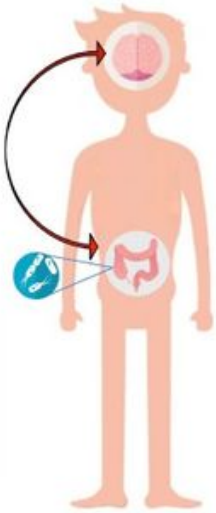
ADHD and the Microbiome

Cheryl le Roux | Educator

24/07/19



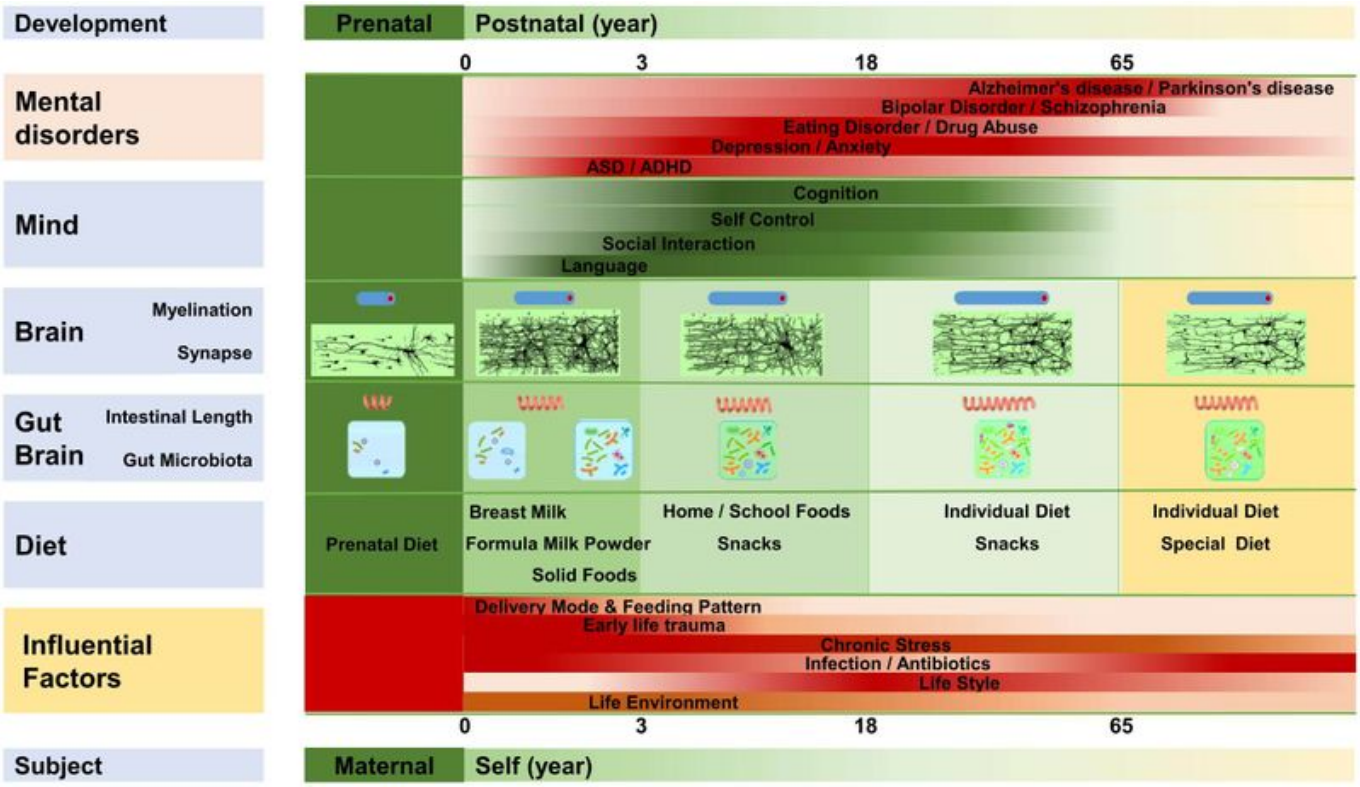
Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric disorder first presenting in childhood (before age 12) with core symptoms of hyperactivity, restlessness, impulsivity, and inappropriate attention ([2]). The disorder persists into adulthood in a considerable number of patients, with a worldwide prevalence of ADHD in adults at 1-4%. Genetic and environmental factors contribute to the disorder, and the microbiome is increasingly investigated for its potential role ([3]).

Approximately 9.4% of children in the US aged 4-17 have been diagnosed with ADHD as of 2016 ([4]). In Australia, as of 2015, 7.4% of children and adolescents fulfilled the criteria for ADHD. The prevalence of ADHD was lower in females aged 12–17 than those aged 4-11 (2.7% vs 5.4%) but about the same for males (9.8% vs 10.9%) ([5]).

Increasing evidence suggests that the gut microbiota plays a key role in the gut-brain communication axis by influencing metabolism, inflammation, the hypothalamic-pituitary-adrenal axis and neurotransmission ([6]). Preclinical research shows promising results in targeting the microbiota, particularly during critical microbial-neural developmental windows, with the potential to prevent later neurodevelopmental deficits ([7]).

A prevailing hypothesis suggests that an unfavourable infant gut microbiota can affect brain development through epigenetic mechanisms ([8],[9]). However, no direct clinical evidence supports a relationship between gut microbiota composition and ADHD symptoms ([10]). Rather, evidence of the role of the microbiome in ADHD is supported by a number of theoretical hypotheses as outlined below. This is emerging into a novel integrative model explaining the aetiology and pathogenesis of ADHD in a microbiota-gut-brain context. In this model, an imbalanced, less rich and/or diverse gut microbiota early in life is a core developmental feature of metabolic, immunologic, cognitive, emotional and behavioural symptoms in ADHD ([11]). Figure 1 highlights the link between early life microbiota disruption and ADHD development.

Figure 1. Microbiota disruption at different life stages and the incidence of different neuropsychiatric disorders ([12])



Microbiome composition in ADHD

Gut microbiome studies in ADHD are in their early days. Initial evidence indicates that there may be a difference in microbiota composition early in life between children, adolescents and adults with ADHD and healthy controls ([13],[14],[15]).

A study found that children diagnosed with ADHD had decreased levels of *Bifidobacterium longum* early in life. The same study found that administration of *Lactobacillus rhamnosus GG* during the first 6 months of life may reduce the risk of ADHD. Despite what seems to be a protective effect of the probiotic, it did not result in significant effects on the microbiota composition ([13]).

A recent study found an abundance of *Faecalibacterium* was negatively associated with parental reports of ADHD symptoms in children. No significant difference in microbiome diversity was found however between the ADHD and control groups ([6]).

If the effect of microbiota composition early in life on ADHD proves to be correct (replicated), major functions of the gut microbiome will be affected ([16]):

- Protection from colonisation of pathogenic bacteria strains
- Strengthening of the intestinal barrier and limiting the penetration of bacteria and toxic content into the body

- Increasing efficiency of nutrient absorption
- Guiding the function and maturation of the immune system

Environmental risk factors

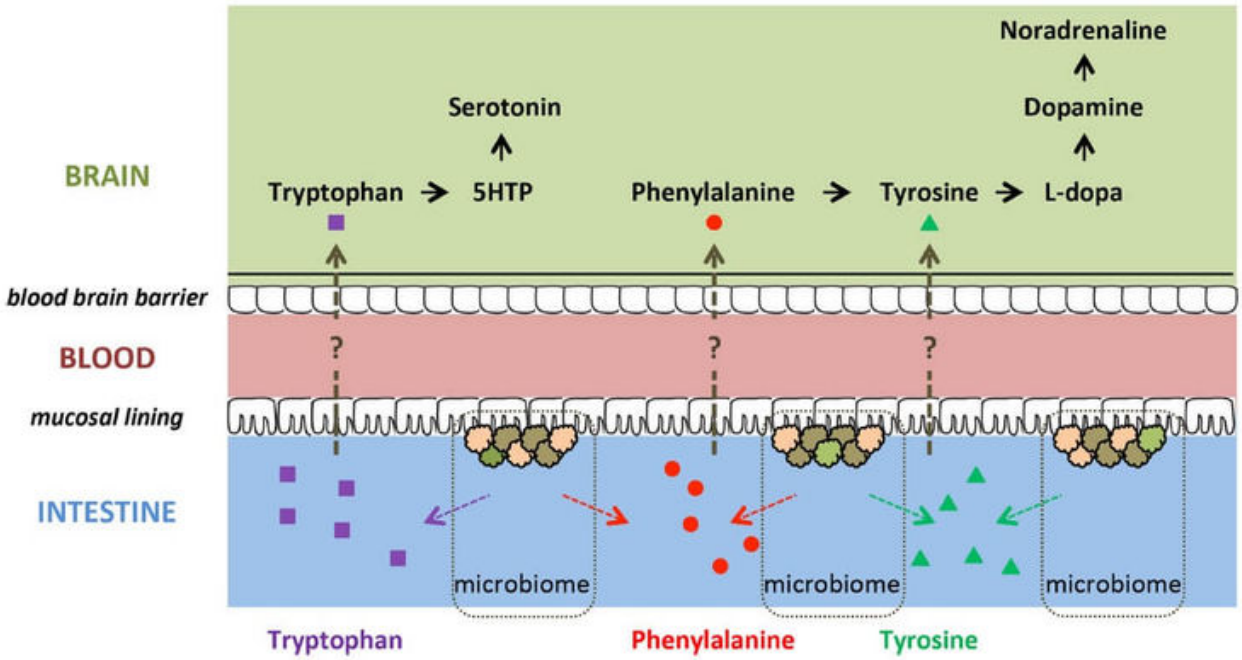
There is strong evidence that industrial chemicals such as toluene, lead, fluoride and methylmercury are neuro-developmentally toxic and capable of causing permanent brain damage at low levels of exposure during sensitive developmental stages ([17]). Childhood exposure to lead and prenatal exposure to organophosphates has been associated with ADHD although further evaluation is needed ([18]). Chemicals are able to cross the blood-brain barrier and be transported to the central nervous system. If barrier functions are reduced in ADHD then it is plausible that there will be increased sensitivity to toxic environmental exposure, as well as to bacterial toxins and food substances such as gluten, which shows endotoxin-mimicking and thus induces inflammation ([19],[20]). It has been proposed that low-grade systemic inflammation may lead to the gradual destruction of the blood-brain barrier and possibly the neuroinflammation seen in ADHD ([10],[21]). There is preliminary evidence of elevated pro-inflammatory cytokines in children and adolescents with ADHD ([22]).

Neurotransmitter synthesis

One proposed mechanism for the effects of gut microbiota on brain and behaviour is through their ability to synthesize neurotransmitter chemicals and their precursors ([23]). Clinical studies have reported altered tryptophan, dopamine, GABA and vitamin B_6 metabolism in ADHD, which suggests that microbial metabolism may be affected, but studies directly addressing this question are needed ([11]).

Preclinical evidence indicates that several members of the gut microbiota produce precursors of monoamines involved in ADHD (i.e. dopamine, tryptophan, noradrenaline, serotonin and GABA) ([24],[25],[26]). These precursors (i.e. phenylalanine, tyrosine, tryptophan) might be absorbed through the intestinal epithelium, entering the portal circulation ([23]) and crossing the blood-brain barrier, potentially influencing host monoamine synthesis (Figure 2). Therefore, differences in abundance and/or metabolic activity of monoamine precursor-producing microbiome bacteria may affect monoamine-related brain functioning and behaviours relevant to ADHD ([15]).

Figure 2. Potential routes in which precursors of monoamines could influence brain functioning ([15])



Immune dysregulation and inflammation

ADHD is linked to altered metabolic and immunologic function, indirectly suggesting that major functions of the gut microbiome may be affected ([11]).

Immune dysregulation in autoimmune disorders and ADHD may be associated with an altered microbiome, low-grade inflammation, and gastrointestinal dysfunction ([27],[28],[29],[30]). Dysbiosis may result in a disproportionate quantity of pro-inflammatory microbes leading to increased intestinal permeability and inflammation, as well as a resultant shift of microbes into the systemic circulation which may lead to low-grade systemic inflammation and immune dysregulation ([3]).

Allergic disease (e.g. atopic eczema) is associated with an increased risk of ADHD ([31]–[33]). Conversely, alteration in the microbial colonisation during early life has been suggested to play an important role in susceptibility to developing allergies ([34]).

Gastrointestinal disturbance in ADHD

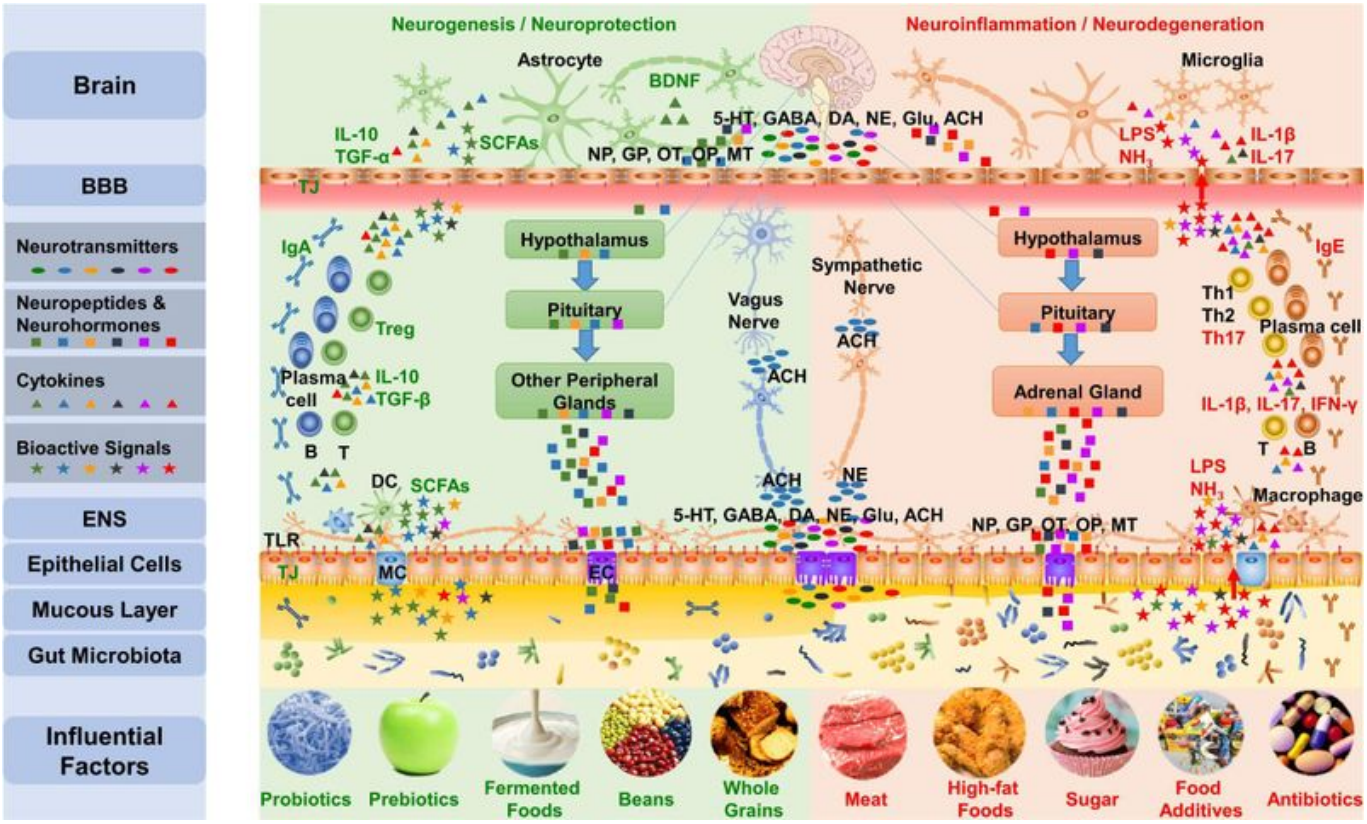
A small but growing body of evidence describes an increased incidence of gastrointestinal symptoms (constipation and flatulence) in individuals with ADHD which may be suggestive of an altered microbiome ([3]).

Dietary Effects on ADHD

It is well known that dietary factors are associated with childhood behavioural disorders such as ADHD ([35]). Diet might influence behaviour and ADHD symptoms by affecting the gut

microbiome ([36],[37]). Meta-analyses show that the elimination of potential allergens through restriction diets in ADHD may lead to a significant reduction in symptoms, although there is a large degree of variety across studies ([38],[39],[40]). Figure 3 highlights influential dietary factors affecting the gut microbiota and their effect on the brain which might conceivably influence the development of ADHD.

Figure 3. Dietary factors and their effect on gut-brain communication ([12]) CC BY 4.0



Aetiological factors of ADHD

The risk of developing ADHD has been suggested to be associated with many perinatal risk factors which are able to shape the gut microbiota composition. Maternal factors affect in-utero brain development while early childhood factors affect brain function and behaviour ([10],[37]).

Table 1. Environmental factors influencing the development of infant gut microbiota ([10])

Maternal factors	Early childhood factors
• Maternal diet and obesity • Maternal health • Maternal infections and stress • Antibiotic/drug exposure	• Gestational age • Delivery mode • Early life infections and stress • Milk-feeding patterns • Complementary feeding/diet • Genetic influences • Antibiotic/drug exposure

Takeaway on ADHD and the Microbiome

- The gut-brain axis may be a potential intervention target for treating developmental disorders including ADHD ([10])
- Initial clinical results indicate an altered composition of gut microbiota in ADHD in early life, but more research is needed ([11])
- Preliminary human studies suggest that dietary components modulating gut microbiota may influence ADHD development or symptoms ([10])
- If dysbiosis/decreased biodiversity of the microbiome and an unfavourable microbiota development in early life is a controlling mechanism driving ADHD development and symptom severity, any intervention reducing inflammation can be predicted to reduce symptoms ([11])

References

1 Cerdó T, Ruíz A, Suárez A, Campoy C. Probiotic, Prebiotic, and Brain Development. Nutrients. 2017 Nov 14;9(11).

2 Klein M, Berger S, Hoogman M, Dammers J, Makkinje R, Heister AJGAM, et al. Meta-analysis of the DRD5 VNTR in persistent ADHD. Eur Neuropsychopharmacol. 2016;26(9):1527–32.

3 Ming X, Chen N, Ray C, Brewer G, Kornitzer J, Steer RA. A Gut Feeling: A Hypothesis of the Role of the Microbiome in Attention-Deficit/Hyperactivity Disorders. Child Neurol Open. 2018;5:2329048X18786799.

4 CDC. ADHD Data & Statistics [Internet]. Centers for Disease Control and Prevention. 2018 [cited 2018 Dec 2]. Available from: https://www.cdc.gov/ncbddd/adhd/data.html

5 Lawrence D, Johnson S, Hafekost J, Boterhoven de Haan K, Sawyer M, Ainley J, et al. The mental health of children and adolescents: report on the second Australian Child and Adolescent Survey of Mental Health and Wellbeing. [Internet]. 2015. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/9DA8CA21306FE6EDCA257E2700016945/$File/child2.pdf

6 Jiang H, Zhou Y, Zhou G, Li Y, Yuan J, Li X, et al. Gut microbiota profiles in treatment-naïve children with attention deficit hyperactivity disorder. Behavioural Brain Research. 2018 Jul;347:408–13.

7 Borre YE, O'Keeffe GW, Clarke G, Stanton C, Dinan TG, Cryan JF. Microbiota and neurodevelopmental windows: implications for brain disorders. Trends in Molecular Medicine. 2014 Sep;20(9):509–18.

8 Mayer EA, Tillisch K, Gupta A. Gut/brain axis and the microbiota. J Clin Invest. 2015 Mar 2;125(3):926–38.

9 Stilling RM, Bordenstein SR, Dinan TG, Cryan JF. Friends with social benefits: host-microbe interactions as a driver of brain evolution and development? Front Cell Infect Microbiol. 2014 Oct 29;4.

10 Cenit MC, Nuevo IC, Codoñer-Franch P, Dinan TG, Sanz Y. Gut microbiota and attention deficit hyperactivity disorder: new perspectives for a challenging condition. Eur Child Adolesc Psychiatry. 2017 Sep;26(9):1081–92.

11 Sandgren AM, Brummer RJM. ADHD-originating in the gut? The emergence of a new explanatory model. Med Hypotheses. 2018 Nov;120:135–45.

12 Liang S, Wu X, Jin F. Gut-Brain Psychology: Rethinking Psychology From the Microbiota–Gut–Brain Axis. Front Integr Neurosci. 2018 Sep 11;12.

13 Pärtty A, Kalliomäki M, Wacklin P, Salminen S, Isolauri E. A possible link between early probiotic intervention and the risk of neuropsychiatric disorders later in childhood: a randomized trial. Pediatr Res. 2015 Jun;77(6):823–8.

14 Prehn-Kristensen A, Zimmermann A, Tittmann L, Lieb W, Schreiber S, Baving L, et al. Reduced microbiome alpha diversity in young patients with ADHD. PLoS ONE. 2018;13(7):e0200728.

15 Aarts E, Ederveen THA, Naaijen J, Zwiers MP, Boekhorst J, Timmerman HM, et al. Gut microbiome in ADHD and its relation to neural reward anticipation. PLoS ONE. 2017;12(9):e0183509.

16 Wang Y, Kasper LH. The role of microbiome in central nervous system disorders. Brain Behav Immun. 2014 May;38:1–12.

17 Grandjean P, Landrigan PJ. Neurobehavioural effects of developmental toxicity. Lancet Neurol. 2014 Mar;13(3):330–8.

18 Yolton K, Cornelius M, Ornoy A, McGough J, Makris S, Schantz S. Exposure to neurotoxicants and the development of attention deficit hyperactivity disorder and its related behaviors in childhood. Neurotoxicol Teratol. 2014 Aug;44:30–45.

19 Bengmark S. Gut microbiota, immune development and function. Pharmacol Res. 2013 Mar;69(1):87–113.

20 Nikulina M, Habich C, Flohé SB, Scott FW, Kolb H. Wheat gluten causes dendritic cell maturation and chemokine secretion. J Immunol. 2004 Aug 1;173(3):1925–33.

21 Donev R, Thome J. Inflammation: good or bad for ADHD? Atten Defic Hyperact Disord. 2010 Dec;2(4):257–66.

22 Mitchell RHB, Goldstein BI. Inflammation in children and adolescents with neuropsychiatric disorders: a systematic review. J Am Acad Child Adolesc Psychiatry. 2014 Mar;53(3):274–96.

23 Lyte M. Microbial Endocrinology in the Microbiome-Gut-Brain Axis: How Bacterial Production and Utilization of Neurochemicals Influence Behavior. PLoS Pathog. 2013 Nov 14;9(11).

24 Clayton TA. Metabolic differences underlying two distinct rat urinary phenotypes, a suggested role for gut microbial metabolism of phenylalanine and a possible connection to autism. FEBS Lett. 2012 Apr 5;586(7):956–61.

25 Desbonnet L, Garrett L, Clarke G, Bienenstock J, Dinan TG. The probiotic Bifidobacteria infantis: An assessment of potential antidepressant properties in the rat. J Psychiatr Res. 2008 Dec;43(2):164–74.

26 Gertsman I, Gangoiti JA, Nyhan WL, Barshop BA. Perturbations of tyrosine metabolism promote the indolepyruvate pathway via tryptophan in host and microbiome. Mol Genet Metab. 2015 Mar;114(3):431–7.

27 Chung H, Kasper DL. Microbiota-stimulated immune mechanisms to maintain gut homeostasis. Curr Opin Immunol. 2010 Aug;22(4):455–60.

28 Felix KM, Tahsin S, Wu H-JJ. Host-microbiota interplay in mediating immune disorders. Ann N Y Acad Sci. 2018 Apr;1417(1):57–70.

29 Mandl T, Marsal J, Olsson P, Ohlsson B, Andréasson K. Severe intestinal dysbiosis is prevalent in primary Sjögren's syndrome and is associated with systemic disease activity. Arthritis Res Ther. 2017;19.

30 Yadav SK, Boppana S, Ito N, Mindur JE, Mathay MT, Patel A, et al. Gut dysbiosis breaks immunological tolerance toward the central nervous system during young adulthood. Proc Natl Acad Sci U S A. 2017 Oct 31;114(44):E9318–27.

31 Chang HY, Seo J-H, Kim HY, Kwon J-W, Kim B-J, Kim HB, et al. Allergic Diseases in Preschoolers Are Associated With Psychological and Behavioural Problems. Allergy Asthma Immunol Res. 2013 Sep;5(5):315–21.

32 Genuneit J, Braig S, Brandt S, Wabitsch M, Florath I, Brenner H, et al. Infant atopic eczema and subsequent attention-deficit/hyperactivity disorder--a prospective birth cohort study. Pediatr Allergy Immunol. 2014 Feb;25(1):51–6.

33 Tsai M-C, Lin H-K, Lin C-H, Fu L-S. Prevalence of attention deficit/hyperactivity disorder in pediatric allergic rhinitis: a nationwide population-based study. Allergy Asthma Proc. 2011 Dec;32(6):41–6.

34 Lynch SV. Gut Microbiota and Allergic Disease. New Insights. Ann Am Thorac Soc. 2016 Mar;13(Suppl 1):S51–4.

35 Woo H, Kim D, Hong Y-S, Kim Y-M, Seo J-H, Choe B, et al. Dietary Patterns in Children with Attention Deficit/Hyperactivity Disorder (ADHD). Nutrients. 2014 Apr 14;6(4):1539–53.

36 David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014 Jan 23;505(7484):559–63.

37 Thapar A, Cooper M, Eyre O, Langley K. Practitioner Review: What have we learnt about the causes of ADHD? J Child Psychol Psychiatry. 2013 Jan;54(1):3–16.

38 Nigg JT, Lewis K, Edinger T, Falk M. Meta-Analysis of Attention-Deficit/Hyperactivity Disorder or Attention-Deficit/Hyperactivity Disorder Symptoms, Restriction Diet, and Synthetic Food Color Additives. J Am Acad Child Adolesc Psychiatry. 2012 Jan;51(1):86-97.e8.

39 Pelsser LM, Frankena K, Toorman J, Savelkoul HF, Dubois AE, Pereira RR, et al. Effects of a restricted elimination diet on the behaviour of children with attention-deficit hyperactivity disorder (INCA study): a randomised controlled trial. Lancet. 2011 Feb 5;377(9764):494–503.

40 Sonuga-Barke EJS, Brandeis D, Cortese S, Daley D, Ferrin M, Holtmann M, et al. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. Am J Psychiatry. 2013 Mar;170(3):275–89.