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# Infant microbiota and short chain fatty acids

## Relation to lifestyle and effect on health

Akademisk avhandling

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av

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Avhandlingen baseras på följande delarbeten

- I. **Gio-Batta M**, Sjöberg F, Yazdanshenas S, Nookaew I, Hesselmar B, Saalman R, Adlerberth I, Wold A. E. Delayed acquisition of typical commensal anaerobes is associated with various early life exposures and allergy development. Manuscript.
- II. **Gio-Batta M**, Sjöberg F, Jonsson K, Barman M, Lundell A-C, Adlerberth I, Hesselmar B, Sandberg A-S, Wold A. E. Fecal Short Chain Fatty Acids in Children Living on Farms and a Link between Valeric Acid and Protection from Eczema. *Scientific Reports* 2020; 10: 22449.
- III. **Gio-Batta M**, Spetz K, Barman M, Bråbäck L, Norin E, Björkstén B, Wold A. E, Sandin A. Low concentration of fecal valeric acid at one year of age is linked with eczema and food allergy at 13 years of age – findings from a Swedish birth cohort. *International Archives of Allergy and Immunology* 2022; 183(4):398-408.
- IV. Barman M, **Gio-Batta M**, Andrieux L, Stråvik M, Saalman R, Fristedt R, Rabe H, Sandin A, Wold A. E and Sandberg A-S. Short-chain fatty acids (SCFA) in infant plasma – relation to SCFA levels in breast milk and plasma and to subsequent food allergy, atopic eczema or sensitization in a prospective birth-cohort study. Manuscript (submitted)
- V. **Gio-Batta M**, Thordarson T, Sjöberg F, Bry K, Wold A. E, Elfvin A, Adlerberth I. Establishment of early gut, oral and skin microbiota in extremely preterm infants – a comprehensive culture-based study. Manuscript.



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# Infant microbiota and short chain fatty acids

Relation to lifestyle and effect on health

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## ABSTRACT

The commensal microbiota has both beneficial and negative effects on the host. It is a source of infectious and inflammatory microorganisms, but may also provide immune stimulation during a critical period during early infancy that possibly offers protection against allergy and other immune mediated diseases. Here, we examine four birth cohorts to investigate the interplay between lifestyle factors, microbiota acquisition and maturation, production by the microbiota of immunomodulatory short chain fatty acids (SCFA) and allergy development. The FARMFLORA birth cohort consists of children raised on small family-owned dairy farms and non-farming controls from the same rural areas, the BAS cohort followed infants born in Jämtland until 13 years of age, the NICE cohort includes infants born in Norrbotten, and the ÖFLORA cohort consists of extremely preterm infants cared for at a neonatal intensive care unit in Göteborg. Our hypotheses were that preterm neonates acquire a microbiota that may predispose to sepsis and the inflammatory condition necrotizing enterocolitis, while a microbiota dominated by anaerobic bacteria yields protection from allergy development, in part through production of SCFAs. Using 16S rRNA gene sequencing, we demonstrate that growing up on a farm, with pets, or with elder siblings are all associated with enrichment of core anaerobic commensals, which in turn is reflected in more complex SCFAs in feces and protection from allergy at 3 and 8 years of age. The SCFA valeric acid was associated with protection from allergy in later childhood, a finding confirmed in the BAS cohort. Using newly developed highly sensitive liquid chromatography-mass spectroscopy, we measured SCFAs in infants' blood plasma at 4 months of age, as well as corresponding samples of mother's milk and blood plasma in the NICE cohort. Plasma levels of several SCFAs were lower in infants who later became allergic and/or sensitized. Interestingly, the SCFAs butyrate and caproate were enriched 100-fold in mother's breast milk compared to her blood plasma, suggesting selective transport into the milk to serve the demands of the infant. Further, isobutyrate and valerate were also enriched (4-fold) in milk, while other SCFAs were less prevalent in milk than in maternal blood plasma. Lastly, characterization of the gut, oral and skin microbiota of extremely preterm infants revealed a microbiota with a profound lack of anaerobes, dominated by Gram-positive facultatives, especially coagulase-negative staphylococci, and with a high prevalence of yeasts. Treatment with antibiotics affected microbiota development, as also did the degree of prematurity. The characteristics of the preterm microbiota may increase the risk of infectious and inflammatory conditions. Taken together, our results suggest that early life exposures impact on the composition of the infant gut microbiota and that SCFAs might be mediators contributing to immune maturation and protection against allergy.

**Keywords:** microbiota, gut, oral, skin, short chain fatty acids, allergy, siblings, farm, pets, extremely preterm, quantitative culture, 16S rRNA gene sequencing

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