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Immune health

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Summary

Optimal functioning of the immune system is a prerequisite for a healthy live. The immune system produces a variety of very different molecules that all play a different role in reacting to e.g., bacterial or viral infections that can cause illness. Normally these reactions are tightly regulated and well-balanced, but they can also be exaggerated, compromised or disbalanced, which can increase the risk at certain diseases. Previous studies have shown that certain plasma markers from dietary origin may reflect immune function, further referred to as dietary determinants of immune function. In addition, dietary approaches – such as the use of certain supplements or changing dietary patterns – are promising interventions to improve immune health.

Serum non-cholesterol sterols reflect cholesterol metabolism when standardized for serum total cholesterol concentrations. Non-cholesterol sterols that reflect intestinal cholesterol absorption can be retrieved from the diet (plant sterols, plant stanols) or are metabolites associated with cholesterol absorption (cholestanol). Contrary, non-cholesterol sterols that reflect endogenous cholesterol synthesis are intermediates of the human cholesterol synthesis pathways (lathosterol, lanosterol, desmosterol). Previous studies have shown that non-cholesterol sterols are able to affect immunological processes. For example, plant sterols and stanols have been shown to improve immune cell behavior in a subset of disbalanced immune cells typical for asthma patients. In addition, desmosterol was shown to reduce inflammatory responses of macrophages. Based on these previous findings, the aim of this thesis was to study the effects of dietary approaches and determinants on immune health throughout life, with special attention to the mediating effects of non-cholesterol sterols.

First, the potential of non-cholesterol sterols as dietary determinants that reflect or predict immune function throughout life was studied. Non-cholesterol sterols (standardized for creamatocrit) were analyzed in breast milk samples one month post partum and associations between non-cholesterol levels in breast milk and allergic outcomes in the first two years of life of breastfed children were analyzed (Chapter 3). The odds of developing eczema during the first two years of life were significantly lower with higher concentrations of cholestanol, lanosterol, lathosterol, and stigmasterol in breast milk one-month postpartum. In addition, the odds of being allergically sensitized (an early stage of allergy) to common allergens at age 2 were significantly lower with a higher concentration of campesterol in breast milk. None of the sterols in breast milk were associated with the development of wheeze during the first two years of life. In Chapter 4, serum non-cholesterol sterols (standardized for total cholesterol to reflect cholesterol metabolism) were measured in two studies that included children with or without asthma. The ADEM study included children aged 3 years and followed them until the age of 6 years. Then it was determined if these children had asthma, transient wheeze, or no complaints. Serum non-cholesterol sterols were measured at age 3 years. Characteristics of cholesterol metabolism were not associated with asthma-related

parameters in these children at the age of 3 or 6 years, nor with airway inflammation. The MIKADO study included children aged 6-16 years (mean age: 12 years). These children had obesity and either already had a confirmed asthma diagnosis or were at increased risk of developing asthma. Obesity was based on BMI-SDS scores, which is a measure of relative weight adjusted for age and sex, which can be determined using growth curves. Serum non-cholesterol sterols were measured before and after weight loss. At baseline, children with a lower BMI-SDS score had an higher intestinal cholesterol absorption (and vice versa). Only in children at risk of developing asthma, a higher cholesterol absorption associated with better lung function. After weight loss, the associations between changes in cholesterol metabolism and changes in lung function were opposite in children with a confirmed asthma diagnosis versus children at risk of developing asthma. Weight loss induced increases in cholesterol absorption related to improved lung function in children at risk of developing asthma. Contrary, weight loss induced decreases in endogenous cholesterol synthesis related to decreases in lung function in children with a confirmed asthma diagnosis. It is unknown why these associations differed in children with or without a confirmed asthma diagnosis, but these results indicate a possible relation between cholesterol metabolism with asthma development or disease progression.

Furthermore, the potential of dietary approaches to improve immune health was studied. In Chapter 2, dietary interventions that simultaneously evaluated effects on asthma-related outcomes and immunological parameters were systematically reviewed. Studies from the clusters "herbs, herbal mixtures, and extracts" and "omega-3 long-chain polyunsaturated fatty acids (LCPUFAs)" showed the highest potential to improve asthma-related outcomes via immunomodulation. However, it should be noted that only three studies were able to induce clinically relevant improvements in asthma-related outcomes. Contrary to these beneficial effects, it was suggested that soy isoflavones worsened asthma-related outcomes via immunomodulation. In Chapter 5, the potential of plant stanols as a dietary approach to improve immune function was studied in a randomized placebo-controlled double-blind intervention study in a population at risk of severe COVID-19 complications. Here, products enriched with plant stanols (4 g/day) or control were provided to people with overweight or obesity starting two weeks before receiving the COVID-19 vaccination until four weeks after the vaccination. Several immunological parameters were studied (e.g., anti-COVID-19 IgM and IgG titers, cytokine production), as well as metabolic parameters (e.g., serum lipid and lipoprotein concentrations, plasma glucose, serum insulin). After consuming 4 g of plant stanols per day, anti-COVID-19 IgM Spike antibody titers increased up to 139% in adults with overweight or obesity. Only in people that showed IgG seroconversion, plant stanol consumption also increased anti-COVID-19 IgG Spike titers. Furthermore, a decrease in stimulated cytokine production was observed, indicating that overall inflammatory responses where decreased, while simultaneously antibody production was increased. No changes in metabolic parameters were observed compared to control. These results imply that people with overweight or obesity at high risk of severe COVID-19 complications could benefit from plant stanols added to their diet to improve their

immune function. In Chapter 6, it was studied if plant stanols would affect immune cell behavior – and thereby potentially disturbed the balanced immune responses – in immunologically healthy volunteers. Samples from two studies were analyzed, either at recommended (2.5 g/day) or high (9.0 g/day) intakes of plant stanols and compared to placebo. Circulating levels of non-cholesterol sterols, lipids, and lipoproteins were also analyzed, as well as stimulated cytokine production. The results of this chapter showed that, as expected, plant stanol intakes lowered circulating serum total and LDL cholesterol concentrations. Cytokine production remained unaffected, indicating that plant stanols might only restore immune function when Th1/Th2 immune responses are imbalanced.

To summarize, the main conclusions of this thesis are:

1. Higher levels of non-cholesterol sterols (standardized for creamatocrit) in breast milk are associated with decreased risk of developing eczema and allergic sensitization in the first to years of life in breastfed children.
2. A high cholesterol absorption is associated with better lung function in children with obesity at risk of asthma. After weight loss, increases in cholesterol absorption are associated with improvements in lung function in children with obesity at risk of asthma. This association was opposite in children with a confirmed asthma, i.e., decreases in cholesterol synthesis were associated with decreases in lung function. Exact mechanisms and causality need to be determined.
3. Omega-3 LCPUFAs and certain herbs, herbal mixtures, and extracts are promising dietary interventions that can induce improvements in asthma-related outcomes via immunomodulation, whereas soy isoflavones induced a worsening in asthma-related outcomes via immunomodulation.
4. Plant stanols are promising dietary components to improve immune health in those with compromised immune responses. Although the exact mechanism by which plant stanols affect immune health remains unclear, LDL cholesterol lowering effects of plant stanols is not a likely explanation.
5. A higher dietary intake of plant stanols does not disturb the balanced immune response in immunologically healthy adults.