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Cerebrovascular and peripheral vascular function in adults

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Impact

The findings of this dissertation provide evidence that improved vascular function in the brain and in the periphery are important mechanisms by which exercise training and soy nuts reduce the risk for cardiovascular disease (CVD) and cognitive impairment. Additionally, inorganic nitrate may acutely increase brain insulin action, which may be important as brain insulin resistance is considered a characteristic of both dementia and type 2 diabetes mellitus (T2D). Our findings are important as the worlds' population, the proportion of older people (1), and the incidence of CVD (2), cognitive impairment (3, 4) and (T2D) are estimated to further increase the coming years. Therefore, it is crucial to develop strategies to lower the risk for developing age-related non-communicable diseases (5). The potential scientific, societal, environmental and economic relevance, and the implications for the translation into practice of the findings described in this thesis will be discussed in the following paragraphs.

Scientific relevance

Exercise training and soy nuts improved regional cerebral blood flow (CBF), which may underlie the observed beneficial effects on cognitive performance. Therefore, further evidence was provided that CBF as measured with arterial spin labeling (ASL) magnetic resonance imaging (MRI) is a sensitive non-invasive marker, which can be used to assess lifestyle-induced changes in cerebrovascular function. Also, exercise training improved endothelial function in a major elastic conduit (i.e., carotid) and peripheral muscular (i.e., brachial) artery, thereby lowering CVD risk (6-8). Due to the proven sensitivity of these markers, they may be used in the future for identification of people at risk of disease and, for example, to track the progression of diseases. Moreover, inorganic nitrate acutely increased brain insulin action, and this finding should now be further investigated in future longer-term studies.

Societal relevance

An unhealthy lifestyle, consisting of a sedentary lifestyle and an unhealthy diet, is a major cause of CVD and cognitive impairment (9). CVD is the leading cause of death worldwide accounting for 17.9 million deaths in 2016 (2), while an impaired cognitive performance is the fastest growing condition reaching 82 million people suffering from this condition globally in 2030 (3, 4). Worldwide, on average 25% of the adult population does not meet the global recommendations for physical activity set by the World Health Organization (10). Depending on the economic development of a country, this can be as high as 70%, due to changing patterns of transportation, increased use of technology and urbanization (10). Approximately 5.3 million deaths every year are attributable to physical inactivity (11), which doubles the risk of CVD, type 2 diabetes, and obesity (12), and is also associated with decreased cognitive performance (13). An unhealthy diet is another leading cause of disability and mortality. Eleven million disability-adjusted life-years could be attributed to dietary risk factors in 2017 (14). Improvement of diet could potentially prevent one out of five deaths globally, which is more than any other risk globally. Specifically, consumption of plant-based diets has been associated with improvements in cognitive performance across

different cognitive domains (3, 15). This highlights the importance of a healthy diet in preventing or attenuating the development of these age-related conditions.

The observed effects of exercise training and soy nuts on top of a recommended diet contribute to the reduced risk of CVD and increased cognitive performance. Results from prospective epidemiological studies suggested that the observed exercise-induced improvement in brachial endothelial function reduces CVD risk by about 24% (23). Besides, vasodilation of the carotid artery increased after exercise training to a level previously observed in healthy young individuals. In addition, the beneficial effects of exercise training and soy nuts on regional CBF and cognitive performance may therefore have a great societal impact. Inorganic nitrate acutely increased brain insulin action in regions that were shown to be impaired in populations with neurodegenerative diseases and T2D, and were related to eating behavior (16-18).

Human aging is another important risk factor for the development of the non-communicable conditions mentioned above. The population aged over 65 years will almost double by the year 2050 accounting for 1.5 billion people (1). Physical activity and a healthy diet are effective modifiable lifestyle factors that can be implemented at any age to reduce the duration and exposure to risk factors for age-related conditions, thereby attenuating or preventing those disease outcomes (19, 20). Therefore, it is important to understand how these lifestyle factors affect healthy aging. In this thesis we showed that not only cerebrovascular and peripheral vascular function improved, but also perceivable benefits, including cognitive performance and physical fitness. Moreover, reducing the risk for cognitive impairment also beneficially impacts the psychosocial consequences of this condition for both the individuals and their relatives.

Economic relevance

The total numbers of deaths due to CVD increased with 14.5% to 17.6 million people globally between 2006 and 2016 (21). The CVD-related economic costs were estimated to be 169 billion dollar translating to 230 dollar per person in 2004, of which 68% were direct costs (e.g., hospitalization) and the remaining indirect costs were mainly due to losses of productivity and short- or long-term disability (22). Exercise training may reduce these costs by decreasing the risk for CVD via its effects on peripheral vascular function. Additionally, reduced risk for cognitive impairment may be realized by exercise and soy nuts via beneficial effects on cerebrovascular function. The rapidly growing incidence of cognitive impairment is also a global public health problem. Around 50 million people suffer from cognitive impairment worldwide, which is projected to reach 82 million in 2030 and 152 million in 2050 (3). Not only governments are faced with increased costs due to cognitive impairment, but also whole communities, families and individuals are affected. The global societal cost of cognitive impairment was estimated to be 818 billion dollar (3). Stimulating a healthy lifestyle, consisting of increased physical activity levels and a healthy diet, is a cost-effective intervention and prevention strategy. Costs for health care systems attributable to physical inactivity were estimated to be 54 billion dollar worldwide (23), which already yielded cost savings when a reduction of inactivity rates by about 20% was realized (24). Besides, it was

estimated that 45% of the cost associated with cardiometabolic diseases is related to an unhealthy diet, accounting for more than 50 billion dollar in the United States (25). Approximately 1.93 million CVD events could be prevented and 39.7 billion dollars in healthcare costs would be saved in the United States, if a 30% subsidy would be provided on healthful foods, including fruit and vegetables and plant-based foods (26). This clearly highlights the economic relevance of a healthy lifestyle by lowering the health care costs of non-communicable diseases in the aging population.

Target groups

The two longer-term intervention studies were performed in older adults aged 60 to 70 years. The study investigating the effect of aerobic exercise training included sedentary overweight and obese men, while normal-to-overweight men and women participated in the soy study. These populations were expected to have a reduced cerebrovascular and peripheral vascular function at baseline, thereby allowing for improvement by lifestyle interventions. Multimodal interventions in aging overweight and obese participants may effectively attenuate the societal, economic, and psychosocial consequences of the age-related conditions. Whether the observed effects of exercise training also translate to a broader population consisting of young adults and CVD patients requires further study. The study investigating the acute effects of inorganic nitrate on brain insulin action focused on apparently healthy men that were aged 18 – 60 years and may benefit most from lifestyle interventions. However, this research did not include women to eliminate possible gender differences, which obviously reduces the generalizability of the outcomes. Future research should now also investigate whether the findings also translate to populations with subjective cognitive decline and reduce the progression to mild cognitive impairment and eventually dementia.

Translation into practice

Intervention and prevention trials in humans are essential for the development of knowledge about processes that lead to health problems, and how these problems can be prevented. The translational research performed in this thesis showed that aerobic exercise training can already have beneficial effects on vascular function, cognitive performance, and glucose metabolism after eight weeks in older men. The compliance to the intervention was excellent, although feasibility over a prolonged period with a larger population may be more challenging. However, other physical activity protocols may also be beneficial, which should be confirmed in future studies. Additionally, soy nuts on top of a healthy diet showed beneficial effects on cerebrovascular function and cognitive performance, which emphasizes the benefits of shifting to a more plant-based diet. The soy nuts were well tolerated, while body weight remained stable and no (serious) adverse events were observed. Participants were requested to consume soy nuts. However, similar beneficial effects may also be observed with other soy products which requires further study. Finally, inorganic nitrate acutely increased brain insulin action. These results may also apply to whole foods rich in nitrate, such as beetroot and leafy green vegetables (16), but this needs

to be confirmed by follow-up research. Additionally, improvements in perceivable benefits (e.g., physical fitness and cognitive performance) may also assist in adherence to the intervention in practice. Finally, the outcomes of this study may be relevant for the development of dietary and physical activity recommendations that will aid in the reduction in prevalence of CVD and cognitive impairment. The observed results may also be interesting for the food industry to develop, for example, healthy evidence-based food formulations and concepts.

The findings described in one of the chapters are published in Siemens FLASH, which is primarily read by clinicians. The first study was already published open-access, to increase visibility and reuse of knowledge. The other studies described in this dissertation will also be published in peer-reviewed scientific journals and have already been presented at scientific conferences to increase awareness and share knowledge, which functions as a foundation for future research. The findings may also be used to create more awareness for, and to promote, a healthy lifestyle.

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