Lifestyle, Alzheimer's disease pathophysiology and cognition

Summary

Alzheimer's disease (AD) is a common neurodegenerative disease that is characterized by abnormal accumulation of the amyloid and tau protein. While AD dementia remains a clinical diagnosis, evidence of AD pathology can be detected from as early as twenty years before cognitive symptom onset using biomarkers for amyloid and tau. There are no established prevention or treatment strategies for AD. While both lifestyle-based interventions and anti-amyloid therapies have shown promising results, we need to improve our understanding of the underlying mechanisms and determine which individuals would benefit from these strategies at what stage of the disease. The aim of thesis, therefore, was to contribute to protection and prevention of AD by characterizing the role of lifestyle health in AD pathophysiology (**part I, chapters 2 through 5**) and leveraging pooled data to help inform clinical trial design for anti-amyloid therapies (**part II, chapter 6 and 7**).

In **chapter 1**, we introduce AD, its clinical stages and biomarkers and provide background information on lifestyle health in AD and AD clinical trials. We introduce the research questions that are addressed in this thesis and the datasets we used to answer these questions.

In **Part I**, we further characterized the role of lifestyle health in AD pathophysiology by studying the association between lifestyle health and AD biomarkers. In **chapter 2**, we used data from the Amyloid Biomarker Study to assess the associations of alcohol consumption, smoking behavior, sleep quality, physical activity, cognitive activity, and social activity with amyloid pathology. We found that, in the group of persons with normal cognition (NC), those who were cognitively active were less likely to have amyloid pathology than those who were not. In the group of individuals with mild cognitive impairment (MCI), those who had ever smoked or had sleep problems were less likely to have amyloid pathology than those who did not.

In **chapter 3**, we built on these findings and studied whether a composite measure of late-midlife lifestyle was associated with longitudinal biomarker changes and cognitive changes when accounting for change in biomarkers using data from the Wisconsin Registry for Alzheimer's Prevention. We also examined whether changes where similar between individuals on the AD continuum (amyloid pathology) vs. the non-AD continuum (no amyloid pathology). We found that, in the age- and disease-range studied, lifestyle did

not exhibit a meaningful effect on AD or vascular biomarker accumulation and did not affect the primary longitudinal cognitive outcome.

In **chapter 4**, we focused specifically on depressive symptoms and investigated whether the presence and severity of depressive symptoms was associated with amyloid pathology in persons without dementia included in the Amyloid Biomarker Study. We found that depressive symptoms were not consistently associated with amyloid pathology in persons with NC but were associated with a lower likelihood of amyloid pathology in persons with MCI.

We conclude that there is no direct association between lifestyle health and biomarkers for AD in persons without dementia, although lifestyle health may be associated with cognitive decline through other mechanisms.

In **chapter 5**, we describe the methodology used in setting up the Netherlands Consortium of Dementia Cohorts (NCDC). We took the first steps toward improving the findability, accessibility, interoperability, and reusability (FAIR) of data from nine Dutch memory and aging cohorts through establishment of ethical and legal frameworks for data sharing, development of harmonization strategies and implementation of software allowing for federated analysis. Results from **chapter 5** indicate that data-pooling initiatives may greatly benefit from the identification or appointment of dedicated study personnel at each study site. The establishment of the ethical and legal frameworks needed for data sharing may be the largest barrier to the successful formation of such initiatives.

In **Part II**, we helped inform clinical trial design for anti-amyloid therapies by studying the association between amyloid pathology and cognitive decline and the association between cerebral microbleeds and amyloid pathology. In **chapter 6**, we studied the association of amyloid pathology with decline in global cognition, clinical functioning, and immediate and delayed memory recall in individuals without dementia included in the Amyloid Biomarker Study. We found that individuals with MCI and amyloid pathology performed worse and declined faster on all cognitive outcomes studied when compared to MCI individuals without amyloid pathology. A similar pattern was observed in persons with NC for global cognition and functional performance (not memory), but this was only apparent in individuals who had both amyloid and tau pathology.

In **chapter 7**, we examined the association between cerebral microbleeds and amyloid pathology and provided prevalence estimates of cerebral microbleeds given amyloid status, *APOE ε4* copy number and age using data from the Amyloid biomarker Study. We found that amyloid pathology and, additively, *APOE ε4* copy number, were associated with higher odds of cerebral microbleeds in individuals with MCI and AD dementia, and with higher odds of lobar cerebral microbleeds only in persons with NC. Prevalence estimates ranged from 6% at age 50 (*APOE ε4* non-carrier, no amyloid pathology, NC) to 52% at age 90 (*APOE ε4* homozygote, amyloid pathology, MCI/AD dementia).

We conclude that adaptions in the design of clinical trials of anti-amyloid therapies would be warranted if initiation of treatment in earlier clinical stages would be considered. The prevalence estimates provided in **chapter 7** may also inform sample size calculations for clinical trials of anti-amyloid therapies.

In **chapter 8**, we place these results in the broader context of the existing work and developments in the field. We note that future research should continue to focus on exploring the mechanisms that may underlie the association between lifestyle health and dementia risk. For clinical trials of anti-amyloid therapies, it is vital to continue to work on finding a balance between benefit and harm as well as safety and generalizability of results. The combination of expertise and data across studies and research sites may be key in answering these questions.