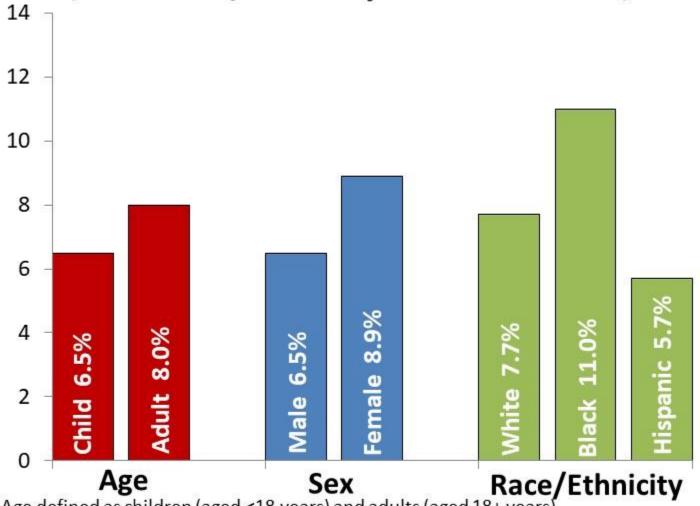


Benchmarks of Good Asthma Control

- No coughing or wheezing
- No shortness of breath or rapid breathing
- No waking up at night
- Normal physical activities
- No school absences due to asthma
- No missed time from work for parent or caregiver



Percentage of People With Current Asthma by Age¹, Sex^{2,3}, and Race/Ethnicity³: United States, 2021



¹Age defined as children (aged <18 years) and adults (aged 18+ years)

Source: National Health Interview Survey, National Center for Health Statistics, Centers for Disease Control and Prevention



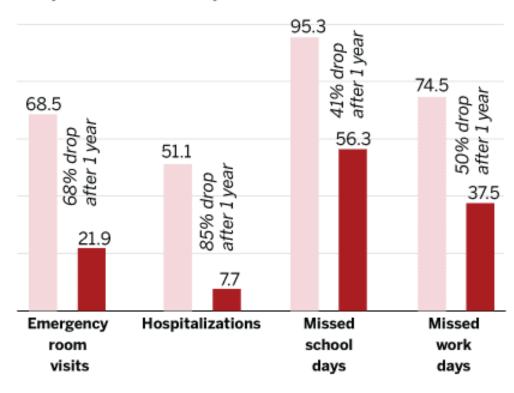
²Sex is defined as persons who answered "male" or "female" to the question "Are you male or female?"

³Sex and race/ethnicity include all ages



Workers taught patients and their families how to properly use asthma medications and checked their homes for environmental triggers.

- Percentage of patients with one or more incidents in the year before the study
- Percentage of patients with one or more incidents 12 months after the visits





SOURCE: Children's Hospital Boston

GLOBE STAFF

Conclusion

- Asthma is a very common disease in the United States
- Asthma exacerbations cause a matrix of problems
- There are many barriers to achieving successful asthma management
- Developing an asthma action plan can help achieve successful asthma symptom control
- Assessing asthma outcome metrics can help direct and maintain beneficial programs
- Asthma prevalence may increase in the future



Questions





References

- Global Asthma Network (GAN). The Global Asthma Report. http://www.globalasthmareport.org (2018).
- Piloni D, Tirelli C, Domenica RD, Conio V, Grosso A, Ronzoni V, Antonacci F, Totaro P, Corsico AG. Asthma-like symptoms: is it always a pulmonary issue? Multidiscip Respir Med. 2018;13:21. [PMC free article] [PubMed]
- Aggarwal B, Mulgirigama A, Berend N. Exercise-induced bronchoconstriction: prevalence, pathophysiology, patient impact, diagnosis and management. NPJ Prim Care Respir Med. 2018 Aug 14;28(1):31. [PMC free article] [PubMed]
- Yii AC, Soh AZ, Chee CBE, Wang YT, Yuan JM, Koh WP. Asthma, Sinonasal Disease, and the Risk of Active Tuberculosis. J Allergy Clin Immunol Pract. 2019 Feb;7(2):641-648.e1. [PMC free article] [PubMed]
- D'Amato M, Molino A, Calabrese G, Cecchi L, Annesi-Maesano I, D'Amato G. The impact
 of cold on the respiratory tract and its consequences to respiratory health. Clin Transl
 Allergy. 2018;8:20. [PMC free article] [PubMed]