Vascular function and insulin sensitivity in the brain and periphery

Impact

In this dissertation, the results from two well-controlled human intervention studies and one systematic literature review have been described and discussed. The overall aim of the dissertation was to investigate the effects of dietary intervention strategies on vascular function and insulin sensitivity of the brain and periphery in adults. The potential impact of this research will be discussed from a scientific, socio-economic and environmental perspective, as well as the translation of the findings into practice.

Scientific relevance

Our research has made significant contributions to the scientific understanding of age-related metabolic and cognitive health, in particular through the further implementation of a non-invasive neuroimaging technique at the research facilities in Maastricht. This technique is sensitive for mapping nutritional effects. It allowed us to quantify (regional) cerebral blood flow (CBF) using arterial spin labeling magnetic resonance imaging (ASL-MRI) under resting conditions and following intranasal insulin administration to study respectively brain vascular function and brain insulin sensitivity [1]. Our randomized controlled trial with mixed nut supplementation indeed provided evidence that regional CBF was beneficially affected through this nutritional intervention, further highlighting the relevance of these measurements to investigate mechanisms through which a healthy diet can improve cognitive performance. The results further underscores the importance of studying brain health together with peripheral vascular and metabolic effects of dietary interventions, as age-related comorbidities, including cardiovascular disease (CVD), type 2 diabetes (T2D), and dementia, often share common risk factors. Especially, our research has shed light on specific brain regions that are activated in response to insulin, suggesting their important role in cognitive processes. Future research should however also focus on other functional outcomes, such as CBF in brain regions involved in the regulation of appetite and satiety, which were also affected. Moreover, our research has emphasized the importance of age and metabolic disorders, such as obesity and T2D, on brain insulin sensitivity. However, future investigations are warranted to further explore differences - and their importance - in brain insulin sensitivity across different patient populations. This will further unravel mechanisms through which therapeutic and lifestyle interventions may enhance brain insulin sensitivity, subsequently leading to improved cognitive performance and appetite regulation.

Socio-economic relevance

The population of adults aged 60 years and older is expected to double from 1.2 billion in 2022 to 2.1 billion by the year 2050 [2]. This demographic shift will have profound socio-economic and public health implications, primarily due to the expected rise in the prevalence and economic burden of age-related disorders, such as CVD, T2D, and dementia [3], which are all closely related to cognitive decline [4, 5]. Notably, the number of patients with dementia is expected to

triple worldwide from 57.4 million in 2019 to 152.8 million in 2050 [6]. The global economic burden associated with dementia is high, with an estimated global cost exceeding €250 billion in 2019, despite that only a fourth of cases is diagnosed and treated [7]. The costs can be split into 16% for direct medical costs, 34% for direct social sector costs, such as long-term care, and 50% for time and efforts of informal caregivers [8]. The direct global cost of dementia-related care is projected to reach €1.5–2.2 trillion by 2050 [7]. Additionally, it should be acknowledged that the total costs related to age-related cognitive decline extend beyond dementia and will be much higher. To address the global socio-economic burden of age-related disorders, it is important to promote a healthy diet - and lifestyle in general - for managing risk factors. Research has demonstrated that an unhealthy diet is responsible for up to 45% of cardiometabolic disease deaths [9]. Our trial provided insights in the beneficial effects of mixed nut consumption on cardiometabolic and brain health, and cognitive performance. These findings further support for the inclusion of nuts in the diet as a healthy aging strategy for the general population, which results in perceivable benefits that have implications for the prevention or delay of metabolic and cognitive disorders [10]. Moreover, lower nut consumption may contribute significantly to annual diet-related cardiometabolic costs [11], highlighting the relevance of nuts for improving not only health outcomes, but also for reducing the socio-economic burden of age-related disorders. Finally, even though we did not report convincing health benefits of long-term NWT-03 supplementation, an egg-protein hydrolysate, on (peripheral) arterial stiffness or cardiometabolic risk markers, a recent publication from our research group demonstrated that NWT-03 intake significantly improved cognitive performance within the executive function domain [12]. These findings suggest that NWT-03 intake may also contribute to the reduction of the burden of cognitive decline.

Environmental relevance

It is essential to consider aspects related to sustainability into dietary recommendations and the development of dietary guidelines [13]. Agricultural food production worldwide is responsible for about 30% of global greenhouse gas (GHG) emissions, contributes to nutrient pollution affecting ecosystems, and consumes a significant amount of freshwater resources [14]. When formulating dietary guidelines for nut consumption, it is important to account for their environmental footprint. The Netherlands Nutrition Centre recommends consuming nuts at a dose of 15-25 g/day [10], while the mixed nut study used a higher daily dose of 60 g. Although nuts generally have a low environmental impact in terms of GHG emissions and pollution compared to other food products, they do have a relatively high impact on scarcity-weighted water use [13]. For instance, the water requirements per kilogram of nuts are comparable to those of less environmentally sustainable food products like red meat. However, when considering the averaged relative environmental impact in relation to the relative risk of mortality, the environmental impact of nut consumption

may not be as significant as that of (un)processed red meat [13]. Furthermore, the environmental impact vary depending on the type of nut. Walnuts consistently demonstrate positive sustainability performance across various criteria, while cashews showed relatively poorer scores [15]. Finally, considering the potentially beneficial longer-term effects of NWT-03 on cognitive performance, it is important to discuss the environmental impact when increasing the production of NWT-03. This should take into account all environmental considerations at the production facilities, including operational and logistic aspects.

Target groups

The study on the effects of mixed nut consumption included older men and women aged 60 to 70 years old who were overweight or obese, while the NWT-03 study included adults with the metabolic syndrome. These populations are known to have an increased risk of metabolic diseases and to develop cognitive impairment [16]. Importantly, it should be emphasized that the participants in our studies did not have existing cognitive complaints. Furthermore, our systematic review revealed differences in regional brain insulin responsiveness associated with aging and obesity. Interestingly, we found that these regions were beneficially affected in our study population through the consumption of mixed nuts. However, future research is needed to generalize these results also to other study populations, such as individuals with or without (pre-)diabetes, subjective cognitive decline, and to explore its potential in reducing the progression to mild cognitive impairment (MCI) and ultimately dementia.

Translation into practice

Clinical studies involving humans play a crucial role in translating findings derived from cell or animal studies to real-life human settings. The described randomized, controlled intervention trials showed excellent study compliance and food products were well-tolerated, indicating that incorporating these products into the diet for extended periods is feasible and safe. To ensure long-term feasibility and success, the inclusion of nuts as part of healthy diet or egg-protein hydrolysates in other food products could be considered as an option for extended periods. Most research findings presented in this thesis have already been published in international open-access journals, such as Neuroendocrinology [17] and Clinical Nutrition [18], or are currently undergoing the peer-review process. As a result, the obtained knowledge is readily accessible to scientists, health professionals, patient organizations and the general public worldwide, thereby promoting further investigation into the effects of healthy foods and food products on brain and metabolic health. Furthermore, the clinical relevance of these results has been presented at national and international conferences, further disseminating the findings to relevant stakeholders. Thus, the research conducted in this dissertation is not only important from a health perspective, but also from socio-economic, environmental and public health perspectives. In this

context, these findings may also be relevant for policymakers in the development of healthy food-based dietary guidelines.

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