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THE GUT-LUNG AXIS AND NEUROIMMUNE DYSREGULATION: EXPLORING THE ROLE OF GUT MICROBIOME DYSBIOSIS IN CHILDHOOD ASTHMA AND AUTISM SPECTRUM DISORDERS

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ABSTRACT Autism is the fastest-growing developmental disability in the world. Gut microbiota is either directly or indirectly linked to autism..Therapeutic approaches that target microbiota can help in the management of autism.Emerging research underscores the pivotal role of the gut microbiome in modulating immune responses and neurodevelopment. Dysbiosis, or imbalance in gut microbial communities, has been implicated in the pathogenesis of various conditions, including childhood asthma and autism spectrum disorders (ASD). This article explores the interconnectedness of the gut-lung axis and neuroimmune pathways, highlighting how alterations in gut microbiota composition can influence respiratory health and neurodevelopmental outcomes.

KEYWORDS :

INTRODUCTION

Ischemic stroke is an acute cerebrovascular disease caused by cerebral artery occlusion. Although this disease has a great impact on public health, its exact etiological and pathological processes are not directed and precise (1)

Currently, researchers believe that a complex series of neuropathological events, such as excitotoxicity, oxidative stress, neuroinflammation, apoptosis, immune response, acidosis, and mitochondrial damage, result in brain damage in ischemic stroke (2,3)

Severe changes in local circulation lead to the accumulation of cell debris, and extensive infiltration of immune cells in the brain tissue also induces the secondary progression of cell injury. However, there is no single answer to the mechanisms of ischemic stroke, because of which there is considerable ambiguity regarding the direction of stroke treatment (4)

Despite alternative treatments such as thrombus removal to allow tissue reperfusion, the limited treatment window and inadequate response lead to the poor prognosis of many patients.

Ischemia of the local brain tissue has been regarded as causing significant inflammation and has been studied in the past(5)

From the perspective of the brain, resident glial cells act as the main immune defense by eliminating injured or necrotic parts, while the intestinal tract and lung also assist the process via additional pathways, by translocation of immune cells and changing the central response through some metabolites (6).

Normally, microglia dynamically supervise changes in brain homeostasis and can be activated to eliminate cellular debris and release abundant cytokines, neurotransmitters, or other molecules to save both neurons and synapse functions (7)

Previous studies have fully distinguished the roles between M1 and M2 phenotypes, and suggested that M2 microglia are the earliest cell type to be activated when the stroke occurs (8,9)

While some studies have confirmed the proinflammatory role of M1 microglia at the beginning of ischemic stroke, it should be made clear that such discrepancy probably depends on the primary ischemia condition, reperfusion time, lesion location, and research time (10)

Additionally, another essential role of microglia is the interaction with endothelial cells, astrocytes, and oligodendrocytes (11)

Activated microglia will induce A1-reactive astrocytes in vitro and in vivo by releasing interleukin (IL)-1α, tumor necrosis factor-α (TNF-α), and complement component subunit 1q (12)

The Autism and Developmental Disabilities Monitoring Network reported that the estimated prevalence of ASD increased from 0.67% in 2000 to 1.46% in 2012b (13).

Autism spectrum disorder (ASD) is a complex neuro-developmental disorder characterized by deficits in social interaction, language, and communication, as well as the presence of restricted repetitive behaviors.

The prevalence of ASD in US children has steadily increased over the past decades (14)

A recent study using data from the National Health Interview Survey (NHIS) found that the prevalence of ASD in US children aged 3 to 17 years was 2.24% in 2014, 2.41% in 2015, and 2.76% in 2016 (15)

The etiology of ASD involves both genetic and environmental risk factors, and it is estimated that up to 40% to 50% of the variance in ASD liability might be attributed to environmental risk factors (16)

Immunologic dysfunction is a potential link between environmental risk factors and ASD (17)

Symptoms of immune function abnormalities, such as frequent infections and increased prevalence of autoimmune conditions, were frequently reported among children with ASD (18,19)

Available evidence has shown that early-life immune activation can adversely influence certain neuro-developmental processes, such as neuron growth, through multiple pathways, including altered expression of cytokines and chemokines (20)

Gut Microbiota

Microbiota in general refers to commensal, pathogenic, and symbiotic microbes that are found in multicellular organisms, which include not just bacteria but also other microbes such as protists, fungi, and viruses. (21)

The gut acts as the major habitat of human microbiota and depicts microbial populations inhabiting the length and width of the mammalian gastrointestinal (GI) tract. The human gut consists of approximately 500–1000 bacterial species, and healthy gut flora is largely responsible for maintaining an individual's overall health status (22)

There are manifold functions performed by the gut microbiota that include: maintaining the integrity of the intestinal barrier, stimulating regeneration of epithelium through the production of short-chain fatty acids (SCFAs) and some other metabolites, leading to the production of mucus, fermentation of non-digestible carbohydrates, and a lot more (23,24)

Enteric Nervous System--Second brain

Recent studies on the gut–brain axis suggested that the gut contains millions of nerve cells, eventually forming an extensive network called the enteric nervous system (ENS). This enteric nervous system is also considered our second brain (25)

The ENS and the central nervous system (CNS) are mainly connected via the vagus nerve and form the gut–brain axis (26)

The communications within the gut–brain axis occur through the autonomic nervous system, enteric nervous system, neurotransmitters, hormones, and immune responses (27)

Neurotransmitters produced in the gut influence our emotions by regulating the gut–brain axis. Around 90% of neurotransmitters, such as serotonin, are produced in the gut (28)

The human gut microbiome consists of trillions of bacterial cells, which are 10-fold more significant than human body cells (29)

The average human gut contains 1 kg of diverse groups of bacteria that mostly perform beneficial activities, often involved in metabolite production and transportation, and maintenance of gut homeostasis (30,31)

Earlier, the majority of microbiota could not be classified by traditional cultural techniques. Researchers have overcome this limitation by using next-generation sequencing technology and metagenomic sequencing to identify unculturable microorganisms(32)

Our intestines harbor numerous beneficial bacteria that generate many neurotransmitters and active metabolites in the gut by utilizing the consumed foods. The essential amino acid tryptophan found in food acts as a precursor of a neurotransmitter called serotonin. Over 1%–2 % of Dietary tryptophan is converted into serotonin(33)

Beneficial gut bacteria such as Bifidobacterium infantis convert tryptophan into serotonin, regulating emotions and behavior(34)

Clostridium sporogenes increases the production of tryptophan metabolites called indole-3-propionic acid (IPA), a bioactive molecule that increases the production of antioxidant and neuroprotectant molecules inside the gut (35)

The gut can also be invaded by various pathogenic microbes, leading to the development of gastrointestinal problems following the presence of Clostridium bolteae (36,37)

Asthma--Autism

Asthma, a chronic inflammatory disorder of the airways, affects approximately 10% of children globally, making it one of the most prevalent childhood chronic diseases (38)

With a multifactorial etiology involving genetic and environmental factors, asthma poses a substantial global health burden (39)

The diagnosis of asthma in children younger than 2 years of age poses a considerable challenge due to the absence of age-specific diagnostic tools (40)

Additionally, accurately predicting the severity of asthma remains an ongoing obstacle in effective asthma management (41)

The complex pathogenesis of asthma also contributes to the absence of well-defined therapeutic strategies, primarily stemming from an incomplete understanding of the underlying mechanisms (42)

Recent studies have shed light on the interplay between the gut microbiota and the innate and adaptive immune systems, revealing their potential as crucial determinants in the etiology of asthma (43,44)

There is a well-established relationship between the trillions of microbes that inhabit the human gut and organism-level health.(45)

Animal studies have provided compelling evidence that the gut microbiota and its metabolites play an influential role in the development of allergy disorders, particularly in infancy.(46,47)

Asthma and autism are distinctly different medical conditions. Asthma is a chronic respiratory disease, while autism is a developmental disorder. There is some evidence that autism spectrum disorder (ASD) frequently co-occurs with immune-mediated conditions, including asthma. Multiple studies have found that autism spectrum disorder (ASD) can co-occur with certain immune-mediated conditions, including asthma. Other studies have found that children with asthma may have a slightly higher risk of developing autism compared to those without asthma. Research has also looked at common factors

that may play a role in the development of both autism and allergic diseases, such as maternal asthma and allergies, gut microbiome imbalance, diet, diabetes during pregnancy, exposure to air pollution, and sleep disturbances. There is also research that suggests an asthma-autism link may begin during pregnancy with the use of certain asthma medications.

Gut Microbiome and Childhood Asthma

Asthma is a chronic inflammation of the lining of the lungs' airways. It makes these airways contract easily. Several studies have demonstrated that early-life gut microbiome composition significantly impacts the risk of developing asthma. A systematic review indicated that higher bacterial diversity in the gut is protective against asthma in children. Conversely, reduced diversity and specific microbial profiles have been linked to increased asthma risk. Notably, colonization by Clostridium difficile in infancy has been associated with wheezing and asthma development by school age. Furthermore, the presence of bacteria such as Faecalibacterium, Lachnospira, Veillonella, and Rothia (collectively referred to as FLVR) in early life has been inversely correlated with asthma risk, suggesting their potential protective role.

Gut Microbiome and Autism Spectrum Disorders

Autism Spectrum Disorder (ASD) ranked in the top ten causes of non-fatal health burden among young people below 20, says a new study from the Global Burden of Diseases, Injuries and Risk Factors (GBD), 2021, published in The Lancet Psychiatry.Autism spectrum disorder (ASD) is a highly complex neurodevelopmental disorder characterized by deficits in sociability and repetitive behaviour, however, there is a great heterogeneity within other comorbidities that accompany ASD. Recently, the gut microbiome has been pointed out as a plausible contributing factor for ASD development, as individuals diagnosed with ASD often suffer from intestinal problems and show a differentiated intestinal microbial composition.(48)

The gut-brain axis represents a bidirectional communication system between the gastrointestinal tract and the central nervous system. In ASD, gut microbiome alterations have been observed, with studies reporting increased abundance of certain bacterial families, such as Lactobacillaceae, and decreased levels of beneficial metabolites like short-chain fatty acids (SCFAs). A recent study highlighted that autistic children exhibited altered levels of tryptophan metabolites, particularly reduced kynurenate, which is associated with neuroprotective functions. These metabolic changes correlated with differences in emotional and sensory brain activity, underscoring the gut-brain connection in autism.

Interconnection Between Asthma and ASD via Gut Dysbiosis

The co-occurrence of asthma and ASD in children suggests shared underlying mechanisms, potentially mediated by gut microbiome dysbiosis. Both conditions have been linked to immune system dysregulation and inflammatory responses originating from the gut. Early-life factors, such as antibiotic exposure and cesarean delivery, can disrupt gut microbial balance, leading to increased susceptibility to both asthma and ASD.

Many studies have shown that the development of asthma in AD patients is more common, although the exact causative factors are not yet clear. In a study conducted by Pourpak et al., the prevalence of asthma in patients with AD was 27,5%.(49)

The exact pathogenesis of asthma and AD is not entirely understood. Both diseases are associated with chronic inflammation. In asthma patients, cytokines and other inflammatory mediators are found in bronchial washings. Both diseases can be IgE-mediated, which suggests genetic predisposition, as atopy refers to the familial tendency to produce IgE. Imbalance in the Th1/Th2 ratio is associated with higher production of IgE in atopic patients. By producing IL-2 and IL-13, Th2 cells promote the production of IgE by B-cells in response to an antigen trigger. This leads to hyperreactive responses of the airways in asthma patients and skin inflammation in AD patients. Mast cells play a major role in allergic and inflammatory disorders (50)

The many similarities between AD and asthma in terms of pathogenesis and immunological imbalance often lead us to consider each disease in the context of the other.

A Canadian study, published in 2018, found that AD increased the risk of asthma in children at the age of 3 years only if AD was accompanied by sensitization to inhalants, foods or both at the age of 1 year (51).

These observations had led to the necessity of defining phenotypes and endotypes within the AD patient population, to predict future development of atopic march. Classifying AD patients into phenotypes can be directly related to their risk of developing other atopic diseases in the future. Based on the age of the patient: infantile, childhood, adolescent/adult, and elderly, AD has been defined, each with its characteristic clinical features. (52)

Nutrition--Autism

Eating regular meals containing fiber and having 6-8 drinks a day will help with digestion problems in autistic people. Newborns with low blood levels of Vitamin D were 33% more likely to later be diagnosed with autism than those born with high blood levels of vitamin D. Vitamin D is essential for the development of the brain, and studies have shown that children with autism who have low levels of Vitamin D have more severe symptoms than those with normal levels Vitamin B6 is important for producing neurotransmitters, which are chemicals that transmit signals in the brain. Studies have shown that children with autism often have low levels of vitamin B6. Supplementing with vitamin B6 has been shown to improve behavior and social interaction in children with autism. Vitamin B12 is important for forming red blood cells and the proper functioning of the nervous system. Studies have shown that children with autism often have low levels of vitamin B12. Supplementing with vitamin B12 has been shown to improve language and behavior in children with autism. Folic acid is important for the proper development of the nervous system. Studies have shown that children with autism often have low levels of folic acid. Supplementing with folic acid has been shown to improve language and behavior in children with autism. In addition to the vitamins mentioned above, other nutrients may benefit children with autism. Magnesium is one such nutrient. It is important for the proper functioning of the nervous system, and studies have shown that children with autism often have low levels of magnesium. Supplementing with magnesium has been shown to improve behavior and social interaction in children with ASD. Zinc is another nutrient that may be beneficial for children with autism.

Food Allergy

AD is associated with food allergy (FA), asthma, and allergic rhinitis (AR), with or without the occurrence of elevated IgE levels (53)

This gradual transition of one atopic disease into another in an almost specific age range is known as atopic march. AD is considered the first step as a disrupted skin barrier, inflammation, and bacterial dysbiosis lead to sensitization required for the development of other atopic diseases (5, 55)

However, AD can follow asthma and AR. FA develops early in

life; it can precede or follow the AD, and may in some cases be the first sign of the atopic march. FA often occurs before the appearance of AR or asthma (56,57)

A dysfunctional skin barrier in AD could lead to food sensitization, or FA could accompany AD. Either way, food sensitization could be a marker for AD severity, an endotype, which could suggest a more probable transition to other atopic comorbidities (asthma and AR) (58)

Autism Food allergy plays an important role in the pathophysiology of autism because, in some cases, clinical hypersensitivity reactions result when certain foods are eaten by autistic children. This evidence suggests a role for neuroimmune mechanisms in the pathophysiology of autism. Lactobacillus might be the critical link in regulating the gut-immune-brain axis in the intestinal, immunological, and psychiatric ASD-like symptoms seen in our model of CMA-induced autism. Changes in gut microbiota, especially Lactobacillus attenuation and mTOR signalling activation in the brain, may be an important mechanism linking allergic reactions and autistic behaviours.

Mechanisms Linking Gut Dysbiosis to Inflammation

Dysbiosis can compromise the intestinal barrier, allowing translocation of microbial products that trigger systemic inflammation. This inflammatory cascade can affect distant organs, including the lungs and brain, contributing to the pathophysiology of asthma and ASD. Additionally, altered microbial metabolites can influence immune cell differentiation and cytokine production, further exacerbating inflammatory responses.

Therapeutic Implications and Future Directions

Understanding the role of gut microbiome dysbiosis in asthma and ASD opens avenues for novel therapeutic interventions. Strategies such as probiotic supplementation, dietary modifications, and fecal microbiota transplantation (FMT) are being explored to restore microbial balance and mitigate symptoms. Personalized approaches considering individual microbial profiles may enhance treatment efficacy.

CONCLUSION

Human health is an ever-interesting topic. Several studies have been carried out on the same, exploring the various genera involved, their association, and their importance in maintaining good health. The healthy human gut is colonised mainly by organisms belonging to two phyla, namely Bacteroidetes and Firmicutes. They have been found to play inevitable roles in host nutrient metabolism, maintaining the integrity of gut mucosa, and protection from invading pathogens.

The gut microbiome's influence extends beyond the gastrointestinal tract, impacting respiratory and neuro-developmental health. Addressing gut dysbiosis presents a promising strategy in managing and potentially preventing conditions like asthma and ASD. Further research is warranted to elucidate the complex interactions within the gut-lung-brain axis and to develop targeted microbiome-based therapies. Extensive studies have observed gut disturbances in lung diseases, including allergy, asthma, chronic obstructive pulmonary disease, cystic fibrosis, and lung cancer.

REFERENCES

1. Pluta R, Januszewski S, Czuczwar SJ. The role of gut microbiota in an ischemic stroke. Int J Mol Sci. 2021;22:915. doi: 10.3390/ijms22020915. [DOI] [PMC free article] [PubMed] [Google Scholar]
2. Wang L, Wang L, Wang H, Zhu T. Investigation into the potential mechanism and molecular targets of Fufang Xueshuantong capsule for the treatment of ischemic stroke based on network pharmacology and molecular docking. Front Pharmacol. 2022b;13:949644. doi: 10.3389/fphar.2022.949644. [DOI] [PMC free article] [PubMed] [Google Scholar]
3. Zhao SC, Wang C, Xu H, Wu WQ, Chu ZH, Ma LS, Zhang YD, Liu F. Age-related differences in interferon regulatory factor-4 and -5 signaling in ischemic brains of mice. Acta Pharmacol Sin. 2017;38:1425–1434. doi: 10.1038/aps.2017.122. [DOI] [PMC free article] [PubMed] [Google Scholar]
4. Xiong XY, Liu L, Yang QW. Refocusing neuroprotection in cerebral reperfusion era:new challenges and strategies. Front Neurol. 2018;9:249. doi: 10.3389/fneur.2018.00249. [DOI] [PMC free article] [PubMed] [Google Scholar]
5. Cuenca-López MD, Brea D, Segura T, Galindo MF, Antón-Martínez D, Agulla J, Castillo J, Jordán J. Inflammation as a therapeutic agent in cerebral infarction:cellular inflammatory response and inflammatory mediators. Rev Neurol. 2010;50:349–359. [PubMed] [Google Scholar]
6. Singh V, Beer A, Kraus A, Mang F, Zhang X, Xue J, Hagemann N, Hermann DM, Gunzer M. Stroke increases the expression of ACE2, the SARS-CoV-2 binding receptor, in murine lungs. Brain Behav Immun. 2021;94:458–462. doi: 10.1016/j.bbi.2021.01.039. [DOI] [PMC free article] [PubMed] [Google Scholar]
7. Borst K, Dumas AA, Prinz M. Microglia:Immune and non-immune functions. Immunity. 2021;54:2194–2208. doi: 10.1016/j.immuni.2021.09.014. [DOI] [PubMed] [Google Scholar]
8. Li M, Chen S, Shi X, Lyu C, Zhang Y, Tan M, Wang C, Zang N, Liu X, Hu Y, Shen J, Zhou L, Gu Y. Cell permeable HMGB1-binding heptamer peptide ameliorates neurovascular complications associated with thrombolytic therapy in rats with transient ischemic stroke. J Neuroinflammation. 2018;15:237. doi: 10.1186/s12974-018-1267-5. [DOI] [PMC free article] [PubMed] [Google Scholar]
9. Umahara T, Uchihara T, Hirokawa K, Hirao K, Shimizu S, Hashimoto T, Terasi H, Hanyu H. Time-dependent and lesion-dependent HMGB1-selective localization in brains of patients with cerebrovascular diseases. Histol Histopathol. 2018;33:215–222. doi: 10.14670/HH-11-914. [DOI] [PubMed] [Google Scholar]
10. Alawieh A, Langley EF, Tomlinson S. Targeted complement inhibition salvages stressed neurons and inhibits neuroinflammation after stroke in mice. Sci Transl Med. 2018;10:eaao6459. doi: 10.1126/scitranslmed.aao6459. [DOI] [PMC free article] [PubMed] [Google Scholar
11. Xu S, Lu J, Shao A, Zhang JH, Zhang J. Glial cells: role of the immune response in ischemic stroke. Front Immunol. 2020;11:294. doi: 10.3389/fimmu.2020.00294. [DOI] [PMC free article] [PubMed] [Google Scholar]
12. Liddelow SA, Barres BA. Reactive astrocytes: production, function, and therapeutic potential. Immunity. 2017;46:957–967. doi: 10.1016/j.immuni.2017.06.006. [DOI] [PubMed] [Google Scholar]
13. Christensen DL, Baio J, Van Naarden Braun K, et al. ; Centers for Disease Control and Prevention (CDC) . Prevalence and characteristics of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2012. MMWR Surveill Summ. 2016;65(3)
14. Zablotsky B, Black LI, Maenner MJ, Schieve LA, Blumberg SJ. The estimated prevalence of autism and other developmental disabilities following questionnaire changes in the 2014 National Health Interview Survey. Natl Health Stat Report. 2015;87:1-20.
15. Xu G, Strathearn L, Liu B, Bao W. Prevalence of autism spectrum disorder among US children and adolescents, 2014-2016. JAMA. 2018;319(1):81-82.
16. Lai MC, Lombardo MV, Baron-Cohen S. Autism. Lancet. 2014;383(9920):896-910.
17. Modabbernia A, Velthorst E, Reichenberg A. Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. Mol Autism. 2017;8:13.
18. Onore C, Careaga M, Ashwood P. The role of immune dysfunction in the pathophysiology of autism. Brain Behav Immun. 2012;26(3):383-392.
19. Nardone S, Elliott E. The interaction between the immune system and epigenetics in the etiology of autism spectrum disorders. Front Neurosci. 2016;20:329.
20. Xu N, Li X, Zhong Y. Inflammatory cytokines: potential biomarkers of immunologic dysfunction in autism spectrum disorders. Mediators Inamm. 2015;2015:531518.
21. P. Luczynski, K.A. McVey Neufeld, C.S. Oriach, G. Clarke, T.G. Dinan, J.F. Cryan,Growing up in a bubble: using germ-free animals to assess the influence of the gut microbiota on brain and behavior,Int J Neuropsychopharmacol, 19 (8) (2016), pp. 1-17
22. J.F. Cryan, K.J. O'Riordan, C.S. Cowan, et al.The microbiota-gut-brain axis.Physiol Rev, 99 (2019), pp. 1877-2013
23. A.P. Allen, W. Hutch, Y.E. Borre, et al.Bifidobacterium longum 1714 as a translational psychobiotic: modulation of stress, electrophysiology and neurocognition in healthy volunteers,Transl Psychiatry, 6 (11) (2016), pp. 1-7 24. Desbonnet, G. Clarke, A. Traplin, et al.Gut microbiota depletion from early adolescence in mice: implications for brain and behaviourBrain Behav Immun, 1 (2015), pp. 165-173
25. Gershon M. (1999). The Enteric Nervous System: A Second Brain. Hosp. Pract. 34 (7), 31–52. doi: 10.3810/hp.1999.07.153 [DOI] [PubMed] [Google Scholar]
26. Cryan J., Dinan T. (2012). Mind-Altering Microorganisms: The Impact of the Gut Microbiota on Brain and Behaviour. Nat. Rev. Neurosci. 13 (10), 701–712. doi: 10.1038/nrn3346 [DOI] [PubMed] [Google Scholar]
27. Dinan T., Stilling R., Stanton C., Cryan J. (2015). Collective Unconscious: How Gut Microbes Shape Human Behavior. J. Psychiatr. Res. 63, 1–9. doi: 10.1016/j.jpsychires.2015.02.021 [DOI] [PubMed] [Google Scholar]
28. Warner B. (2018). The Contribution of the Gut Microbiome to Neurodevelopment and Neuropsychiatric Disorders. Pediatr. Res. 85 (2), 216–224. doi: 10.1038/s41390-018-0191-9 [DOI] [PubMed] [Google Scholar]
29. Chauhan N., Nain S., Sharma R. (2017). Identification of Arsenic Resistance Genes From Marine Sediment Metagenome. Indian J. Microbiol. 57 (3), 299–306. doi: 10.1007/s12088-017-0658-0 [DOI] [PMC free article] [PubMed] [Google Scholar]
30. Dinan T., Stilling R., Stanton C., Cryan J. (2015). Collective Unconscious: How Gut Microbes Shape Human Behavior. J. Psychiatr. Res. 63, 1–9. doi: 10.1016/j.jpsychires.2015.02.021 [DOI] [PubMed] [Google Scholar]
31. Kumar Mondal A., Kumar J., Pandey R., Gupta S., Kumar M., Bansal G., et al. (2017). Comparative Genomics of Host–Symbiont and Free-Living Oceanobacillus Species. Genome Biol. Evol. 9 (5), 1175–1182. doi:

10.1093/gbe/evx076 [DOI] [PMC free article] [PubMed] [Google Scholar]
32. Chauhan N. (2017). Human Gut Microbiome: An Imperative Element for Human Survival. Curr. Trends In Biomed. Eng. Biosci. 6 (1). doi: 10.19080/ctbeb.2017.06.555680 [DOI] [Google Scholar]
33. Jennis M., Cavanaugh C., Leo G., Mabus J., Lenhard J., Hornby P. (2017). Microbiota-Derived Tryptophan Indoles Increase After Gastric Bypass Surgery and Reduce Intestinal Permeability In Vitro and In Vivo . Neurogastroenterol.& Motil. 30 (2), e13178. doi: 10.1111/nmo.13178 [DOI] [PubMed] [Google Scholar]
34. Desbonnet L., Garrett L., Clarke G., Bienenstock J., Dinan T. (2008). The Probiotic Bifidobacterium Infantis: An Assessment of Potential Antidepressant Properties in the Rat. J. Psychiatr. Res. 43 (2), 164–174. doi: 10.1016/j.jpsychires.2008.03.009 [DOI] [PubMed] [Google Scholar]
35. Javier Díaz-García F., Flores-Medina S., Mercedes Soriano-Becerril D. (2020). Interplay Between Human Intestinal Microbiota and Gut-To-Brain Axis: Relationship With Autism Spectrum Disorders. Microorganisms, 318. doi: 10.5772/intechopen.89998 [DOI] [Google Scholar]
36. Tsai P., Hull C., Chu Y., Greene-Colozzi E., Sadowski A., Leech J., et al. (2012). Autistic-Like Behaviour and Cerebellar Dysfunction in Purkinje Cell Tsc1 Mutant Mice. Nature 488 (7413), 647–651. doi: 10.1038/nature11310 [DOI] [PMC free article] [PubMed] [Google Scholar]
37. Rosenfeld, C. (2015). Microbiome Disturbances and Autism Spectrum Disorders. Drug Metab. Disposition 43 (10), 1557–1571. doi: 10.1124/dmd.115.063826 [DOI] [PubMed] [Google Scholar]
38. The global asthma report, 2022 Int J Tuberc Lung Dis. 2022;26(suppl 1):1–104. doi: 10.5588/ijtld.22.1010. [DOI] [PubMed] [Google Scholar]
39. Reddel H.K., Bacharier L.B., Bateman E.D., Brightling C.E., Brusselle G.G., Buhl R., et al. Global Initiative for Asthma Strategy 2021: executive summary and rationale for key changes. Am J Respir Crit Care Med. 2022;205:17–35. doi: 10.1164/rccm.202109-2205PP. [DOI] [PMC free article] [PubMed] [Google Scholar]
40. Ducharme F.M., Tse S.M., Chauhan B. Diagnosis, management, and prognosis of preschool wheeze. Lancet. 2014;383:1593–1604. doi: 10.1016/S0140-6736(14)60615-2. [DOI] [PubMed] [Google Scholar]
41. Suarez C.J., Parker N.J., Finn P.W. Innate immune mechanism in allergic asthma. Curr Allergy Asthma Rep. 2008;8:451–459. doi: 10.1007/s11882-008-0085-8. [DOI] [PubMed] [Google Scholar
42. Lambrecht B., Hammad H. The immunology of asthma. Nat Immunol. 2015;16:45–56. doi: 10.1038/ni.3049. [DOI] [PubMed] [Google Scholar]
43. Huang Y.J., Boushey H.A. The microbiome in asthma. J Allergy Clin Immunol. 2015;135:25–30. doi: 10.1016/j.jaci.2014.11.011. [DOI] [PMC free article] [PubMed] [Google Scholar]
44. Frati F., Salvatori C., Incorvaia C., Bellucci A., Di Cara G., Marcucci F., et al. The role of the microbiome in asthma: the gut–lung axis. Int J Mol Sci. 2018;20:123. doi: 10.3390/ijms20010123. [DOI] [PMC free article] [PubMed] [Google Scholar]
45. Lynch S.V., Pedersen O. The human intestinal microbiome in health and disease. N Engl J Med. 2016;375:2369–2379. doi: 10.1056/NEJMra1600266. [DOI] [PubMed] [Google Scholar
46. Liu M.Y., Yang Z.Y., Dai W.K., Huang J.Q., Li Y.H., Zhang J., et al. Protective effect of Bifidobacterium infantis CGMCC313-2 on ovalbumin-induced airway asthma and beta-lactoglobulin–induced intestinal food allergy mouse models. World J Gastroenterol. 2017;23:2149–2158. doi: 10.3748/wjg.v23.i12.2149. [DOI] [PMC free article] [PubMed] [Google Scholar]
47. Raftis E.J., Delday M.I., Cowie P., McCluskey S.M., Singh M.D., Ettorre A., et al. Bifidobacterium breve MRx0004 protects against airway inflammation in a severe asthma model by suppressing both neutrophil and eosinophil lung infiltration. Sci Rep. 2018;8 doi: 10.1038/s41598-018-30448-z. [DOI] [PMC free article] [PubMed] [Google Scholar]
48. Lucia N. Peralta-Marzal, David Rojas-Velazquez,et al.A robust microbiome signature for autism spectrum disorder across different studies using machine learning, Scientific Reports Volume 14, Article number: 814 (2024)
49. Pourpak Z, Mozaffari H, Gharagozlou M, Daneshmandi Z, Moin M. Asthma in patients with atopic dermatitis. Indian J Pediatr. 2008;75(2):139–41. https://doi.org/10.1007/s12098-008-0021-x.
50. P Kolkhir D Elieh-Ali-Komi M Metz et al 2021Understanding human mast cells: lessons from therapies for allergic and non-allergic diseasesNat Rev Immunol https://doi.org/10.1038/s41577-021-00622-y
51. Tran M, Lefebvre D, Dharma C, Dai D, Lou W, Subbarao P, et al. Predicting the atopic march: results from the Canadian Healthy Infant Longitudinal Development study. J Allergy Clin Immunol. 2018;141(2):601–7. https://doi.org/10.1016/j.jaci.2017.08.024 (e8).
52. Bieber T, Bussmann C. Atopic dermatitis. In: Bolognia JL, Lorizzo JL, Schaffer JV, editors. Dermatology. St Louis: Mosby; 2012. p. 203–16.
53. Pinart M, Benet M, Annesi-Maesano I, von Berg A, Berdel D, Carlsen KC, et al. Comorbidity of eczema, rhinitis, and asthma in IgE-sensitised and non-IgE-sensitised children in MeDALL: a population-based chort study. Lancet Respir Med. 2014;2:131–40. https://doi.org/10.1038/s41572-018-0001-z.
54. Paller A, Kong H, Seed P, Naik S, Scharschmidt T, Gallo R, et al. The microbiome in atopic dermatitis. J Allergy Clin Immunol. 2019;143(1):26–35. https://doi.org/10.1016/j.jaci.2018.11.015.
55. Paller A, Spergel J, Mina-Osorio P, Irvine A. The atopic march and atopic multimorbidity: Many trajectories, many pathways. J Allergy Clin Immunol. 2019;143(1):46–55. https://doi.org/10.1016/j.jaci.2018.11.006.
56. Hill D, Grundmeier R, Ram G, Spergel J. The epidemiologic characteristics of healthcare provider-diagnosed eczema, asthma, allergic rhinitis, and food allergy in children: a retrospective cohort study. BMC Pediatr. 2016;16:133. https://doi.org/10.1186/s12887-016-0673-z.
57. Ziyab A, Hankinson J, Ewart S, Schauberger E, Kopec-Harding K, Zhang H, et al. Epistasis between FLG and IL4R genes on the risk of allergic sensitization: results from two population-based birth cohort studies. Sci Rep. 2018;8(1):3221. https://doi.org/10.1038/s41598-018-21459-x.
58. Tsakok T, Marrs T, Mohsin M, Baron S, du Toit G, Till S, et al. Does atopic dermatitis cause food allergy? A systematic review. J Allergy Clin Immunol. 2016;137(4):1071–8. https://doi.org/10.1016/j.jaci.2015.10.049.