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

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Summary

Alzheimer’s disease (AD) is one of the most common and impactful diseases in the elderly and only increases in prevalence. AD is characterized by amyloid plaques and tau tangles in the brain, which can be measured using biomarkers in CSF or on PET. Diabetes and vascular burden often co-occur in AD, but it remains unclear what role diabetes and vascular burden play in AD pathophysiology and its related cognitive decline. Within this thesis, we aimed to (1) assess associations of diabetes and vascular burden with common biomarkers of AD, including amyloid and tau, and (2) how combined profiles of diabetes/vascular burden and AD biomarkers contribute to cognitive decline.

This thesis consists of two parts. In **part I** (chapter 2-5), we explored whether diabetes is associated with AD biomarkers of amyloid and tau, neurodegeneration markers, and vascular burden, and we zoom in on the association between cerebral microbleeds and amyloid biomarkers. In **part II** (chapter 6-7), we explored how amyloid pathophysiology in combination with diabetes or vascular burden might impact cognitive decline.

In **chapter 1**, the general introduction, we provide a global background on AD, its diagnostics and biomarkers, and potential vascular contributions to AD with a special focus on diabetes and vascular burden on MRI. We introduced four research questions, that we will discuss below along with the findings.

**PART I – Associations with amyloid and tau biomarkers**

*Are diabetes and glucose metabolism associated with amyloid and tau pathophysiology?*

In **chapter 2**, we summarized existing studies on the associations of diabetes and glucose metabolism measures with AD biomarkers of amyloid and tau through a systematic review and meta-analysis. We found that a diagnosis of diabetes and impaired blood glucose are overall not associated with biomarkers of amyloid but show an association with decreased amyloid biomarkers in persons within memory clinic settings. Diabetes diagnosis and impaired blood glucose were associated with increased levels of tau, especially in population settings.

In **chapter 3**, we explored whether measures of glucose metabolism are associated with amyloid and tau on PET later in life, in participants from the Framingham Heart Study. We found that elevated levels of blood glucose were associated with increased tau 14 years later, whereas higher levels of insulin and insulin resistance were related to decreased amyloid biomarkers later in time.
In chapter 4, we large-scale explored the association of diabetes with AD biomarkers, neurodegeneration, and MRI vascular burden by pooling data from ten European memory clinic and aging cohorts in collaboration with multiple European universities (PRIME project). Here, we demonstrated that diabetes was associated with less amyloid pathology in persons with dementia, but with more tau pathology and medial temporal atrophy (MTA) in cognitively normal persons with normal amyloid. Diabetes was not associated with MRI vascular burden.

Are cerebral microbleeds related to amyloid pathophysiology?
In chapter 5, we explored relationships between cerebral microbleeds and amyloid biomarkers using data from the Amyloid Biomarker Study, combining data from 15 centers worldwide. We found that cerebral microbleeds are closely associated with amyloid biomarkers, and that microbleeds prevalence increases in persons with higher age and abnormal amyloid.

PART II – Associations with cognitive decline
Do diabetes and amyloid pathophysiology synergistically contribute to cognitive decline?
In chapter 6, we assessed whether diabetes and amyloid contribute to cognitive decline synergistically or independently, using the same cohorts as in chapter 4 (as part of PRIME). We found that abnormal biomarkers of amyloid are major contributors to cognitive decline across multiple cognitive domains. Diabetes did not predict cognitive decline. Diabetes was however associated with decreased baseline performance on attention, executive functions, and language, whereas amyloid abnormality was associated with baseline global cognition and memory.

Do vascular burden and amyloid pathophysiology synergistically contribute to cognitive decline?
In chapter 7, we assessed whether MRI vascular burden and amyloid biomarkers are synergistically or independently related to cognitive decline in a Dutch-German memory clinic setting. We found that abnormal amyloid is the major contributor to cognitive decline, while vascular burden on MRI and vascular comorbidities only showed a minor contribution in this setting.

In chapter 8, the general discussion, we summarized and discussed our findings in the light of recent literature.

In short, we conclude that diabetes is not associated with AD pathophysiology and that diabetes and AD show independent and different patterns of cognitive functions. Vascular burden, especially cerebral microbleeds, are closely associated with AD but
do not contribute to cognitive decline in a memory clinic setting. With this knowledge, we can improve diagnostics and prognostics in persons with diabetes and/or vascular burden. Moreover, our findings underline the importance of preventing diabetes and controlling blood glucose. It also informs future clinical (drug) trials for AD, updates current theoretical frameworks, and shows the strength of pooling data. Future studies should further explore vascular contributions, their underlying pathways, and their role in AD or other types of dementia.