

Metabolic health and vascular function in adults

Citation for published version (APA):

Tischmann, L. (2021). *Metabolic health and vascular function in adults: effects of a high-protein diet and soy nuts*. [Doctoral Thesis, Maastricht University]. Gildeprint Drukkerijen.
<https://doi.org/10.26481/dis.20210428lt>

Document status and date:

Published: 01/01/2021

DOI:

[10.26481/dis.20210428lt](https://doi.org/10.26481/dis.20210428lt)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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- The final published version features the final layout of the paper including the volume, issue and page numbers.

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IMPACT

The main objective of this dissertation was to investigate the effects of dietary interventions with a mixed high-protein content or soy nuts on several metabolic health and vascular function markers in adults. This thesis support previous findings that a higher dietary protein intake lowers hunger perception and provides novel insights for the involvement of the endocannabinoid-system in energy-intake regulation. The impact of 2-arachidonoylglycerol (2-AG) concentrations in protein-related appetite regulation might be of great interest for future research as it appeared to be a contributor to the appetite-modulating effects in our study. However, the protein intervention or the endocannabinoid-system had no impact on cardiometabolic health and vascular function markers in our study. In contrast, soy nut consumption improved endothelial function and lipoprotein concentrations and therefore lowered cardio-vascular disease (CVD) risk in older adults. As the worlds' population, the proportion of the elderly, and also the diabetes incidence are expected to further increase in the coming years, it is crucial to find strategies to lower the risk for developing non-communicable diseases [1-3]. This thesis's potential impact in terms of scientific, societal and economic relevance, and implications for the translation into practice will be discussed in the following paragraphs.

Societal relevance

Malnutrition, caused by a diet providing too many or too few nutrients, represents a global threat to human health and can result in overweight and obesity or under-nutrition [4]. Worldwide, the consumption of unhealthy diets with, amongst others, high amounts of red meat increases and has been related to an estimation of 990 000 deaths in 2017 [5]. Globally, the prevalence of obesity is rapidly increasing and as it is one of the main modifiable risk factors for non-communicable diseases, those numbers are expected to concurrently increase. Diabetes incidence is enormously growing from a prevalence of 4.7% in adults in 1980 to 8.5% in 2014 and caused 1.6 million deaths in 2016. Approximately 90% of all diabetes cases are assigned to type 2 diabetes mellitus (T2DM), which is mostly associated with overweight and unhealthy lifestyle. Therefore, lifestyle improvements, such as improvements in body weight, physical activity, and a healthy diet, are useful tools in preventing disease development [1]. Even if there are several ways to reduce body weight successfully, weight maintenance after weight loss remains exceptionally challenging due to activated biological responses to prevent further weight loss, amongst other causes. Therefore, it is crucial to find strategies to

improve and simplify body weight maintenance to increase the chances of successful weight management and lower disease risk. In this context, the high-protein diet of the PREVIEW study showed promising results concerning weight management and metabolic parameters [6]. Additionally, this thesis shows that an altered hunger perception possibly contributed to these beneficial effects and weight management improvement.

Next to promoting T2DM development, obesity strongly relates to the development of CVD risk factors, such as hypertension and dyslipidemia [7]. CVD is the most common cause of death worldwide, leading to an estimated 17.9 million deaths annually [2]. As most CVD are caused by modifiable risk factors, such as an unhealthy diet and obesity, powerful prevention strategies could immensely reduce the burden of CVD. In one of our studies, we found that the addition of soy nuts to a healthy diet improved various risk factors for CVD development, such as an improvement in endothelial function, blood pressure, and the lipid profile. The effect on endothelial function, for example, can be associated with an overall 12% decreased CV event risk [8].

Another important risk factor for the above-mentioned non-communicable diseases is aging. In the last years, the aging pace of the world's population is increasing. Due to enhanced longevity worldwide, the proportion of the elderly is increasing. According to the WHO, the population of 60+ years is expected to increase from 12% to 22% between 2015 and 2050 [3]. Aging is associated with an increased risk of disease development, e.g., T2DM due to gradual cellular damage, meaning that a further increase in disease incidence can be expected in the coming years. However, healthy aging can, at least partly, be promoted by improving behavior and the environment at younger age already. This can be done by behavioral changes such as regularly eating a healthy, balanced diet and being physically active [3]. Therefore, it is of enormous importance to understand the aging process in more detail and find optimal strategies to promote healthy aging at the early onset to prevent the development of non-communicable diseases [3]. Multiple organ systems and influencing factors are involved in many age-related conditions. Those conditions often have shared co-morbidities, indicating underlying mutual causes which simultaneously implies the possibility of shared solutions.

According to the soy study in the current thesis, promising cardiovascular effects in persons aged 60 - 70 years has been shown when soy nuts were added on top of a healthy diet compared to the healthy diet without any soy product, suggesting that the simple addition of soy nuts to the diet may promote healthy aging. In this study, multiple possible working mechanisms were analyzed to understand in more detail why the consumption of plant-based foods beneficially affects health.

Economic relevance

Due to the highly increasing numbers of CVD and diabetes patients, health care costs are increasing accordingly and are expected to rise even higher in the future. The diabetes-related costs increase to USD 760 billion in 2019 and have been estimated to increase to USD 825 billion in 2030 [9]. While the global CVD-related costs added up to USD 863 billion in 2010, they are expected to rise to USD 1044 billion in 2030 [10]. Stimulating a healthier lifestyle and a healthier body weight by using dietary intervention strategies as described in the current thesis can lower the disease development risk and thereby reduce the economic burden of non-communicable diseases. A healthier diet, e.g., with more plant-based proteins, could stimulate a healthier aging process and lower the need for medical treatments while being relatively cheap and easily accessible for many people. It, therefore, contains the possibility of a substantial economic relevance by lowering the health care costs of non-communicable diseases in the aging population significantly.

Environmental relevance

Globally, more than 820 million people have insufficient access to food and even more are regularly consuming an unhealthy diet, contributing to a high food-related morbidity [11]. Currently, 462 million adults are underweight, another form of malnutrition. This number will even increase when no changes in the food production systems are made, as the world's population is further increasing to an expected population of around 10 billion people by 2050 [4,11]. It has been proposed that around 70 - 100% more foods will be required in 2050 than produced now [12]. Several adaptations are necessary to feed the increasing world's population within the planetary boundaries, such as a change to more sustainable agricultural systems. Additionally, the change to a less resource-intensive diet by reducing animal-based products and including more protein-rich plant-products instead, such as pulses and soybeans, may help to manage the increasing need for food supply in the future [13].

A shift towards a predominantly plant-based diet combined with improved food production and a reduction in food waste is necessary to provide a healthy diet, in particular for a growing world population. For both, human and planetary health, a shift from animal products to plant-based diets is vital as those diets need fewer resources for their production and are therefore more sustainable [14]. Especially the dietary protein is a huge point of discussion for shifting to those diets. However, with the increased use of nuts, soy, and legumes, protein targets can be achieved with a plant-based diet [11]. Plant-based products rich in protein, such as soy products, have a better

nutrient profile-low climate index than animal-protein sources according to the sustainable nutrient-rich food index [15]. It has been shown that water use increases with the amount of animal protein in the diet. Furthermore, around two-thirds of agricultural and one-third of arable land are currently used for livestock farming. When compared to the production of 1 kg rice or potatoes, 1 kg of beef production uses approximately 18 times more water and 163 times more land. Additionally, the CO₂eq production can be reduced by 53% with an entirely plant-based diet compared with a typical US diet [16].

Target groups

Both studies presented in this thesis were performed in adults and older adults. While the first study with a high-protein diet was completed in pre-diabetic, overweight and obese adults, the soy nut study was performed in persons aged 60 to 70 years with a normal to overweight BMI and no signs of impaired glucose tolerance or CVD. Multidimensional solutions are needed to tackle the medical, economic, and psychosocial consequences of a growing aging population indicating the special need for studies in the elderly to find effective, evidence-based dietary intervention strategies. However, to translate those results to a broader population, e.g., young adults or patients with established CVD, more research is needed. Next to the scientific impact for patients, the outcomes of these studies are also interesting for the food industry to launch healthy, evidence-based food concepts for e.g., plant-based products.

Translation into practice

Clinical studies in humans are critical for translating findings from cell or animal studies to a real-life setting in participants. The protein intervention investigated in this dissertation has already been used for an extended period during the PREVIEW study [17]. Following the high-protein intervention over three years turned out to be difficult, but the dietary intervention still successfully reduced T2DM risk. In contrast, the soy study's compliance was excellent, indicating that merely adding a product to the diet may be easier to follow over a more extended period. Additionally, this study showed beneficial effects of soy nuts despite a healthy diet, possibly pointing out the benefit of shifting the diet to a more plant-based origin. The soy nuts provided in this study were well tolerated, no serious adverse events occurred, and body weight remained stable even when simply adding the product to the regular diet. The daily amount of soy nuts was relatively high but feasible for the study period. For a more extended period, however, it might be an option to incorporate other soy products to promote this

intervention's long-term feasibility and success. Next to the effects on CVD risk, the role of plant-based foods in the prevention of other age-related conditions should get much more attention in future research.

This dissertation's results are or will be published in peer-reviewed scientific journals and have been presented at scientific conferences to increase awareness of this topic, share knowledge, and stimulate further research. These results may be used in a general population's advice to promote healthy dietary choices of individuals. Different patient organizations or societies could help to inform and provide awareness within specific population groups. During both studies, regular dietary guidance for the participants was provided to stimulate and promote compliance to the intervention. We strongly suggest to include dietary guidance into practice to stimulate a balanced and healthy diet and high success rate.

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