The maternal microbiota is shaping the future generations

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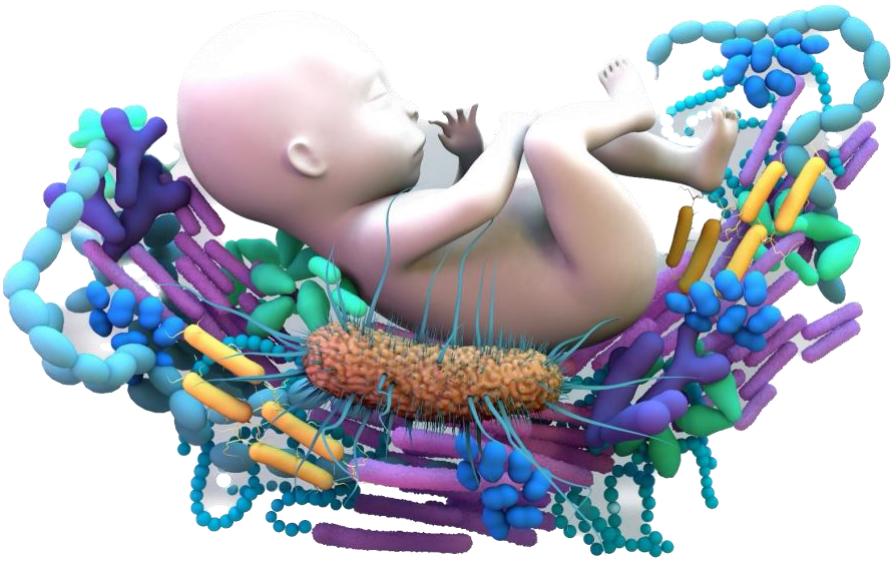

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Abstract

The human microbiota is defined as organisms that use a particular location in the human body as their habitat. Dysregulation of this microbiota has been linked to underdevelopment of the immune system. This can have several consequences, such as allergic diseases. This study aimed to investigate the impact of the maternal microbiota on the development of allergic diseases in the offspring, focusing on asthma, food allergies and atopic dermatitis (AD). It was hypothesized that the maternal microbiota may have a potential influence on allergy development through environmental, genetic and other maternal factors during both the prenatal and post-natal phases.
The sterility of the infant at birth is a topic of ongoing investigation. There are different perspectives on the presence or absence of microbial colonization in the infant at birth. Therefore the understanding of initial exposure to microbial communities and its potential influence on the development of allergic diseases remains unknown. Several maternal factors may play a role in allergy development in the offspring, such as environmental factors. High microbial exposure during pregnancy, such as farming, may contribute to a diverse maternal microbiota and protect against allergic diseases in the offspring. Besides environmental factors, also genetic factors may have a potential role in this, but several studies show that these factors are relatively weak compared to environmental influences.
Also maternal antibiotic use can alter the composition and diversity of the maternal microbiota and potentially impact the offspring's immune system and in turn lead to allergy development, in specifically asthma. Another maternal factor that may disrupt normal immune development in the offspring is maternal obesity, which is shown to decrease microbial diversity, further supporting the relationship between the maternal microbiota and the development of allergic diseases in the offspring. Conversely, a high-fiber diet during pregnancy has been associated with protection against asthma development in the offspring.
Food allergies are associated with the oral and gut microbiota. Maternal factors such as delivery method and breastfeeding can influence the composition of the oral microbiota and reduce the risk of food allergies in the offspring.
Lastly, also the skin and gut microbiota may play significant role in the development of allergic diseases, in particular AD. The skin microbiota interacts with the immune system, suggesting that infants with greater diversity of their skin microbiota, may have a reduced susceptibility to allergic diseases. Interestingly, delivery method of birth may not have a strong influence on the development of AD, unlike other allergic diseases.
In conclusion, the maternal microbiota may influence the development of allergic diseases in offspring through various maternal factors. However, it is necessary to perform future research, like early-life interventions and longitudinal studies to gain better knowledge about the development of allergic diseases and the influence of the maternal microbiota. This knowledge can lead to targeted interventions and personalized approaches to reduce the risk of allergic diseases in offspring.

Introduction

Bacteria, viruses, archaea and eukaryotes live inside the human body. As it may sound weird, but we need these organisms to survive. They namely form the human microbiota (Ogunrinola et al., 2020). A complex term that is used to define organisms that use a particular location in the human body as their habitat. This has implications beyond the negative, because these organisms have effects on the human body both in health and disease (Ogunrinola et al., 2020). Locations of the habitats of these organisms can be the skin, the gastrointestinal tract, and the respiratory tract. The microbiome is another term which refers to the genomic content of these organisms. The microbiota evolves fast over time and lifestyle, hormonal changes, nutrition and genes can have a lot of impact. A drastic change can lead to life-threatening situations (Ogunrinola et al., 2020).

Over the years, there is an increased interest in how dysregulation of the microbiota plays a part in the development of the immune system and therefore also in the allergy development (Bunyavanich & Berin, 2019).
An allergic disease is characterized by an aberrant immune response to a certain substance which is identified by the body as harmful, but in most cases it is not (Allergies - Symptoms and Causes - Mayo Clinic, 2022). These substances which cause an allergic reaction are called allergens and they are linked to the antibody immunoglobulin E (IgE), produced by the body (Allergies and the Immune System, 2021). The invasion of microbes and substances is quickly recognized by the innate immune system (Institute for Quality and Efficiency in Health Care (IQWiG), 2020). This system activates intra- and extracellular downstream signaling pathways, like activation of CD4+ T cells and T-helper type 2 (Th2) cells (Lamiable et al., 2020). These cells activate an inflammatory immune response (Maeda et al., 2019b). When you encounter an allergy, high amounts of IgE are produced against an benign substance, IgE travels to the cells and discharge chemicals which initiates a chain of events resulting in a allergic immune response (Janeway & Travers, 1994). Food allergies, asthma and atopic dermatitis (AD) are allergies that are very common. Not only genetic factors, but also environmental factors contribute to the dysregulation of the immune system and therefore potentially to the development of allergic diseases (Liu et al., 2009).
The link between the development of the microbiota and allergic diseases are elucidated by different hypothesis. In 1989 Dr. David Strachan formulated the “hygiene hypothesis” which states that children in larger households and younger siblings had decreased chances of developing allergic diseases like AD and asthma. The reason for this is that being infected, e.g. with diverse bacteria, in early childhood can prevent the development of allergic diseases. (Van Tilburg Bernardes & Arrieta, 2017). Additional hypothesis are the “old friends” hypothesis and the “biodiversity hypothesis”. They state that the reason for increased rate in allergies worldwide is because of the decreased commensal relationship between humans, parasites and bacteria (Hanski et al., 2012), (Rook, 2012).

Since there may be a relationship between the microbiota and the development of allergic disease, it is crucial to acknowledge the influential role of maternal factors in this context.
After pregnancy the offspring is exposed to the maternal microbiota via e.g. birth and breastfeeding, which suggest that there are post-natal maternal factors that play a role in the development of the microbiota of the offspring. Besides that, there are speculations that the development of the microbiota of the offspring initiates during the prenatal phase, implying

there is a maternal influence already before birth, potentially contributing to the development of the microbiota of the offspring (Abrahamsson et al., 2015). This means that not solely the exposure to maternal microbial communities during the initial months of life have an impact on allergy development, but also the microbial exposure during pregnancy may play an important part in the prevention of allergic diseases. The maternal microbiome goes beyond the well-being of the mother, because these indications suggest it also affects the health of the infant. Since this is a currently widely discussed topic, the primary focus of this paper revolves around how the maternal microbiota influences allergic diseases in the offspring, focussing on asthma, food allergies and AD.
It is hypothesized that the maternal microbiota has a significant impact on the development of allergic diseases in the offspring, via environmental, genetic and other maternal factors. This influence is not limited to post-natal exposure through birth and breastfeeding, but also extends to the prenatal phase, suggesting a dual role of maternal microbial exposure in preventing allergic diseases.

Research findings

The development of the microbiota

The gut microbiome consists of an enormous number of commensal bacteria and these microorganisms exert influence on the host's state during homeostasis and disease. Several factors lead to colonization of intestinal bacteria, which can play a crucial role in maintaining immune and metabolic homeostasis (Thursby & Juge, 2017). The gut microbiota is composed of various phyla, with *Bacteriodetes* and *Firmicutes* being dominant, while also *Proteobacteria*, *Actinobacteria*, *Fusobacteria* and other phyla are present (Carding et al., 2015). These different phyla are regulators of intestinal inflammation by expansion of regulatory T cells (Treg), stimulation of anti-inflammatory cytokines and regulation of pro-inflammatory cytokines (Bryant, 2019). Dysbiosis of the gut microbiota defines a reduction in microbial diversity in combination with the loss of beneficial bacteria, such as *Firmicutes* (Humphreys, 2020). An altered gut microbiota has therefore been associated with inflammatory diseases and infections, such as autoimmune diseases (Thursby & Juge, 2017). This demonstrates a correlation between a healthy gut microbiota and the overall health and well-being (Jandhyala et al., 2015).
The importance of the microbiota is evident, as its colonization has great impact on the development of the immune system (Rodríguez et al., 2015). Therefore it makes sense that the human microbiota gained attention. There are different studies that are debating whether the microbiota is formed pre- or postnatally.
It has been assumed for a long time that the human fetus is sterile and that bacterial exposure starts in the birth-canal. In this location, the newborn will get their first microbial exposure from their mother. Neonates born vaginally, obtain mostly *Lactobacillus* and *Prevontella*, which are bacteria that are highly present in the maternal vaginal microbiome. This differs from neonates born via a caesarean section, who acquire mostly *Staphylococcus*, which is the predominant microbe on the skin (Dominguez-Bello et al., 2010). These bacteria would colonize the skin, mouth, intestine and upper airways.
Although this dogma was widely accepted, recent studies show different outcomes, demonstrating that they found bacterial communities already present in the placenta, amniotic fluid, and meconium in healthy pregnancies (Stinson et al., 2019). These findings

suggests that the microbiota formation of the infant already starts in utero, but underlying contamination issues cause reasons for debate. The study from Stinson et al. uses methods that reduce contamination in the microbiome and therefore has more valid results. The findings of this study shows that DNA and short-chain fatty acids (SCFAs) are detected in utero, and may potentially regulate the development of the fetal immune system (Stinson et al., 2019). In addition to that, another study also shows that a low diversity and low richness of *Proteobacteria* was found in the maternal placenta and amniotic fluid, which suggests a transfer of microbes between the feto-maternal interface (Collado et al., 2016). This study concludes development of the microbiota, independent on the delivery mode, is initiated prenatally in the placenta and amniotic fluid. The Ardissone et al. study adds that colonization of the infant's gut starts in utero, potentially through the ingestion of amniotic fluid (Ardissone et al., 2014).
These studies are still ongoing and therefore there is no definite proof regarding the infants sterility at birth. However, the maternal influence on the development of the microbiota of the offspring remains significant. Numerous prenatal and post-natal maternal factors have been identified that can potentially have impact on the composition of the microbiota in the offspring, consequently influencing the development of allergic diseases.

Maternal influence

Several studies have been done that link the maternal microbiome to allergic disease in the offspring. Even though the underlying immunologic mechanisms are poorly understood, there is growing interest in investigating the potential impact of environmental factors on the maturation of the maternal microbiota. Exposure to environmental factors through inhalation, absorption, and ingestion can be contributing factors in this process (Bolte et al., 2022). To get a deeper understanding of the relationship between environmental factors and the development of allergic diseases, Schaub et al. study initiated a research on analyzing the activation of regulatory T (Treg) cells in cord blood (Schaub et al., 2009). Findings show that exposure to farming during pregnancy is associated with higher expression of Treg cells in cord blood. Treg cells promote the development of the fetal immune system and play a role in the protection against the development of allergic diseases. Therefore it can be suggested that maternal environmental exposure of certain bacterial communities may have an impact on immunity development via Treg cells and therefore may have a protective effect against AD and potentially other allergic diseases in the offspring. The potential involvement of environmental factors in the development of allergic diseases is further supported by an additional study which performed a research on the first-pass meconium (Tapiainen et al., 2018). They found that having more furry pets during pregnancy led to an increase in the variety of the microbiota, the total count of operational taxonomic units (OTUs), and the relative abundance of OTUs, which belong to the *Bacteriodetes phylum* and *Fecalibacterium genes.* This observation suggests that a higher level of diversity in the prenatal maternal living environment, enhances the diversity of the microbiome in the offspring. It also suggests the in utero transfer of microbes.
The two studies mentioned above provide evidence that environmental factors may have an influence on the maturation of the microbiota development in the offspring. Considering the involvement of the microbiota on the development of the immune system and therefore association with allergic diseases, it can be speculated that environmental factors might contribute to the development of allergic diseases.

There is ongoing research about the involvement of genetic factors in the development of the microbiota and therefore their correlation with allergic diseases. In order to focus on genetic influences exclusively, environmental factors need to be minimized as much as possible. One effective approach that was done in human studies, were Twin studies (Kurilshikov et al., 2017). These provided valuable insight into the heritability of the microbiome by comparing monozygotic (MZ) and dizygotic (DZ) twins. Throughout these studies it is assumed that the twins experience similar environmental conditions in order to emphasize genetic influences only. Over the years, there are some variabilities between different studies. Earlier studies showed results indicating no significant difference in the composition of the gut microbiome between MZ and DZ twins (Turnbaugh et al., 2009). Conversely, more recent studies used an increased sample size, and therefore suggest that the host genetics of the gut microbiome can influence the development of the gut microbiome (Goodrich et al., 2014). Using 16S rRNA gene-based analysis, these studies were able to identify the most heritable microbial community family called *Christensenellaceae (phylum Firmicutes).* It was found that transplanting the microbiome with this particular taxon to an obese-associated microbiome, resulted in the reduction in weight gain in transplanted germ-free mice. These findings suggest that there is a link between host genetics, the composition of the human gut microbiome, and therefore suggesting it may influence the development of allergic diseases, such as food allergies. Another twin study study showed evidence for the heritability of different microbial taxa and functional modules in the gut microbiome (Xie et al., 2016). These modules can be related to susceptibility to complex diseases, including allergic diseases. Additionally, this study found that as twins were experiencing different environmental factors, the microbial similarity between the twins decreased, suggesting that environmental influences play a predominant role in shaping the composition of the gut microbiome. Another study provide additional evidence that support this statement. It shows that non-twins have a similar bacterial similarity when sharing a household. For family members who did not share a household, this similarity in bacterial composition is not observed (Song et al., 2013).
These findings indicate that genetic factors may only have a modest impact on the microbiome development, and environmental factors play a dominant role in this process.
In addition to human studies, also mouse models were used to achieve more control over genetic and environmental factors. A research performed on mice, demonstrated via a murine mice model that inbred lines with genetic variations had a different microbiota, while reciprocal hybrids with identical genetics showed a more similar microbiota (Korach-Rechtman et al., 2019). This is one finding that provides evidence that host genetics influences the composition of the gut microbiota.
The findings of these studies indicate evidence that besides environmental factors, also genetic factors play a minor role in the development of the maternal microbiota, subsequently influencing the development of the microbiota in the offspring. Consequently, it can be suggested that genetic factors may have an influence on the development of allergic diseases.
Besides environmental and genetic factors that may have an impact on allergy development, there are several other maternal factors can have an impact on the immune development of the infant and their ability to tolerate different antigens.

Asthma

Asthma is referred to as a chronic respiratory condition that affects the airways in the lungs. It is characterized by inflamed and narrowed airways. Individuals with asthma experience difficulties in breathing out (*What Is Asthma? | NHLBI, NIH*, 2022).

Maternal antibiotic use during pregnancy gained interest due to its potential impact on the health of both the mother and the offspring. Antibiotics can alter the composition and diversity of the maternal microbiota and therefore have consequences for the offspring (Blaser & Bello, 2014). A meta-analysis and showed that maternal antibiotic use during pregnancy may increase the risk of asthma and AD, but not food allergy, and therefore that prenatal use of antibiotics increases the risk of developing allergic diseases in the offspring (Zhong et al., 2021), (Jedrychowski et al., 2006), (Stokholm et al., 2014). It has been found that maternal antibiotic use has a profound impact on the infants gut microbiota (Patangia et al., 2022). Antibiotics are helpful in targeting harmful bacteria, but they also decrease the microbial diversity of the infant's gut and disrupt the balance of microbial communities (Patangia et al., 2022). Diversity of the microbiota is crucial for the development of the infant's immune system.

Therefore, maternal antibiotic use during pregnancy may have big consequences on the infant's gut microbiota, causing it to be out of balance and less diverse which lead to an increase risk of immune-related conditions, including asthma. However, the severity of this respiratory disease depends on the dose, type and timing of the antibiotic use (Loewen et al., 2018). This is due to the potential development of antibiotic resistance. Misusage of antibiotics can lead to the survival of bacteria which can acquire bacterial resistance. Underuse and incomplete treatment courses can therefore lead to continuous proliferation of the bacterial community, which has an impact on the severity of respiratory diseases (Davison et al., 2000).

The influence of maternal factors on the development of asthma in the offspring is well-established. In addition to antibiotic use during pregnancy, maternal obesity may also be a potential risk factor for the development of asthma in the offspring (Forno et al., 2014).

The association between maternal obesity and the development of allergic diseases, revolved around multiple factors and remains a bit unclear. It is thought that maternal obesity can influence the immune system by altering the balance of pro-inflammatory and anti-inflammatory factors, which can potentially disrupt the normal immune development in utero (Thakali et al., 2014), (Castellana et al., 2018). On top of that, there are multiple studies showing that individuals with obesity tend to have a less diverse microbial community compared to those without obesity (Gong et al., 2022). Overall, there is one key risk factor identified, which is the decrease in diversity of microbes shown in people with obesity (Harpsøe et al., 2013). This suggests that there is a link between maternal obesity and the reduced diversity of the microbiota. Given the suggestion that the maternal microbiota influences the establishment of the microbiota in the offspring and therefore is also implicated in allergic disease, it may be plausible to speculate that maternal obesity may contribute to the development of allergic disease, specifically asthma, in the offspring.

Since maternal obesity can increase the risk of asthma development on the offspring, the Thorburn et al. study shows the importance of the maternal diet during pregnancy. They show that the significance of a high-fiber diet can provide protection against the development of asthma in the offspring (Thorburn et al., 2015b). A high-fibre diet, increases the SCFA production and additionally another study shows that SCFA may have beneficial effects on the immune system and suggests that supplementing can help the maturation of dendritic cells

(Trompette et al., 2014). These cells will then be less likely to trigger certain immune responses in the lungs that are associated with asthma.
From these results can be speculated that maternal antibiotic use, maternal obesity and diet can play a big role in the development of allergic disease in the offspring.

Food allergies

Food allergies are characterized by an adverse immune response after exposure to a specific type of food (Moore et al., 2017). The immune response can lead to various symptoms like hives, itching, swelling and difficulties breathing. There is an increased research interest in the relationship between food allergies and the oral and gut microbiota (Tuniyazi et al., 2022). Multiple studies suggest that alterations of the microbiota may potentially contribute to the development of food allergies (Ling et al., 2014), (Rivas et al., 2013).
During the birth process, maternal factors can influence the development of food allergies, as the delivery method has an impact on the composition of the oral microbiota. A research by Holgerson et al. suggests that infants delivered vaginally acquire an oral microbiota which closely resembles the mother's vaginal microbiota, while infants born via a cesarean section show a oral microbiota with resemblance to the microbiota found on the skin (Holgerson et al., 2011).
Further more, another study shows that during the initial 18 months of life, the oral microbiota of the infants was shaped by their parents. The bacteria shared were both associated with health and disease (Jo et al., 2021). Therefore it can be postulated that factors such as breastfeeding and exposure to a varied microbial environment may have a great impact on the development of the immune system, subsequently decreasing the risk of allergic diseases (Von Mutius & Vercelli, 2010). Breastfeeding is recognized as a maternal factor that potentially influences the risk of food allergies in infants by having a protective effect. It consists of varying levels of oligosaccharides, immuno-active molecules, vitamins, metabolites and microbes (Boquien, 2018). The microbiota in breastmilk differs per individual and therefore it can be said that exclusive breastfeeding infants still have a change of developing food allergies. However, there are bacterial communities present in breastmilk that are associated with food allergies in infants. (Wang et al., 2022). The mechanism how breastmilk decreases the susceptibility of developing food allergies in infants, is not yet well understood. Wang et al. shows several hypothesis showing the potential mechanisms involved. *Bifidobacterium*, a beneficial bacteria present in breastmilk, may influence the development of food allergies by intestinal colonization. In one study, it is recognized that Bifidobacterial supplementation to pregnant women prevents allergy development in the infant (Enomoto et al., 2014). The reason for this may be because *Bifidobacteria* expands the diversity of certain polysaccharides targeted by degradated bacteroides and additionally activates certain genes in the host which are involved in innate immunity (Turroni et al., 2008). Therefore, breastfeeded infants that obtain an increase in *Bifidobacterium* are more likely to have a better developed innate immune system and are more protected against the development of allergic diseases. Besides beneficial bacteria present, also butyrate-producing bacteria are found in breastmilk. These bacteria, such as *Fusobacterium* and *Ruminococcus*, produce butyrate (Wang et al., 2022). Butyrate is found to have a protective immune and non-immune response against food allergies (Di Costanzo et al., 2021). However, the full working mechanism of these bacteria are not well understood.
Based on these findings, it can be suggested that maternal factors play a significant role in the prevention of allergic diseases, such as food allergies, in the offspring. The mode of delivery

during childbirth has been shown to impact the bacterial diversity within the infant's oral microbiota. Since the composition of the oral and gut microbiota might contribute to the development of allergic disease, it can be said that the maternal factor 'mode of delivery' can influence the development of allergic disease in the offspring. Furthermore, the presence of specific bacterial communities present in breast milk has been associated with food allergies. This suggests that breastfeeding may also have a role in preventing allergic diseases in the offspring. However, the precise mechanisms are not yet completely understood.

Atopic Dermatitis (AD)

Atopic dermatitis (AD), is often referred to as eczema. It is a chronic inflammatory skin condition, characterized by redness, irritation and inflammation. Symptoms of AD can be intense itching which can lead to further symptoms like skin redness, swelling and scaling (Branch, 2023). The skin and gut microbiota are found to be closely related to the development of AD (Park et al., 2020). Research shows that the bacteria on our skin interacts with our immune system and therefore can affect how our skin functions as a protective barrier (Wollina, 2017).

Interestingly, AD is not strongly associated with being born through cesarean section, unlike other allergic diseases (Laubereau, 2004). This could be because *Staphylococcus* and *Corynebacterium* are highly present in operating room in the hospital environment (Shin et al., 2015), which are beneficial microbes found on the skin (Carmona-Cruz et al., 2022). This suggests that being in touch with these bacteria can protect the infant from being colonized by bacteria that might trigger AD. Besides skin microbiota involvement in AD, also the gut microbiota is involved (Craig, 2016). It was found that children with AD have less abundance of certain bacterial species in their gut, in specific *Lachnobacterium* and *Faecalibacterium* (Galazzo et al., 2020). These findings suggest that adjusting the balance of bacteria in the gut, might prevent the development of AD. This is done by Rø et al. showing that oral supplementation of *Lactobacillus* and *Bifidobacterium* can reduce the change of developing AD in infants (Rø et al., 2017).

These findings suggest that the maternal factor 'mode of delivery' does not have an immediate impact on protecting against the development of AD. Additionally, as previously mentioned, the composition of the gut microbiota is an important factor in the development of AD, primarily due to its influence on the maturation of the immune system. The maternal gut microbiota may potentially shape the microbiota of the infant, suggesting that maternal factors may contribute to the preventing of allergic diseases, such as AD, in their offspring.

Discussion

Dysregulation of the microbiota has emerged as a critical factor associated with the development of the immune system and the pathogenesis of allergic diseases (Bunyavanich & Berin, 2019). Allergic diseases are characterized by an aberrant immune response to substances, known as allergens, which are identified by the body as harmful, although they are typically nots (Allergies - Symptoms and Causes - Mayo Clinic, 2022). Maternal factors may have a substantial influence in the development of allergic diseases in the offspring, given that the infants are exposed to the maternal microbiota through several routes.

This study aimed to clarify the impact of the maternal microbiota on the development of allergic diseases in the offspring, with a particular focus on asthma, food allergies and AD. It was hypothesized that the maternal microbiota affects the development of allergic diseases in

the offspring through a combination of environmental, genetic, and other maternal factors, both during the prenatal as the post-natal phase.

Since the microbiota has a crucial role in the immune system development, there is an increased interest about its formation and colonization (Rodríguez et al., 2015). Traditionally it was believed that the human fetus was sterile until birth, and obtained its first bacterial exposure during delivery (Dominguez-Bello et al., 2010). Nevertheless, there are recent studies challenging this notion, suggesting that the infant already is exposed to microbial communities in utero. Even though there is a lack of definitive proof of the infants sterility at birth, there are speculations about the influential role of maternal factors shaping the offspring's microbiota and potentially impacting the development of allergic diseases. Future research should further investigate the sterility of the infant at birth to gain a better understanding about the presence or absence of microbial colonization. This exploration will be advancing for our comprehension of the maternal influence on the infants microbiota during both the prenatal and postnatal phases and therefore can give insights in the development of allergic disease in the offspring.

Exposure to environmental factors may contribute to the development of the maternal microbiota (Schaub et al., 2009). In this paper contradictory findings have been reported, indicating that environmental factors may not be associated with the development of the maternal microbiota. Consequently, suggesting that high microbial environmental exposure during pregnancy can not prevent allergic diseases (Kortekangas et al., 2020). However, there were other studies suggesting that exposure to a rich microbial environment, like farming, can contribute to the development of a diverse maternal microbiota and can therefore protect against development of allergic diseases in the offspring (Tapiainen et al., 2018). Overall, most researches indicate that environmental factors play a role in the development of the maternal microbiota and therefore it can be suggested that environmental factors may play a role in allergy development in the offspring. Future research is required to get a perfect understanding about the complex interaction between environmental factors, maternal microbiota development and the risk of allergic disease in the offspring.
Besides environmental factors, there is also ongoing research about the influence of genetic factors on the development of the microbiota and their correlation with allergic diseases. Findings of the studies indicate that environmental influences play a dominant role over genetic factors in shaping the composition of the gut microbiome (Xie et al., 2016). This suggest that genetic factors influences are relatively weak on the microbiome development. Besides that, several studies cited in this paper utilized mouse models, raising the question of how representative these models are for human microbiome research. Hence, it is crucial to conduct further investigations to deepen the understanding of the impact of genetic factors on microbiota development in the offspring and their potential association with allergic diseases.

Several studies in this paper indicate that maternal factors, such as antibiotic use and maternal obesity can increase the risk of asthma development in the offspring. Maternal antibiotic use can alter the composition and diversity of the maternal microbiota, potentially impacting the offspring's immune system (Zhong et al., 2021). Maternal obesity may play a risk factor for asthma development in the offspring, possibly due to disruption of normal immune development (Thakali et al., 2014), (Castellana et al., 2018). A decrease in microbial diversity

in individuals with obesity further support this relationship (Harpsøe et al., 2013). Additionally, a high-fiber diet during pregnancy has been associated with a protective effect against asthma development in the offspring, potentially due to increased SCFA production (Trompette et al., 2014), which have a beneficial effects on the immune system. These findings together suggest that there are several maternal factors, such as antibiotic use, maternal obesity and diet, that may contribute to the development of allergic diseases in the offspring. However, to gain a better understanding of this relationship, long-term follow-up studies need to be performed and track the development of the offspring from pregnancy to adulthood. This can provide valuable insight into the long-term effects of maternal factors on allergic disease.
On top of that, there is growing interest in the relationship between food allergies and the oral and gut microbiota (Tuniyazi et al., 2022). There are several maternal factors that may contribute to the risk of developing food allergies. First, during birth the infant is exposed to the maternal microbiota and therefore the delivery method may affect the composition of the oral microbiota (Holgerson et al., 2011). Besides that, also breastfeeding is shown to play a significant role as a maternal factor that can potentially reduce the risk of food allergies in infants due to containment of several components. However, the complex mechanism through which breast milk decreases the susceptibility to food allergies is not yet well understood. Therefore it is necessary to do early life interventions and further investigate the microbiota and immune system of the offspring during early life, which may give promising strategies for preventing food allergies. Certain studies that may give potential results can be about probiotic or prebiotic supplementation, dietary interventions or other targeted microbial therapies.

Lastly, the skin and gut microbiota have been found to play a significant role in the development of AD (Park et al., 2020). The microbiota on the skin can interact with the immune system (Wollina, 2017). This suggests that infants exhibiting a greater diversity of their skin microbiota, have a better developed immune system, which in turn may lead to a reduced susceptibility to the onset of allergic diseases. Interestingly, AD is not strongly associated with a cesarean section, unlike other allergic diseases, possibly due to the presence of beneficial microbes in the hospital environment (Shin et al., 2015). Therefore it can be concluded that delivery method does not play a role in the development of AD in the offspring, but it can for other allergic diseases. Furthermore, the gut microbiota also influences development of AD and therefore supplementation of certain microbes can potentially lead to reduction in the risk of developing AD in the offspring(Rø et al., 2017).

Overall, it can be concluded that the maternal microbiota influences the development of allergic disease in the offspring, mediated through various maternal factors. However, future research is needed to expand the understanding in this field. Longitudinal studies tracking the development of allergic diseases in offspring from pregnancy to adulthood are essential to gain a better understanding of the long-term effects of maternal microbiota involvement on allergic diseases in the offspring. These kind of studies can help provide valuable insights into the interactions between the maternal microbiota, environmental factors, genetic factors and other maternal factors involved in the development of allergic diseases. By understanding these complex mechanisms, there can be targeted interventions and personalized approaches be developed to reduce the risk of allergic diseases in the offspring. These future directions will improve our knowledge and cause improvements in preventing allergic diseases, specifically in the context of the maternal microbiota.

Afterword

Dear readers,

as I am closing my thesis, I would like to take a moment to reflect and share a few words with you. Throughout my academic journey, there was one course in particular that gained my interest: Endocrinology. This course fascinated me and I knew I wanted to deepen my knowledge in this field of the biology. The course coordinator of this course is Marijke Faas, so when I had to write my thesis, I was very grateful that Marijke Faas was willing to supervise me. When looking for a subject, I came across the involvement of the microbiota in allergic diseases, which piqued my curiosity. This exploration became the foundation of my thesis, and I am very thankful to Marijke Faas for guiding me in this direction.

Writing this thesis served as one of the final courses in completing my Bachelor's degree in Biology with a major in Biomedical Sciences. I thoroughly enjoyed writing my thesis and still am delighted with the topic I chose. As I conclude this chapter of my academic journal, I carry with me a sense of accomplishment, but also recognize that there is still much more to learn and discover.

Thank you for taking time to read my words.

With gratitude and warm regards,

Ruth Hommels

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