OPEN ACCESS

Asthma, classical conditioning, and the autonomic nervous system – a hypothesis for why children wheeze

Gary James Connett

National Institute for Health Research, Southampton Biomedical Research Centre, Southampton Children's Hospital, Southampton, UK

Correspondence to
Professor Gary James Connett, National Institute for Health Research, Southampton Biomedical Research Centre, Southampton Children's Hospital, Southampton, UK; gary.connett@uhs.nhs.uk

Received 7 February 2023
Accepted 26 July 2023
Published Online First 30 August 2023

ABSTRACT

Paediatric asthma is an increasing global healthcare problem for which current treatments are not always effective. This review explores how abnormal triggering of the autonomic diving reflex might be important in explaining research findings and the real-world experience of asthma. It hypothesises that the way in which stress during pregnancy is associated with childhood asthma could be through effects on the developing nervous system. This results in increased parasympathetic responsiveness and specifically, excessive triggering of the diving reflex in response to wetting and cooling of the face and nose as occurs with upper airway infections and allergic rhinitis. In aquatic mammals the reflex importantly includes the contraction of airway smooth muscle to minimise lung volume and prevent nitrogen narcosis from diving at depth. Misfiring of this reflex in humans could result in the pathological airway narrowing that occurs in asthma. The diving reflex, and possibly also smooth muscle, is a vestigial remnant of our aquatic past. The hypothesis further suggests that classically conditioned reflex responses to neutral cues and contexts that were present at the same time as the stimuli that initially caused symptoms, become of themselves ongoing triggers of recurrent wheeze. Symptoms occurring in this way, irrespective of the presence of allergens and ongoing airway sensitisation, explain why allergen avoidance is poorly effective in alleviating wheeze and why asthma is made worse by stress. Interventions to suppress the diving reflex and to prevent reflex conditioned wheezing could result in more effective asthma management.

INTRODUCTION

Asthma is the most common chronic disease among children globally and the number of children affected is increasing in developing countries.[1 2] UK data from the Royal College of Physicians' national asthma audit suggests that children are presenting with more severe asthma attacks than recorded in previous audits.[3] UK asthma mortality is much higher than other European countries. These concerns have driven efforts to improve the delivery of asthma care.[4] Exploring new hypotheses about the cause of asthma might usefully result in changes in treatment to the benefit of patients. This paper explores the possibility that asthma might occur because of antenatally determined changes in autonomic development resulting in increased triggering of the parasympathetic components of the diving reflex and its subsequent triggering by classically conditioned reflex responses. Such a hypothesis might explain counterintuitive findings from research into asthma heritability, the role of allergy and the ineffectiveness of inflammometry.

Registry-based twin studies, using well-established methods to estimate the relative genetic (nature) versus environmental (nurture) determinants of asthma, suggest that genetic factors account for approximately 60%–80% of asthma susceptibility, with only a modest or no effect attributable to environmental effects shared between family members.[5] Despite such findings, genome-wide and epigenome-wide association studies fall short of explaining the disease's polygenic heritability.[6 7]

Atopy is highly associated with asthma, but there is little evidence that the association is causal. Studies comparing changes in asthma incidence within geographical locations over time show significant rises in the number of patients with asthma, with little change in the incidence of atopy and vice versa.[8] Authors of British Thoracic Society (BTS) asthma guidelines do not recommend allergen avoidance to treat asthma symptoms and highlight the paradoxical effects of removing cats and dogs from the homes of children with evidence of sensitisation to their pets.[9] Metanalyses of allergen avoidance confirm a lack of evidence for the benefits of allergen control in treating asthma and allergic rhinitis.[10 11] Such findings suggest that while allergically triggered symptoms might be important in initiating asthma, they are less important as an ongoing cause of symptoms.

While there is good evidence that airways inflammation is associated with the asthma phenotype, there are significant shortcomings in managing asthma according to indices of airways inflammation. Raised fractional exhaled nitric oxide (FeNO) levels in steroid-naive patients might usefully suggests an asthma diagnosis, but paediatric studies have found that such levels are insensitive and will miss up to 50% of affected children.[12] Randomised controlled trials consistently fail to demonstrate benefits for FeNO levels in decision making about the use of asthma therapies.[12] Routine measurement of FeNO as part of asthma care is not recommended in BTS/Scottish Intercollegiate Guidelines Network guidelines. While this failure of inflammometry to improve asthma outcomes is commonly attributed to poor adherence, it might also be due to the limited efficacy of high-dose versus low-dose steroids. Cochrane analyses of dose responses to inhaled corticosteroids identified 89 studies with

Check for updates

To cite: Connett GJ. *Arch Dis Child* 2024;**109**:462–467.

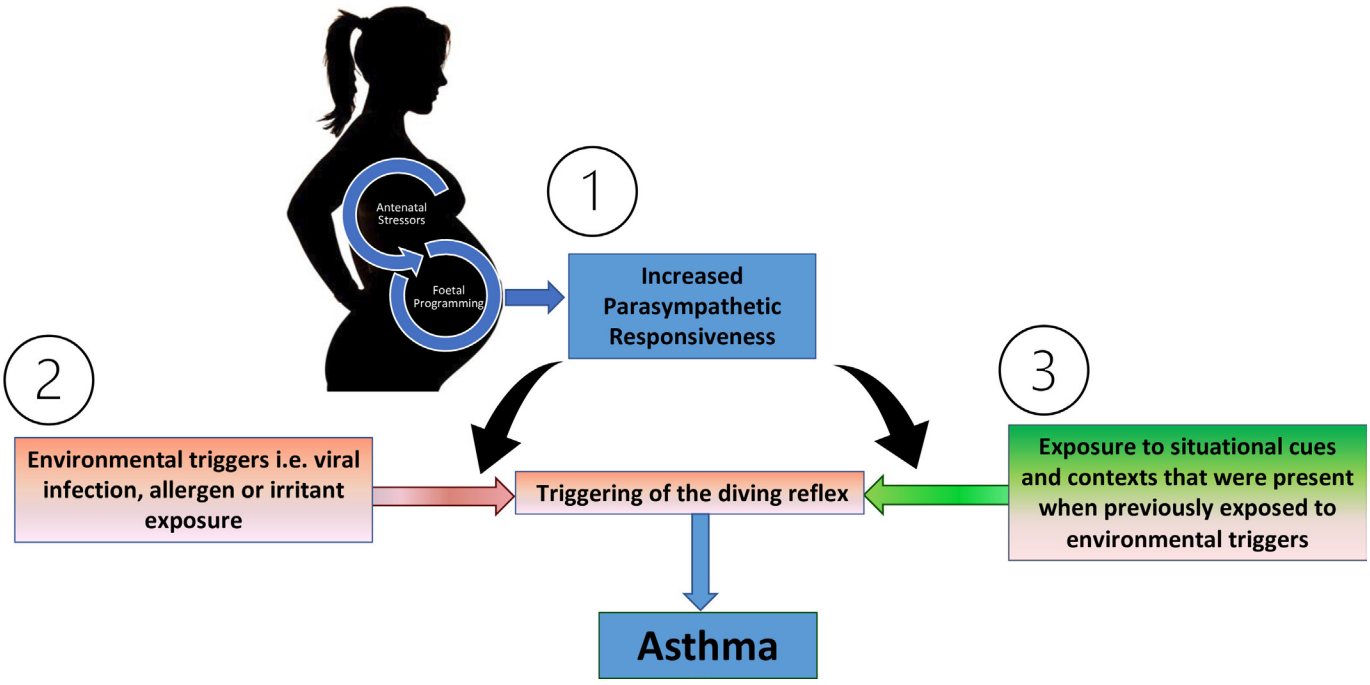

Figure 1 The autonomic basis for asthma. (1) Prenatal stressors alter autonomic development favouring parasympathetic pathways. (2) Increased vagal responsiveness after exposure to environmental triggers cause triggering of the diving reflex. (3) Situational cues and contexts cause reflex bronchoconstriction without the need for allergic sensitisation.

negative results for clinically important outcome measures and just one study suggesting high doses versus low doses of budesonide reduced acute exacerbations in severe asthma.[13–15]

These findings are difficult to explain within the prevailing narrative of asthma as a genetically determined, allergically driven, inflammatory disease process. The following hypothesis addresses these shortcomings. Three components are suggested as relevant to the development and persistence of asthma (figure 1). The first is the impact of maternal stressors on early life development during pregnancy. These stressors affect the antenatal development of the nervous system favouring increased parasympathetic stress responses. The second is the impact of this predisposition on the bronchoconstrictive component of the diving reflex as triggered by wetting and cooling of the face and nostrils. Third, classically conditioned autonomic reflexes result in recurrent wheezing. These reflexes occur in response to neutral stimuli that were present at the time of initial wheezy episodes.

Step 1: Antenatal stressors result in fetal programming favouring increased parasympathetic responsiveness

This hypothesis builds on the developmental origins of disease concept proposed by Barker.[16] His observation that nutritional indices at birth were associated with chronic diseases in later life, spurred many prospective cohort studies to identify the important risk factors for diseases across the life course. Antenatal stress has been consistently identified as an important risk factor for childhood asthma[17] but the cause is not clear.[18] Suggested mechanisms include effects on immune, neuroendocrine and oxidative stress systems. Effects on the development of the autonomic nervous system might also be important. Vulnerable fetuses, stressed in utero at a critical period for the development of autonomic homoeostatic mechanisms, could be predisposed to neurally derived mechanisms which, when triggered by postnatal factors, result in asthma.

An important component of acute asthma attacks is neurally driven contraction of bronchial smooth muscle via the vagus nerve. The anticholinergic drug ipratropium bromide works as a bronchodilator in addition to the effects of β-2 agonist drugs by blocking these neural pathways.[19] Heart rate variability indices have been used in many studies as a marker of parasympathetic responsiveness. These markers are associated with increased asthma severity.[20]

There is evidence suggesting the sympathetic part of the autonomic nervous system, (the classical 'fight or flight' response), is diminished in patients with asthma. While circulating epinephrine levels in heart failure, septicaemia and hypoglycaemia typically increase to 17 times above basal levels, in acute asthma attacks epinephrine levels have been reported to be at the lower end of the normal range.[21] Although findings are not consistent across all studies, patients with asthma have reduced adrenergic responses after exercise, antigen bronchoprovocation and hyperventilation.[22]

Antenatal stress might be an important confounder for other antenatal risk factors for asthma (table 1). For example, extreme preterm birth is highly associated with asthma.[23] While chronic lung disease of prematurity among such infants might adversely impact on lung growth and result in bronchial hyper-reactivity, these infants spend what would have been their third trimester ex utero. They have therefore been exposed to more stressful circumstances than most infants during this critical period for the development of the autonomic nervous system.[24] Studies characterising outcomes for autonomic function after preterm birth are inconsistent. However in one, a subgroup of premature infants who went on to have acute life-threatening events had distinct autonomic development trajectories characterised by increased parasympathetic and decreased sympathetic tone.[25] Similar trajectories might be important risk factors for asthma.

A maternal history of asthma is strongly associated with asthma in her offspring. Many studies report that anxiety

Table 1 Antenatal risk factors for the early life origins of asthma

Risk factors for wheeze in childhood	OR (95% CI)	Outcome
Maternal stress/stressors[17] *	1.56 (1.36 to 1.80)	Childhood asthma or wheeze
Maternal smoking[62] *	1.23 (1.12 to 1.36)	Asthma aged >5 years
Socioeconomic status[63] *	1.38 (1.37 to 1.39)	Asthma prevalence
Low birth weight[64] *	1.13 (1.01 to 1.27)	School-aged asthma
Maternal history of asthma* Paternal history of asthma[65] *	3.15 (2.53 to 3.93) 2.60 (2.28 to 2.96)	Asthma aged >5 years
Prematurity (22–31 weeks)* Prematurity (32–36 weeks)[23] *	4.92 (2.91 to 8.31) 2.04 (1.38 to 3.01)	Asthma aged 6–9 years
Exposure to inhaled pollutants[33]	1.28 (1.15 to 1.41)	Diagnosed asthma by 6 years (male only)
Emergency caesarean section* Elective caesarean section[66] *	1.18 (1.07 to 1.29) 1.23 (1.20 to 1.26)	Childhood asthma
Caesarean section without medical indication[67]	1.58 (1.17 to 2.13)	Asthma aged 4–12 years
Pre-eclampsia[68]	1.23 (1.07 to 1.43)	Ever or recurrent wheeze (up to 24 months)
Maternal obesity (BMI≥30 kg/m^2)[69]	1.36 (1.08 to 1.68)	Current asthma or wheeze (14 months to 16 years)

*Asterisk labelled references are the most recently published systematic reviews or metanalyses for antenatal risk factors. Non-asterisked references are case series addressing risk factors for which there are no published systematic reviews.
BMI, body mass index.

disorders are more common in patients with asthma and particularly among women. Anxiety increases the perception of respiratory symptoms and thus the likelihood of an asthma diagnosis.[26] Although smokers state that cigarettes help them relax, there is good evidence that tobacco dependency is associated with higher stress levels.[27] There are similar associations for obesity[28] and pre-eclampsia.[29]

Although it has been suggested that the association between caesarean section (CS) and asthma might be due to changes in microbiota, recent research suggests that maternal vaginal strains make up a small and transient fraction of the neonatal intestinal microbiota after birth.[30] A systematic review has shown that women who request a CS have significantly raised anxiety and depression.[31] These feelings are not alleviated by them knowing they can have their chosen mode of delivery. There are many confounding medical factors determining whether women opt for a CS, but the only published study assessing the risk of childhood asthma in women opting for CS without medical indication, had a higher OR for childhood asthma than all other CS studies (OR 1.58; 95% CI 1.17 to 2.13).[31]

Exposure to air pollutants is increasingly recognised as having adverse respiratory health effects, but thus far antenatal exposure appears to only have a weak association with subsequent asthma[32] except in male offspring with mothers who had experienced antenatal stress.[33]

Step 2: Increased vagal responsiveness after exposure to environmental triggers results in an exaggerated diving reflex

The parasympathetic nervous system subserves more complex functions than 'rest and digest' as is commonly popularised. It is active in many autonomic reflexes including the diving reflex. This is present in all mammals. It is greater in infants, who instinctively trigger the response when submerged, and aquatic mammals. In clinical settings, cold water facial immersion is used to trigger the reflex to treat supraventricular tachycardia. The resulting bradycardia is part of an adaptive survival response to maximise time spent underwater.[34] The reflex is triggered by chilling or wetting the nostrils and face. Studies in rats have shown how the reflex is initiated by excitation of nerves in the anterior nasal passages.[35]

Less well appreciated is that bronchoconstriction is part of the diving reflex. Reducing lung volume through airway narrowing reduces the systemic absorption of nitrogen when diving at depth to prevent nitrogen narcosis—the bends.[36] There is no good explanation for why humans and other land mammals have smooth muscle in their airways. It might be that its presence is an evolutionary remnant of our aquatic past. The diving reflex in humans, when exaggerated by increased parasympathetic responsiveness, might be the mechanism whereby bronchospasm occurs in relation to being exposed to cooling and wetting of the face and nostrils as occurs after coryzal or allergic symptoms.

Bradycardia, as elicited by the diving reflex, is increased in a subgroup of patients with asthma compared with non-asthmatic controls and decreases in heart rate are associated with the underlying degree of hyper-responsiveness measured by methacholine challenge.[37] One small study has demonstrated that bronchoconstriction is also a component of the diving response in man but whether this occurs to a greater extent in patients with asthma has not been studied.[38] Asthma prevalence is high among elite swimmers and winter sports athletes, but this is thought to be largely an effect of breathing at high ventilation rates and volumes.[39] Swimming in public pools is also associated with increased asthma but this is likely to be due to chlorine exposure. Interestingly, there is emerging evidence that open water swimming alleviates asthma.[40] This might be due to improvements in mental well-being but might also occur through resetting of the diving reflex after repeat immersions in the cold water environment within which it originated.

The most important postnatal risk factors for asthma are wheezy illnesses in early childhood, often caused by rhinovirus, and evidence of allergic sensitisation. Initial wheezy illnesses are unresponsive to bronchodilators.[41] Why the pathophysiology changes, and reversible smooth muscle contraction becomes a cause of recurrent viral-associated wheeze, has not been explained. It is possible that initial infections predispose to the development of reflex vagal bronchoconstriction in response to further episodes of wetting of the nostrils. The association between asthma and allergic rhinitis might also be due to wetting of the nostrils by nasal secretions.

Step 3: Situational cues and contexts cause recurrent, classically conditioned activation of the diving reflex

Classical conditioning is a form of associative learning. Subjects learn something about the causal fabric of their environment or, in an experimental setting, the relationship of stimuli. Stimuli can be arranged so that one stimulus provides information about the likely occurrence of another. Over time learning becomes incorporated into the nervous system's autonomic brainstem pathways and causes involuntary physiological changes in response to what were previously neutral stimuli.

Classical conditioning is also known as Pavlovian conditioning in recognition of research by the Russian physiologist Ivan Pavlov.[42] He elicited an involuntary parasympathetic reflex; salivation, in response to a previously neutral stimulus; the sound of a bell. Similarly, asthma could be an involuntary parasympathetic reflex in response to neutral stimuli present at a time

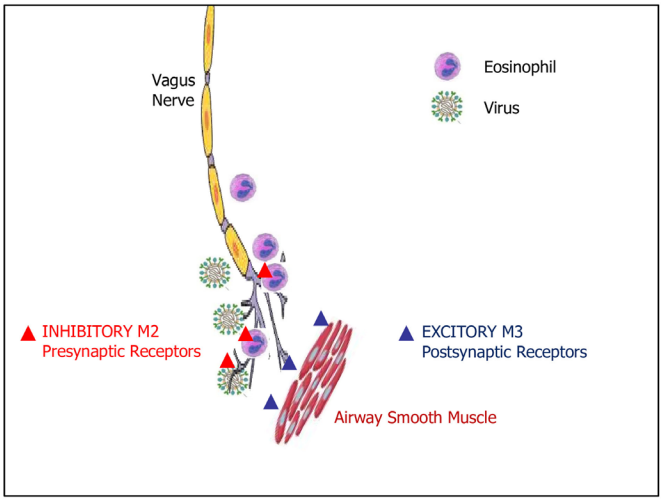

Figure 2 Vagal nerve impulses excite M3 post synaptic receptors and cause smooth muscle contraction.Viruses and eosinophils increase cholinergic induced airways obstruction through blocking M2 receptor inhibition of the vagus nerve.

when airways obstruction occurred after infection or allergen exposure.

This type of reflex is well characterised in guinea pig research models of asthma.[43–45] Animals can be sensitised to egg albumen by intraperitoneal injections of egg white. Two weeks later, placing the animals in a chamber and exposing them to a fine mist of egg white produces asthma-like symptoms. Most develop tolerance to the mist after repeated exposure but among those that don't, many develop respiratory symptoms after inhaling saline mist and eventually just by being in the chamber. This is an example of cue and context conditioning. The cue is the saline aerosol mist, and the context is the chamber in which the mist had previously been given. Smaller chambers cause more severe symptoms.

Studies have used other neutral stimuli as cues introduced at the same time as the albumen mist including bells and smells. Responses to these stimuli are accompanied by rises in histamine levels and prevented by atropine injection.[41] Wheezing is greater in stressed animals but stressing animals without exposure to a conditioned stimulus does not cause respiratory symptoms. Such findings have implications for the way in which stress during childhood might exacerbate wheezing but is not the underlying cause.

Similar cue and context conditioning occurs in adults with allergic rhinitis after just one learning session exposing subjects to a strong smell at the same time as an unconditioned stimulus (allergen) to which the subjects were sensitised.[46] Such studies have not been replicated in patients with asthma but patients with asthma have been induced to have asthma attacks by suggestion after inhaling saline which they believe is a solution of an allergen to which they are allergic.[47] Symptoms occurred in almost half of those challenged and reversed after inhaling normal saline which the subjects were told was a bronchodilator. Patients with asthma, having associated inhaling specific allergens with the occurrence of asthma attacks, might reasonably be assumed to have suffered airways obstruction through a classically conditioned reflex.

The significant improvements in lung function in the placebo arms of randomised controlled asthma trials might also be explained as a cue conditioned response to taking an inhaler for which there is belief in there being a high probability of effectiveness. There are likely to be individuals who continue to have asthma symptoms because of ongoing allergic sensitisation, but the extent to which this occurs might be less than appreciated.[9]

Implications

If asthma has a significant neurobehavioural component, the highly inheritable nature of asthma, as suggested by twin studies in which identical twins are far more likely to both have asthma than non-identical twins, could be due to mimicry. While psychologists define mimicry as the unconscious automatic repetition of behaviour performed by others, mimicry can also result in the repetition of autonomic responses.[48 49] Identical twins are more empathic to each other than non-identical twins. An identical twin is therefore more likely to have autonomically driven bronchoconstriction than a non-identical twin when confronted by their wheezy sibling. Such a mechanism might explain why the heritability of asthma cannot be explained genetically.[5]

While allergic nasal symptoms as a trigger for the diving reflex might in part explain the relationship between atopy and asthma, this relationship is far more complex. There is now increasing epidemiological evidence suggesting that the atopic march's prevalence has been overstated and that the hygiene hypothesis is incorrect. These findings have reignited discussion about alternative models to better explain the pathophysiological and epidemiological processes that result in what may or may not be ongoing allergic disease.[50]

There is a strong association between stress and asthma but the extent to which this occurs in developing countries and the associated morbidity is underappreciated.[51] Similarly, there is evidence for an association between post-traumatic stress disorders and asthma most clearly demonstrated among 9/11 responders to the destruction of the twin towers in New York.[52] In the few studies that have investigated the phenomena, asthma is increased in war zones.[53] Mirroring the association between inequality and poor mental health, there is an association between asthma and increasing inequality at a national level.[54] These data are consistent with the way in which asthma is increasingly recognised in many parts of the developing world and becoming more severe in developed countries where young people increasingly suffer from stress-related mental health problems.

Vagally induced bronchoconstriction is exacerbated by viral infections[55] and eosinophil mediators.[56] The anti-inflammatory benefits of inhaled corticosteroids could be through downregulating such mechanisms. The lack of a dose response for inhaled corticosteroids[57] could be because these drugs do not prevent ongoing reflex vagal excitation of smooth muscle. The effectiveness of precision biologics might be a result of anti-inflammatory effects that restore presynaptic M2 receptor suppression of vagal activity (figure 2).

High doses of anticholinergics are effective adjuncts to β-2 agonists for acute asthma but are less effective than β-adrenergics. This is because they act on the neurogenic cause of bronchoconstriction as opposed to directly reversing the contraction of smooth muscle. Regular use of the anticholinergic tiotropium for chronic asthma has modest clinical benefits although it has been shown to be as effective as long-acting β-2 agonists in preventing symptoms in adults.[58] The limited efficacy of anticholinergics is probably due to insufficient dose and the non-selective blocking of receptors that inhibit the vagal nerve as well as those causing smooth muscle contraction (figure 2).[59 60] The development of selective M3 postsynaptic receptor antagonists might result in more effective treatment.[61]

CONCLUSION

This hypothesis is consistent with much of what is known about asthma. The evidence base in support of it is limited but studies could readily be done to confirm or refute it. These might usefully further characterise how the autonomic nervous system is altered in patients with asthma, the extent to which bronchoconstriction exists as a component of the diving reflex in patients with asthma, and whether cue and context conditioning occurs in the same way it has been demonstrated in allergic rhinitis. Interventional studies to suppress the diving reflex and classically conditioned wheezing might result in new effective treatments with less reliance on medication.

X Gary James Connett @garyconnett

Acknowledgements The author thanks Professor Stephen Holgate for his encouragement to pursue this hypothesis, Dr Vanessa Hewertson for her help in developing it and Dr Woolf Walker for reviewing the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing is not applicable as no data sets were generated and/or analysed for this study.

ORCID iD

Gary James Connett http://orcid.org/0000-0003-1310-3239

REFERENCES

1 WHO. Human Papillomavirus vaccines: WHO position paper. *Biologicals* 2009;37:338–44.
2 Dharmage SC, Perret JL, Custovic A. Epidemiology of asthma in children and adults. *Front Pediatr* 2019;7:246.
3 RCP. Available: https://www.nacap.org.uk/nacap/welcome.nsf/reportsPA.html2021
4 HSIB. 2021. Available: https://www.hsib.org.uk/investigations-cases/management-chronic-asthma-children-aged-16-years-and-under/
5 Thomsen SF. Exploring the origins of asthma: lessons from twin studies. *Eur Clin Respir J* 2014;1.(Suppl 1)
6 Vicente CT, Revez JA, Ferreira MAR. Lessons from ten years of genome-wide Association studies of asthma. *Clin Transl Immunology* 2017;6:e165.
7 Sheikhpour M, Maleki M, Ebrahimi Vargoorani M, *et al*. A review of epigenetic changes in asthma: methylation and Acetylation. *Clin Epigenetics* 2021;13:65.
8 Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to Atopy *Thorax* 1999;54:268–72.
9 British Thoracic Society and Scottish Intercollegiate Guidelines Network (SIGN). British guideline on the management of asthma. A national clinical guideline [SIGN publication no.158]. n.d. Available: https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/
10 van Boven FE, de Jong NW, Braunstahl G-J, *et al*. A meta-analysis of baseline characteristics in trials on mite Allergen avoidance in Asthmatics: room for improvement. *Clin Transl Allergy* 2020;10:2.
11 Tomé M, Lourenço O. Avoidance measures for patients with allergic rhinitis: A Scoping review. *Children (Basel)* 2023;10:300.
12 Gaillard EA, Kuehni CE, Turner S, *et al*. European respiratory society clinical practice guidelines for the diagnosis of asthma in children aged 5-16 years. *Eur Respir J* 2021;58:2004173.
13 Adams NP, Bestall JC, Jones P, *et al*. n.d. Beclomethasone at different doses for chronic asthma. *Cochrane Database Syst Rev*;1999.
14 Adams NP, Bestall JC, Jones P, *et al*. Fluticasone at different doses for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2008;2008:CD003534.
15 Adams N, Bestall J, Jones PW. Budesonide at different doses for chronic asthma. *Cochrane Database Syst Rev* 2001;2000:CD003271.
16 Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* 1986;1:1077–81.
17 van de Loo KFE, van Gelder MMHJ, Roukema J, *et al*. Prenatal maternal psychological stress and childhood asthma and wheezing: a meta-analysis. *Eur Respir J* 2016;47:133–46.
18 Lee A, Wright RJ. Prenatal stress and childhood asthma risk: taking a broader view. *Eur Respir J* 2016;47:406–9.
19 Griffiths B, Ducharme FM. Combined inhaled Anticholinergics and Short-Acting Beta2-Agonists for initial treatment of acute asthma in children. *Cochrane Database Syst Rev* 2013;2013:CD000060.
20 Emin O, Esra G, Aysegül D, *et al*. Autonomic nervous system dysfunction and their relationship with disease severity in children with Atopic asthma. *Respir Physiol Neurobiol* 2012;183:206–10.
21 Ind PW, Causon RC, Brown MJ, *et al*. Circulating catecholamines in acute asthma. *BMJ* 1985;290:267–9.
22 Barnes PJ. Endogenous catecholamines and asthma. *J Allergy Clin Immunol* 1986;77:791–5.
23 He H, Butz A, Keet CA, *et al*. Preterm birth with childhood asthma: the role of degree of Prematurity and asthma definitions. *Am J Respir Crit Care Med* 2015;192:520–3.
24 Schneider U, Bode F, Schmidt A, *et al*. Developmental milestones of the autonomic nervous system revealed via longitudinal monitoring of fetal heart rate variability. *PLoS One* 2018;13:e0200799.
25 Nino G, Govindan RB, Al-Shargabi T, *et al*. Premature infants Rehospitalized because of an apparent life-threatening event had distinctive autonomic developmental Trajectories. *Am J Respir Crit Care Med* 2016;194:379–81.
26 ten Thoren C, Petermann F. Reviewing asthma and anxiety. *Respir Med* 2000;94:409–15.
27 Parrott AC. Does cigarette smoking cause stress *Am Psychol* 1999;54:817–20.
28 Scott KA, Melhorn SJ, Sakai RR. Effects of chronic social stress on obesity. *Curr Obes Rep* 2012;1:16–25.
29 Vianna P, Bauer ME, Dornfeld D, *et al*. Distress conditions during pregnancy may lead to pre-Eclampsia by increasing Cortisol levels and altering lymphocyte sensitivity to glucocorticoids. *Med Hypotheses* 2011;77:188–91.
30 Fricke WF, Ravel J. More data needed on neonatal Microbiome seeding. *Microbiome* 2022;10:88.
31 Olieman RM, Siemonsma F, Bartens MA, *et al*. The effect of an elective cesarean section on maternal request on Peripartum anxiety and depression in women with childbirth fear: a systematic review. *BMC Pregnancy Childbirth* 2017;17:195.
32 Wang B, Chen H, Chan YL, *et al*. Why do Intrauterine exposure to air pollution and cigarette smoke increase the risk of asthma *Front Cell Dev Biol* 2020;8:38.
33 Lee A, Leon Hsu H-H, Mathilda Chiu Y-H, *et al*. Prenatal fine particulate exposure and early childhood asthma: effect of maternal stress and fetal sex. *J Allergy Clin Immunol* 2018;141:1880–6.
34 Godek D. Physiology diving reflex. In: *StatPearls*. Treasure Island (FL), 2022.
35 McCulloch PF, Lahrman KA, DelPrete B, *et al*. Innervation of the nose and nasal region of the rat: implications for initiating the mammalian diving response. *Front Neuroanat* 2018;12:85.
36 Kooyman GL, Ponganis PJ. The physiological basis of diving to depth: birds and mammals. *Annu Rev Physiol* 1998;60:19–32.
37 Sturani C, Sturani A, Tosi I. Parasympathetic activity assessed by diving reflex and by airway response to Methacholine in bronchial asthma and rhinitis. *Respiration* 1985;48:321–8.
38 Mukhtar MR, Patrick JM. "Bronchoconstriction: a component of the 'diving response' in man". *Eur J Appl Physiol Occup Physiol* 1984;53:155–8.
39 Mountjoy M, Fitch K, Boulet L-P, *et al*. Prevalence and characteristics of asthma in the aquatic disciplines. *J Allergy Clin Immunol* 2015;136:588–94.
40 Greenfield K, Verling W, Larcombe T, *et al*. n.d. Case report: open water swimming as a possible treatment for asthma. *Front Med*;10.
41 Jackson DJ, Gangnon RE, Evans MD, *et al*. Wheezing Rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008;178:667–72.
42 Rehman I, Mahabadi N, Sanvictores T, *et al*. Classical conditioning. In: *StatPearls*. Treasure Island (FL), 2022.
43 Justesen DR, Braun EW, Garrison RG, *et al*. Pharmacological differentiation of allergic and classically conditioned asthma in the guinea pig. *Science* 1970;170:864–6.
44 Ottenberg P, Stein M, Lewis J, *et al*. Learned asthma in the guinea pig. *Psychosomatic Medicine* 1958;20:395–400.
45 Smit M, Zuidhof AB, Bos SIT, *et al*. Bronchoprotection by Olodaterol is synergistically enhanced by Tiotropium in a guinea pig model of allergic asthma. *J Pharmacol Exp Ther* 2014;348:303–10.
46 Besedovsky L, Benischke M, Fischer J, *et al*. Human sleep consolidates allergic responses conditioned to the environmental context of an Allergen exposure. *Proc Natl Acad Sci U S A* 2020;117:10983–8.
47 Luparello T, Lyons HA, Bleecker ER, *et al*. Influences of suggestion on airway reactivity in asthmatic subjects. *Psychosom Med* 1968;30:819–25.
48 Prochazkova E, Kret ME. Connecting minds and sharing emotions through Mimicry: A Neurocognitive model of emotional contagion. *Neurosci Biobehav Rev* 2017;80:99–114.

49 Ardizzi M, Umiltà MA, Evangelista V, *et al*. Less Empathic and more reactive: the different impact of childhood Maltreatment on facial Mimicry and vagal regulation. *PLoS One* 2016;11:e0163853.
50 Aw M, Penn J, Gauvreau GM, *et al*. Atopic March: Collegium Internationale Allergologicum update 2020. *Int Arch Allergy Immunol* 2020;181:1–10.
51 Cruz ÁA, Stelmach R, Ponte EV. Asthma prevalence and severity in low-resource communities. *Curr Opin Allergy Clin Immunol* 2017;17:188–93.
52 Kim H, Baidwan NK, Kriebel D, *et al*. Asthma among world trade center first responders: A qualitative synthesis and bias assessment. *IJERPH* 2018;15:1053.
53 Boulet LP. War-time asthma: lessons from Syria. *J Thorac Dis* 2017;9:3412–4.
54 Connett G, Rudrappa S. P150 Increased national mortality rates for asthma are associated with increased financial inequality as calculated by the GINI index. British Thoracic Society Winter Meeting 2019, QEII Centre, Broad Sanctuary, Westminster, London SW1P 3EE, 4 to 6 December 2019, Programme and Abstracts; December 2019
55 Jacoby DB, Xiao HQ, Lee NH, *et al*. Virus- and interferon-induced loss of inhibitory M2 muscarinic receptor function and gene expression in cultured airway parasympathetic neurons. *J Clin Invest* 1998;102:242–8.
56 Drake MG, Lebold KM, Roth-Carter QR, *et al*. Eosinophil and airway nerve interactions in asthma. *J Leukoc Biol* 2018;104:61–7.
57 Beasley R, Harper J, Bird G, *et al*. Inhaled corticosteroid therapy in adult asthma. time for a new therapeutic dose terminology. *Am J Respir Crit Care Med* 2019;199:1471–7.
58 Wechsler ME, Yawn BP, Fuhlbrigge AL, *et al*. Anticholinergic vs long-acting beta-agonist in combination with inhaled corticosteroids in black adults with asthma: the BELT randomized clinical trial. *JAMA* 2015;314:1720–30.
59 Fryer AD, Jacoby DB. Muscarinic receptors and control of airway smooth muscle. *Am J Respir Crit Care Med* 1998;158(5 Pt 3):S154–60.
60 Moulton BC, Fryer AD. Muscarinic receptor antagonists, from folklore to pharmacology; finding drugs that actually work in asthma and COPD. *Br J Pharmacol* 2011;163:44–52.
61 Pavord ID, Beasley R, Agusti A, *et al*. After asthma: redefining Airways diseases. *Lancet* 2018;391:350–400.
62 Burke H, Leonardi-Bee J, Hashim A, *et al*. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. *Pediatrics* 2012;129:735–44.
63 Uphoff E, Cabieses B, Pinart M, *et al*. A systematic review of socioeconomic position in relation to asthma and allergic diseases. *Eur Respir J* 2015;46:364–74.
64 Sonnenschein-van der Voort AMM, Arends LR, de Jongste JC, *et al*. Preterm birth, infant weight gain, and childhood asthma risk: a meta-analysis of 147,000 European children. *J Allergy Clin Immunol* 2014;133:1317–29.
65 Lim RH, Kobzik L, Dahl M. Risk for asthma in offspring of asthmatic mothers versus fathers: a meta-analysis. *PLoS One* 2010;5:e10134.
66 Darabi B, Rahmati S, HafeziAhmadi MR, *et al*. The association between Caesarean section and childhood asthma: an updated systematic review and meta-analysis. *Allergy Asthma Clin Immunol* 2019;15:62.
67 Chu S, Chen Q, Chen Y, *et al*. Cesarean section without medical indication and risk of childhood asthma, and Attenuation by Breastfeeding. *PLoS One* 2017;12:e0184920.
68 Zugna D, Galassi C, Annesi-Maesano I, *et al*. Maternal complications in pregnancy and wheezing in early childhood: a pooled analysis of 14 birth cohorts. *Int J Epidemiol* 2015;44:199–208.
69 Forno E, Young OM, Kumar R, *et al*. Maternal obesity in pregnancy, gestational weight gain, and risk of childhood asthma. *Pediatrics* 2014;134:e535–46.