Elective Cesarean section, microbiome and asthma

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Abstract

Background There has been an increase in the frequency of elective cesarean section (CS) during the last decades. Also the number of children diagnosed with asthma has increased. It has been discussed if there is any relation between being delivered by elective CS and developing asthma. It has been suggested that the gut microbiome of the newborn affects the risk of developing asthma later in life, and that the mode of delivery has an impact on the microbiome of the newborn.

Method This study investigates possible correlations between elective CS and the microbiome of the newborn and the development of asthma. A systematic literature search resulted in the four articles used.

Results Two articles find an association between asthma and elective CS. This is indicated by several variables; higher salbutamol prescription, asthma requiring hospital admission, wheezing and increases in FeNO levels in air exhaled. One article finds that children born by elective CS have a different composition of fecal microbiome compared with children born by vaginal delivery (VD). This is also seen
in another article, which found a less diverse microbiome in allergic children. The findings are seen for *Bifidobacterium* especially.

**Discussion** There are many confounding factors to keep in mind, for example, differences in breastfeeding and the socio-economic background of the mothers. The size of the study group and the length of follow-up period are discussed, concerning bias. Furthermore, local variations in pre-operative use of antibiotics and the normal bacterial flora may bias the results.

**Conclusion** All together, the four articles indicate an association between elective CS, microbiome diversity and the development of asthma. This is in accordance with earlier findings, but needs to be further investigated in the future to establish a causal link.

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**Abbreviations:** CS, cesarean section; VD, vaginal delivery; FeNO, fractional exhaled nitric oxide.

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**Introduction**

The frequency of elective cesarean section (CS) has increased during the last decades. At the same time, the number of children diagnosed with asthma has increased. It has therefore been speculated that a causal link might exist between elective CS and asthma.\(^1\)\(^2\) It has been hypothesized that the gut microbiome of the newborn affects the risk of developing asthma later in life.\(^3\) It is known that children delivered by CS avoid the exposure to bacteria in the mother’s vaginal and anal tracts that occurs in a vaginal delivery (VD). This difference in exposure has been shown to alter the microbiome of the newborn.\(^4\)

The newborn infant is exposed to a wide range of new bacteria in the world outside the womb. According to the hygiene hypothesis, our clean modern world causes the immune system to react on our own bodies, thereby increasing the risk of developing asthma and other diseases. The infant’s first contact with vaginal and anal bacteria in the mother during VD may thus play a protective role.

Several studies have found regional differences in the colonizers of the newborn’s gut.\(^5\)\(^6\)\(^7\)

Some bacteria, such as *Bifidobacteria, Enterococci* and *Lactobacilli*, seem to protect against allergy.\(^8\) In contrast, colonization with *Clostridium species* has been associated with development of allergy.\(^9\)\(^10\) Children born by CS are seen to have a different gut microbiome, dominated by environmental bacteria.\(^7\)

The aim with this study is to assess the hypothesis that the altered gut microbiome in children born by elective CS results in a higher incidence of asthma, compared with children born by VD. This is done by a systematic study of the literature on this topic.
Methods

LITERATURE SEARCH

A systematic literature search was performed using PubMed and Web of Science. A PICO-schedule (Population, Intervention, Comparison and Outcomes) was used to help defining and structuring the search (Figure 1). To minimize confounding factors, the study population was defined as healthy women of maximum 35 years of age with full-term and uncomplicated pregnancies. The intervention was either elective cesarean section (CS) or vaginal delivery (VD). The newborns were followed up to school age. This was considered sufficient since most asthma patients develop their first symptoms during the first 5 years of life.

Three combinations of search terms were used:

A: “(Caesarian OR Cesarean section) AND asthma”

B: “(Caesarian OR Cesarean section) AND microbiome OR microbiota”

C: “(Microbiome OR microbiota) AND asthma AND controlled”

Articles older than 10 years were excluded. Abstracts were read, and articles not clearly defining elective CS were excluded, as were reviews and meta studies. PubMed did not retrieve as many articles as Web of Science, especially for the search profile PICO C (Figure 1). Reference lists from selected articles from PubMed were read, using Web of Science to find additional relevant articles.

The articles were read, and finally four articles, which included all of the PICO search terms, were selected (Figure 1). Citation counts, journal reputation, use of probiotics and country of research institution were considered relevant factors in selecting articles (Figure 2-4).

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Figure 1. PICO-structure for article search.
Figure 2. Flowchart for article search using PICO A.

Figure 3. Flowchart for article search using PICO B.

Figure 4. Flowchart for article search using PICO C.
Results

The four articles that were selected based on the three search profiles (Figure 1) are summarized in Table 1. A more detailed version is found in Appendix.

Both van Berkel et al. and Black et al. find an association between elective CS and asthma, compared with VD. The association is seen for several different asthma indications; a higher incidence of salbutamol inhaler prescription during the first 5 years of life (adjusted HR 95% CI: 1.13 (1.01-1.26)), asthma requiring hospital admission (adjusted HR 95% CI: 1.22 (1.11-1.34)), increased prevalence of wheezing during the first 3 years of life (95% CI: 1.43 (0.99-2.05)), and persistent wheezing until 6 years of age (95% CI: 1.56 (0.99-2.46)). Also an increase of FeNO levels is found (sympercents 95% CI 12.7 (0.6-24.8)).

Lui et al. find that the mode of delivery has an influence on the composition of the intestinal microbiome in Chinese newborns, in accordance with the findings from other studies (see Introduction). Children born by elective CS had Staphylococcus, Clostridium, Enterobacter and Streptococcus species as dominant microbes. In contrast, children born by VD had Escherichia coli, Bifidobacterium longum and Bacteroides species as dominant microbes. (See Table 2.)

Sjögren et al. conclude that a more diverse gut microbiome in early childhood might prevent allergy development. This may be associated with an inverse relationship between allergy and family size or endotoxin exposure. The fecal samples from allergic children were less colonized with Lactobacilli, Bifidobacterium and Clostridium. (See Table 2.)
Table 1. Summarized results for all articles used. A more detailed version is found in Appendix.

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<tr>
<td>Van Berkel et al.</td>
<td>Prospective cohort study. 6 218 children. Data from registries. Follow-up on self-reported wheezing, asthma diagnosed by a physician until age 6. Airway-inflammation and resistance measured. Adjusted for difference in information on the mothers, breastfeeding and lower respiratory tract infections.</td>
<td>Elective CS was associated with increased risk of wheezing (early and persistent) and more airway inflammation (higher FeNO level), compared with VD.</td>
<td>Elective CS, compared with VD, was associated with higher risk of wheezing during the 3 first years of life, as well as persistent wheezing until 6 years of age. The increased FeNO levels, indicating airway inflammation, could be one explanation.</td>
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<tr>
<td>Black et al.</td>
<td>Retro-perspective cohort study. 321 287 children. Clinical databases used. Follow-up on asthma requiring hospital admission and salbutamol inhaler prescription until 5 years of age. Adjusted for difference in information on the mothers and breastfeeding.</td>
<td>Elective CS was associated with higher risk of asthma requiring hospital admission, and use of salbutamol inhaler, compared with VD.</td>
<td>Elective CS, compared with VD, was associated with more use of salbutamol inhaler and asthma requiring hospital admission.</td>
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<td>Lui et al.</td>
<td>Cross-sectional study. 25 Chinese newborns by VD, 16 by elective CS. Fecal samples collected day 2 and 4 after delivery, and analyzed. All children received a combination of breast milk and formula feeding.</td>
<td>A significant difference, between CS and VD, of the composition of fecal microbiome on day 2 and 4. See Table 2.</td>
<td>The mode of delivery has an influence on the composition of the newborns microbiome.</td>
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<tr>
<td>Sjögren et al.</td>
<td>Prospective cohort study, following 47 Swedish newborns until 5 years of age. Fecal samples collected 1 week, 1 month and 2 months after delivery. Information on self-reported allergic symptoms, asthma diagnosed by a physician, skin prick test and exposure to allergenes.</td>
<td>Children developing allergy had a different composition of the fecal microbiome, compared with children without allergy. See Table 2.</td>
<td>A more diverse composition of microbiome in newborns may prevent allergy development.</td>
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Discussion

ELECTIVE CS AND ASTHMA

An association between elective CS and asthma, compared to VD, is found both by van Berkel et al. and Black et al. (Table 1). The strength of this association is that multiple ways to diagnose asthma were used, and all are found positively related to elective CS. The results were adjusted for confounding factors such as breastfeeding, parental history of asthma, smoking during pregnancy and maternal education level. This makes the results less likely to be biased, and prevents effect modification, which could have given a false positive association and lead to a type I error.

Black et al. is a retro-perspective study using clinical data registers. A retro-perspective study, compared to a perspective study, is more prone to bias due to recall problems and lack of information on adjustment factors. However, this does not seem to be the case here, since the database used had a quality assurance up to 98% and the population-based study design minimized the risk of selection bias. In both Black et al. and van Berkel et al. mothers with missing data were seen to differ from those with complete data (younger, higher BMI, lower educated, multiparas and psychological distress during pregnancy). This was adjusted for to avoid bias and to strengthen the study power. Another strength in the study of Black et al. is that only nulliparas (first time mothers) were included, which avoided confounding by parity and related pregnancy complications. Van Berkel et al. did not restrict their study to nulliparas, but they did adjust for parity. The indication for elective CS is not described in the two studies, and probably some of them are because of “mother’s request”. Women requesting elective CS without any medical indication may differ from women not wanting CS in, for example, education level, age, and smoking during pregnancy. This could be a confounding factor. However, adjustments were done for covariates of the mothers in both studies.

Only 3.8% (Black et al.) or 5.2% (van Berkel et al.) of the examined children were born by elective CS. This small proportion of the study population gives a relatively small information base, and could lead to bias. Since children are more often born by VD than by elective CS, it is important to study a large population cohort to strengthen the statistical power. Van Berkel et al. used a relatively small population, compared with Black et al. A small sample size gives a high risk for making a type II error. However, this does not seem to be the case; the studies do find an association between asthma and CS. Van Berkel et al. observe that mothers with CS differed from VD in many ways. They had higher age, and pre-pregnancy BMI, lower education, more often a history of asthma. Their children had a lower birth weight and were less breastfed. Although the study adjusted for many of these confounding factors, they should be kept in mind when concluding a possible association between CS and asthma.

A remarkably high prevalence of mothers smoking during pregnancy is seen in both Black et al. and van Berkel et al. In the UK the prevalence was 20.5% in mothers with elective CS versus 26.3% in VD. In the Netherlands: 25.2% in elective CS versus 25.8% in VD. Even more notable is the large difference in breastfeeding, which is well known to be an important protective factor for later development of allergic symptoms. In the UK only 37.8% of the children born by elective CS were breastfed 6 weeks after birth, versus 34.6% for the VD group. Significantly more children in the Netherlands were breastfed after 6 and 12 months: 88.1% for elective CS versus 92.0% for VD. The striking difference between the two countries may be related to the mode of information collection: via data from the Child Health Surveillance in the UK, and via self-reported questionnaires in the Netherlands. Dutch mothers might over-report breastfeeding, since this is an important and sensitive part in becoming a mother. There may also be differences in asthma prevalence.
between the UK and the Netherlands. As discussed in van Berkel et al. perinatal factors such as preterm birth and low birth weight increase the risk of developing asthma. This finding may be explained by the fact that children born by CS more often are preterm, with a lower birth weight. Given that both studies had to be corrected for multiple confounding factors, the observed significant, but relatively weak association between elective CS and asthma, compared to VD, must be viewed with caution until a causal link is established. Since the underlying mechanisms are unknown, it should be kept in mind that the interplay between asthma, delivery mode and childhood factors might be more complex.

ELECTIVE CS AND MICROBIOME

Lui et al. find that the mode of delivery has an influence on the composition of the intestinal microbiome in Chinese newborns. Children born by elective CS had *Staphylococcus, Clostridium, Enterobacter* and *Streptococcus* species as dominant microbes, whereas children born by VD had *Escherichia coli, Bifidobacterium longum* and *Bacteroides* species as dominant microbes (Table 2).

A weakness of the study is that the study population is very small (25 children by VD and 16 by elective CS). This may lead to a type II error. But the study did find a significant difference in the composition of fecal microbiome in elective CS versus VD.

An important confounding factor, not adjusted for, is that all CS cases were “mother’s request”. As mentioned above, women requesting elective CS without any medical indication may differ from women not wanting CS. This would lead to bias. All the mothers were given flucloxacillin before CS. Pre-operative administration of antibiotics is a normal procedure for elective CS. However, different antibiotics may have been used according to the local guidelines of the various hospitals. (For example Cefuroxim is used in Aarhus, Denmark). This could alter the composition of the newborns fecal microbiome, and be an important confounding factor to adjust for. Lui et al. did adjust for some confounding factors by excluding children with active infections, receiving antibiotics. No information on parity was noted. This could lead to confounding by parity and related pregnancy complications.

The short time of follow up (2 and 4 days after birth), and the fact that more than 50% of the VD children dropped out after day 2, compared to 1.1 % of the CS children, weakens the study. This variation was explained by different length of hospitalization: 2 days for VD and 3-4 days for CS. VD children leaving hospital before day 4 were excluded because the environmental microbes outside the hospital could alter the microbiome composition. All children received a combination of breast milk and formula feeding during the first 4 days of life. The results may have been different if the children were exclusively fed by breast.

In the future it could be interesting to see if these findings persist in a larger population group, with longer follow-up time. It would also be interesting to compare results from different regions, with different normal environmental microbes and different use of pre-operative antibiotics.

ASTHMA AND MICROBIOME

Sjögren et al. conclude that a more diverse gut microbiome in early childhood might prevent allergy development. The fecal samples from allergic children were less colonized with *Lactobacilli, Bifidobacterium adolescentis* and *Clostridium* (Table 2). This may be associated with an inverse relationship between allergy and family size or endotoxin exposure. The findings were for allergy in general (especially atopic dermatitis, AD) and not specifically for asthma, where no difference in microbiome was found. The small number (7) of children in the study who developed asthma could be one explanation. Also children with only AD may develop asthma after 5 years of age.
The study was based on a small population (47 Swedish children), but had a long follow-up time. Fecal samples were collected 1 week, 1 month and 2 months after delivery, this strengthens the results. The children were followed until 5 years of age for any symptoms of bronchial obstruction, of which at least one was diagnosed by a physician. Asthma was defined as three or more episodes of bronchial obstruction during the last 12 months. This also strengthens the study since most patients with asthmatic problems develop their first symptoms during the first 5 years of life. The use of hospital diagnosed asthma, and not only self-reporting questionnaires, makes self-over- or under-reporting bias unlikely. The demographic data collected were similar for children with allergy and for children not developing allergy. Thus, there seem to be no risk of confounding. 96% of the children were exclusively breastfed, again reducing the likelihood of confounding. The fecal samples were collected at home so any incidental pollution could have biased the findings.

The findings that allergic children were less colonized with Lactobacilli, Bifidobacterium and Clostridium, especially at 1 week after birth (Table 2) supports the hypothesis that Bifidobacteria and Lactobacilli protect against asthma.8 Whether Clostridium, which is found to be associated with asthma, is a significant finding has to be investigated.4-10 Sjögren et al. suggest that the explanation could be the low rate of Clostridium colonization and relatively few allergic children.

Sjögren et al. found that the number of family members was related to the number of Bifidobacterium species in fecal samples at 1 week and 2 months after birth. This indicates that more siblings and larger families protect against asthma, in accordance with the hygiene hypothesis. Earlier studies also found a lower diversity of gut microbiome in children developing allergy.13-15 This indicates that a diverse gut microbiome in early childhood protects against allergy. Whereas the same association exists for all types of allergic disease, including asthma, remains to be determined.

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<th>Protects against allergy</th>
<th>Born by VD</th>
<th>Not allergy</th>
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<td>Bifidobacteria, Entero cocci and Lactobacilli</td>
<td>Born by elective CS</td>
<td>Clostridia</td>
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<tr>
<td>Entero cocci and Lactobacilli</td>
<td>Born by elective CS</td>
<td>Not allergy</td>
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<tr>
<td>Lactobacilli</td>
<td>Born by elective CS</td>
<td>Not allergy</td>
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**Table 2. Findings on dominant bacteria.**

ELECTIVE CS, MICROBIOME AND ASTHMA

**Conclusion and future studies**

Altogether, the articles examined in this study indicate that a diverse composition of the fecal microbiome of the newborn is an important factor for protection from allergy development. Sjögren et al. find that allergic children were less colonized with Bifidobacteria and Lui et al. find that children born by elective CS were less colonized with Bifidobacteria (Table 2). This is in accordance with earlier studies, and strengthens the hypothesis that altered microbiome of the newborn explains the observed association between asthma and CS. Whether it is a more diverse composition of the microbiome, or specific bacterium that is protective, has to be further investigated.

However, it is important to remember that the association could be multifactorial and biased by many confounding factors. For example, as mentioned in van Berkel et al., it has been suggested that VD alters mechanical forces induc-
ing higher levels of catecholamine, cortisol and pulmonary surfactant in the child. This would stimulate the post-natal lung to a proper development, thus reducing the risk of developing asthma.\textsuperscript{16, 17, 18}

In future investigations of the association between elective CS, microbiome and asthma, prospective studies should be carried out with large populations of children born by elective CS, collecting fecal samples and asthmatic symptoms, and comparing with those born by VD. To avoid confounding, full information about the mother (age, smoking, gestational age, parity, history of allergy/asthma, breastfeeding) and pregnancy-related complications should be documented. Differences in local use of antibiotics and clinical guidelines, as well as local differences in bacterial flora should also be taken into account.

Such studies may give a clearer picture of long-term side effects of CS, and better clinical guidelines for choosing between VD and elective CS. Further studies may also provide better support for (or against) bacterial seeding, where vaginal- and anal bacteria from the mother are implanted into the newborn’s mouth after CS delivery.
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APPENDIX : Summarized results from articles used. Tables 1a and 1b (Pico A; Cesarean section-asthma), Table 2 (PICO B; Cesarean section –microbiome), and Table 3 (PICO C; Asthma-microbiome).

**Table 1a. Pico A; Cesarean section-asthma**

**Article**
Van Berkel et al. Mode of delivery and childhood fractional exhaled nitric oxide, interrupter resistance and asthma: the Generation R study.

**Methods**

Population-based prospective cohort study, including 6 218 children. Information on delivery (mode, sex, gestational age at birth, birth weight) was taken from midwife and hospital registries. The children were followed up at age 1, 2, 3, 4 and 6 on information of any wheezing (i.e. sibilant rhonchi) in the previous 12 months. Wheezing was defined as 1) early if appearing in the first 3 years of life, 2) late if appearing after 3 years of age and 3) persistent if appearing both before and after 3 years of age. The information was collected by questionnaires. At 6 years age, any asthma diagnose by a physician were collected, and airway inflammation or resistance were measured using fractional exhaled nitric oxide (FeNO) and interrupter resistance technique during tidal breathing (Rint), respectively. Also information on lower respiratory tract infections (i.e., pneumonia, bronchi-tis, bronchiolitis or pertussis) was collected at the age of 6 years. Questionnaire-based information on the mother was obtained, including age, pet keeping, pre-pregnancy BMI, parity, distress during pregnancy, smoking during pregnancy, gestational diabetes, pre-eclampsia or pregnancy-induced hypertension, and history of atopy or asthma. At 6 and 12 months after birth, information on breastfeeding was collected.

The questionnaire-based covariates were used to adjust the results, via polynomial, logistic and linear regression models. Adjustment for breastfeeding, inhalant allergies, eczema and lower respiratory tract infections were also conducted.

**Results**

Elective CS was associated with increased risk of early and persistent wheezing, compared with VD (OR early wheezing 95% CI: 1.43 (0.99-2.05), OR persistent wheezing 95% CI: 1.56 (0.99-2.46)). There was no increased risk of late wheezing, compared with VD.

Elective CS was associated with higher FeNO level (sympercents 95% CI 12.7 (0.6-24.8), compared with VD. No significant association was found between elective CS and asthma or Rint.

**Conclusions**

The study found that elective CS, compared with VD, is associated with increased risk of wheezing during the first 3 years of life, as well as persistent wheezing until 6 years of age. The increased levels of FeNO, indicating airway inflammation, in children born by elective CS may be one of many explanations.
Table 1b. Pico A: Cesarean section-asthma

| Article  | Black et al. Planned Cesarean Delivery at Term and Adverse Outcomes in Childhood Health. |

Methods

A population-based retro-perspective cohort study including 321,287 children born in Scotland between 1993 and 2007. Databases containing social and clinic data on all deliveries since 1980 were used to find the study cohort and information on outcomes. Children with missing data on date and mode of delivery, gestation age, birth weight or sex were excluded. Follow-up until February 2015 with outcomes of any asthma requiring hospital admission and any salbutamol inhaler prescription at 5 years of age.

Elective CS was defined as “scheduled delivery” in the database. Information was collected on the mother’s age at delivery, BMI in pregnancy, social class, and smoking during pregnancy, use of salbutamol inhaler and breastfeeding status at 6 weeks after delivery.

Statistical analyses and sensitivity analyses were performed and hazard ratio (HR) was calculated for each outcome, via Cox regression. Adjustment for the collected covariates was done.

Results

Elective CS was associated with higher risk of asthma requiring hospital admission, compared with VD (3.73% vs. 3.41%, adjusted HR 95% CI: 1.22 (1.11-1.34)).

The use of salbutamol inhaler during the first 5 years of life was higher after elective CS compared with VD (10.34% vs. 9.62%, adjusted HR 95% CI: 1.13 (1.01-1.26)).

Conclusions

Children born by elective CS, compared with VD, were associated with a higher risk of salbutamol inhaler prescription during the first 5 years of life and asthma requiring hospital admission.
**Table 2: Pico B: Cesarean section – microbiome**

| Article | Liu et al. Bacterial Community Structure Associated With Elective Cesarean Section Versus Vaginal Delivery in Chinese Newborns. |

**Methods**

Cross-sectional study including 25 children born by VD and 16 born by elective CS. Fecal specimens collected on day 2 and 4 after delivery. The children were matched for gestational age, birth weight, head circumference, and body length. All children received a combination of breast milk and formula feeding. Polymerase chain reaction (PCR), rRNA gene sequencing and gel electrophoresis were used to analyze the fecal samples.

**Results**

A significant difference in the composition of the fecal microbiome between VD and elective CS was found on day 2 and 4, after birth. Children born by VD had *Escherichia coli*, *Bifidobacterium longum* and *Bacteroides species* as dominant microbes. Children born by elective CS had *Staphylococcus*, *Clostridium*, *Enterobacter* and *Streptococcus species* as dominant microbes.

**Conclusions**

The study concludes that the mode of delivery has an influence on the composition of the intestinal microbiome in Chinese newborns.
Table 3: Pico C; Asthma-microbiome

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<td>Sjögren et al. Altered early infant gut microbiota in children developing allergy up to 5 years of age.</td>
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Methods

Prospective cohort study following 47 Swedish newborns until 5 years of age. Fecal samples were collected at 1 week, 1 month and 2 months after birth. Primers binding to specific bacteria and PCR were used to analyze fecal microbiome composition. Questionnaires were used to collect information on allergic symptoms and use of antibiotics. Children with allergic symptoms (asthma, atopic dermatitis or rhinitis/conjunctivitis) and positive skin prick test (allergens: cow’s milk, egg white, cat, birch and timothy) up to 5 years old were defined as allergic. Asthma was defined as three or more episodes of bronchial obstruction, of which at least one was diagnosed by a physician.

Information was collected on environmental factors, such as family size, breastfeeding, pet keeping, allergic or atopic parents, and endotoxin levels in house dust.

Results

Children who developed allergy had a different fecal microbiome composition during the first 2 months of life, compared with children without allergy. The fecal samples from allergic children were less colonized with Lactobacilli, Bifidobacterium adolescentis and Clostridium. At 1 week after delivery, 92% of the non-allergic children were colonized with Bifidobacterium adolescentis and 48% with Lactobacilli. In contrast only 62% of the allergic children were colonized with Bifidobacterium adolescentis and 8% with Lactobacilli.

Children, who grew up in large families and with high exposure to endotoxin were more often colonized with Bifidobacterium in their fecal samples.

Conclusions

The study concludes that a more diverse gut microbiome in early childhood might prevent allergy development. This may be associated with an inverse relationship between allergy and family size or endotoxin exposure.