The role of diabetes and vascular burden in Alzheimer's disease

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Impact paragraph

Within this thesis, the main aim was to unravel contributions of diabetes and vascular burden to Alzheimer's disease (AD). Therefore, we assessed (1) whether diabetes and vascular burden are associated with AD pathophysiology, and (2) how diabetes and vascular burden in combination with AD pathophysiology contribute to cognitive decline. This impact paragraph describes the societal and scientific impact of the findings within this thesis.

Main findings

In part I, we have shown that diabetes and AD are two distinct diseases with independent disease processes. The diseases might show similarities regarding tau pathology and temporal atrophy, but overall diabetes and AD were associated with different combined profiles of amyloid and tau pathologies as well as distinctive patterns of cognitive decline at different stages. AD was associated with amyloid and tau pathology and presence of these biomarkers strongly predicts cognitive decline across multiple cognitive domains. Diabetes was associated with tau pathology and neurodegeneration, especially in cognitively normal and population settings, but not with amyloid. Persons with diabetes did not show a strong decline in cognitive functions but did show lower cognitive performance in attention and executive functions domains already in early stages. These findings might suggest that diabetes is associated with cognitive impairment and dementia, but not AD.

In part II, we demonstrated that cerebral microbleeds are closely associated with amyloid pathophysiology, and that its prevalence increases with age and amyloid abnormality. Amyloid biomarkers were shown to be the major driver of cognitive decline in a memory clinic setting, as compared to vascular burden on MRI. It can be questioned whether markers such as cerebral microbleeds and WMH represent vascular pathologies in the context of AD, i.e. have a vascular cause, or whether they represent AD pathologies instead.

Societal impact

AD is currently one of the most common and impacting diseases in the elderly and only increases in prevalence in the upcoming years. The disease can have a great impact on cognition and behavior, and thereby on the personal life and independent functioning of patients. This does not only impact the patient, but also their informal caregivers and family. In advanced stages of the disease, patients cannot continue working, are not able to live independently anymore, and need continuous healthcare, which is a great burden.
for society and healthcare systems. With the current increasing burden and healthcare costs, it becomes a great challenge to provide appropriate and timely healthcare to all persons who need it. It is therefore important to improve healthcare through developing suitable treatments in early stages and invest in dementia prevention. Targeting early stages is particularly important, as treatments in this phase are often less invasive and of lower costs. To do so, knowledge on the mechanisms behind AD are necessary, as well as knowledge on risk factors causing AD pathophysiology and its related cognitive decline. Our findings are therefore of great relevance for (a) clinicians and patients, (b) adult individuals (at-risk for AD), and (c) healthcare insurances and companies.

For clinicians and patients, there is need for better and more efficient diagnostic and prognostic procedures, in which we can predict the risk and course of AD based on low cost and non-invasive methods. Our findings help to better understand how diabetes and vascular burden contribute to a diagnosis of AD and how combined profiles of AD and vascular markers can lead to cognitive decline. As differences in individual characteristics can change associations, the ultimate goal would be to predict the course of AD and cognitive decline based on individualized profiles of demographics, genetics, biomarkers, and risk factors such as vascular comorbidities (including diabetes) and vascular burden.

Our findings demonstrate that AD is not affected by diabetes status and therefore cannot be described as diabetes type 3, as claimed by previous studies. Diabetes is predominantly associated with lower performance in non-memory domains such as attention, executive functions, and language. These are slow and subtle effects as when compared to biomarkers of AD, which more strongly predict cognitive decline across both memory and non-memory domains. Having both abnormal AD biomarkers and diabetes does not further accelerate cognitive decline. This implies that diabetes and AD are independent entities that should be diagnosed separately and have a different prognosis. Diabetes may however lower the threshold for a clinical diagnosis of dementia. Regarding vascular burden, we have shown that cerebral microbleeds are closely related to AD pathology but do similarly not contribute to accelerated cognitive decline. As it becomes more apparent that AD and vascular pathologies often co-exist, this knowledge is highly relevant for clinicians when defining the prognosis of patients with mixed pathologies. An accurate prognosis is important to plan appropriate and timely treatments and care, to improve the quality of life for patients and their informal caregivers.

For adult individuals, our finding that diabetes and elevated blood glucose is associated with tau and neurodegeneration highlights the importance of preventing diabetes and managing blood glucose, also in stages before diabetes. This will help
to prevent future neurodegeneration and cognitive impairment (in attention, executive functions, and language). Thereby, it may reduce chances to develop AD in later life and increase the quality of life for individuals and their families.

Improving diagnostic and prognostic procedures is also relevant for healthcare companies and insurances, by enabling better guidelines and providing relevant knowledge for appropriate individualized healthcare packages with the goal to reach an optimal balance in costs and benefits. Preventing people to develop dementia (and vascular diseases) will on the long-term relieve burden on healthcare systems and substantially reduce its costs.

**Scientific impact**

This thesis provides novel and relevant perspectives for researchers and gives directions for future research in the field. We question the current belief that diabetes increases AD risk. While diabetes might contribute to cognitive impairment and a clinical diagnosis of AD, this does not seem to be true for underlying pathways of AD as defined by the ATN framework and amyloid cascade hypothesis. Our findings indicate that diabetes is associated with tau but not amyloid pathology. This indicates that cognitive impairment induced by a vascular cause should be targeted differently. This is an important ground to further study the role of diabetes and vascular burden in relation to pathophysiological profiles and different (sub)types of dementia. Our thesis also suggests that the role of peripheral insulin in AD should be further explored and underlines the importance of assessing differences between populations and persons to develop personalized healthcare.

We also provide relevant information for pharmaceutical companies, by providing information and guidelines on participant selection and safety evaluations in anti-amyloid trials. We have demonstrated that cerebral lobar microbleeds are closely related to amyloid pathology. As current anti-amyloid medication options can induce amyloid-related imaging abnormalities (ARIA) as side effect, it is of great importance to select participants on low microbleed burden for safe inclusion procedures. It is currently unknown what would be a good selection criterium. Our study suggests that selecting participants on <2 microbleeds might be better than the currently used <4 cutoff. Using this cutoff, clinical trials could safely include amyloid positive persons that are APOE ε4 positive. In addition, we have shown that a diagnosis of diabetes or the presence of vascular burden might not impact trial outcomes when assessing cognitive decline as outcome.

Both parts of this thesis, show that data sharing and pooling is of high relevance and importance for research, as it allows to study differences between subgroups on a
large-scale and can lead to novel perspectives. Researchers should more often reuse data through sharing and pooling to increase the impact of research and bring more efficient and faster solutions.

**Dissemination activities**

We disseminated our findings through scientific publications (as reported for each chapter) and presentations at conferences and scientific events. We presented the results in oral presentations at the Alzheimer’s Association International Conference (AAIC) in 2021, 2022, and 2024, and a poster presentation in 2023. Other oral presentations on our findings were given at VasCog 2021 and the European College of Neuropsychopharmacology (ECNP) conference in 2022 through a symposium with PRIME consortium members, which was also published in a conference report by Medicom Medical Publishers. We also shared knowledge with a more general audience through a two-episode podcast for ECNP. Results were also presented at local events such as the MHeNs research days (2021-2022), EURON PhD days (2022-2023) and a symposium for the inaugural lecture of Prof. Dr. Pieter Jelle Visser (2023). Presentations to lay audience were given at an online event for patients and caregivers organized by Alzheimer’s Association ISTAART ambassadors (2021), the Pint of Science festival Maastricht (2022) and in “dementia dialogues” at MUMC+ (2023). We also shared our findings through social media platforms like LinkedIn, ResearchGate, and Kudos. In addition, we shared our knowledge and findings through teaching activities to bachelor and master’s students at Maastricht University in the faculties of Health, Medicine, and Life Sciences (FHML) and Psychology and Neuroscience (FPN).