

Novel perspectives from existing data on early Alzheimer's disease pathology and dementia care use

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IMPACT PARAGRAPH

The main aim of the research described in this thesis was to examine relevant outcomes and endpoints related to Alzheimer's disease (AD) pathology in pre-dementia stages, and to examine the disease trajectory and care duration after a dementia diagnosis. To this means, existing data were re-used, and different data sources and data types ranging from biomarker data to registry data were included. This impact paragraph describes the scientific and societal impact of our main findings.

Main findings

In Part I we focused on amyloid abnormality in preclinical and prodromal AD. The methodology to define amyloid abnormality cutoffs influences prevalence estimates, and it has appeared recently that some cerebrospinal fluid (CSF) values gradually increased over the past two decades indicating that older cutoffs might be too conservative. Using cohort-provided cutoffs to determine amyloid abnormality, amyloid abnormality prevalences were similar to our 2015 estimates for individuals without dementia, and similar across positron emission tomography (PET) and CSF estimates, while for clinical AD dementia estimates were higher for PET than CSF. When amyloid abnormality was examined using adjusted, data-driven cutoffs, CSF estimates were on average 10% higher than PET-estimates in non-dementia stages, while estimates were comparable for PET and CSF in AD dementia. This implies that preclinical and prodromal AD may be more prevalent than previously estimated. We also showed that amyloid abnormality estimates are similar in persons with normal cognition (NC) and persons with subjective cognitive decline (SCD) and that there is large variability in the frequency of amyloid pathology in persons with SCD between different cohorts. In preclinical AD, characteristics of SCD are associated with amyloid pathology but often depend on age and setting. These low-cost characteristics may aid identification of individuals that might benefit from disease-modifying treatment, but due to their small effect sizes provide limited added value next to age and apolipoprotein (*APOE*)- $\epsilon 4$ carriership. Cognitive decline was closely associated with amyloid abnormality in persons with prodromal AD, but was similar in amyloid-abnormal and amyloid-normal persons with NC across all domains (global cognitive functioning, clinical functioning, episodic memory). This suggests that anti-amyloid treatments in preclinical AD are not likely to show short-term cognitive improvements compared with amyloid-normal persons with NC.

Part II first provided an integrated overview of how different European real-world AD data sources capture outcomes that are considered a priority by patients, caregivers, and healthcare professionals. No single data source identified contained information



on all outcomes across the full AD disease spectrum. Then, using registry data from the Netherlands, we estimated the duration of different care types in persons with dementia and compared these with estimates from controls. Total care duration was 3.5 years in 85-year-old men and 5.4 years in 85-year-old women. In men, the duration of home care was longer compared with no formal care and institutional care. The duration of no formal care was longer in persons not living alone, without prescribed dementia medication, with a non-Western migration background, or with a higher income. The duration of home or institutional care was longer in women, persons without polypharmacy, in those living alone, or those with a Western background. Median time from diagnosis until institutionalization and until death for people with dementia was considerably shorter than for controls, whereas median time to death once institutionalized was longer for persons with dementia than for controls.

Societal impact

The findings described in this thesis are relevant to our society. The number of persons affected by AD dementia and other dementias continues to increase and poses a great burden not only on patients and caregivers, but also on healthcare systems and the general society. Dementia prevention has become a public health priority as the economic impact of dementia is enormous. Next to prevention of dementia, successful disease-modifying treatments that halt or delay disease progression remain the ultimate goal. This would relieve the burden posed to persons living with dementia, caregivers, and social care systems because these treatments would have direct medical costs instead of the current indirect costs and costs of social care. Clinicians, patients, caregivers, policy makers, and healthcare insurers can employ our findings in several ways, which are listed below.

Clinicians, patients, and caregivers can benefit from our findings. Our prevalence estimates of amyloid abnormality and its associations with AD risk factors as well as cognitive decline can contribute to timely diagnosis and can improve accuracy of prognoses. Clinicians can use our findings to help interpret biomarker and clinical data, and therefore our results are also of relevance to patients and caregivers. For example: the setting in which a patient is presenting is an important factor to consider in persons with SCD, the amyloid biomarker modality used might influence the ability to capture earlier disease stages, and decline in immediate and delayed recall memory performance in persons with MCI might be most sensitive to indicate future progression to dementia. Currently, providing accurate prognoses is not yet possible, as there are uncertainties regarding the link between amyloid biomarkers and cognitive outcomes at an individual level. Our results reduced this uncertainty by increasing knowledge on the relations between amyloid biomarkers, risk factors, characteristics of subjective complaints, and

cognitive decline. Our results on specific characteristics of SCD might assist in directing patient-tailored cognitive by training those specific complaints a patient is presenting with. As those complaints were associated with AD biomarker abnormality in our study, these interventions might delay or slow the onset of pathologic cognitive decline. Our results on care use and mortality can be used to assess risk of institutionalization and mortality more precisely, and ultimately to link those at higher risk to suitable services in a timely manner to improve quality of life of both patients and caregivers. General practitioners can also utilize our sex- and age-specific estimates to better inform patients and caregivers about a probable care trajectory. Those patients might benefit from closer monitoring and healthcare providers might use our duration estimates in discussing more sensitive topics such as care planning, nursing home placement, and mortality risk. Still, the predictive value at an individual level remains unclear, and this uncertainty should be considered by clinicians when interpreting and communicating individual results. It is also important to consider an individual patient's expectations, values, and reasons for seeking help.

Policy makers can employ the transition rates between formal care types in persons with dementia which incorporate the influence of several individual characteristics in health-economic assessments of treatments. These assessments are important to compare the influence of a treatment on calculated formal dementia-care related costs based on our transition rates with the direct medical costs associated with a treatment and likely provide valuable insights. Thereby our estimates can also assist governments and healthcare insurers in selecting treatments and reimbursements most likely to result in the maximum societal health gain. The estimates of care duration and the role of demographic and health-related factors can be used to facilitate the identification of persons with dementia that are likely to have a shorter duration without home care for example.

Scientific impact

The findings described in this thesis are also relevant to researchers and pharmaceutical companies. Our prevalence estimates described in Part I contribute to improved recruitment strategies for trials on future treatments. Since our results contribute to the identification of persons that are in an early stage of AD and likely to benefit from treatment, our findings are relevant to reduce screen-failure rates. The future aim to share the Amyloid Biomarker Study data on an online platform will contribute to scientific research as well, by allowing other researchers to use this rich data source to answer future research questions.

The findings described in Part II are relevant to researchers and pharmaceutical companies in a number of ways. Researchers can use our findings and especially the integrated overview of European AD-relevant data sources and outcomes in the form



of a Data cube as a starting point to select appropriate data sources for different types of research questions and to design future studies. Also, the Data cube could be used to drive future data collection by identifying gaps in the availability of priority outcomes in different data sources. Designers of clinical trials can incorporate the identified outcomes that are currently collected least to ensure that future treatments can effectively improve outcomes relevant to persons living with AD, their caregivers, and healthcare professionals. Researchers can also use our reported transition rates to predict future care needs in the Netherlands, for example by forecasting the number of persons living in the Netherlands that will need home or institutional care in the next decade.

There are a number of future research questions that our studies were unable to answer, such as whether CSF-based estimates are indeed more sensitive than PET-based estimates for amyloid abnormality among people without dementia, whether rates of cognitive decline differ when amyloid abnormality is based on PET versus CSF, whether SCD-characteristics within persons with amyloid abnormality are associated with cognitive outcomes over time, how other AD biomarkers fit into our results, and how formal care duration is influenced by other factors such as dementia type, severity, and informal care. Research on these topics will contribute to improving trial recruitment strategies, contribute to timely diagnoses, and eventually decrease the burden of AD on patients, caregivers, and the society.

Dissemination activities

Our findings were disseminated to the scientific community through publications in scientific journals, as well as poster and oral presentations at local (MHeNs research day 2018-2021, Geriatriedagen 2020, Future of a data-driven society symposium 2018) and international scientific conferences (Alzheimer's Association International Conference 2018-2021, Innovative Medicine Initiatives symposium 2018, European Medical Frameworks Initiative symposium 2018, Optimizing multi-study integrative research conference 2019). We also disseminated our findings to researchers through online platforms such as ResearchGate and LinkedIn and reports publicly available on the Real-World Outcomes across the AD spectrum for better care (ROADMAP) project website. Our findings were disseminated to pharmaceutical companies involved in the ROADMAP project, and served as input to Biogen project meetings through reports, regular meetings, and scientific dissemination. Our research results were also disseminated through teaching of Bachelor and Master students at the Faculty of Health, Medicine and Life Sciences, the Faculty of Psychology and Neuroscience, and the Maastricht Science Programme. Our results were communicated to patients, caregivers, and the general public through presentations at local community centers at the Alzheimer Café Maastricht and in the Alzheimer Center Limburg newsletter.