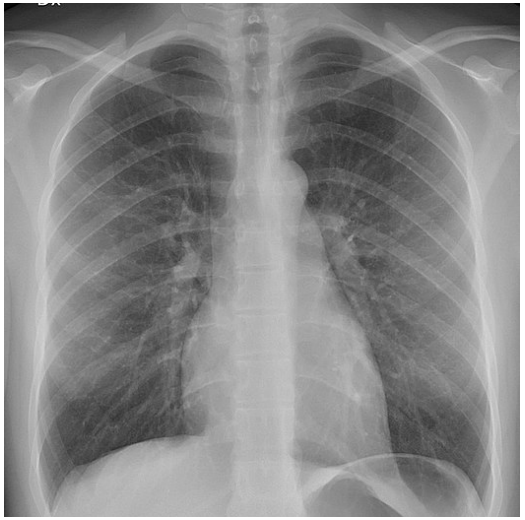
Asthma and other chronic lung diseases.



Christopher Whitty

Gresham College 2018

Chronic diseases: genes, environment, chance.

- Genes change slowly, if at all (mainly through migration). Environment can change fast.
- Environment includes infections disease agents, living space, occupation.
- Three conditions with different relative importance of genetic and environmental factors: asthma, COPD and cystic fibrosis.

City of London C1630. Now- Colin Kim Hansen

Asthma. The commonest chronic lung disease.

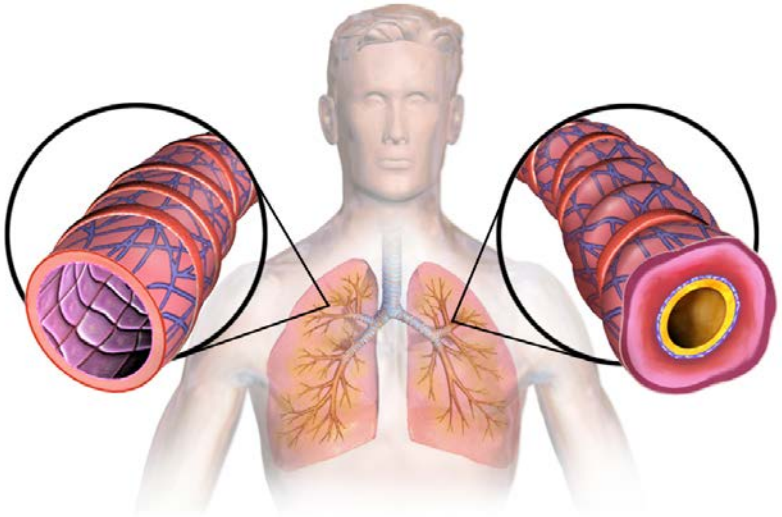
Data Asthma UK / WHO

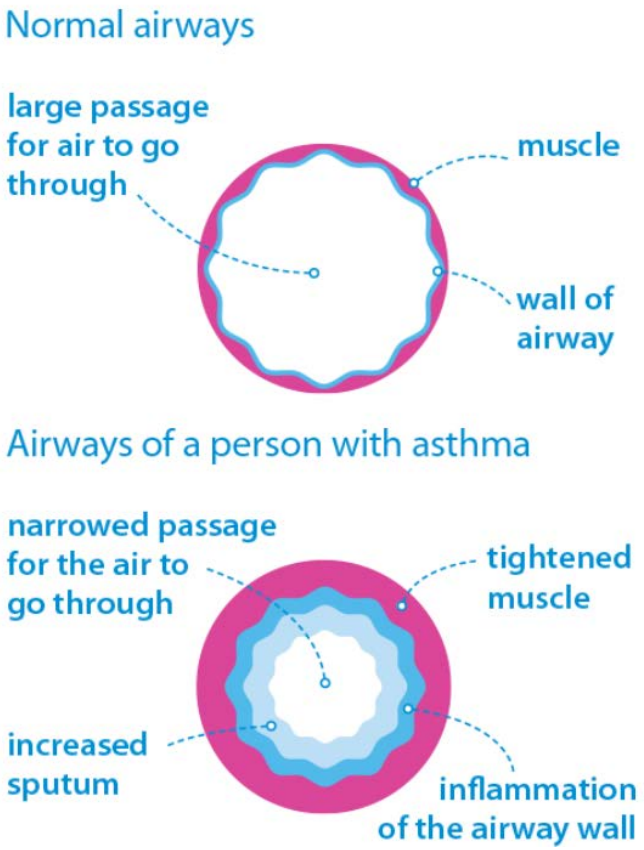
- 5.4 million people in the UK currently receiving treatment.
- 1.1 million children (1:11) and 4.3 million adults (1:12).
- In some children asthma gets better with age, but in many it does not.
- NHS spends around £1 billion a year on asthma.
- 235–334 cases, around 250,000 million cases worldwide a year.

Asthma has proved no bar to many who require remarkable respiratory control- sport.

Or public speaking or music.

What asthma does- narrow the airways.

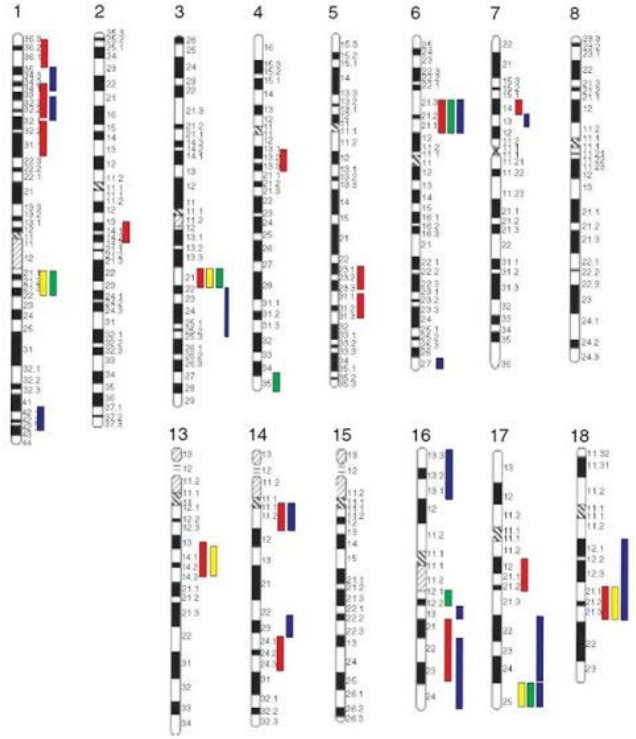




BruceBlaus

Asthma, inheritance and genes.

- Clustering in families.
- More likely if both parents have asthma, and from mother.
- If someone has asthma, an identical twin has around a 20-30% chance of asthma.
- Over 100 genes have been associated with asthma.
- Gene-environment combination.
- Gene-drug combinations.



Asthma

Atopic dermatitis

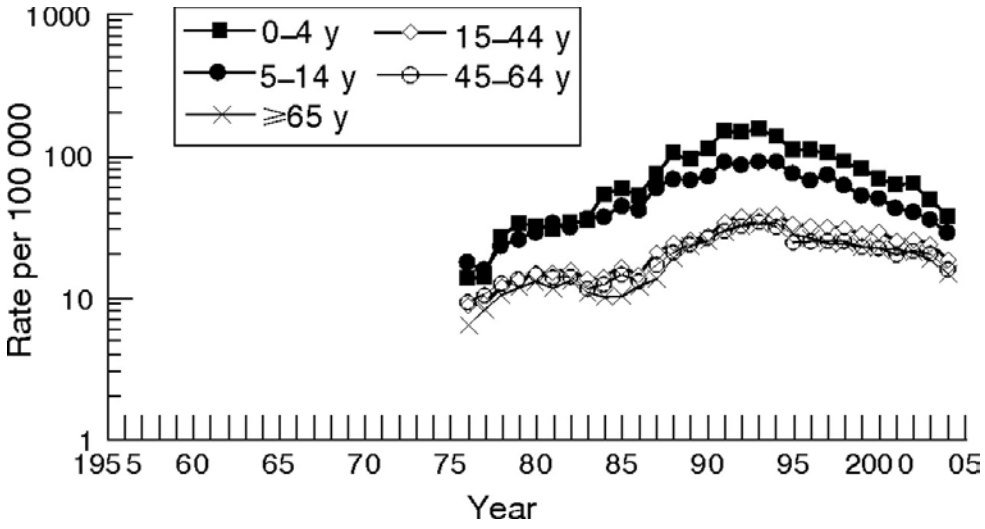
Triggers for asthma attacks. Avoiding them all is tricky.

Include:

- Infections
- Allergens
- Drugs (eg aspirin)
- Cold
- Exercise
- Chemical fumes
- Stress
- Pollution

7Mike5000

Is new asthma going up or down?

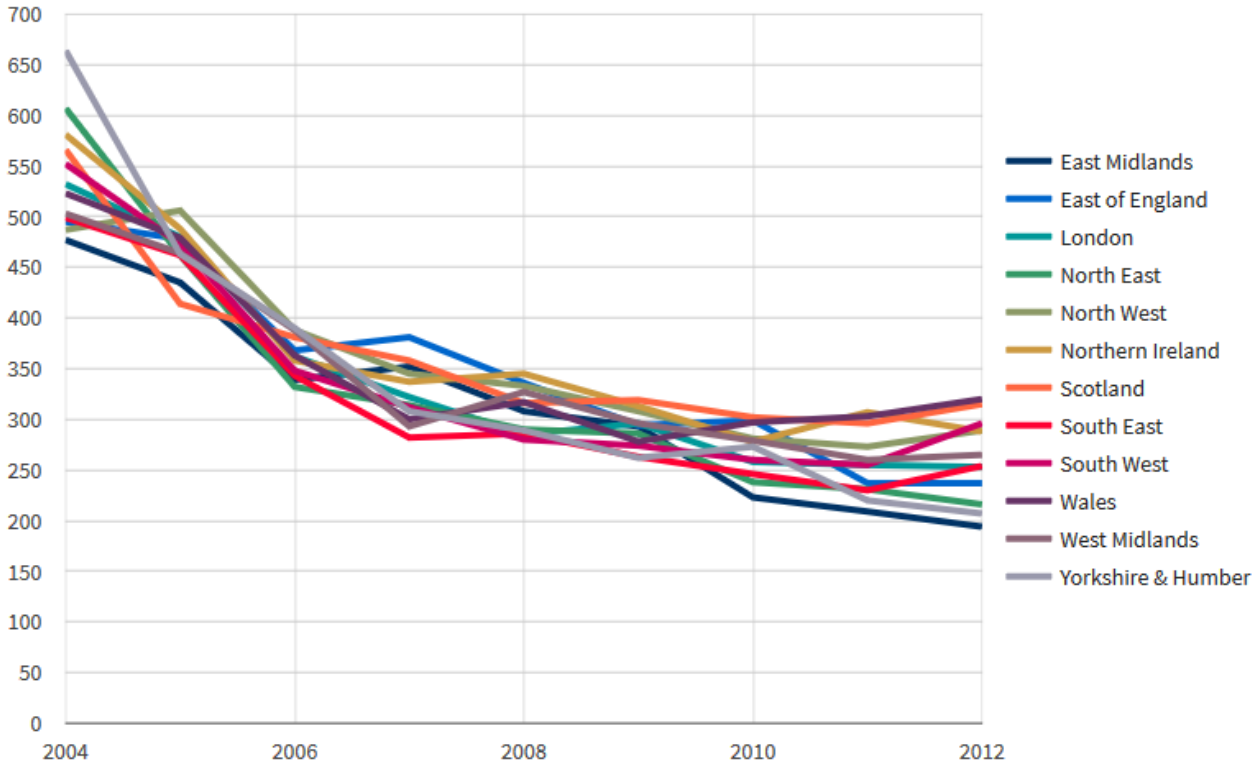


Anderson et al, Thorax, 2006

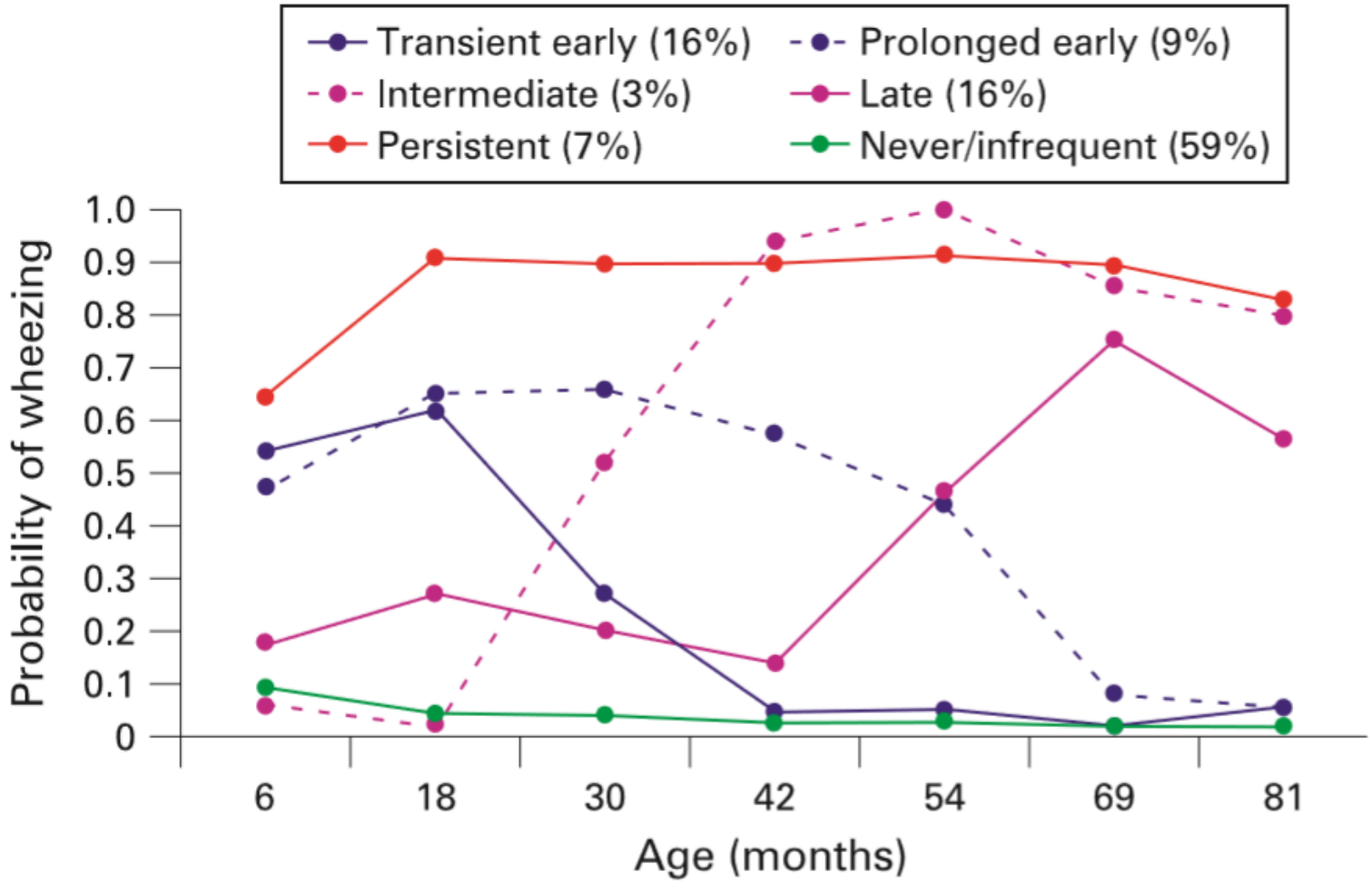
- There appeared to be an increase in the 1980s, peaking in the 1990s.
- Data on mean weekly new episodes of asthma presenting to general practice, by age, England and Wales 1976–2004. (England and Wales).

There has also been a fall in new diagnoses in the last 10 years, although levelling out.

Number of people per 100,000 newly diagnosed with asthma, by UK region, 2004–12

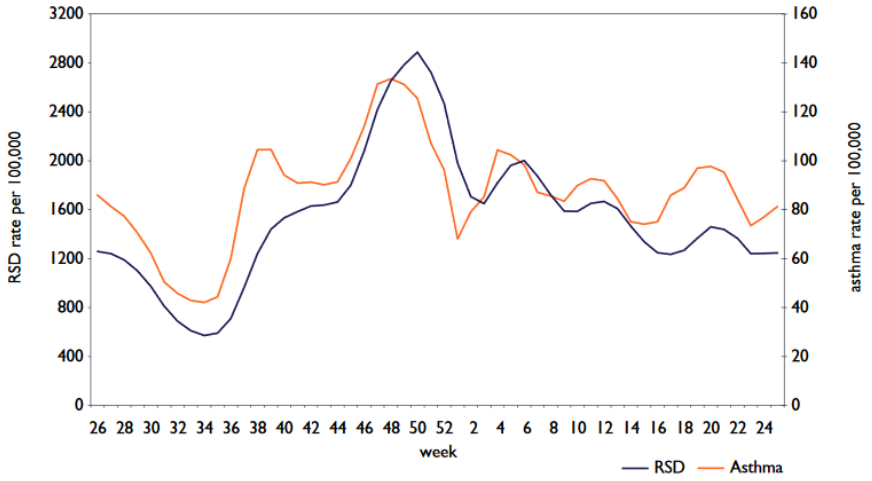


Variation over the lifecourse. Wheeze can be transient in childhood, persist, or start in adulthood. *Henderson et al 2007*

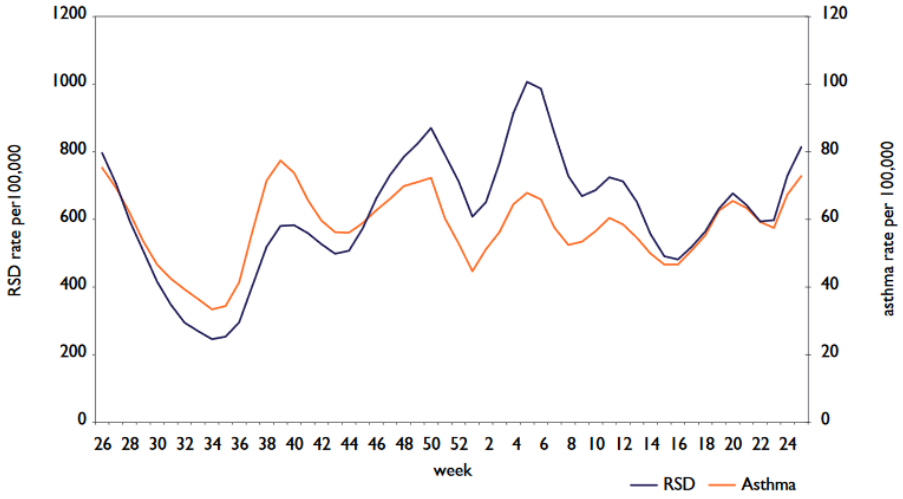


There is a winter peak in asthma GP diagnoses, linked mainly to infection.

HPA data, 10 year average.



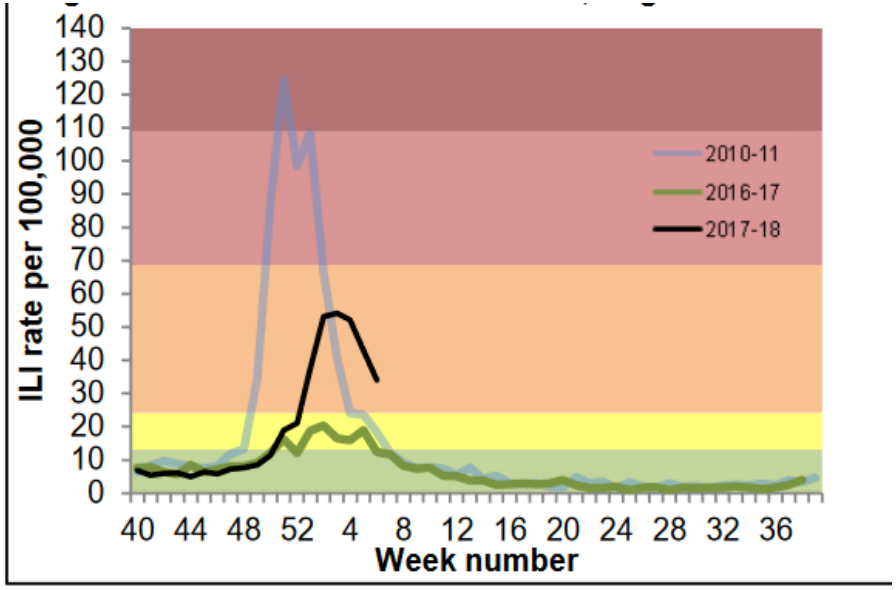
Children 0-4

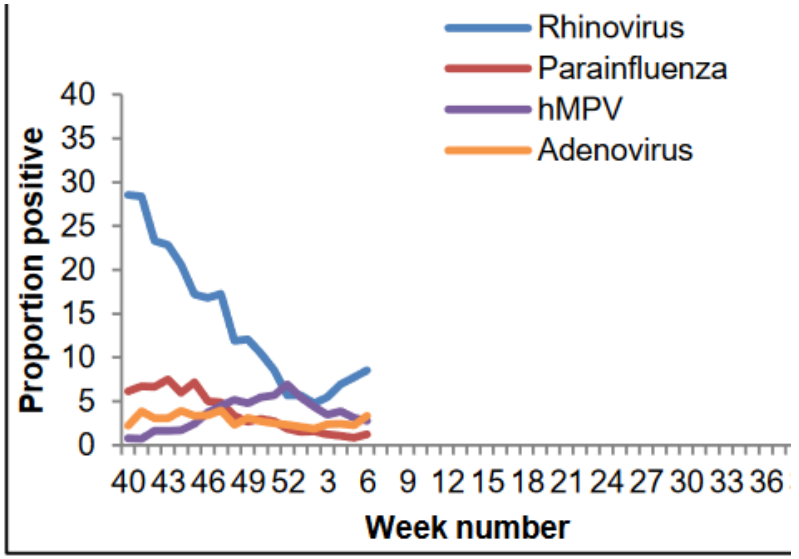


Children 4-15

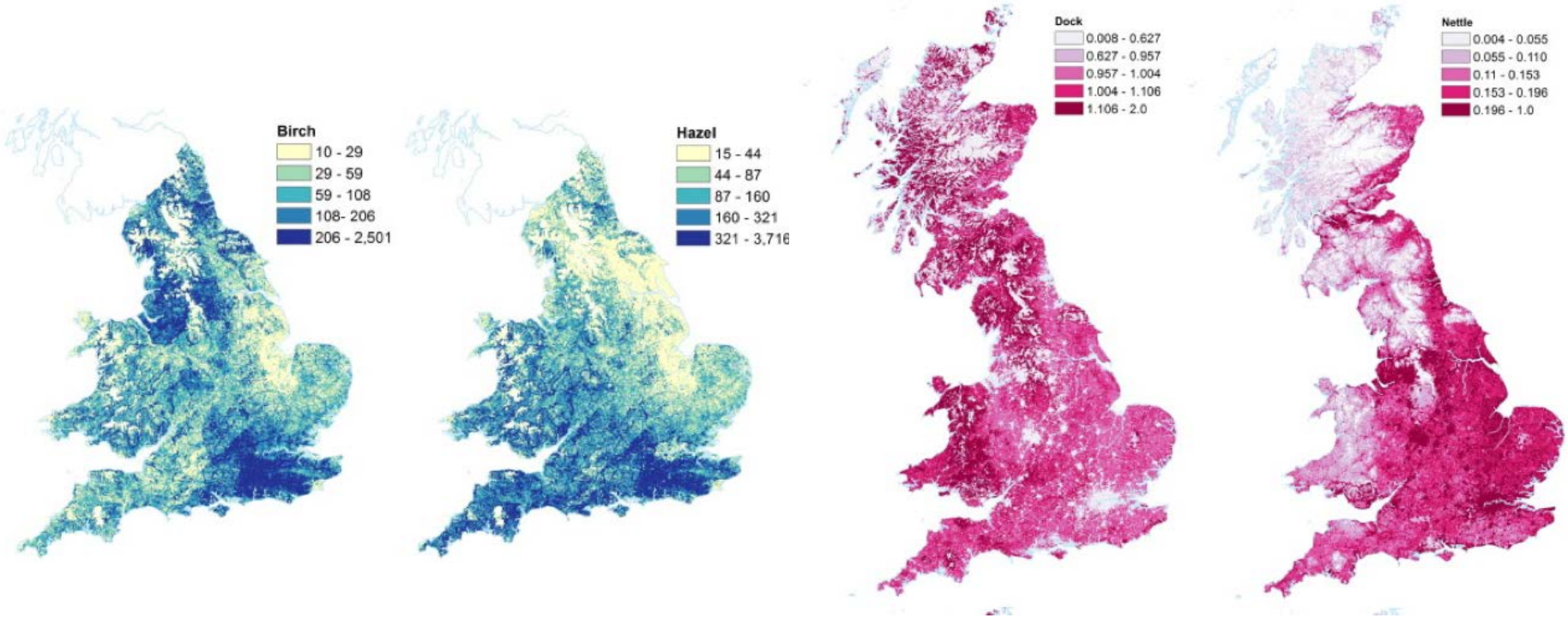
Respiratory viruses vary within year and between year. Influenza-like GP visits (L), other viruses (R).

PHE 2018

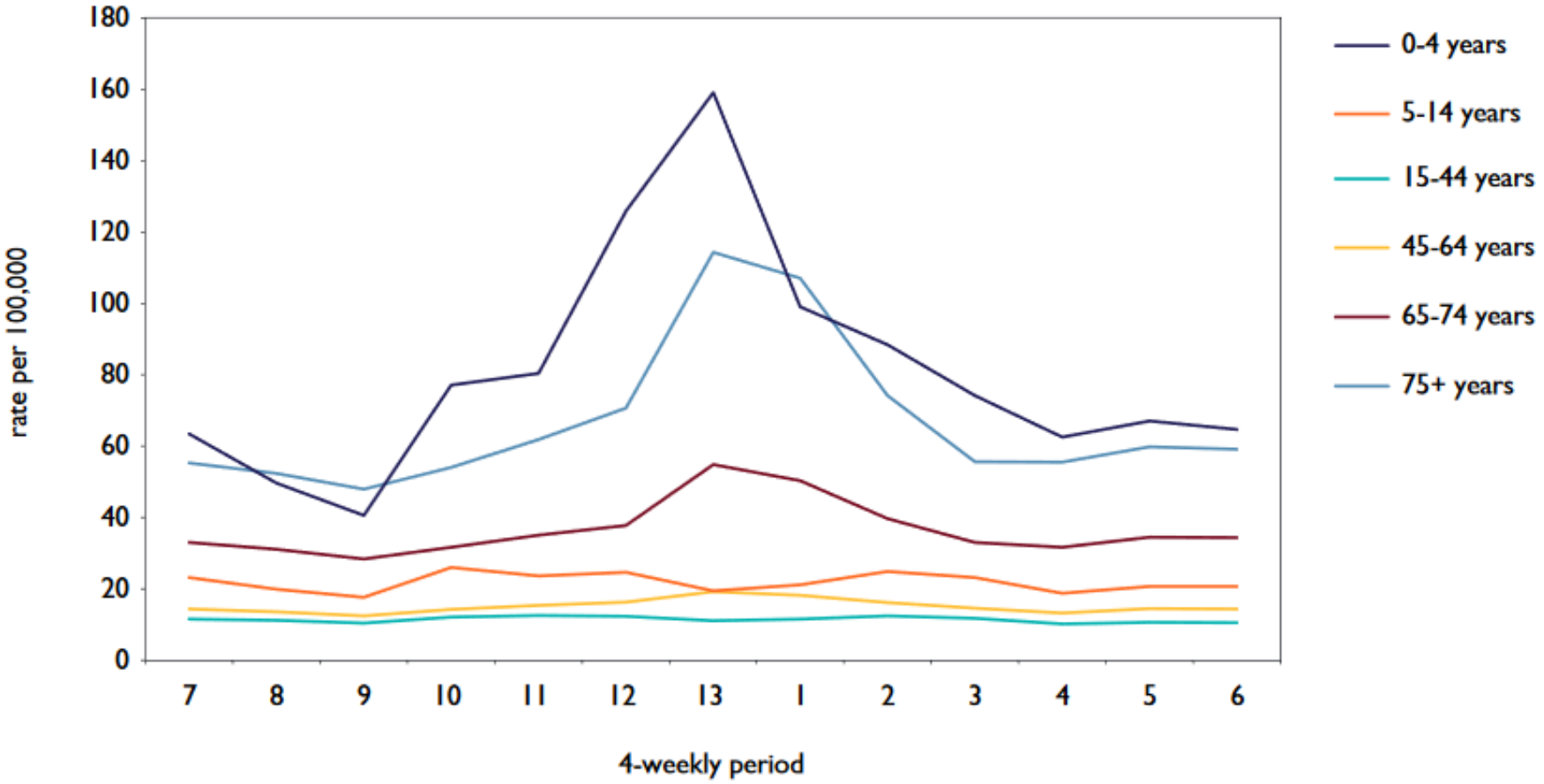




Examples of potential hay fever triggers. Birch (Mar-May), hazel (Feb-Mar), dock (June-Jul), nettle (June-Aug). *(Met Office/ U. Exeter)*



A peak in respiratory admissions to hospital- in the young and old. (HPA data, 10 year average).



The diagnosis of asthma is sometimes difficult.

- Asthma is sometimes obvious.
- Milder cases can be difficult to diagnose.
- The first attack of wheeze in a child is often not asthma.
- Whether symptoms responds to treatment important to diagnosis.

Spirometry

Peak flow

Effective, safe treatment for asthma only started in a widespread way from the 1950s.

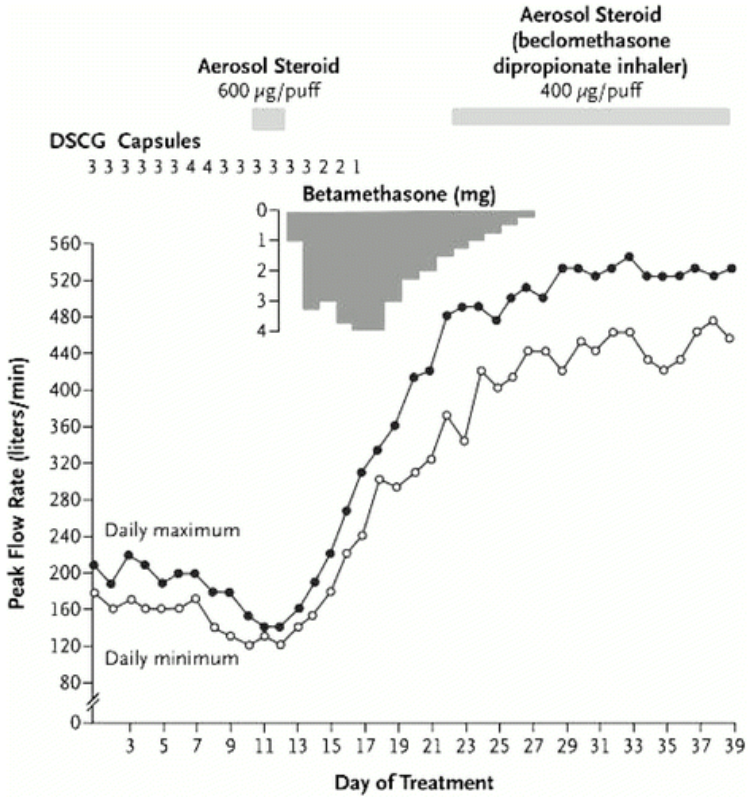
Current drugs for asthma. Relief (rescue) treatment: β2-adrenergic agonists.

- It had been known from at least 1910 that injected adrenaline could have an effect on asthma.
- Current mainstay salbutamol, developed in 1966 in Ware by Sir David Jack (in a predecessor of GSK). Much more selective.
- Relax bronchial smooth muscle. Some anti-inflammatory activity.
- Other drugs in this class terbutaline and salmeterol.

Inhalatorium

Inhaled steroids- the main anti-inflammatory prevention drugs.

- Studies in 1950s with injected hormone corticotrophin showed prolonged effect on asthma.
- By 1970s oral steroids used.
- Mid 1970s inhaled steroids introduced.
- Major trials, most influential in 1991 showed inhaled steroids superior to β agonists.



Brown et al, BMJ 1972.
1 patient.

In praise of inhaled steroids. *If* people take them, *and* they have reasonable technique transformational.

The anticholinergic inhalers.

- Smoking stramonium, dried Thorn-apple / devils snare, from 1900s.
- Active ingredient alkaloids of Belladonna (deadly nightshade), an anticholinergic. *E.G*. atropine.
- A stable form, ipratropium bromide, developed for inhalation.
- Can make β-agonists more effective. Sometime combinations.

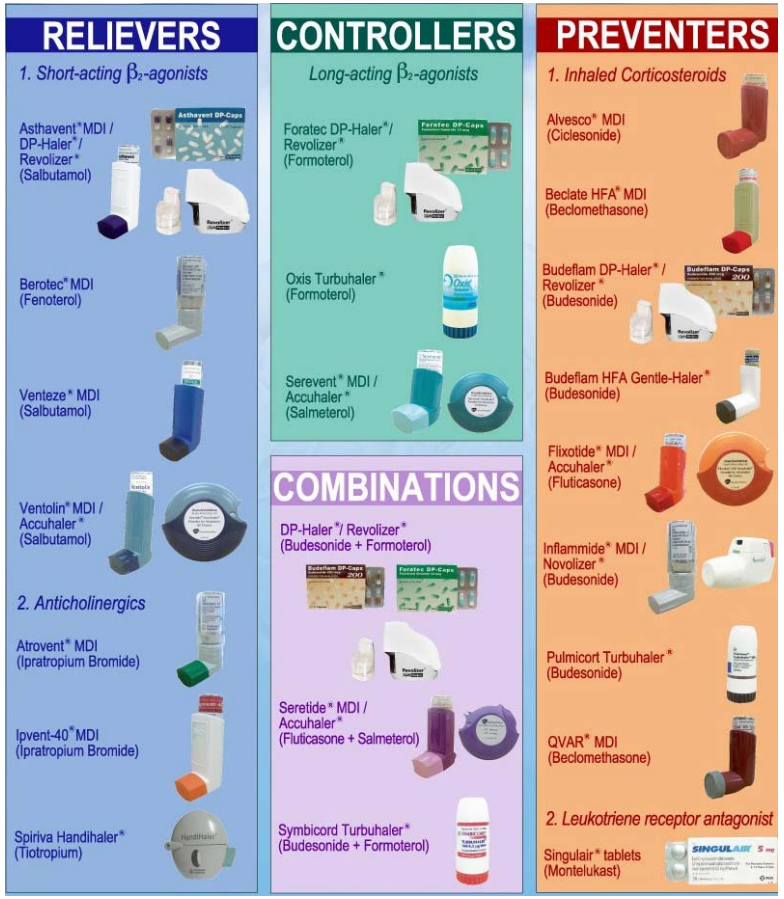
Several other drugs, used more rarely include:

- Theophylline, originally extracted from tea leaves. First used as a diuretic.
- Antileukotriene and anti-IgE treatments deliberately designed based on understanding of asthma.
- Khellin, a chemical from *Ammi visnaga* (Bishops weed), from traditional medicine, gave rise to sodium chromoglycate.

Tea plant (Kohler), Ammi visnaga

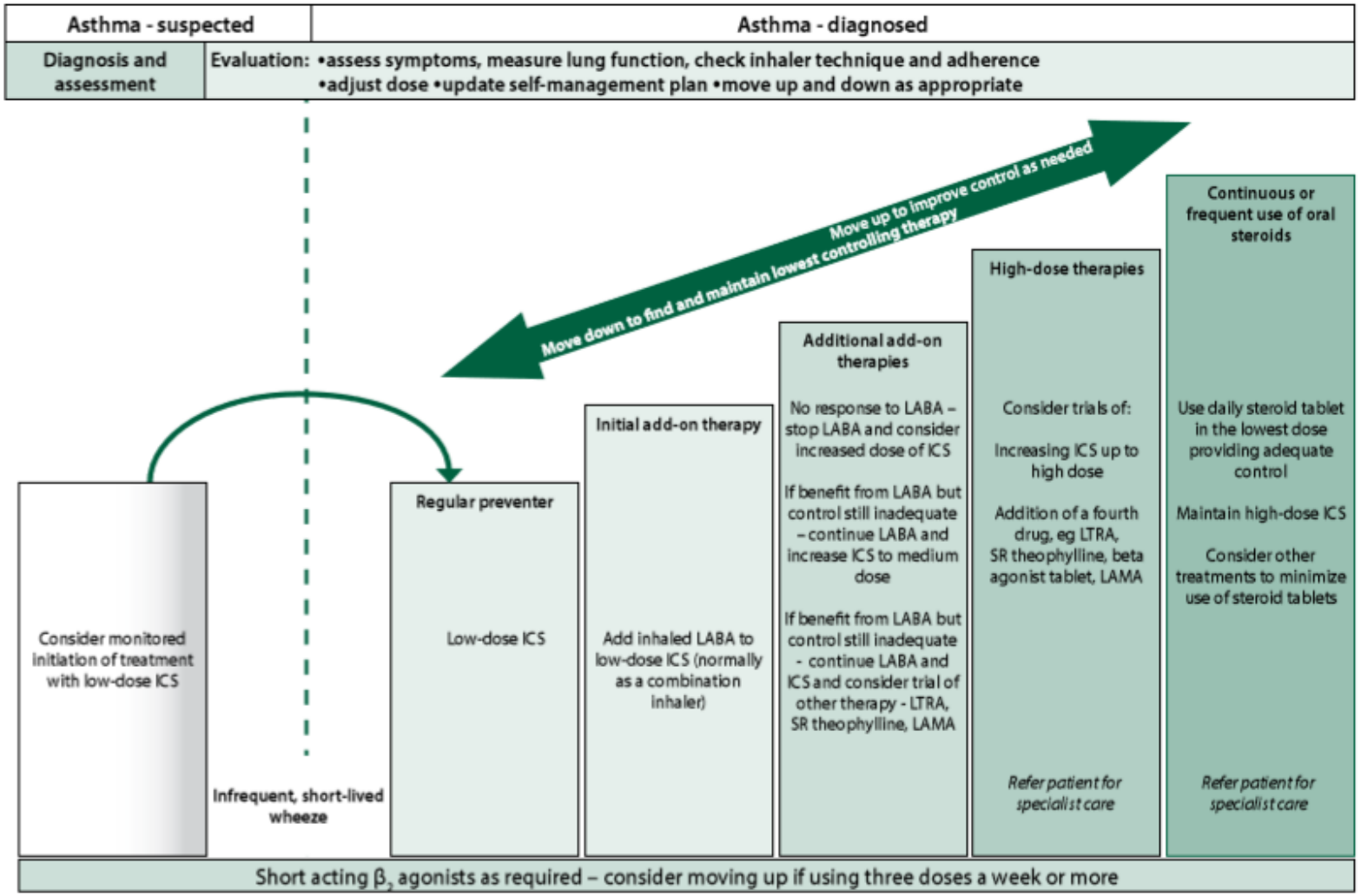
The inhaled drugs form the mainstay of most people's asthma treatment.

- All will have a short-acting β-agonist reliever.
- The great majority will have an inhaled steroid preventer.
- For most children and adults that is enough.
- If necessary additional long-acting controller or anticholinergic.



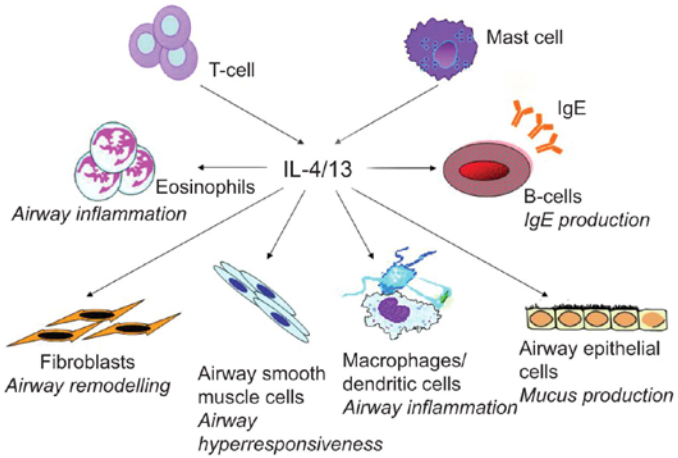
Examples of inhalers *(CIPLA)*

Current UK guidelines on moving up or down ladder of intervention.



New advances in asthma- the biologics.

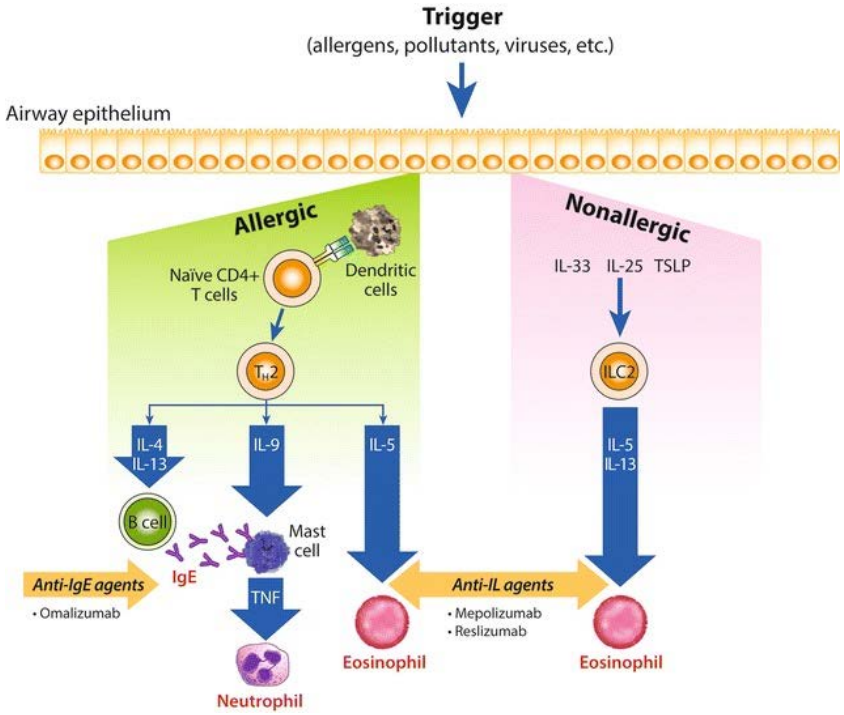
- Biologic agents (monoclonal antibodies) are revolutionising inflammatory diseases.
- Asthma is starting to benefit.
- Antibodies target specific parts of the immune system such as IgE or interleukins.
- Early trials are promising in severe asthma. Examples dupilumab (IL4/13), omalizumab (IgE).



Oh et al. (2010). European Respiratory Review.

Mild-moderate asthma can probably still be treated as one disease (it is not). For severe asthma we will need to differentiate.

Category	Phenotype
Trigger-induced asthma	(1) Allergic (2) Non-allergic (3) Aspirin-exacerbated respiratory disease (AERD) (4) Infection (5) Exercise-induced
Clinical presentation of asthma	(6) Pre-asthma wheezing in infants Episodic (viral) wheeze Multi-trigger wheezing (7) Exacerbation-prone asthma (8) Asthma associated with apparent irreversible airflow limitation
Inflammatory markers of asthma	(9) Eosinophilic and neutrophilic asthma



Kiley et al 2009

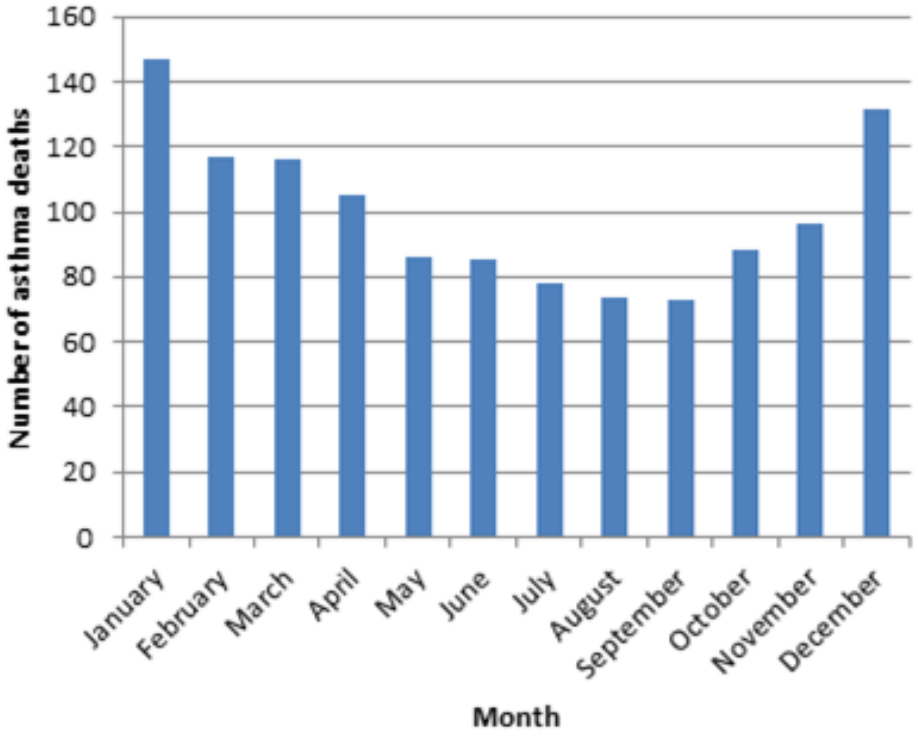
Kim et al 2017

Severe asthma attacks.

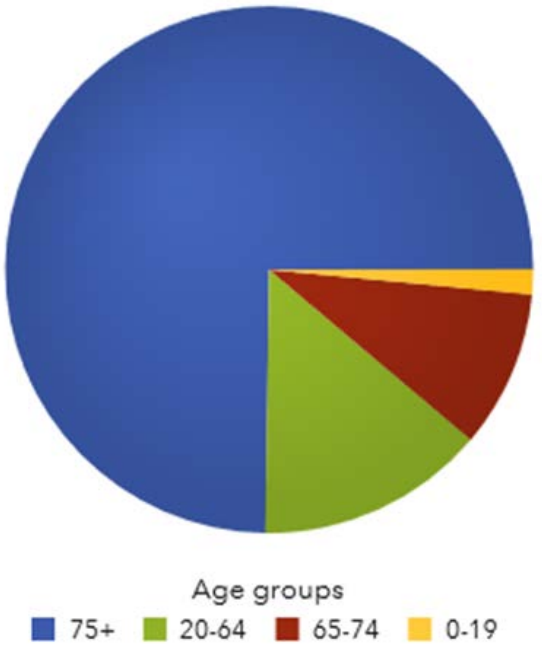
- Only a small minority of people with asthma ever need hospitalisation. But asthma is common.
- Severe asthma, which tends to recur in some people, is life-threatening.
- Initial treatment is oxygen, oral steroids and high doses of the bronchodilator drugs by face-mask nebuliser.
- May need temporary respiratory support or artificial ventilation.

In 2016 1,410 people in UK died from asthma. Mortality concentrated in age and time of year.

Asthma UK



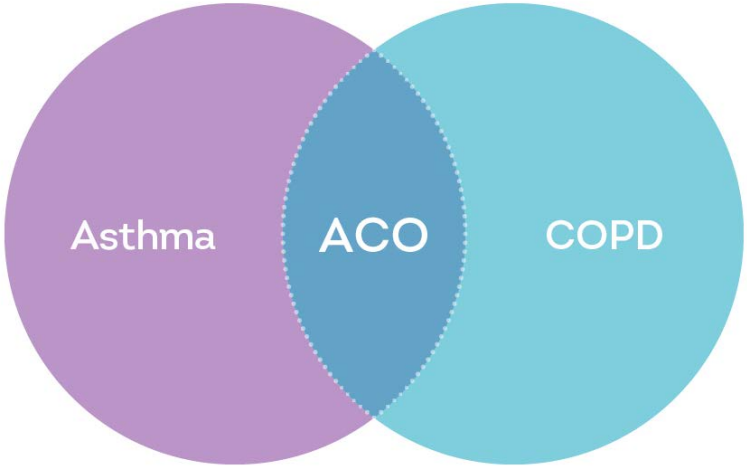
Monthly average asthma deaths decade 2005-14.



Mortality from asthma by age, UK

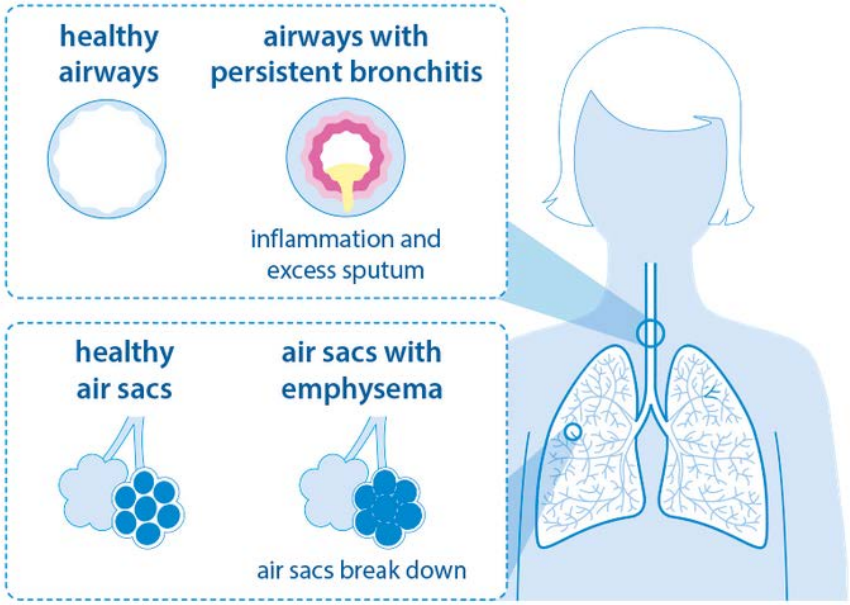
Asthma and chronic obstructive pulmonary disease (COPD) overlap.

- They are different diseases. Most have one, or the other; a few have both (ACO).
- If this is not recognised treatment will not be optimal.
- Uncontrolled asthma can lead to COPD.



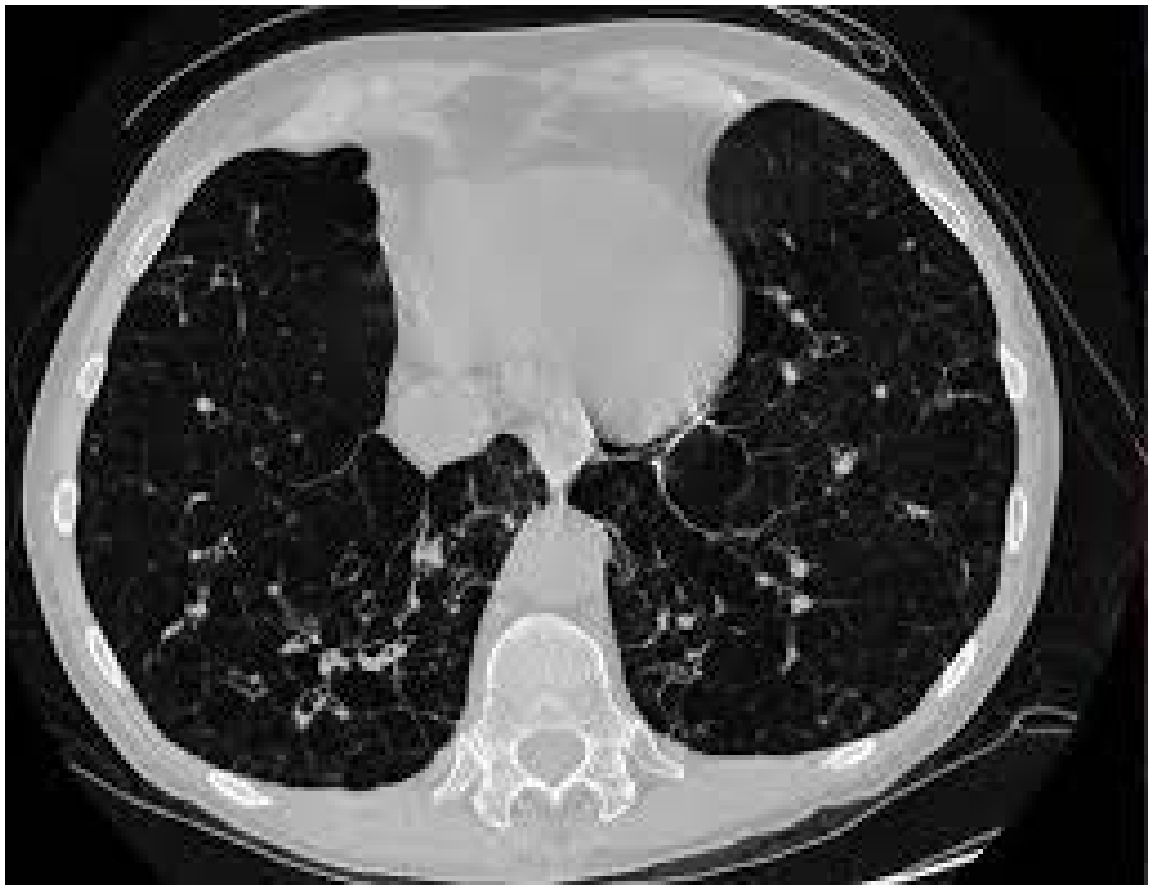
COPD is a broad term for a group of lung conditions where there is damage to the lung.

- Major ones
- emphysema (damage to lung sacs)
- chronic bronchitis (inflammation of airways).
- Tends to come on in middle or old age.
- Shortness of breath, chronic cough.
- Get gradually worse over time, with exacerbations (flare ups).



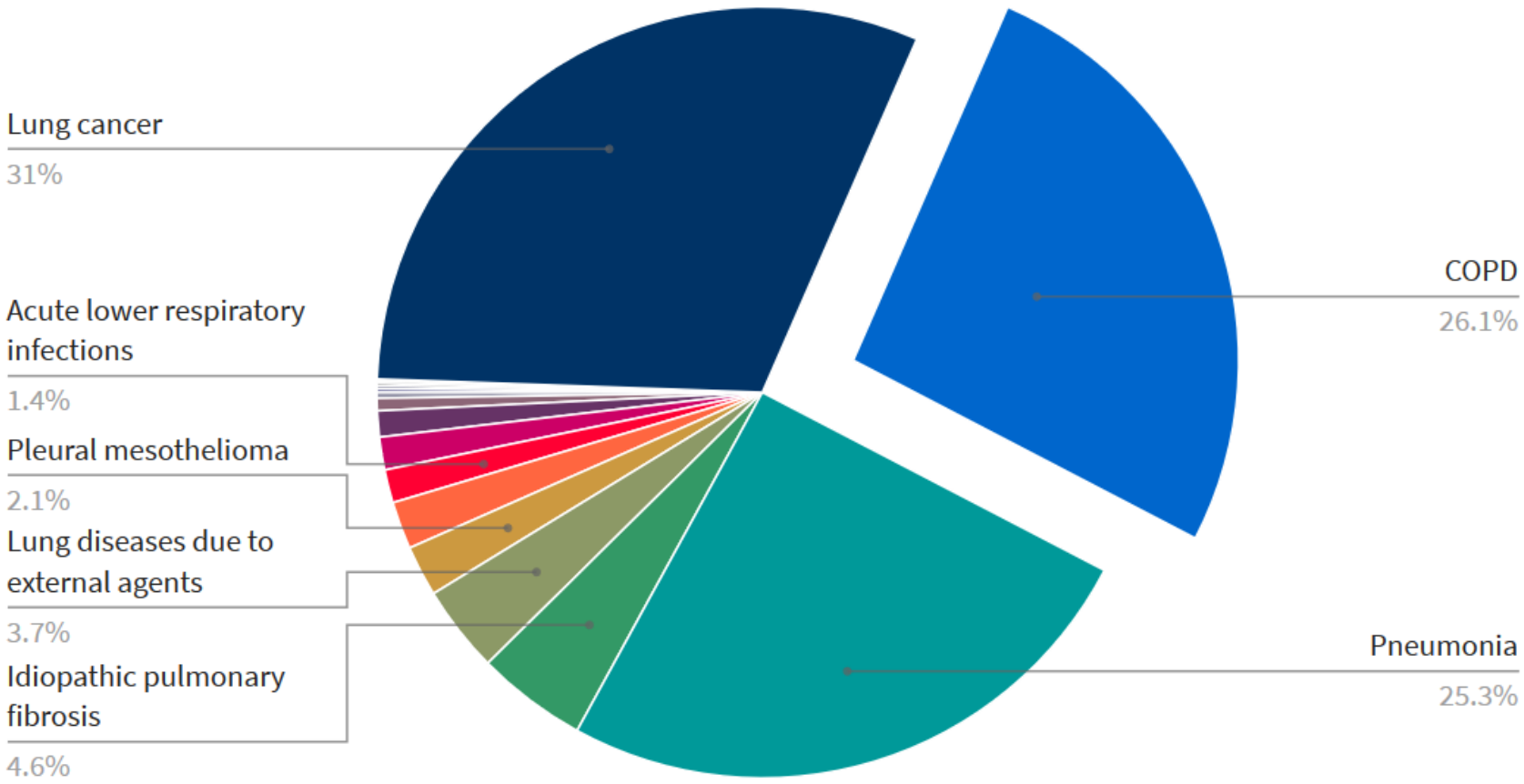
British Lung Foundation

In severe cases substantial destruction of the lung. People highly restricted in what they can do.

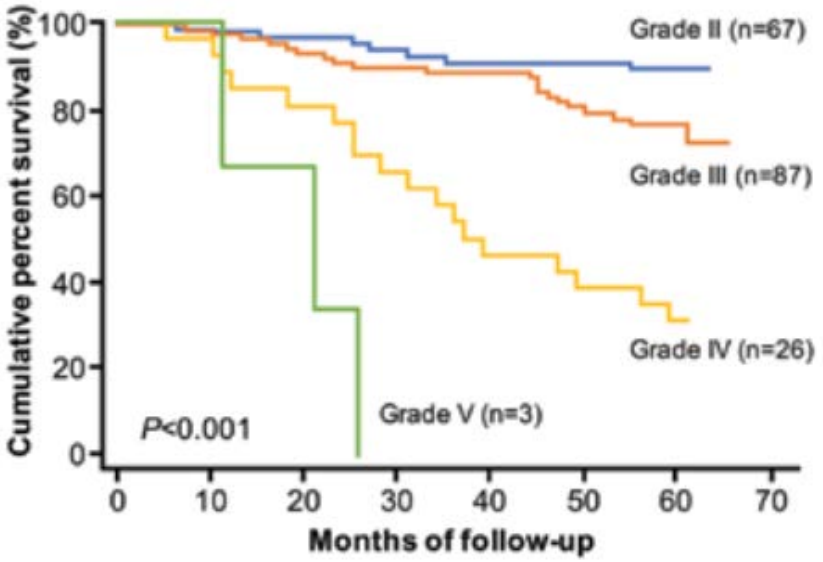


COPD a major cause of mortality. Around 29,000 deaths a year, 5% of all deaths. WHO estimates 3rd most important cause of death globally by 2030.

(British Lung Foundation data).



Dying is not the only issue; COPD substantially reduces quality of life through breathlessness.



Survival by MRC grade.
(Nishimura et al)

MRC COPD grade.

- Grade 2. Short of breath when hurrying on the level or walking up a slight hill.
- Grade 4. Stops for breath after walking 100 yards, or a few minutes on level ground.
- Grade 5. Too breathless to leave the house, breathless when dressing/undressing.

There are several potential environmental causes. Indoor and outdoor air pollution, occupation.

- Historically in all countries, and still in many countries, indoor cooking / heating.
- Outdoor air pollution.
- Occupations which increase risk include mining, brick making, welding, stonemasonry, flour and grain workers, agriculture, foundry workers, textiles.

Bruce Kirenga, Lancet. Uganda.

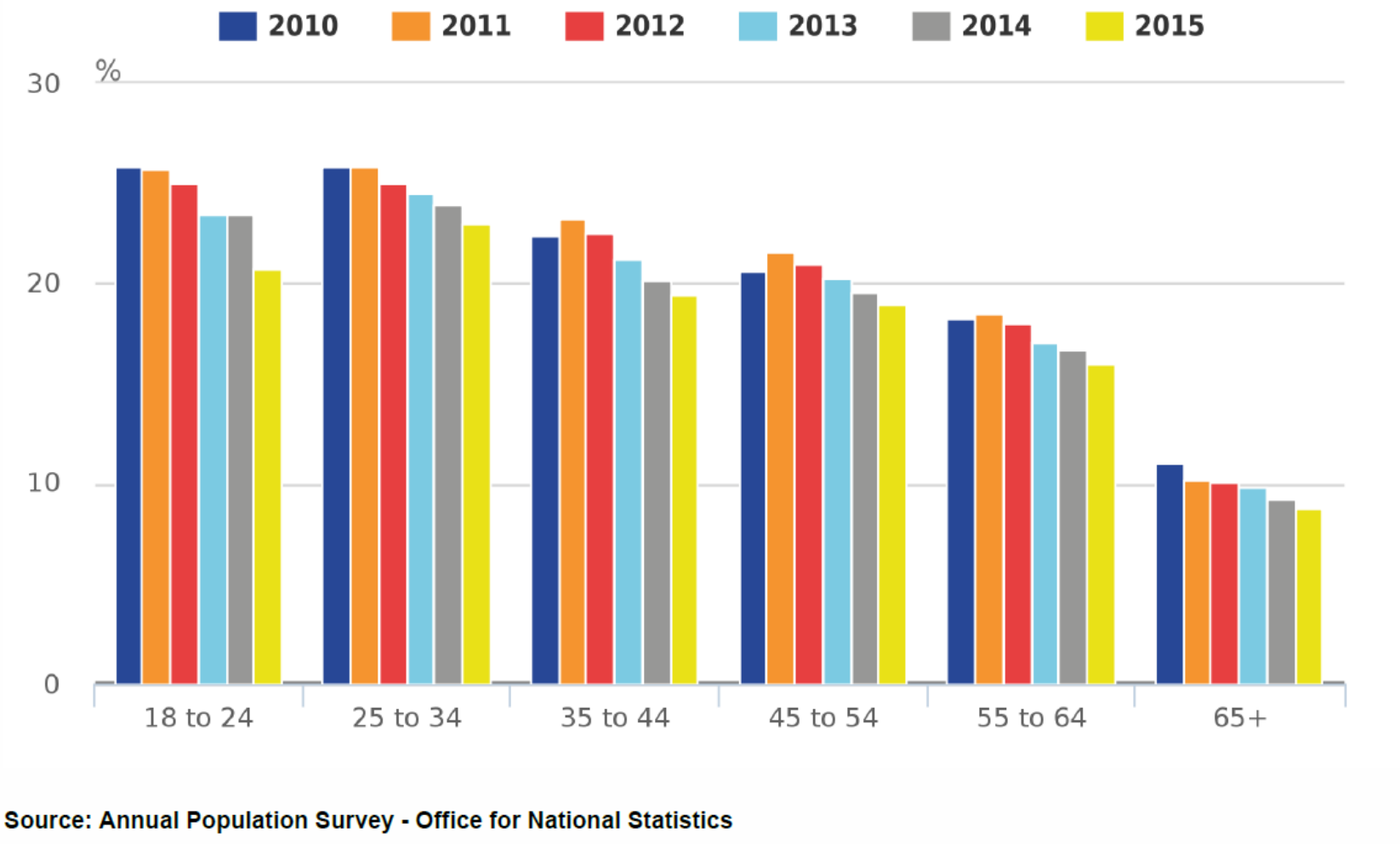
In high-income countries the great majority of COPD cases now in smokers.

- In the UK smoking probably responsible for 9 out of every 10 cases of COPD.

- Therefore the epidemiology of COPD is largely the epidemiology of smoking.

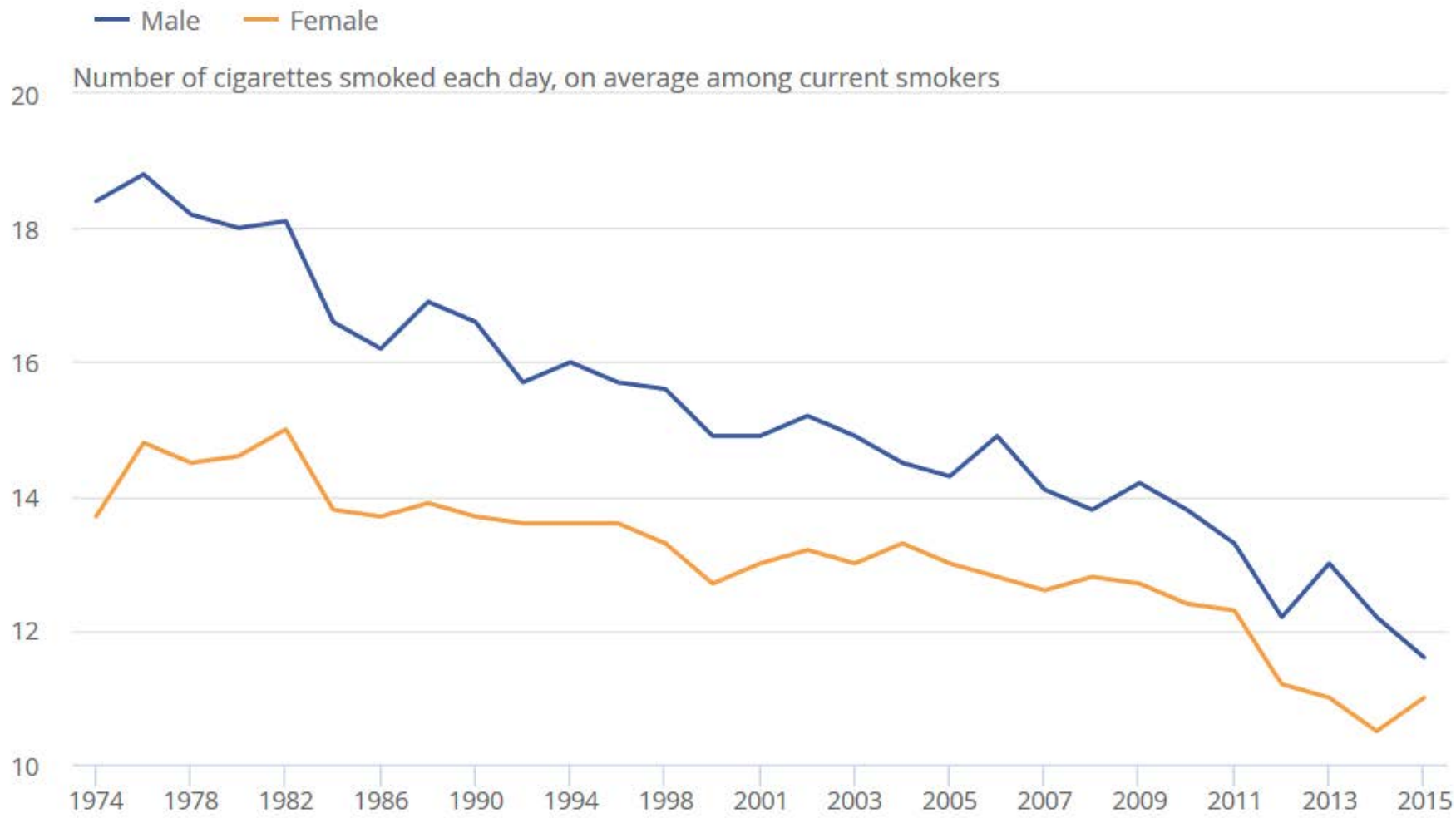
Vincent van Gogh

Current proportion (%) smokers by age, UK *(ONS).*



Source: Annual Population Survey - Office for National Statistics

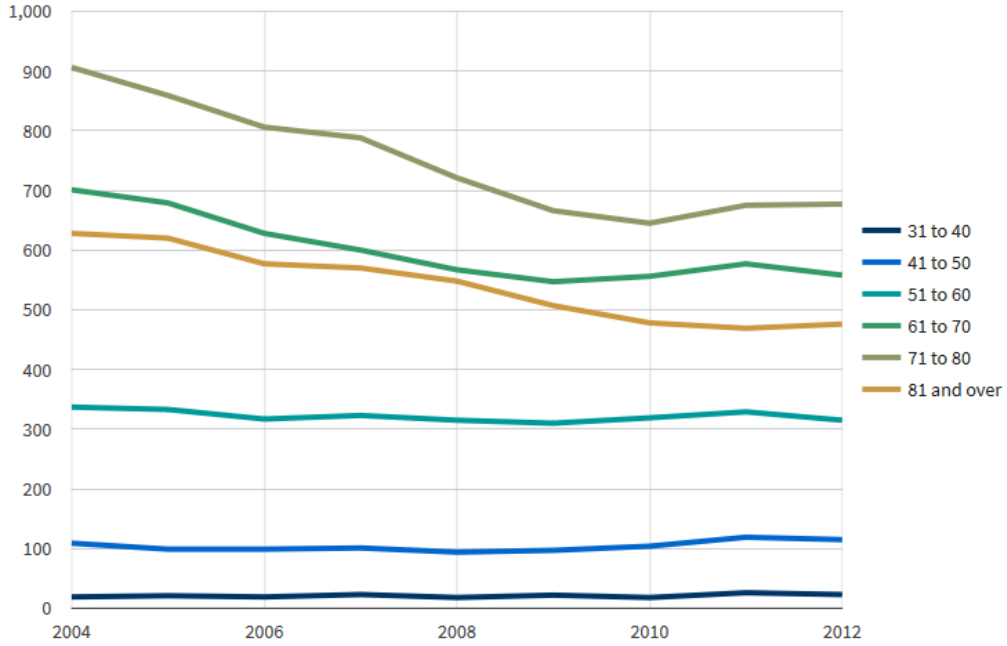
Amount smoked in smokers decreasing. *(ONS)*



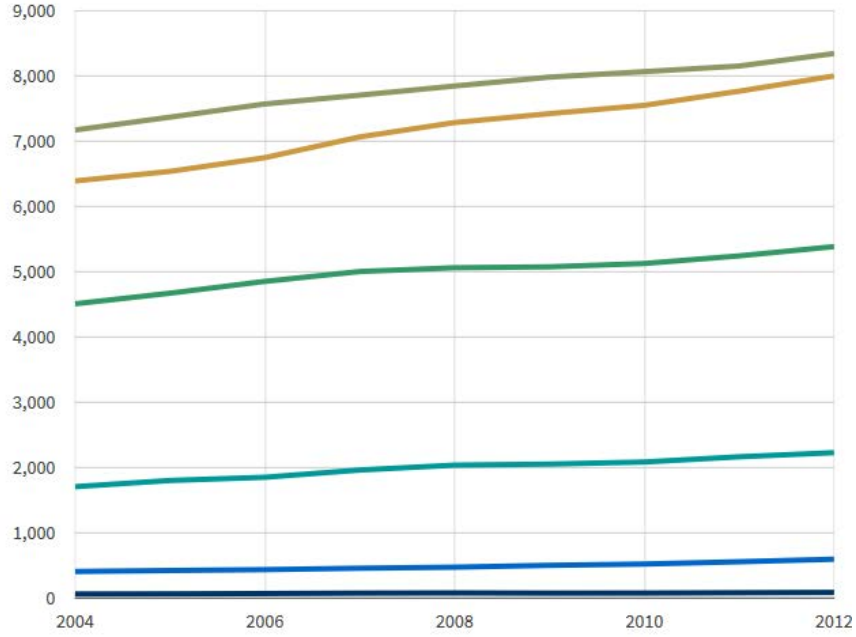
Change in COPD since 2004, UK. Estimated 1.2M people living with COPD in the UK.

(British Lung Foundation)

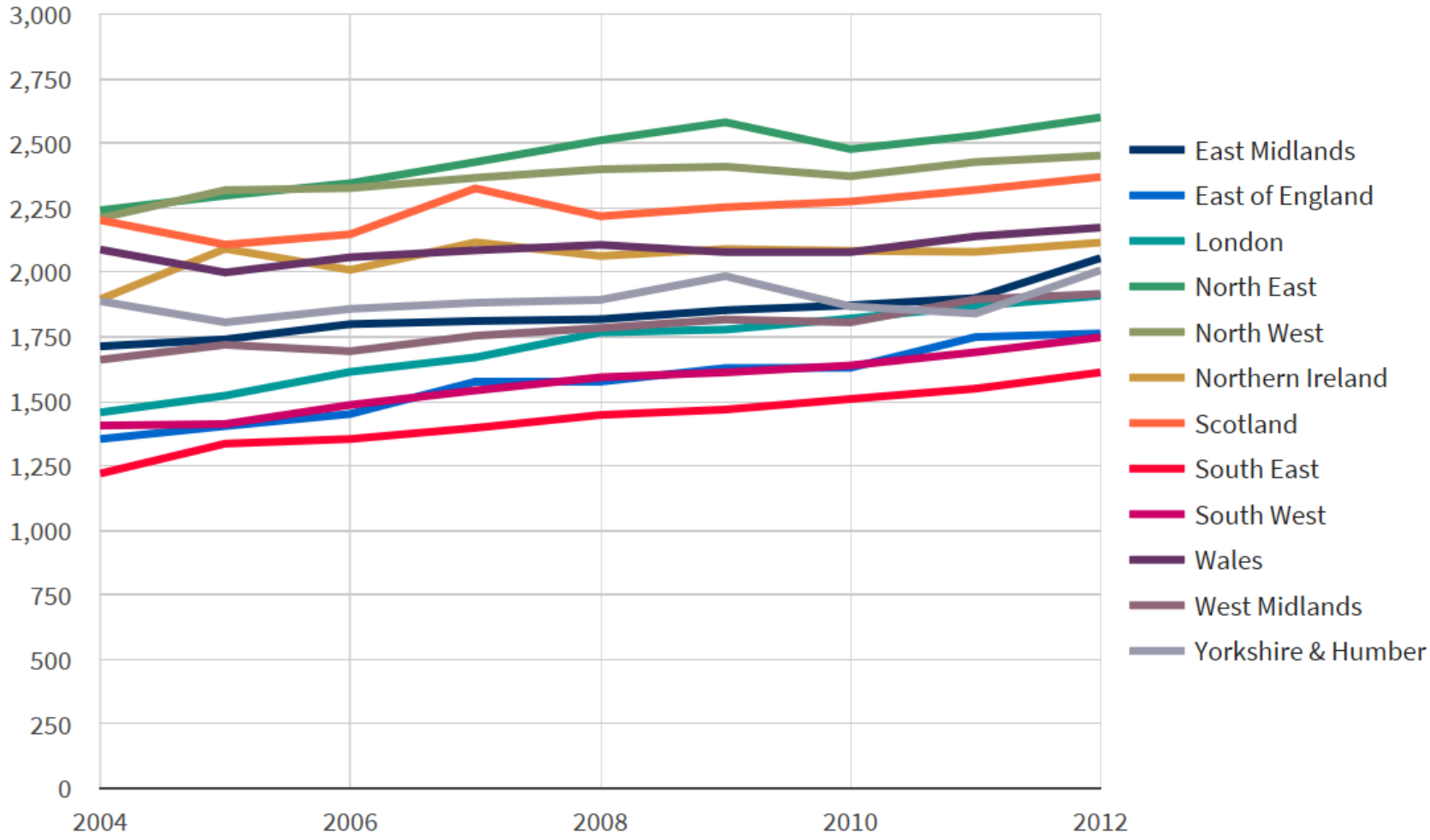
New diagnoses with COPD / 100,000 by age over time (incidence).



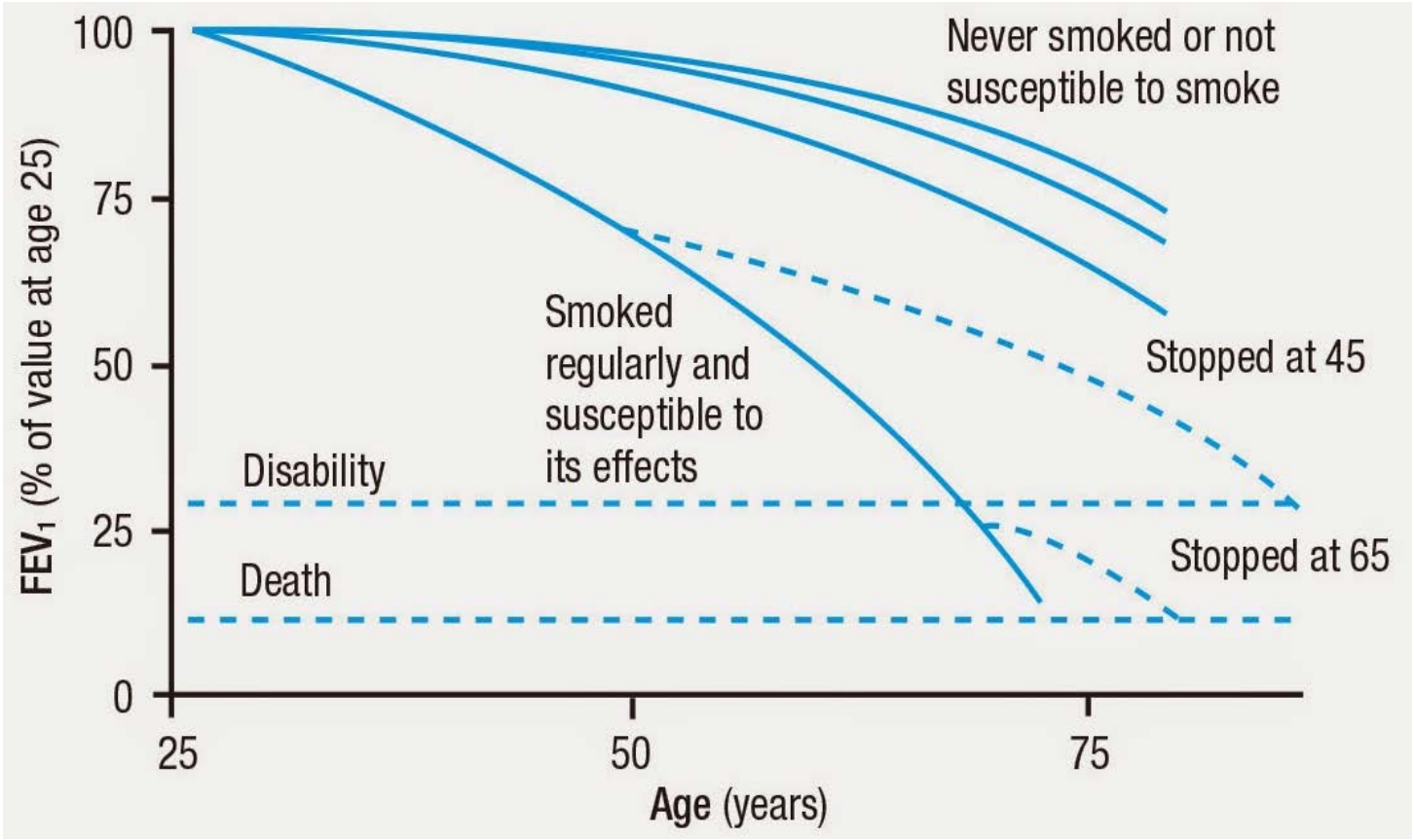
People living with COPD /100,000 by age (prevalence).



People/100,000 with COPD by region.



By some distance the most important thing is to stop smoking. Short- and long-term benefits.

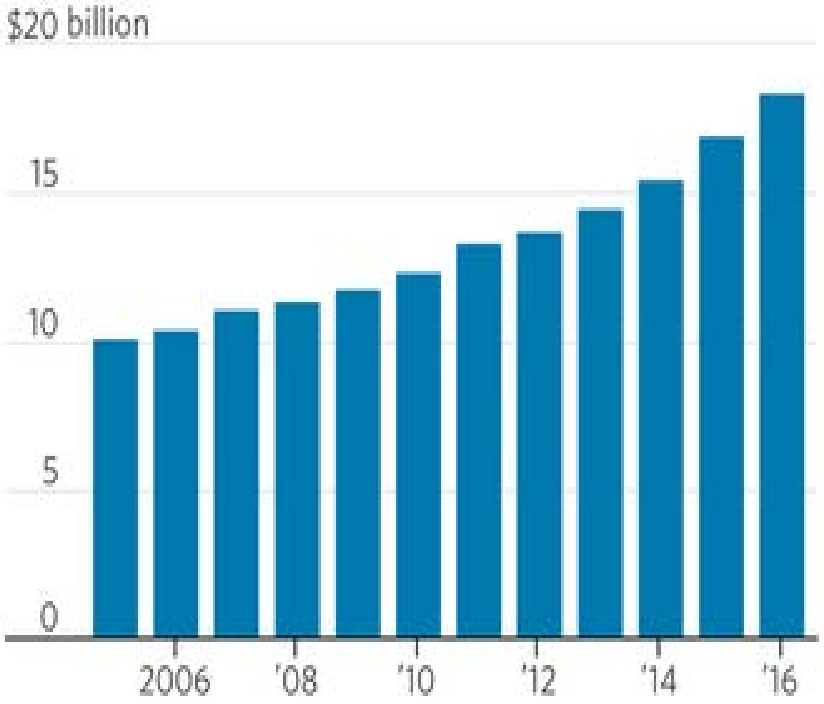


Fletcher & Peto, BMJ 1977

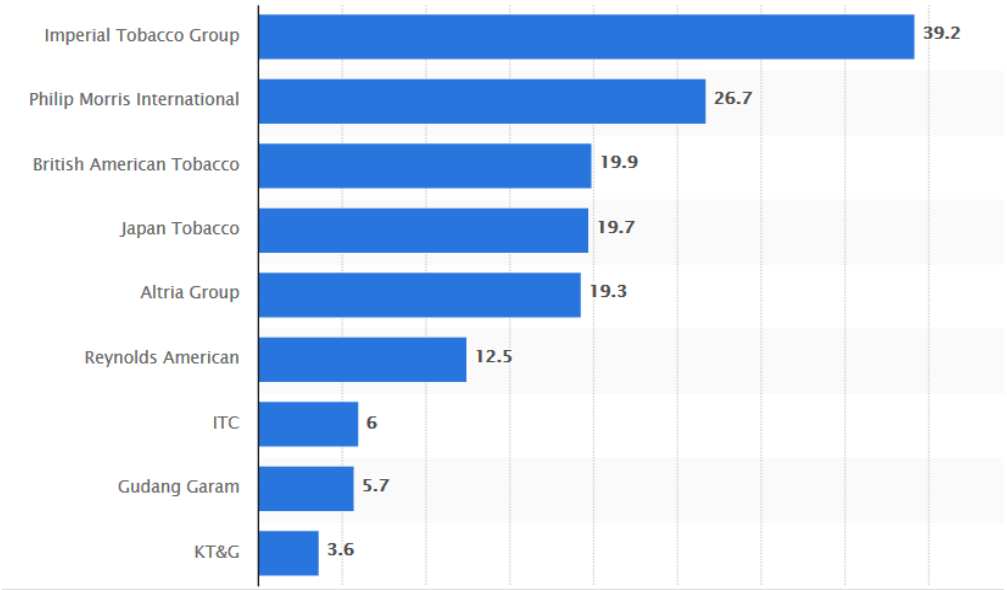
People with COPD often blame themselves for smoking. They should not. One of the wealthiest and most powerful industries in the world worked hard to get them addicted to nicotine at a young age, and keep them there.

Total US tobacco profit pool, $

(WSJ 2017)

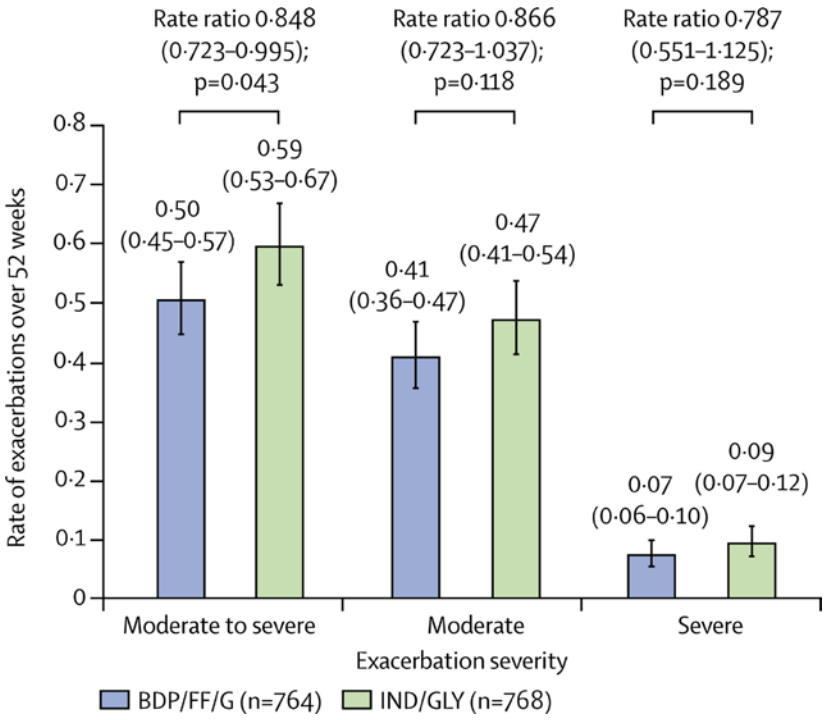


Top 10 tobacco companies net worldwide $ sales 2017 *(Statistica)*



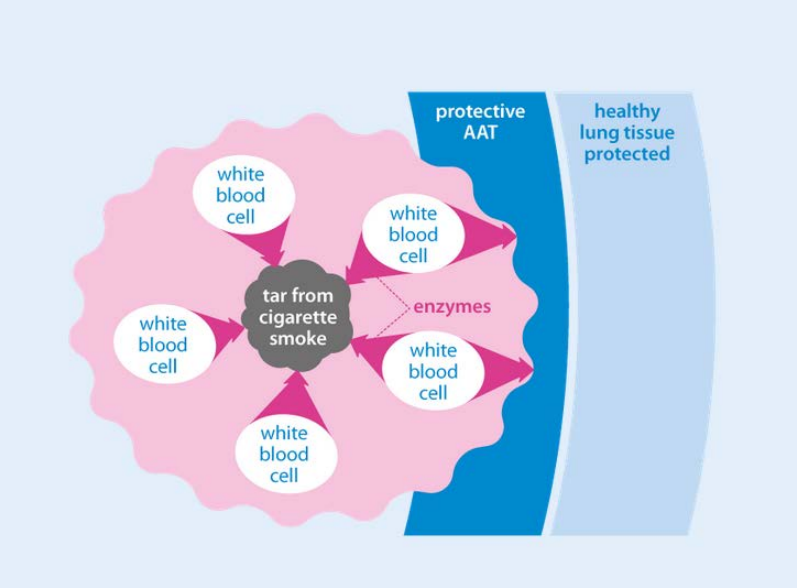
Avoiding triggers of exacerbations and drugs help.

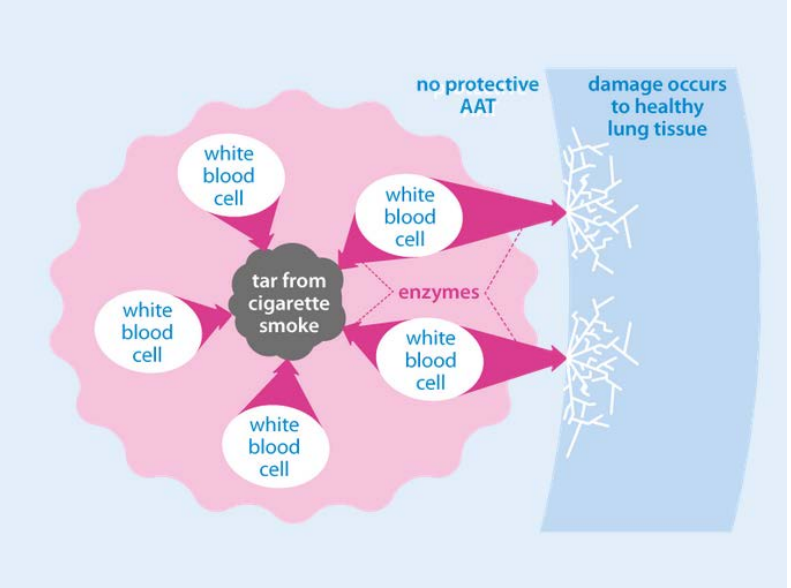
- 'Flu and pneumococcal vaccines. Possibly others.
- Exercise.
- Long-acting drugs more important than asthma.
- Long-acting antimuscarinic inhalers (LAMA) and long-acting B-adrenergic inhalers (LABA).
- Combinations improving (R). Steroids have a place.



Papi et al Lancet 2018

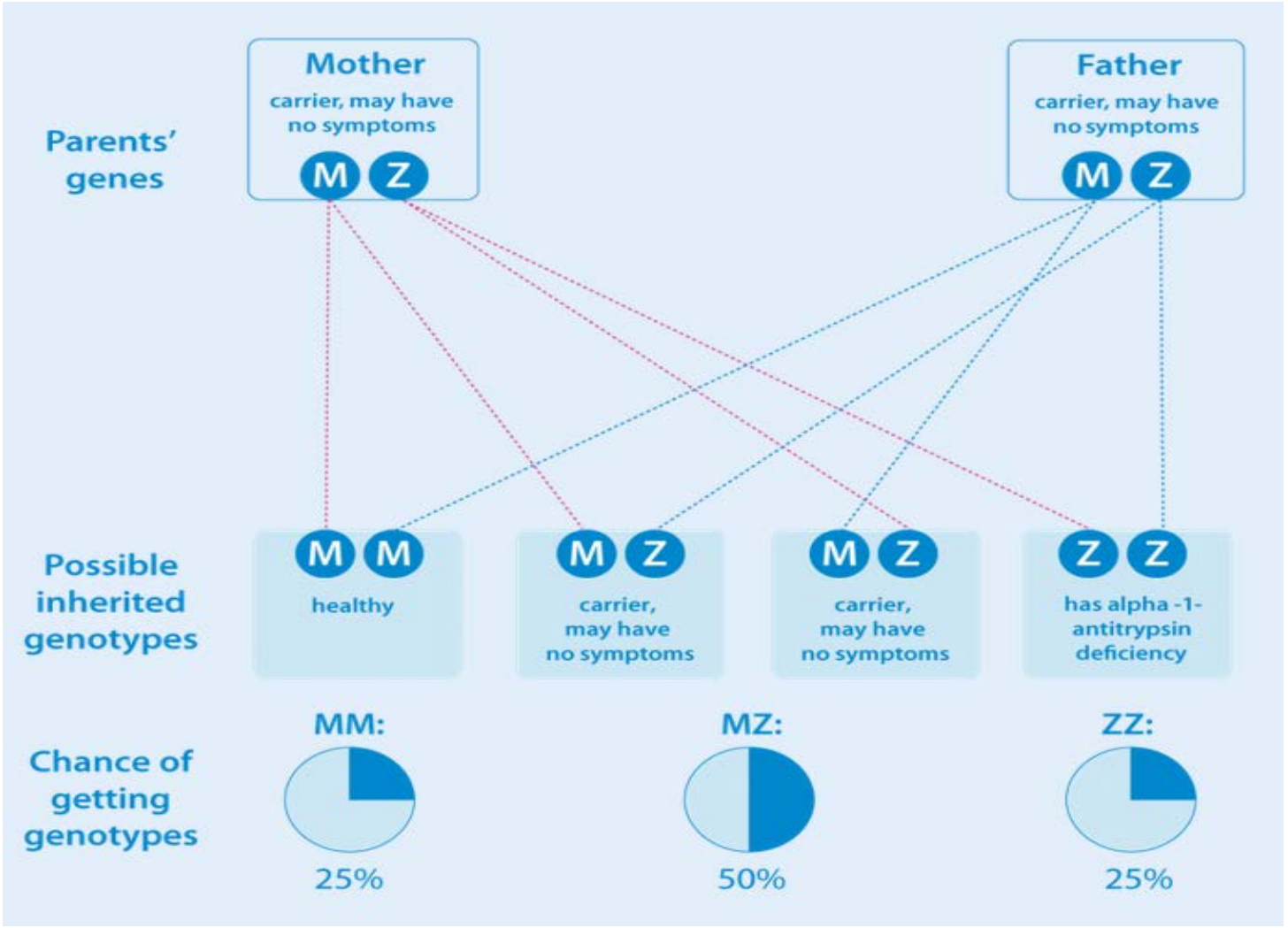
Alpha-1-antitrypsin (A1AT) deficiency. Around 25,000 people in the UK. Most asymptomatic. Around 1% of people with COPD have A1AT.





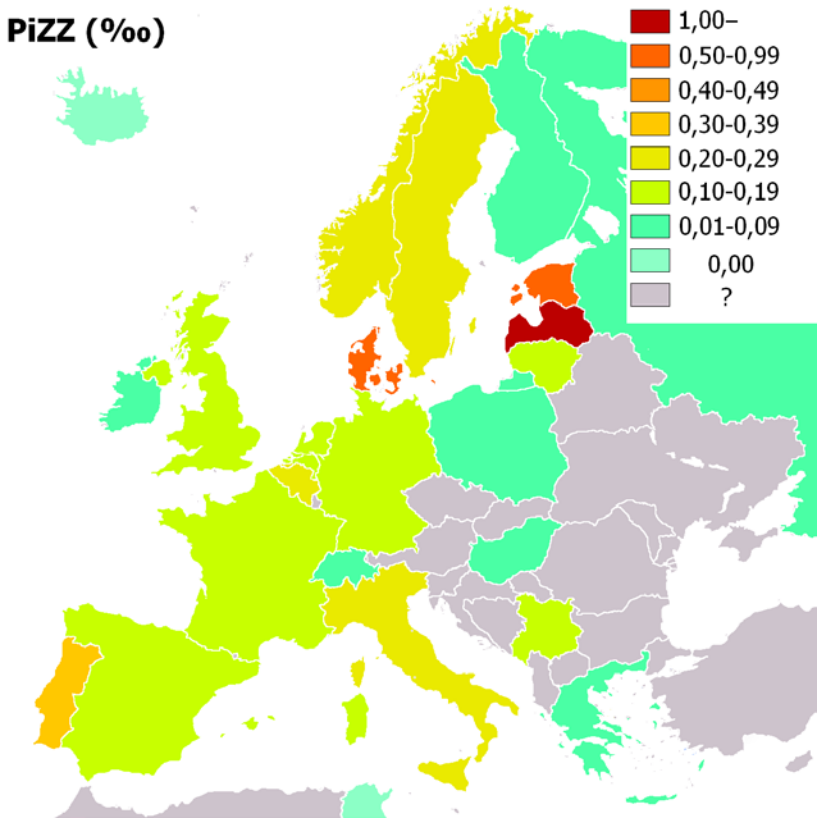
British Lung Foundation

Alpha-1-antitrypsin deficiency inheritance. 93% population MM. Those who are ZZ have about 10% A1AT levels.

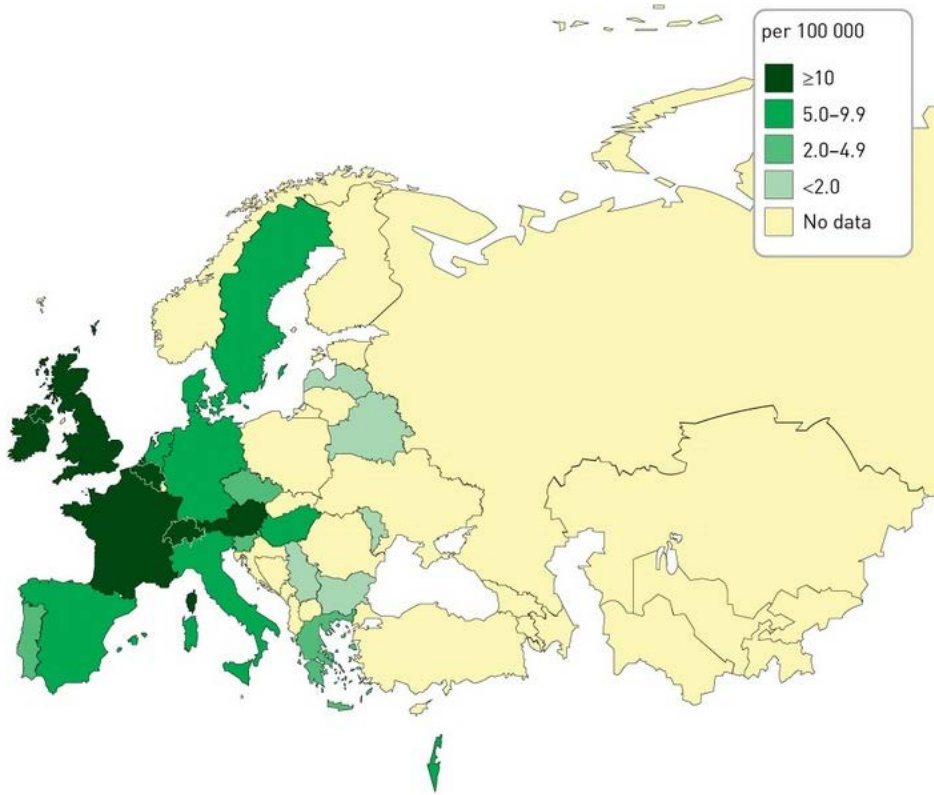


BLF

Genetic variants vary by geography.
A1AT PiZZ (L) and CF (R).



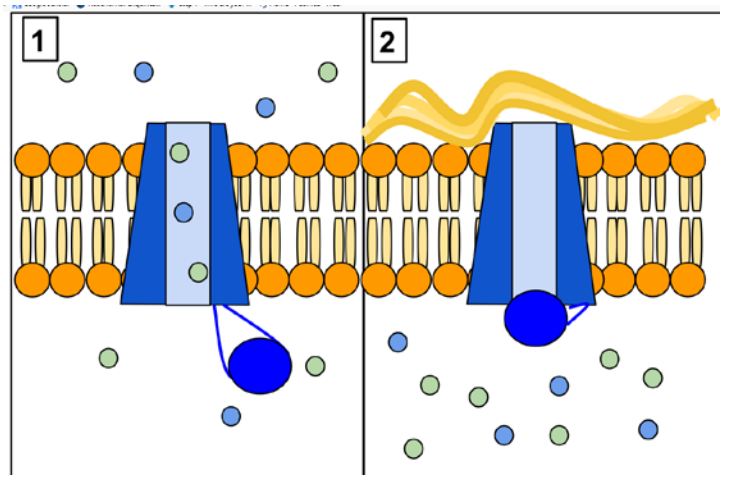
Olve Utne



European Lung Foundation

Cystic fibrosis: the commonest autosomal recessive condition in Caucasians.

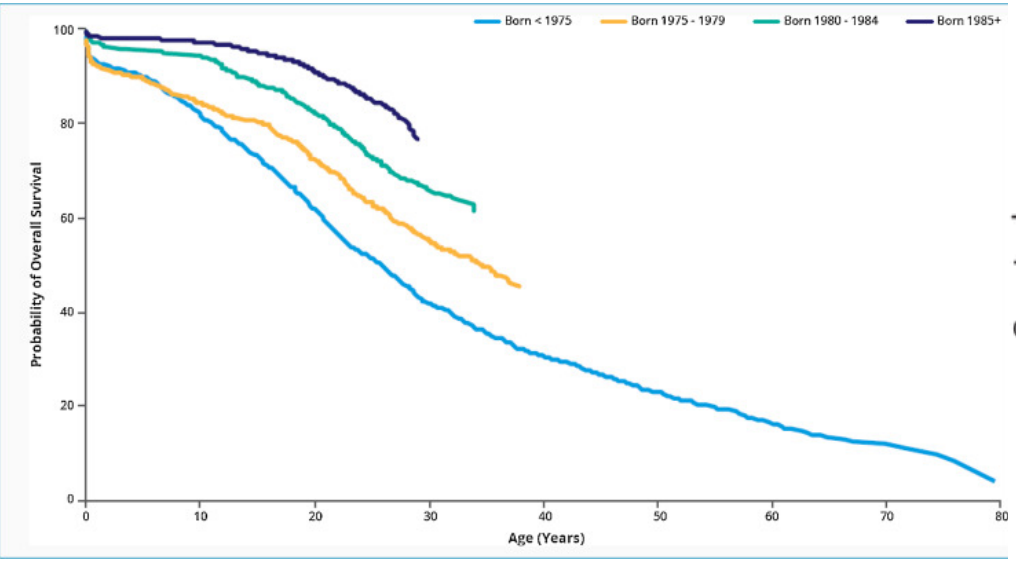
- 1:25 people in UK carry faulty gene. Over 2000 mutations.
- Around 10,500 people (1:2500 babies) have CF- two faulty genes in UK.
- Abnormal handling of chloride and water in cells.
- Leads to buildup of thick mucus.
- Repeated, atypical infections of the lungs and other effects.
- Most die of lung complications.

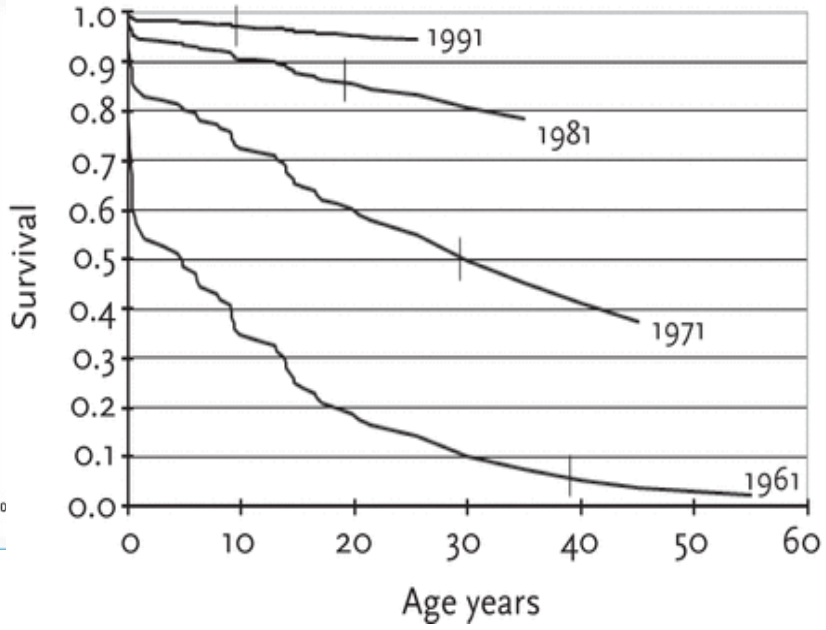


CFTR protein abnormal.
Chloride and H2O cannot pass freely.

Lbud14

Every decade has led to improved survival in CF patient cohorts worldwide.





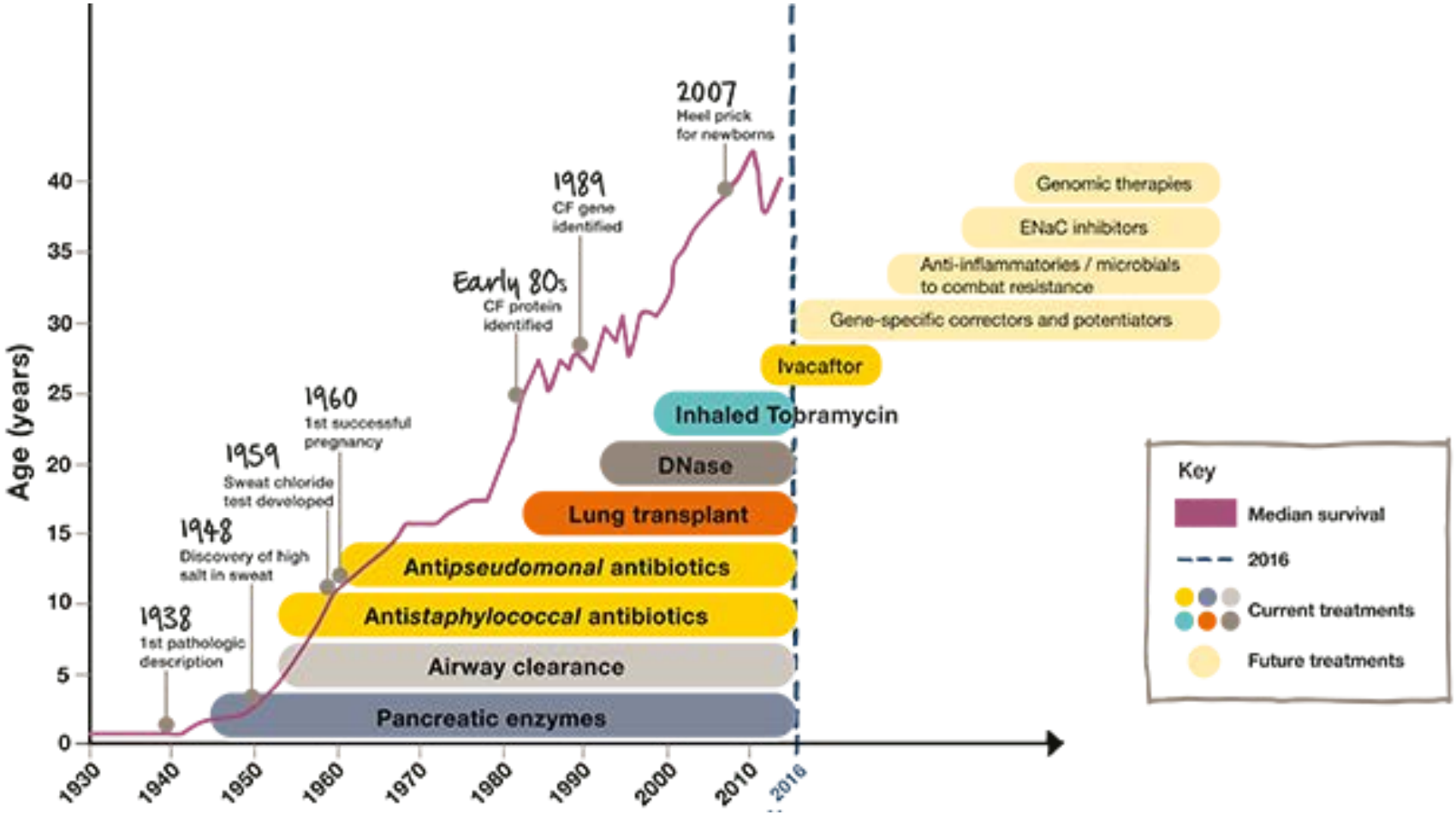
Canadian data.

Stephenson et al 2017.

Swedish data.

Lannefors et al 2002

This improvement has been built on a series of incremental advances in CF management.

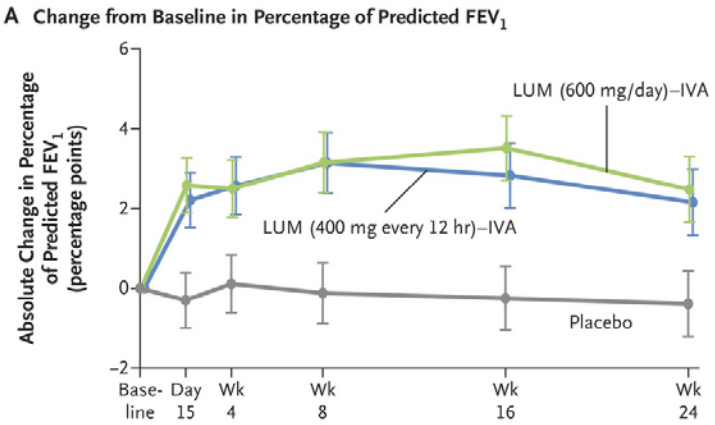


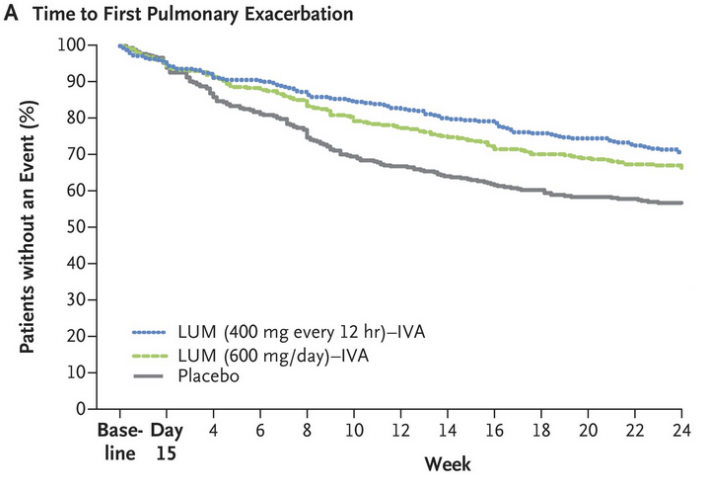
Cystic Fibrosis Trust

Advances in targeting the CFTR protein directly.

(Wainwright et al NEJM 2015)

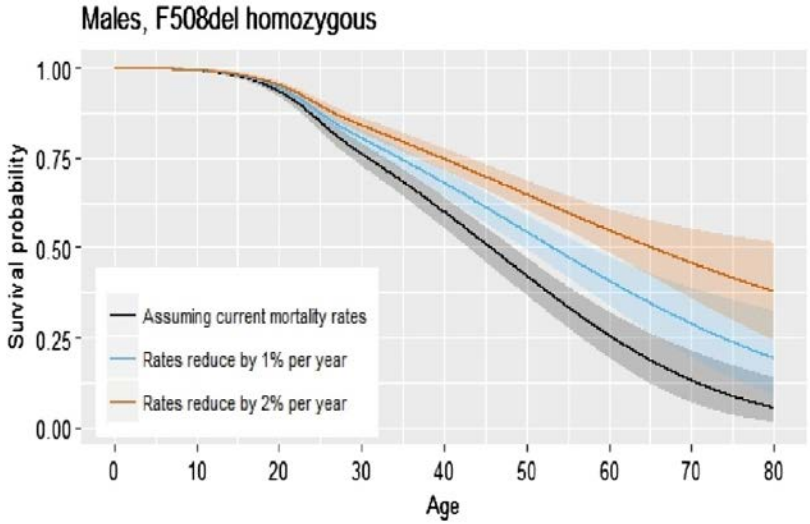
- Phe508de mutation most common: 45% CF homozygous.
- An example lumacaftor–ivacaftor (Orkambi). Combined CFTR corrector and potentiator.
- Rate of pulmonary events 30-39% lower.
- Complex results, and initially $259,000 a year. But undoubtedly a step forward.
- Other drugs targeting CFTR on the way.





If rates of progress continue, improvements in survival in CF will be substantial.

- Mortality rates dropped 2% a year 2006–2015.
- Median survival from birth in F508del homozygotes 46 years (male), 41 years (female).
- If survived to 30, median survival age rises to 52 (male), 49 (female).
- Over half of CF babies born today can expect to survive into at least their fifth decade.



Keogh et al 2018

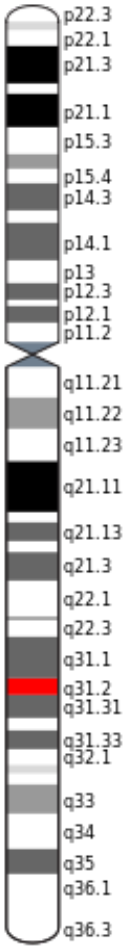
Gene editing and repair in CF?

- In principle possible to correct faulty genes in people living with CF.
- Still experimental, but has been achieved in other diseases.
- Two possible approaches:

-insert a normal gene in addition to the faulty ones

-edit the faulty gene by cutting out and replacing the abnormal section.

- In theory it would be possible to edit the early embryo so no CF. But ethical issues, and not currently legally possible.



CFTR gene
Chromosome 7

Chronic respiratory disease including asthma, COPD, CF: genes, environment, chance.

Wikimedia