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Windows of Influence: Investigating the Impact of Early Life Factors on Gut Microbiome Development and Autism Risk

Bachelor Thesis Life Sciences

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Abstract

Autism Spectrum Disorder (ASD) is a condition characterized by repetitive behaviours and communication impairments. While genetic factors contribute to its aetiology, environmental factors also play a significant role. Individuals with ASD exhibit a distinct gut microbiota, with an altered Bacteroidetes/Firmicutes ratio and a decreased abundance of *Bifidobacteria*. These findings highlight the importance of the gut-brain axis, as gut dysbiosis can affect neurodevelopment. Conversely, it's also possible that specific behaviors linked to ASD can lead to an altered gut microbiota, which gives rise to the paradoxical relationship between the gut and ASD. This review aims to investigate which early life factors affect the gut microbiome, and when and how they influence the development of ASD. The results suggests that an interplay between different pre-, peri-, and postnatal factors can result in gut dysbiosis, and therefore add to ASD risk. Gut bacteria that are affected by these factors include *Bifidobacteria*, *Lactobacillus* and *Clostridium*. Besides, it appeared that especially mode of delivery is an important factor for the establishment of a healthy gut and normal neurodevelopment. Investigating the exact timeframe in which these factors influence the gut microbiota, could facilitate early life interventions. In this way, the gut microbiota of infants can be restored, which could prevent ASD from developing.

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Introduction

Autism Spectrum Disorder (ASD) is condition characterized by traits such as repetitive sensory-motor behaviors, neurocognitive and social cognitive impairments (Hajri et al., 2022). Approximately one out of every 100 children worldwide is thought to have autism (World Health Organization: WHO, 2023), though the exact cause is still unknown. The aetiology of ASD is believed to involve an interplay between genetic and environmental factors. Up to 60% of the cases are attributed to genetic risk, according to research, but prenatal, perinatal and postnatal factors can affect this genetic risk (Ostrowski et al., 2024). There are several comorbidities linked to ASD, of which gastrointestinal (GI) problems are most frequently reported (Madra et al., 2021). A study conducted by Ye et al. (2021), found that children with ASD have a gut microbiota development that differs from neurotypical children or children with other developmental delays, this finding will be discussed later on in more depth (Ye et al., 2021).

The trillions of microorganisms that live in the human gut make up the ecological community known as the gut microbiota. These gut microbes can, for instance, support healthy immune function and produce a variety of neurotransmitters (Lozupone et al., 2012; Góralczyk-Bińkowska et al., 2022). The two bacterial phyla Firmicutes and Bacteroidetes make up 90% of the gut microbiota. Other phyla include Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia. The phylum Firmicutes consist of many genera, including *Lactobacillus, Bacillus, Clostridium, Enterococcus, and Ruminicoccus*. Of the phylum Bacteroidetes, the two most predominant genera are *Prevotella* and *Bacteroides.* The phylum Actinobacteria is less abundant, and the genus *Bifidobacterium* is the primary representative here (Rinninella et al., 2019). There is interpersonal variation in the composition of the gut microbiota and it may fluctuate, especially during early development. The gut microbiota changes dramatically during early life and remains relatively stable after the age of three (Lozupone et al., 2012b). In general, the microbiota's ability to resist outside threats increases with its diversity and richness (Rinninella et al., 2019b). The degree of community differentiation along habitat gradients is known as beta diversity, while the richness of a particular sample is explained by the alpha diversity (Ding et al., 2021)**.**

A reduction in diversity or abnormal composition of the microbiota is not only connected to intestinal disorders, but also to neurological disorders (Milani et al., 2017). This is supported by a case-control study conducted by Ye and colleagues (2021), that compared the gut microbiota of Chinese children with ASD to that of neurotypical children. According to the findings, children with ASD had an increase in Firmicutes and a decrease in Bacteroidetes. This decreased Bacteroidetes/Firmicutes ratio is typical for patients with ASD and is associated with gastrointestinal problems. Besides, a lower abundance of *Bifidobacteria* was shown in the ASD group. Accordingly, this study demonstrates that the gut microbiota of individuals with ASD differs from that of neurotypical individuals. Furthermore, a correlation between alterations in the gut and the severity of ASD symptoms was found, which supports the idea that there is bidirectional communication between the gut and the brain (Ye et al., 2021b).

The bidirectional communication between the enteric nervous system and central nervous system is known as the gut-brain axis. This network encompasses many pathways, through which the brain can affect intestinal activities while the gut can affect mood and cognition (Appleton, 2018). This raises the paradox: do changes in the gut microbiota cause ASD, or do behaviors associated with ASD change the composition of the gut? (Kurokawa et al., 2024). Consequently, the question emerged which early life factors shape the gut microbiome, and when and how do they influence the development of ASD? Colonisation of the gut microbiota starts *in utero,* since microbes are discovered in the placenta and meconium. However, the first three years of life are also critical for the development of a stable and healthy microbiota (Srikantha & Mohajeri, 2019). Early in life, breastfeeding promotes *Bifidobacteria* abundance which characterizes a healthy gut. With the introduction of solid foods, the diversity of the gut increases and adopts adult-like characteristics (Laursen et al., 2017). Studies have showed that modifying the microbiome can correct behavioural abnormalities caused by a dysbiosis in the gut, indicating that the gut microbiota may be a contributing factor to the development of ASD (Madra et al., 2021b). However, the exact timing of the microbiome's establishment and, consequently, which factors are more likely to affect the microbiome's development and cause altered neurodevelopment, are still unknown (Dogra et al., 2021).

In this review, a distinction is made between pre-, peri- and postnatal factors. It is essential to investigate which early life factors have a greater influence on the microbiota's development, because doing so could allow for early life interventions. These early life treatments may stop microbiota scarring, which could prevent the development of ASD (Park et al., 2023). Considering all of this led to the following research question: **"Which early life factors impact the gut microbiome, and when and how do they influence the development of Autism Spectrum Disorder?".**

1. Prenatal factors

The prenatal period extends from conception to delivery (Santiago & Huffman, 2015). Interactions between the mother and fetus characterize this stage, during which the fetal gut is shaped by various maternal factors (Adamczak et al., 2024). In this section, the effect of prenatal factors on the child's gut microbiome, and how this contributes to the development of ASD, is discussed.

Maternal BMI

Research has indicated that a mother's pre-pregnancy weight may impact the child's neurodevelopment (Sanchez et al., 2017). A study was conducted by Guzzardi and colleagues (2021), to assess newborns gut microbiota, their cognitive development, along with potential links to maternal obesity during pregnancy. Researchers followed 90 families with newborns, from birth to an age of five. For analysis, faecal samples were collected and cognitive tests were conducted. The findings of this study showed that there was a significant difference in the composition of the gut microbiota in offspring from overweight mothers, compared to lean mothers. A reduction in *Eubacterium* and *Bifidobacterium*, and an increase in *Faecalibacterium* and *Clostridium* were observed in the gut microbiota of children born to overweight mothers. In general, maternal weight had the greatest impact on bacteria in the Firmicutes phylum. Also, it was found that maternal pre-pregnancy overweight was significantly correlated with lower practical reasoning scores. Lower *Bifidobacteria* abundance was discovered to be the primary factor associated with the declined cognitive development (Guzzardi et al., 2021).

The altered gut microbiome in children born to overweight mothers can be linked to the development of ASD. The study by Guzzardi et al. (2021) suggested that maternal overweight during pregnancy may increase the likelihood that the offspring will have an obesity-related gut microbiota as well. The increased Firmicutes/Bacteroidetes ratio that is seen in obese adults (Ley et al., 2006), is also observed in individuals with ASD (Lewandowska-Pietruszka et al., 2023). Additionally, children of overweight mothers had lower levels of *Eubacterium* and *Bifidobacteria*, and the same distinct gut microbiota is observed in individuals with ASD (Ye et al., 2021c). The presence of *Eubacterium* is important due to their ability to produce short chain fatty acids (SCFAs) which improves gut health (Mukherjee et al., 2020). A lack of SCFAs can cause problems by disrupting the epithelial barrier function and by increasing blood brain barrier (BBB) permeability. These disruptions in turn increase the risk of developing ASD, since decreased epithelial barrier function in the gut and increased BBB permeability was found in children with ASD (Bojović et al., 2020).
A significant correlation between maternal pre-pregnancy overweight and cognitive impairment in offspring was also found, with a reduction of *Bifidobacteria* as an important determinant (Guzzardi et al., 2021b). By synthesizing neurotransmitters, *Bifidobacteria* have the ability to directly or indirectly impact the brain's cognitive processes (Y. Chen et al., 2021). As mentioned in the introduction, individuals with ASD have a lower amount of Bifidobacteria (Ye et al, 2021d), and often neurocognitive deficits (Hajri et al., 2022b). This therefore fits the results that were found.
Lastly, the study by Guzzardi et al. (2021) showed that infants born to overweight mothers had higher levels of *Clostridium*. Certain *Clostridium* species can produce harmful toxins, which can reach the brain once it passes through the intestinal barrier, where they can influence the production of neurotransmitters (Argou-Cardozo & Zeidán-Chuliá, 2018). Studies have indicated that individuals with ASD harbour higher levels of *Clostridium* compared to neurotypical individuals (Zuffa et al., 2023). Therefore, *Clostridium* species can, via various mechanisms, play a role in neurodevelopment and thus the onset of ASD.

Maternal diet

Another factor that affects the composition of the mother's own microbiome and, therefore, the microbial bacteria that can be passed on to the child, is her diet (Chu et al., 2016). A study conducted by Liu et al. (2021) found results that align with previously discussed literature on maternal BMI. In this experiment, female mice were given a high-fat diet (mHFD) or a control diet (mCD), after which male and female mice were paired to create offspring. The offspring was given a control diet (oCD) after three weeks (Figure 1A). The Y-maze and novel object recognition test were used to evaluate working memory and long-term memory. Additionally, in the three-chamber sociability test, the sociability of the offspring were tested. It was found that offspring of overweight mothers (mHFD-oCD) exhibited poorer sociability, working memory and long term memory (Figure 1B-E).
Another intriguing finding of this study was that consumption of maternal dietary fiber, rich in *Bifidobacterium animalis* and *Prevotella,* protected their offspring from the cognitive and social behavioural impairments brought on by maternal obesity (Liu et al., 2021). Individuals with ASD have lower levels of *Bifidobacteria* and *Prevotella*, highlighting the importance of these bacteria for social behaviour (Kang et al., 2013; Hajri et al., 2022c).
In a study by Bruce Keller et al. (2017) it has been shown that, even across generations, a HFD diet could contribute to ASD-like behaviour in male offspring (Bruce-Keller et al., 2017). In light of sex bias in autism (Werling & Geschwind, 2013), the sex differences that were found in this study will be discussed later on.

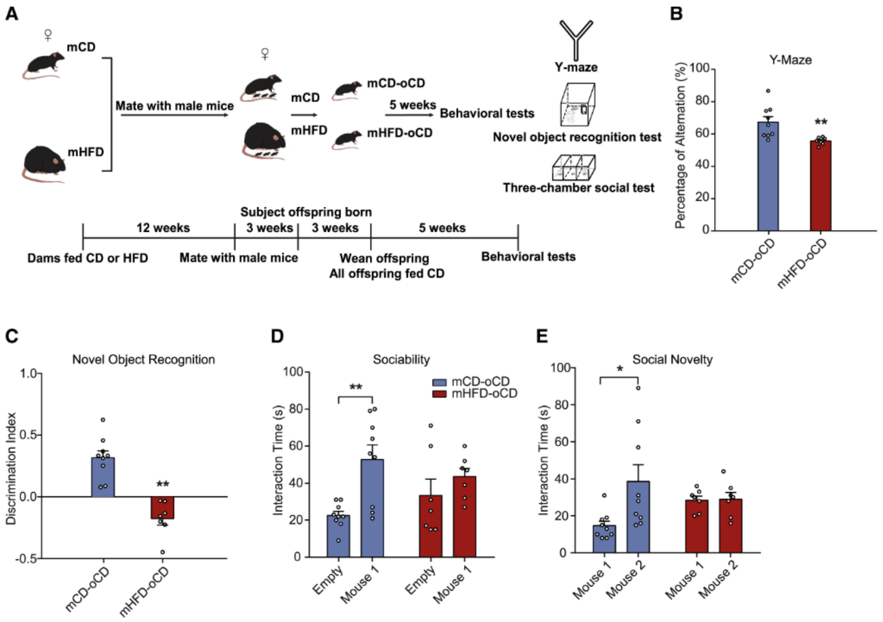

Figure 1: The social and cognitive behaviors of mouse offspring are influenced by maternal obesity. (A) Overview of breeding pattern and diet regimen. (B) Percentage of spontaneous alternations in the Y-maze. mHFD-oCD offspring had fewer spontaneous alternations compared to mCD-oCD offspring. (C) The discrimination index in the novel object recognition test was close to -0.2 for the mHFD-oCD offspring, this indicates that both working memory and long-term memory are impaired. (D) Here the time spent interacting with either a mouse or an empty wire cage was measured, revealing impaired sociability in mHFD-oCD offspring. (E) In the social novelty test, the mHFD-oCD offspring showed no preference for social novelty (Liu et al., 2021).

Human studies have examined the role of maternal diet as a possible risk factor for ASD as well. A case-control study investigated this using 354 typically developing (TD) children and 474 children with ASD. The findings demonstrated a significant correlation between ASD and maternal unbalanced eating practices, such as eating primarily vegetables or meat. Additionally, it was discovered that calcium consumption considerably decreased the likelihood of ASD in children (Li et al., 2018). Reduced calcium intake by the mother can increase the likelihood of developing ASD in offspring, by exacerbating obesity which increases the Firmicutes/Bacteroidetes ratio (Marotte et al., 2013). This altered Firmicutes/Bacteroidetes ratio brought on by obesity is consistent with previously discussed literature, and a feature of ASD (Lewandowska-Pietruszka et al., 2023b). In conclusion, a nutritious diet is crucial during pregnancy, to lower the chance of developing disorders such as ASD in offspring (Borge et al., 2017).

Maternal antibiotic use

Approximately one in four pregnant women worldwide use antibiotics (Orwa et al., 2024). Despite being a necessary treatment option for bacterial infections, antibiotics have long been known to affect the human microbiome. They can alter the microbial composition by reducing microbial diversity, and favouring antibiotic-resistant strains which increases host susceptibility (Patangia et al., 2022).

Antibiotic-induced maternal dysbiosis is believed to be passed on to offspring, with long-term effects on the development of the child's gut microbiome and overall health (Miyoshi & Hisamatsu, 2021). For example, a study conducted by Chen and colleagues (2021) tested the effect of maternal antibiotic use on offspring, in which pregnant mice were given either sterile drinking water or drinking water that contained antibiotics. The administration of antibiotics was stopped right after birth, and on the seventh postnatal day the GI tract of the neonates were analysed. The results were as follows; when compared to the control group, the quantity of commensal bacteria in the gut of neonates were significantly reduced by maternal antibiotic treatment. In particular, the amount of Bacteroidetes and Firmicutes in the intestine decreased when maternal antibiotic treatment was administered, while the amount of Proteobacteria increased. Besides, neonates born to mothers treated with antibiotics had less goblet cells in the epithelium, compared to mice born to controls (Chen et al., 2021). Thus, it can be concluded from this study that the intake of antibiotics by pregnant mice, changes the composition of the offspring's gut microbiota by altering commensal gut bacteria. Interesting to note is that a study that used an ASD-like mouse model, found that treatment with the commensal *Bacteroides fragilis*, resulted in improved anxiety-like behaviours (Hsiao et al., 2013).

Alternatively, another mechanism by which antibiotic use can affect the offspring is by altering the mucous layer. The mucous layer is a barrier that prevents against bacterial invasion, controls epithelial hydration and shields the epithelium from injury. Goblet cells are intestinal cells that produce and maintain this mucous layer, and it has been discovered that treating mothers with antibiotics caused fewer goblet cells in the epithelium of neonates (Franco et al., 2021). Besides, in *Chd8L*$^{+/-}$ mice, a mouse model similar to ASD, a reduced amount of goblet cells was found, which resulted in a thinner mucous layer and increased intestinal permeability (Chatterjee et al., 2023). Individuals with ASD frequently exhibit abnormalities in the intestinal epithelial barrier, which can lead to "leaky gut syndrome" (Dargenio et al., 2023). A reduced amount of goblet cells, induced by antibiotic use, can therefore be a contributing factor to the gastrointestinal problems associated with ASD (Franco et al., 2021b).

In summary, several prenatal factors are covered in the preceding sections. It was found that children born to obese mothers are more likely to develop ASD due to an altered Firmicutes/Bacteroidetes ratio. Also, it was found that mice offspring of HFD mothers exhibited ASD-like behavior. Lastly, administering antibiotics to pregnant mice altered the offspring's gut microbiome, increasing their risk to develop ASD. Importantly, it was found that ASD-like behaviour is reversible when correcting the gut's composition. Treatment with the human commensal *Bacteroides fragilis*, or the intake of dietary fiber, protected the offspring from behavioral abnormalities. This further strengthens the idea that prenatal factors influences behaviour by altering the gut microbiota. Considering the timing, in the study by Chen et al. (2021), antibiotics were administered to mice from gestational day 15 until delivery, highlighting the specific timing of this intervention. In contrast, the effects of maternal BMI and diet impacted the entire pregnancy. In conclusion, it was found that prenatal factors shape the gut microbiota through maternal influence, which affects ASD risk. In the following section, the effect of perinatal factors will be discussed.

2. Perinatal factors

In this review, the perinatal period will be limited to the time of giving birth (Ellenbroek & Youn, 2016), even though it can be more widely defined to include the entire pregnancy and the first four weeks postpartum (Koukopoulos et al., 2019). How the infant's gut microbiota is affected by mode of delivery, and how this influences ASD risk, will be covered next.

Mode of delivery

Research has indicated that mode of delivery is one of the most important factors influencing the composition of the neonatal gut microbiota (Zhang et al., 2021). The gut microbiota of infants born vaginally are similar to their mothers' vaginal microbiota, with a predominance of *Lactobacillus* and *Prevotella*. However, infants born via caesarean section (CS) have a gut microbiota that resembles the skin microbiota of the mother, which is dominated by *Propionibacterium*, *Corynebacterium*, and *Staphylococcus* (Dominguez-Bello et al., 2010).

A study was designed to look into how mode of delivery affected the composition of the gut microbiota in infants. In this study, faecal samples were taken on the third day of life from infants who were delivered vaginally (n=23) and infants who were delivered by CS (n=23). Both groups displayed a distinct gut microbiota, that was significantly impacted by mode of delivery. While no *Bifidobacteria* and *Bacteroidetes* were detected in any of the infants delivered by CS, a wide variety of these bacteria were discovered in the gut microbiota of infants born vaginally. This study emphasizes how important the mode of delivery can be and how, at this early age, it is more significant for modifying the composition of the gut microbiota than for example the type of nutrition (Biasucci et al., 2010). Furthermore, it is crucial to note that according to research, lactations starts later after CS. This implies that infants born through CS also do not receive the benefit of breastmilk, which is a stimulant for the development of a healthy microbiota (Dewey et al., 2003).

Similar results were found in the next study by Reyman et al. (2019). Here, faecal samples were collected from 120 infants, of whom 46 were delivered via CS, and 74 were delivered vaginally. According to the findings, infants born vaginally had greater *Bifidobacteria* levels than infants born via CS. An important remark here, is that breastfeeding did not fully make up for the delayed colonization of *Bifidobacteria* in infants born by CS. This implies that obtaining important bacterial species like *Bifidobacteria* requires maternal transmission during vaginal delivery (Reyman et al., 2019).
In addition, infants that are delivered vaginally also have higher levels of *Lactobacillus* (Dominguez-Bello et al., 2010b). *Bifidobacteria* and *Lactobacillus* are two genera that fall under the category of "psychobiotics" (Darwesh et al., 2024). Psychobiotics are probiotics that are known to have beneficial effects on the host's mental health (Del Toro-Barbosa et al., 2020). Two *Lactobacillus* species (*L. reuteri and L. plantarum*), were found to be significantly less abundant in autistics individuals, according to research (Darwesh et al., 2024b). It has become clear in previous sections that *Bifidobacteria* are crucial for neurodevelopment and that people with ASD have lower levels of these bacteria (Abuaish et al., 2021). Since vaginal delivery supports the colonization of beneficial bacteria such as *Bifidobacteria* and *Lactobacillus*, it supports the development of a gut microbiome that decreases the risk of developing ASD.

To further prove the relation between CS delivery and autism risk, a case control study was conducted. In this study, a correlation was found between ASD diagnosis and CS delivery; a higher risk of ASD was associated with CS delivery (Al-Zalabani et al., 2019). This study also highlights different mechanisms through which CS can be linked to ASD. First, the gut-brain axis; delivery modes are known to alter gut microbiota composition, and animal studies have shown the effect of microbiota changes on social interaction through this gut-brain axis (Vuong & Hsiao, 2016). Secondly, the role of oxytocin appears to be important. Among other things, oxytocin is a hormone that affects social behaviour (Olff et al., 2013), and fetal levels of this hormone are significantly higher during vaginal delivery than during CS (Kenkel, 2020). Additionally, it has been found that oxytocin plasma levels are lower in people with ASD compared to neurotypical individuals (Husarova et al., 2016). Thus, oxytocin dysregulation is thought to impact the infants' brain development and raise their risk of developing ASD (Gialloreti et al., 2014).

In conclusion, mode of delivery appears to be one of the most significant factors affecting the gut microbiota. A clear correlation between CS and ASD risk was found, and it was discovered that CS delivery negatively changes the gut microbiome by lowering levels of *Lactobacillus* and *Bifidobacteria.* Breastfeeding was unable to fully make up for these alterations, underlining the importance of a vaginal birth. In the following section, the effect of postnatal factors on gut microbiota development and ASD risk will be discussed.

3. Postnatal factors

The postnatal period is officially defined as the first six weeks following delivery (World Health Organization, 2010). However, here the postnatal period is defined up to 3 years following delivery, since postnatal factors continue to have an influence by this time, as evidenced by several studies (Somaraki et al., 2024; Korpela et al., 2016). The infant’s gut microbiota experiences colonization and maturation right after birth (Pantazi et al., 2023). Postnatal factors linked to gut microbiome dysbiosis and ASD risk are reviewed in this section.

Diet early years

The choice of whether to use infant formula or breastfeed is highly personal and depends on a variety of factors. Breastfeeding is recommended, since research indicates that it offers numerous advantages, such as modulating postnatal intestinal function and brain development (Savino et al., 2013).

The differences in gut microbiota of healthy infants that were either exclusively breast fed or formula fed have been investigated in a study by Ma et al. (2020). In this study 91 infants were recruited and given either formula or breastmilk for more than 4 months after birth. The results showed that prevalence of *Bifidobacteria* were significantly higher in the breastfed group, while the prevalence of *Streptococcus* and *Enterococcus* were significantly lower. The microbiota of formula fed infants was associated with a higher abundance of *Clostridia* and *Veillonella* (Ma et al., 2020). Overall, the results showed that over the first few months the microbiota of breastfed infants is less diverse compared to formula fed infants, due to the predominance of *Bifidobacteria*. Low diversity of the gut microbiota in adults is linked to illnesses, but high levels of *Bifidobacteria* are advantageous in infants since they play an important role in, for example, the development of the immune system (Derrien et al., 2019; Stuivenberg et al., 2022). Important to note is that some diseases, such as asthma, have been coupled to early life low diversity. However, *Bifidobacteria* abundance or breastfeeding have not been coupled to these diseases (Laursen et al., 2017b).

As discussed before, the microbes in the gut can play a role in neurodevelopmental disorders. It was found that the formula fed group had a higher abundance of the class Clostridia. The genus *Clostridium*, can produce a compound called p-cresol, which can have toxic effects (Stuivenberg et al., 2022b). According to a rodent model of autism, increased levels of p-cresol can amplify the autism-like behaviour in these rats (Pascucci et al., 2020). This theory is further supported by the finding that autistic children have higher levels of p-cresol in their urine (Persico & Napolioni, 2012). *Bifidobacteria*, which were more abundant in the breastfed group, can have protective effects against p-cresol (Stuivenberg et al., 2022c), and therefore guard against autism-like behaviour. The idea that *Bifidobacteria* can protect against neurodevelopmental disorders like ASD, is further evidenced by another experiment, where rats exhibiting behavior similar to ASD were given probiotic *Bifidobacterium longum* treatment. During the course of the treatment, the rats' social impairment was corrected, their microbial diversity was increased, and the high levels of *Clostridium perfringens* were normalized (Abuaish et al., 2021b). Breastfeeding can promote the growth of *Bifidobacteria*, since human milk oligosaccharides (HMOs) provide an optimal environment (Bakshani & Crouch, 2023). In addition to this, a recent meta-analysis revealed that breastfeeding, for any length of time, significantly reduced the risk of ASD by 58% (Ghozy et al., 2019). Thus, the development of a gut microbiome that promotes normal neurodevelopment, may be facilitated by breastfeeding.

Another crucial aspect of an infant's diet that can have long-term health effects, is the introduction to solid foods (Kuo et al., 2010). In a study by Homann et al. (2021), it was assessed how dietary decisions made at the time of solid food introduction, relate to gut bacterial dynamics in a group of healthy, full term, vaginally born babies. It was discovered that *Bifidobacterium* members were positively correlated with dietary diversity (Homann et al., 2021). Since *Bifidobacteria* can protect against neurodevelopmental disorders (Abuaish et al., 2021c), eating a more varied diet might be beneficial. Also the timing of introduction to solid foods seems to be important. In a French cohort, feeding practices of 8511 families were evaluated monthly. The findings indicated that lower neurodevelopmental scores at ages 1, 2 and 3,5 are associated with late introduction to solid foods (i.e. after 10 months) (Somaraki et al., 2024b). Many children diagnosed with ASD exhibit neurodevelopment regression in infancy as well (Martin-Borreguero et al., 2021). Although the results of this study do not support a cause-and-effect relationship, it is possible that there is some correlation between the timing of introduction to solid foods and neurodevelopmental outcomes.

Antibiotic use early years

Previously it was concluded that maternal antibiotic use can alter the gut microbiota of the offspring, and increase ASD risk (Miyoshi & Hisamatsu, 2021b). A study by Korpela et al. (2016) investigated the impact of macrolides and penicillin on the gut microbiota in 142 Finnish children during childhood. In this study, the samples were categorized according to the use of antibiotics: children in the control group (C) had little exposure to antibiotics, while children in the early life group (E) had regular early antibiotic use but no recent exposure. Three other macrolide groups were divided by timing: M6 (use within 6 months), M12 (6–12 months), and M24 (12–24 months). Samples of children who had taken penicillin were organized similarly.
The following results were found; treatment with macrolides was more obviously linked to a change in the composition of the microbiota than treatment with penicillin. Group M6 had a higher abundance of Bacteroidetes and Proteobacteria, and less *Bifidobacteria* in their gut. These alterations were mostly resolved in the M12 and M24 groups, suggesting that the microbiota stabilized again within a year. However, for up to two years following a macrolide course, other changes, including the abundances of *Lactobacillus* as well as the overall richness and maturity of the microbiota, remained decreased (Figure 2). Group E was associated with an increased risk of obesity, which implies that even brief disruptions to a child’s microbiome during infancy could have a lasting impact on their health. Overall, it seemed that it took longer for the gut microbiota to fully recover after an antibiotic course, than the typical time between courses. If antibiotics are used once a year or more, the microbiota might not have time to recover, and the disturbed composition might persist (Korpela et al., 2016b).

Given that gut dysbiosis is associated with altered development of the brain (Mallick et al., 2024), frequent antibiotic use in early stages of life might be harmful for neurodevelopment. The reduced maturity and decreased microbial richness following macrolide use can be associated with ASD, since individuals with ASD exhibit an early immature microbiota (Lou et al., 2021). Additionally, macrolide use decreased the abundance of *Bifidobacteria* and *Lactobacillus*. As previously discussed, research has indicated that infants at a higher risk of developing ASD, have lower levels of *Bifidobacteria* (Zuffa et al., 2023b). A decreased amount of *Lactobacillus*, might contribute to the development of ASD-like symptoms, since treatment with *Lactobacillus reuteri* restored the social deficits of ASD in a rat model. Here *Lactobacillus reuteri* treatment was started from birth, and administered once a day for three weeks (Wang et al., 2024). Given the timing, it seems to be important to start with the treatment right after birth, in order prevent the development of ASD.

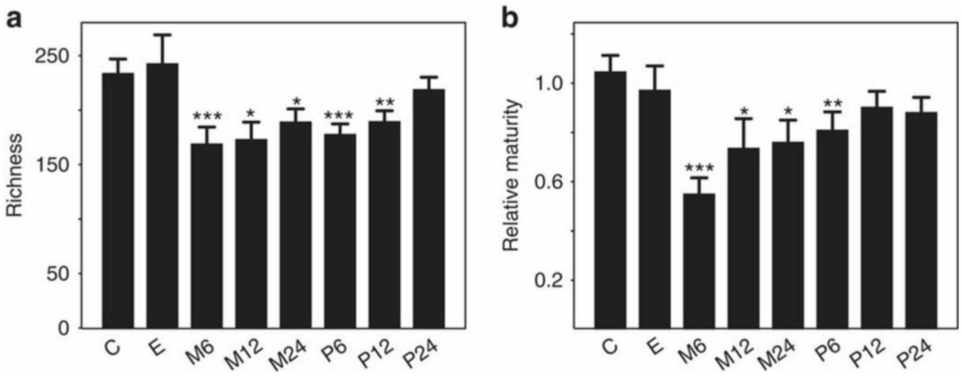

Figure 2: Richness and maturity of the microbiota in relation to age in various groups. (a) Illustrates microbiota richness. Antibiotic use was associated with a long-term depletion of microbial richness, especially for macrolide. (b) Illustrates the maturity index of the microbiota, adjusted for age. Maturity of the microbiota was reduced after exposure to macrolides even after 24 months, and in group P6. The latter indicates that the microbiota restored after a penicillin course within 6-12 months. Significance compared to the control group (C) is denoted using Asterisks: *P<0.05, **P<0.01, ***P<0.001, determined using linear models. Mean values are displayed with error bars representing standard errors (s.e.). N=257 for both panels (Korpela et al., 2016).

A study by Tanaka et al. (2009) examined how Japanese infants' intestinal microbiota developed as a result of early antibiotic exposure. The control group (AF) included 18 subjects who had vaginal deliveries with no antibiotic exposure, while the AT group included five subjects that received cefalexin in their first four days. The CD group was delivered via CS, whose mothers were injected with an antibiotic, cefotiam, postpartum. Compared to the control group, both group AT and CD had a lower gut microbiota diversity that persisted for at least 2 months. The AT group showed reduced *Bifidobacteria* and *Bacteroidaceae,* and increased *Enterococcus* and *Enterobacteriacea ((*Tanaka et al., 2009)*,* which is similar to a gut microbiota composition seen in ASD (Abuljadayel et al., 2024). Group CD showed similar patterns compared to the AT group, indicating that the infant's microbiota is impacted by the mother's postpartum antibiotic treatment. This could be explained by transfer via breast milk, but evidence is lacking demonstrating cefotiam transfer into breastmilk (Tanaka et al., 2009b).

In summary, several postnatal factors are discussed. The first section covered the diet of an infant during their early life, and it has been discovered that breastfeeding facilitates the development of a gut microbiome that promotes healthy neurodevelopment. Additionally, a correlation between the length of breastfeeding and the likelihood of ASD was found, as was the significance of introducing solid foods. Dietary diversity is positively correlated with *Bifidobacteria*, a type of bacteria that guards against neurodevelopmental disorders. Research on the effects of antibiotic use in early life, revealed that antibiotic use causes gut dysbiosis by reducing the amount of *Lactobacillus* and *Bifidobacteria*. This is associated with altered brain development and an increased risk of ASD. However, treatment with *Lactobacillus*, directly after birth, restored the social deficits that were found in an ASD rat model.

Discussion

In this review, the impact of different pre-, peri- and postnatal factors on the gut microbiota are discussed, along with how these factors affect the development of ASD. The research question was as follows: “Which early life factors impact the gut microbiome, and when and how do they influence the development of Autism Spectrum Disorder?”.

To start, the literature showed that all three factors can shape the gut microbiome of the infant. This became evident from several studies demonstrating that these factors significantly alter the composition of the gut, by changing its diversity and richness (Guzzardi et al., 2021c; C. Chen et al., 2021b; Reyman et al., 2019b; Ma et al., 2020b). Since various gut microbes can have a significant impact on neurodevelopment, disruptions brought on by these factors can result in conditions like ASD (Milani et al., 2017b). Figure 3 illustrates the different factors that are discussed in this review on a timeline, according to the corresponding papers.

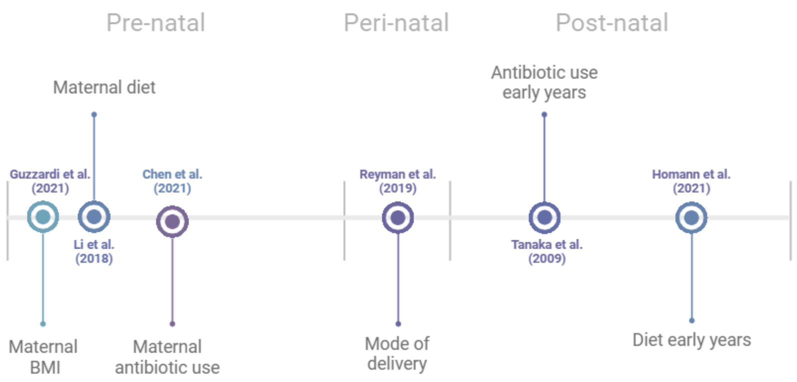

Figure 3: Overview of the different pre-, peri- and postnatal factors. The factors are depicted on a timeline according to some of the papers that were mentioned in this review. Created by BioRender.com.

In order to answer which early life factors have the greatest influence on a gut microbiome that causes ASD, the most crucial bacteria for neurodevelopment and factors that affect the establishment of these bacteria must be identified. A few bacteria have been brought up frequently in relation to neurodevelopment, according to the literature. These are *Bifidobacteria*, *Lactobacillus* and *Clostridium*. Low *Bifidobacteria* was found to be the main factor linked to cognitive decline (Guzzardi et al., 2021d), and the same pattern is seen in people with ASD, who frequently have neurocognitive impairments and a lower abundance of *Bifidobacteria* (Hajri et al., 2022d). The importance of *Bifidobacteria* was further demonstrated when it was shown that treating rats with *Bifidobacteria* improved their social impairment (Abuaish et al., 2021d), and that traits similar to ASD are linked to lower levels of *Bifidobacteria* (Liu et al., 2021b). Lastly, it was illustrated that *Bifidobacteria* can prevent neurodevelopmental disorders, by defending against harmful substances like p-cresol (Stuivenberg et al., 2022d). *Lactobacillus* seems to be crucial for healthy neurodevelopment as well. Together with *Bifidobacteria,* these bacteria are so-called psychobiotics, and they can have an impact on the host's mental well-being (Del Toro-Barbosa et al., 2020b). It became evident that treatment with *Lactobacillus* could alleviate symptoms similar to ASD (Wang et al., 2024b). Finally, research revealed that *Clostridium* contributes to neurodevelopment and the onset of ASD. It was discovered that some *Clostridium* species are capable of producing toxins that enter the brain and affect neurodevelopment (Argou-Cardozo & Zeidán-Chuliá, 2018b). P-cresol is one of these toxins, and it was found that its production heightens the behavior linked to ASD (Pascucci et al., 2020b).

This review's literature demonstrated that the establishment of these bacteria is influenced by a number of factors, rather than just one. With the mother's influence, the gut microbiota's foundation is formed *in utero*. On the other hand, the gut microbiota undergoes significant changes after birth, which are driven by postnatal factors. Thus, it appears that there is an interplay between pre-, peri-, and postnatal factors that increase ASD risk, since multiple windows are identified. However, this interaction is not considered in many of the papers that are discussed in this review. In these papers, solely the effects of one factor were considered (Guzzardi et al., 2021e; Li et al., 2018b; C. Chen et al., 2021c; Biasucci et al., 2010c; Homann et al., 2021b). Therefore, I suggest that in order to identify the most crucial period for gut microbiota development and ASD risk, this interaction should be examined in more depth in future research.

When taking into account the critical window in which the gut and the brain develop, it could be speculated that postnatal factors are more important for shaping the gut microbiota to influence the development of ASD. The first 1000 days after birth (Pantazi et al., 2023b), are a crucial time for the gut's development and this window coincides with the development of the brain (Srikantha & Mohajeri, 2019b). However, based on the findings in this review, no clear evidence was found that postnatal factors increase the risk of ASD more than prenatal factors do. Yet, it does seem that especially the perinatal period is important. A study conducted by Reyman et al. (2019), demonstrated that breastfeeding was insufficient to make up for the decreased levels of *Bifidobacteria* in the guts of children born via CS (Reyman et al., 2019c). This suggested that the gut microbiome is more influenced by mode of delivery than by the diet of the infant.

Early life interventions might stop disorders such as ASD from developing. An example of such an intervention is treatment with probiotics. It became evident that infants born via CS and infants that received antibiotics in early life, had a disturbed microbiota characterized by lower *Bifidobacteria* (Biasucci et al., 2010b; Korpela et al., 2016c). Treatment with probiotics could potentially help restore the microbiota of these infants (Manzoor et al., 2022). Probiotics are live organisms that can have health benefits for the host (Hill et al., 2014), by increasing the amount of beneficial bacteria such as *Lactobacillus* and *Bifidobacteria*, and decreasing the amount of potential harmful bacteria such as *Clostridium* (Huang et al., 2024).
Because of their therapeutic potential, probiotic treatment has been the subject of studies. In a study conducted by Korpela et al. (2018), pregnant women were randomized to either the treatment group, which received probiotics, or the control group, which received a placebo. The probiotic was made up of *Lactobacillus rhamnosus*, *Propionibacterium freundenreichii*, and *Bifidobacterium breve*. For six months following delivery, the infants were given either the same probiotic or a placebo. The findings illustrated that in the placebo group, mode of delivery and use of antibiotics were linked to changes in the microbiota composition, with specifically a decrease in the amount of *Bifidobacteria*. In the group treated with probiotics, the effects of antibiotic use or mode of delivery on the gut microbiota were either eliminated or reduced. Besides, the findings show that the best outcomes for promoting a healthy gut microbiota in infants, was obtained when breastfeeding is combined with probiotic supplementation (Korpela et al., 2018). Therefore, I believe that probiotic treatment is a promising intervention. Especially for children who lack essential bacteria that cannot be compensated for by, for example, breastfeeding (Reyman et al., 2019d). However, more research with adequate power

should be conducted, as there is still little information on this subject, and how it will affect neurodevelopment (Kamphorst et al., 2022).

Another important issue, is determining the ideal timing to reduce breastfeeding and introduce solid foods. Early in life, a healthy gut microbiota is characterized by an abundance of *Bifidobacteria* which is supported by breastfeeding. After being exposed to solid foods, microbial diversity rises and the microbiota eventually takes on more adult-like characteristics (Laursen et al., 2017c). Then, rather than taking probiotics, wouldn't it be more crucial to concentrate on supplementing infants with a well-timed diet to support gut health? To identify the optimal feeding-strategy, longitudinal studies on breastfeeding duration and solid food introduction should be conducted. This could raise breastfeeding awareness, and determine the ideal timing for solid food introduction to maximize brain development of the infant.
However, children with ASD are found to be breastfed for a shorter duration and introduced to solid foods later, since they accept them less well (Xiang et al., 2023). This is an interesting finding with regard to the paradoxical relationship between ASD and the gut, since it implies that behaviours associated with ASD, can lead to an altered gut microbiota. Even though this review provides evidence that alterations in the gut may lead to the development of ASD, it should not be ignored that it can also be the other way around. Or that rather than being causative, the relationship between the gut and ASD is correlative. That would imply that there is an additional factor, such as genetics, that influences the gut and the development of ASD at the same time. Thus, to be able to find the best strategies to improve gut health and neurodevelopment, it is important to investigate this conflicting relationship between the gut and ASD first.

The topic of sex-bias found in ASD will be covered next. In the literature on maternal diet, the altered gut microbiota and behavior of offspring whose mothers consumed a high-fat diet were found to differ by sex. In this study, male mice represented a particular lower amount of Firmicutes phylum members and displayed more ASD-like behaviour compared to the female offspring (Bruce-Keller et al., 2017b). Sex differences in autism is an highly discussed topic. Research indicates that ASD is more common in males than females, with a 4:1 ratio (Nag et al., 2018). This imbalance can be explained in a number of ways, one of which is that males are more susceptible to environmental factors during pregnancy, which alters their behavioral outcomes compared to females (Mueller & Bale, 2007). Since males and females can react differently to prenatal stressors, the composition of the gut can also be shaped in a sex-dependent manner (Valeri & Endres, 2021), which makes males potentially more susceptible for developing a gut microbiome that leads to ASD (Salia et al., 2024). The sex-bias found in the development of the gut microbiota and ASD, highlights the importance of incorporating sex-specific research and treatment options. In order to do this, a cross-disciplinary approach is needed to understand the mechanisms underlying ASD and how the gut microbiota is shaped differently in males and females.

To conclude, this review provides evidence on how an interplay between pre-, peri-, and postnatal factors shape the gut microbiome, which raises the risk of ASD. However, many studies in this review have focussed on one single factor. Therefore, future studies would benefit from studying the interplay between these factors, to determine the critical timeframe for promoting a healthy gut and neurodevelopment. There are some promising strategies in research on ASD, such as probiotic treatment, however, in order to better guide prevention strategies it is important to first resolve the relationship between the gut and ASD. Thus, addressing the “chicken or egg” dilemma, at the core of this paradox.

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