Immune health

Impact

The aim of this thesis was to study the effects of dietary approaches and determinants on immune health throughout life, with special attention for non-cholesterol sterols. A systematic review, a randomized-controlled trial, and secondary analyses using data of two observational studies and three randomized-controlled trials have been described in this thesis. Briefly, higher non-cholesterol sterol levels in breast milk were associated with decreased risk of developing eczema (cholestanol, lanosterol, lathosterol, stigmasterol) and allergic sensitization (campesterol) in the first two years of life of breastfed children. Moreover, serum non-cholesterol sterols as markers for cholesterol metabolism were associated with lung function, but in opposite directions for children with or without asthma. In children with asthma, decreased cholesterol synthesis after weight loss was associated with decreased lung function. In children at risk of asthma with obesity, higher cholesterol synthesis (before weight loss) was associated with better lung function. Weight loss induced increases in cholesterol absorption related to improved lung function in children at risk of developing asthma, whereas weight loss induced decreases in cholesterol synthesis related to decreases in lung function in children with a confirmed asthma diagnosis. The associations in children at risk of developing asthma were as expected, since weight loss is associated with increased cholesterol absorption and improvements in asthma complaints. However, it remains unknown why the associations were opposite in children with a confirmed diagnosis in asthma. When used as dietary approach to improve immune function, consuming diets enriched with plant stanol esters improved immunological parameters in adults with overweight or obesity with a skewed immune system. An important question is what the effects of plant stanol consumption are in immunological healthy adults. We here showed that recommended or high intakes of plant stanols did not alter cytokine production in immunologically healthy adults. Based on our systematic review we concluded that other promising dietary interventions for those with compromised immune responses, such as asthma patients, included omega-3 long-chain polyunsaturated fatty acids (LCPUFAs), and certain herbs and extracts. The results described in this thesis will be discussed in this paragraph from a scientific and societal perspective.

Scientific relevance

The low-density lipoprotein (LDL) cholesterol lowering effects of plant sterols and stanols are well-known [1]. However, these non-cholesterol sterols that are derived from the diet may have other effects on human health, such as effects on the immune system [2-6]. This thesis showed that a relation between cholesterol metabolism and lung function, although causality was not determined. In addition, this thesis showed that plant stanols are a suitable dietary approach to increase specific antibody titers upon COVID-19 vaccinations and improve immune cell behavior in those with compromised immune responses. Exact underlying mechanisms remain unclear, although the findings

in Chapter 5 indicate that the LDL cholesterol lowering effects of plant stanols are not involved in immunomodulatory mechanisms. The results described in this thesis can be used to design new studies to further explore the involvement of non-cholesterol sterols in asthma. For example, it is unclear whether plant stanol supplementation in early life is safe on the long term and can prevent asthma development in children. In addition, underlying mechanisms of immunomodulatory effects of plant stanols should be further explored, more specifically the role of changes in cholesterol absorption and if plant stanols act on the immune system via changes in immune cell behavior or the gut microbiome. Finally, this thesis highlights the potential for plant stanol interventions to induce a multiple health effects in those with suboptimal immune and/or metabolic health. All studies presented in this thesis have been published or are in the process of being published in international peer-reviewed scientific journals. In addition, the results of the studies included in this thesis have been or will be presented at (inter)national conferences to scientific peers. These publications and presentations contribute to scientific knowledge utilization and is available for all scientists and other (health) professionals interested.

Societal relevance

A well-functioning immune system is a prerequisite for a healthy life, as dysfunctions in the immune system underlie various health problems. Dysfunctions in the immune system, and more specifically in T cell function, may translate into diseases such as asthma. Asthma is the most prevalent chronic respiratory disease in the youngest children [7, 8], severely affecting their quality of life [9]. From 1990 to 2017 the prevalence of chronic respiratory diseases has increased by 39.8% [10]. Moreover, in 2017, chronic respiratory diseases affected 544.9 million people globally and were ranked as third leading cause of death. Specifically for asthma, global prevalence was 3.6%, which surprisingly remained relatively stable since 1990 [10]. Although prevalence did not really increase, absolute numbers of cases have risen due to an increase in the global population. Therefore, it remains of importance to improve asthma-related complaints and quality of life of these patients.

There are various risk factors for asthma development, ranging from air pollution and antibiotics use during infancy to overweight and obesity [11]. Overweight and obesity are examples of modifiable risk factors, and several weight-loss interventions have already proven to be successful in improving the incidence and severity of asthma-related outcomes [12-14]. Overweight, obesity, and asthma have all been shown to contribute to an increased risk of cardiovascular diseases [15]. Especially for asthma, this increased risk relates to shared pathological mechanisms [15]. Since plant stanols also lower serum LDL cholesterol concentrations, which is a causal risk factor for CVD [16], the results of this thesis imply that plant stanols are promising dietary approaches to improve immune health and metabolic health simultaneously. As plant stanols interventions target multiple health outcomes simultaneously, they could potentially provide multiple health benefits.

A healthy immune system is also relevant for the economy. For example, the COVID-19 pandemic had an enormous impact on health care costs. A study in the USA showed that hospitalized COVID-19 patients had a median stay of 5 days in the hospital, with median hospital charges of $43 986, but in extreme cases reaching $198 394 [17]. Asthma also comes with a high economic burden, with estimated mean yearly costs per patient ranging from $1 900 in Europe to $3 100 in the USA [18]. These costs include direct costs of treatment, but also indirect costs, such as temporary or permanent disabilities or even early mortality [18]. This thesis highlights the relation between dietary determinants in early life (e.g., non-cholesterol sterol levels in breast milk) and asthma, although causality was not determined. It also highlights the relevance of dietary approaches to increase specific antibody titers to vaccinations and reduce asthma severity. Therefore, dietary determinants and approaches should be incorporated in health care to dampen the economic burden of diseases related to a compromised immune function.

Non-cholesterol sterols can either be produced by the human body (cholesterol synthesis markers, cholestanol) or are present in our diet (plant sterols and stanols). Food sources contributing most to plant sterol and stanol intake in the Netherlands are bread, vegetable oils, fruit, and vegetables [19]. Dietary intake of plant sterols is approximately 300 mg/day [19, 20]. People following (largely) plant-based diets are known to have the highest intakes of plant sterols and stanols, up to approximately 600 mg/day [21]. Diets containing more plant-based products than animal-based products – such as an ovolactovegetarian diet – or a completely plant-based vegan diet are more environmentally sustainable compared to (largely) animal-based diets. For example, greenhouse gas emissions are 35% lower for ovolactovegetarian diets, and even 50% lower for vegan diets, compared to omnivorous diets [22]. In general, these diets also require less land and water use compared to omnivorous diets [22]. Therefore, plant-based diets rich in plant sterols and stanols could contribute to increased environmental sustainability. Other dietary components that improved immune health described in this thesis include omega-3 LCPUFAs and herbs, herbal mixtures, and extracts. These approaches can also be incorporated into plant-based and environmentally sustainable diets, especially if omega-3 LCPUFAs are obtained from a plant-based source, such as (micro)algae [23].

Target groups

The effects of plant stanol interventions in diverse target groups were studied in this thesis: children with and without asthma, adults with overweight or obesity, and immunologically healthy adults. Based on the results of this thesis, those with compromised or skewed immune responses – e.g., people with obesity [24, 25], older adults [26], patients with HIV [27] or asthma [28] – may benefit most from dietary approaches to improve immune health. Immunologically healthy people might use these approaches to sustain immune health, as there were no undesired effects on cytokine production in immunologically healthy adults after plant stanol interventions, even at higher than recommended intakes (**Chapter 6**). Moreover, the LDL cholesterol

lowering effects of plant stanol interventions are well-known. Therefore, those with compromised immune health as well as metabolic health may benefit from a double health benefit of plant stanol interventions. These populations include e.g., patients with asthma and/or obesity, as both conditions are often characterized by elevated serum LDL cholesterol concentrations [29, 30], which is a risk factor for developing cardiovascular diseases [16].

Translation into practice

This thesis described two studies where non-cholesterol sterols were considered as dietary determinants to reflect or predict immune function, either as nutrients in breast milk or as characteristics of cholesterol metabolism. Higher concentrations of non-cholesterol sterols as nutrients in breast milk were associated with a decreased risk of developing eczema or allergic sensitization in the first two years of life. These results could be used in the future to update dietary recommendations for pregnant or lactating women. However, these results should first be confirmed using larger studies. Non-cholesterol sterol supplementation can be safe for pregnant or lactating women and their children [31], although the long-term safety should be confirmed before these results can be used in practice. The correlations observed between characteristics of cholesterol metabolism and lung function in children with asthma or at risk of developing asthma might suggest a link between cholesterol metabolism and asthma development / disease progression. Especially after weight loss, correlations between weight loss induced changes in cholesterol metabolism and lung function showed opposite patterns in children with a confirmed asthma diagnosis versus children at risk of developing asthma. In clinical practice, patterns in cholesterol metabolism might be used as indication to also check if the child suffers from asthma. It should also be explored if consumption of functional foods enriched with plant sterols or stanols could be beneficial for asthma patients. In addition, interventions to alter cholesterol metabolism might contribute to lowering asthma complaints, but well-designed randomized-controlled trials should be performed first to show causality between changes in cholesterol metabolism and asthma outcomes. This thesis also described three studies using dietary approaches to improve immune health. In summary, these studies showed that those with compromised immune responses benefit from dietary approaches, whereas those with healthy immune responses did not show adverse effects in immune function. Dietary approaches that may be used to improve immune health in populations with compromised immune health include plant stanols, omega-3 LCPUFAs, and herbal interventions. These results could be used to update dietary recommendations for asthma patients, as these guidelines are now limited to consuming a healthy diet rich in fruit and vegetables, and to lose weight for asthma patients with obesity. Clinicians and dietitians could use these recommendations in daily practice. However, as the underlying mechanisms of these dietary approaches remain unclear, these should be unraveled first before updating dietary recommendations.

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