

Nutritional strategies to improve endothelial function during the fasting and postprandial phase

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Impact



In this thesis, the results of two meta-analyses and three human intervention trials have been described. The main aim of these studies was to investigate effects of dietary strategies on postprandial and long-term fasting vascular endothelial function. Most studies assessed vascular endothelial function by brachial artery flow-mediated vasodilation (FMD) in humans, as changes in fasting brachial artery FMD can be linked to CVD risk [1]. We provided evidence that long-term fasting vascular endothelial function is beneficially affected by whole food products as well as by supplementing specific nutrients, while postprandial vascular endothelial function was not affected. The potential impact of the research in the current thesis will be discussed from a social, economic, environmental and commercial perspective in this chapter.

Social impact

Cardiovascular disease (CVD) is still the number one cause of death world-wide with an estimated annual death of 3.9 million in Europe. Even more patients are diagnosed with CVD and have to deal with the consequences on a daily basis [2]. Therefore, the social impact of CVD is large, and prevention of CVD is very important.

Our diet is one of the most important factors that affect our CVD risk [3], and previous research has already clearly shown that modifying our diet is an effective approach for the prevention of CVD [4]. This highly stresses the importance of studies investigating dietary strategies that can lower our risk of developing CVD. Assessing postprandial FMD responses may be of importance since a significant part of the day is spent in the postprandial state. Postprandial challenges may be used as a tool to assess early perturbations in endothelial function, even though it still remains to be investigated whether postprandial changes are of clinical importance for long-term cardiovascular health [5]. In line with previous research, we observed no significant differences in effects between a high-fat, high-carbohydrate and high-protein mixed-meal on postprandial endothelial function. However, a meta-analysis of *Thom and colleagues* [6] clearly showed that especially patients with cardiometabolic disease who have high baseline FMD values have more pronounced reductions in postprandial FMD responses as compared with apparently healthy individuals with either high or low baseline values. Although no different postprandial effects were observed in our study, the macronutrient composition of the meals should still be considered as an important determinant for our lifelong risk on developing CVD [7]. Moreover, in this thesis we examined postprandial effects of dietary nitrate and L-arginine added to a high-fat mixed-

meal, but no beneficial effects were found. Contrary, we showed in our meta-analysis that tree nuts and groundnuts, that are whole food products containing relatively high amounts of L-arginine, do beneficially affect longer-term fasting FMD. Interestingly, effects on FMD can be translated to a nine-to-fourteen percent reduced risk of developing CVD. Further, longer-term L-arginine supplementation reduced the risk on CVD by four to seven percent.

Besides tree nuts and groundnuts, L-arginine is also present in poultry, soybeans, fish and dairy products. Effects of these whole food products have been studied less extensively as compared with tree nuts and groundnuts. A recent study showed that non-fat and full fat milk attenuated postprandial impairments in brachial FMD [8]. In addition, long-term soy nut consumption significantly improved brachial FMD in type 2 diabetes patients [9]. Moreover, *Jackson et al.* [10] observed that nitrate supplementation and beetroot juice consumption improved endothelial function, as assessed by FMD. In both our meta-analysis and the meta-analysis of *Jackson and colleagues* [10], L-arginine and nitrate are one of the several bioactive compounds that are provided by nuts and beetroot juice [11, 12]. Besides beetroot juice, other green leafy vegetables, such as spinach and rocket salad, are also good sources of dietary nitrate [13]. Effects of spinach and rocket salad on endothelial function, however, have been studied less. A previous study found that a nitrate-rich spinach meal improved postprandial FMD as compared with the low-nitrate control meal [14]. In line with this, research has shown that the Mediterranean diet, which is high in nuts, fish, and green leafy vegetables, has a protective role on cardiovascular events [15]. Therefore, consuming L-arginine and nitrate rich food products might reduce the longer-term risk to develop CVD.

Economic impact

In Europe, the annual CVD-related costs are estimated to be €210 billion. Around €111 billion is related to health care costs, and €54 billion is due to productivity losses by CVD patients. The remaining costs are related to costs from time and effort given by informal caregivers, such as family members [2]. To reduce health care costs and the overall economic burden of CVD it is of importance to prevent the development of CVD. The prevention of CVD can be divided in primordial, primary, secondary and tertiary prevention. Primordial prevention consists of risk factor reduction in the entire population, especially via social and environmental approaches. Primary prevention targets the entire population and aims to prevent a disease from occurring. Secondary prevention targets patients at increased risk to develop diseases and aims for early disease detection. Finally, tertiary prevention is implemented in patients to reduce disease severity and associated sequelae [16]. A

study by *Lee and colleagues* [17] showed that incentives on fruit and vegetables intakes as well as a healthy diet including nuts, whole grains and plant oils on top of fruit and vegetables may generate substantial benefits regarding CVD risk and are highly cost-effective. Theoretically, the fruit and vegetable strategy was able to prevent 1.93 million CVD events in the United States and would save \$39.7 billion in health care costs. The healthy diet approach even showed to prevent 3.28 million CVD cases and reduced health care costs by \$100.2 billion. The research in this thesis showed that dietary strategies are effective in reducing CVD risk and thus can be implemented as primordial and primary prevention strategies. Our meta-analysis showed that longer-term consumption of tree nuts and groundnuts reduced the risk of developing CVD by nine-to-fourteen percent. Although the number of included studies was relatively low, our meta-analysis observed a seven-to-ten percent reduced risk on CVD after longer-term watermelon consumption. Though further research is needed, dietary strategies increasing L-arginine, nitrate and L-citrulline rich food products (i.e., nuts and vegetables) can be implemented at low costs and may eventually result in reduced medical health care costs.

Environmental impact

Making more healthy food choices is not only beneficial for our own (cardiovascular) health, but also contributes to a healthy and sustainable planet. Besides our general health, sustainability became a factor in developing nutritional guidelines. We showed that long-term tree nut and groundnut consumption beneficially affects our cardiovascular health. The dose of tree nuts and ground nuts ranged between 15 and 85 grams per day and is higher than the daily recommendation of a handful (around 15 to 25 grams depending on age) by the Dutch Nutritional Center. However, it is not recommended to further increase the daily portion of nuts, since we did not observe a dose-response relationship between nut intake and long-term vascular endothelial function. Besides, the amount of water needed for each kilogram of nuts is equal to less-environmentally sustainable food products, such as meat [18]. Therefore, increasing the daily recommended portions of nuts will not necessarily beneficially affect our health, but in turn will decrease the sustainability of our diets.

In addition, long-term consumption of watermelon, an L-citrulline-rich food product, might positively affect our cardiometabolic health. Most studies provided L-citrulline-enriched watermelon juice or watermelon extract, as an unfeasible high amount of fresh watermelon would be needed in order to reach beneficial effects on cardiovascular health. Watermelon is a vegetable [19], mostly consumed during the spring and summer months. As fruits and vegetables are part

of a healthy diet, watermelon consumption might contribute to our general health. Watermelon farms have minimal environmental impact and can therefore be watermelon part of a sustainable diet [20].

No postprandial effects of nitrate and L-arginine supplementation were observed, while we did not assess long-term effects of dietary nitrate supplementation or nitrate-rich food products. However, previous research has shown that shifting to a more plant-based diet, which is high in nuts and (green leafy) vegetables, will beneficially affect our cardiovascular health [21]. Moreover, nuts and vegetables have a lower environmental impact as compared with an animal-based diet [22]. Thus, replacing animal-based products with L-arginine-rich and nitrate-rich food products could benefit our cardiovascular health and improve the sustainability of our diets.

Commercial impact

Nutritional research often focuses on specific nutrients instead of examining effects of whole food products or combinations of nutrients. The research presented in this thesis focus on a combination of single nutrients as well as on the combination of nutrients and whole food products. An advantage of combining specific nutrients is that additive effects can be present and therefore lower amounts that can be achieved by our diet are needed to exert beneficial effects. Dietary supplements often contain high amounts of specific (micro)nutrients above the daily acceptable intake. In the Netherlands, almost half of the adult population has stated to take one or more dietary supplements [23]. Therefore, companies can consider to develop and produce supplements containing lower amounts of multiple specific nutrients. However, we showed that combining low amounts of L-arginine and nitrate did not affect postprandial brachial FMD, but a tendency for an improved FMD after the nitrate-containing meals was found as compared with the meals without nitrate. Longer-term effects of combining low amounts of nitrate and L-arginine have not been established and warrants further study.

Target groups

The three human intervention trials presented in this thesis included apparently healthy overweight or abdominally obese men. Overweight or abdominally obesity increases the risk of developing CVD, but it should be emphasized that these men did not suffer from CVD [24]. This particular part of the population is therefore hypothesized to benefit most from the development of dietary strategies aimed to reduce the risk on CVD events. Moreover, the number of people with overweight and obesity is still rising. The need of finding effective and scientific-based dietary

strategies to prevent the development of CVD is thus increasing. In this thesis only overweight or abdominally obese men were included as this population has already disturbed postprandial responses at baseline and is at increased risk of developing CVD. Moreover, in the meta-analyses in this thesis we stratified findings for populations groups. No differential effects were found for diseased or overweight people as compared with healthy individuals. The findings of the research in the current thesis might also be applicable for CVD patients. However, if findings between CVD patients and patients at risk are comparable should be investigated in future well-designed studies.

Translation into practice

The aim of this thesis was to investigate effects of dietary strategies on vascular endothelial function. We found that longer-term vascular function markers were beneficially affected by the consumption of tree nuts and groundnuts. More research is needed to investigate the potential beneficial effect of watermelon consumption on long-term CVD risk. Although beneficial long-term effects were observed, no effects of L-arginine and nitrate supplementation on postprandial endothelial function were found.

The findings of the studies presented in this thesis have been published or are in the process of being published in peer-reviewed, open access, scientific journals. The obtained knowledge is therefore commonly accessible for scientists, other health professionals, patient organizations, and even the general public. This will hopefully stimulate more research on the effects of dietary strategies on both postprandial and long-term fasting vascular endothelial function. Additionally, the results have been presented on conferences to a scientific audience to share the obtained findings and increase awareness of the importance of dietary strategies on postprandial and long-term vascular function as marker for CVD risk. Thus, the research presented in this thesis is not only important from an individual's perspective, but also from an economic, environmental and public health point of view (e.g., integrated lifestyle interventions, changes in food or supplement formulations, dietary recommendations).

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