

Lifestyle, Alzheimer's disease pathophysiology and cognition

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Impact paragraph

Main findings

In this thesis, we conclude that there is no direct association between lifestyle health and biomarkers for Alzheimer's disease (AD) in persons without dementia, although lifestyle health may be associated with cognitive decline through other mechanisms (**part I**). We further observed clear associations between amyloid pathology and cognitive decline in persons with MCI and found that the prevalence of CMBs ranged from 6% at age 50 to 52% at age 90, which helps inform design of clinical trials for anti-amyloid therapies (**part II**).

Societal impact

AD is highly prevalent, and the number of individuals affected by AD is expected to increase incrementally in the coming years.¹ AD therefore poses a significant societal and healthcare burden. There are no established treatments for AD. Lifestyle-based interventions and anti-amyloid therapies have shown promising results, although it is still unclear for which patients and at what disease stages these may be most effective. The results of this thesis help inform the design of lifestyle prevention strategies as well as clinical trials for AD therapies. Therefore, results are relevant for clinicians, patients and persons at risk of developing AD as well as pharma and health insurance companies.

Clinical impact

Our observation that there is no association between depressive symptoms and AD biomarkers may inform prognosis in a clinical setting, benefiting clinicians and patients. The negative associations we observed between lifestyle health factors and amyloid pathology in individuals with MCI generally suggest that it remains important to consider evaluation of the presence of depressive symptomatology and other lifestyle health factors in elderly persons presenting with cognitive problems.

We note that individuals who receive an MCI diagnosis in a memory clinic setting increasingly express interest in lifestyle advice. The observation that there is no direct association between lifestyle health and AD biomarkers will help to better inform clinicians and patients of the potential benefits of adopting or adhering to healthy lifestyle behaviors in this stage, clarifying that

it may have beneficial effects on cognition but will not delay the appearance or progression of the underlying AD pathology.

Adaptation of clinical trial design for anti-amyloid therapies may affect eligibility for trial inclusion. As such, optimization of trial design may have important consequences for treatment access. Currently, only around 17% of its target population is eligible for inclusion in trials in trials for the amyloid therapy Lecanemab.²

Scientific impact

This thesis contributes to our knowledge of the associations between lifestyle health and AD biomarkers, AD biomarkers and cognition and amyloid pathology and cerebral microbleeds, which can inform future research in these areas. This thesis also establishes barriers to and facilitators for the establishment of data pooling initiatives and provides insight into strategies that could be used to improve the findability, accessibility, interoperability, and reusability (FAIR) of cohorts and research data. This may facilitate and promote scientific collaboration and open science.

Dissemination activities

Dissemination activities for the work presented in this thesis include publications in peer-reviewed journals (chapters 2-7) and presentations at conferences and other scientific events. Aspects of this work were presented at AAIC 2021, 2022, 2023 and 2024 (poster presentations) and AD/PD 2022 (oral presentation). Presentations at other scientific events have included an oral presentation at the EURON PhD days (2022) and the MHeNS research day (2021, 2022, 2023) as well as Pint of Science (2022; public event), the Alzheimer Centrum Limburg webinar (2023; public event) and the dementia dialogues series at the Maastricht UMC (2023; public event). We also shared our knowledge and findings when teaching and supervising bachelor's and master's students from Maastricht University.

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