What causes asthma? What we know, don't know and suspect

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Asthma is a chronic inflammatory disease of the lungs where the airways become so obstructed the sufferer struggles to breathe. It's vastly more prevalent in Western societies, and usually develops in childhood. But

what do we know about what causes it?

Given asthma is about five times more common in Western societies, this suggests lifestyle plays a major role. And as it usually develops in childhood, many studies have attempted to look at the events that transpired in infants who did or did not develop asthma by school age.

The immune system

A common finding in those who developed asthma is that they had experienced a severe respiratory viral infection or "viral bronchiolitis" in early life. Other studies have shown respiratory viruses trigger asthma exacerbations or "attacks" in those who already have asthma. So in already susceptible individuals, respiratory virus infections contribute to the onset, progression, and exacerbations of asthma.

Our immune system has a number of mechanisms to fight viruses. One of these is the production of proteins called interferons – so called because they interfere with viral replication. In some studies, cells from patients with asthma produced lower levels of interferons, suggesting this may make someone more susceptible to a respiratory virus, and then asthma.

It's also important to recognise not all asthma is the same. We now know there are different sub-types of the disease, which may have different causes.

The dominant subtype, which affects around 50% of asthmatics is referred to as "eosinophilic asthma". Research in the past two decades has led to the identification of a number of proteins found in abundance in people with eosinophilic asthma.

Several new therapies involving antibodies that neutralise or absorb these

proteins are now entering the market. Some are available now, including one called "anti-interleukin-5".

Importantly, some of these new drugs are effective in patients with severe asthma. Severe asthma is poorly controlled by mainstay treatments such as steroids, which work by reducing the inflammation of the airways.

Our saliva, breath and blood contain biomarkers (such as interleukin-5 and exhaled nitric oxide) that can tell a doctor which drugs may work best for us. But this remains imperfect, and we'll hopefully find better biomarkers in the future.

We don't know quite as much about the less dominant forms of asthma, but inroads are being made in this area too. One recent landmark study, for example, reported that including azithromycin (an antibiotic) as an add-on therapy reduced the number of exacerbations in patients with eosinophilic asthma, but also those with non-eosinophilic asthma.

It's doubtful the beneficial effects of azithromycin relate solely to its antibiotic activity, but these findings highlight the importance of the microbiota – the bugs that reside on our skin and in our lungs and gut.

The microbiota

The majority of known risk factors for asthma onset – for example, poor diet (low fibre/high sugar), urban living, smaller family size, Caesarean births, formula feeding and greater antibiotic use – affect the diversity of our microbiota.

In the late 80s an observation was put forward that younger siblings in large families have a lower risk of developing allergies, and this could be because they were exposed to more germs. This was known as the

"hygiene hypothesis".

The hygeine hypothesis is now thought to be more of a "microbiota hypothesis" as the microbiota assembles and matures in early life. Recent studies show infants who are at high risk of developing asthma have an imbalanced gut microbiota at one month of age.

Because the prevalence of asthma has increased so rapidly over the past 50 years, this means our genetic make-up alone cannot be responsible.

The composition of the microbiota can change rapidly (within days), contains 150 times more genes than our genome, and is heavily influenced by our mother's microbiota, particularly in early life. This is now placing the spotlight on Western lifestyle choices, and how these influence the metagenome (which is our genome together with the multitude of microbial genomes).

We now need to find out how the microbiota affects our immune system to confer protection or susceptibility to respiratory virus infections, and later asthma.

A number of elegant studies, largely performed in animal models, have demonstrated that diet affects the composition of the gut microbiota, which in turn, affects gut health but also all other organs and tissues.

This is because the feeding microbiota generates break-down products or "metabolites" that enter our blood stream. So these microbial byproducts can influence the development and maturation of our immune system, as well as non-immune cells, and thereby affect our immunity upon encounter with external exposures, such as a respiratory virus infection.

A study found treatment of mice with antibiotics (which disturb the microbiota) diminishes their ability to produce interferon proteins in

response to influenza virus infection.

And a recent study showed poor maternal diet in the third trimester of pregnancy increases the severity of viral bronchiolitis in the offspring. The investigators of this large study didn't explore whether this effect was associated with alterations to the microbiota, which is the likely explanation, and this is something we need to find out.

Once we know more about the link between asthma and the bugs that reside within and on us, we'll be better able to treat and hopefully prevent asthma.

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