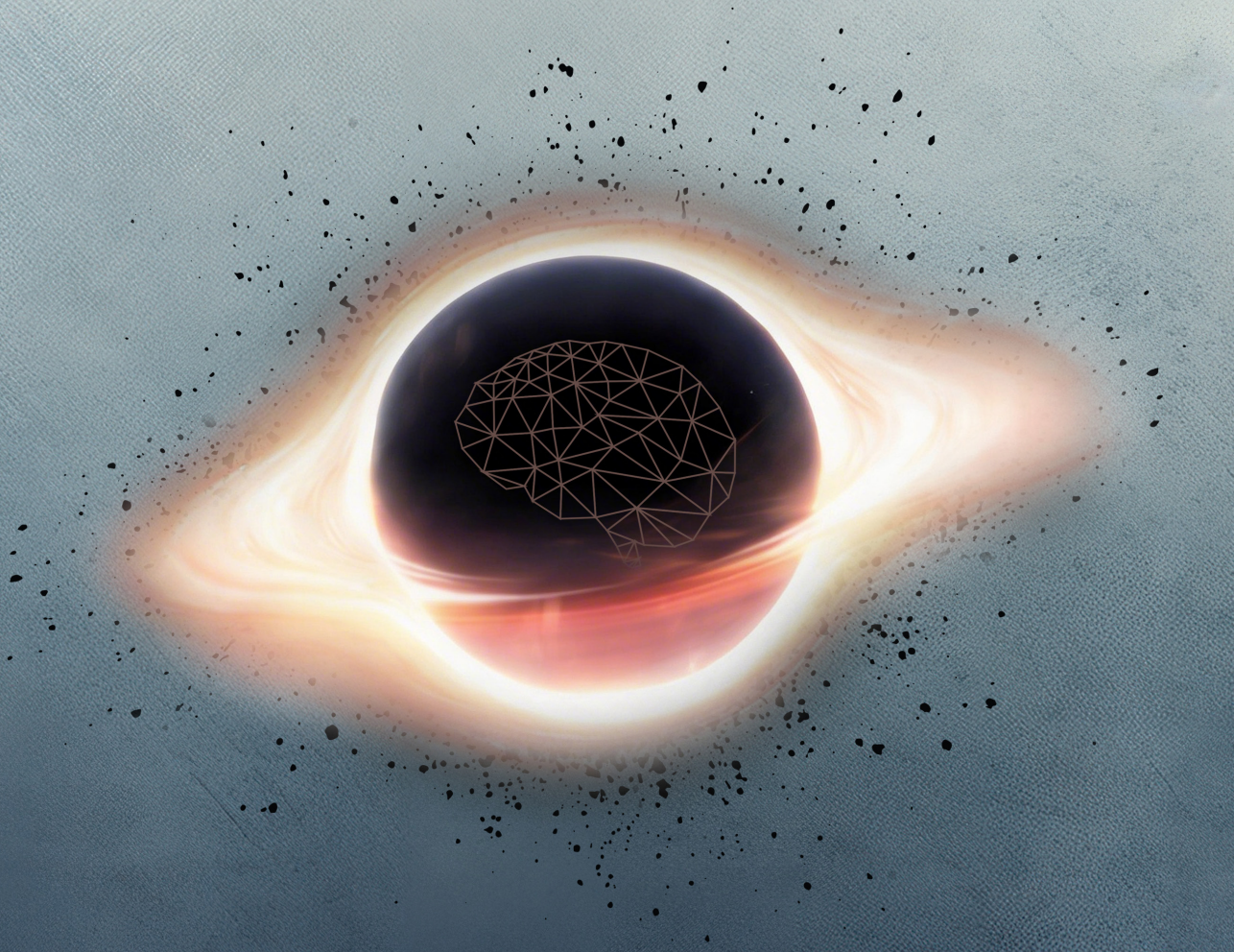
IMAGING THE FUTURE BRAIN

Neuroimaging markers for dementia prediction



MATHIJS T. ROSBERGEN

PROPOSITIONS

Accompanying the doctoral thesis

IMAGING THE FUTURE BRAIN

Neuroimaging markers for dementia prediction

BASED ON THIS THESIS:

1. When using MRI for dementia risk stratification, multiple MRI modalities are necessary, as a single modality cannot capture the diversity of disease processes.
2. Advanced cortical thickness signatures do not outperform hippocampal volume for dementia risk stratification.
3. Amygdala volume independently predicts dementia, beyond grey matter and hippocampal atrophy.
4. The desire to know one's dementia risk is significantly influenced by the perceived ability to take actionable steps.
5. Easily obtainable predictors, which are applicable in primary care, can be used to distinguish between low- and high-risk individuals for dementia.

BEYOND THIS THESIS:

6. If a picture is worth more than a thousand words, scientific publishing should put a greater emphasis on informative visual representations rather than elaborate textual explanations.
7. Dementia should be viewed as a mixed-pathology syndrome rather than a single-pathology disease.
8. Impactful science listens to people, not just to data.
9. Replication and validation are essential for the identification of robust biomarkers.
10. Individuals without symptoms should not be diagnosed with Alzheimer's disease, even in the presence of pathology.

11. The only way of discovering the limits of the possible is to venture a little way past them into the impossible. – Arthur C. Clarke

MATHIJS T. ROSBERGEN

Imaging the Future Brain

Neuroimaging markers for dementia prediction

Mathijs T. Rosbergen

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Imaging the Future Brain

Neuroimaging markers for dementia prediction

Beeldvorming van de toekomstige hersenen

Neuroimaging markers voor de voorspelling van dementie

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr.ir. A.J. Schuit

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

dinsdag 9 juni 2026 om 13:00 uur

door

Mathijs Thomas Rosbergen
geboren te Capelle aan den IJssel.

Erasmus University Rotterdam

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CHAPTER 1

GENERAL INTRODUCTION



Imagine attempting to look into a black hole: a mysterious phenomenon far away, whose inner workings remain largely hidden from view. To get close to such a celestial body, you would have to travel for many years. Similarly, predicting dementia is like trying to look into the unknown and you can only be sure if the prediction is accurate when you wait for many years. We know there are clinical signs which suggest the onset of neurodegeneration, but dementia often hides its early stages until it's too late. On top of that, dementia is not a single disease but a spectrum of conditions with different causes and trajectories, making prediction of dementia very complex and difficult.

Dementia epidemiology

Dementia is a syndrome characterized by a progressive loss of cognitive abilities that are severe enough to interfere with daily life and activities. Besides memory loss, individuals with dementia experience problems with language, behavior, emotions, organizing, orientation, and other cognitive skills. Currently, there are living 57 million people with dementia in the world[1], with 310.000 in the Netherlands[2]. Although prevalence of dementia seems to be stable or even declining[3], absolute numbers will still increase rapidly due to a growing population of elderly[4]. Dementia is one of the largest health problems, not only due to its high prevalence but also of its substantial economic burden. In the Netherlands, dementia care costs exceeded 10 billion euros in 2019, accounting for over 10% of the overall healthcare costs. In addition, many individuals with dementia are dependent on informal caregivers of which over half of them is severely burdened in the Netherlands.[2]



Figure 1. Dementia numbers of the global and Dutch population.

Early identification of high-risk individuals

Identifying individuals at high risk of dementia is becoming increasingly important as the field of targeted prevention and treatment is emerging. Since dementia has a long presymptomatic disease trajectory[5, 6], detecting signs in an early stage offers an opportunity for delaying the onset of dementia and reducing its impact, both for affected individuals and for society. Although severe side effects may occur, anti-amyloid drug trials have shown promising results in patients with early Alzheimer's disease[7] raising the question whether similar drugs may be more effective if administered earlier, before symptoms have occurred. However, the solanezumab trial, which targeted symptom-free individuals with elevated amyloid levels in the brain, failed to show clinical benefit[8], underscoring how challenging early intervention is. Since not all individuals with amyloid pathology will develop dementia[9-11], these trials need the identification of those who will develop dementia.

Besides treatment, early identification empowers individuals in making informed decisions for care planning and in engaging in preventive strategies regarding lifestyle. A large, randomized controlled trial has already shown that a multidomain approach, combining lifestyle interventions with vascular risk monitoring, could improve or maintain cognitive functioning in older adults.[12] Moreover, the Lancet Commission on dementia prevention estimated that 14 modifiable risk factors account for 45% of dementia cases.[13] Within this publication, two new risk factors were identified showing that the field keeps identifying new biomarkers. Although various prediction models for dementia have been developed and validated, like ANU-ADRI[14], CAIDE[15], and two models from the Rotterdam Study[16], further research is needed to determine how novel biomarkers could improve these dementia prediction models.

Advances in multimodal MRI and analytical methods

Imaging markers have already demonstrated their value in predicting dementia, but similar to the evolution of tools for exploring and observing outer space, neuroimaging has advanced significantly over the past decades. These advancements allow for the identification of new markers, which could ultimately improve current prediction models. While other types of biomarkers, including blood biomarkers, also show to

be promising in predicting dementia, magnetic resonance imaging (MRI) can offer complementary information in a non-invasive manner.

Conventional MRI techniques provide the ability to observe structural changes in the brain, such as tissue loss, which are established hallmarks of neurodegeneration and dementia.[17, 18] However, these methods typically capture downstream markers of neurodegeneration that appear relatively close to the clinical stage of dementia. Since the detection of early, presymptomatic brain changes are essential for accurate dementia prediction, conventional imaging methods offer limited value for prediction. Moreover, structural changes, including white matter hyperintensities, often reflect only the tip of the iceberg regarding underlying pathologies.

More recent developments have enabled us to study the brain beyond structural changes. Advanced techniques such as functional MRI, arterial spin labelling, and diffusion MRI provide the ability to investigate brain function, cerebral perfusion, and microstructural integrity. In the context of white matter deterioration, diffusion MRI is particularly interesting due to its ability to assess connectivity and microstructural changes. These microstructural changes have been shown to precede macrostructural changes, such as tissue loss and white matter hyperintensities[19, 20], making diffusion MRI a promising tool for early prediction. This ongoing development of imaging techniques has also contributed to the understanding that dementia is not only a disease of the cortical gray matter. Increasing evidence suggests that that subcortical gray matter structures and white matter integrity also play essential roles in the progression to dementia.[21, 22] Using these advanced imaging techniques, we can further investigate the role of both white matter and gray matter in prediction of dementia.

Similar to imaging techniques, analytical methods have developed the last decades. In particular, machine learning methods, such as unsupervised learning, are rapidly evolving and open new possibilities in the analysis of imaging data. These data-driven methods enable us to unravel patterns by combining multiple markers, rather than focusing on individual markers. By integrating both established and novel imaging markers from multiple MRI modalities, these methods could offer a more comprehensive overview of brain changes. Ultimately, this could provide us with the tools to capture subtle early changes in the brain preceding the onset of dementia symptoms.

Implementation of dementia prediction models

Although numerous clinical prediction models have been developed in the past, relatively few have been successfully implemented into clinical practice. To successfully implement a prediction model, it is important that prediction models are developed using data that closely reflect the target population. To capture the entire continuum from cognitively unimpaired individuals to those in the prodromal stages of dementia, data should ideally be drawn from both population-based cohorts that are representative of the general population, and memory clinic cohorts. Therefore, the majority of this thesis is based on data from the population-based Rotterdam Study, including individuals aged 45 years or older. These data are further complemented by data from memory clinic cohorts. Another requirement for successful implementation is identifying the needs and barriers of various stakeholders. This is especially important since prediction models should be tailored to the context in which they will be applied. For example, prediction models for primary care should be different than those for specialized settings, where the use of imaging markers is more appropriate.

Overall aim and outline

The overall aim of this thesis is to investigate the role of magnetic resonance imaging in identifying individuals at high risk of dementia, to assess how neuroimaging can enhance the performance of dementia prediction models, and to explore strategies for the implementation of such models in clinical practice.

Chapter 2 focusses on the role of white matter characteristics, as measured on MRI, in predicting neurodegeneration within the population-based Rotterdam Study. In **Chapter 2.1**, I investigate distinct white matter signatures using multimodal brain MRI. We subsequently assess the underlying risk profiles of the signatures and their risk of dementia, stroke, and mortality. **Chapter 2.2** compares the predictive value of multiple diffusion imaging measures for dementia and cognitive decline.

Chapter 3 revolves around volumetric measurements of grey matter and which areas have an important role in dementia prediction. In **Chapter 3.1**, I investigate which subcortical grey matter structures are independently associated with risk of dementia across multiple cohorts, consisting of individuals with subjective cognitive decline or mild cognitive impairment. **Chapter 3.2** presents a replication study assessing the prognostic value of a novel cortical thickness signature for dementia, comparing its

predictive performance with other grey matter measures, including hippocampal volume and cortical thickness of the whole brain.

Chapter 4 sheds light on the development and potential implementation of a dementia prediction model in clinical practice. In **Chapter 4.1**, I investigate the attitude of the public towards dementia risk prediction models. **Chapter 4.2** focusses on the development and validation of a prediction model for dementia.

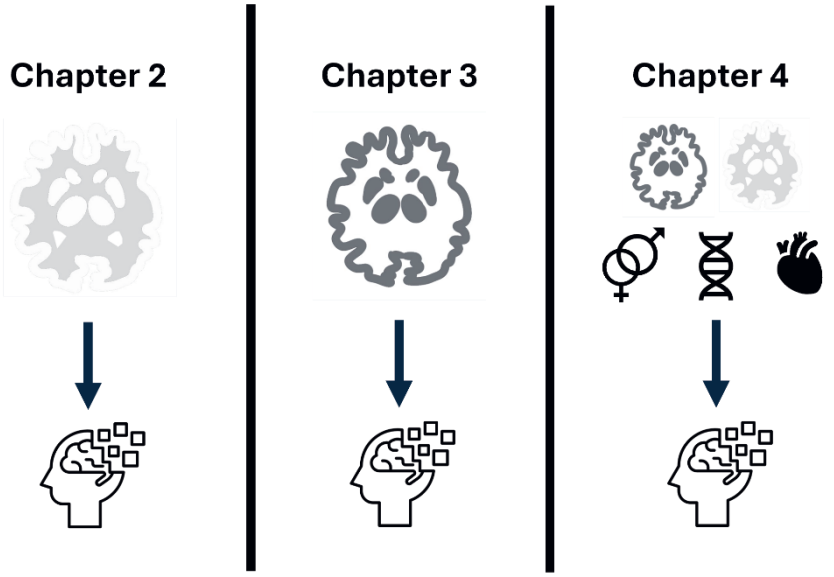

Figure 2. Graphical overview of the outline of this thesis.

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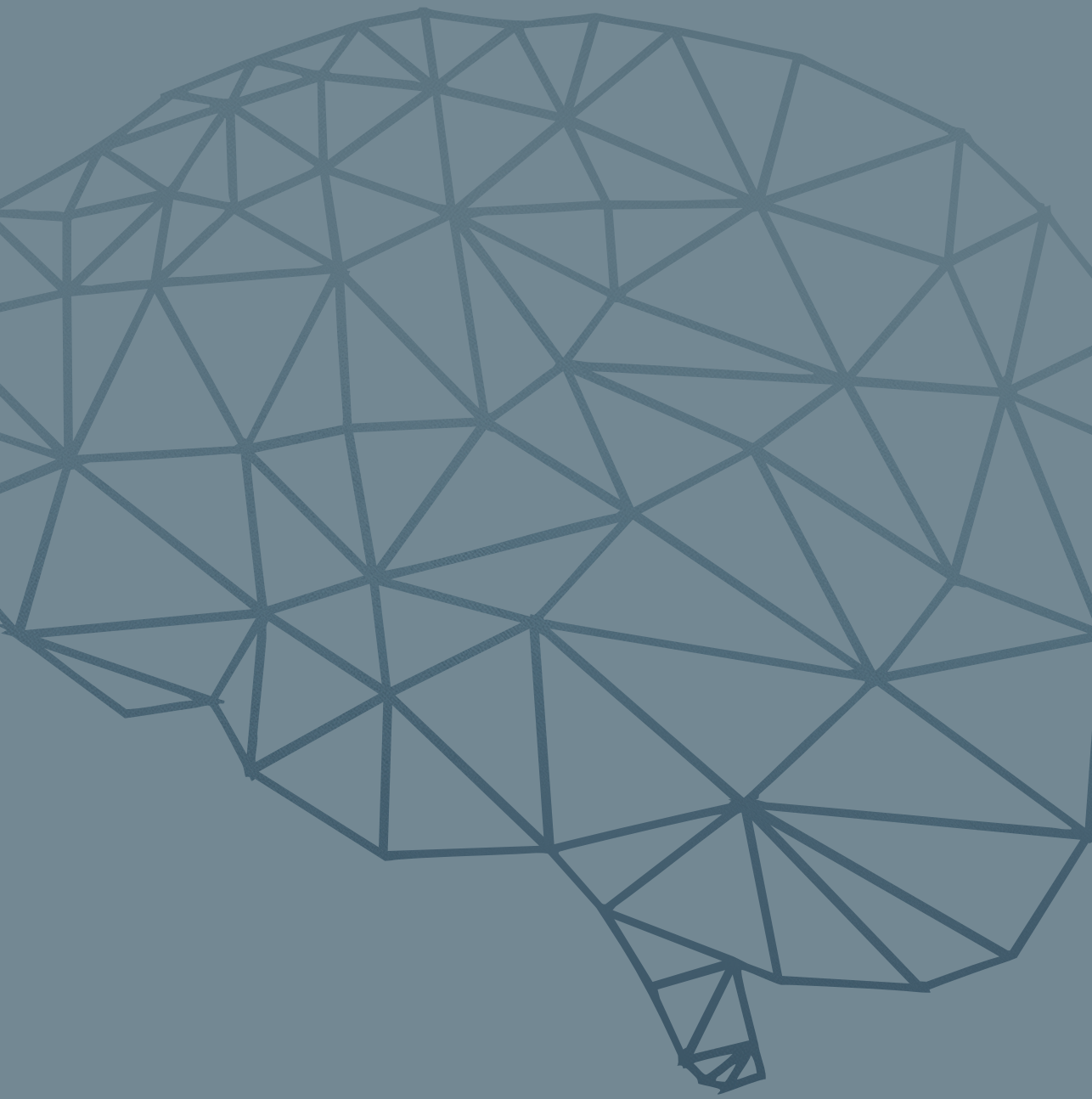
CHAPTER 2

WHITE MATTER BIOMARKERS OF BRAIN HEALTH





CHAPTER 2.1

CLUSTER-BASED WHITE MATTER SIGNATURES AND THE RISK OF DEMENTIA, STROKE, AND MORTALITY

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ABSTRACT

Background: Markers of white matter injury on brain MRI are important indicators of brain health. Different patterns of white matter (WM) atrophy, white matter hyperintensities (WMH), and microstructural integrity could reflect distinct pathology and disease risk, but large-scale imaging studies investigating WM signatures in relation to disease outcomes are lacking. The aim of this study was to identify distinct white matter signatures using both structural and diffusion MRI, and determine underlying risk factor profiles. Moreover, we will assess the clinical outcomes of these signatures in relation to the risks of dementia, stroke, and mortality.

Methods: Between 2005-2016, we measured WMH volume, WM volume, fractional anisotropy (FA) and mean diffusivity (MD) on brain MRI in the population-based Rotterdam study. We used hierarchical clustering to identify separate clusters of white matter injury, and determined for each cluster the risk of dementia, stroke and mortality using Cox proportional hazard models.

Results: We included 5279 participants (mean age 65.0 years, 56.0% women) and identified four distinct data-driven white matter signatures: (1) above-average microstructural integrity and little WM atrophy and WMH, (2) above-average microstructural integrity and little WMH, but substantial WM atrophy, (3) poor microstructural integrity and substantial WMH, but little WM atrophy, and (4) poor microstructural integrity with substantial WMH and WM atrophy. Prevalence of cardiovascular risk factors, lacunes, and cerebral microbleeds was higher in clusters 3 and 4 than in clusters 1 and 2. During a median 10.7 years of follow-up, 291 participants developed dementia, 220 had a stroke, and 910 died. Compared to cluster 1, dementia risk was increased for all clusters, notably cluster 3 (hazard ratio [HR]:2.53 [95%CI:1.74-3.60]), followed by cluster 4 (HR:1.83 [1.26-2.67]), and cluster 2 (HR:1.58 [1.11-2.23]). Compared to cluster 1, risk of stroke was higher only for cluster 4 (HR:1.70 [1.14-2.54]), whereas mortality risk was moderately increased in all clusters (HR cluster 2: 1.23[1.03-1.48], HR cluster 3: 1.46[1.19-1.79], HR cluster 4: 1.45[1.19-1.77]), compared to cluster 1. Models including clusters instead of an individual imaging marker, showed a superior goodness of fit for dementia and mortality, but not for stroke.

Conclusion: Machine-learning methods can derive white matter signatures that are differentially associated with dementia, stroke and mortality risk.

INTRODUCTION

Cerebral white matter injury is a heterogeneous process of pathophysiological changes, reflected by white matter atrophy, white matter hyperintensities (WMH), and loss of microstructural integrity on brain MRI. To assess these changes non-invasively, MRI is a useful technique using imaging sequences, such as T1-weighted imaging and T2-weighted fluid-attenuated inversion recovery (FLAIR) imaging for macrostructural properties. More recently, diffusion tensor imaging (DTI) has been proven to be an useful MRI technique in obtaining microstructural properties of cerebral white matter. Fractional anisotropy (FA) and mean diffusivity (MD) are commonly used DTI measures which reflect the directional constraint and the magnitude of water diffusion.1 Previous research has established that these markers are all associated with the risk of dementia, stroke and mortality.2-8 However, published studies mostly investigated individual imaging markers of white matter, leaving undetermined how these imaging markers co-occur and how their interplay affects clinical outcome within individuals.

Novel data-driven techniques may aid to unravel white matter patterns on the basis of multimodal imaging data, hereafter referred to as white matter signatures. Studies focusing on cognitive decline and brain atrophy have used machine learning approaches on multimodal imaging markers.9-11 These studies showed that imaging based clusters are associated with cognitive patterns both in a cross-sectional manner and in terms of cognitive decline. Although these studies focused on imaging-based clusters, they included supplementary cerebrospinal fluid markers in their clustering methodology or focused on a specific population and did not consider to primarily focus on non-invasively obtainable white matter imaging markers within the general population.

Despite increasing literature regarding individual white matter imaging markers and imaging based clusters, it lacks comprehensive exploration into the diverse patterns of white matter injury and how these patterns may reflect different underlying pathologies. Moreover, the extent to which these patterns of white matter injury contribute to differential risks for dementia, stroke, and mortality remains largely unexplored.

The aim of this study was to identify distinct white matter signatures using both structural and diffusion MRI, and determine underlying risk factor profiles. Moreover, we will assess the clinical outcomes of these signatures in relation to the risks of

dementia, stroke, and mortality. Through this approach, we aim to unravel the origins and diverse manifestations of white matter injury, ultimately contributing to a better understanding of their implications for health outcomes.

METHODS

Study population

This study was embedded in the Rotterdam Study, an ongoing prospective population-based cohort study in the city of Rotterdam, the Netherlands.12 Residents of the Ommoord district aged ≥45 were invited to participate since 1990, with follow-up every 4 years. Participants underwent routine brain magnetic resonance imaging (MRI) from 2005 onwards. Changes to the diffusion imaging sequence were implemented in the first year, therefore the current study includes all participants with brain MRI between 29th March 2006 and 29th June 2016.

Ethical approval

The Rotterdam Study has been approved by the institutional review board (Medical Ethics Committee) of the Erasmus Medical Center and by the Ministry of Health, Welfare and Sports of the Netherlands, implementing the “Wet Bevolkingsonderzoek: ERGO (Population Screening Act: Rotterdam Study)”. All participants provided written informed consent to participate in the study.

MRI acquisition, preprocessing and appraisal

Brain MRI scanning was performed in all participants on a 1.5 Tesla MRI scanner (Signa Excite II, General Electric Healthcare) with an eight-channel head coil. The scan protocol and sequence details of the Rotterdam Study have been described elsewhere.12 For volumetry, T1-weighted (voxel size 0.49x0.49x1.6 mm3), proton density-weighted (voxel size 0.6x0.98x1.6 mm3), and FLAIR (voxel size 0.78x1.12x2.5 mm3) scans were used for automated segmentation of supratentorial white matter, WMH, and intracranial volume.13,14 All segmentations were visually inspected and manually corrected if necessary. White matter volume was defined as total supratentorial white matter, including WMH. White matter volume and WMH volume were divided by supratentorial intracranial volume to adjust for head size. For microstructural measures, diffusion tensor imaging (voxel size 3.3x2.2x3.5 mm3) was

used to quantify global FA and global MD of normal-appearing white matter. Data were processed using a standardized pipeline15 and combined with tissue segmentation, providing global FA and MD values in normal-appearing white matter, where FA ≥ 0.2 to minimize involvement of partial volume effects arising from gray matter or cerebrospinal fluid.

All scans were rated by trained researchers, blinded to clinical data, for the presence of lacunes, cortical infarcts and microbleeds. Lacunes were defined as focal parenchymal lesions ≥ 3 mm and < 15 mm in size with similar signal intensity as cerebrospinal fluid on all sequences, and – when located supratentorial – with a hyperintense rim on FLAIR images.16 To differentiate lacunes from dilated perivascular spaces, symmetry of the lesions, sharp demarcation, and absence of a hyperintense rim on the FLAIR sequence supported presence of a dilated perivascular space.17 Microbleeds were rated as focal areas with a very low intensity on a 3D T2*-weighted gradient-recalled echo MRI scan (voxel size 0.78x1.12x1.6 mm3), which were not accompanied by signal abnormalities on other sequences.18

Clinical characteristics and other variables

Information regarding educational attainment, smoking habits, alcohol intake, and medication use was obtained by trained interviewers during baseline home interviews. Educational attainment was categorized into four groups, ranging from primary to higher education (higher vocational education or university). Smoking was categorized into three groups: former smoker, current smoker or never-smoker. Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters. Blood pressure was measured twice at the right arm with the participant in seated position. The mean of two consecutive measurements was used. Serum total cholesterol and high-density cholesterol (HDL) were measured during visits at the research center. Diabetes mellitus was defined as a fasting blood glucose concentration of ≥ 7.0 mmol/L or as use of anti-diabetic drugs. APOE genotype was determined using polymerase chain reaction or bi-allelic Taqman assay.

Assessment of dementia, stroke and mortality

All participants were followed for the onset of dementia, stroke, and mortality until 1st January 2020, through a combination of repeated in-person assessment and

linkage with electronic medical records. Follow-up for each participant started at the time of their MRI scan, which was between 29th March 2006 and 29th June 2016.

During each visit to the research center, participants were screened for dementia with the Mini–Mental State Examination (MMSE) and the Geriatric Mental State Schedule (GMS) organic level. Participants with a MMSE < 26 or a GMS > 0 underwent an examination and informant interview with the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX). Electronic linkage of the study database with medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care provided additional, continuous surveillance for dementia for the entire cohort.19 A consensus panel, led by a consultant neurologist, decided on the final dementia diagnosis in all cases, in accordance with the Diagnostic and Statistical Manual of Mental Disorders III-R criteria. Participants were censored at date of dementia diagnosis, death, loss to follow-up or January 1st, 2020, whichever came first. Dementia follow-up was near complete until January 1st, 2020 (91.2% of potential person years).

Definition of stroke was based on World Health Organization criteria,20 describing a syndrome of rapidly developing symptoms of focal or global cerebral dysfunction lasting 24 hours or longer or leading to death, with apparent vascular cause. Prevalent stroke was assessed at baseline during interview, and we verified these data with medical records from the general practitioner. In the Netherlands, general practitioners serve as gatekeepers and have access to comprehensive clinical data for their patients. From baseline onward, we continuously monitored participants for incident stroke through linkage of the study database with files from general practitioners. Files of nursing home physician's and files from general practitioners of participants who moved out of the district were also checked. We obtained additional information from hospital records. When potential strokes were found, they were reviewed by research physicians and verified by an experienced neurologist. Subarachnoid haemorrhages attributed to ruptured aneurysms were excluded. Participants were censored at date of stroke diagnosis, death, loss to follow-up or January 1st, 2020, whichever came first. Stroke follow-up was near complete until January 1st, 2020 (97.8% of potential person years).

We assessed all-cause mortality by obtaining information on vital status from municipal records and clinical follow-up data collection. Coded information on all-cause mortality until 1st January 2020 was used for this study.

Data analysis

Missing data on covariables (maximum 7.0%) were imputed using 5-fold multiple imputation. Distribution of variables were similar in the imputed and non-imputed datasets.

We performed quantile regression to obtain age-adjusted measures of global FA, global MD, WMH volume and white matter volume by predicting 1000 quantiles of the regression function for each imaging marker (ranging from 0 to 1), and assigning each individual to their closest predicted quantile. This results in higher quantile scores for individuals with high values of an imaging marker, compared to their counterparts of the same age. We accounted for nonlinearity in the trajectories by using natural cubic splines of age with 1 knot for all imaging markers.

To identify different white matter signatures, we then performed unsupervised hierarchical agglomerative clustering with age-adjusted global FA, global MD, WMH volume and white matter volume as input parameters for each participant. As sensitivity analysis we repeated this clustering method without adjusting the imaging markers for age prior to clustering. Within agglomerative hierarchical clustering, each individual starts as a cluster of one person, after which clusters are iteratively merged based on similarity, determined by maximizing or minimizing an objective function and a metric for distance between individuals based on their imaging marker quantiles. This approach will result in every participant being clustered into only one of the clusters and no participant will be left unclassifiable. We assessed cluster tendency in our data using the Hopkins statistic, which provides a value ranging from 0 (uniformly distributed data) to 1 (highly clustered data). The Hopkins statistic was 0.86, indicating a clustered distribution of white matter pathology in the cohort, persisting after assigning age-quantiles. We then performed hierarchical clustering, which is an effective method for datasets that are not excessively large and where the inherent structure is not overly complex. We used Ward linkage as objective function aiming to minimize the total within-cluster variance and to create internally cohesive and well-defined clusters. Euclidean distance was adopted as the distance metric since it is the most common and intuitively straightforward distance measure. To determine the optimal number of clusters, we used the R package NbClust , which applies various cluster validity metrics, such as the gap statistic, Dunn index, and Silhouette score, to assess validity for different cluster numbers. The optimal number is determined by selecting the number with the highest frequency of metrics

suggesting its optimum cluster validity. After performing the clustering, we assessed the stability of clusters by using bootstrapping, generating 100 subsamples (90% of the original dataset) for repeating the clustering analysis on each subsample. The Adjusted Rand Index, ranging from -1 to 1, was then calculated to evaluate the consistency with which individuals were clustered together across the subsamples, with higher values indicating a greater degree of agreement between clustering results compared to random chance. The Adjusted Rand Index was calculated to compare the cluster labels of every subsample with the cluster labels of the full sample. Subsequently, we calculated the mean Adjusted Rand Index across all subsamples.

Next, we compared several participant characteristics between clusters, using t-tests for continuous variables and Chi-squared tests for categorical variables. We used Cox proportional hazard models to obtain hazard ratios and 95% confidence intervals (CI) for the association between clusters and risk of dementia, stroke and mortality. For all Cox models, we tested the proportional hazard assumption using Schoenfeld residuals. We constructed three different models: a crude analysis (model 1), an analysis adjusted for age, sex and education (model 2), and an analysis with additional adjustment for APOE genotype, lacunes, microbleeds and cardiometabolic risk factors, including BMI, smoking status, alcohol intake, systolic blood pressure, diastolic blood pressure, use of blood pressure-lowering drugs, diabetes, serum total cholesterol, serum HDL and use of lipid-lowering drugs. In sensitivity analyses, we i) additionally adjusted for gray matter volume, and ii) compared the associations of the clusters with clinical outcomes to a similar model assessing each imaging marker individually. Performance of the models was compared using Akaike's Information Criterion (AIC). All analyses were performed using R, version 4.1.2 (packages: fmsb, gplots, gridExtra, hopkins, mice, mclust, NbClust, quantreg, sjmiscc, survival). This study adhered to the STROBE guidelines for observational studies.21

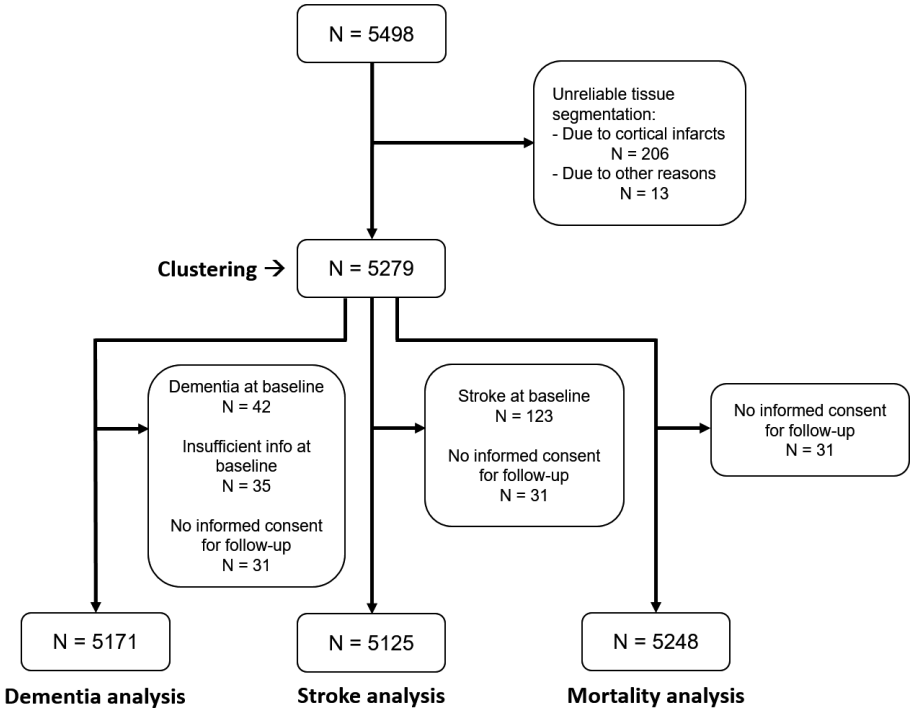
Data availability statement

Requests for the anonymised data underlying this report can be directed to data manager Frank J.A. van Rooij (secretariat.epi@erasmusmc.nl).

RESULTS

During the study period, 5498 participants underwent brain MRI, of whom 5279 could be included in the present study (Figure 1). Baseline characteristics of all participants included in the clustering analyses are presented in Table 1. The mean age at time of MRI scan was 65.0 years and 56.0% of the participants were women.

Figure 1 Flowchart of the inclusion of participants.



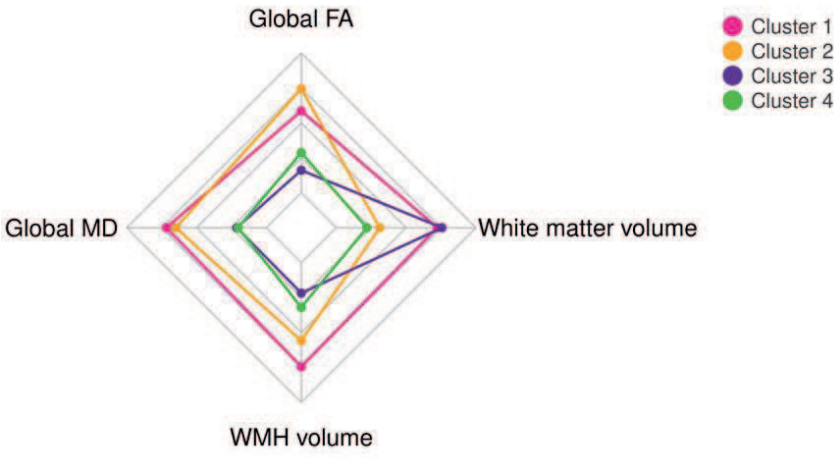
White matter signatures

We identified four different clusters of white matter characteristics, including between 956 and 1791 individuals each. The acquired dendrogram and results of determining the optimal number of clusters are presented in Supplementary Materials. Four distinct white matter signatures emerged (Figure 2). Participants in cluster 1 had above-average microstructural integrity and little WM atrophy and WMH. Participants in cluster 2 had equally above-average microstructural integrity and an average WMH burden, but with substantial WM atrophy. Participants in cluster 3 had poor microstructural integrity and a relatively high burden of WMH, but

displayed little WM atrophy. Participants in cluster 4 also had poor microstructural integrity, yet with substantial WM atrophy and WMH burden. These characteristics can also be seen in Figure 3, which shows MR images of participants, typical for each cluster.

Figure 4 shows the distribution of the different white matter imaging markers across clusters. For microstructural integrity and WM volume, clusters generally discriminated well between clusters, distinguishing at least two of four clusters from one another. Distributions were more overlapping for WMH volume, with a wide range of WMH especially in cluster 2.

Figure 2 Composition of the different white matter clusters.



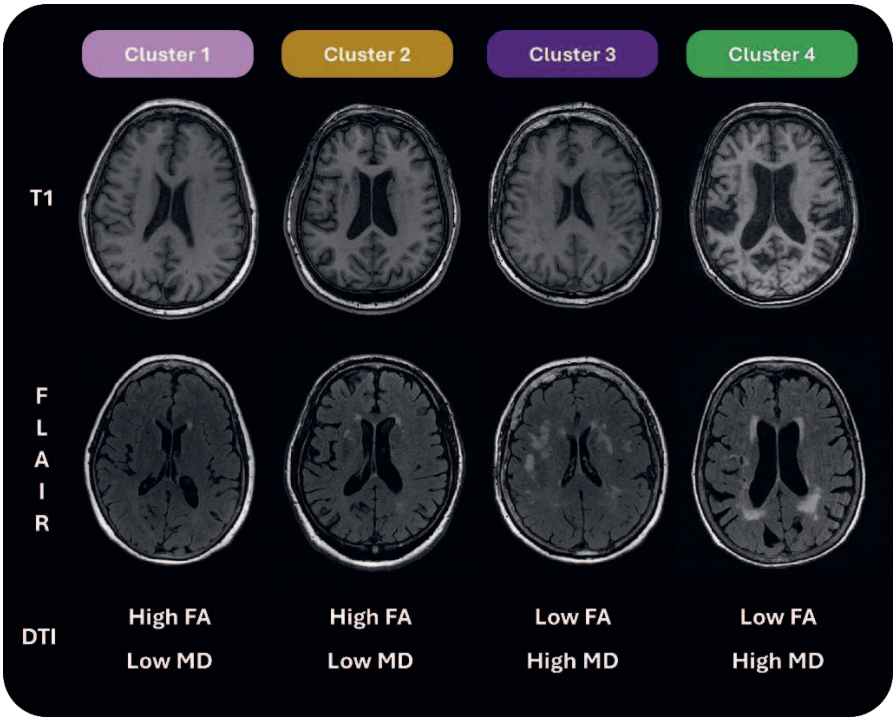
Radar plot showing median values of white matter imaging markers for each cluster. Outer rim values represent favorable values (i.e., smaller WMH volume, larger white matter volume, higher global FA and lower global MD). Abbreviations: FA = fractional anisotropy, MD = mean diffusivity, WMH = white matter hyperintensities.

Table 1. Characteristics of the total study population and white matter clusters.

Characteristic	Total (N=5279)	Cluster 1 (N=1457)	Cluster 2 (N=1791)	Cluster 3 (N=956)	Cluster 4 (N=1075)	P-value
Age, years	65.0 (11.0)	65.0 (11.0)	64.9 (11.0)	65.6 (11.0)	64.9 (10.8)	0.424
Sex, female	2957 (56.0)	777 (53.3)	945 (52.8)	618 (64.6)	617 (57.4)	<0.001
Education						0.038
Primary only	470 (8.9)	109 (7.5)	176 (9.8)	96 (10.0)	89 (8.3)	
Lower vocational	2018 (38.2)	556 (38.2)	659 (36.8)	388 (40.6)	415 (38.6)	
Intermediate vocational / higher general	1594 (30.2)	470 (32.3)	550 (30.7)	250 (26.2)	324 (30.1)	
Higher vocational/ university	1197 (22.7)	322 (22.1)	406 (22.7)	222 (23.2)	247 (23.0)	
Body mass index, kg/mm^2	27.4 (4.1)	27.1 (3.7)	27.7 (4.2)	27.3 (4.2)	27.7 (4.3)	<0.001
Systolic blood pressure, mmHg	139.6 (21.4)	137.7 (21.5)	139.2 (20.6)	141.3 (22.3)	141.2 (21.4)	<0.001
Diastolic blood pressure, mmHg	82.5 (11.0)	81.5 (10.7)	82.2 (10.7)	83.6 (11.4)	83.5 (11.5)	<0.001
Blood pressure lowering medication	1869 (35.4)	432 (29.6)	603 (33.7)	387 (40.5)	447 (41.6)	<0.001
Smoking						0.056
Never	1622 (30.7)	439 (30.1)	545 (30.4)	314 (32.8)	324 (30.1)	
Former	2601 (49.3)	736 (50.5)	913 (51.0)	440 (46.0)	512 (47.6)	
Current	1056 (20.0)	282 (19.4)	333 (18.6)	202 (21.2)	239 (22.2)	
Alcohol intake*, g/day	6.43 [0.54-10.00]	6.43 [0.57-8.57]	6.43 [1.25-14.93]	6.43 [0.54-8.57]	6.43 [0.71-11.93]	<0.001
Total cholesterol, mmol/L	5.53 (1.05)	5.57 (1.01)	5.54 (1.07)	5.53 (1.07)	5.47 (1.05)	0.111
HDL cholesterol, mmol/L	1.45 (0.42)	1.46 (0.41)	1.43 (0.42)	1.48 (0.43)	1.45 (0.43)	0.006
Lipid lowering medication	1291 (24.6)	353 (24.2)	420 (23.5)	233 (24.4)	299 (27.8)	0.089
Diabetes mellitus	675 (12.8)	147 (10.1)	235 (13.1)	126 (13.2)	167 (15.5)	0.001
APOE genotype						0.097
ε3/ε3	3002 (56.9)	844 (57.9)	1034 (57.7)	537 (56.2)	587 (54.6)	
ε2/ε2 or ε2/ε3	876 (16.6)	227 (15.6)	288 (16.1)	163 (17.1)	198 (18.4)	
ε4-carrier (heterozygous)	1294 (24.5)	363 (24.9)	438 (24.5)	225 (23.5)	268 (24.9)	
ε4-carrier (homozygous)	107 (2.0)	23 (1.6)	31 (1.7)	31 (3.2)	22 (2.0)	
Cerebral microbleeds (any)	1063 (20.1)	257 (17.6)	311 (17.4)	247 (25.8)	248 (23.1)	<0.001
Lacunes (any)	396 (7.5)	57 (3.9)	109 (6.1)	104 (10.9)	126 (11.7)	<0.001
Gray matter volume, proportion of ICV	0.47 (0.03)	0.46 (0.03)	0.48 (0.03)	0.45 (0.03)	0.47 (0.03)	<0.001

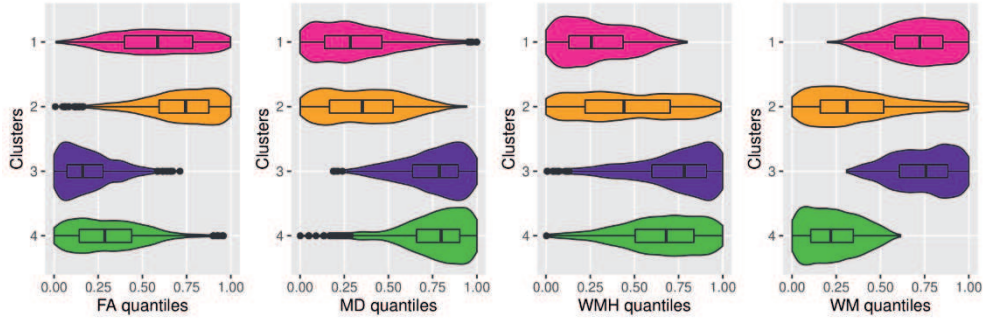
Continuous variables are presented as means (standard deviations) and categorical variables as number (percentages). * = variable with skewed distribution. Median [interquartile range] is shown instead of mean (standard deviation). Abbreviations: HDL=high density lipoprotein; ICV=intracranial volume

Figure 3 Typical MR images of the brain for each cluster.



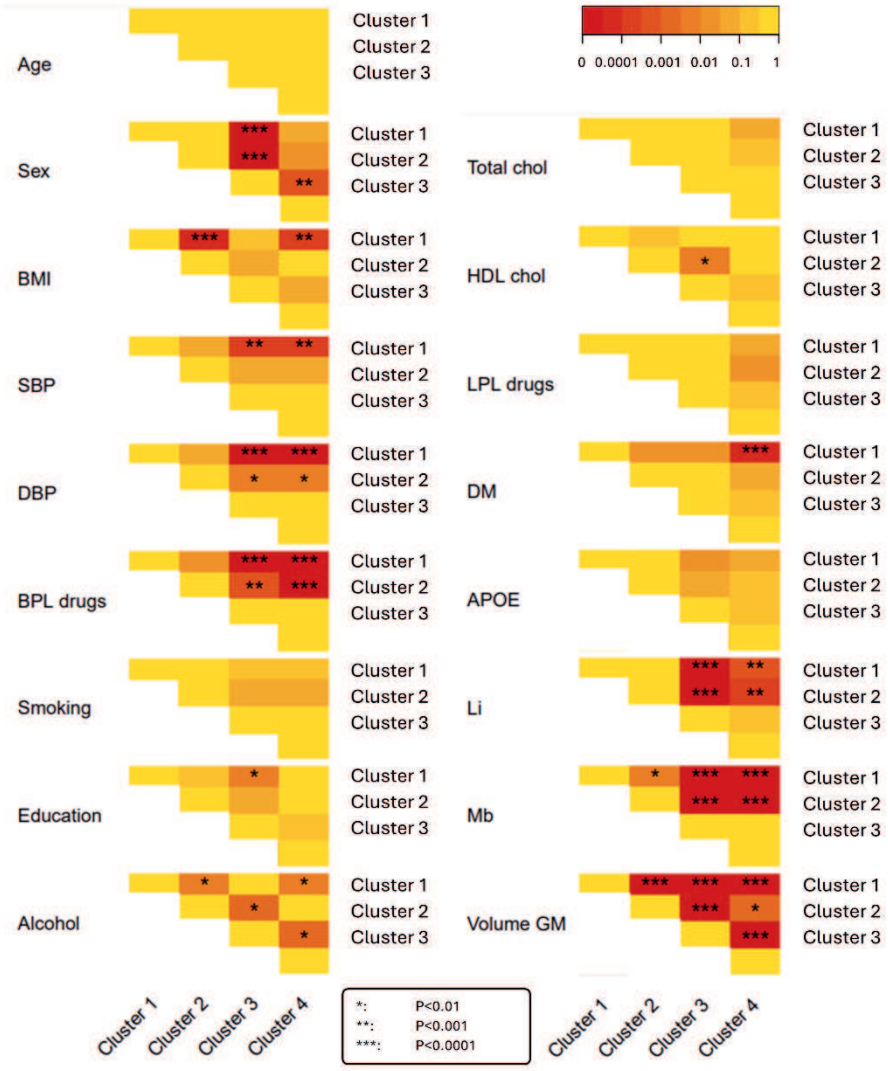
For each cluster, MR images of a single participant in that cluster are shown to demonstrate typical MR images of the brain for each cluster. Microstructural properties derived from DTI were shown as text rather than images since diffusion-weighted images for fractional anisotropy and median diffusivity are difficult to interpret intuitively. Abbreviations: FLAIR = fluid-attenuated inversion recovery, DTI = diffusion tensor imaging, FA = fractional anisotropy, MD = mean diffusivity.

Figure 4 Distributions of imaging markers across clusters.



Violin plots showing the probability density function of white matter imaging markers for each cluster, with age-adjusted quantiles on the x-axis. Box plots are shown as overlay. Abbreviations: FA = fractional anisotropy, MD = mean diffusivity, WMH = white matter hyperintensities, WM = white matter volume.

Figure 5 Pairwise comparisons of determinants.



Heatmap of p-values of pairwise comparisons among clusters for various determinants. Abbreviations: BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, BPL = blood pressure lowering, chol = cholesterol, HDL = high density lipoprotein, LPL = lipid lowering, DM = diabetes mellitus, Li = lacunes, Mb = microbleeds, GM = gray matter.

The mean Adjusted Rand Index of 0.30 (standard deviation: 0.07) suggested poor cluster stability. Nevertheless, visual inspection revealed that signatures, particularly

for clusters 3 and 4, were quite stable across clustered subsamples, implying that etiological insights can be validly derived from them.

The sensitivity analysis in which we performed clustering without age-adjustment of imaging markers prior to clustering resulted in the identification of four clusters.(eFigure 3) However, the cluster patterns were different than those with age-adjustment prior to clustering. Without adjusting imaging markers for age, the clusters show a gradual increase of white matter pathology with older age (eTable 1).

Determinants of white matter clusters

Owing to the age standardization, clusters were well matched on age (Table 1 and Figure 5). Cluster 3 contained more women than the other clusters. Prevalence of cardiovascular determinants was generally lower in cluster 1 than in any of the other clusters, notably for hypertension, diabetes, and BMI. Concordantly, markers of small vessel disease were more prevalent in clusters 3 and 4 than in clusters 1 and 2. HDL cholesterol on average was slightly lower in cluster 2 than in cluster 3, whereas total cholesterol and use of lipid lowering medication did not differ between clusters. Smoking habits, alcohol consumption, educational attainment, and APOE genotype were also similarly distributed among clusters.

Risk of dementia, stroke and mortality

Participants were followed up for a median 9.9 years for dementia (cluster 1: 9.9 years; cluster 2: 10.2 years; cluster 3: 9.6 years; cluster 4: 9.9 years), 10.8 years for stroke (cluster 1: 10.8 years; cluster 2: 10.9 years; cluster 3: 10.6 years; cluster 4: 10.6 years) and 10.8 years for mortality (cluster 1: 10.8 years; cluster 2: 10.9 years; cluster 3: 10.6 years; cluster 4: 10.7 years). During this follow-up, 291 participants developed dementia, 220 participants had a stroke, and 910 participants died. Associations between white matter signatures and event risks of model 1, 2 and 3 are presented in eTable 2, eTable 3 and Table 2, respectively.

Risk estimates were generally higher for dementia than for stroke and mortality. In fully adjusted models, dementia risk was increased most for cluster 3 (HR: 2.50 [95%CI: 1.74-3.60]), followed by cluster 4 (HR: 1.80 [95%CI: 1.24-2.63]), and to a lesser extent cluster 2 (HR: 1.57 [95%CI: 1.10-2.23]), compared to cluster 1. In addition, cluster 1, 2 and 3 showed to be statistically distinct from one another in terms of dementia risk, while cluster 4 was only statistically different from cluster 1.

Compared to cluster 1, incidence of stroke was higher for clusters 3 (HR: 1.84 [95%CI: 1.21-2.79]) and 4 (HR: 2.03 [95%CI: 1.37-3.01]). After further adjustment for cardiovascular risk factors, the only significant between-cluster difference for stroke was between clusters 1 and 4 (Table 2). Mortality risk was moderately increased for clusters 2, 3 and 4 compared to cluster 1, without any significant differences between clusters 2, 3, and 4 (Table 2).

Fully adjusted Cox proportional hazard models using the clustered data had higher AIC values than similar models using individual white matter imaging markers for dementia risk (AIC > 4465.84), indicating a superior goodness of fit for the cluster model (AIC: 4462.90). In contrast, models incorporating only WMH (AIC: 3504.11) or MD (AIC: 3509.67) as independent variables for incident stroke showed a better goodness of fit compared to the cluster model (AIC: 3510.11). For mortality risk too, the clusters-based model (AIC: 14265.81) yielded a lower AIC value than the models using individual white matter imaging markers (AIC > 14266.05) (eTable 4).

Further adjustment for gray matter volume showed broadly similar patterns, though it led to slightly higher effect estimates for cluster 2 on dementia and cluster 4 on mortality (eTable 5).

Table 2. Risk of dementia, stroke and mortality by white matter cluster.

		Reference cluster			
		1	2	3	4
Dementia HR [95% CI]	Cluster 1	-	**0.60 [0.42-0.85]**	**0.33 [0.23-0.47]**	**0.43 [0.30-0.63]**
	Cluster 2	**1.67 [1.17-2.38]**	-	**0.55 [0.40-0.75]**	0.72 [0.52-1.00]
	Cluster 3	**3.06 [2.12-4.42]**	**1.83 [1.34-2.51]**	-	1.33 [0.95-1.85]
	Cluster 4	**2.31 [1.58-3.37]**	1.38 [1.00-1.91]	0.75 [0.54-1.05]	-
Stroke HR [95% CI]	Cluster 1	-	0.74 [0.50-1.08]	**0.64 [0.42-0.98]**	**0.52 [0.35-0.77]**
	Cluster 2	1.36 [0.93-1.98]	-	0.87 [0.60-1.28]	**0.70 [0.49-1.00]**
	Cluster 3	**1.55 [1.02-2.37]**	1.14 [0.78-1.67]	-	0.80 [0.54-1.18]
	Cluster 4	**1.94 [1.30-2.89]**	**1.43 [1.00-2.04]**	1.25 [0.85-1.84]	-
Mortality HR [95% CI]	Cluster 1	-	**0.79 [0.65-0.94]**	**0.60 [0.49-0.74]**	**0.57 [0.47-0.69]**
	Cluster 2	**1.27 [1.06-1.53]**	-	**0.77 [0.64-0.93]**	**0.72 [0.61-0.86]**
	Cluster 3	**1.65 [1.35-2.03]**	**1.30 [0.08-1.57]**	-	0.94 [0.77-1.14]
	Cluster 4	**1.76 [1.44-2.15]**	**1.38 [1.16-1.65]**	1.06 [0.87-1.30]	-

Hazard ratios of model 3, which are adjusted for age, sex, education, *APOE* genotype, lacunes, microbleeds and cardiometabolic risk factors. Each cluster is used as reference once for determining hazard ratios. Bold font indicates significant estimates. Abbreviations: HR = hazard ratio, CI = confidence interval.

DISCUSSION

In this study, we demonstrate that heterogeneity in imaging markers of white matter in the general population can be clustered in etiologically meaningful white matter signatures based on MRI data. Differences between clusters in determinants and clinical outcomes suggest different underlying pathologies, which may have utility for risk stratification and targeted intervention.

Clustering methods are commonly used in brain MRI research for tissue segmentation on a voxel level, but as we have shown, they can be applied also to identify distinct white matter signatures based on structural and diffusion MRI. Unraveling white matter signatures, above and beyond investigating individual imaging markers, can be helpful to identify interrelated pathophysiological processes and interactions between individually measured markers. Prior studies that used clustering on MRI markers generally focused on cognitive decline or other clinical outcomes in specific patient populations. Consequently, these studies considered a broader range of biomarkers for clustering, including cerebrospinal fluid in addition to gray and white matter traits on brain imaging.9-11 Whilst this may be useful for outcome prediction, we focused on imaging markers of cerebral white matter to gain insight specifically in the etiologic role of white matter pathology. The validation against several clinical outcomes underlines that differences between such signatures can be clinically meaningful, in particular regarding dementia. This may reflect a more complex role of white matter pathology in development of dementia, as compared to stroke or mortality.

The variation between clusters in underlying pathology is further supported by differences in several clinical determinants. Vascular pathology was a hallmark of clusters 3 and 4, coinciding with pronounced reduction of microstructural integrity and the largest WMH volume. These findings align with the notion that reduced white matter integrity and WMH burden are at least in part attributable to cerebrovascular disease.22-25 Interestingly, APOE genotype was similar across clusters, suggesting limited impact on white matter signatures as identified in this study. However, previous research linked APOE to WMH volume in subcortical regions, but not periventricular,26 which could explain the absence of APOE differences since we did not include spatial information of WMH.

The identified signatures show that deterioration of a single white matter imaging marker does not necessarily imply the deterioration of other white matter imaging

markers. This stands in contrast to clusters formed through clustering without prior adjusting imaging markers for age, where cluster patterns reveal a gradual increase in white matter pathology with older age. This confirms our hypothesis that adjusting imaging markers for age was necessary to unravel heterogeneity of imaging markers and to avoid clusters primarily driven by age. This heterogeneity could be related to temporal evolution of pathology, which remains to be determined in future studies using longitudinal imaging data. Based on previously reported changes in brain MRI markers over time,27,28,29 it is plausible that individuals from cluster 1 may later shift to cluster 2, 3 or 4, and individuals from cluster 2 and 3 may shift to cluster 4. Although it is interesting to investigate the stability of cluster type over time, this aspect was beyond the scope of our study and remains to be explored in future research. Some of the observed differences, however, do not seem explicable solely by temporal changes. An interesting observation in that respect is the higher risk of dementia in clusters 3 and 4, despite difference in white matter atrophy (substantial in cluster 4, but not in cluster 3). The dementia risk difference was only partially explained by smaller gray matter volumes in cluster 3, indicating an increased risk of dementia.30,31 It raises the question whether these clusters may reflect different etiological subtypes of dementia and could be further investigated through cluster correlation with disease specific biomarkers. Alternatively, we cannot rule out that white matter volume segmentations might be influenced by coinciding gray matter atrophy.

Strengths of our study include the long-term, prospective ascertainment of dementia, stroke and mortality in a large, population representative sample with multimodal brain MRI. Despite the new insights from the clustering approach, it is important to acknowledge the methodological imperfections and future challenges. First, some of the imaging marker values within clusters, particularly WMH burden in cluster 2, exhibited broad distributions. This might explain the relatively poor Adjusted Rand Index across subsamples, as white matter imaging patterns in clusters 3 and 4 were more stable than cluster 1 and 2. However, the goal of our clustering was not to assign individuals perfectly into clusters, but to infer etiological clues from white matter signatures; in this respect, the various iterations of clustering provided rather consistent results based on visual inspection of white matter signatures. Second, we only included global markers of brain structure. Future studies may also benefit from spatial information of imaging markers. Previous studies have already shown that spatial information of WMH is associated to different underlying pathologies and

specific cognitive deficits.32,33 This could also apply for white matter atrophy and microstructural deterioration (e.g., tract-specific FA and MD). Moreover, for similar volume of WMH, different locations may lead to different global FA or global MD values due to some regions of white matter having a larger impact on the global FA or MD than other regions. Third, scans with cortical infarcts, causing tissue segmentation issues, had to be excluded, potentially introducing selection bias. Based on the observed clusterification, these individuals are expected to be in clusters 3 or 4, possibly leading to slightly underestimated disease risks of these clusters in the current analyses. Fourth, although >80% of individuals who attended the study center also underwent brain MRI, the selection may have led to a somewhat more healthy study population. Fifth, we have not externally validated the presented white matter signatures.

In conclusion, heterogeneity in imaging markers of white matter in the general population can be clustered in distinct and etiologically meaningful white matter signatures based on MRI data. Differences among clusters in determinants and clinical outcomes suggest different underlying pathologies, which adds to understanding of disease pathophysiology, and may hold future utility for risk stratification.

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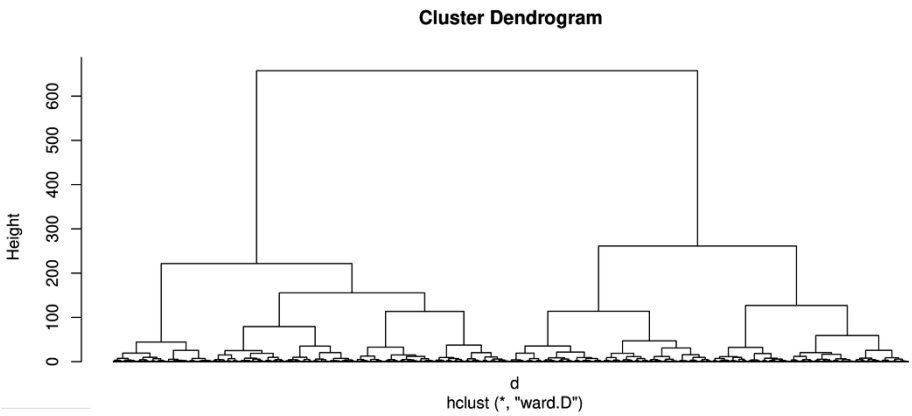
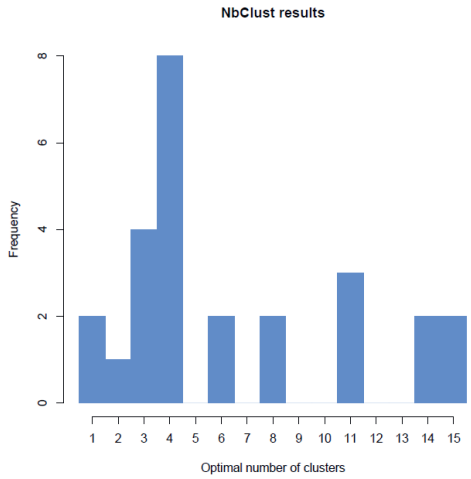
SUPPLEMENTARY MATERIALS

eFigure 1. Cluster dendrogram



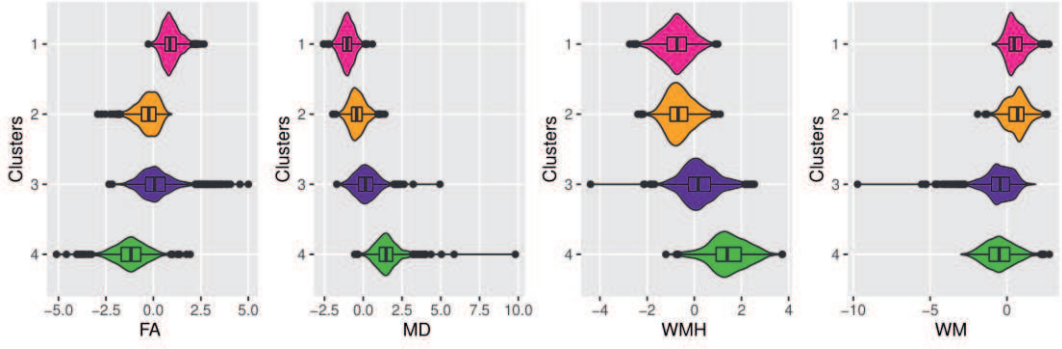
Dendrogram visualizing the hierarchical clustering process of the included individuals.

eFigure 2 Determining optimal number of clusters



Histogram of cluster validity metrics within the NbClust package determining the optimal number of clusters within our data. This is done by applying a variety of cluster validity metrics which determine the optimal number of clusters. The optimal number of clusters is the number which had the highest frequency of cluster validity metrics suggesting this number as optimum. The majority of metrics determined 4 as the optimal number of clusters.

eFigure 3 Distributions of imaging markers across clusters when no age adjustment prior to clustering was applied.



Violin plots showing the probability density function of white matter imaging markers for each cluster when clustering was performed without age-adjustment of imaging markers prior to clustering. Box plots are shown as overlay. Abbreviations: FA = fractional anisotropy, MD = mean diffusivity, WMH = white matter hyperintensities, WM = white matter volume.

eTable 1. Characteristics of white matter clusters when no age adjustment prior to clustering was applied.

Characteristic	Cluster 1 (N=1004)	Cluster 2 (N=1356)	Cluster 3 (N=2129)	Cluster 4 (N=790)	P-value
Age, years	57.2 (7.2)	58.1 (6.8)	69.1 (9.9)	76.1 (8.3)	<0.001
Sex, female	480 (47.8)	815 (60.1)	1165 (54.7)	497 (62.9)	<0.001
Education					<0.001
Primary only	66 (6.6)	101 (7.4)	209 (9.8)	94 (11.9)	
Lower vocational	340 (33.9)	487 (35.9)	853 (40.1)	337 (42.7)	
Intermediate vocational / higher general	307 (30.6)	397 (29.3)	655 (30.8)	238 (30.1)	
Higher vocational/ university	291 (29.0)	371 (27.4)	412 (19.4)	121 (15.3)	
Body mass index, kg/mm^2	27.3 (4.2)	27.3 (4.1)	27.6 (4.1)	27.2 (4.0)	0.022
Systolic blood pressure, mmHg	131.6 (17.5)	132.4 (19.2)	143.5 (21.0)	151.2 (21.9)	<0.001
Diastolic blood pressure, mmHg	81.5 (10.1)	82.4 (11.0)	82.4 (11.1)	84.3 (11.8)	<0.001
Blood pressure lowering medication	213 (21.2)	335 (24.7)	872 (41.0)	449 (56.8)	<0.001
Smoking					<0.001
Never	314 (31.3)	422 (31.1)	635 (29.8)	259 (32.8)	
Former	450 (44.8)	608 (44.8)	1121 (52.7)	415 (52.5)	
Current	240 (23.9)	326 (24.0)	373 (17.5)	116 (14.7)	
Alcohol intake*, g/day	6.43 [1.61-15.00]	6.43 [1.61-8.57]	7.14 [0.54-12.14]	6.43 [0.54-8.57]	<0.001
Total cholesterol, mmol/L	5.55 (1.04)	5.62 (1.04)	5.53 (1.05)	5.38 (1.07)	<0.001
HDL cholesterol, mmol/L	1.42 (0.42)	1.47 (0.44)	1.45 (0.41)	1.48 (0.41)	0.007
Lipid lowering medication	202 (20.1)	288 (21.2)	566 (26.6)	242 (30.6)	<0.001
Diabetes mellitus	74 (7.4)	117 (8.6)	318 (14.9)	163 (20.6)	<0.001
APOE genotype					0.264
ε3/ε3	563 (56.1)	784 (57.8)	1236 (58.1)	431 (54.6)	
ε2/ε2 or ε2/ε3	162 (16.1)	207 (15.3)	346 (16.3)	150 (19.0)	
ε4-carrier (heterozygous)	263 (26.2)	339 (25.0)	496 (23.3)	195 (24.7)	
ε4-carrier (homozygous)	16 (1.6)	26 (1.9)	51 (2.4)	14(1.8)	
Cerebral microbleeds (any)	102 (10.2)	178 (13.1)	452 (21.2)	331 (24.9)	<0.001
Lacunes (any)	22 (2.2)	35 (2.6)	169 (7.9)	170 (21.5)	<0.001
Gray matter volume, proportion of ICV	0.47 (0.03)	0.47 (0.03)	0.47 (0.03)	0.45 (0.03)	<0.001

Continuous variables are presented as means (standard deviations) and categorical variables as number (percentages). * = variable with skewed distribution. Median [interquartile range] is shown instead of mean (standard deviation). Abbreviations: HDL=high density lipoprotein; ICV=intracranial volume

eTable 2. Risk of dementia, stroke and mortality by white matter cluster.

		Reference cluster			
		1	2	3	4
Dementia HR [95% CI]	Cluster 1	-	**0.65 [0.46-0.92]**	**0.37 [0.26-0.52]**	**0.50 [0.35-0.73]**
	Cluster 2	**1.54 [1.09-2.18]**	-	**0.56 [0.42-0.76]**	0.78 [0.57-1.06]
	Cluster 3	**2.74 [1.92-3.91]**	**1.78 [1.32-2.39]**	-	**1.38 [1.00-1.90]**
	Cluster 4	**1.98 [1.37-2.87]**	1.29 [0.94-1.76]	**0.72 [0.52-1.00]**	-
Stroke HR [95% CI]	Cluster 1	-	0.74 [0.51-1.08]	**0.57 [0.38-0.86]**	**0.51 [0.34-0.75]**
	Cluster 2	1.35 [0.92-1.97]	-	0.77 [0.53-1.11]	**0.68 [0.48-0.97]**
	Cluster 3	**1.76 [1.16 [2.66]**	1.30 [0.90-1.88]	-	0.89 [0.61-1.31]
	Cluster 4	**1.97 [1.33-2.92]**	**1.46 [1.03-2.06]**	1.12 [0.76-1.65]	-
Mortality HR [95% CI]	Cluster 1	-	**0.77 [0.64-0.93]**	**0.62 [0.51-0.76]**	**0.61 [0.50-0.74]**
	Cluster 2	**1.29 [1.08-1.55]**	-	**0.81 [0.67-0.97]**	**0.79 [0.67-0.94]**
	Cluster 3	**1.60 [1.31-1.96]**	**1.24 [1.04-1.49]**	-	0.98 [0.81-1.19]
	Cluster 4	**1.63 [1.35-1.99]**	**1.26 [1.06-1.50]**	1.02 [0.84-1.24]	-

Hazard ratios of model 1, which are unadjusted. Each cluster is used as reference once for determining hazard ratios. Bold font indicates significant estimates. Abbreviations: HR = hazard ratio, CI = confidence interval.

eTable 3. Risk of dementia, stroke and mortality by white matter cluster.

		Reference cluster			
		1	2	3	4
Dementia HR [95% CI]	Cluster 1	-	**0.66 [0.47-0.94]**	**0.38 [0.26-0.54]**	**0.51 [0.35-0.73]**
	Cluster 2	**1.52 [1.07-2.15]**	-	**0.57 [0.42-0.77]**	0.77 [0.56-1.05]
	Cluster 3	**2.65 [1.85-3.79]**	**1.75 [1.30-2.36]**	-	1.34 [0.97-1.85]
	Cluster 4	**1.97 [1.36-2.85]**	1.30 [0.95-1.78]	0.74 [0.54-1.03]	-
Stroke HR [95% CI]	Cluster 1	-	0.73 [0.51-1.06]	**0.54 [0.36-0.82]**	**0.49 [0.33-0.73]**
	Cluster 2	1.35 [0.92-1.96]	-	0.73 [0.51-1.06]	**0.66 [0.47-0.94]**
	Cluster 3	**1.84 [1.21-2.79]**	1.37 [0.95-1.98]	-	0.91 [0.62-1.33]
	Cluster 4	**2.03 [1.37-3.01]**	**1.51 [1.07-2.13]**	1.10 [0.75-1.62]	-
Mortality HR [95% CI]	Cluster 1	-	**0.78 [0.65-0.93]**	**0.59 [0.48-0.72]**	**0.59 [0.48-0.71]**
	Cluster 2	**1.29 [1.07-1.54]**	-	**0.76 [0.63-0.91]**	**0.76 [0.64-0.90]**
	Cluster 3	**1.69 [1.38-2.07]**	**1.31 [1.10-1.58]**	-	1.00 [0.82-1.21]
	Cluster 4	**1.70 [1.40-2.07]**	**1.32 [1.11-1.57]**	1.00 [0.83-1.22]	-

Hazard ratios of model 2, which are adjusted for age, sex and education. Each cluster is used as reference once for determining hazard ratios. Bold font indicates significant estimates. Abbreviations: HR = hazard ratio, CI = confidence interval.

eTable 4. AIC values of fully adjusted cox models (model 3) with clusters or individual imaging markers.

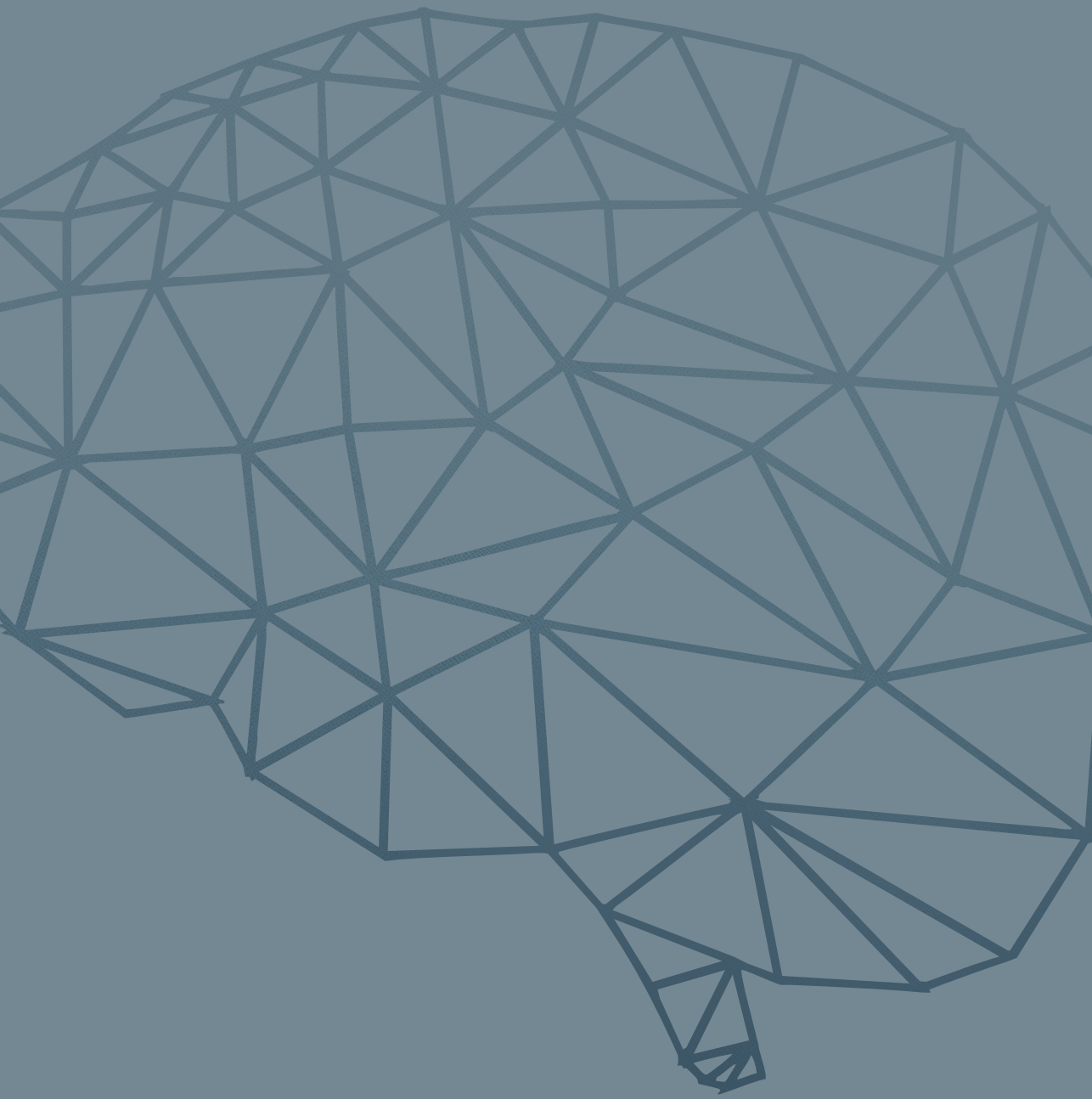
	Clusters	FA	MD	WMH	WM
Dementia	4462.90	4475.65	4465.84	4474.13	4481.10
Stroke	3510.11	3511.87	3509.67	3504.11	3511.47
Mortality	14265.81	14279.18	14275.32	14266.05	14279.23

Akaike Information Criterion (AIC) values showing the goodness of fit of the fully adjusted cox models (model 3) for each outcome, comparing models with clusters or individual imaging markers as dependent variable. A lower AIC value represents a better goodness of fit.

eTable 5. Risk of dementia, stroke and mortality by white matter cluster, additionally adjusted for gray matter volume.

		Reference cluster			
		1	2	3	4
Dementia HR [95% CI]	Cluster 1	-	**0.56 [0.39-0.80]**	**0.41 [0.29-0.60]**	**0.49 [0.33-0.72]**
	Cluster 2	**1.80 [1.25-2.58]**	-	0.75 [0.54-1.03]	0.88 [0.64-1.22]
	Cluster 3	**2.42 [1.68-3.48]**	1.34 [0.97-1.86]	-	1.19 [0.84-1.67]
	Cluster 4	**2.04 [1.39-2.99]**	1.13 [0.82-1.56]	0.84 [0.60-1.19]	-
Stroke HR [95% CI]	Cluster 1	-	0.72 [0.49-1.06]	0.69 [0.45-1.06]	**0.56 [0.37-0.84]**
	Cluster 2	1.39 [0.94-2.05]	-	0.96 [0.65-1.43]	0.77 [0.54-1.10]
	Cluster 3	1.45 [0.94-2.21]	1.04 [0.70-1.55]	-	0.80 [0.54-1.20]
	Cluster 4	**1.80 [1.20-2.70]**	1.29 [0.91-1.84]	1.24 [0.83-1.86]	-
Mortality HR [95% CI]	Cluster 1	-	**0.71 [0.59-0.85]**	**0.71 [0.58-0.87]**	**0.61 [0.50-0.75]**
	Cluster 2	**1.41 [1.17-1.71]**	-	1.00 [0.83-1.22]	0.87 [0.72-1.03]
	Cluster 3	**1.41 [1.15-1.73]**	1.00 [0.82-1.21]	-	0.86 [0.70-1.06]
	Cluster 4	**1.64 [1.33-2.00]**	1.16 [0.97-1.38]	1.16 [0.95-1.42]	-

Model 4 is additionally adjusted for gray matter volume. Bold font indicates significant estimates. Abbreviations: HR = hazard ratio, CI = confidence interval.



CHAPTER 2.2

COMPARING STRUCTURAL CONNECTIVITY MEASURES FOR COGNITIVE DECLINE AND DEMENTIA RISK

Mathijs T. Rosbergen, Frank J. Wolters, M. Arfan Ikram, Meike W. Vernooij

Submitted as:
Head-to-head comparison of structural connectivity measures for cognitive decline and risk of dementia: the population-based Rotterdam Study.

ABSTRACT

Diffusion tensor imaging (DTI) is a promising tool for early detection of white matter deterioration, but the optimal DTI marker for assessing risk of cognitive decline and dementia is undetermined. The aim of this study was to compare the predictive value of multiple diffusion measures for cognitive decline and dementia risk in a population-based study.

We measured peak-width skeletonized mean diffusivity (PSMD), normal-appearing white matter mean diffusivity (MD), and fractional anisotropy (FA) in participants aged 45 years and older who underwent 1.5T MRI between 2006-2015 as part of the ongoing prospective population-based Rotterdam Study. In a head-to-head comparison between DTI markers, we determined risk of cognitive decline and dementia during follow-up, using linear regression and Cox proportional hazard models, respectively, that also include age, sex, education and presence of lacunes or microbleeds.

Of 5230 participants (mean age: 65.0 years +/-10.9 [standard deviation], 55.8% women), 286 developed dementia during a median follow-up of 9.8 years. For dementia risk, PSMD and global MD were superior regarding model fit, with the highest hazard ratio for global MD (HR: 1.74 [95%CI: 1.53-1.98]). Similarly, PSMD and MD had the highest discriminatory value (C-statistic, for PSMD: 0.886, and for MD: 0.882), albeit differences with other measures were small. Of all participants, 4433 (84.3%) had complete data on all cognitive tests at baseline, of whom 2800 (63.2%) completed their follow-up visit after on average 5.6 years. For global cognition both at time of MRI and at follow-up, PSMD was superior in terms of model fit and showed the highest regression coefficients, followed by tract-specific measures of MD and FA.

In conclusion, when directly comparing structural connectivity measures, PSMD is superior to MD and FA for prediction of cognition and cognitive decline, while PSMD and MD perform best with respect to dementia risk.

INTRODUCTION

Dementia represents significant and growing public health challenges, with an increasing burden on aging populations worldwide.[1] Cognitive decline and dementia are characterized by progressive loss of cognitive abilities such as memory, attention, and executive function, which are due in part to deterioration of white matter networks.[2] Quantitative assessment of this white matter injury in an early stage could improve timely identification of individuals at risk of cognitive decline and dementia. Although white matter hyperintensities (WMH) volume on conventional magnetic resonance imaging (MRI) techniques is predictive of future cognitive decline and dementia[3], it reflects only the tip of the iceberg of white matter injury.[4] Diffusion tensor imaging (DTI) has emerged as a key modality for assessing white matter integrity in a more fine-grained manner[5], detecting microstructural changes in normal-appearing white matter (NAWM) years before they manifest as WMH.[6] As such, DTI measures are a promising marker for early risk stratification, but implementation of DTI in clinical practice is limited, due in part to uncertainty about the optimal DTI parameters for assessment of risk of cognitive decline.

Of the commonly used DTI metrics, fractional anisotropy (FA) and mean diffusivity (MD) have demonstrated associations with cognitive decline and dementia,[2, 7, 8], but they are limited by their susceptibility to noise and artifacts. A more recent diffusion imaging marker, peak-width skeletonized mean diffusivity (PSMD), has gained attention for its ability to robustly quantify microstructural changes in white matter.[9] Instead of averaging diffusivity values, PSMD quantifies the width of the distribution of diffusivity values across the white matter skeleton. The width of the skeletonized MD histogram may be more sensitive to early, localized damage in the white matter than the global MD value. Moreover, PSMD is fully automated and standardized, ensuring highly reproducible across different scanners and settings[10], which enhances its potential for widespread clinical application. Several studies have explored the relationship between PSMD and cognitive decline[11-13], or dementia risk,[14] but none directly compared the prognostic value of PSMD to conventional diffusion imaging markers, such as FA and MD.

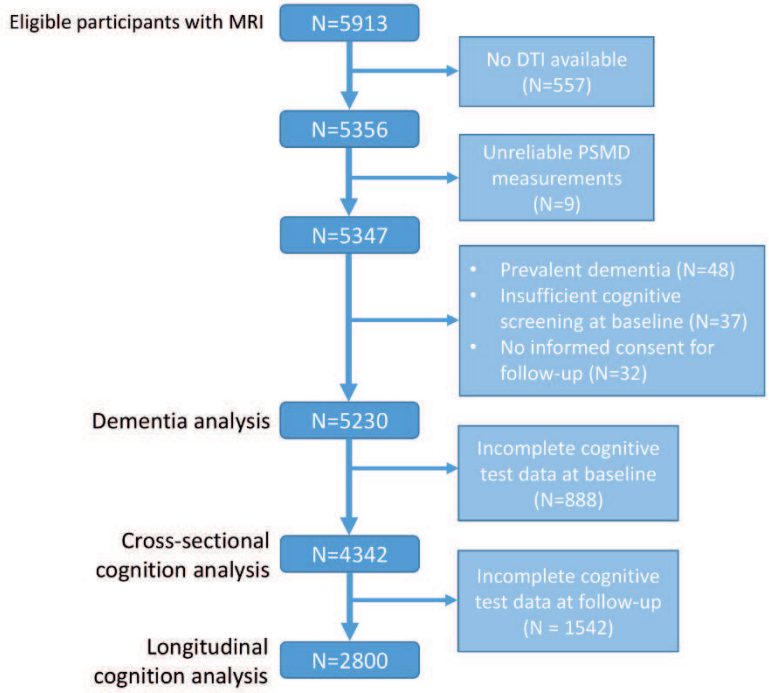
The aim of this study was to provide a head-to-head comparison of the predictive value of multiple diffusion measures for cognitive decline and dementia risk in a population-based study.

METHODS

Study Population

This research was embedded in the Rotterdam Study, an ongoing prospective population-based cohort in the Netherlands[15] that started in 1990, enrolling residents aged ≥45 years in the Ommoord district in Rotterdam with follow-up every 4 to 6 years. Participants overlapped with prior DTI studies[7, 8], but we focused on directly comparing the predictive value of DTI markers, including PSMD. However, Of the 5913 participants who underwent brain MRI, we included 5230 participants with brain MRI between March 29, 2006, and September 22, 2015 (Figure 1). The Rotterdam Study received approval from the institutional review board of the Erasmus Medical Center and by the Ministry of Health, Welfare and Sports of the Netherlands, implementing the "Wet Bevolkingsonderzoek: ERGO (Population Screening Act: Rotterdam Study)." All participants provided written informed consent for their participation in the study.

Figure 1 Flowchart of the inclusion of participants



MRI Acquisition, Preprocessing, and Appraisal

All participants underwent brain MRI using a 1.5 Tesla MRI scanner (Signa Excite II; General Electric Healthcare) with an 8-channel head coil. The scan protocol and sequence details of the Rotterdam Study have been described elsewhere.[15, 16] For volumetry, T1-weighted, proton density-weighted, and FLAIR scans were used for automated segmentation of supratentorial white matter, WMH, and intracranial volume.[17, 18] Two raters visually inspected and manually corrected the segmentations if necessary.

Microstructural integrity was assessed using DTI to derive global FA and MD in NAWM, using a standardized pipeline [19] and including only voxels with FA ≥ 0.2 to minimize partial volume effects.[19] PSMD was derived using an automated pipeline (v0.95)[9] and the white matter skeleton.[20] FA values ≥ 0.2 and subsequently MD values were projected on this skeleton. PSMD was then calculated as the difference between the 95th and 5th percentiles of voxel-based MD values. MRI scans with unreliable PSMD values (>0.0007) were excluded based on previous research.[21] We included tract-specific FA and MD measures[22] for tracts that were most strongly related to poor cognition in previous research, namely the inferior front-occipital fasciculus from the association tracts, and the posterior thalamic radiation from the projection tracts[7].

All scans were rated by trained researchers, for the presence of lacunes and microbleeds according to predefined criteria.[16, 23, 24]

Educational attainment

Information regarding educational attainment was obtained during baseline home interviews and categorized into 4 groups.

Assessment of Cognition

Assessment of cognitive function was routinely performed at center visits every 4 to 6 years through a cognitive test battery, including the Stroop test[25], measuring processing and attention, the Word Fluency test (WFT)[26], measuring efficiency of searching long term memory, the Letter Digit Substitution test (LDST)[27], measuring processing speed and executive function, 15-word verbal learning test (15-WLT)[28], measuring verbal learning and memory, and Purdue Pegboard test (PPB)[29], measuring dexterity and fine motor speed. Additionally, we derived a global cognition measure (g-factor) from principle component analysis of available test scores,[30]

defined as the first unrotated component, explaining 49.8% of variance in cognition in our sample. A higher g-factor indicates a better cognitive performance. Participants with incomplete data for all five cognitive tests were excluded.

Assessment of Dementia

All participants were followed for the occurrence of dementia through a combination of repeated in-person assessment and linkage with electronic medical records. Participants were screened for dementia at baseline and every 3-6 years during follow-up examinations. Those with abnormal scores were further examined and a consensus panel, led by a neurologist, confirmed dementia diagnoses using DSM-III-R criteria. Participants were censored at dementia diagnosis, death, loss to follow-up or January 1, 2020, whichever occurred first.

Data Analysis

Missing covariate data (≤1.0%) were imputed using 5-fold multiple imputation. We modeled age nonlinearity using natural cubic splines of age with 1 knot. All diffusion measures were standardized and FA measures were inverted to ease comparison.

In our primary analysis, we used Cox proportional hazard models to obtain HRs and 95%CIs for the association between global DTI (PSMD, global MD, global FA) measures and risk of dementia. Additionally, we calculated the Akaike Criterium Information (AIC) and C-statistic. We included in all models age, sex, education, and the presence of lacunes and/or microbleeds. We then determined the cross-sectional association between global DTI measures and the g-factor, using linear regression models including the same variables as before. For longitudinal models, we assessed the association between baseline global DTI measures and g-factor at the next follow-up visit, adjusting for baseline g-factor and follow-up time.

In a post-hoc analysis, we assessed the C-statistic with both MD and PSMD included.

In secondary analyses, we assessed tract-specific measures of FA and MD in relation to dementia risk and cognitive decline. Cognition analyses were repeated for each of the cognitive tests separately.

In a sensitivity analysis, we stratified dementia risk analyses by follow-up time. All analyses were performed using R, version 4.3.3 (packages: dplyr, ggplot2, mice,

sjmisc, splines, survival). Requests for computer codes can be directed to secretariat.epi@erasmusmc.nl.

RESULTS

Baseline characteristics of all participants with available data on all DTI measures are shown in Table 1. The mean age at time of MRI was 65.0 years, and 55.8% of the included participants were women. Correlations (Pearson) between the included diffusion measures ranged between 0.46 and 0.85 (Supplemental Figure 1).

Table 1 Characteristic of the total study population

Characteristic	Total (N=5230)
Age, y	65.0 (10.9)
Sex, female	2919 (55.8%)
Education	
Primary only	445 (8.5%)
Lower vocational	2000 (38.2%)
Intermediate vocational/higher general	1599 (30.6%)
Higher vocational/university	1186 (22.7%)
Body mass index, kg/m^2	27.4 (4.1)
Systolic blood pressure, mm Hg	139.8 (21.4)
Diastolic blood pressure, mm Hg	82.9 (11.0)
Blood pressure lowering medication	1893 (36.2%)
Smoking	
Never	1617 (30.9%)
Former	2550 (48.8%)
Current	1063 (20.3%)
Alcohol intake[a], g/d	6.43 (0.54-8.57)
Total cholesterol, mmol/L	5.52 (1.06)
HDL cholesterol, mmol/L	1.45 (0.42)
Lipid lowering medication	1323 (25.3%)
Diabetes mellitus	672 (12.8%)
APOE genotype	
ε3/ε3	2931 (56.0%)
ε2/ε2 or ε2/ε3	864 (16.5%)
ε4-carrier (heterozygous)	1262 (24.1%)
ε4-carrier (homozygous)	173 (3.3%)
Cerebral microbleeds (any)	1064 (20.3%)
Lacunes (any)	421 (8.0%)

Abbreviations: HDL = high-density lipoprotein; ICV = intracranial volume. Continuous variables are presented as mean (SD) and categorical variables as n (%). [a] Variable with skewed distribution. Median (interquartile range) is shown instead of mean (SD).

Risk of dementia

During a median follow-up of 9.8 years, 286 participants developed dementia. All diffusion imaging markers were significantly associated with risk of dementia (Figure 2), with the best goodness of fit for models including MD and PSMD (AIC for MD: 4088.8; and for PSMD: 4089.4). These values were better than for global FA, tract-specific MD or tract-specific FA measures (all AIC>4101.1). The model with PSMD achieved a slightly higher C-statistic (0.886 [95%CI: 0.871-0.900]) than models with MD (C-statistic$_{MD}$: 0.882 [0.867-0.897]) and FA (C-statistic$_{FA}$: 0.876 [0.860-0.891]) (Supplemental Table 1).

When stratifying analyses by follow-up period, models including global MD were superior until 5 years of follow-up, after which global MD and PSMD were comparable in terms of AIC (Supplemental Table 2). HRs were consistently somewhat higher for global MD than for other diffusion measures. In a post-hoc analysis, we assessed the C-statistic of a model including both PSMD and MD which achieved a slightly higher C-statistic (0.889 [95%CI: 0.874-0.903]) than PSMD alone (0.886 [0.871-0.900]).

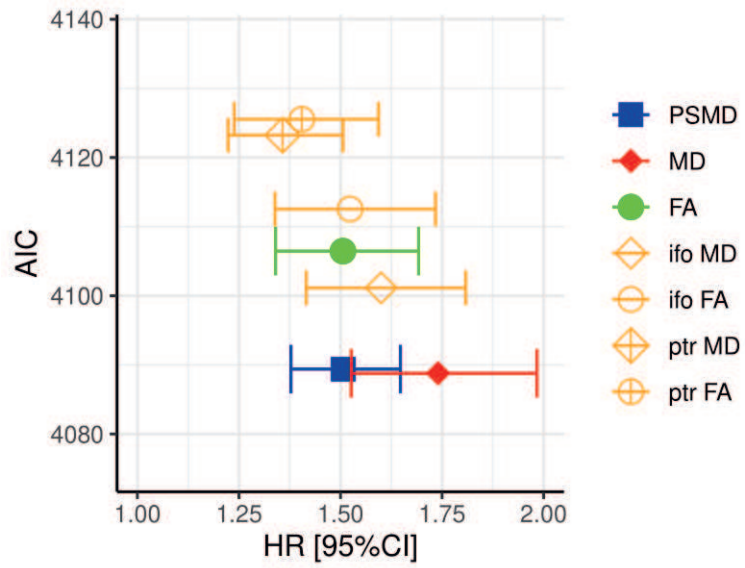
Cross-sectional cognition

Of all 5230 participants, 4342 (84.3%) completed on the entire cognitive assessment at time of MRI. Compared to participants who did not complete the entire neuropsychological assessment, those who did were on average younger and had a lower burden of vascular risk factors (Supplemental Table 3).

All diffusion imaging measures were significantly associated with global cognition at time of MRI (Figure 3A). For global cognition, the regression coefficient for PSMD (β [95%CI]: -0.22 [-0.26- -0.19]) was higher than coefficients for global MD (β [95%CI]: -0.13 [-0.16- -0.10]) and global FA (β [95%CI]: -0.10 [-0.12- -0.07]). Regression coefficients of tract-specific diffusion measures were also inferior to those of PSMD. Moreover, the goodness-of-fit was superior for the model including PSMD (AIC: 9700.9), compared to models with other diffusion imaging measures (AIC>9753.7).

Similarly, for individual cognitive tests, PSMD had the highest regression coefficients and superior model fit, compared to global MD and global FA. Tract-specific diffusion measures showed a superior model fit for the Word Fluency Test and Word Learning Test (Supplemental Figure 2).

Figure 2 Risk of dementia for diffusion imaging markers



HR=Hazard ratio, CI=confidence interval, AIC=Akaike Information Criterion, PSMD=Peak-width skeletonized mean diffusivity, MD=mean diffusivity, FA=Fractional anisotropy, ifo=inferior fronto-occipital fasciculus, ptr=posterior thalamic radiation; lower AIC reflects better model performance.

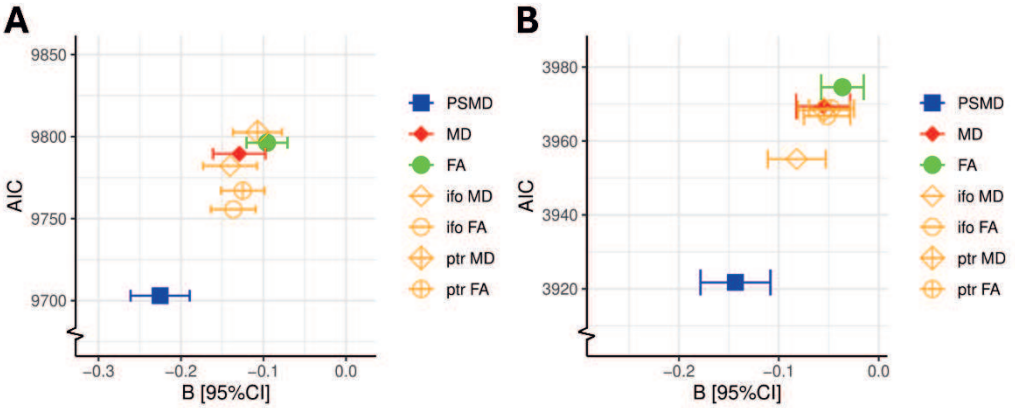
Longitudinal cognition

Of 4342 participants with complete cognitive assessment at baseline, 2800 (64.5%) completed the entire cognitive assessment during reassessment after on average 5.6 years (Supplemental Figure 3).

All diffusion imaging measures were significantly associated with global cognition (Figure 3B). The regression coefficient and goodness-of-fit were highest for PSMD (β [95%CI]: -0.14 [-0.18- -0.11]; AIC: 3922.0), compared to MD (β: -0.06 [-0.08- -0.03]; AIC: 3969.6) and FA (β: -0.04 [-0.06- -0.01]; AIC: 3964.8). Tract-specific diffusion measures were also inferior to PSMD regarding global cognition.

Consistent with global cognition, PSMD had the highest regression coefficients and superior model fit across all cognitive tests, compared to other global and tract-specific diffusion measures (Supplemental Figure 4).

Figure 3 Cognition and diffusion imaging markers



A: Cross-sectional global cognition (g-factor) and diffusion imaging markers. **B**: Longitudinal global cognition (g-factor) and diffusion imaging markers. B=Bèta (regression coefficient), CI=confidence interval, AIC=Akaike Information Criterion, PSMD=Peak-width skeletonized mean diffusivity, MD=mean diffusivity, FA=Fractional anisotropy, ifo=inferior fronto-occipital fasciculus, ptr=posterior thalamic radiation; lower AIC reflects better model performance.

DISCUSSION

In this direct head-to-head comparison of DTI measures in a large population-based imaging study, we demonstrated that both PSMD and MD are superior for predicting dementia, and PSMD is superior in predicting cognitive decline. PSMD also outperformed tract-specific measures of MD and FA, except for cross-sectional performance in verbal fluency and the 15-word learning test.

Our study confirms earlier associations of PSMD with cognitive decline[11-13, 31] and dementia risk[14, 31], and adds the insight that these associations for PSMD are at least equal, if not stronger, than for other diffusion imaging measures. This confirms our hypothesis that PSMD may be more sensitive to microstructural damage of cerebral white matter. Based on this rationale, PSMD is expected to be particularly effective in predicting dementia or cognitive decline over longer follow-up periods. This was supported by our results on cross-sectional cognition and cognition at follow-up. In cross-sectional analyses, tract-specific measures outperformed PSMD in the Word Fluency Test and the Word Learning Test. However, when assessing cognitive decline during follow-up, PSMD was stronger than other diffusion imaging markers for all cognitive tests. Furthermore, while models including MD had the best

fit for dementia at follow-up up to 5 years, models including PSMD caught up and showed comparable model fit at longer follow-up durations.

Tract-specific diffusion measures were inferior to PSMD regarding predicting general cognition or dementia, but performed well in cross-sectional analyses of specific cognitive domains. Particularly for the Word Fluency Test and the Word learning Test, the models including the global FA or MD value of the inferior fronto-occipital fasciculus were superior, which can be attributed to the important role this structure has in language processing.[32] For other cognitive tests, PSMD was superior, which is in line with previous clinic-based and population-based studies, which showed that PSMD is cross-sectionally associated with processing speed, executive function, visuospatial ability, verbal memory and general cognition.[12, 33, 34] Moreover, one of these studies showed that PSMD is significantly associated with processing speed and memory at 3-year follow-up.[12] Although our follow-up for cognitive decline was longer, these associations were also seen in our results regarding individual cognitive tests at follow-up (Supplemental Figure 4). In the current study, PSMD had the strongest association with all cognitive tests at follow-up, compared to other global and tract-specific diffusion measures.

In addition to being a strong predictor for cognitive decline and dementia, PSMD offers several strengths over other diffusion imaging measures. Both global FA and MD measures may be affected by crossing fibers, and are based on all FA or MD values across the normal-appearing white matter, making them more susceptible to noise or artefacts. In contrast, PSMD offers greater robustness due to its skeletonized approach and its use of the 5th to 95th percentile of the MD histogram. Consequently, previous research showed that PSMD has excellent inter-rater reliability (between different sites), test-retest repeatability, and inter-scanner reproducibility.[10] The robustness and automated extraction of PSMD[9] along with its predictive value in the current study, may favour PSMD as the preferred measure of structural white matter integrity in prediction, and early diagnosis of cognitive decline and dementia. Although DTI has not been widely adopted in clinical practice yet, our comparative evidence may guide the implementation of the most appropriate diffusion measures for prediction of cognitive decline and dementia.

Strengths of our study include the long-term, prospective ascertainment of dementia and cognition in a large population-representative sample with diffusion brain MRI. However, it is important to acknowledge some methodological limitations. First,

excluding participants with incomplete cognitive test data potentially introduced some selection bias. Participants excluded from cross-sectional cognition analysis were a bit older with more vascular risk factors than those with complete data on all cognitive tests (Supplemental Table 1). Second, although >80% of individuals who attended the study center also underwent brain MRI, the selection may have led to a healthier study population, potentially attenuating our estimates but not affecting the comparison between markers. Thirdly, as the focus of our study was on the head-to-head comparison between diffusion imaging measures, we did not investigate predictive accuracy above and beyond other conventional neuroimaging markers like volumetric measurements. Further studies should investigate the added value of PSMD combined with structural MRI markers, such as the hippocampus, that already proved to be important in prediction of dementia.[35] Fourth, our findings were not validated in other populations or MRI protocols, which future research should address.

In conclusion, in our head-to-head comparison of structural connectivity measures, PSMD is superior to MD and FA for prediction of cognition and risk of cognitive decline, while both PSMD and MD are superior with respect to dementia risk. Given its robustness, PSMD may be the preferred imaging marker for predicting cognitive decline in clinical practice.

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SUPPLEMENTARY MATERIALS

Supplemental Table 1 Discriminatory power regarding dementia prediction when using different diffusion measures

	PSMD	MD	FA	Ifo MD	Ifo FA	Ptr MD	Ptr FA
C-statistic [95%CI]	0.886 [0.871-0.900]	0.882 [0.867-0.897]	0.876 [0.860-0.891]	0.881 [0.866-0.896]	0.877 [0.862-0.893]	0.875 [0.860-0.890]	0.876 [0.860-0.891]

PSMD=Peak-width skeletonized mean diffusivity, MD=mean diffusivity, FA=Fractional anisotropy, ifo=inferior fronto-occipital fasciculus, ptr=posterior thalamic radiation; higher C-statistic reflects a stronger discriminatory power.

Supplemental Table 2 Risk of dementia for diffusion imaging markers with increasing follow-up time.

Follow-up	At risk/ Cumulative dementia	PSMD		MD		FA		ifo MD		Ifo FA		Ptr MD		Ptr FA	
		HR [95%CI]	AIC	HR [95%CI]	AIC	HR [95%CI]	AIC	HR [95%CI]	AIC	HR [95%CI]	AIC	HR [95%CI]	AIC	HR [95%CI]	AIC
3 years	4968/55	1.38 [1.15-1.67]	833.2	1.96 [1.49-2.57]	**821.4**	1.41 [1.10-1.81]	835.7	1.60 [1.25-2.05]	830.0	1.45 [1.10-1.91]	836.0	1.30 [1.04-1.62]	837.8	1.32 [1.00-1.74]	838.8
4 years	4847/79	1.48 [1.27-1.72]	1183.0	1.90 [1.52-2.39]	**1175.3**	1.47 [1.19-1.81]	1190.8	1.71 [1.40-2.10]	1179.3	1.55 [1.23-1.96]	1189.9	1.39 [1.16-1.67]	1191.8	1.44 [1.14-1.81]	1193.9
5 years	4652/108	1.45 [1.27-1.65]	1592.9	1.78 [1.46-2.17]	**1587.5**	1.35 [1.13-1.62]	1606.6	1.65 [1.38-1.97]	1589.5	1.51 [1.24-1.85]	1601.0	1.41 [1.21-1.65]	1600.5	1.48 [1.21-1.81]	1602.5
6 years	4417/151	1.53 [1.38-1.71]	**2212.6**	1.83 [1.55-2.17]	2213.5	1.47 [1.26-1.71]	2235.4	1.66 [1.43-1.93]	2220.3	1.57 [1.33-1.87]	2232.0	1.36 [1.19-1.56]	2241.1	1.50 [1.26-1.78]	2237.7
7 years	4151/179	1.49 [1.34-1.65]	**2623.5**	1.73 [1.48-2.04]	2624.1	1.37 [1.19-1.58]	2648.0	1.58 [1.37-1.83]	2631.2	1.50 [1.28-1.76]	2641.5	1.31 [1.16-1.49]	2650.4	1.39 [1.19-1.62]	2649.9
8 years	3729/206	1.49 [1.35-1.64]	**3018.5**	1.72 [1.48-2.00]	3019.9	1.43 [1.25-1.63]	3040.1	1.61 [1.41-1.84]	3024.1	1.57 [1.36-1.82]	3031.4	1.34 [1.19-1.50]	3046.2	1.42 [1.23-1.65]	3044.8
9 years	3157/243	1.51 [1.37-1.65]	3555.8	1.78 [1.55-2.05]	**3552.5**	1.46 [1.29-1.66]	3578.1	1.62 [1.42-1.84]	3564.6	1.59 [1.38-1.82]	3570.7	1.36 [1.21-1.51]	3587.0	1.41 [1.23-1.62]	3588.6
10 years	2502/264	1.51 [1.38-1.65]	**3820.4**	1.73 [1.51-1.99]	3822.2	1.48 [1.31-1.67]	3841.6	1.60 [1.42-1.82]	3831.7	1.55 [1.36-1.77]	3840.4	1.34 [1.20-1.49]	3856.1	1.40 [1.23-1.59]	3856.6
11 years	1751/278	1.51 [1.38-1.65]	**3991.3**	1.73 [1.51-1.97]	3992.9	1.50 [1.33-1.68]	4009.8	1.59 [1.40-1.80]	4004.7	1.53 [1.34-1.74]	4014.0	1.34 [1.21-1.49]	4027.4	1.40 [1.23-1.59]	4027.4
12 years	1046/285	1.51 [1.38-1.65]	4076.5	1.75 [1.53-1.99]	**4075.3**	1.51 [1.34-1.69]	4093.4	1.60 [1.41-1.81]	4088.5	1.51 [1.33-1.72]	4101.0	1.36 [1.22-1.51]	4110.5	1.41 [1.24-1.59]	4112.6

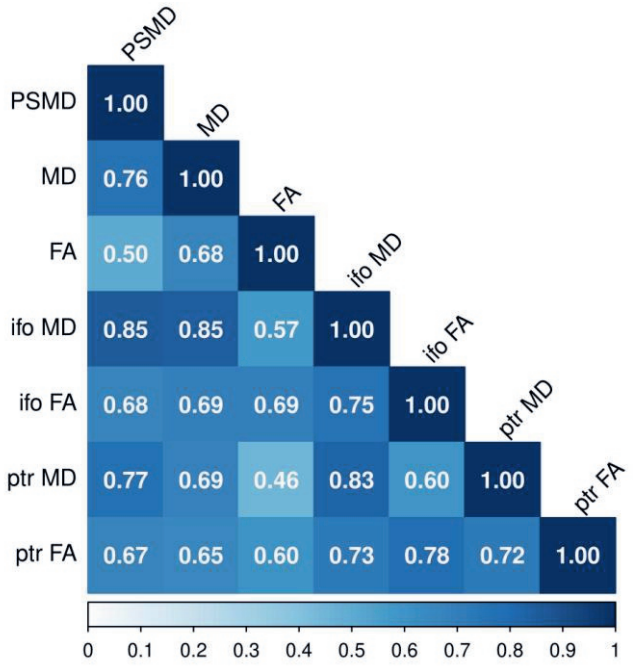
HR=Hazard ratio, CI=confidence interval, AIC=Akaike Information Criterion, PSMD=Peak-width skeletonized mean diffusivity, MD=mean diffusivity, FA=Fractional anisotropy, ifo=inferior fronto-occipital fasciculus, ptr=posterior thalamic radiation; lower AIC reflects better model performance.

Supplemental Table 3 Characteristics of the population included in cognition analyses

Characteristic	Participants included in cross-sectional cognition analysis (N=4342)	Participants excluded from cross-sectional cognition analysis due to incomplete data on all cognitive tests (N=853)
Age, y	64.1 (10.7)	69.3 (11.1)
Sex, female	2436 (56.1%)	465 (54.5%)
Education		
Primary only	335 (7.7%)	101 (11.8%)
Lower vocational	1659 (38.2%)	324 (38.0%)
Intermediate vocational/higher general	1330 (30.6%)	266 (31.2%)
Higher vocational/university	1018 (23.4%)	162 (19.0%)
Body mass index, kg/m^2	27.4 (4.1)	27.7 (4.2)
Systolic blood pressure, mm Hg	139.0 (21.2)	143.7 (22.5)
Diastolic blood pressure, mm Hg	82.8 (10.9)	83.3 (11.8)
Blood pressure lowering medication	1473 (33.9%)	402 (47.1%)
Smoking		
Never	1337 (30.8%)	270 (31.7%)
Former	2126 (49.0%)	408 (47.8%)
Current	879 (20.2%)	175 (20.5%)
Alcohol intake[a], g/d	6.43 (0.54-10.00)	6.43 (0.54-8.57)
Total cholesterol, mmol/L	5.54 (1.06)	5.44 (1.07)
HDL cholesterol, mmol/L	1.45 (0.42)	1.45 (0.42)
Lipid lowering medication	1059 (24.4%)	257 (30.1%)
Diabetes mellitus	519 (12.0%)	148 (17.4%)
APOE genotype		
ε3/ε3	2426 (55.9%)	492 (57.7%)
ε2/ε2 or ε2/ε3	707 (16.3%)	143 (16.8%)
ε4-carrier (heterozygous)	1067 (24.6%)	188 (22.0%)
ε4-carrier (homozygous)	142 (3.3%)	30 (3.5%)
Cerebral microbleeds (any)	844 (19.4%)	213 (25.0%)
Lacunes (any)	326 (7.5%)	90 (10.6%)

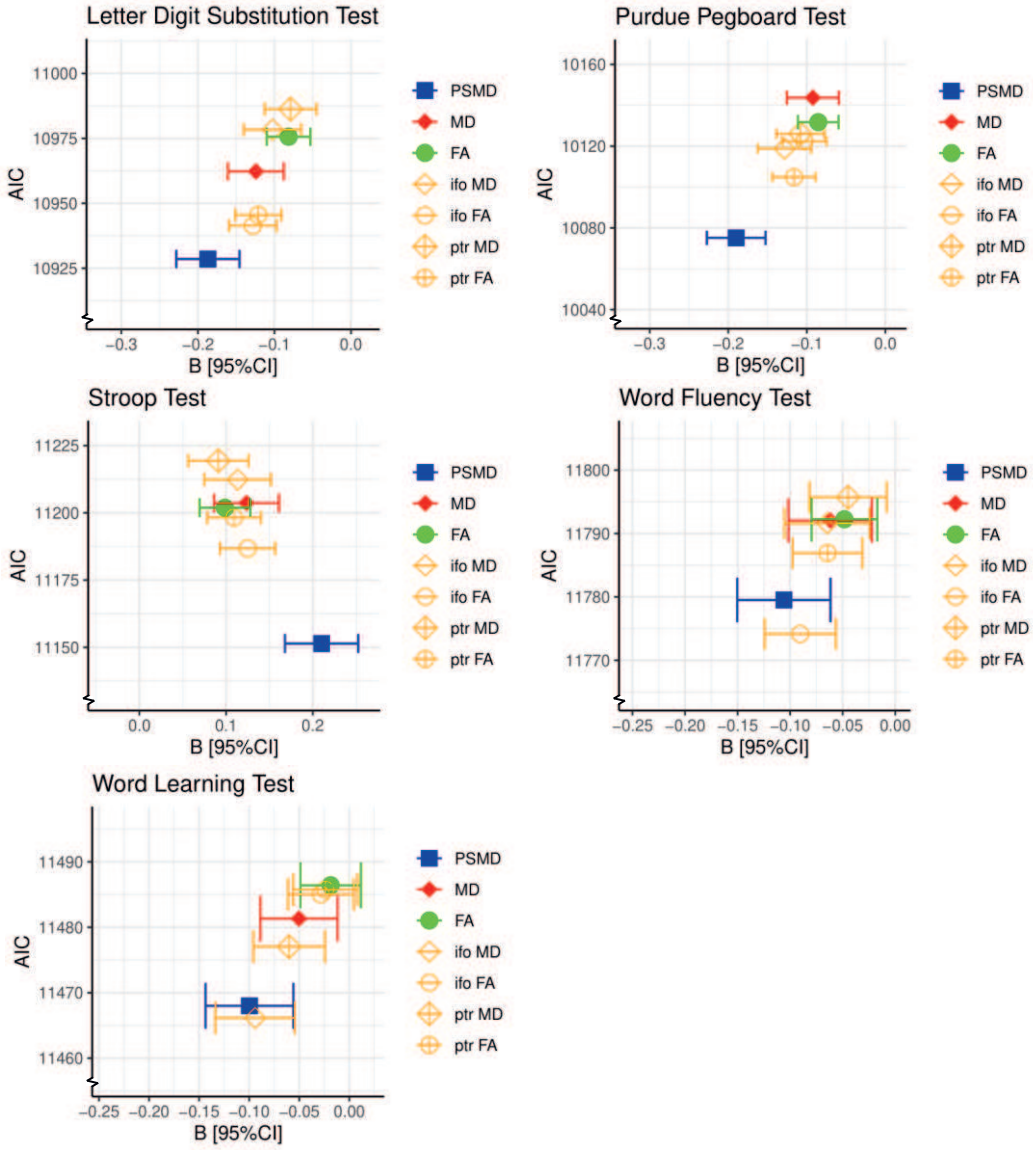
Abbreviations: HDL = high-density lipoprotein; ICV = intracranial volume. Continuous variables are presented as mean (SD) and categorical variables as n (%). [a] Variable with skewed distribution. Median (interquartile range) is shown instead of mean (SD).

Supplemental Figure 1: Correlation plot of diffusion imaging markers



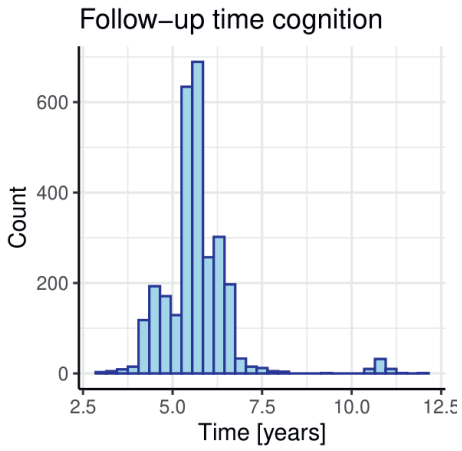
PSMD=Peak-width skeletonized mean diffusivity, MD=mean diffusivity, FA=Fractional anisotropy, ifo=inferior fronto-occipital fasciculus, ptr=posterior thalamic radiation.

Supplemental Figure 2: Cross-sectional cognition and diffusion imaging markers for each cognitive test separately

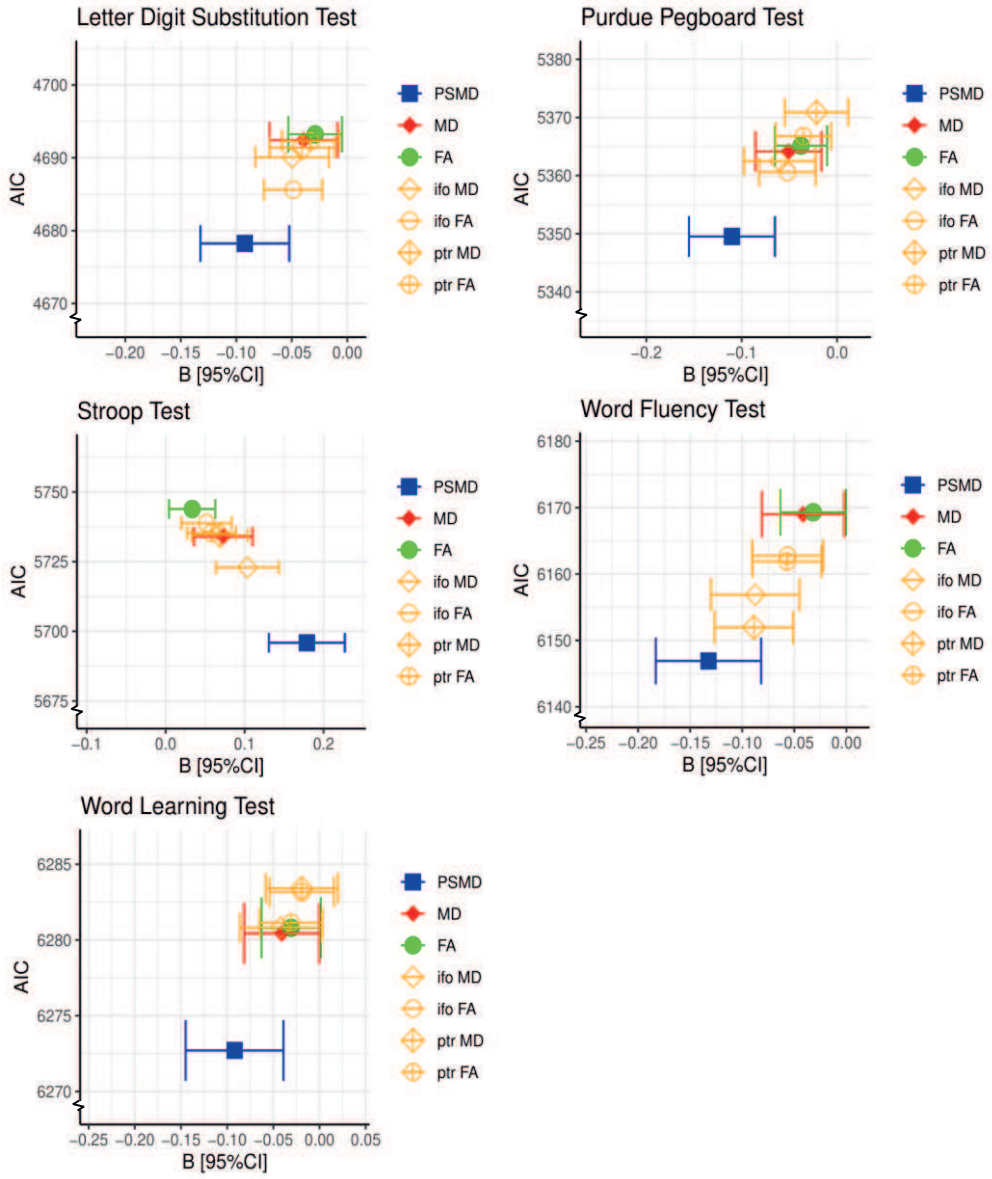


B=Bèta (regression coefficient), CI=confidence interval, AIC=Akaike Information Criterion, PSMD=Peak-width skeletonized mean diffusivity, MD=mean diffusivity, FA=Fractional anisotropy, ifo=inferior fronto-occipital fasciculus, ptr=posterior thalamic radiation; lower AIC reflects better model performance.

Supplemental Figure 3: Histogram of follow-up time between MRI and cognitive performance measured at next follow-up visit.



Supplemental Figure 4: Longitudinal cognition and diffusion imaging markers for each cognitive test separately

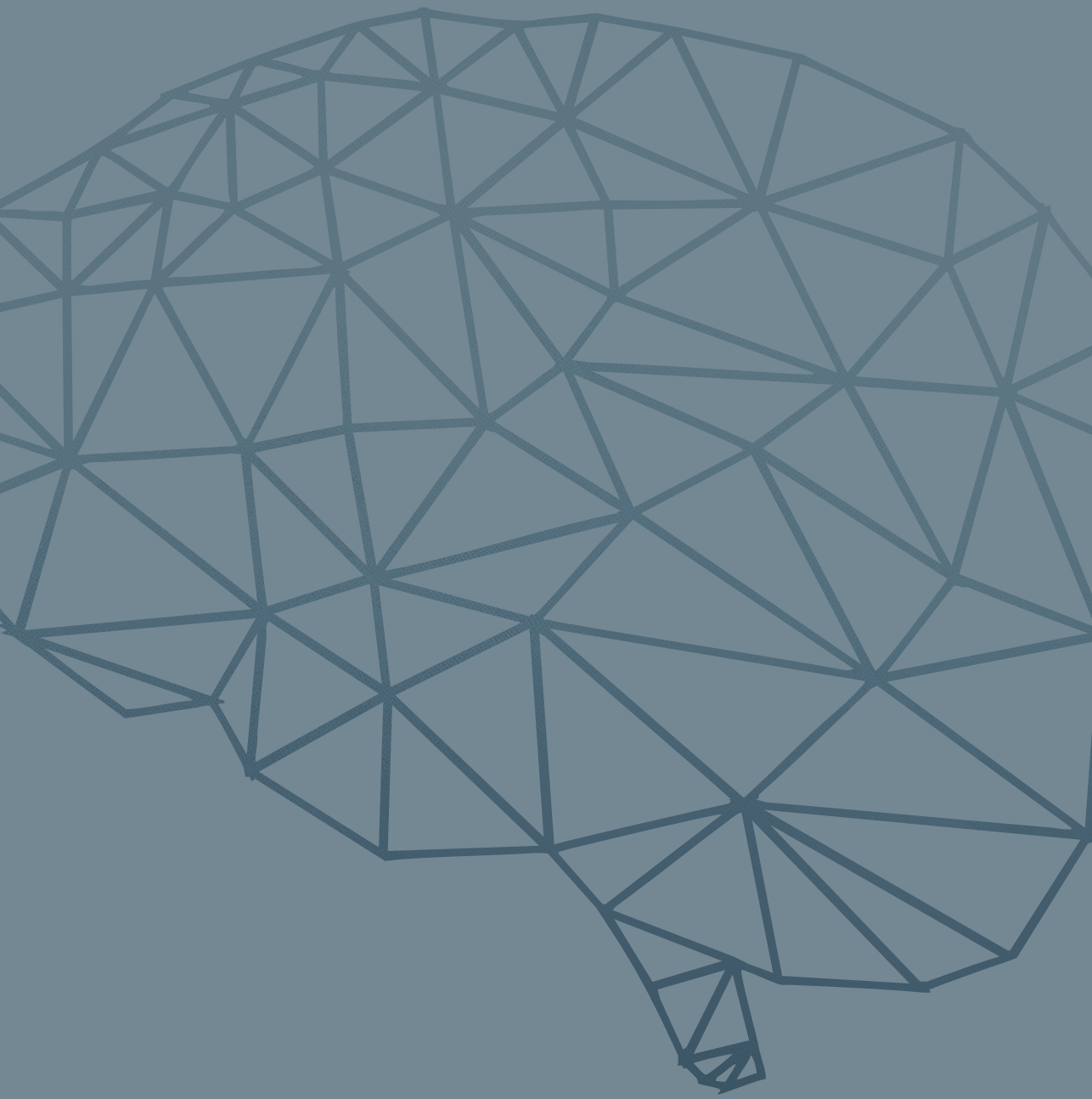


B=Bèta (regression coefficient), CI=confidence interval, AIC=Akaike Information Criterion, PSMD=Peak-width skeletonized mean diffusivity, MD=mean diffusivity, FA=Fractional anisotropy, ifo=inferior fronto-occipital fasciculus, ptr=posterior thalamic radiation; lower AIC reflects better model performance.

CHAPTER 3

GREY MATTER INDICATORS OF DEMENTIA RISK





CHAPTER 3.1

SUBCORTICAL GREY MATTER AND DEMENTIA RISK

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Subcortical grey matter volumes and 5-year dementia risk in individuals with subjective cognitive complaints or mild cognitive impairment: a multi-cohort analysis.

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ABSTRACT

Introduction: The prognostic value of subcortical grey matter structures for dementia beyond the hippocampus remains unclear.

Methods: We included participants with subjective cognitive decline or mild cognitive impairment from two memory clinic-based cohorts (Amsterdam Dementia Cohort and National Alzheimer's Coordinating Center) and one population-based cohort (Rotterdam Study). We assessed volumes of subcortical structures on MRI, and determined 5-year dementia risk using Cox models.

Results: Of 7076 participants (mean age: 66-69 years, 58.8-61.0% women; N_{SCC}=5425, N_{MCI}=1661), 622 developed dementia within 5 years. Smaller volumes of the hippocampus and amygdala were consistently associated with increased dementia risk, independent of other subcortical structures. Smaller hippocampal volume was predominantly associated with clinical diagnosis of Alzheimer's disease, but prognostic value did not differ by amyloid status.

Discussion: Hippocampal and amygdalar volume are consistently associated with dementia risk in individuals with subjective cognitive decline or mild cognitive impairment, which may hold potential for personalized prognosis.

INTRODUCTION

Dementia is one of the leading causes of disability and dependency worldwide, with 55 million people living with dementia globally.[1] Diagnosis primarily relies on clinical symptoms, but is often supported by neuroimaging to differentiate from non-degenerative causes of cognitive impairment and characterize disease etiology. For example, atrophy of the medial temporal lobe and the hippocampus are commonly observed with Alzheimer's disease (AD),[2] and widely acknowledged as an important marker of Alzheimer's pathology in clinical diagnosis. Applied to prognosis for people with subjective cognitive decline[3] or mild cognitive impairment, such markers could tailor follow-up strategies and care planning, as well as inclusion in trials of disease-modifying therapy. Yet, the significance of imaging measures for determining prognosis is uncertain, depending on reliable assessment methods and sufficient discriminatory value that is unlikely achieved by any single imaging marker on its own.[4] The increasing application of volumetric brain assessment in clinical practice offers new possibilities for improving prognostic information to patients. In particular, volumetric assessment allows for the assessment of subcortical grey matter structures that cannot be measured through visual ratings scales, taking risk assessment beyond the hippocampus alone.

Prior neuroimaging studies have suggested that various subcortical brain structures play a key role in dementia pathophysiology.[5] These grey matter structures, which are not part of the neocortex, include the nucleus accumbens, amygdala, caudate nucleus, hippocampus, globus pallidum, putamen and thalamus. They are highly connected to each other and cortical grey matter, and involved in a wide range of functions, including cognition, emotion, autonomic control, and language[6], all of which are often affected in individuals with dementia. Despite their functional relevance, few longitudinal studies have assessed the prognostic value of subcortical brain structure volumes in dementia risk beyond the hippocampus. Evidence from these studies is inconsistent,[7-10] which could be attributable to differences in studied populations, disease stage, follow-up, and brain imaging. Moreover, the role of subcortical brain structures may differ between AD and other causes of dementia, depending on the underlying dementia etiology.[11-13] Therefore, larger studies covering a wide range of the neurodegenerative disease spectrum are needed to determine the role of early neurodegenerative changes within subcortical grey matter structures in risk assessment for different causes of dementia.

In this study, we aimed to determine the prognostic value of several subcortical grey matter volumes for progression to dementia in individuals with subjective cognitive decline (SCD) or mild cognitive impairment (MCI). Specifically, we assessed volumes of the nucleus accumbens, amygdala, caudate nucleus, hippocampus, globus pallidum, putamen and thalamus in two clinic-based cohorts and one population-based cohort from the United States and Europe.

METHODS

Study population

We included participants with SCD and MCI from two memory clinic-based cohorts (Amsterdam Dementia Cohort and the Alzheimer's Disease Research Centers of NACC: National Alzheimer's Coordinating Center, funded by NIA/NIH Grant U24 AG072122) and one population-based cohort (the Rotterdam Study). Details of the design and characteristics of participating studies have been described previously[14-16], and are summarised below. All studies were approved by the relevant institutional review boards, and written informed consent was obtained from all participants.

Amsterdam Dementia Cohort – Since the year 2000, all patients attending the Alzheimer Center Amsterdam of Amsterdam UMC, in Amsterdam, are asked to participate in the Amsterdam Dementia Cohort and consent for their clinical data to be used for scientific purposes. Patients undergo a standardized one-day screening battery, including neuropsychological evaluation, brain magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) sampling.[15] Participants with SCD are invited for annual follow-up visits in the context of the SCIENCe project[17], while MCI patients are invited for clinical follow-up visits at which their clinic status is reassessed. The current study includes all participants with available MRI data and who were diagnosed with SCD or MCI between 2001 and 2022.

National Alzheimer's Coordinating Center (NACC) – NACC includes data from 41 past and current National Institute on Aging (NIA)-supported Alzheimer's Disease Centers across the United States. Data of these centers have been collected since 2005 into a large database of standardized clinical and neuropathological research data, including data on brain MRI if available. Follow-up data was collected annually during in-person visits and telephone calls. For the current study, we included all

participants who were labelled as normal cognition, SCD or MCI and underwent brain MRI between 2005 and 2022.

Rotterdam Study – The Rotterdam Study is an ongoing, population-based cohort study in the city of Rotterdam, the Netherlands. Residents aged ≥40 years living in the Ommoord district, were invited to participate across four recruitment waves from 1990 onwards. Participants were examined extensively at the study research center every 5 years, including routine cognitive assessment and brain MRI from 2005 onwards.[14, 18] For the present study, we included participants with SCD or MCI who underwent brain MRI between 2005 and 2015.

MRI acquisition and processing

MRI in the **Amsterdam Dementia Cohort** was performed on site using 1T and 1.5T scanners before 2008 (Magnetom Avanto, Impact, and Sonata, Siemens; Signa, GE Healthcare) and using 3T scanners from 2008 onwards (Magnetom Siemens; Discovery MR750, Signa General Electric Medical Systems; Ingenuity TF PET/MR, Philips Medical Systems; and Titan, Toshiba Medical Systems). All scans within this cohort were performed using a standardized imaging protocol.[15] MRI scans in **NACC** were performed with 1.5T and 3.0T scanners (General Electric Healthcare, Siemens and Philips). Different scan protocols were used among different research centers. MRI scans in the **Rotterdam Study** were performed on the same 1.5T scanner (Signa Excite II, General Electric Healthcare) throughout the study duration. The scan protocol and sequence details of the Rotterdam Study have been previously described elsewhere.[18]

To obtain volumetric measurements, T1-weighted MRI scans were processed using Freesurfer. MRI scans of **Amsterdam Dementia Cohort** were processed with Freesurfer 7.0, while MRI scans of **NACC** and the **Rotterdam Study** were processed using Freesurfer 6.0. For the current study, we used volumetric measurements of nucleus accumbens, amygdala, caudate nucleus, hippocampus, globus pallidum, putamen, thalamus, cortical grey matter, and intracranial volume.

Diagnostic assessment and follow-up for dementia

Within **Amsterdam Dementia Cohort**, diagnoses of dementia and MCI were made in a multidisciplinary consensus meeting.[15] Diagnosis of all-cause dementia was entirely based on clinical evaluation, while subtyping the specific etiologies, such as

AD, is supported by biomarker data, including hippocampal atrophy. All diagnoses fulfilled the core clinical criteria National Institute of Aging in the Alzheimer's Association (NIA-AA) criteria.[19, 20] Patients with MCI fulfilled the criteria defined by Petersen.[19, 21] When clinical investigations showed no impairment (i.e., criteria for MCI, dementia or any psychiatric disorder were not met), patients were considered to have a SCD diagnosis and were reassessed in person during annual follow-up visits. The diagnostic procedure within **NACC** varies between centers, from consensus panel diagnosis to a single physician's assessment, all adhering to standardized clinical criteria as outlined by the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) and National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA). Diagnosis of MCI was made predominantly via a consensus conference using modified Petersen criteria.[21] Diagnoses status were re-evaluated during annual data collection. In the **Rotterdam Study**, participants were screened for dementia at baseline and during follow-up examinations every 5 years using the Mini-Mental State Examination (MMSE) and the Geriatric Mental Schedule (GMS) organic level. All participants underwent a brief neuropsychological examination,[22] with additional CAMDEX and informant interview upon indication. A consensus panel, led by a consultant neurologist, decided on the final dementia diagnosis in all cases, in accordance with the DSM-III-R criteria for dementia and the NINDS-ADRDA criteria for clinical AD dementia. All participants were also continuously monitored for diagnosis of dementia through continuous linkage to electronic medical records. Classification of SCD and MCI was based on interview questions and cognitive assessment during research center visits. During interview, three questions regarding memory decline (difficulty remembering, forgetting what one had planned to do and difficulty finding words) were asked. One confirmative answer to any of these questions was considered a SCD. MCI was defined using criteria based on the criteria by Petersen et al.[23] and a detailed description of the MCI assessment in the Rotterdam Study has been published previously.[24]

Across cohorts, volumetric measures were not used for baseline diagnosis in this sample. Although diagnosis of dementia was entirely based on clinical evaluation, neuroradiologist assessment of global atrophy and medial temporal lobe atrophy were part of routine work-up to determine etiologic diagnoses, including AD, in the Amsterdam Dementia Cohort and NACC.

Assessment of educational attainment and amyloid status

In **Amsterdam Dementia Cohort**, data on educational attainment was obtained during baseline visit using the Verhage scale.[25] To enhance comparability of characteristics in Table 1, the 7 categories of the Verhage scale were transformed into four groups similar to the education categories of the Rotterdam Study. Educational attainment within **NACC** was measured at baseline visit as total years of education. Transforming this measurement into education categories was unfortunately not possible. Information regarding educational attainment in the **Rotterdam Study** was obtained by trained interviewers during baseline home interviews, and categorized into four groups, ranging from primary to higher education (higher vocational education or university). In the **Amsterdam Dementia Cohort**, data on amyloid positivity in a subset of participants were obtained through CSF or amyloid-PET. Before 2018, sandwich enzyme-linked immuno sorbent assays (ELISA) were used (Innotest, Fujirebio, Gent, Belgium). From 2018 onward, CSF was analysed using Elecsys (Roche, Rotkreuz, Swiss). Amyloid PET imaging was performed using 3-Tesla Ingenuity TF PET/MRI, Ingenuity TF PET/CT and Gemini TF PET/CT scanners (Philips healthcare, the Netherlands) with the 11C-Pittsburg Compound B (PiB), 18F-flutemetamol and 18F-Florbetaben compounds.[26-28] Participant were labelled as amyloid positive when either their CSF or amyloid-PET was positive.

Data analysis

We imputed missing data on covariables separately for each cohort. In the Amsterdam Dementia Cohort and the Rotterdam Study, data for educational attainment was missing for 0.1% and 0.9%, respectively. Within NACC, some data was missing for MRI scanner and field strength (<13.9%). For imputation, we used the mice package in R (version 4.3.3 and version 4.4.2.) to perform 5-fold multiple imputation with the number of iterations set to default (n=5). To assess the quality of the imputation, we examined the density plots, which showed that the distributions of variables were similar in the imputed and non-imputed datasets. We standardized subcortical volumes to facilitate comparison across structures and provide hazard ratios (HR) per standard deviation (SD) increase of the volume of each subcortical structure. For bilateral structures, we used the mean of both values for analyses. Follow-up time was measured in years from the date of MRI until dementia diagnosis, death, loss-to-follow-up, or censoring at 5 years of follow-up, whichever came first. Information on death was only used for data from the Rotterdam Study; for the

Amsterdam Dementia Cohort and NACC, censoring occurred at time of the last clinical assessment.

Primary analysis consisted of Cox proportional hazard models to obtain HRs and 95% CI for the association between subcortical volumes and risk of dementia in each cohort. For all Cox models, we tested the proportional hazard assumption. In secondary analyses, we stratified i) between AD and other causes of dementia as an outcome, ii) by baseline amyloid positivity in the subsample of the Amsterdam Dementia Cohort with CSF or amyloid-PET, and iii) by baseline diagnosis of SCD versus MCI.

Following the primary analysis, we performed a post-hoc analysis in which we compared the C-statistic between different models: a basic model including age, sex, and education; the basic model including hippocampal volume as additional predictor; and the basic model including hippocampal volume and amygdalar volume as additional predictors. We performed this analysis to determine the improvement in prognostic value when using hippocampal volume and both hippocampal and amygdalar volume. Models including volumetric measurements were additionally adjusted for different MRI scanner, field strengths, and intracranial volume.

We further did sensitivity analyses, i) stratifying by sex, while testing for multiplicative interactions between volume of each subcortical structure and sex, ii) repeating primary analysis on a subsample from NACC consisting of participants who visited the research center for clinical evaluation, excluding those who volunteered solely research participation, iii) repeating primary analysis on subsamples from NACC and the Amsterdam Dementia Cohort consisting of participants who underwent brain MRI with a field strength of 3.0T, and vi) repeating primary analysis with adjusting for different MRI scanners and field strengths by applying neuroCombat harmonization on the extracted volumes instead of adjustment through covariates. The second sensitivity analysis was performed to select within the NACC population on a clinical sample, similar to the Amsterdam Dementia Cohort. All of these sensitivity analyses included participants classified as SCD as well as participants classified as MCI.

For all analyses, we constructed three different models: adjusting for intracranial volume, MRI field strength and MRI scanner (model 1), adjusting for intracranial volume, MRI field strength, MRI scanner age, sex and education (model 2), and additionally adjusting for volumes of other subcortical structures and global cortical grey matter volume (model 3) to investigate if there is an independent effect. In the

Rotterdam Study, we did not adjust for MRI field strength and MRI scanner, as all participants within this cohort were scanned with the same field strength and MRI scanner. We did not meta-analyze risk estimates across studies, because we anticipated heterogeneity and intended to demonstrate associations in both clinic-based and community-based setting.

All analyses were performed in R (version 4.3.3 and version 4.4.2.; packages: haven, dplyr, mice, tableone, survival, neuroCombat). Alpha was set at 0.0

RESULTS

We included a total of 7076 participants with SCD or MCI of whom 1964 participants originated from the Amsterdam Dementia Cohort, 2207 participants from NACC, and 2905 from the Rotterdam Study. Baseline characteristics for each cohort are presented in Table 1.

Mean age at time of the MRI scan ranged from 61.9 to 68.9 years, and in each cohort around 60% of participants were women. In the clinic-based Amsterdam Dementia Cohort and NACC, around one third of participants had MCI, compared to 8% in the population-based Rotterdam Study.

During the maximum follow-up time of 5 years, dementia was diagnosed in 701 (9.9%) individuals. Progression to dementia occurred in 249 (12.7% of cohort; N_{SCD}=31 [2.5% of SCD in cohort]; N_{MCI}=218 [30.7% of MCI in cohort]) individuals in ADC, 292 (13.2% of cohort; N_{SCD}=26 [1.8% of SCD in cohort]; N_{MCI}=266 [36.8% of MCI in cohort]) in NACC, and 81 (2.8% of cohort; N_{SCD}=62 [2.3% of SCD in cohort]; N_{MCI}=19 [8.3% of MCI in cohort]) in the Rotterdam Study. Dementia incidence per time point is shown in Table A1.

Table 1. Demographic and imaging characteristics for the Amsterdam Dementia Cohort, National Alzheimer's Coordinating Center cohort, and the Rotterdam Study

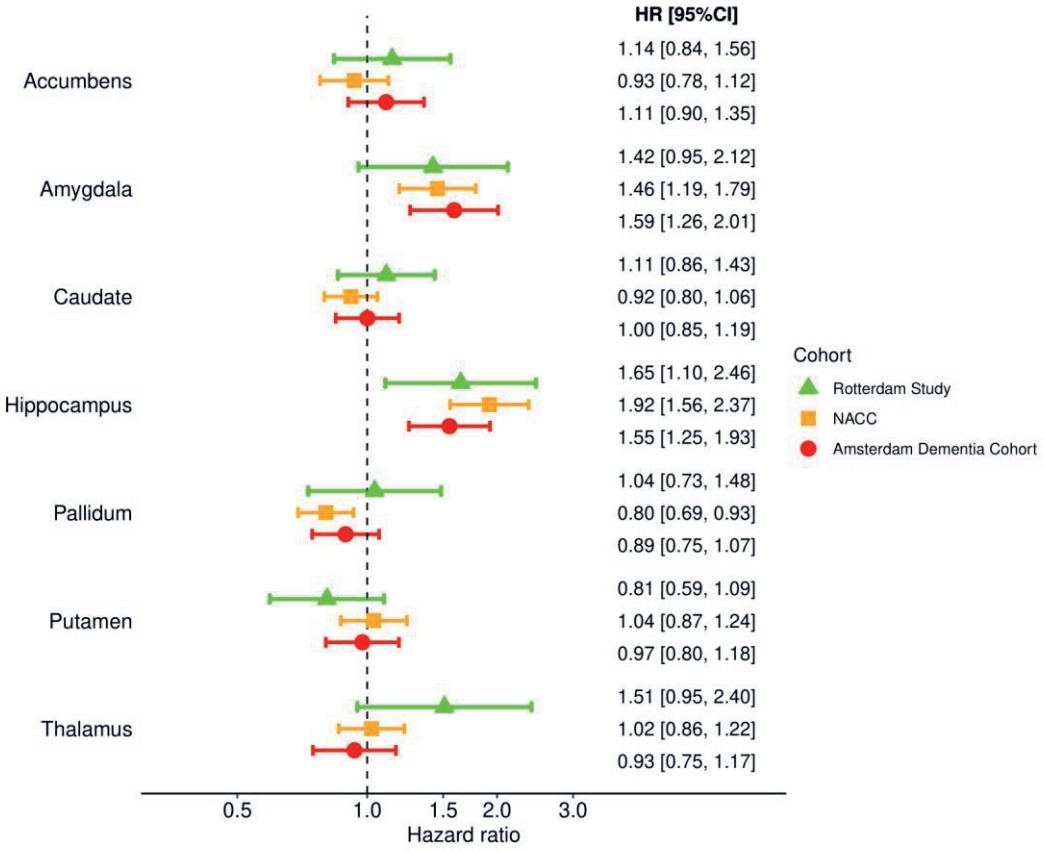
	Amsterdam Dementia Cohort (N=1964)	**NACC (N=2207)**	**Rotterdam Study (N=2905)**
Age, years	61.9 [9.1]	68.9 [11.0]	66.1 [11.0]
Sex, female	1170 [59.6%]	1347 [61.0%]	1708 [58.8%]
Education duration, years	n.a.	15.8 [6.0]	n.a.
Education			
Primary only	20 [1.0%]	n.a.	283 [9.7%]
Lower vocational	154 [7.8%]	n.a.	1147 [39.5%]
Intermediate vocational / higher general	830 [42.3%]	n.a.	877 [30.2%]
Higher vocational/ university	958 [48.8%]	n.a.	598 [20.6%]
Subjective cognitive decline	1254 [63.8%]	1485 [67.4%]	2686 [92.1%]
Mild cognitive impairment	710 [36.2%]	722 [32.6%]	229 [7.9%]
MRI field strength			
0.95 Tesla	340 [17.3%]	0	0
1.5 Tesla	212 [10.8%]	774 [35.1%]	2,905 [100.0%]
3.0 Tesla	1,412 [71.9%]	1,428 [64.7%]	0
Unspecified	0	5 [0.2%]	0
Brain structure volumes			
Accumbens volume, ml	0.47 [0.11]	0.44 [0.11]	0.49 [0.09]
Amygdala volume, ml	1.54 [0.27]	1.46 [0.26]	1.42 [0.20]
Caudate volume, ml	3.40 [0.54]	3.29 [0.52]	3.31 [0.51]
Hippocampus volume, ml	3.85 [0.52]	3.65 [0.50]	3.84 [0.42]
Pallidum volume, ml	1.88 [0.25]	1.77 [0.25]	1.57 [0.22]
Putamen volume, ml	4.48 [0.62]	4.19 [0.62]	4.13 [0.56]
Thalamus volume, ml	6.79 [0.85]	6.42 [0.77]	6.48 [0.71]
Cortical grey matter volume, ml	543.20 [63.0]	528.77 [58.09]	536.30 [50.25]
Amyloid status			
Negative	827 [68.1%]	-	-
Positive	387 [31.9%]	-	-

Continuous variables are presented as means [standard deviations] and categorical variables as number (percentages). Abbreviations: NACC=National Alzheimer's Coordinating Center, ml=milliliter

Subcortical structures and risk of dementia

Results from the crude models and models adjusted for age, sex and education are shown in Table 2. Consistently across cohorts, smaller hippocampal volume was significantly associated with an increased dementia risk (HR [95%CI] in the Rotterdam Study: 1.65 [1.10-2.46]; in NACC: 1.92 [1.56-2.37]; and in ADC: 1.55 [1.25-1.93]) in fully adjusted models (Figure 1, Table 2). Similarly, smaller amygdalar volume was associated with increased dementia risk in both clinic-based cohorts (HR [95%CI] in NACC: 1.46 [1.19-1.79]; and in ADC: 1.59 [1.26-2.01]), with similar effect estimates in the population-based cohort (HR [95%CI]: 1.42 [0.95-2.12]). Smaller volume of the pallidum, was significantly associated with decreased dementia risk in NACC, but not in either of the other cohorts (Table 2). Smaller volume of the thalamus was not associated with dementia risk in the clinic-based cohorts, while a moderate, not statistically significant increase was observed in the Rotterdam Study (HR [95%CI]: 1.51 [0.95-2.40]). None of the other structures showed an association with dementia risk in any of the studies. In a post-hoc analysis, hippocampal volume improved the C-statistic substantially across cohorts, compared to the basic models (Table A2). In both memory clinic cohorts, adding amygdalar volume on top of hippocampal volume improved again the C-statistic, compared to the model with hippocampal volume alone.

Figure 1. Subcortical structures and the risk of dementia.



Hazard ratio per standard deviation decrease of subcortical structure volume, adjusted for age, sex, education, MRI field strength, MRI scanner, intracranial volume, cortical grey matter and volumes of all other subcortical structures. Error bars depict 95% confidence intervals.

Table 2. Subcortical structures and risk of dementia.

	Cohort	Model 1 HR [95%CI]	Model 2 HR [95%CI]	Model 3 HR [95%CI]
Accumbens	Rotterdam Study	2.57 [1.99-3.32]	1.42 [1.07-1.89]	1.14 [0.84-1.56]
	NACC	2.01 [1.75-2.31]	1.60 [1.37-1.87]	0.93 [0.78-1.12]
	ADC	1.89 [1.61-2.21]	1.59 [1.36-1.87]	1.11 [0.90-1.35]
Amygdala	Rotterdam Study	3.95 [3.07-5.08]	2.27 [1.69-3.05]	1.42 [0.95-2.12]
	NACC	2.70 [2.39-3.04]	2.49 [2.18-2.84]	1.46 [1.19-1.79]
	ADC	2.45 [2.11-2.83]	2.35 [2.01-2.74]	1.59 [1.26-2.01]
Caudate	Rotterdam Study	0.74 [0.59-0.91]	1.07 [0.85-1.33]	1.11 [0.86-1.43]
	NACC	1.09 [0.95-1.25]	1.10 [0.97-1.25]	0.92 [0.80-1.06]
	ADC	1.20 [1.02-1.41]	1.12 [0.97-1.29]	1.00 [0.85-1.19]
Hippocampus	Rotterdam Study	4.03 [3.20-5.07]	2.37 [1.76-3.18]	1.65 [1.10-2.46]
	NACC	2.96 [2.61-3.35]	2.71 [2.36-3.12]	1.92 [1.56-2.37]
	ADC	2.31 [2.01-2.65]	2.15 [1.87-2.48]	1.55 [1.25-1.93]
Pallidum	Rotterdam Study	2.22 [1.68-2.94]	1.27 [0.95-1.69]	1.04 [0.73-1.48]
	NACC	1.22 [1.05-1.38]	0.99 [0.87-1.14]	0.80 [0.69-0.93]
	ADC	1.19 [1.03-1.39]	1.10 [0.95-1.26]	0.89 [0.75-1.07]
Putamen	Rotterdam Study	2.02 [1.55-2.63]	1.13 [0.88-1.45]	0.81 [0.59-1.09]
	NACC	1.61 [1.41-1.83]	1.31 [1.14-1.51]	1.04 [0.87-1.24]
	ADC	1.46 [1.25-1.70]	1.27 [1.10-1.48]	0.97 [0.80-1.18]
Thalamus	Rotterdam Study	4.47 [3.19-6.27]	2.05 [1.37-3.06]	1.51 [0.95-2.40]
	NACC	2.09 [1.79-2.44]	1.62 [1.36-1.92]	1.02 [0.86-1.22]
	ADC	1.75 [1.48-2.08]	1.50 [1.26-1.79]	0.93 [0.75-1.17]

Model 1: adjusted for MRI scanner (settings) and intracranial volume
Model 2: adjusted for MRI scanner (settings), intracranial volume, age, sex and education
Model 3: adjusted for MRI scanner (settings), intracranial volume, age, sex, education, other subcortical structure volumes and cortical grey matter volume.
Abbreviations: ADC=Amsterdam Dementia Cohort, NACC=National Alzheimer's Coordinating Center, HR=hazard ratio, CI=confidence interval

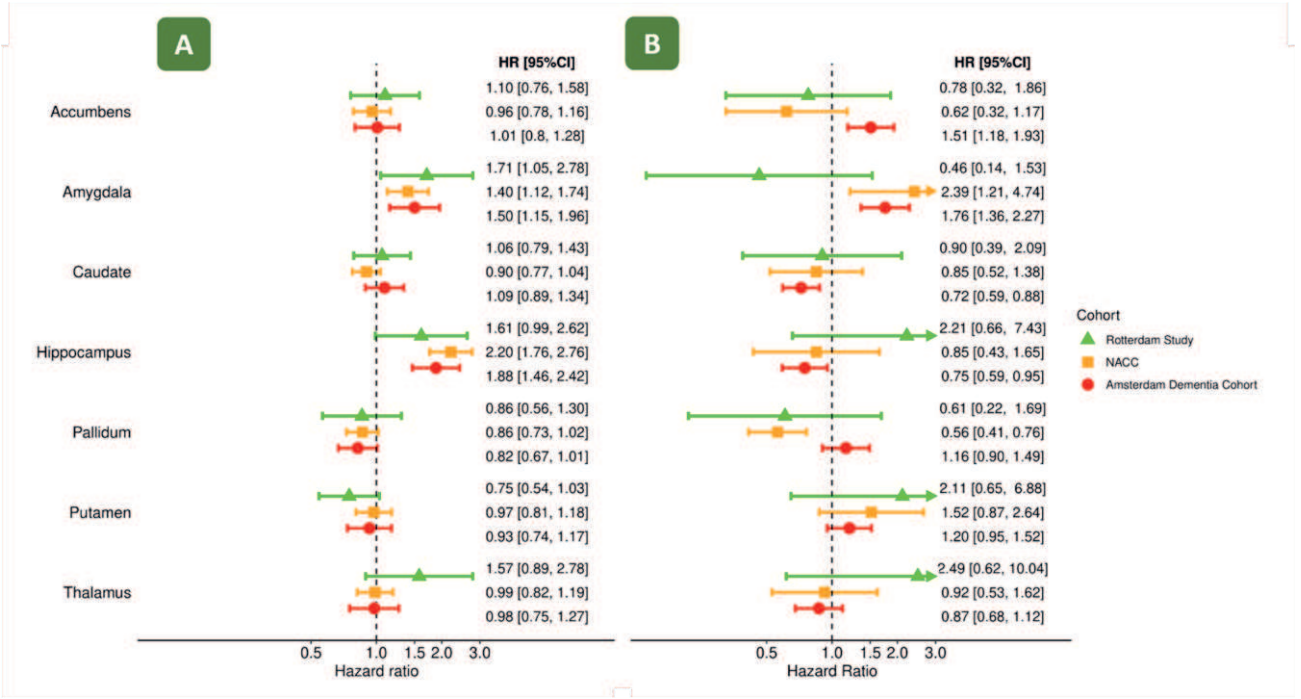
Alzheimer's disease versus other types of dementia

Of all dementia cases, most were diagnosed as AD (76.7% of the dementia cases in the Amsterdam Dementia Cohort, 60.6% in NACC and, 70.3% in the Rotterdam Study). Amyloid-β42 information was available in the Amsterdam Dementia cohort from CSF in 1246 (63.4%) participants and from amyloid PET imaging in 360 (18.3%) participants. Taken together, information on either measurement was available for 1214/1964 individuals of whom 387 (31.9%) were amyloid-positive.

In the population-based cohort, risk estimates for the hippocampus were similar for AD and non-AD dementia (Figure 2). In both clinic-based cohorts, a smaller hippocampus was associated with increased risk of dementia due to AD (HR [95%CI] in NACC: 2.20 [1.76-2.76]; and in ADC: 1.88 [1.46-2.42]) but not with dementia due to other causes (HR [95%CI] in NACC: 0.85 [0.43-1.65]; and in ADC: 0.75 [0.59-0.95]) (Figure 2). However, risk estimates for hippocampal volume did not differ between amyloid-positive and amyloid-negative patients in ADC (Table A3).

Lower volume of the amygdala in the clinic-based cohorts was associated with risk of dementia due to clinical AD (HR [95%CI] in NACC: 1.40 [1.12-1.74]; and in ADC 1.50: [1.15-1.96]) as well as other dementia types (HR [95%CI] in NACC: 2.39 [1.21-4.74]; and in ADC 1.76 [1.36-2.27]). Similar patterns were seen when stratifying by amyloid positivity (Table A3). In contrast, in the population-based cohort, amygdalar volume was associated with risk of dementia due to AD (HR [95%CI]: 1.71 [1.05-2.78]), but not other causes of dementia (HR [95%CI]: 0.46 [0.14-1.53]).

Figure 2. Subcortical structures and risk of dementia due to A) Alzheimer's disease and B) other causes of dementia.



Hazard ratio per standard deviation decrease of subcortical structure volume, adjusted for age, sex, education, MRI field strength, MRI scanner, intracranial volume, cortical grey matter and volume of all other subcortical structure. Error bars depict 95% confidence intervals. Abbreviations: HR=hazard ratio, NACC=National Alzheimer's Coordinating Center, MRI=magnetic resonance imaging.

Disease stage

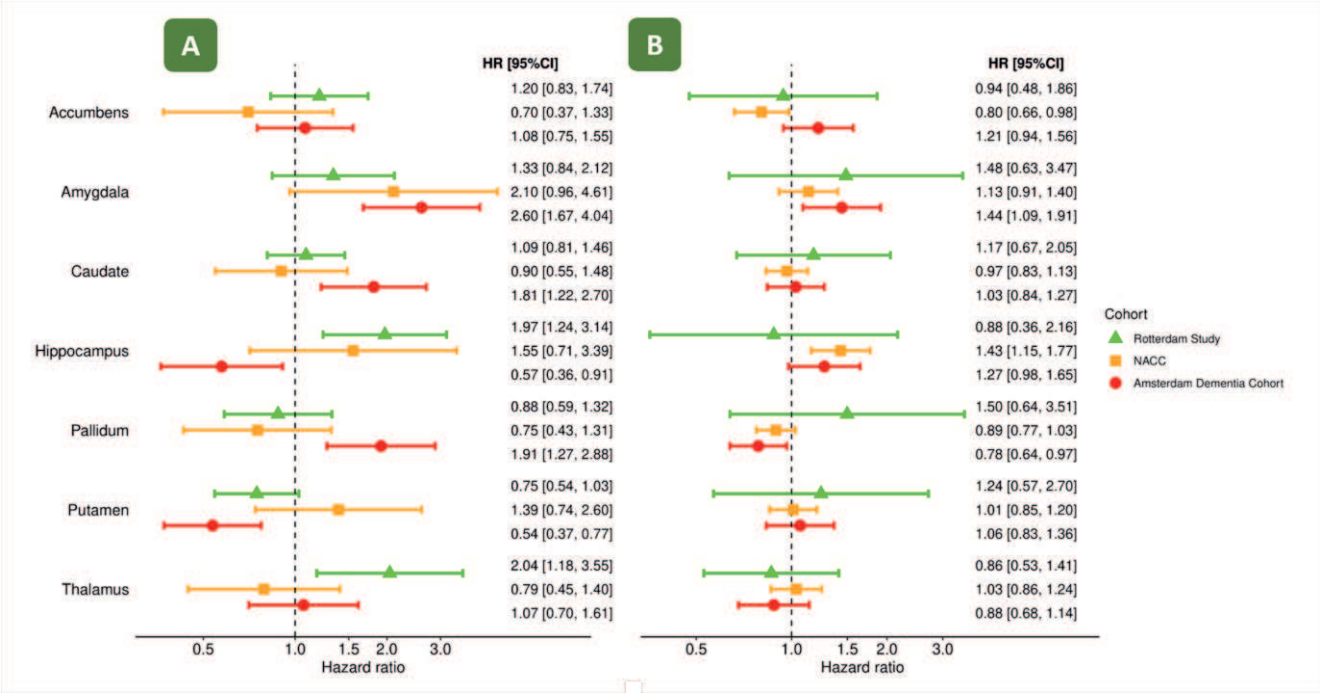
When stratifying by SCD and MCI, no consistent major differences were observed (Figure 3). In both clinic-based cohorts, we observed slightly higher risk estimates for the amygdala in individuals with SCD than with MCI, but this was not seen in the population-based cohort (Figure 3). For the hippocampus, risk estimates appeared higher with SCD than with MCI in the population-based cohort, but confidence intervals around the MCI estimate were wide and no differences were observed in both clinic-based cohorts (Figure 3). For the putamen, risk estimates suggested a slightly decreased dementia risk with lower volumes among individuals with SCD rather than MCI in the Amsterdam Dementia Cohort and Rotterdam Study, but this was not observed in NACC (Figure 3).

Sensitivity analyses

Results from the sensitivity analysis showed no major differences in risk estimates when restricting analyses in NACC to participants who visited the research center solely for clinical evaluation (Table A4).

There were no consistent differences in associations between men and women. Interaction between sex and subcortical structures was statistically significant only for the hippocampus (P=0.01) and thalamus (P=0.02) in the Amsterdam Dementia Cohort, but interaction went in the opposite direction in the other two cohorts (Table A5). Risk estimates did not change between adjustment for different MRI scanners and field strength through either neuroCombat harmonization of the volumes or through adding them as covariates in the Cox model (Table A6).

Figure 3 Subcortical structures and risk of dementia, stratified by clinical diagnosis of (A) subjective cognitive decline and (B) mild cognitive impairment .



Hazard ratio per standard deviation decrease of subcortical structure volume, adjusted for age, sex, education, MRI field strength, MRI scanner, intracranial volume, cortical grey matter and volume of all other subcortical structure. Error bars depict 95% confidence intervals. Abbreviations: HR=hazard ratio, NACC=National Alzheimer's Coordinating Center, MRI=magnetic resonance imaging.

DISCUSSION

In this study of 7076 participants with subjective cognitive decline and mild cognitive impairment from three large cohorts, we found that hippocampal and amygdalar volumes are consistently associated with 5-year risk of dementia, independent of other subcortical structures and cortical grey matter volume. No consistent associations were observed with other subcortical grey matter structures.

Our analysis across cohorts robustly shows that volumes of the amygdala as well as the hippocampus are related to progression from SCD and MCI to dementia. While the hippocampus is widely acknowledged as marker for risk of dementia[29-32], the role of the amygdala in progression to all-cause dementia was less established. A prior analysis among 511 participants of the Rotterdam Study showed that manual segmentations of the amygdala were associated with all-cause dementia risk, while another clinic-based study suggested smaller amygdala volume increases the short-term,[33] 1-year risk of progression to AD dementia.[34] These results align with a more recent multi-cohort analysis, which demonstrated a significant association between amygdalar or hippocampal volume and the risk of AD dementia.[32] Our study supports the notion that prognostic value of hippocampal and amygdalar volume extend to 5 years of follow-up. Hippocampal volume appeared more strongly associated with AD dementia than with non-AD dementia, but this was driven by the clinic-based cohorts, in which use of hippocampal volume or visual rating scales for diagnosing AD caused some circularity and may have influenced the outcome assessment for the hippocampus. Notably, when stratifying by amyloid status, no clear differences in risk of dementia were observed between amyloid-positive and amyloid-negative individuals for hippocampal volume.

None of the other subcortical grey matter structures showed a clear association with risk of dementia across cohorts. On the basis of prior studies, we had hypothesized a more profound role of the thalamus, which has an important relay function between other subcortical structures. Among cognitively healthy individuals from the Rotterdam Study sample, thalamic volume was strongly associated with dementia risk.[7] Lower volumes of the thalamus are observed during the early stage of MCI,[10, 35] and seem to remain stable from late MCI to AD dementia.[35] This may explain why we did not observe significant associations between thalamic volume and dementia risk in our current study of mostly later stage MCI [36]. Remarkably, the observed associations in the current study were thus confined to structures part of

the limbic system.[37] This may reflect involvement of the limbic system in AD, but perhaps more likely reflects contributions of Limbic-predominant Age-related TDP-43 Encephalopathy (LATE) to dementia risk. Misclassification of LATE as AD happens frequently in daily clinical practice, due to the similarity in symptoms and the absence of LATE-specific diagnostic markers in vivo.[38] Further research is needed to link our clinical observations to underlying pathologies, measured post-mortem or – ideally – in vivo capitalizing on development of liquid or imaging biomarkers. Advances in imaging resolution and processing may in this regard lead to more fine-grained observations of the hippocampus and amygdala, as well as other smaller structures that may currently not be captured in sufficient detail.

Our findings support further consideration of the amygdalar volumes for clinical decision-making, in addition to assessment of the hippocampus. Volumetric segmentations increasingly allow for incorporation of the amygdala in diagnostic and prognostic tools. As visual rating scales for medial temporal lobe atrophy may be more easily applied in clinics than volumetric assessment of the hippocampus, proper comparison of these two assessment methods is needed to determine possible added value of hippocampal volumetry. In any case, our findings imply that future research using volumetrics should go beyond the hippocampus alone, to evaluate the joint role of the amygdala and hippocampus for dementia prognosis and prediction. Moreover, such studies could explore whether repeated measurements of subcortical volumes over time could improve dementia predictive accuracy. Additionally, investigating the sequence of deterioration in various subcortical structures is important for understanding their prognostic value throughout the pre-clinical disease trajectory.

Our study is strengthened by the inclusion of three large cohorts, including both memory clinic-based and community-based individuals, with comprehensive information on brain imaging and cognitive status. It is also important to consider some methodological limitations when interpreting our findings. First, different versions of FreeSurfer (i.e., 6.0 and 7.0) were used for volumetric segmentation in the included cohorts, which may have led to heterogeneity between cohorts. However, intraindividual correlation between Freesurfer 6.0 and 7.0 segmentations of subcortical structures was high in a subsample of the Rotterdam Study (ICC ranging from 0.76 to 0.97). Second, variation in scanners, including in MRI field strength, may have induced measurement error as shown in previous research[39], despite adjustment in multivariable models. Yet, risk estimates were similar when restricting

analyses to the 3.0T scans in the clinic-based cohorts (Table A7). Third, the low number of dementia cases not attributed to AD and the relatively low number of individuals with MCI in the community-based sample, resulted in less precise estimates for these analyses. In addition, due to the non-collapsibility properties of hazard ratios[40], some findings in the stratified analyses are difficult to compare directly to the primary analysis. Fifth, misclassification bias might have been introduced due to the absence of amyloid biomarker data for definite diagnosis of AD in most participants. Sixth, differential attrition may have induced selection bias, most likely attenuating findings to the null if nonresponse was related to worse cognitive status. Finally, we did not have continuous follow-up data until death for dementia of participants in NACC and ADC, precluding computation of absolute risks using competing risk modelling.

In conclusion, hippocampal and amygdalar volume are consistently associated with dementia risk in individuals with subjective cognitive decline or mild cognitive impairment, which holds potential for personalized prognosis. Other subcortical grey matter structures showed no consistent associations with dementia risk.

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SUPPLEMENTARY MATERIAL

Table A1. Incidence of dementia for each year follow-up.

Time point	Amsterdam Dementia Cohort			NACC			Rotterdam Study		
	At risk	Cumulative cases	New cases	At risk	Cumulative cases	New cases	At risk	Cumulative cases	New cases
Baseline	1964	0	-	2207	0	-	2905	0	-
Year 1	1122	33	33	1709	57	57	2873	7	7
Year 2	857	104	71	1487	139	82	2811	19	12
Year 3	640	180	76	1240	215	76	2738	39	20
Year 4	478	226	46	996	265	50	2662	60	21
Year 5	355	249	23	821	292	27	2553	81	21

Numbers include time till last assessment, which may have underestimated the speed of progression in some participants who for example missed their 2-year examination before being diagnosed with dementia at the year-3 visit.

Table A2. Predictive power when adding hippocampal volume and amygdalar volume.

Model	C-statistic [95%CI] NACC	C-statistic [95%CI] ADC	C-statistic [95%CI] Rotterdam Study
Age + sex + education	0.703 [0.675-0.731]	0.635 [0.599-0.670]	0.847 [0.817-0.877]
Age + sex + education + hippocampus	0.790 [0.765-0.815]	0.745 [0.715-0.775]	0.870 [0.842-0.898]
Age + sex + education + hippocampus + amygdala	0.800 [0.776-0.824]	0.761 [0.731-0.790]	0.870 [0.840-0.901]

Abbreviations: ADC=Amsterdam Dementia Cohort, NACC=National Alzheimer's Coordinating Center, HR=hazard ratio, CI=confidence interval

Table A3. Subcortical structures and risk of dementia, stratified by amyloid positivity

Subcortical structure	Amyloid status	N (%)	HR [95%CI]	P interaction
Accumbens	Positive	387 (31.9)	1.24 [0.88-1.74]	0.29
	Negative	827 (68.1)	1.55 [0.89-2.69]	
Amygdala	Positive	387 (31.9)	1.56 [1.10-2.21]	0.12
	Negative	827 (68.1)	2.58 [1.42-4.71]	
Caudate	Positive	387 (31.9)	0.92 [0.72-1.17]	0.41
	Negative	827 (68.1)	0.96 [0.62-1.48]	
Hippocampus	Positive	387 (31.9)	1.26 [0.91-1.74]	0.32
	Negative	827 (68.1)	1.17 [0.64-2.13]	
Pallidum	Positive	387 (31.9)	0.74 [0.53-1.02]	0.78
	Negative	827 (68.1)	0.81 [0.49-1.36]	
Putamen	Positive	387 (31.9)	1.12 [0.81-1.55]	0.94
	Negative	827 (68.1)	1.05 [0.62-1.75]	
Thalamus	Positive	387 (31.9)	1.04 [0.75-1.45]	0.57
	Negative	827 (68.1)	0.52 [0.25-1.07]	

Results from a subsample of the Amsterdam Dementia Cohort. Hazard ratio per standard deviation increase of volume. P interaction shows p-value for interaction between volume of subcortical structures and amyloid status. Abbreviations: HR=hazard ratio, CI=confidence interval.

Table A4 Subcortical structures and risk of dementia for participants in the National Alzheimer's Coordinating Center cohort.

	NACC, all participants HR [95%CI] N=2207	**NACC, participants who attended research center for clinical evaluation HR [95%CI] N=507**
Accumbens	0.93 [0.78-1.12]	1.08 [0.75-1.57]
Amygdala	1.46 [1.19-1.79]	1.45 [1.00-2.08]
Caudate	0.92 [0.80-1.06]	1.07 [0.78-1.46]
Hippocampus	1.92 [1.56-2.37]	1.51 [1.05-2.17]
Pallidum	0.80 [0.69-0.93]	0.76 [0.59-0.96]
Putamen	1.04 [0.87-1.24]	0.78 [0.56-1.08]
Thalamus	1.02 [0.86-1.22]	0.95 [0.67-1.34]

Results from a Cox regression model for all participants in the National Alzheimer's Coordinating Center cohort and a subset of participants who visited the research center solely for a clinical evaluation. Hazard ratios adjusted for MRI scanner (settings), intracranial volume, age, sex, education, other subcortical structure volumes and cortical grey matter volume. Abbreviations: NACC=National Alzheimer's Coordinating Center, HR=hazard ratio, CI=confidence interval

Table A5 Subcortical structures and the risk of dementia stratified by sex.

Subcortical structure	Sex	Rotterdam Study		NACC		Amsterdam Dementia Cohort	
		HR [95%CI]	P interaction	HR [95%CI]	P interaction	HR [95%CI]	P interaction
Accumbens	Female	1.18 [0.78-1.79]	0.81	0.98 [0.74-1.31]	0.83	1.10 [0.76-1.59]	0.86
	Male	1.17 [0.71-1.93]		0.96 [0.75-1.23]		1.23 [0.94-1.60]	
Amygdala	Female	1.76 [1.02-3.03]	0.78	1.94 [1.41-2.67]	0.77	1.33 [0.87-2.04]	0.59
	Male	1.12 [0.60-2.09]		1.23 [0.94-1.62]		1.79 [1.32-2.43]	
Caudate	Female	0.92 [0.66-1.30]	0.25	0.99 [0.80-1.21]	0.79	0.96 [0.66-1.38]	0.33
	Male	1.43 [0.95-2.16]		0.88 [0.72-1.07]		1.04 [0.85-1.27]	
Hippocampus	Female	1.34 [0.79-2.28]	0.55	1.74 [1.27-2.37]	0.49	2.28 [1.52-3.43]	0.01
	Male	2.19 [1.13-4.24]		1.99 [1.49-2.66]		1.23 [0.94-1.65]	
Pallidum	Female	0.94 [0.59-1.48]	0.36	0.74 [0.59-0.93]	0.19	0.92 [0.67-1.27]	0.44
	Male	1.18 [0.64-2.18]		0.83 [0.68-1.01]		0.90 [0.72-1.14]	
Putamen	Female	0.98 [0.67-1.42]	0.86	0.89 [0.68-1.16]	0.15	0.83 [0.55-1.27]	0.55
	Male	0.58 [0.32-1.04]		1.14 [0.89-1.45]		0.98 [0.78-1.23]	
Thalamus	Female	0.99 [0.53-1.84]	0.11	0.88 [0.68-1.13]	0.08	1.31 [0.88-1.94]	0.02
	Male	3.07 [1.43-6.6]		1.22 [0.93-1.60]		0.78 [0.60-1.02]	

Hazard ratio per standard deviation increase of volume. P interaction shows p-value for interaction between volume of subcortical structures and sex. Abbreviations: HR = hazard ratio, CI = confidence interval, NACC=National Alzheimer's Coordinating Center.

Table A6. Subcortical structures and risk of dementia for different types of adjustment for the variety of MRI scanners.

	NACC		Amsterdam Dementia Cohort	
	NeuroCombat harmonization HR [95%CI]	**Adjusting in Cox model HR [95%CI]**	**NeuroCombat harmonization HR [95%CI]**	**Adjusting in Cox model HR [95%CI]**
Accumbens	0.94 [0.79-1.13]	0.93 [0.78-1.12]	1.07 [0.88-1.31]	1.11 [0.90-1.35]
Amygdala	1.46 [1.19-1.79]	1.46 [1.19-1.79]	1.57 [1.25-1.96]	1.59 [1.26-2.01]
Caudate	0.92 [0.80-1.05]	0.92 [0.80-1.06]	1.08 [0.91-1.28]	1.00 [0.85-1.19]
Hippocampus	1.95 [1.58-2.40]	1.92 [1.56-2.37]	1.53 [1.22-1.93]	1.55 [1.25-1.93]
Pallidum	0.78 [0.68-0.90]	0.80 [0.69-0.93]	0.88 [0.73-1.07]	0.89 [0.75-1.07]
Putamen	1.04 [0.88-1.25]	1.04 [0.86-1.22]	0.95 [0.78-1.16]	0.97 [0.80-1.18]
Thalamus	1.05 [0.88-1.24]	0.93 [0.75-1.17]	0.87 [0.70-1.09]	0.93 [0.75-1.17]

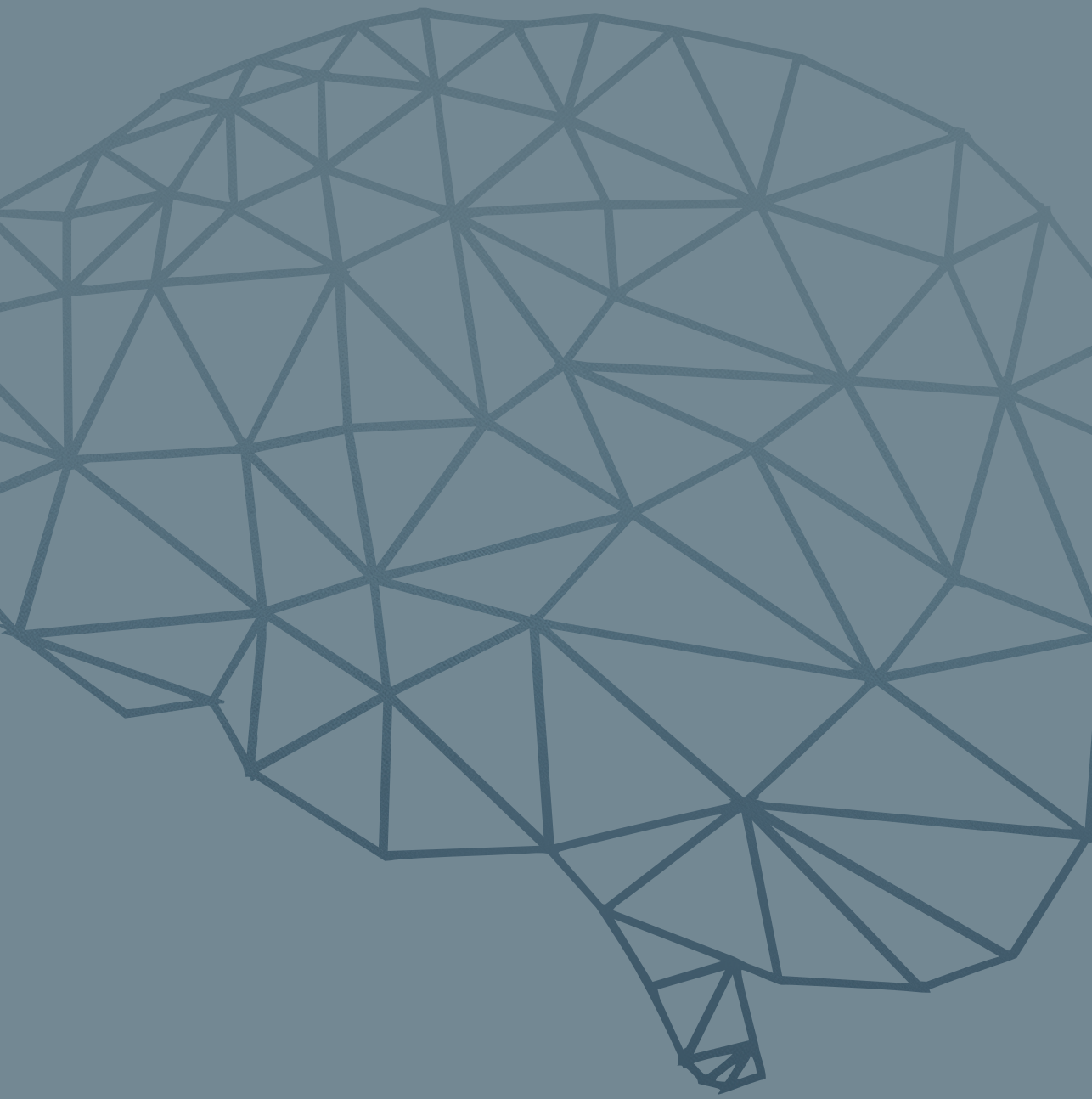
Hazard ratios adjusted for intracranial volume, age, sex, education, other subcortical structure volumes and cortical grey matter volume. Adjustment for MRI scanner was performed by either as covariate in the Cox proportional hazards model or by harmonizing imaging measurements using NeuroCombat harmonization.

Abbreviations: NACC=National Alzheimer's Coordinating Center, HR=hazard ratio, CI=confidence interval, MRI=magnetic resonance imaging

Table A7. Subcortical structures and risk of dementia for different MRI field strengths.

	NACC		Amsterdam Dementia Cohort	
	All participants HR [95%CI] N=2207	**Participants with 3.0T MRI HR [95%CI] N=1316**	**All participants HR [95%CI] N=1964**	**Participants with 3.0T MRI HR [95%CI] N=1410**
Accumbens	0.93 [0.78-1.12]	0.87 [0.67-1.13]	1.11 [0.90-1.35]	1.15 [0.90-1.46]
Amygdala	1.46 [1.19-1.79]	1.57 [1.20-2.05]	1.59 [1.26-2.01]	1.84 [1.38-2.44]
Caudate	0.92 [0.80-1.06]	0.96 [0.79-1.17]	1.00 [0.85-1.19]	1.11 [0.91-1.37]
Hippocampus	1.92 [1.56-2.37]	1.94 [1.47-2.56]	1.55 [1.25-1.93]	1.51 [1.16-1.96]
Pallidum	0.80 [0.69-0.93]	0.80 [0.66-0.97]	0.89 [0.75-1.07]	0.88 [0.70-1.10]
Putamen	1.04 [0.87-1.24]	1.02 [0.79-1.33]	0.97 [0.80-1.18]	0.98 [0.77-1.24]
Thalamus	1.02 [0.86-1.22]	1.19 [0.91-1.54]	0.93 [0.75-1.17]	0.79 [0.61-1.03]

Hazard ratios adjusted for MRI scanner, intracranial volume, age, sex, education, other subcortical structure volumes and cortical grey matter volume.
Abbreviations: NACC=National Alzheimer's Coordinating Center, HR=hazard ratio, CI=confidence interval, MRI=magnetic resonance imaging



CHAPTER 3.2

VALIDATION OF A NOVEL NEUROIMAGING MARKER FOR DEMENTIA

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ABSTRACT

Background: A novel neuroimaging signature of regional cortical thickness on brain MRI recently showed high potential for Alzheimer's disease and related dementias (ADRD) risk stratification in the community. How these findings translate to other populations, remains undetermined.

Objective: We aimed to replicate this novel ADRD neuroimaging marker in the population-based Rotterdam Study.

Methods: We included all participants from the population-based Rotterdam Study with brain-MRI between 2005–2016, and derived the signature using FreeSurfer. We computed hazard ratios and C-statistics for 10-year dementia risk, and betas for cross-sectional associations with cognition, comparing the novel signature to hippocampal volume, mean cortical thickness, and another cortical thickness signature (Dickerson's).

Results: Of 3249 participants (mean age 71.3 ± 8.0 years), 294 developed dementia (74.8% clinical AD) during a mean follow-up of 8.1 years. The novel ADRD signature had similar magnitude of associations as Dickerson's signature and cortical thickness for AD dementia (HR per 1-SD increase 0.87;0.78–0.96), but performed worse than all markers for all-cause dementia. Of the four neuroimaging markers, hippocampal volume showed the strongest associations with both risk of all-cause dementia and clinical AD dementia. The ADRD had the weakest association with general cognitive function (β per 1-SD increase 0.04;0.02–0.06), and executive function (β per 1-SD increase 0.02;0.00–0.04), followed by cortical thickness and Dickerson's, and hippocampal volume showed the strongest associations.

Conclusions: In this community-based study, the novel cortical thickness signature did not outperform hippocampal volume for dementia risk stratification. The importance of replication studies underlines the value of the current study. Replicating research findings is essential to establish robust biomarkers for dementia risk prediction.

INTRODUCTION

Dementia is among the largest health problems, with around 57 million people currently living with dementia worldwide.[1] With no current treatment available, early risk stratification could enable targeted prevention and assist in personalized selection for treatment in clinical trials. Brain magnetic resonance imaging (MRI) is a non-invasive investigative tool that can relatively easily be applied to large populations at risk of dementia for risk stratification. While the body of literature on novel brain MRI biomarkers for dementia risk is growing, few are replicated and translation to routine clinical practice remains challenging.[2]

Recently, a novel neuroimaging signature for Alzheimer's disease and related dementias (ADRD) was identified from cortical thickness maps in the Framingham Heart Study (FHS).[3] This signature showed high risk estimates for all-cause dementia and AD dementia, that went above and beyond established MRI biomarkers including hippocampal volume, mean cortical thickness and cortical thickness in Dickerson's signature.[4] The investigators replicated analyses in the same report using data of the University of California Davis Alzheimer's Disease Research Center (UCD-ADRC) cohort, with similar results.[3] However, it remains undetermined how these findings translate to other populations across the globe.

We therefore aimed to determine the association between the novel cortical thickness neuroimaging biomarker and cognition and dementia risk in the population-based Rotterdam Study.

METHODS

Study design

The Rotterdam Study is an ongoing prospective population-based cohort study investigating determinants and occurrence of disease in persons aged 40 years and older. The study started in 1990 and now comprises 17,931 individuals living in the Ommoord suburb of Rotterdam, the Netherlands. The design of the Rotterdam Study has been described in detail previously.5 In brief, participants are invited for interview and extensive in-person examination at a dedicated research center every 3–6 years. For the current study, we included all participants who underwent brain MRI between 2005 and 2016 (N = 5862), of whom 5586 had valid measurement of either

hippocampal volume, overall mean cortical thickness or mean cortical thickness in Dickerson's or the ADRD signature. We excluded individuals with previous stroke (n = 180), insufficient information on dementia at time of first scan (n = 68) or prevalent dementia at time of MRI (n = 57). For analyses of dementia risk, we included only participants over the age of 60 (n = 3254/5586). For cross-sectional analyses of cognition, we excluded 221/5586 (4.0%) participants who did not undergo cognitive assessment.

Ethics approval

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the Population Screening Act: Rotterdam Study.

Brain MRI acquisition and processing

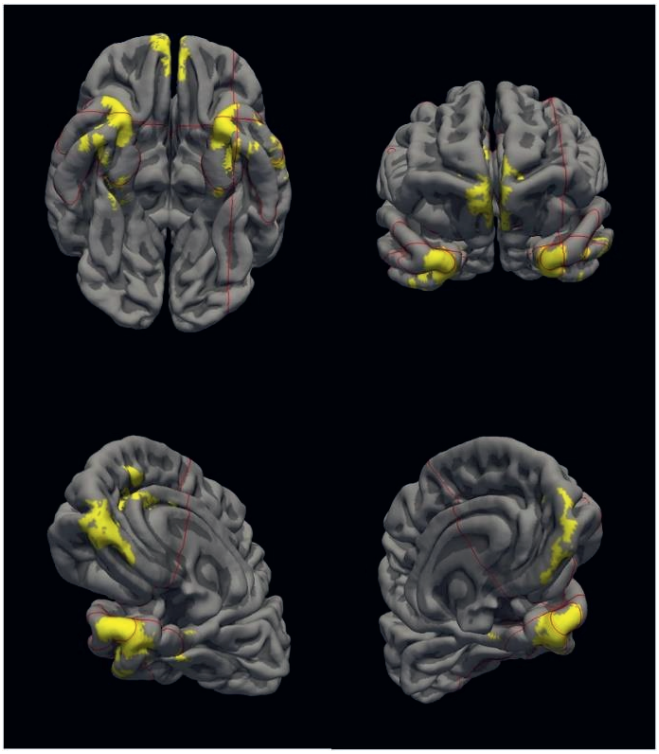
All participants underwent scanning on a 1.5-T MRI device (GE Healthcare) using a multisequence protocol consisting of T1-weighted, proton density-weighted, fluid-attenuated inversion recovery, and T2-weighted sequences. For brain volumetry, T1-weighted (voxel size 0.49 × 0.49 × 1.6 mm3), proton density–weighted (voxel size 0.6 × 0.98 × 1.6 mm3), and the fluid-attenuated inversion recovery (FLAIR) (voxel size 0.78 × 1.12 × 2.5 mm3) scans were used for automated segmentation of supratentorial gray matter, white matter, cerebrospinal fluid (CSF), and white matter hyperintensities, using an in-house segmentation method.6,7 All segmentations were visually inspected, and manually corrected if needed. Total brain volume was the sum of gray matter, normal-appearing white matter, and white matter hyperintensity volume. Supratentorial intracranial volume was estimated by summing gray and white matter (consisting of the sum of normal-appearing white matter and white matter lesion volume) and CSF volumes.7 Additionally, all T1-weighted MR images were processed using FreeSurfer (version 6.0) to obtain hippocampal volume8 and cortical thickness measurements. Hippocampal volume was defined as the sum of the left and the right hippocampal volumes. Total brain volume was defined as the sum of white and gray matter as a percentage of the total intracranial volume. We used the mean cortical thickness and the surface area-weighted average of the AD cortical thinning signature defined by Dickerson and colleagues.4 This signature consists of multiple regions, including the entorhinal cortex, parahippocampus, inferior parietal lobe, pars opercularis, pars orbitalis, pars triangularis, inferior temporal, temporal

pole, precuneus, supramarginal gyrus, superior parietal and superior frontal regions.

ADRD signature

Satizabal and colleagues previously derived an ADRD signature from cortical thickness maps using brain MRI of participants with AD dementia and matched controls from the Framingham Heart Study.3 They determined the cortical thickness in MRI scans using the DiReCT diffeomorphism-based application.9 Further details on the development of the ADRD signature have been described previously.3 For the current study, we have used the region of interest (ROI) of the signature in MNI space as provided by Satizabal and colleagues (private correspondence). To determine the mean cortical thickness within this ROI, we registered the ROI from MNI space to FreeSurfer space, and processed Rotterdam Study imaging using FreeSurfer 6.0 to determine for each study participant mean cortical thickness within the ADRD signature ROI. The ROI in FreeSurfer space is shown in Figure 1.

Figure 1. Visualization of the ADRD signature.



ADRD signature ROI projected on white matter volume in 3D in the population-based Rotterdam study. ADRD: Alzheimer's disease related dementias; ROI: region of interest.

Dementia ascertainment

Participants were screened for dementia at baseline and every 3–6 years during follow-up examinations using the Mini-Mental State Examination (MMSE) and the Geriatric Mental Schedule (GMS) organic level. Those with an MMSE score of <26 or a GMS organic level score of >0 were further examined using the Cambridge Examination for Mental Disorders in the Elderly diagnostic interview. Additionally, participants were continuously under surveillance for dementia through the electronic linkage between the study database and medical records from general practitioners and the Regional Institute of Outpatients Mental Health Care. The general practitioner functions as a gatekeeper within the Dutch healthcare system, receiving written information of any medical specialists' consultations of their patients. The final diagnosis of dementia and its most common subtypes was made by a consensus panel led by a neurologist based on the standard criteria for all-cause dementia (DSM-III-R) and clinical Alzheimer's disease (NINCDS-ADRDA).

Cognitive assessments

Assessment of cognitive function was routinely performed at center visits through a cognitive test battery, including the Stroop test,10 measuring processing and attention, the Word Fluency test (WFT),11 measuring efficiency of searching long term memory, the Letter Digit Substitution test (LDST),12 measuring processing speed and executive function, 15-word verbal learning test (15-WLT),13 measuring verbal learning and memory, and Purdue Pegboard test (PPB),14 measuring dexterity and fine motor speed. In this study, we derived a measure of global cognition (g-factor) from principle component analysis of available test scores.15 The g-factor is defined as the first unrotated component of the principle component analysis. A higher g-factor indicates a better cognitive performance. Executive function was defined as the mean of standardized values of the Stroop test, the WFT and the LDST (weighted half). Episodic memory was defined as the score from the 15-WLT.

Assessment of APOE genotype

Apolipoprotein E (APOE) genotype was determined using polymerase chain reaction on coded DNA samples or using biallelic TaqMan assays (TaqMan Gene Expression Assays; Thermo Fisher Scientific, Waltham, MA) (rs7412 and rs429358).16,17 APOE-ε4 carriers were defined as carrying at least one ε4 allele (ε3/ε4, ε2/ε4 and ε4/ε4).

Statistical analyses

Missing data on cognitive testing was imputed using 5-fold multiple imputation when data of at least one cognitive test of the test battery was available, based on age, sex, education, MMSE and other available cognitive tests. Imaging markers included mean cortical thickness within the ADRD signature and Dickerson's signature, overall mean cortical thickness (averaged over the entire cortex) and hippocampal volume. In line with the previous report by Satizabal et al.,.3 we modelled all markers as continuous measures (for hazard ratios [HR] with 95% confidence intervals [CI] per 10 units increase), and comparing the bottom quartile to the upper three quartiles. To enhance comparability between measures, we additionally standardized measures of each imaging marker to provide HRs with 95% CIs per standard deviation (SD) increase of each imaging marker.

Follow-up time was measured in years from the date of the MRI examination until dementia diagnosis, death, loss-to-follow-up, or censoring at 10 years of follow-up, whichever came first (in line with the report by Satizabal et al.).3 We performed Cox proportional hazard models to compute HRs for each imaging marker across the 10-year incidence of all-cause and AD dementia. All models were adjusted for age and sex, and additional models also for other brain MRI markers of dementia (total brain volume, hippocampal volume, and white matter hyperintensities as percentage of intracranial volume). The C-statistic was computed to quantify the predictive discrimination.

Next, we determined the cross-sectional association of imaging markers with cognitive function (episodic memory, executive function and global cognition), using linear regression.

We stratified all analyses by sex and tested for multiplicative interactions between the ADRD signature and sex in the Cox regression models, and additive interaction in the linear regression models for cognition. Last, we performed linear regression models to relate APOE-ε4 carrier status to the ADRD signature.

All analyses were performed in R (version 4.2.1; packages: tidyverse, dplyr, lubridate, here, rio, survival).

RESULTS

Participants characteristics

We included 5060 participants for analyses on cognition (mean age 64.7 ± 10.8 years, 55.6% women) and 3249 for analyses on dementia risk (mean age 71.3 ± 8.0 years, 55.8% women) (Table 1).

Table 1 Participant's characteristics

	Cognition sample (N=5,060)	Dementia sample (N=3,249)
Age, mean (±SD)	64.7 (10.8)	71.3 (8.0)
Women, n (%)	2,813 (55.6)	1,814 (55.8)
Education, n (%)		
Lower	444 (8.8)	307 (9.4)
Intermediate	3,452 (68.2)	2,312 (71.2)
Higher	1,131 (22.4)	585 (18.0)
APOE ε4 carriers, n (%)	1,426 (28.2)	836 (26.5)
MRI markers, mean (SD)		
ADRD signature ROI, mm	2.93 (0.14)	2.92 (0.14)
Dickerson's signature, mm	2.49 (0.10)	2.46 (0.10)
Cortical thickness, mm	2.45 (0.09)	2.42 (0.09)
Hippocampal volume, cm^3	7.78 (0.85)	7.56 (0.84)
Total brain volume, cm^3	942.09 (105.28)	920.86 (103.41)
WMH volume, cm^3, median (IQR)	3.04 (4.70)	4.56 (7.17)
Cognitive measures*, mean (SD)		
Executive function	0.03 (0.78)	-0.04 (0.50)
Episodic memory	0.03 (0.99)	-0.18 (0.95)
General cognition	0.04 (0.98)	-0.32 (0.95)

Abbreviations: AD, Alzheimer's disease; SD, standard deviation; ADRD, Alzheimer's disease related dementias; APOE, apolipoprotein E; MRI, magnetic resonance imaging; ROI, region of interest; WMH, white matter hyperintensities; IQR, interquartile range. *Represents standardized values.

Among the neuroimaging markers, overall cortical thickness and Dickerson's cortical thickness showed a high correlation (Supplemental Figure 1). In contrast, hippocampal volume demonstrated the weakest correlation with the other three measures.

Incident dementia

Of 3249 participants, 303 developed dementia within 10 years from baseline, during a mean follow-up of 8.7 (±2.1) years. Follow-up for incident dementia was virtually complete (96.0% of potential person-years). Increased cortical thickness in the ADRD signature was associated with lower incidence of all-cause dementia (HR [95%CI] per

1-SD increase: 0.89 [0.90–1.00]) and clinical AD dementia (HR: 0.83 [0.72–0.95]; Table 2). Compared to individuals in the upper three quartiles, those in the lowest quartile of the ADRD signature had higher risk of both all-cause dementia and clinical AD dementia in models adjusting for age and sex (Table 2). However, risk estimates for the ADRD signature were similar or lower than those for mean cortical thickness, the Dickerson's signature, and hippocampal volume (Table 2).

After further adjustment for total brain volume, hippocampal volume and volume of WMH, estimates attenuated for all measures of cortical thickness, driven by effects of hippocampal volume. Consequently, the risk estimate of the ADRD signature in the quartile analysis was no longer statistically significant (HR: 1.21 [95% CI: 0.96–1.54]) and lower than for the other cortical thickness measures (Table 2). For clinical AD dementia, the categorized ADRD signature showed similar performance compared to Dickerson's and cortical thickness, although risk was still highest for individuals in the lowest quartile of hippocampal volume. Discriminatory value, as measured by the C-static, was similar across imaging markers (Table 2), due in large part to a large contributing value of age to these models.

Risk estimates for the lowest quartile of the ADRD signature tended to be higher for women than for men, both for all-cause dementia (women: HR 1.53 [1.14–2.05]; and men: HR 1.14 [0.79–1.74]) and clinical AD dementia (women: HR 1.97 [1.39–2.79]; and men: HR: 1.53 [0.90–2.60]), but neither interaction was statistically significant (pinteraction = 0.15 and 0.11, respectively).

Cognitive outcomes

Increased thickness in the ADRD signature cortical was associated with better general cognitive function (per 1-SD increase β: 0.04; 95% CI: 0.02–0.06), executive function (per 1-SD increase β: 0.02; 95% CI: 0.00–0.04), and episodic memory (per 1-SD increase β: 0.07; 95% CI: 0.05–0.10) (Table 3). In line with the results on dementia, hippocampal volume showed the strongest association with general cognition, followed by cortical thickness, Dickerson's signature, and the ADRD signature (Table 3). Results were similar in the quartile analyses of all imaging markers. Lower quartiles of hippocampal volume (β −0.27; 95% CI: −0.32–-0.22), Dickerson's (β: −0.18; 95%CI: −0.23–-0.14) and cortical thickness (β: −0.18; 95%CI: −0.23–-0.13) were associated with lower standardized values of executive function, but only marginally for the lowest quartiles of the ADRD signature (−0.04; −0.09–0.00). Only for

episodic memory, the lowest quartile of the ADRD signature showed the strongest association of all four markers (β: −0.13; −0.19–-0.07), but this difference was not observed in the continuous analyses per standard deviation (Table 3).

Similar to the dementia analyses, we observed slightly stronger associations between the ADRD marker and cognition in women than in men, though interactions were non-significant (episodic memory: pinteraction = 0.84; executive functioning: pinteraction = 0.72, general cognitive function: pinteraction = 0.29).

Association with APOE ε4 carriership

We observed no significant associations between the presence of at least one APOE-ε4 allele and the ADRD signature, neither in the sample for dementia analyses (β 0.008 [± standard error (SE) 0.015], p-value 0.63), nor in the sample for analyses on cognitive assessment (β 0.007 [± SE 0.016], p-value 0.68).

Table 2 Head-to-head comparison of neuroimaging markers of 10-year dementia risk in the Rotterdam Study

		ADRD signature	Dickerson's	Cortical thickness	Hippocampal volume
All-cause dementia					
Dementia N/Total N		303/3,249	303/3,249	303/3,249	303/3,249
Model 1	**Continuous:** *HR (95% CI)*	0.86 (0.80-0.93)	0.75 (0.66 – 0.85)	0.73 (0.64 – 0.83)	0.94 (0.93 – 0.96)
	C-statistic	0.79	0.80	0.80	0.80
	Standardized: *HR (95%CI)*	0.82 (0.73-0.91)	0.75 (0.66 – 0.85)	0.76 (0.67 – 0.85)	0.61 (0.52-0.71)
	C-statistic	0.79	0.80	0.80	0.80
	Q1 vs Q2-4: *HR (95% CI)*	1.39 (1.10-1.76)	1.89 (1.47 – 2.42)	1.89 (1.48 – 2.42)	1.66 (1.27 – 2.17)
	C-statistic	0.79	0.80	0.80	0.80
Model 2	**Continuous:** *HR (95% CI)*	0.92 (0.85-1.00)	0.81 (0.71 – 0.92)	0.79 (0.69 – 0.91)	0.95 (0.93 – 0.96)
	C-statistic	0.81	0.81	0.81	0.81
	Standardized: *HR (95% CI)*	0.89 (0.80-1.00)	0.81 (0.71 – 0.92)	0.82 (0.72 – 0.92)	0.62 (0.53-0.72)
	C-statistic	0.81	0.81	0.81	0.81
	Q1 vs Q2-4: *HR (95% CI)*	1.21 (0.96-1.54)	1.69 (1.31 – 2.18)	1.67 (1.30 – 2.14)	1.63 (1.24 – 2.13)
	C-statistic	0.81	0.81	0.81	0.80
Clinical AD dementia					
AD N/Total N		215/3,249	215/3,249	215/3,249	215/3,249
Model 1	**Continuous:** *HR (95% CI)*	0.81 (0.73-0.90)	0.73 (0.63 – 0.86)	0.73 (0.62 – 0.87)	0.94 (0.92 – 0.96)
	C-statistic	0.81	0.81	0.81	0.82
	Standardized: *HR (95% CI)*	0.75 (0.66-0.86)	0.74 (0.63 – 0.86)	0.76 (0.65 – 0.88)	0.60 (0.50-0.73)
	C-statistic	0.81	0.81	0.81	0.82
	Q1 vs Q2-4: *HR (95% CI)*	1.82 (1.36-2.44)	1.89 (1.38 – 2.59)	1.81 (1.33 – 2.47)	1.81 (1.29 – 2.56)
	C-statistic	0.81	0.81	0.81	0.81
Model 2	**Continuous:** *HR (95% CI)*	0.87 (0.78-0.96)	0.80 (0.68 – 0.94)	0.80 (0.68 – 0.96)	0.94 (0.92 – 0.97)
	C-statistic	0.82	0.82	0.82	0.82
	Standardized: *HR (95% CI)*	0.83 (0.72-0.95)	0.80 (0.69 – 0.94)	0.83 (0.71 – 0.96)	0.61 (0.51-0.74)
	C-statistic	0.82	0.82	0.82	0.82
	Q1 vs Q2-4: *HR (95% CI)*	1.58 (1.17-2.12)	1.67 (1.21 – 2.30)	1.57 (1.14 – 2.15)	1.78 (1.26 – 2.51)
	C-statistic	0.82	0.82	0.82	0.82

Continuous represents hazard ratios per tenth point of the imaging marker. Standardized represents hazard ratios per standard deviation increase of the imaging marker. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, and MRI markers

Table 3 Head-to-head comparison of neuroimaging markers of cognitive test performance in the Rotterdam Study

		ADRD signature	Dickerson's	Cortical thickness	Hippocampal volume
Episodic memory*					
Model 1	**Continuous: β**	0.05 (0.03-0.07)	0.07 (0.04-0.10)	0.08 (0.04-0.11)	0.01 (0.00-0.01)
	Standardized: β	0.07 (0.05-0.10)	0.07 (0.04 – 0.10)	0.07 (0.04 – 0.10)	0.04 (0.01 – 0.08)
	Q1 vs Q2-4: β	-0.13 (-0.19- -0.07)	-0.07 (-0.14 – -0.01)	-0.10 (-0.17 – -0.04)	-0.07 (-0.14 – 0.00)
Model 2	**Continuous: β**	0.04 (0.02-0.06)	0.06 (0.02-0.09)	0.06 (0.03-0.10)	0.00 (0.00-0.01)
	Standardized: β	0.06 (0.03-0.08)	0.06 (0.02 – 0.09)	0.06 (0.03 – 0.09)	0.04 (0.01 – 0.07)
	Q1 vs Q2-4: β	-0.10 (-0.16- -0.04)	-0.05 (-0.12 – 0.01)	-0.08 (-0.15 – -0.02)	-0.07 (-0.13 – 0.00)
Executive function*					
Model 1	**Continuous: β**	0.02 (0.00-0.03)	0.08 (0.06-0.10)	0.10 (0.07-0.12)	0.02 (0.01-0.02)
	Standardized: β	0.02 (0.00-0.04)	0.08 (0.06 – 0.10)	0.09 (0.06 – 0.11)	0.13 (0.11 – 0.16)
	Q1 vs Q2-4: β	-0.04 (-0.09 – 0.00)	-0.18 (-0.23 – -0.13)	-0.18 (-0.23 – -0.14)	-0.27 (-0.32 – -0.22)
Model 2	**Continuous: β**	0.01 (0.00-0.03)	0.07 (0.05-0.09)	0.09 (0.06-0.11)	0.01 (0.01-0.02)
	Standardized: β	0.02 (0.00-0.04)	0.07 (0.05 – 0.09)	0.08 (0.05 - 0.10)	0.12 (0.10 – 0.15)
	Q1 vs Q2-4: β	-0.03 (-0.08-0.01)	-0.16 (-0.20 – -0.11)	-0.16 (-0.21 – -0.11)	-0.25 (-0.30 – -0.20)
General cognitive function*					
Model 1	**Continuous: β**	0.03 (0.01-0.05)	0.10 (0.08-0.13)	0.12 (0.09-0.15)	0.02 (0.01-0.02)
	Standardized: β	0.04 (0.02-0.06)	0.10 (0.08 – 0.13)	0.11 (0.08 – 0.13)	0.14 (0.12 – 0.17)
	Q1 vs Q2-4: β	-0.06 (-0.11 – -0.01)	-0.20 (0.26 – -0.14)	-0.23 (-0.28 – -0.17)	-0.28 (-0.34 – -0.23)
Model 2	**Continuous: β**	0.02 (0.00-0.04)	0.09 (0.06-0.11)	0.10 (0.07-0.13)	0.02 (0.01-0.02)
	Standardized: β	0.03 (0.00-0.05)	0.09 (0.06 – 0.11)	0.09 (0.07 – 0.12)	0.13 (0.10 – 0.16)
	Q1 vs Q2-4: β	-0.04 (-0.09-0.01)	-0.16 (-0.22 – -0.11)	-0.19 (-0.24 – -0.13)	-0.26 (-0.32 – -0.21)

Continuous represents betas per tenth point of the imaging marker. Standardized represents betas per standard deviation increase of the imaging marker. Model 1: adjusted for age and sex
Model 2: adjusted for age, sex, and MRI markers
* Cognitive outcomes were modeled as standardized values.

DISCUSSION

In this large population-based cohort, we confirmed associations of the novel ADRD signature imaging marker with cognition and risk of dementia. However, in our head-to-head comparison of four neuroimaging markers, associations for the ADRD signature were not greater than for other AD-related imaging markers. Overall, hippocampal volume showed stronger associations with dementia and cognition than any of the cortical thickness measures.

Risk estimates of the ADRD signature for cognition and dementia were less profound in the Rotterdam Study cohort than in FHS and UCD-ADRC. This discrepancy could, in part, stem from differences in our study sample, comprising community-dwelling Europeans, compared to the U.S. population in the FHS and the clinic-based sample of the replication cohort at UCD-ADRC. Additionally, we used FreeSurfer rather than the DiReCT method employed by the FHS, which might contribute to the observed disparities due to differences in the underlying techniques between both approaches.3 However, our results for the Dickerson's signature and mean cortical thickness, which also rely on these methods, were similar compared to those in the FHS report. Notably, FreeSurfer is a widely used openly available neuroimaging analysis tool, and its application in our validation study probably reflects the performance of the ADRD signature if it were implemented in real-world populations.18

In the original study by Satizabal et al., the development of the ADRD signature was meticulously executed, including all necessary steps and external validation in a separate cohort.3 Despite these thorough efforts, our findings emphasize a critical reality, namely that results may not consistently replicate across different populations, due either to methodological differences or heterogeneity in the studied populations. The discrepancy between our findings and those from the FHS and UCD-ADRC cohort may however in fact also be explained by a third factor, namely chance. Results from one study will not always be replicated based on statistical chance alone. Replication studies are essential to establish robust biomarkers for dementia risk stratification, and external validation to determine in which setting they may or may not apply.

The current study is strengthened by its large, population representative sample of individuals with brain imaging and long-term follow-up for dementia. Some limitations need to be acknowledged. First, brain MRI was incorporated at the last stage (i.e.,

third day-visit) of each examination round of the Rotterdam Study, which might have led to selection of more healthy participants who underwent MRI. However, any selection would influence all four imaging markers equally and should not affect the head-to-head comparison. Second, the ADRD signature is developed using MRI data acquired with scanners different than ours and partly with different field strengths. Use of FreeSurfer rather than the DiReCT method might also have contributed to the observed disparities. Such methodological differences are important to consider, especially as translation to a real-world setting may depend on robustness of measures across different MRI scanners and algorithms.

In conclusion, in this population-based study the novel cortical thickness signature did not outperform hippocampal volume in the magnitude of the association with cognition and for dementia risk stratification. The importance of replication studies underlines the value of the current study. Replicating research findings is vital to establish robust biomarkers for dementia risk prediction.

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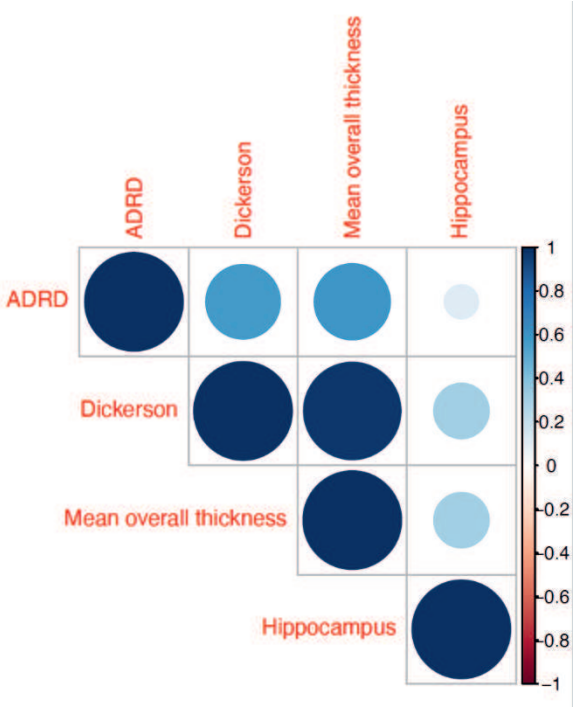
SUPPLEMENTARY MATERIALS

Supplemental Figure 1. Correlation between the neuroimaging signatures.

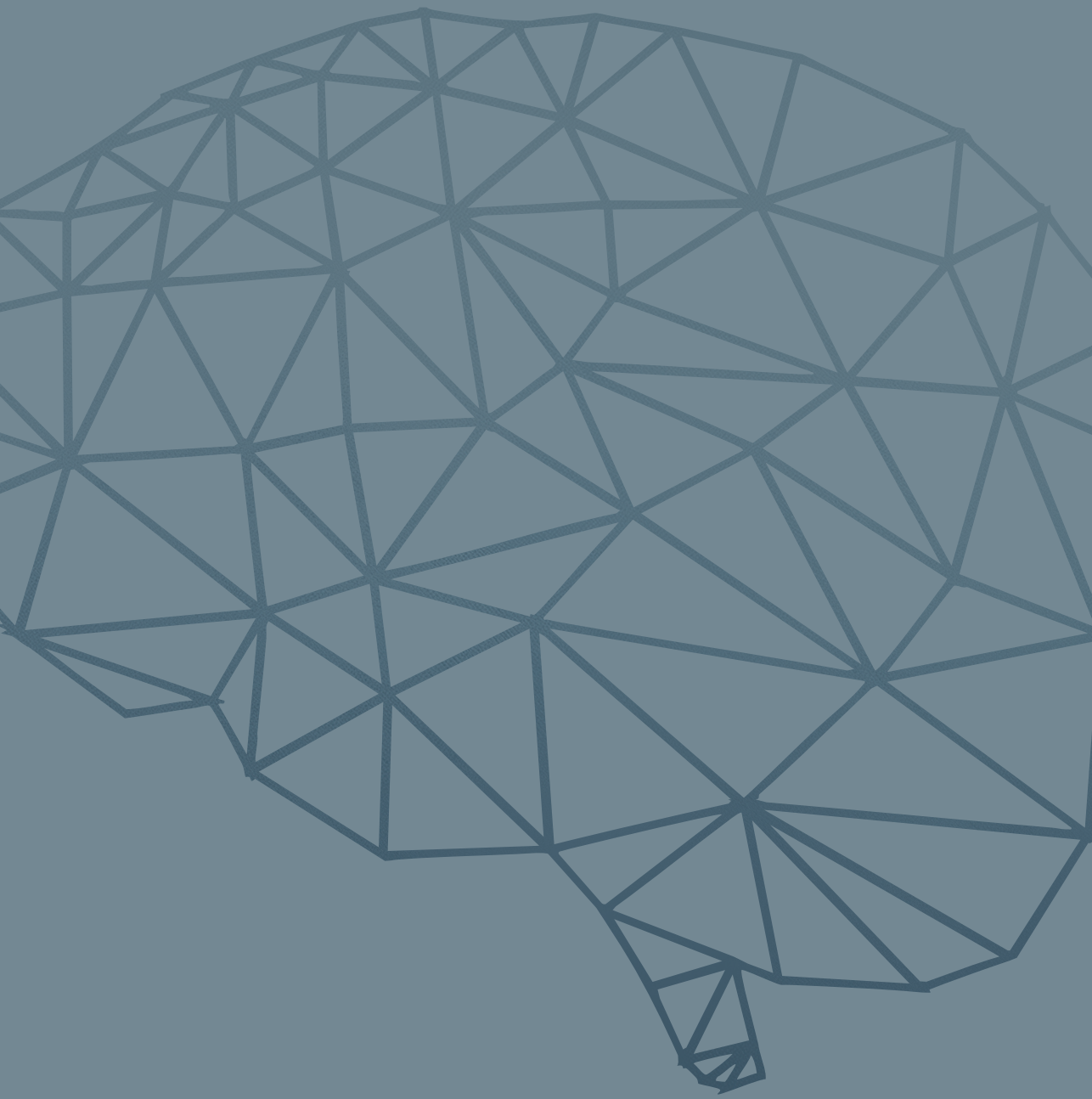


This figure displays the correlation matrix between four neuroimaging measures: the Alzheimer's Disease Related Dementias (ADRD) signature, the Dickerson signature, mean overall cortical thickness, and hippocampal volume. Each cell in the matrix represents the Pearson correlation coefficient, ranging from -1 (strong negative correlation) to 1 (strong positive correlation). The diagonal elements of the matrix represent perfect correlations (correlation coefficient = 1) between the same measures. Off-diagonal elements show the correlations between different neuroimaging signatures, highlighting the relationships among these variables. The strength and direction of the correlations provide insight into how these neuroimaging markers are related in the context of neurodegenerative processes.

CHAPTER 4

PREDICTING DEMENTIA: MODELS AND PERSPECTIVES





CHAPTER 4.1

PUBLIC ATTITUDES TOWARDS DEMENTIA PREDICTION

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ABSTRACT

Introduction: Numerous dementia risk prediction models have been developed, but uptake in clinical practice is poor.

Methods: We determined public attitude towards dementia risk prediction, through means of a focus group (n=9) and subsequent online survey (n=687). Thematic content analysis was used for focus group data, and descriptive statistics for survey responses.

Results: Focus group participants expressed reluctance to knowing dementia risk due to fear, emotional burden, and belief that prevention was impossible. Conversely, practical benefits, and maximizing present quality of life motivated others to know dementia risk. Of survey respondents, 66.1% would want to know their 10-year risk at present, increasing to 82.3% if preventive medication were available. People perceived their 10-year risk as rather high, yet lower still than their own personal threshold for considering preventive action.

Discussion: Development and implementation of dementia risk prediction models may benefit from personal actionability and emotional impact of risk communication.

BACKGROUND

Accurate prediction an individual's risk of dementia enables personalized approaches to diagnostics, care planning, treatment options, and participation in preventive trials. Over the past 10 years alone, more than 50 new dementia risk prediction models have been developed to identify individuals at high risk, but only a quarter of these models have undergone external validation.(1-3) The fraction of prediction models that make it into clinical practice remains very limited, and no tools are routinely used in clinical practice.

The successful adoption of prediction models in clinical settings typically relies on factors related to the prediction tool as well as the health care setting in which it is applied. First and foremost, prediction tools need to align with the needs of patients and health care providers in routine clinical practice. Other relevant factors for uptake are the model's predictive accuracy, the accessibility of obtaining or measuring the predictors in clinical practice, implementation costs, ease and understandability of risk estimates for both patients and caregivers, and actionability on the basis of the results. Given the complexity and challenges involved in communicating dementia risk(4), engagement with the target users is essential for the development and implementation of useful risk prediction models in clinical practice. Several studies have examined attitudes and preferences toward dementia screening, primarily focusing on detecting (prodromal) dementia, rather than predicting dementia risk years before symptom onset.(5, 6) No published studies have assessed the barriers and facilitators of individualized risk prediction models in clinical settings, leaving unanswered whether individuals want to know their risk years prior to a potential diagnosis. The needs of patients and the understandability and actionability of risk information in particular require further investigation.

Using a mixed-methods approach, we aimed to better understand the needs, beliefs, and concerns of community-dwelling individuals regarding risk prediction of dementia in clinical practice.

METHODS

Study design, sample and recruitment

We conducted a mixed-methods study to explore the perspectives of community-dwelling individuals on dementia risk prediction models and their implementation in clinical practice. We first organized a focus group with non-demented community-dwelling individuals (age range 61-74 years), and subsequently sent out a survey.

For the focus group, participants were recruited from the participant panel of the Rotterdam Study, an ongoing population-based cohort study investigating determinants and occurrence of disease in persons aged 40 years and older. The study started in 1990 and now comprises 17,931 individuals living in the Ommoord suburb of Rotterdam, the Netherlands. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the Population Studies Act: Rotterdam Study. The design of the Rotterdam Study has been described in detail previously.(7) The participant panel consists of 21 individuals who expressed interest in actively contributing to the study's design, practical aspects, and discussions related to scientific research. For the current focus group, these participants received an invitation letter by email. Of the 21 invitees, 4 did not respond, and 7 declined due to lack of interest or time constraints, and one participant initially agreed but did not attend. A total of 9 participants joined the focus group, and all 9 participants provided written informed consent before the focus group commenced.

For the survey, we collaborated with the Dutch Alzheimer's Association patient organization (Alzheimer Nederland; www.alzheimer-nederland.nl), who distributed the survey through their social media channels, including Facebook, LinkedIn, and X. All respondents to the survey provided online informed consent prior to proceeding to the actual survey questions.

Focus group

A focus group consists of individuals who gather in an informal setting to discuss a specific topic determined by the researcher. While the facilitators ensure the conversation stays on topic, they take a non-directive approach, allowing the participants to freely explore various perspectives on the subject.(8) The focus group was held on July 10th, 2024, at the research center of the Rotterdam Study in

Ommoord, Rotterdam, the Netherlands. Prior to the focus group, we introduced the topic of dementia, highlighting its occurrence, and our research aim to understand whether people want to know their dementia risk and how they prefer to receive this information. The session lasted 90 minutes and was facilitated by two medically trained researchers, with two additional staff members from the Rotterdam Study in attendance. One of these staff members actively contributed to the discussion, while the other served as the participant coordinator. Before the focus group, we developed a topic list, which was used to structure the session. The list covered four main areas: knowledge about dementia, knowledge about methods for calculating disease risk, attitudes toward dementia risk prediction models, and the implications of knowing one's dementia risk. These topics were introduced using open-ended questions (see Supplemental Table A). The focus group themes were designed based on identified gaps in the literature and prior discussions with healthcare professionals, including general practitioners, elderly care specialists, and geriatricians. The topics were not disclosed to participants prior to the session. The focus group was audio-recorded, and the recordings were transcribed verbatim independently by two investigators (JJC and MTR). Any coding discrepancies were discussed between the authors for consensus, consulting if needed a third researcher who was not present during the focus group (MJS). The transcripts were not returned to participants for review or correction.

Survey

To quantitatively assess the perspectives gathered in the focus group within a larger population, we developed a survey consisting of 15 questions, enabling broader validation of the viewpoints discussed in the focus group. After familiarization with the focus group data, investigators JJC and MTR rephrased the focus group results into closed-ended questions for the survey. We structured the survey into five subsections: 1) demographic information and living situation, 2) perception of personal dementia risk, 3) modifiability of dementia risk through lifestyle, 4) attitudes towards risk prediction, and 5) reasons for wanting or not wanting to know personal dementia risk. We provided a short information text at the beginning of the survey to ensure basic knowledge of dementia and instructions on how to fill out the survey. The questions were subsequently discussed among the research team, after which it was tested among 10 individuals >50 years from our personal network, resembling the target audience. After minor adjustments, this resulted in the final version of the

questionnaire (Supplemental Material C). The survey was distributed as described above and remained open for three weeks.

Data analysis

Qualitative data analysis were performed according to the guidelines by Braun and Clarke.(9) Authors JJC and MTR reviewed all codes to identify patterns and generate overarching themes. MTR drafted the initial summary of these themes. JJC then drafted the initial version of the results section, incorporating illustrative quotes from the focus group. This summary was then reviewed against the initial codes by three researchers (JJC, MTR, and MJS), and revised accordingly to provide the best possible reflection of the focus group discussion. Coding was performed using Atlas.ti version 22.

We used descriptive statistics to summarize the baseline characteristics of focus group participants and survey respondents, as well as to quantify survey responses. Proportions, along with their 95% confidence intervals (CI), were computed using the standard normal approximation. Proportions were compared using chi-square tests, and medians were compared using the Wilcoxon Rank Sum test. All statistical analyses were conducted using R (version 4.3.2), with the significance level set at $\alpha = 0.05$.

Research team and reflexivity

The focus group discussions were facilitated by JJC and MTR, both of whom are PhD candidates specializing in dementia risk prediction. JJC is a White female medical doctor and epidemiologist from the Netherlands, who brings clinical experience to the study with a specific focus on dementia risk prediction. MTR is a White male technical physician and epidemiologist from the Netherlands, who contributes a technical perspective to the study, emphasizing the integration of risk prediction tools into clinical practice. Academic backgrounds of the coauthors include sociology (MJS), epidemiology (MJS, FJW, MAI, MWV), neurology (FJW) and radiology (MWV).

The backgrounds of the facilitators, including their ongoing PhD work on dementia risk prediction, may have influenced their approach to and interpretation of the discussions. For instance, it may have prompted the researchers to seek reasons why participants would want to know their predicted dementia risk and how they envision this information being used in clinical practice. To move beyond our own perspective,

we engaged in discussions with various stakeholders, including medical professionals (e.g., general practitioners, elderly care specialists, and geriatricians) and the patient organization Alzheimer Nederland.

RESULTS

We included a total of 9 participants in the focus group, and 687 people responded to our survey. Focus group participants were older (mean age, standard deviation [SD]: 67.2 [3.4] years) than survey respondents (51.1 [13.3] years), and included more men (85.7% versus 55.6%)(Table 1). Most focus group participants and survey respondents were higher educated (Table 1). Focus group participants more often lived alone (5/9; 55.6%) than survey respondents (112/687; 16.3%).

From the focus group, we identified three overarching themes, namely A) motivations for willingness to know dementia risk, B) reasons for avoiding dementia risk information, and C) considerations for clinical implementation of risk prediction models (Supplemental Table B). In the next paragraphs, we will first summarize the survey results on dementia knowledge and risk perception. We then explore the focus group themes in more detail, integrating the qualitative results from the focus group discussions and the quantitative survey findings.

Table 1. Demographics

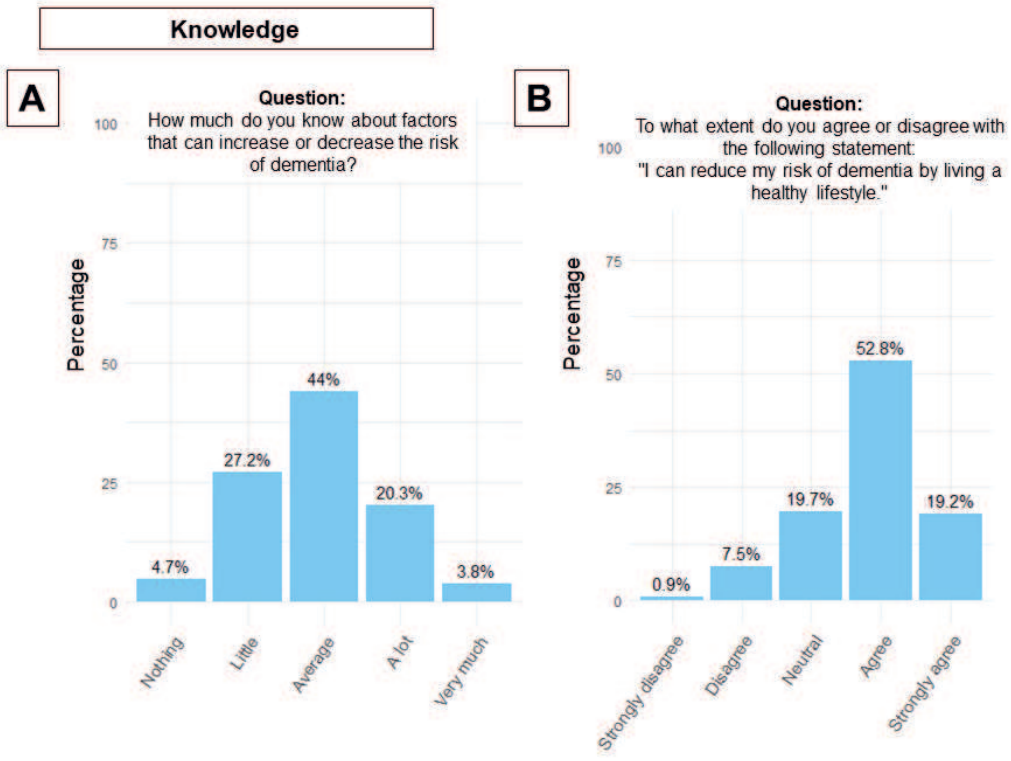
Characteristic	Focus group participants N = 9	Survey respondents N = 687
Age (years), mean (SD)	67.2 (3.4)	51.1 (13.3)
Sex, female	5 (55.6)	558 (85.7)
Education		
Primary/Lower	0 (0.0)	122 (17.8)
Intermediate	4 (44.4)	218 (31.8)
Higher	4 (44.4)	343 (50.0)
Unknown	1 (11.1)	3 (0.4)
Living situation		
Alone	5 (55.6)	112 (16.3)
With partner	4 (44.4)	499 (72.6)
With children	0 (0.0)	57 (8.3)
Other	0 (0.0)	19 (2.3)

SD=standard deviation.

Knowledge of dementia risk reduction

Of all 682 survey respondents, 299 (43.8%) rated their knowledge of factors influencing dementia risk as average, whereas 181 (26.9%) called it lower than average, and 202 (29.6%) as higher than average. The majority of survey respondents (492/684; 72.0%) agreed to the proposition that they could reduce their risk of dementia by living a healthy lifestyle (Figure 1). This pattern was consistent across age and sex, but differed with educational attainment. Respondents with higher education more often agreed that a healthy lifestyle can reduce dementia risk (287/343; 84.4%) than those with intermediate education (134/218; 61.5%), primary/lower education (69/122; 56.6).

Figure 1 Survey response distribution on questions about knowledge of dementia

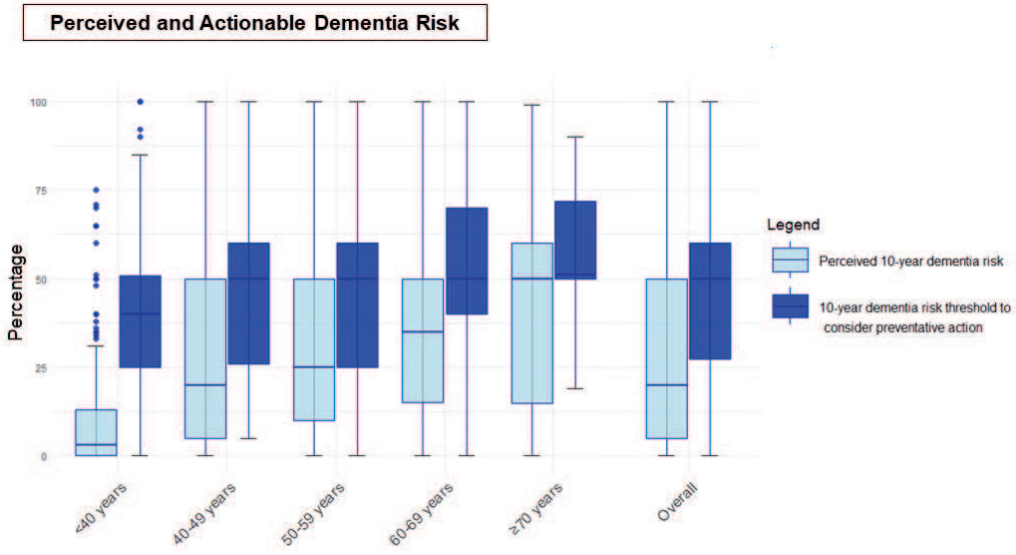


Distribution of responses to survey questions among respondents (N=687). Percentages indicate the proportion of respondents selecting each response option.

Dementia risk perception

Survey respondents estimated their 10-year risk of developing dementia at median 20.0% (interquartile range 5.0-50.0). Perceived risk increased with age, ranging from 11.4% (IQR 3.0-13.0) in those younger than 40, to 50.0% (14.8-60.0) in individuals over 70 years old (Figure 2). Most survey respondents (299/682; 43.8%) estimated their dementia risk to be similar to others of the same age, while 202 (29.6%) thought their risk was higher (24.5% slightly higher and 5.1% much higher), and 181 (26.6%) considered it lower (15.7% slightly lower and 10.9% much lower).

Figure 2 Perceived 10-year risk of dementia compared to personal thresholds at which one considers preventive measures, among survey respondents



Boxplots represent the distribution of responses to survey questions (N=453), stratified by age. The number of respondents per age category are: <40 years (N=147), 40-49 years (N=132), 50-59 years (N=231), 60-69 years (N=121), >70 years (N=56), and the overall population (N=453). Whiskers extend to the 95% percentiles, with data points beyond this range plotted as individual observations. Perceived risk was enquired by asking: “How high do you estimate your chance of developing dementia in the next 10 years?”. Risk thresholds refer to the question: “At what level of dementia risk would you take measures to reduce your risk?”.

Perceived risk was closely linked to how respondents compared themselves to their peers. Those who believed their risk was much higher than their peers estimated their 10-year dementia risk at 65.0% (50.0-77.5), while estimates were lower among those who saw their risk as only slightly higher (36.0% [14.5-56.5]), similar to others (17.0%

[5.0-50.0]), slightly lower (15.0% [3.5-35.0]), or much lower (2.5% [0.0-18.5]). Education also played a role in risk perception. Respondents with higher education estimated a lower 10-year dementia risk (12.0% [2.0-50.0]) compared to those with only primary education (40.0% [11.0-57.0]), lower intermediate education (47.5% [7.25-50.0]), or intermediate education (25.0% [2.0-50.0]). Respondents who believed that a healthy lifestyle could reduce dementia risk did not perceive their own risk as very different compared to those who did not believe in the modifiability of dementia risk (26.0% [22.1-29.9] versus 31.6% [25.0-38.2], respectively). These patterns did not differ with age or between men and women. Of 687 survey respondents, 570 indicated a 'risk threshold' at which they would take measures to reduce their dementia risk. This threshold was median 50.0% (IQR 27.3-60.0%), which in the vast majority of respondents was higher than their perceived 10-year risk (Figure 2). This was consistent across age groups.

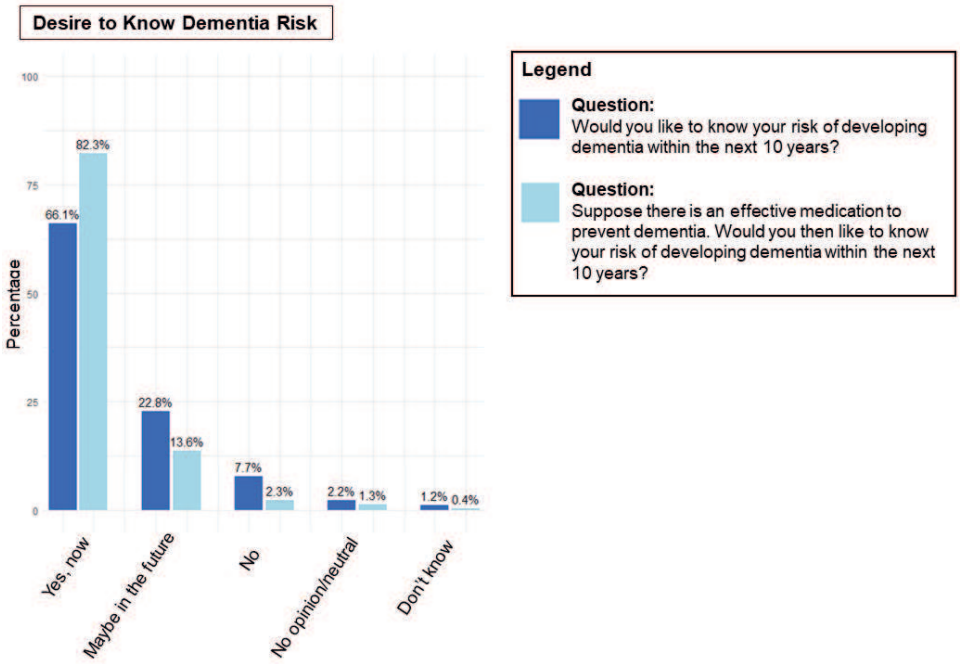
Desire to know dementia risk

A total of 451 survey respondents (66.0%) expressed a desire to know their dementia risk, and an additional 156 respondents (22.7%) indicated they might want to know in the future (Figure 3). Only 53 respondents (7.8%) stated they did not want to know their dementia risk. These numbers did not differ substantially for older respondents (age ≥70: 33/47, 70.2%) compared to their younger counterparts (age 50-69: 239/352, 68.5%; <50 years: 174/279, 62.6%). Presuming an effective medication to prevent dementia were available, the share respondents interested in knowing their dementia risk increased from 66.0% (451/683) to 82.3% (562/683), with only 2.3% preferring not to know their 10-year dementia risk (Figure 3).

Prior beliefs about dementia risk reduction were unrelated to the attitude towards risk prediction; individuals who believed lifestyle could modify their dementia risk were just as willing to hear about their dementia risk (65.1%) as those who did not (68.2%). Similarly, participants who perceived their risk factor knowledge as higher than average would like to be informed equally (61.2%) as those with lower than average self-perceived knowledge (67.6%). Respondents who were interested in knowing their current dementia risk estimated their 10-year risk slightly higher (median 25%, IQR 6.5-50.0%) than those who were not interested in knowing their risk (median 15.0%, IQR 3.0-40.5%; p-value=0.667). Results were similar between women and men. Desire to know dementia risk was slightly lower among respondents with higher education (60.5%), compared to intermediate education (73.4%) and lower/primary

education (69.7%).

Figure 3. Desire to know one's dementia risk among survey respondents



Distribution of responses to survey questions among respondents (N=687). Percentages indicate the proportion of respondents selecting each response option.

Reasons for wanting to know one's dementia risk

Participants in the focus groups mentioned several reasons for wanting to know their predicted dementia risk. One key reason was the practical utility of this information (Table 2.a.; quote 1). Another reason was to help prepare family and friends. Additionally, some participants emphasized the importance of enjoying the present moment (Table 2.a.; quote 2). Other motivations included having a family history of dementia and wanting to adopt a healthier lifestyle while there is still time to make changes. Curiosity about personal health also emerged as a reason (Table 2.a.; quote 3). However, focus group participants were also unsure how they would react if they heard their personal dementia risk (Table 2.a.; quote 4).

In the survey, 381 of 687 respondents (55.5%) indicated "Dementia runs in my family" as a reason for wanting to know their risk (Figure 4). Similarly, 379 (55.2%) stated that

knowing their risk would help them manage practical matters, such as preparing a living will or advance directives. Additionally, 255/687 respondents (37.1%) wanted to know their risk to prepare family and friends for the possibility of dementia. Finally, 234/687 (34.1%) mentioned that knowing their risk would motivate them to adopt a healthier lifestyle.

Reasons against wanting to know one's dementia risk

Common reasons cited in the focus group for not wanting to know predicted dementia risk included concerns about emotional distress, the fear that an increased risk of dementia could heighten anxiety (Table 2.b.; quote 5), and the potential for stigma associated with having a high risk of dementia (Table 2.b.; quote 6). Other reasons against wanting to know dementia risk included the belief that dementia risk cannot be mitigated by lifestyle (Table 2.b.; quote 7), and difficulties interpreting one's predicted risk. Some participants shared experiences of close relatives who developed dementia despite a healthy lifestyle, reinforcing the belief that preventive actions might be futile.

One third of survey respondents (214/687, 31.1%) did not want to know their risk because they believed nothing could be done to reduce it (Figure 4). This included 100 participants who earlier agreed to the statement that a healthy lifestyle could reduce dementia risk. In addition, 139/687 (20.2%) respondents reported being afraid of dementia, and 68/687 (9.9%) expressed concern about frightening family and friends.

Figure 4. Reasons for and against wanting to know one's dementia risk



Distribution of responses to survey questions among respondents (N=687), for A) the most important reasons to know dementia risk, and B) the most important reasons against knowing dementia risk. Counts indicate the number of respondents that selected each response option. Individual respondents could provide multiple answers.

Table 2. Focus group quotes

A. Focus group participants reasons for wanting to know dementia risk	
Quote 1	"But for practical reasons, because I am single, [...] I might still take some actions."
Quote 2	"There's nothing more to be done about it. Go and enjoy life."
Quote 3	"I want to know everything about my body"
Quote 4	"Do you want to know or not? I would think yes, but I have no idea how I would react if I heard it."
B. Focus group participant reasons for avoiding dementia risk information	
Quote 5	"You can't let it go, and everyone says, 'Hey, enjoy life while you still can,' but you're completely gripped by that fear."
Quote 6	"The term [dementia] immediately carries a stigma."
Quote 7	"She [a close friend] was the epitome of healthy living, and yet, she still eventually started experiencing forgetfulness."
C. Considerations regarding clinical implementation of risk prediction	
Quote 8	"It remains, of course, a very personal choice."
Quote 9	"But with the possibility of a cure, I think many people would be more inclined to take further steps in general."
Quote 10	"I would find it very risky to do that [a self-test] myself."
Quote 11	"Yes, I would definitely consult with my GP on this to get their perspective. It's important to have another opinion alongside your own."

Considerations for clinical implementation of risk prediction

The focus group participants emphasized that deciding whether to know your dementia risk is a deeply personal choice (Table 2.c.; quote 8), including the timing of when one wants to obtain this information. Most participants indicated a willingness to undergo more invasive testing, if there was a possibility of reducing their dementia risk (Table 2.c.; quote 9). The idea of a self-test was put forward, but focus group participants were generally opposed to a self-test for dementia (Table 2.c.; quote 10), preferring a more personalized approach to learning about their risk from their healthcare provider (Table 2.c.; quote 11). Similarly, two thirds (454/685; 66.3%) of survey respondents preferred to learn about their dementia risk from their healthcare

provider, chiefly from a medical specialist (43.6%) or general practitioner (22.6%). Yet, nearly one in five survey respondents would consider a self-test (129/685; 18.8%).

Supposing their predicted risk would turn out higher than expected, a majority of survey respondents would consider changing their lifestyle and habits (567/687; 82.5%) or taking medication (367/687; 53.4%) in order to reduce their dementia risk. The most frequently chosen actions were more regular exercise (67.8%), participating in memory training (61.3%), maintaining a healthier diet (61.1%), and staying socially active (55.3%). While half of respondents would be willing to take preventative medication with no or limited side effects, only a small minority indicated they would take medication with significant side effects (41/687; 6.0%).

DISCUSSION

In this mixed-methods study, we explored public perspectives on dementia risk prediction and identified key reasons for and against wanting to know one's dementia risk. In the focus group, predominant hesitancy to know one's dementia risk was attributed to fear and emotional concerns, and a perceived lack of actionability. Among the survey respondents, the majority wanted to know their risk, especially if effective preventive medication were available.

Response to the survey was overwhelmingly in favor of personalized risk disclosure, somewhat at odds with the impression from our focus group. Survey respondents were likely more interested in dementia due to their engagement with the Dutch Alzheimer Association, whereas focus group participants were drawn from a population-representative cohort, and were not selected based on dementia interest. The survey respondents represent a subgroup of the population that can be effectively reached with education on dementia risk. Nearly three quarters believed a healthy lifestyle could help reduce dementia risk, which supports the notion that this may be a relatively well-informed group.(10-12) Yet, survey respondents generally estimated their 10-year dementia risk much higher than commonly cited 10-year risks in the general population, with an average estimate of 19.0% among those under 50 and more than 50% after age 70. In reality, 10-year dementia risk at age 50 is generally <1%, and ranges between 12-35% at age 80.(13) Accurate risk information could help alleviate public anxiety among those overestimating their own predicted dementia

risk. Indeed, respondents who wanted to know their predicted risk, perceived their 10-year risk as higher than those who did not want to know.(14) At the same time, it should be prevented that communicating these risks inadvertently reduces motivation for beneficial lifestyle changes.

Actionability emerged as an important argument for knowing one's dementia risk in both the focus group and the survey. This aligns with anecdotal information from an earlier group conversation we had with general practitioners, who were more inclined to use risk prediction tools with clear clinical implications. Actionability could relate to lifestyle changes, medication prescription, or sometimes enrolment in clinical trials. If an effective medication were available, nearly all respondents would want to know their dementia risk. This highlights the importance of developing risk assessment tools and risk communication strategies for clinical practice, in anticipation of targeted disease-modifying therapies.(15) It should be noted that many survey respondents perceived their own 10-year risk as too low to take action, which could explain a lack of personal motivation for lifestyle changes, and may also imply that people with mild cognitive impairment at low predicted risk of disease progression could be reluctant towards active treatment. In any case, the often limited knowledge on modifiability on dementia risk underscores the need for greater public education, for example through public awareness campaigns.(16)

Our findings emphasize that the desire to know one's dementia risk is a deeply personal decision, with individuals citing various reasons for either wanting or not wanting to know. Focus group participants were generally hesitant towards knowing risk, often due to concerns about anxiety over test results and the stigma associated with dementia. Prior studies on public opinion regarding dementia screening (in prodromal stages), rather than risk prediction, have shown similar views, with anxiety about test results and concerns over stigma being common themes.(5, 6) In our study, participants mentioned practical benefits, emotional relief, and the opportunity to maximize present-day quality of life as motivating factors for knowing their risk. Similarly, in screening studies, individuals expressed belief in potential benefits, the chance to make lifestyle changes, and family pressure for a diagnosis as key motivators.(5, 6)

Clear and understandable communication of disease risk to patients and caregivers can be challenging,(17) and difficulties in interpreting dementia risk came up as a potential barrier during our focus group discussion. This emphasizes the importance

of consulting a healthcare professional to avoid the potential risks of misinterpreting self-test results, and may underlie the fact that 80% of survey respondents would not consider a self-test. We believe effective and empathetic communication by healthcare providers is important to properly address the complexity of interpreting dementia risk and its actionability.(17) The substantial variation in patients' personal preferences advocate for shared decision-making with patients and their relatives.(18-21) Percentages and probabilities can be challenging to understand, and the use of visual aids, such as visual arrays, can help enhance comprehension of risk probabilities.(22) Disclosure of genetic risk was not explicitly discussed during our focus group, but should be considered explicitly in clinical setting, in particular because of the wide variety in social acceptability of genetic testing across cultures.

Whilst our study offers valuable insights into public perspectives on dementia risk prediction, several limitations should also be considered. First, observer bias may have affected the thematic analysis of focus group data, despite the assessment of transcripts by two independent raters. Second, the survey population predominantly consisted of more highly educated women, potentially limiting generalizability. Third, survey respondents were likely more interested and engaged with dementia than the general public, which may be reflected in more knowledge on dementia and a greater desire to know one's predicted risk. Focus group participants were also involved in research and therefore potentially better informed. Lastly, while we consulted healthcare providers, including general practitioners and geriatricians, to develop the focus group topics, we only formally investigated opinions from the general public. Input from other stakeholders, such as clinicians and policymakers, is also important to guide the development and uptake of dementia risk prediction models.

Among citizens with particular interest in dementia, many are keen to learn more about their personal dementia risk, particularly in the presence of effective preventive measures. However, hesitancy remains due to fear, emotional burden, and uncertainty or unfamiliarity about the efficacy of preventive interventions. Development and implementation of dementia prediction tools can benefit from a keen eye for individual preferences, and tap into actionable reasons for wanting to know one's dementia risk.

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SUPPLEMENTARY MATERIALS

Supplemental Table A. Topic list focus group

Subject	Question	Possible follow-up questions	Aim of question(s)
Knowledge	What do you know about dementia?	• What do you think are the most common symptoms of dementia? • How likely do you think it is that you will develop dementia? • How likely do you think it is that a 50-year-old has dementia? • How likely do you think it is that an 80-year-old has dementia?	To gain insight into participants' knowledge, awareness, and personal perspectives on dementia.
Knowledge	Have you ever heard about ways to calculate the likelihood of getting a certain disease?	• Can you give examples of such methods? • What do you think about these methods? • Do you think these methods are useful or not?	To understand participants' knowledge of prediction models.
Attitude	There are prediction models for dementia, but they are currently mainly used for scientific purposes and not yet in clinical practice. We are investigating whether they could be useful in general practice or hospitals. What are your thoughts on this?	• Can you imagine a situation where you would want to know your risk of dementia? • Would you want to know this for dementia specifically, or are there other diseases you would be interested in knowing your risk for? • What reasons should these models be used for? • Why would you want to know your risk? • Is it to provide clarity about your health? • Would you want to know this only if you have symptoms, or even if you don't have any yet? • Might your interest change in the future? • What if better treatments become available? • How far in advance would you want to know the prediction? • Would you use this service if it required an out-of-pocket payment? • What kind of information would you be willing to provide for this calculation? • Would you be willing to have a blood test? • Would you undergo an MRI scan?	To gain insight into participants' attitudes toward dementia risk prediction models.

Implications	Suppose the doctor calculates your risk of developing dementia. What would you do with this information?	• What would you do if you were found to have an increased risk of dementia? • What would you do if your risk was 50%? • What would you expect from the person who tells you your risk? • From whom would you want to hear your risk? • Who should administer the test (GP, specialist, yourself)? • At what level of dementia risk would you feel reassured? • At what level of dementia risk would you start to worry? • What do you need to properly understand this information? • Suppose the prediction model says your dementia risk is 90%; how would you interpret that? • Is that risk irreversible? • Would you change your diet? • Would you quit smoking? • Would you take your medication for blood pressure more diligently? • What would you advise your partner/father/mother?	To understand what participants might do with this information, for the benefit of themselves and society.

Supplemental Table B. Themes and categories focus group

Themes		Subthemes
A.	Motivations for willingness to know dementia risk	Practical benefits of knowing the risk
		Alleviating emotional burden of uncertainty
		Curiosity about personal health
		Desire for actionable information
B.	Reasons for avoiding dementia risk information	Emotional distress from knowing the risk
		Confidence in current preventive measures
		Belief that risk cannot be mitigated
C.	Considerations for clinical implementation of risk prediction	Willingness to undergo invasive testing if it significantly reduces risk
		Preference to learn about dementia risk from healthcare professionals
		Need for thorough and sensitive communication by healthcare providers
		Personal choice regarding the timing of receiving risk information

Supplemental Material C. English translation of original survey
The survey was drafted in Dutch layman language and clarity of questions and provided information was evaluated through a feedback round with two professionals working at Alzheimer Nederland.

Dementia Risk Prediction
Welcome to the survey: Dementia Risk Prediction
1 in 5 people will develop dementia. We are getting better at predicting who will and who won't develop dementia. This can be useful to know, but also difficult to understand or process.

Through this study, we want to better understand whether people want to know their risk of developing dementia and how this risk can best be communicated to them. This questionnaire is not being used to determine your risk of dementia.

The questionnaire consists of 15 questions.

Please note: click on 'Done' when you have finished filling out the questionnaire.

Question 1: What is your sex?
- Male
- Female
- Prefer not to say
- Other, namely:

Question 2: What is your age?
Open ended.

Question 3: What is the latest level of education you have completed?
- No diploma or primary school
- Secondary school: MULO, ULO, LTS, household school, mavo, vmbo
- Secondary school: HBS, havo, vwo
- Vocational education: mbo
- Scientific education: hbo, university
- Prefer not to say
- Other, namely:

Question 4: What is your living situation?
(Multiple answers are possible.)
- Alone
- With a partner
- With children
- Other

Question 5: How high do you estimate the chance that you will develop dementia within the next 10 years?
Slider from 0-100.

Question 6: Compared to the average person of your age, how high do you estimate the chance that you will develop dementia within the next 10 years?
- Much lower
- Somewhat lower

- About the same
- Somewhat higher
- Much higher

Question 7: How much do you know about factors that can increase or decrease the risk of dementia?
- Nothing
- A little
- Average
- A lot
- Very much

Question 8: To what extent do you agree or disagree with the following statement:
"I can reduce my risk of dementia by living a healthy lifestyle."
- Strongly disagree
- Disagree
- Neutral
- Agree
- Strongly agree

Question 9: Would you like to know how high your risk is of developing dementia within the next 10 years?
- Yes, I want to know
- Not now, but maybe in the future
- No, I don't want to know
- No opinion / Neutral
- I don't know

Question 10: Suppose there is an effective medication to prevent dementia. Would you then want to know how high your risk is of developing dementia within the next 10 years?
- Yes, I want to know
- Not now, but maybe in the future
- No, I don't want to know
- No opinion / Neutral
- I don't know

Question 11: What are the most important reasons for you to want to know your risk of dementia?
(Multiple options are possible.)
- Prepare family and friends for dementia
- Dementia runs in my family
- Healthier living (so I can still do something about it)
- Arrange practical matters (e.g., living will or advance directives)
- Enjoy the here and now more
- I don't know
- I don't want to know
- Other, namely:

Question 12: What are the most important reasons for you to <u>not</u> want to know your risk of dementia?
(Multiple options are possible.)

- I am afraid of dementia
- I don't want to scare my family and friends
- There's nothing I can do about it anyway
- I don't know
- I do want to know
- Other, namely:

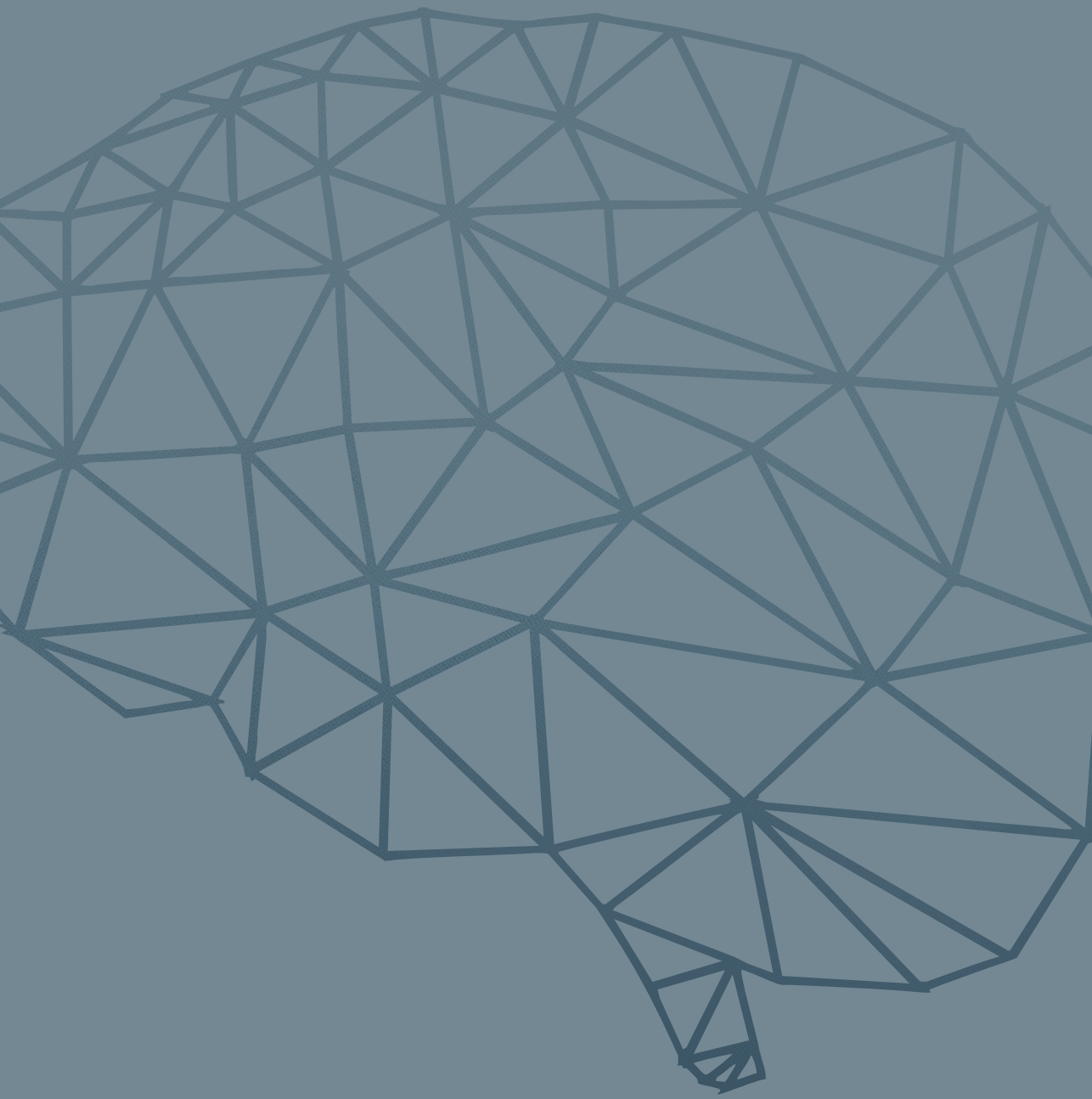
Question 13: How would you like to find out about your risk of dementia?
(Even if you don't want to know the risk now, we are interested in your answer.)

- Through a self-test (e.g., an app or finger prick)
- Through a commercial service (e.g., a total body scan)
- Through the general practitioner
- Through a medical specialist (e.g., neurologist, geriatrician)
- No opinion / Neutral
- I don't know

Question 14: Suppose your risk of dementia is higher than you expected. What would you do to reduce your risk of dementia?
(Multiple options are possible.)

- Nothing
- I believe I am already doing enough to reduce my risk
- Eating healthily
- Exercising enough
- Being socially active
- Memory training, puzzles, bridge, etc.
- Taking medication with no or mild side effects (e.g., blood pressure pill, cholesterol pill)
- Taking medication with many side effects
- None of the above

Question 15: At what level of dementia risk would you take measures (as in the previous question) to reduce your risk of dementia?
Slider from 0 – 100%.
If you do not wish to take any measures, please do not answer this question.



CHAPTER 4.2

DEVELOPMENT OF A DEMENTIA PREDICTION MODEL

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Development of a dementia prediction model for individuals with cognitive complaints or familial history.

In preparation

ABSTRACT

Background: Accurate prediction of dementia risk can facilitate clinical trial recruitment and tailored prevention and care. However, implementation of these models in clinical practice remains limited, partly because current models are not developed in the target populations, and insufficiently account for competing mortality risk.

Methods: From the population-based Rotterdam Study, we included between 2009 and 2013 dementia-free individuals over 60 years of age, who reported either subjective memory complaints or a positive family history of dementia. We derived a basic model, with prespecified candidate predictors that can be easily acquired in primary care. For an extended model, we included additional, more advanced predictors, including neuropsychological assessment, genetics, and brain imaging. We used subdistribution hazard models to determine risk of dementia within 5 and 10 years using C-statistics and calibration plots, compared with a reference model using age alone. Additionally, we computed sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), and determined the optimal threshold using Youden's index.

Results: We included 1963 individuals (mean age: 71.7, 55.1% women), of whom 159 developed dementia during a mean follow-up of 6.7 years. The basic prediction model included age, Mini-Mental State Examination, and walking speed out of 19 candidate predictors, resulting in a C-statistic of 0.91 [95%CI: 0.87-0.96] for 5-year, compared to 0.77 [0.73-0.84] for age alone. For 10-year prediction, a C-statistic of 0.82 [0.77-0.87] was reached, compared to 0.59 [0.50-0.64] for age alone. Calibration showed an underestimation of absolute risks. In the extended model, brain imaging (white matter volume, white matter hyperintensities volume, amygdala volume, presence of brain infarcts, and cerebral blood flow), APOE, polygenic risk score, and neuropsychological assessment slightly improved calibration and did not substantially improve discrimination, with C-statistics of 0.92 [0.86-0.97] at 5 years, and 0.80 [0.73-0.85] within 10 years. At the optimal risk threshold for 5-year prediction, the basic model achieved 0.90 sensitivity and 0.78 specificity, similar for the 10-year window, and changing to a sensitivity of 0.82 and specificity of 0.88 for the extended model. Tailoring the extended model to high-risk individuals alone according to the basic model, calibration improved while C-statistics were somewhat lower at 0.70 [0.64-0.80] and 0.70 [0.43-0.86] for both 5- and 10-year prediction.

Discussion: Among individuals with cognitive complaints or a family history of dementia, easily obtainable clinical predictors have high discriminatory value but underestimate dementia risk at a 5- and 10-year horizon. Further incorporation of cognitive, genetic, and imaging data did not substantially improve discrimination overall, but did lead to somewhat better calibration within 5 years, and may contribute in further refining risk estimation within high-risk groups.

INTRODUCTION

Dementia is one of the most significant health challenges of this century, affecting an estimated 57 million people globally. Timely and accurate identification of those at highest risk for dementia can enable early intervention with personalized preventative strategies and aid in the design of clinical trials. Additionally, we have previously shown that two-thirds of the surveyed individuals expressed a desire to know their dementia risk,[1] underscoring the demand among the general public for dementia prediction models that accurately provide tailored information on their dementia risk. Interestingly, that same study showed that individuals tend to overestimate their dementia risk, suggesting that dementia prediction models may help provide reassurance for those concerned.

Although numerous dementia risk prediction models have been developed over the past few years, [2, 3] implementation of prediction models in clinical practice remains limited. One explanation is that these models are often developed on population-based cohorts, which do not necessarily reflect the specific target populations in which such tools will be ultimately applied. In practice, physicians are mostly confronted with questions regarding dementia risk by individuals with subjective cognitive complaints or a family history of dementia. Another reason may be that existing risk prediction models often do not satisfy the needs of routine clinical care. Predictors like cognitive test batteries, genotyping, and neuroimaging are typically available only in specialized settings, making them less applicable to primary care. A two-step prediction model, with one model specifically designed for primary care and a second model for specialized care, might better align with the processes in dementia care. Moreover, existing models have not incorporated recently identified predictors, such as advanced neuroimaging markers[4-8], which have been established as important predictors for dementia and could potentially enhance

predictive performance.[9] Finally, questions regarding methodological validity existing models may arise, especially when considering dementia in the context of mortality as a competing risk from a prognostic perspective.[10, 11] This could potentially lead to an overestimation of dementia risk and compounding concerns among patients and caregivers.

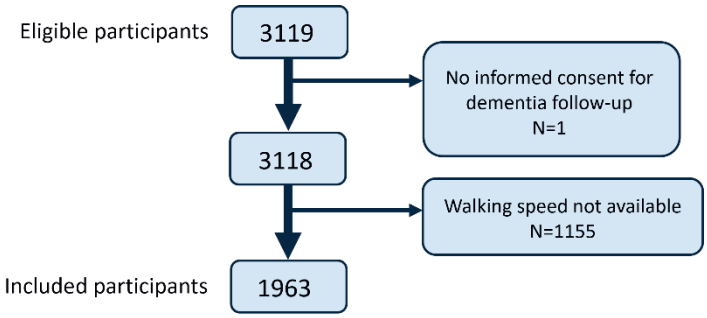
In this study, we aimed to develop a dementia risk prediction model for community-dwelling individuals with subjective cognitive complaints or a familial history of dementia and assess its performance for 5- and 10-year prediction horizons. Taking a staged, two-step approach, we first developed a model using easily obtainable clinical predictors suitable for primary care. Subsequently, we created an extensive dementia risk prediction model incorporating advanced established predictors, including genotyping, cognitive testing and neuroimaging.

METHODS

Study design

This study was embedded within the Rotterdam Study, an ongoing prospective population-based cohort study investigating determinants and occurrence of disease in persons aged 40 years and older. The study started in 1990 and now comprises 17,931 individuals living in the Ommoord suburb of Rotterdam, the Netherlands. The design of the Rotterdam Study has been described in detail previously.[12] In brief, participants are invited for interview and extensive in-person examination at a dedicated research centre every 3-6 years. For the current study, we included all participants from the fifth examination wave (2009-2013) who were aged 60 years or older, were free of dementia, had follow-up data for incident dementia until January 1, 2020, and had either subjective memory complaints or a positive family history of dementia. We excluded participants who did not provide informed consent to access medical records (N=1) (Figure 1). We additionally excluded participants whose walking speed was not collected (N=1155), primarily due to logistical reasons. After these exclusions, a total of 1963 participants were included in the analysis for the basic model. All participants provided written informed consent to participate in the study.

Figure 1 Flowchart of the inclusion of participants.



Ethics approval

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the Population Screening Act: Rotterdam Study.

Candidate predictors

We prespecified candidate predictors based on literature review, expert opinion, and their availability in clinical practice. We decided to include prodromal features as well to capture early disease manifestations that may improve short-term predictive accuracy. For the basic model, we considered predictors which can be easily acquired in primary care: age, sex, education level, body mass index (BMI), systolic blood pressure, smoking status, presence of memory complaints, need for assistance with finances or medication, Mini-Mental State Examination (MMSE) score, non high-density lipoprotein (non-HDL) cholesterol, presence of depressive symptoms, walking speed, hand grip strength, presence of hearing loss, history of stroke, presence of diabetes, presence of atrial fibrillation, and presence of coronary heart disease.

For the extended model, we included additional predictors which are more advanced but often available (or can be acquired) in memory clinic settings, namely a measure for general cognition, various brain imaging markers and genetic information. The brain imaging markers included total white matter volume, total gray matter volume, white matter hyperintensity volume, hippocampus volume, amygdala volume, peak-width of skeletonized mean diffusivity (PSMD), presence of any infarcts and total

cerebral blood flow. Genetic information consisted of APOE-ε4 carrier ship and a polygenic risk score for dementia. Detailed information on all predictors are provided in Supplementary Materials.

Assessment of dementia

Participants were screened for dementia at baseline and every 3-6 years during follow-up examinations using the MMSE and the Geriatric Mental Schedule (GMS) organic level. Those with an MMSE score of <26 or a GMS organic level score of >0 were further examined using the Cambridge Examination for Mental Disorders in the Elderly diagnostic interview including informant interview. Additionally, participants were continuously under surveillance for dementia through the electronic linkage between the study database and medical records from general practitioners and the Regional Institute of Outpatients Mental Health Care. The general practitioner functions as a gatekeeper within the Dutch healthcare system, receiving written information of any medical specialists' consultations of their patients. The final diagnosis of dementia and its most common subtypes was made by a consensus panel led by a neurologist based on the standard criteria for all-cause dementia (DSM-III-R) and clinical Alzheimer's disease (NINCDS-ADRDA).

Statistical analyses

Missing data on predictors (<15.0%, Supplemental Table 1) were imputed using 5-fold multiple imputation, after which we merged the imputed datasets into a single analysis dataset. Skewed distributions of white matter hyperintensity volume and MMSE score were transformed to normal distributions using a log transformation and reverse log transformation (log(max(X+1)-X)), respectively.

For the development of both the basic and extended model, we used subdistribution hazard models as proposed by Fine and Gray[13] to determine risk of dementia, taking death into account as competing risk. We accounted for potential nonlinear effects of age by adding an age-squared term, after scaling age prior to squaring to reduce collinearity.

We first checked the proportional hazards assumption using Schoenfeld residuals and, when necessary, added time interaction terms for variables violating this assumption. Next, we used the least absolute shrinkage and selection operator (LASSO) technique[14] in a 10-fold cross-validation to select the most important

predictors for the basic model. Subsequently, we performed LASSO on the selected predictors from the basic model in combination with the additional candidate predictors for the extended model to select the most important predictors for our extended model.

We evaluated discrimination and calibration of all models by computing the C-statistics and calibration plots for survival data with competing outcomes[15] using 10-fold bootstrap cross validation. To assess the added value of additional predictors, we compared each model against a reference model based on age alone. In addition, we explored the use of certain thresholds to classify individuals into risk categories (low risk vs. high risk) for both the basic and extended model. For thresholds set at 2%, 5%, 10%, 15%, 20%, 25%, 30%, and the threshold identified using Youden's index[16], we computed sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). All performance metrics were computed for prediction horizons of 5 and 10 years.

In additional analyses, we applied an existing prediction model, previously developed within the Rotterdam Study[17], to our population, which only consisted of individuals with cognitive complaints or a family history of dementia. This model includes the following predictors: age, subjective memory complaints, history of stroke, and need for help with finances or medication. We subsequently assessed its performance and compared it to our basic model.

Recognizing that certain advanced predictors may not always be readily available in clinical practice, we created alternative versions of the extended model excluding either imaging data or genetic data. These adaptations explore to which extent the models remain applicable even when certain predictors are unavailable.

Finally, we re-developed the extended model restricted to individuals classified as high risk according to the basic model and the corresponding Youden index. By doing this, we test the applicability of the extended model when the basic model is used as referral tool.

All analyses were performed in R (version 4.4.2; packages: haven, readxl, dplyr, survival, glmnet, splines, ggplot2, mice, rio, riskRegression, prodlim).

RESULTS

Of 1963 participants, 159 developed dementia during a mean follow-up of 6.7 (+/-2.2) years. (Supplemental Figure 1) Baseline characteristics of included participants are shown in Table 1. The mean age at baseline was 71.7 years, and 55.1% of the included participants were women.

Model development and performance

After penalized LASSO selection, age, walking speed and MMSE (including MMSE with time interaction) were selected to be included in the final basic prediction model (Table 2). For the extended model, the following predictors were selected after penalized LASSO selection: age, MMSE (including MMSE with time interaction), g-factor, APOE-ε4 carriership, polygenic risk score, white matter volume, white matter hyperintensities volume, amygdala volume (including amygdala volume with time interaction), presence of any brain infarcts, and total cerebral blood flow.

The basic model demonstrated good discrimination for 5-year prediction (0.91 [0.87-0.96]), outperforming the reference model including age alone (0.77 [0.73-0.84]). Discriminatory ability (C-statistic: 0.92 [0.86-0.97) was slightly better for the extended model (Table 3). Calibration plots showed a slight improvement, particularly for lower risk scores, which the majority of individuals fall into, as shown in Figure 2. However, all calibration plots showed a consistent underestimation of absolute risks (Figure 2). As shown in Figure 3, the separation between the predicted risk distributions for individuals who will and will not develop dementia increases when moving from the age-only model to the basic and extended model.

The C-statistic at a 10-year prediction horizon decreased for the age-only reference model (C-statistic: 0.59 [0.50-0.64]), basic model (0.82 [0.77-0.87]) and extended model (0.80 [0.73-0.85]) (Table 3). Similar patterns were observed in the calibration plots.

Table 1 Characteristics of the total study population.

Characteristic	Total (N=1963)
Age, y	71.7 (7.2)
Sex, female	1082 (55.1%)
Education	
Primary only	165 (8.4%)
Lower vocational	800 (40.8%)
Intermediate vocational/higher general	586 (29.9%)
Higher vocational/university	412 (21.0%)
Memory complaints	1846 (94.0%)
Body mass index, kg/m2	27.3 (4.0)
Systolic blood pressure, mm Hg	145.0 (21.6)
Smoking	
Never	585 (29.8%)
Former	1145 (58.3%)
Current	233 (11.9%)
Non-HDL, mmol/L	3.92 (1.03)
MMSE	28 [27-29]
Depressive symptoms	205 (10.4%)
Need for assistence with medication or finances	342 (17.4%)
Walking speed, cm/s	117.0 (20.1)
Hearing loss	1057 (53.8%)
Stroke	85 (4.3%)
Atrium fibrillation	148 (7.5%)
Coronary heart disease	207 (10.5%)
Diabetes mellitus	323 (16.5%)
Hand grip strength, kg	27.4 (9.9)
APOE-ε4 carrier	586 (29.9%)
Polygenic risk score	0.03 (<0.01)
Total white matter volume (corrected for ICV)	0.34 (0.04)
Total gray matter volume (corrected for ICV)	0.46 (0.03)
WMH volume (corrected for ICV)	0.004 [0.002-0.008]
Hippocampus volume (corrected for ICV)*100	0.67 (0.06)
Amygdala volume (corrected for ICV)*100	0.25 (0.03)
Any brain infarct (cortical or lacunes)	263 (13.4%)
PSMD*1000	0.28 (0.07)
Total cerebral blood flow, mL/min	495.9 (86.7)

Continuous variables are presented as mean (SD) and categorical variables as n (%).

Table 2 Candidate selected predictors of basic and extended model.

	Basic model		Extended model	
Predictor	**Selected**	**Standardized HR [95%CI]**	**Selected**	**Standardized HR [95%CI]**
Age	X	2.11 [1.79-2.48]	X	2.81 [1.94-4.03]
Age^2			X	0.61 [0.47-0.79]
Sex (female)			Not considered	
Education (primary/lower vocational/ Intermediate vocational/higher vocational)			Not considered	
Memory complaints			Not considered	
Body mass index			Not considered	
Systolic blood pressure			Not considered	
Smoking (current/former/never)			Not considered	
Non-HDL			Not considered	
MMSE	X	2.34 [1.83-2.97]	X	1.49 [0.90-2.46]
MMSE*time	X	0.48 [0.38-0.60]	X	0.61 [0.36-1.04]
Depressive symptoms			Not considered	
Need for assistance with medication or finances			Not considered	
Walking speed	X	1.03 [0.85-1.23]		
Hearing loss			Not considered	
History of stroke			Not considered	
Atrium fibrillation			Not considered	
Coronary heart disease			Not considered	
Diabetes			Not considered	
Hand grip strength			Not considered	
G-factor	Not considered		X	1.43 [1.21-1.70]
APOE-ε4 carrier	Not considered		X	1.70 [1.19-2.42]
Polygenic risk score	Not considered		X	1.27 [1.09-1.48]
Total white matter volume	Not considered		X	0.93 [0.79-1.09]
Total gray matter volume	Not considered			
WMH volume	Not considered		X	1.16 [0.79-1.09]
Hippocampus volume	Not considered			
Amygdala volume	Not considered		X	0.83 [0.68-1.02]
Amygdala volume*time	Not considered		X	0.81 [0.56-1.17]
Any brain infarct (cortical or lacunes)	Not considered		X	0.45 [0.26-0.76]
PSMD	Not considered			
Total cerebral blood flow	Not considered		X	0.79 [0.66-0.96]

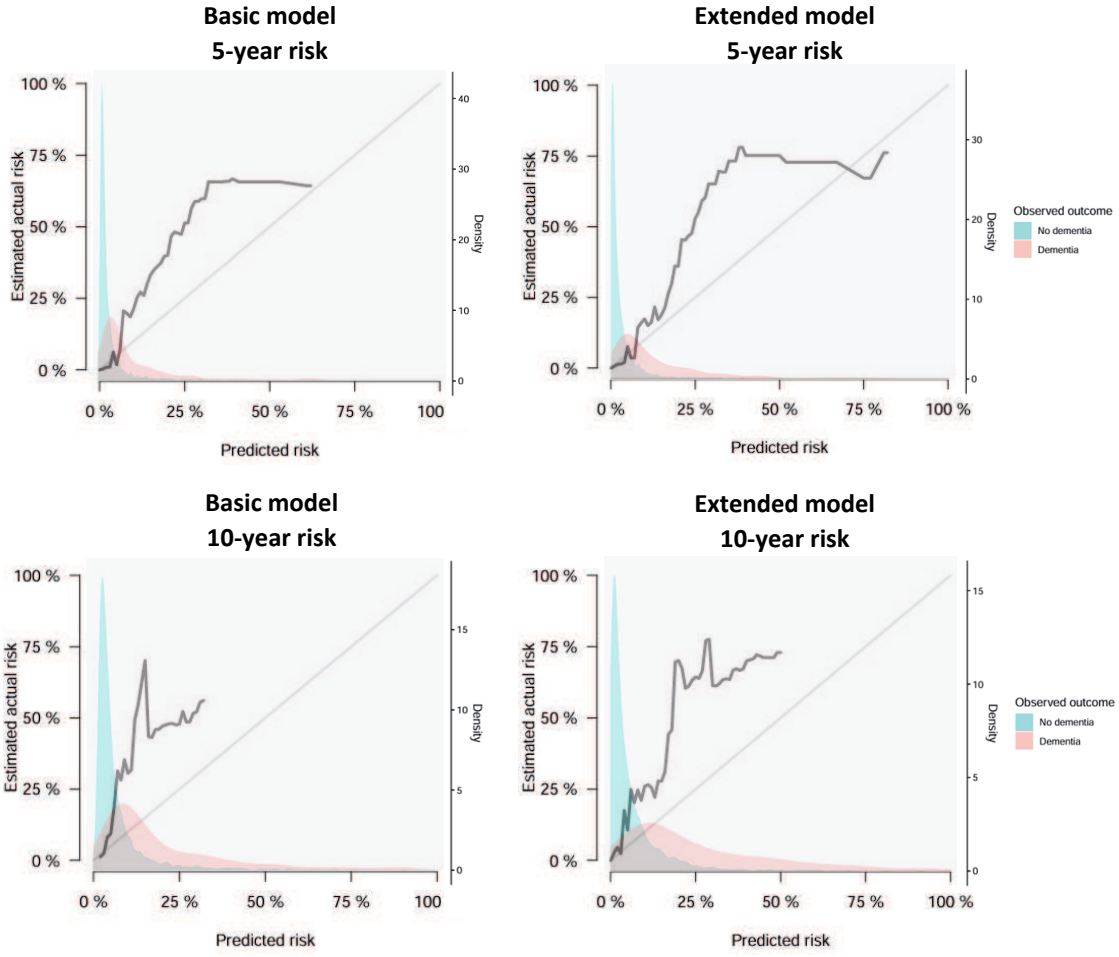
The table on the previous page presents standardized hazard ratios (per one standard deviation increase) derived from the final prediction model including selected predictors.
Abbreviations: HR=hazard ratio, CI=confidence interval, HDL=high-density lipoprotein, MMSE=Mini-Mental State Examination, WMH=white matter hyperintensity; PSMD=peak-width skeletonized mean diffusivity

Table 3 Discriminative ability of the basic and extended dementia prediction models.

	C-statistic [95%CI]		
	Age alone	Basic model	Extended model
5-year	0.77 [0.73-0.84]	0.91 [0.87-0.96]	0.92 [0.86-0.97]
10-year	0.59 [0.50-0.64]	0.82 [0.77-0.87]	0.80 [0.73-0.85]

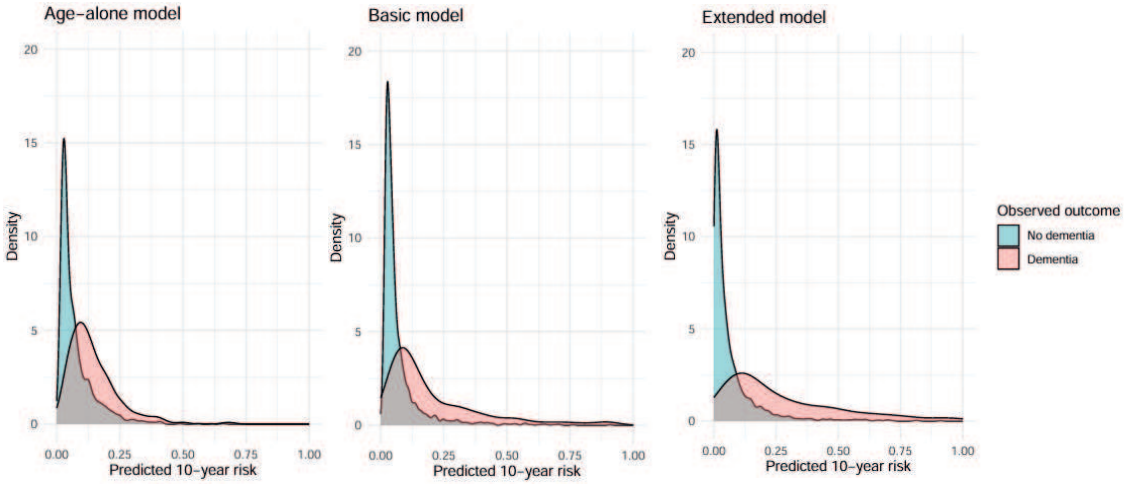
CI=confidence interval
Basic model: age, Mini-Mental State Examination (including time interaction), walking speed.
Extended model: age, Mini-Mental State Examination (including time interaction), g-factor, APOE-ε4 carriership, polygenic risk score, white matter volume, white matter hyperintensities volume, amygdala volume (including time interaction), presence of any brain infarcts, and total cerebral blood flow.

Figure 2 Calibration and density plots of the 5-year and 10-year prediction for the basic model and extended model.



In this figure, density plots are shown as overlay on the calibration plots, showing the relationship between predicted and actual 10-year dementia risk. The calibration plots compare predicted risk (x-axis) with actual risk (y-axis), with the diagonal line representing perfect calibration. The density plots (cyan for "No dementia" and pink for "Dementia") show the distribution of predicted risks for each outcome.

Figure 3 Density of predicted 10-year risk of dementia.



This plot shows the distribution of the predicted 10-year dementia risk, with the area under the curve representing the proportion of data within a range. In this figure, the plots display the predicted 10-year dementia risk for individuals who did not get dementia and those who developed dementia during the following 10 years.

Risk thresholds

The optimal risk threshold for a 5-year prediction horizon of the basic model determined by the Youden index was 0.04. Accordingly, individuals with a 5-year risk higher than 4% were considered high-risk. Within our study population, this resulted in 1480 individuals being classified as low-risk, and 483 classified as high-risk (Table 4). At this cut-off, the sensitivity was 0.903 and specificity was 0.779, while the PPV was 0.135 and NPV was 0.995. Relatively small increases in the risk threshold resulted in a substantially lower sensitivity and a higher specificity (Table 4). For a 10-year prediction horizon, the optimal threshold determined by the calculated Youden index was 7%, resulting in 1362 individuals classified as low-risk and 601 classified as high-risk. The sensitivity was 0.799, the specificity was 0.737, the PPV was 0.211, and the NPV 0.977.

The optimal risk threshold for a 5-year prediction horizon of the extended model determined by the calculated Youden index was 0.07, with a corresponding sensitivity and specificity of 0.819 and 0.877 (Table 5). PPV was 0.202 and NPV was 0.992. For a 10-year prediction horizon, 0.08 was the optimal threshold determined by the calculated Youden index. Accordingly, 1398 individuals were classified as low risk,

while 565 were classified as high risk. The sensitivity, specificity, PPV and NPV were 0.805, 0.758, 0.0.227, 0.978, respectively.

Table 4 Performance metrics at different thresholds for classifying individuals as low or high-risk with the basic model.

Prediction horizon	Threshold low-high risk	N low risk/ N high risk	Sensitivity	Specificity	PPV	NPV
5-year	0.02	1035/928	0.944	0.545	0.073	0.996
	0.04 (Youden index)	1480/483	0.903	0.779	0.135	0.995
	0.05	1628/335	0.792	0.853	0.170	0.991
	0.10	1812/151	0.556	0.941	0.265	0.982
	0.15	1877/86	0.375	0.969	0.314	0.976
	0.20	1910/53	0.278	0.983	0.377	0.973
	0.25	1927/36	0.208	0.989	0.417	0.970
	0.30	1940/23	0.125	0.993	0.391	0.968
10-year	0.02	169/1794	1.000	0.094	0.089	1.000
	0.05	1098/865	0.887	0.599	0.163	0.984
	0.07 (Youden index)	1362/601	0.799	0.737	0.211	0.977
	0.10	1568/395	0.591	0.833	0.238	0.959
	0.15	1721/242	0.428	0.904	0.281	0.947
	0.20	1791/172	0.327	0.933	0.302	0.940
	0.25	1836/127	0.270	0.953	0.339	0.937
	0.30	1865/98	0.220	0.965	0.357	0.934

Number of cases in low-risk group (using Youden index threshold): 7 (5-year); 32 (10-year)
Number of cases in high-risk group (using Youden index threshold): 65 (5-year); 127 (10-year)
PPV=Positive Predictive Value, NPV=Negative Predictive Value

Table 5 Performance metrics at different thresholds for classifying individuals as low or high-risk with the extended model.

Prediction horizon	Threshold low-high risk	N low risk/ N high risk	Sensitivity	Specificity	PPV	NPV
5-year	0.02	1149/814	0.944	0.605	0.084	0.997
	0.05	1570/393	0.861	0.825	0.158	0.994
	0.07 (Youden index)	1671/292	0.819	0.877	0.202	0.992
	0.10	1790/173	0.694	0.935	0.289	0.988
	0.15	1859/104	0.528	0.965	0.365	0.982
	0.20	1889/74	0.444	0.978	0.432	0.979
	0.25	1914/49	0.319	0.986	0.469	0.974
	0.30	1928/35	0.250	0.991	0.514	0.972
10-year	0.02	741/1222	0.962	0.407	0.125	0.992
	0.05	1169/794	0.899	0.639	0.180	0.986
	0.08 (Youden index)	1398/565	0.805	0.758	0.227	0.978
	0.10	1505/458	0.748	0.812	0.260	0.973
	0.15	1664/299	0.572	0.885	0.304	0.959
	0.20	1758/205	0.453	0.926	0.351	0.951
	0.25	1809/154	0.390	0.949	0.403	0.946
	0.30	1844/119	0.327	0.963	0.437	0.942

Number of cases in low-risk group (using Youden index threshold): 13 (5-year); 31 (10-year)
Number of cases in high-risk group (using Youden index threshold): 59 (5-year); 128 (10-year)
PPV=Positive Predictive Value, NPV=Negative Predictive Value

Additional analyses

Applying the prediction model from a previous study resulted in a C-statistic of 0.78 [0.74-0.82] for 5-year prediction and 0.60 [0.55-0.67] for 10-year prediction with moderate calibration in our sample.

Removing *APOE*-ε4 and polygenic risk score from the candidate predictors did not further change the set of selected predictors. The C-statistic and calibration plot for both 5-year (C-statistic: 0.93 [0.89-0.95]) and 10-year prediction (C-statistic: 0.78 [0.73-0.86]) remained similar to the original extended model (Supplemental Figure 2). Alternatively, when we excluded imaging markers as candidate predictors, also the polygenic risk score and the quadratic age term were dropped after penalized LASSO selection. Again, the C-statistic and calibration plot of this alternative model for both 5-year and 10-year were similar to those of the main extended model (for 5-year, C-

statistic: 0.91 [0.86-0.94]; and for 10-year, C-statistic: 0.86 [0.78-0.94]).

Referral pathway approach

For tailoring development of the extended model to high-risk individuals only, we used the 10-year Youden index from the basic model. Among the 601 individuals thus classified as high-risk, penalized LASSO selection resulted in the selection as predictors of age, MMSE, g-factor, APOE-ε4, polygenic risk score, amygdala volume, and total cerebral blood flow.

For 5-year prediction, the extended model achieved a C-statistic of 0.70 [0.64-0.80]. The calibration plot showed a good agreement between predicted and observed risks. Although the C-statistic for 10-year prediction was similar (0.70 [0.43-0.86]), confidence intervals were wider and calibration was poorer than for 5-year prediction.

DISCUSSION

In this study, we demonstrate that a prediction model including easily obtainable clinical predictors achieves high discriminatory value but underestimates dementia risk at a 5- and 10-year horizon among community-dwelling individuals with cognitive complaints or a family history of dementia. Although further incorporation of cognitive, genetic, and imaging data did not substantially improve discrimination overall, it did lead to somewhat better calibration within 5 years, and may contribute in further refining risk estimation within high-risk groups.

Previous studies that developed dementia prediction models in primary care populations using easily obtainable predictors, showed varying model performances, probably due to the inclusion of different predictors.[18-20] Interestingly, among these four primary care models, the model including MMSE had a high AUC, even when validated in external cohorts, whereas two out of the other three models without MMSE report moderate to low AUCs. This was also seen among other late life risk models.[21, 22] Within our basic model, which is specifically designed for primary care, MMSE was selected after penalized LASSO selection, demonstrating its importance as a dementia risk predictor. However, according to a previous systematic review, models based solely on MMSE demonstrate only moderate predictive accuracy,[2] indicating the need to incorporate additional predictors. Because MMSE is frequently used to trigger diagnostic evaluation for dementia, there

is a potential for circular reasoning. This concern is less relevant for prediction, where the aim is risk estimation rather than diagnosis. Although the inclusion of prodromal features might suggest that we are performing early diagnosis, it is important to recognize that prediction is being done at a stage in which symptoms are not yet present or severe enough for the actual diagnostic criteria. Additionally, prediction should be regarded as early diagnosis because individuals, classified as high risk, might get stigmatized or treated differently by their families.

Moreover, it is important to consider that not all primary care patients are inclined to engage in dementia risk assessment. In a previous study, we showed that one of the main reasons for individuals to having a desire for knowing their dementia risk is having a family member with dementia. This underscores the need for models specifically tailored to the target groups who are most likely to present these concerns to their general practitioners.[1]

Although several studies have shown that advanced markers, such as imaging markers and genetics, are related to dementia risk[23-25] and can enhance predictive performance for dementia prediction models,[17, 26, 27] our findings showed only a marginal improvement in performance for our extended model compared to our basic model. One possible explanation for this limited improvement lies in differences in study populations. Whereas previous studies often included participants from the general population, our sample consisted of individuals with cognitive complaints or a family history of dementia, suggesting that these advanced markers could be more effective in detecting subclinical stages of dementia among those without complaints than those with cognitive complaints. Another explanation could be that it is harder to improve predictive performance beyond age, MMSE and walking speed among individuals who may be already at higher risk, like those with cognitive complaints. Nevertheless, our findings show that advanced predictors may still have an important role in further refining risk estimates among high-risk individuals. As expected, the performance of the extended model designed for high-risk individuals was poorer than that of the extended model designed for the general population, as it is more challenging to discriminate among high-risk individuals compared to the total study population with a broader variety of dementia risks. However, the extended model for the referral approach still reaches a fairly good performance for 5-year dementia prediction. Regarding 10-year dementia prediction, the confidence interval widens, suggesting the increased uncertainty is due to longer follow-up. These findings indicate that the inclusion of advanced predictors may be particularly useful for 5-

year prediction when applied in a referral context. This is clinically relevant since it supports a two-step approach that reflects real-world processes in dementia care, where brain imaging is typically not performed in those who are considered low-risk.

Alongside the introduction of new predictors, advanced machine learning methods have also been used to further enhance prediction. However, even when deep learning methods are applied to imaging and genetic features, the improvement in AUC is only marginal,[28] underscoring the complexity in improving dementia prediction beyond fundamental predictors such as age and MMSE. Moreover, their added complexity and limited transparency must be balanced against the need for models that are feasible and clinically applicable.

An interesting observation in our study is that hippocampal volume, known for being an important diagnostic imaging marker of Alzheimer's disease,[29] was not selected in the extended model. This may be due to the inclusion of other imaging predictors, such as amygdalar volume, which correlate with hippocampal volume and therefore already capture its predictive value. Moreover, a recent study showed that amygdalar volume provides additional predictive information beyond hippocampal volume,[25] suggesting that the inclusion of amygdalar volume is sufficient enough to achieve good model performance. This might also apply for the selection of white matter volume as predictor, rather than grey matter volume. The observation that one marker may replace another is important for the implementation of such prediction models as the predictive power of both variables may be similar, but only one is ultimately selected. Therefore, it is crucial to consider not just statistical performance but also the clinical applicability of the chosen marker. Another unexpected finding was the protective association between brain infarcts and the risk of developing dementia. One plausible explanation is that individuals with a brain infarct have a higher risk of mortality and therefore may die before they can develop dementia.

Our findings showed consistently high NPVs for both the basic and extended model, indicating that individuals classified as low risk are very unlikely to develop dementia within the prediction horizon. This is particularly relevant in primary care context, where patients with low-risk scores can be reassured and general practitioners need to decide when further diagnostic evaluation is warranted. In contrast, PPVs were relatively low for both models at the optimal risk threshold according to the Youden index, implying that the model might lead to unnecessary referral of some patients who might otherwise have been reassured on clinical grounds. However, increasing

the risk threshold moderately improved the PPV without substantially reducing the NPV, suggesting that the models can be adapted to the clinical context —whether the goal is to provide reassurance for low-risk individuals or to identify high-risk individuals.

Our study is strengthened by the long-term, prospective ascertainment of dementia, in a large population, and the inclusion of a large variety of predictors, including multimodal brain MRI, genetic information and cognitive assessment. In addition, we focused on a specific population that closely reflects the target population in daily clinical (GP) practice and we took death as competing risk into account to achieve realistic risk estimates. Despite the new insights from our findings, it is important to acknowledge the methodological imperfections and remaining challenges. First, the prediction models presented in this study have not yet been externally validated in independent cohorts, limiting the generalizability of our findings. Future research should aim to validate these models in other populations. Second, we did not differentiate between dementia subtypes. Although relevant predictors may differ between subtypes, the number of cases for non-Alzheimer's dementias in our sample was too small for subtype analyses. Moreover, most individuals with dementia have mixed pathologies making it less likely that distinct dementia prediction models are required, and all-cause dementia arguably is the most relevant patient outcome albeit not necessarily for trial inclusion.[30] Third, we performed penalized LASSO selection to identify the most relevant predictors, but we did not use the shrunken coefficients in our final models as models did not allow for the combination of the shrunken coefficients with C-statistics and calibration plots for survival data with competing mortality outcome. However, this only affects calibration and not discrimination since it will not substantially change the order of predicted risks, but only the scale of the predicted risks resulting in a consistent underestimation in our findings. Fourth, we excluded individuals without data on walking speed. Although missingness was mainly due to logistical causes, some individuals might have declined this test due to health issues leading to a somewhat more healthy study population. Fifth, we did not include blood-based biomarkers, such as amyloid-beta, tau, or neurofilament chain since these measures were not available in our study sample. Nevertheless, our findings suggest that even without such biomarkers, the basic model can already serve as a practical and informative tool. Last, the Rotterdam Study population consists of a predominantly White population, which may limit generalizability to other populations.

In conclusion, easily obtainable clinical predictors can provide insights for individuals with cognitive complaints or family history regarding their 5- and 10-year dementia risks. Although further incorporation of cognitive, genetic, and imaging data did not substantially improve model performance, they may contribute in further refining risk estimation within high-risk groups.

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SUPPLEMENTARY MATERIALS

Detailed information on candidate predictors

Candidate predictors for basic model

Information regarding educational attainment, smoking habits, hearing loss, depressive symptoms, instrumental activities of daily living (IADL), and memory complaints was obtained by trained interviewers during baseline home interviews. **Educational attainment** was categorized into 4 groups, ranging from primary to higher education (higher vocational education or university). **Smoking** was categorized into 3 groups: former smoker, current smoker, or never smoker. The presence of **depressive symptoms** was determined using the Center for Epidemiologic Studies Depression (CES-D) Scale. Depressive symptoms were defined as present with a CES-D score of greater than 16.

Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters. **Blood pressure** was measured twice at the right arm with the participant in the seated position. The mean of 2 consecutive measurements was used. Non high-density lipoprotein (**non-HDL**) cholesterol were measured during visits at the research center.

Walking speed was evaluated using a 5.79-m long walkway (GAITRite Platinum; CIR systems, Sparta, NJ: 4.88-m active area; 120-Hz sampling rate). Participants were instructed to walk at their usual speed. After a practice walk, participants completed 7 normal walks according to a standardized protocol. Walking speed was calculated for each walk by dividing the distance traveled by the ambulation time, after which the overall gait speed was calculated as the average of the 7 walks.

Grip strength was assessed using a handgrip dynamometer and the grip strength was defined as the highest value (kg) of three trials performed in the non-dominant hand.[1]

During each visit to the research center, participants underwent dementia screening with the **Mini-Mental State Examination (MMSE).**

Definition of **stroke** adhered to the World Health Organization criteria,[2] describing a syndrome characterized by the rapid onset of focal or global cerebral dysfunction lasting 24 hours or longer or leading to death, with apparent vascular cause. Prevalent stroke was assessed at during interview, and we verified these data with medical records from the general practitioner. From interview onward, we maintained continuous surveillance for incident stroke through linkage of the study database with files from general practitioners. We obtained additional information from hospital records. When potential strokes were found, they were reviewed by research physicians and verified by an experienced neurologist.

Prevalent **atrial fibrillation** was determined during home interviews and thorough review of medical records. Ten-second 12-lead electrocardiograms (ECGs) were recorded at baseline

and during follow-up visits using an ACTA Gnosis IV ECG recorder (Esaote Biomedical, Florence, Italy) and stored digitally. ECGs were analyzed using the Modular ECG Analysis System (MEANS) software.[3] All ECG diagnoses were independently reviewed by two research physicians blinded to the MEANS results, with a cardiologist consulted to resolve any disagreements.

Coronary heart disease was defined as the occurrence of a fatal or nonfatal myocardial infarction, a percutaneous transluminal coronary angioplasty, a coronary artery bypass graft, other forms of acute or chronic ischemic heart disease, sudden cardiac death, and death due to ventricular fibrillation and congestive heart failure. Two research physicians independently reviewed and coded all reported cardiac events. In cases of disagreement, a medical expert in the field made the final determination.

Diabetes mellitus was defined as a fasting blood glucose concentration of ≥7.0 mmol/L or as use of antidiabetic drugs.

Brain MRI acquisition and processing

All participants underwent scanning on a 1.5-T MRI device (GE Healthcare) using a multisequence protocol consisting of T1-weighted, proton density-weighted, fluid-attenuated inversion recovery, and T2-weighted sequences. For brain volumetry, T1-weighted (voxel size 0.49 × 0.49 × 1.6 mm^3), proton density–weighted (voxel size 0.6 × 0.98 × 1.6 mm^3), and the fluid-attenuated inversion recovery (FLAIR) (voxel size 0.78 × 1.12 × 2.5 mm^3) scans were used for automated segmentation of supratentorial **gray matter**, **white matter**, cerebrospinal fluid (CSF), and **white matter hyperintensities**, using an in-house segmentation method.[4, 5] All segmentations were visually inspected, and manually corrected if needed. Total brain volume was the sum of gray matter, normal-appearing white matter, and white matter hyperintensity volume. Supratentorial intracranial volume was estimated by summing gray and white matter (consisting of the sum of normal-appearing white matter and white matter lesion volume) and CSF volumes.[5] Additionally, all T1-weighted MR images were processed using FreeSurfer (version 6.0) to obtain volumes of the **hippocampus** and **amygdala**[6]. Subcortical volumes were defined as the sum of the left and the right volumes (i.e., hippocampus, amygdala). **Peak-width skeletonized mean diffusivity (PSMD)** was derived using an automated pipeline (v0.95)[7] and the white matter skeleton.[8] fractional anisotropy values ≥ 0.2 and subsequently mean diffusivity (MD) values were projected on this skeleton. PSMD was then calculated as the difference between the 95th and 5th percentiles of voxel-based MD values. MRI scans with unreliable PSMD values (>0.0007) were excluded based on previous research.[9] For **cerebral blood flow** measurement, two–dimensional phase–contrast imaging was performed. A sagittal two–dimensional phase–contrast MRI angiographic scout image was performed (repetition time=24 ms, echo time=9 ms, field of view=32 cm2, matrix=256; 160, flip angle=101, number of excitations=1, bandwidth=8.06 kHz, velocity

encoding=60 cm/s, and slice thickness=60 mm). On this scout image, a transverse imaging plane perpendicular to both the precavernous portion of the internal carotid arteries and the middle part of the basilar artery was chosen for a two–dimensional gradient–echo phase–contrast sequence (repetition time=20 ms, echo time=4 ms, field of view=19 cm2, matrix=256; 160, flip angle=81, number of excitations=8, bandwidth=22.73 kHz, velocity encoding=120 cm/s, and slice thickness=5 mm). Flow (in milliliters per second) was calculated by multiplying the average velocity with the cross-sectional area of the vessel.31 All volumetric measurements were defined as percentage of total intracranial volume.

Cognitive assessments

Assessment of cognitive function was routinely performed at center visits through a cognitive test battery, including the Stroop test[10], measuring processing and attention, the Word Fluency Test (WFT)[11], measuring efficiency of searching long term memory, the Letter Digit Substitution Test (LDST)[12], measuring processing speed and executive function, 15-Word Learning Test (15-WLT)[13], measuring verbal learning and memory, and Purdue Pegboard test (PPB)[14], measuring dexterity and fine motor speed. We derived a global cognition measure (**g-factor**) from principle component analysis of available test scores,[15] defined as the first unrotated component, explaining 49.8% of variance in cognition in our sample. A higher g-factor indicates a better cognitive performance.

Assessment of genetic information

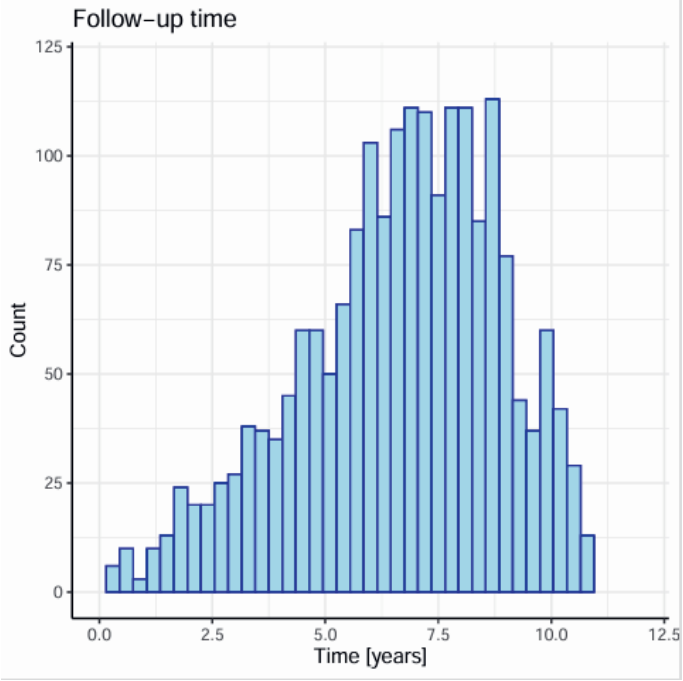
Apolipoprotein E *(APOE*) genotype was determined using polymerase chain reaction on coded DNA samples or using biallelic TaqMan assays (TaqMan Gene Expression Assays; Thermo Fisher Scientific, Waltham, Massachusetts) (rs7412 and rs429358).[16, 17] *APOE*-ε4 carriers were defined as carrying at least one ε4 allele (ε3/ε4, ε2/ε4 and ε4/ε4). The **polygenic risk score** was derived from 75 risk loci for dementia identified by a large genome-wide association study.[18]

Supplemental Table 1 Missing data in population on which both basic and extended model is based on (N=1963).

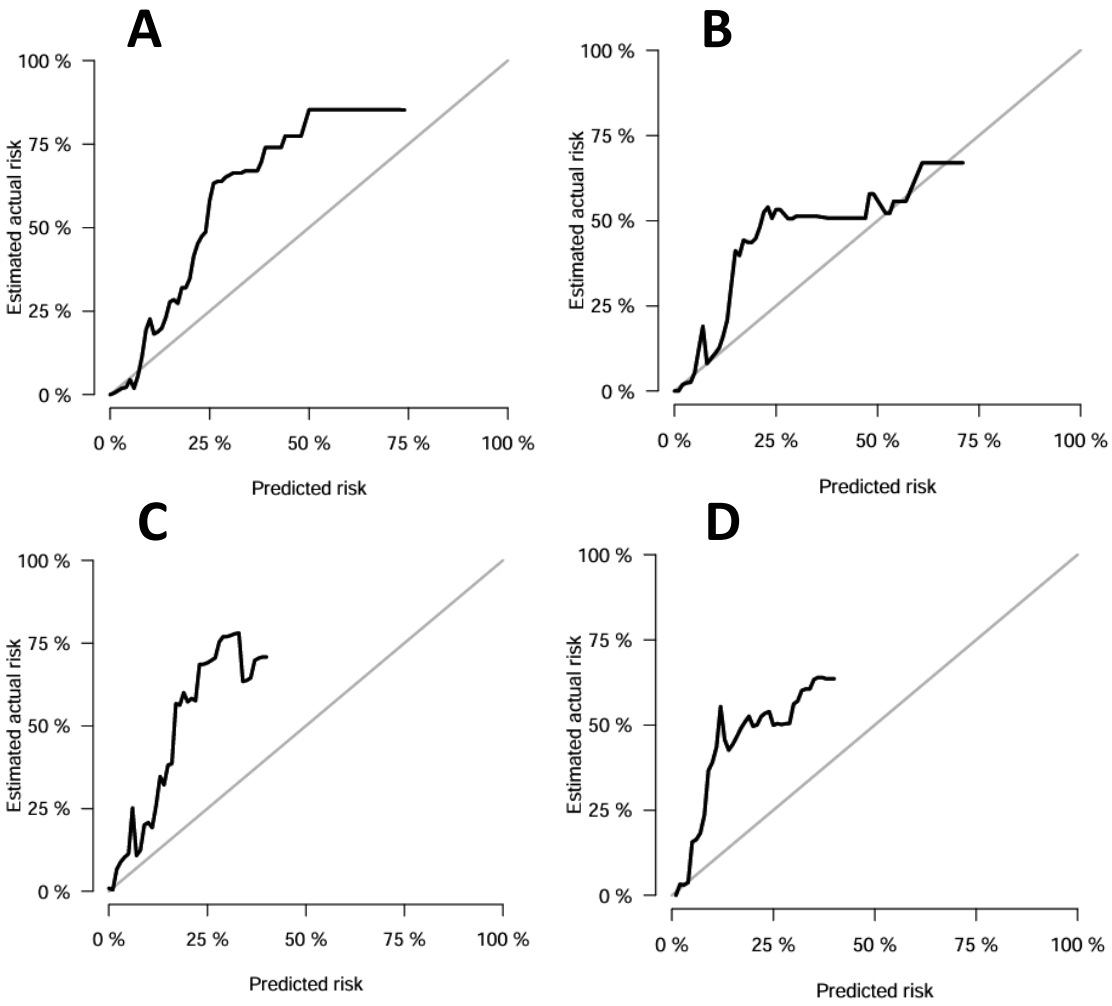
	N missing
Age	0
Sex	0
Education	26 (1.3%)
Memory complaints	12 (0.6%)
BMI	2 (0.1%)
Systolic blood pressure	3 (0.2%)
Smoking (current/former/never)	2 0.1%)
Non-HDL	27 (1.4%)
MMSE	1 (0.1%)
Depressive symptoms	2 (0.1%)
Need for assistance with medication or finances	72 (3.7%)
Walking speed	0 (0.0%)
Hearing loss	195 (9.9%)
History of stroke	0 (0.0%)
Presence of atrium fibrillation	0 (0.0%)
Presence of coronary heart disease	0 (0.0%)
Presence of diabetes	15 (0.8%)
Hand grip strength	33 (1.7%)
G-factor	220 (11.2%)
APOE-e4 carrier	53 (2.7%)
Polygenic risk score	283 (14.4%)
Imaging variables	<217 (11.1%)

Abbreviations: BMI = Body Mass Index, HDL=high density lipoprotein, MMSE=Mini-Mental State Examination, APOE=Apolipoprotein E. Imaging variables include: gray matter volume, white matter volume, white matter hyperintensities volume.

Supplemental Figure 1 Follow-up time of included participants.



Supplemental Figure 2 Calibration plots of the alternative extended dementia prediction models.



A: Calibration plot for 5 year prediction of the extended model without genetics. **B:** Calibration plot for 5 year prediction of the extended model without imaging. **C:** Calibration plot for 10 year prediction of the extended model without genetics. **D:** Calibration plot for 10 prediction of the extended model without imaging.

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CHAPTER 5

GENERAL DISCUSSION



In this thesis I investigated the role of neuroimaging biomarkers in identifying individuals with high risk of dementia. Additionally, I investigated the public's perspective on the use of dementia prediction models in clinical practice and improved current dementia prediction models using novel markers. In this chapter I discuss the main findings of this thesis and place them in a broader perspective. I subsequently discuss methodological considerations, future directions, and clinical implications.

MAIN FINDINGS

White matter biomarkers of brain health

To understand how cerebral white matter affects brain health, it is important to understand which characteristics of the white matter can be measured. Structural MRI enables assessment of macrostructural features, such as white matter volume or white matter hyperintensities (WMH) volume, while diffusion MRI provides information on the microstructural properties. Although these markers have individually been associated with risk of dementia, stroke, and mortality,[1-7] previous research has not clearly addressed how these imaging markers co-occur and how such patterns relate to clinical outcomes. In **Chapter 2.1**, I identified four distinct white matter signatures by applying clustering on structural and diffusion MRI data from a population-based sample of community-dwelling adults. These clusters were differentially associated with dementia, stroke, and dementia risk. Compared to single imaging markers, the identified clusters showed a superior model fit for both dementia and mortality risk models.

Notably, the two clusters with highest risks for all three outcomes had a significantly higher vascular burden and were characterized by high WMH volumes and a reduced microstructural integrity. This support previous evidence that vascular disease contributes to both reduced white matter integrity and WMH.[8-10] Although some of the identified clusters may represent different stages along a shared pathological trajectory, others are unlikely to fit within the same trajectory. Namely, we identified a cluster with relatively good microstructural integrity, but substantial atrophy, while another cluster had poor microstructural integrity and only little atrophy. These findings suggests that distinct white matter patterns may reflect different underlying pathologies.

This is further supported by literature on spatial patterns of WMH, which indicates that their location provides information on underlying pathologies. Specifically, WMH located in the anterior brain regions have been associated with vascular risk factors, while WMH in the posterior brain regions are more frequently associated with amyloid-related pathology such as cerebral amyloid angiopathy.[11, 12] In our study, the cluster with the highest risk of dementia showed a broad range of WMH volumes, suggesting that within this cluster WMH volume alone is not very specific. This suggests that WMH volume needs to be supported by other features, like location, shape[13], or other deep learning features, to reveal more information on underlying pathologies. Although it is interesting to incorporate all these features into models for advancing disease understanding, clinicians generally prefer models which are transparent, rather than a black hole from which it is impossible to understand what is going on. Simple models or explainable artificial intelligence may therefore provide a solution to ensure that the decision-making processes of algorithms are understandable.

A similar clustering approach was performed in a study of the Icelandic ageing population.[14] Although they did not incorporate information on microstructural integrity obtained from diffusion MRI, they did include grey matter imaging markers. The authors confirmed that distinct neuroimaging patterns were associated with varying dementia risks. Both this study and our study in **Chapter 2.1** included healthy participants at baseline and investigated associations with all-cause dementia. Although it is expected to have heterogeneity within dementia as a clinical syndrome, it is interesting that even within a single type of dementia, such as with Alzheimer's disease, heterogeneity can be present. For example, a previous study applied a pattern recognition approach in individuals diagnosed with Alzheimer's disease and identified multiple patterns of brain atrophy.[15] This shows that a variety of trajectories can progress to dementia, emphasizing the need for these multi-biomarker approaches.

Although **Chapter 2.1** already included multimodal MRI data, other imaging modalities, beyond MRI, have also shown their value in dementia research. For example, a previous study combined MRI with positron emission tomography (PET) to disentangle tau and brain atrophy cluster heterogeneity[16], highlighting the potential of multi-modality clustering to unravel heterogeneity in neurodegenerative diseases. These studies underscore the value of clustering approaches for unravelling the co-occurrence of imaging markers rather than relying on individual markers to get a clear

view of underlying pathologies. Identifying such patterns enhance our understanding of disease mechanisms and may also offer improved tools for personalized risk stratification across multiple clinical outcomes. However, it is important to acknowledge that other imaging modalities, such as PET, are invasive and might not be suitable for personalized risk stratification alone.

Although it was established in the first part of **Chapter 2** that diffusion MRI provides valuable insights into brain health, it is important to recognize that diffusion MRI offers a broader range of metrics beyond the commonly used fractional anisotropy (FA) or mean diffusivity (MD). **Chapter 2.2** compares multiple diffusion metrics measured within cerebral white matter to identify the optimal predictors of dementia and cognitive decline. Although previous literature showed that individual diffusion markers are associated with dementia and cognition[17-19], a direct comparison of their predictive value was lacking. The findings from **Chapter 2.2** show that the recently developed marker, peak-width skeletonized mean diffusivity (PSMD), is superior in predicting both baseline cognition and longitudinal cognitive decline among community-dwelling adults. In addition, both PSMD and MD emerged as superior predictors of incident dementia, underscoring that these are the preferred diffusion imaging markers for clinical prediction models. PSMD and MD are also easily acquired without the need of advanced post-processing, making them suitable for clinical implementation.

Taken together, **Chapter 2** highlights the importance of white matter imaging markers in understanding the etiology and prediction of brain health. Additionally, it shows the importance of combining and comparing multiple markers rather than focusing on single markers on their own. As new markers are developed, it is essential to not only focus on their individual value but also to consider how this new puzzle piece fits into the larger puzzle of brain health.

Grey matter indicators of dementia risk

Before diving into the role of grey matter for dementia risk, it is important to understand the different types of grey matter in the cerebral part of the brain. Cortical grey matter is found on the surface of the brain, while grey matter structures located deeper in the brain are considered subcortical grey matter structures, including the hippocampus, amygdala, thalamus, nucleus caudate, putamen, globus pallidum, and nucleus accumbens. These subcortical structures have different functions in the

brains, including memory, emotion regulation, signal relay, motor control, and reward processing. In the context of dementia, research has focused mainly on cortical grey matter and the hippocampus. However, other subcortical structures are increasingly being investigated due to their central role in information integration and network connectivity, combined with their vulnerability to pathological processes such as protein accumulation and vascular damage.[20-22] This raises the question of which subcortical structures are involved in the early brain changes that precede the onset of dementia.

Chapter 3 focusses on both cortical and subcortical grey matter and dementia risk. In **Chapter 3.1**, I demonstrated that lower volumes of the amygdala and hippocampus are each individually associated with an increased 5-year dementia risk in individuals with subjective cognitive complaints or mild cognitive impairment, even after adjusting for other subcortical grey matter and cortical grey matter volume.

According to previous literature, atrophy of the medial temporal lobe and specifically the hippocampus are hallmarks of Alzheimer's disease, in which pathologies accumulate.[23-25] Though the hippocampus was expected to be found associated with dementia risk based on previous studies[26-29], the relationship between amygdala volume and dementia risk beyond hippocampal volume was less established. This inconsistency in previous studies could be attributable to differences in study populations, disease stage, follow-up durations, and imaging parameters. Based on clinical symptoms like memory loss and emotional regulation that typically occur with dementia, it is not surprising that the amygdala, which is an important regulator for these cognitive domains, is damaged in patients with dementia.[30] Previous studies have shown that the amygdala is a site where amyloid-beta (Aβ), tau proteins, and TDP-43 accumulate, playing a key role in the development and progression of Alzheimer's disease pathology.[31, 32] However, vascular risk factors have been shown to modify tau accumulation in the brains in the presence of Aβ during early Alzheimer's disease[33], suggesting that cerebrovascular health could play an important (additional) role in the rate of amygdala atrophy.

A previous study within the Rotterdam Study found that, in addition to the hippocampus and amygdala, the volume of the thalamus was associated with dementia risk among cognitively healthy individuals. However, in **Chapter 3.1**, my findings showed no significant association for the thalamus across all three cohorts. Notably, within the cohort of the Rotterdam Study, the association appeared leaning

toward a significance. Other studies investigating the role of the thalamus in individuals with MCI, showed that thalamic volume loss is present during the early stage of MCI.[34, 35] Furthermore, it is also shown that thalamic volume loss does not further progress from late MCI to AD.[35] This may explain why a significant association with dementia risk was only observed in participants with subjective memory complaints in the population-based cohort (presumably representing an earlier disease stage) rather than in memory clinic populations. Since the thalamus has an important relay function between other subcortical structures, thalamus shrinkage might be the first trigger in a sequential cascade of atrophy in interconnected subcortical structures, such as the amygdala and hippocampus. One possible upstream driver of this process is the locus coeruleus, where tau spreading is believed to originate and spread along white matter tracts that partly connect to the thalamus,[36] potentially initiating a network-wide degeneration sequence.

Transitioning from the deeper to the more superficial structures of the brain, **Chapter 3.2** investigated whether a novel cortical thickness-based signature could outperform hippocampal volume as marker for dementia risk. Although the original study, from which this signature was derived, showed that this signature outperformed conventional measures derived from structural MRI[37], we did not replicate this in our population-based sample.

Cortical thinning in specific regions of cortical grey matter, such as the medial temporal lobe, right anterior cingulate, and middle frontal gyri, has been consistently associated with increased risk of dementia.[38, 39] One prior study proposed a predefined cortical atrophy signature based on combinations of regions in which cortical thinning specifically related to dementia.[40] More recently, the study on which **Chapter 3.2** is based on, used a data-driven approach to define a novel signature using voxel-level cortical thickness data to identify specific voxels related to dementia in their sample.[37] Although this is a sound hypothesis-free approach, our findings suggest that the resulting signature may lack generalizability, as the same associations were not observed in the Rotterdam Study and the novel signature did not outperform more conventional markers like hippocampal volume or the knowledge-based cortical signature.[40] Despite the predictive value of cortical grey matter atrophy, both our study and previous literature have demonstrated that hippocampal volume is a more robust marker, particularly in individuals with MCI.[41] However, imaging signatures which combine multiple regions or information should be not be regarded as irrelevant. As discussed in **Chapter 2**, combining imaging

markers has the potential to complement each other regarding predictive value. This is similar to assessing a runner's performance: looking only at running pace or only at heart rate provides limited insight, but their combination reveals whether the runner is efficient or overexerting. Therefore, dementia research should not always focus on comparing imaging markers, but also on combining imaging markers which may seem less relevant in direct comparisons.

In conclusion, **Chapter 3** shows that both cortical as subcortical grey matter are able to provide valuable information in assessing risk of dementia. However, the hippocampus and amygdala each independently were shown to be strong predictors, with consistent associations across cohorts. By integrating data from multiple cohorts and directly comparing imaging markers, this chapter provides robust evidence supporting the role of these two subcortical structures in dementia risk stratification. Taken together, the hippocampus and amygdala should both be used for dementia risk assessment, while the predictive role of solely cortical grey matter may be more limited in preclinical stages. However, cortical grey matter may add valuable information when combined with other imaging markers and integrated into broader imaging signatures.

Predicting dementia: models and perspectives

Before a prediction model can be successfully implemented in clinical practice, it is important to understand the needs, preferences, and expectations of the target population. Ideally, this is done before the development of the model is initiated. Therefore, we started in **Chapter 4.1** by investigating public perspectives towards dementia risk prediction models. This study revealed how individuals perceive their own risk of developing dementia in the next 10 years and that there is a substantial group of individuals who expressed interest in knowing their 10-year dementia risk. Furthermore, I identified and quantified the reasons why individuals either would or would not want to know their risk. From a practical standpoint, **Chapter 4.1** shows that individuals are willing to undergo more extensive testing if it offers a possibility to reduce their dementia risk. Importantly, participants expressed a clear preference for receiving risk information directly from their healthcare provider, underscoring the need for integrating such models into existing clinical workflows.

Previous literature on perceived dementia risk have shown that the range of perceived lifetime and 10-year risks is broad, with estimates ranging from 0% to 100%.[42, 43]

The majority of participants had a perceived risk between 10% and 50%[43], which align with the results from **Chapter 4.1**. In both previous studies and our study there is a group of participants who perceive their risk as 0%. Within our study, this group was predominantly present in the age group of <40 years, while those participants in other studies were quite older (mean age >68 years). These findings highlight that perceived risk varies a lot within and across populations. Such variability highlights the need for future research into determinants for over- or underestimating dementia risk. Additionally, these results show the importance of tailored risk communication. Given the broad range of perceived risks, it is essential that risk assessments are accompanied by appropriate explanations to ensure that individuals understand their risk in context.

The wide variety in perceived risks may be explained by a lack of knowledge of dementia risk. A recent study showed that dementia knowledge levels among individuals in the general population of the United Kingdom are low.[44] In particular, awareness about the modifiability of dementia risk, for example through lifestyle interventions, is especially lacking.[45, 46] This lack of knowledge and an increased perceived risk are both associated with fear for dementia[47], indicating that fear of dementia might be prevented by increasing awareness. In this context, dementia prediction models, such as presented in **Chapter 4.2**, could be a valuable tool in enhancing awareness and knowledge regarding dementia risk, ultimately reducing fear of dementia.

These insights formed the foundation for the model development in **Chapter 4.2**. Although several dementia prediction models have been developed and validated, they often did not consider newly established predictors and were not specifically designed for clinical implementation.[48-50] Based on our findings in **Chapter 4.1**, the most common reason individuals cited for wanting to know their risk was a family history of dementia. As such, we developed prediction models tailored specifically for individuals with a positive family history or subjective memory complaints since these groups are likely to engage in risk assessment. We decided to develop two prediction models: a basic model, including variables that are easily accessible for a general practitioner or in a primary care setting, and an extended model, including more detailed clinical information suited for a memory clinic setting. The findings in **Chapter 4.2** show that the basic and extended model for 5- and 10-year prediction have very good discrimination among individuals with a family history of dementia or subjective memory complaints. Although the extended model showed an

improvement in discrimination, compared to the basic model, this was very small and presumably clinically not relevant considering the extra burden for patients when undergoing brain MRI and genetic testing. Both models outperformed prediction models including only age, often referred to as the most important risk factor for dementia.

However, translating personalized risk scores into meaningful preventive action is not without challenges. As shown in **Chapter 4.1**, even among individuals who claimed to be aware that dementia risk can be reduced, the threshold at which they would consider taking preventive action was often higher than both their perceived and likely actual risk. This could be solved by proper risk communication, in which individuals are classified in risk categories instead of presenting them risk scores. **Chapter 4.2** reflects on this by using different thresholds for risk categorization, showing that our models have high consistently high negative predictive values. Although the positive predictive value is low, it can be improved by increasing the risk threshold. These findings show that a prediction model can be adjusted for different purposes by changing the thresholds for risk categories. Given that our basic model excels in negative prediction, it is particularly suited for reducing fear in low-risk individuals and assisting primary care providers as gatekeeper for specialized care since referrals could potentially be reduced.

We additionally took the variability in available information in the clinic into account by developing alterative models to accommodate situations where specific information may be missing, enhancing their flexibility and real-world applicability. However, removing either genetics or imaging markers from the extended model did not substantially affect model performance as expected based on the small difference in discriminative power between the basic and extended model. Nevertheless, our findings showed that these advanced markers may be useful in refining risk prediction among individuals identified as high risk according to the basic model. This is particularly relevant as brain imaging or genetic testing is not typically performed in primary care. Therefore, our findings support a two-step approach in which the basic model could serve as an initial referral tool, while the extended model could be used for further risk refinement in a memory clinic setting, aligning with the actual processes in dementia care. Future research should investigate the benefits of such an extended model in an actual memory clinic population so clinicians can provide accurate risk scores across different clinical settings.

In conclusion, **Chapter 4** shows that the basic and extended prediction model for dementia is able to fulfill the needs and expectations of patients across different health care settings. When these insights will be complemented with the needs of healthcare professionals, these models can eventually be used for multiple purposes assisting health care providers, patients, but also by increasing awareness and knowledge regarding dementia risk. Ultimately, they may support the general population in engaging more proactively in dementia prevention.

METHODOLOGICAL CONSIDERATIONS

Although this thesis contains promising findings regarding dementia prediction, it is important to acknowledge certain methodological issues. Specific strengths and limitations for each study have been discussed in their corresponding chapters. In this chapter, I will discuss broader methodological issues that should be taken into account when interpreting these findings.

Selection bias

Although this thesis is predominantly based on data from a large population-based cohort, it is important to recognize that even these studies are prone to various forms of bias, including selection bias[51]. This type of bias originates from the procedures used to select individuals and from factors that may influence their decision to participate or not in a study. This may lead to incorrect conclusions regarding the association between exposure and outcome as this association might differ between those who participated and those who did not, primarily limiting internal validity.

Although it is very difficult to avoid selection bias, the risk of selection bias at baseline is minimized within the Rotterdam Study due to a high overall response rate of 72% within the first three cohorts.[52] However, the studies presented in this thesis were performed within participants who underwent brain imaging. Imaging studies are known for their susceptibility to selection bias, since participants can not have any contraindications for the imaging modality in question. Moreover, it can be an intensive examination, especially compared to other parts of the research visits. For example, interviews are performed at the homes of the participants. In contrast, MRI requires to lay down in a small tunnel with loud noise for over half an hour.

Although brain MRI within the Rotterdam Study is non-invasive, it is likely that frail participants are more likely to decline the imaging due to the discomfort of this part of the research visit. In addition, participants with certain pacemakers or aneurysm clips are not allowed to participate. These reasons potentially introduced a selection bias in which the more healthy participants are included in our imaging studies. In general, approximately half of the participants in the Rotterdam Study participate because they see this as a free health check, suggesting they are more health oriented than those who do not participate. This was also observed within the focus group in which also became clear that some participants participated because they had experience with family members having dementia and having a fear to develop dementia themselves. This might indicate that those focus group participants were at higher risk of developing dementia. In contrast, respondents in our survey were relatively highly educated which is often associated with better health outcomes. This emphasizes the complexity involved in assessing and correcting for selection bias.

Besides baseline selection of individuals, attrition is an important cause contributing to selection bias. The loss of participants during a longitudinal study could be related to the participant's health status, potentially distorting the observed association between exposure and outcome. For example, participants who become more frail during the study may be more likely to withdraw from the study, influencing the results. This shows the importance of carefully considering attrition patterns when interpreting results from longitudinal studies.

Confounding

Another potential threat for internal validity is confounding. This occurs when a variable affects both the exposure and outcome, creating a spurious relationship. For example, whenever the number of ice cream sales increase, so do shark attacks. There is no causal relationship, but the outside temperature acts as a confounder, creating this correlation as it influences both ice cream sales and shark attacks in a similar way. Although confounders can lead to misinterpreting a correlation as a causal relationship, this is not an issue for prediction. A variable that can predict dementia without having a direct casual effect, can still serve as a good predictor. For dementia prediction, it is important to recognize that causal variables are good predictors, but not all predictors need to be causal variables for dementia.

Misclassification

When a patient has dementia, clinicians aim to determine the specific dementia diagnosis, like Alzheimer's disease or vascular dementia. Unfortunately, a substantial number of patients with dementia get a dementia diagnosis which is not entirely accurate. In practice, patients with dementia often have a mix of underlying pathologies, instead of a single pathology causing the dementia. This has been shown in studies investigating the agreement between clinical diagnosis made in vivo and post-mortem diagnoses after autopsy.[53, 54]

While the primary focus of all studies included in this thesis was all-cause dementia, we also explored potential differences in prognostic markers between dementia due to Alzheimer's disease and other dementia subtypes, as well as between all-cause dementia and AD-specific dementia. However, the relatively low incidence of dementias in which non-AD is the predominant subtype, combined with the high likelihood of diagnostic misclassification, make it hard to draw definite conclusions from these subtype-specific analyses. Notably, individuals in our focus groups were generally less concerned with the specific type of dementia they may develop and instead have a greater interest in the overall risk of developing dementia. This suggests that research focused on the prediction of subtypes of dementia might be of less interest for the patients themselves.

Besides misclassification of the outcome, it is important to acknowledge the potential misclassification of predictors. Within Chapter 2 and Chapter 3, the predictors consist of automatically processed imaging markers. Since these markers are processed with a minimal involvement of humans, the misclassification will be very slim. However, specific issues related to imaging predictors are discussed further in this Chapter.

The model in Chapter 4.2 includes a variety of other predictors in which misclassification can occur. For example, information on several predictors were collected through interviews. This type of data collection is especially prone to recall bias,[55] which can lead to differential misclassification when individuals are asked whether they forgot something in past week, and respond "no" because they do not recall their forgetfulness.

Competing risk

In dementia research, accounting for competing events is essential for generating accurate and realistic risk predictions. Traditional time-to-event methods which do not take this properly into account will overestimate the risk of dementia because these models assume that censoring is non-informative. Under this assumption, individuals who are censored due to death are presumed to have the same future risk of developing dementia as those who remain alive. However, in aging populations, death is a major competing risk that prevents the occurrence of dementia. Ignoring this can lead to an overestimation of absolute dementia risk. Therefore, in **Chapter 4.2**, we employed competing risk methods to develop a dementia prediction model that more accurately reflects the probability of developing dementia before death. Without this adjustment, the estimated risks would have been overestimated. This is particularly relevant in light of findings presented in **Chapter 4.1**, where we observed that many individuals experience significant anxiety about developing dementia, especially if they have witnessed the disease among family members or friends. While one might assume that slightly overestimated risks could serve as a motivator for preventive behavior, providing realistic risk estimates could be used to reassure anxious individuals as they already perceive their dementia risk to be higher than it actually is, as shown in **Chapter 4.1**.

Prediction versus diagnosis

Research objectives in quantitative biomedical studies typically fall into three main categories: description, identification, and explanation. In the realm of identification, studies focus on identifying individuals who either have the disease (diagnosis) or are at increased risk of developing a disease (prediction). Accordingly, diagnostic and prediction studies differ in their inclusion criteria. While diagnostic studies typically include both healthy and diseased individuals, prognostic studies include individuals who are disease-free at baseline. This distinction becomes blurred in diseases with gradual onset, such as dementia, where the timing of disease onset is often uncertain. In contrast to acute illnesses with a clear onset, dementia starts with subtle cognitive symptoms that progress slowly to more severe impairment. This prodromal phase of dementia complicates determining who is cognitively healthy and who is in the earliest stage of disease. For example, an older man with cognitive complaints may go to the general practitioner and is subsequently diagnosed with dementia due to Alzheimer's disease at the memory clinic. While the diagnosis is

made at a certain date, it does not reflect the actual onset of symptoms, which may have occurred months earlier. In this thesis, we accounted for this by excluding participants who developed dementia within the first few months following baseline assessment. Other studies, for example that by Walsh et al., have taken a more conservative approach using longer exclusion windows of 5 years.[56] These varying approaches underscore the complexity of determining who is truly disease-free before a clinical diagnosis is made.

While diagnosis revolves around detecting current diseases, prediction focusses on certain outcomes in the future. Nonetheless, prediction models provide risk estimates for an individual in the present. When prediction models are highly accurate, they can closely resemble diagnostic tools since they identify individuals with high certainty of developing a specific disease. According to the National Cancer Institute's definition[57], diagnosis is "the process of identifying a disease, condition, or injury from its signs and symptoms. A health history, physical exam, and tests, such as blood tests, imaging tests, and biopsies, may be used to help make a diagnosis". In contrary, according to the new AA diagnostic criteria, AD can be diagnosed when individuals are cognitively healthy but have 1 AD biomarker.[58] However, recent literature shows that a significant percentage of individuals with amyloid-positivity will not progress to dementia.[59-61] Therefore the Internation Working Group criteria advise to use a combination of biomarkers and clinical symptoms for the diagnosis of AD and use amyloid-positivity as a risk factor.[62] From this perspective, prediction seems similar to diagnosis, but at a stage in which symptoms are not yet present.

This distinction is especially important in the context of dementia. Although risk prediction is valuable for early intervention and prevention, it should not be regarded as early diagnosis. According to the focus group presented in **Chapter 4.1**, some participants expressed they did not want to know their dementia risk due to their fear of being stigmatized when they are considered high risk. For instance, participants were worried their families might treat them differently, such as restricting their driving privileges or overreacting when they forget their keys once. This highlights the need for cautious communication of risk and a clear distinction between predictive modelling and diagnostic certainty.

Imaging acquisition and processing

Within imaging research, specific limitations needs to be considered when interpretating findings. For this thesis, I used predominantly imaging data from the Rotterdam Study that uses a single MRI scanner. This reduces potential differences introduced by using scanners from different manufacturers causing misclassification of exposure. However, a variety of scanners and field strengths were used to acquire volumetric measurements in **Chapter 3.1**. Literature has shown varying results regarding variability in volumetric measurements among different MRI scanners,[63, 64] probably partly due to its dependence on the automated segmentation software used.[65] Regarding field strengths, 3.0T often result in higher subcortical grey matter volumes than with 1.0T,[66] suggesting that 3.0T is the preferred field strength due to higher resolution. Such differences in field strength or scanner primarily represent sources of misclassification of exposure, as they directly influence the accuracy of volumetric measurements. Within **Chapter 3.1**, I accounted for field strength and manufacturer differences by including them as covariates in the models and by applying a harmonization technique on the segmented volumes. For the other chapters including imaging markers it is yet to be determined whether these results can be generalized to settings with other imaging parameters.

A limitation that is more difficult to solve is that volumetric measurements may be slightly incorrect due to partial-volume effects, which may lead to misclassification of some voxels. This is especially true for MRI scanners with lower field strengths. For example, the boundary between white matter and grey matter often passes through a single voxel. The intensity of that voxel contains information on both grey matter and white matter, yet segmentation algorithms classify and segment it as either white matter or grey matter, thereby introducing measurement error.

Another potential issue which is commonly introduced when using volumetric measurements of brain structures is the influence of head size as a confounder. Individuals with smaller head sizes tend to have smaller brain structures.[67] To account for this influence, we adjusted all our volumetric and thickness measurements for intracranial volume.

Replication

A key aspect in identifying robust neuroimaging markers for prediction is conducting replication studies. Replication is crucial to ensure that findings are not specific to a single cohort and can be reproduced in similar populations under similar circumstances. In contrast, external validation assesses whether certain results generalize to different populations or settings, evaluating the broader applicability of markers. Replication can be achieved by reproducing a study using the same methodology in an independent similar cohort or by incorporating multiple cohorts within a single study. In thesis, I used both replication approaches: I replicated an existing study in **Chapter 3.2**, and I investigated multiple cohorts in **Chapter 3.1**.

Despite its importance, replication remains relatively uncommon contributing to the emerging replication crisis. The Dutch funding agency NWO recognize this and has launched a funding scheme for replication studies.[68] **Chapter 3.2** further underscores why replication is required to identify robust neuroimaging markers for the prediction of dementia. Although the study populations seem similar based on their characteristics, the outcomes differed significantly, leading to different conclusions. This discrepancy illustrates that apparent similarities between study populations do not necessarily guarantee consistent results. Therefore, when interpreting results from other studies in this thesis, it is important to acknowledge that replication is still required to ensure the robustness of our results.

FUTURE DIRECTIONS AND CLINICAL IMPLICATIONS

MRI markers in the progression to dementia

In 2014, an updated version of the hypothetical model of Alzheimer's disease biomarkers was presented in *Lancet Neurology*.[69] Both the original and the updated model, conceptualized brain structure and MRI measurements as a single domain of markers which deteriorate just before the onset of symptoms. However, this thesis suggests that brain structure is more accurately represented by a heterogeneous set of MRI markers, each potentially relevant at different stages of disease progression. For example, MD is superior in predicting dementia until 5 years, after which PSMD becomes equally good at predicting dementia. This implies that PSMD may be more important for identifying long-term risk, but not for shorter time windows.

These observations underscore the need for future research to focus on unravelling the sequential order of imaging markers to provide a clear overview of the importance of imaging markers at specific time points. Previous studies have shown the value of disease progression models in identifying the order in which biomarkers become abnormal.[70, 71] These studies have been conducted among individuals with Alzheimer's disease, frontotemporal dementia and mild cognitive impairment, but other studies have extended these models towards cognitively healthy individuals to provide insights into the earliest stages of disease onset.[72, 73] When these models will be complemented with the imaging markers discussed in this thesis, this will provide the tools to move from a simplistic hypothetical model to a more evidence-based, accurate model, of which a conceptual example is showed in Figure 1. In this conceptual model, different imaging markers deteriorate at distinct onset times and progress at varying rates. It also illustrates that certain imaging markers may hold predictive value only at specific stages, as literatures suggests for the thalamus. In this conceptual example, thalamic volume is abnormal only at an early stage. This does not imply that the thalamus regains volume later, but rather that thalamic volume atrophy accelerates in an early stage of dementia and subsequently stabilizes and follows atrophy trajectories similar to those observed in healthy individuals. These models could assist clinicians, not only for prediction of dementia, but also for pinpointing where an individual might be along the disease trajectory.

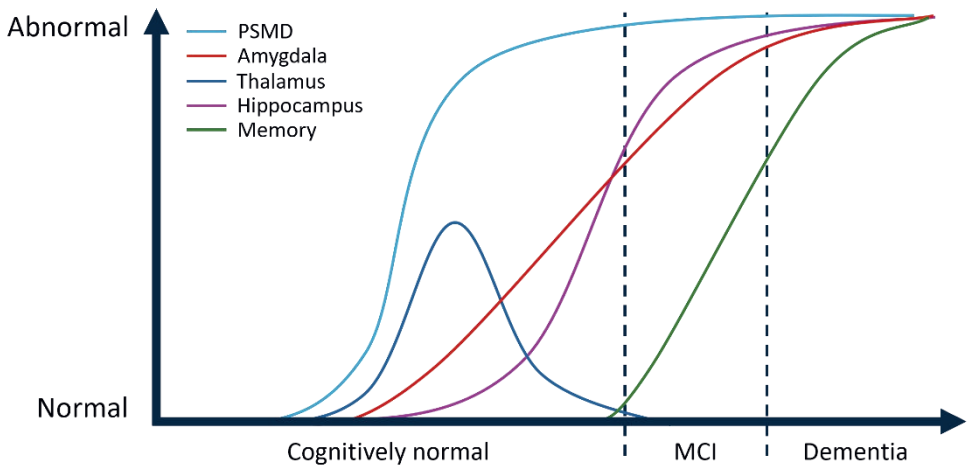

Figure 1. Example of an updated model of MRI biomarkers (and memory) for dementia.

Interplay between white matter and grey matter

Based on **Chapter 2** and **Chapter 3**, we considered several white matter and grey matter imaging markers for the extended prediction model in **Chapter 4**. Both were selected in the final prediction model since each contributed independently to improved prediction of dementia. This suggests that the effect of white matter and grey matter on prediction are complementary.

Dementia is often thought of as a disease of the grey matter, with grey matter atrophy as a significant feature of multiple types of dementia. For example, grey matter loss in the hippocampus and medial temporal lobe is particularly characteristic for Alzheimer's disease[74], while grey matter atrophy in the frontal and temporal lobes is a hallmark for frontotemporal dementia.[75, 76] However, **Chapter 2** shows that certain white matter characteristics also play an important role in dementia risk. The patterns we identified as high risk of dementia, often involved higher WMH volume as well as a higher vascular burden, suggesting that vascular pathologies have an important role in the development of dementia. Nonetheless, not all white matter injury can be attributed to vascular pathologies. Although WMHs are often considered indicative of small vessel disease, recent studies showed that spatial information of WMHs can distinguish between the origin of WMH. These studies showed that anterior WMH are often related to amyloid pathology, while posterior WMH are more often related to vascular pathology.[11, 77, 78] This spatial differentiation implies that WMHs may arise from multiple pathogenic processes, including amyloid, which typically affects cortical grey matter within Alzheimer's disease.[79] This suggests that deterioration of white matter and grey matter areas can have shared underlying pathologies.

Besides shared pathologies, grey matter and white matter likely influence one another based on their anatomical and functional connections. It was already shown that loss of specific tracts predicts grey matter atrophy in the areas connected by those tracts.[80, 81] Other studies have shown the association between microstructural integrity of the white matter with tau and amyloid.[82, 83] This supports the hypothesis that white matter tracts play a crucial role in the spread of neurodegeneration to grey matter regions. In addition, another study showed that the presence of APOE-e4, a genetic risk factor for dementia, modifies the relationship between WMH and grey matter atrophy, which may directly influence the

development of dementia.[84] This indicates a complex interplay between white matter and grey matter deterioration in the development of dementia.

In conclusion, imaging markers of both white matter and grey matter of the brain are important for dementia prediction independently of other predictors, such as age and genetics. Although their added value to prediction seemed small, they may have a crucial role in risk refinement among high-risk groups. Our results in combination with previous literature suggests a complex interplay between white matter and grey matter regarding the development of dementia. Since this interplay is not fully understood yet, future research is necessary to fit these puzzle pieces together. Although disease understanding might not be essential for prediction, it may steer us to discovering new predictors.

Artificial intelligence for dementia prediction

Over the past few decades, research on the use of artificial intelligence (AI) in clinical settings has been evolving rapidly. Radiology, in particular, is a field in which AI applications can be very beneficial, especially in interpreting imaging data across multiple modalities and identifying new patterns.[85] In the field of dementia, AI applications, such as unsupervised learning techniques, can be used to unravel patterns by combining multimodal data leading to a better disease understanding, as shown in **Chapter 2.1**. Additionally, convolutional and deep neural networks can help identify novel imaging biomarkers that are predictive for dementia.

Despite the growing interest in AI and its expanding body of literature, real-world clinical implementation of AI-based technology often remains limited. One of the key barriers to widespread adoption is the limited transparency, particularly regarding model interpretability.[86] Although both deep learning models and traditional statistical methods rely on mathematical operations to reach a certain optimization, understanding how a deep learning model reaches a certain prediction is more complex than with traditional statistical methods. Explainable AI may offer a solution to overcome this issue.[87] Future dementia prediction models might benefit from explainable AI as it might be more accurate than traditional statistical methods and be more interpretable than deep learning networks, which can be seen as black holes where the inner workings remain unclear. However, in addition to transparency, there are other barriers which need to be identified and taken into account in the development of dementia prediction models to achieve successful implementation,

regardless of whether AI is used.

Dementia prediction models in clinical practice

The findings of this thesis have direct implications for the future implementation of dementia prediction models in clinical practice. We identified the needs and expectations of individuals which are essential for a successful implementation. These insights formed the basis of the development of our prediction models. In addition to the patient perspective, we also considered the health care provider by creating two separate models. The basic model is applicable for general practitioners, with predictors easily accessible for them, and the extended model is suited for memory clinic settings in which advanced testing is possible. Since it is not always feasible or desirable in clinical practice to conduct extensive tests on an individual who does not have dementia yet, we created alternative models additionally. These considerations were made to make a future implementation into clinical workflows successful.

Despite our steps towards practical applicability, further research is still necessary. As the field develops, new biomarkers for dementia risk will be discovered. When their predictive value for dementia has been established, existing prediction models should be updated to maintain and enhance predictive accuracy in the near future. Additionally, more research into established markers should be done. For instance, WMH have long been associated with dementia risk, but the location and shape of WMH have recently been shown to play an important role as well.[13, 78]

From a radiology perspective, future implementation of MRI-based dementia prediction models will likely depend on automated, standardized pipelines for image analysis. While diffusion measures such as MD and PSMD provide robust predictive signals, their derivation still requires preprocessing steps not yet integrated in routine clinical workflows. Similarly, spatial characterization of WMH may hold clinical value, but would need to be embedded in structured radiology reporting systems to be actionable. As new biomarkers, such as susceptibility-weighted imaging for microbleeds or arterial spin labeling for perfusion, emerge, multimodal MRI integration may further refine risk stratification. Therefore, translational efforts will need to address not only the predictive validity of imaging markers, but also their clinical interpretability and operational feasibility in radiology settings.

A group of biomarkers that has been gaining increasing attention recently is blood-based biomarkers, including Aβ, p-tau, neurofilament light (NfL), and glial fibrillary acidic protein (GFAP). These markers are cheaper than imaging and easy to collect, making them particularly suitable for prediction models. Although studies have shown that Aβ42, Aβ40, and the Aβ42/40 ratio have a limited role in predicting dementia, p-tau181, p-tau217, NfL, and GFAP were identified as more accurate predictors of dementia.[88-90] Interestingly, p-tau181 alone was more accurate in predicting dementia among cognitively unimpaired individuals than among those with mild cognitive impairment, suggesting that its predictive value may vary along the trajectory towards dementia. However, that study also showed that blood-based biomarkers add little to 5-year dementia risk prediction models which already include MRI markers.[90] Although blood-based biomarkers are easier and cheaper to collect, it is likely that they only reflect global pathological processes in the brain. Imaging could therefore be complementary in providing spatial information for identifying affected regions and may have additional value in predicting symptoms related to those specific regions.

Another important element to consider is the time horizon for the predictions, as this can have a large impact on how risk scores are interpreted. In **Chapter 4.2**, the prediction models were evaluated for 5- and 10-year time horizons. However, based on the focus groups conducted for this thesis, preferences for time horizons varied, ranging from 3 years to lifetime risks. For example, one participant mentioned that a 5 year dementia risk prediction would be sufficient to make necessary arrangements, and that a 10-year risk prediction might be less relevant as a lot of other things could happen during that period. It is also important to recognize that predictions further in the future are always less reliable than those made for shorter time periods. For example, weather predictions for tomorrow are typically more reliable than those for next week. These considerations imply that predictions for shorter time horizons tend to be more preferrable than those for longer time horizons. Nevertheless, the exact time horizon and the its reliability should always be discussed beforehand, highlighting the need for prediction models with flexible time horizons for their predictions and appropriate risk communication.

As risk communication is also an important element for successful implementation in clinical practice, we already started investigating this topic using focus groups with both cognitive healthy individuals and general practitioners, beyond this thesis. These discussions, revealed that the use of color and symbols is a key feature for effective

risk communication. Additionally, cognitive healthy individuals expressed their preference for receiving their risk in a comparative context, such as high or low risk compared to others with the same age. Although these insights are valuable for communicating the risk of dementia, further research should focus on evaluating such prediction models in real-world clinical settings.

Ethical and clinical considerations for dementia prediction

Although dementia prediction models can provide individuals with valuable information, there are several ethical implications of using such models. Previous literature has shown that the ethical principle of respect for autonomy should be taken seriously.[91] Having information on your dementia risk may result in fear and stress. Moreover, **Chapter 4.1** showed that individuals are also afraid of being stigmatized which can result in social isolation. To address how to deal with such ethical concerns, guidelines for clinicians should be developed before dementia prediction models are being implemented.[92]

During the focus groups with individuals and general practitioners, they agreed that implementation of dementia prediction models will have direct implications on discussing prevention with patients. In addition to providing clarity for anxious individuals, these models may serve as tools for initiating conversations regarding modifiable risk factors. Interestingly, participants in the focus groups indicated that they are more afraid of developing dementia than cardiovascular diseases. Since lifestyle risk factors for dementia are shared with other diseases, including cardiovascular diseases, this shows that providing dementia risks could be particularly effective for prevention of many diseases and stimulating health in general.

Besides preventive strategies, dementia prediction could play an important role in treatment research. Recently developed anti-amyloid drugs, like donanemab and lecanemab, have shown small effects on cognition in early Alzheimer's disease, while solanezumab failed to show clinical benefit in symptom-free, amyloid-positive individuals.[93-95] Since most amyloid-positive individuals will not progress to dementia, dementia prediction models may help identify those who will benefit from such treatments. Ultimately, these prediction models could support personalized treatment selection when effective disease modifying therapies will become available.

CONCLUDING REMARKS

This thesis sheds light on the role of brain imaging markers derived from MRI in identifying individuals with high risk of dementia. We investigated imaging markers of both cerebral white matter and grey matter among individuals free of dementia – ranging from cognitively healthy to those with subjective memory complaints and mild cognitive impairment. While our findings highlight the informative value of both white matter and grey matter, the underlying mechanisms of the interplay between these brain tissues needs further research. After we identified the needs for the implementation of a dementia prediction model from a patient perspective, we combined the results of our studies to develop two dementia prediction models: one tailored for use in a primary care setting, and another for memory clinic settings. Still, further research on risk communication and testing such models in clinical practice is required. Even then, prediction models should be regularly updated with new insights on already existing or newly discovered MRI biomarkers. Ultimately, dementia prediction models can play an important role in targeted prevention, reducing anxiety, treatment selection, and informing both individuals and healthcare providers with evidence-based and realistic risk estimates.

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CHAPTER 6

SUMMARY/SAMENVATTING



Summary

Dementia is a complex syndrome characterized by progressive cognitive decline that interferes with daily life. Its variety of causes and trajectories make early prediction challenging and it often goes undetected during early stages. Absolute numbers of dementia are growing, with 57 million individuals affected worldwide, including 310.000 in the Netherlands.

Early identification of individuals at high risk for dementia is crucial for improving treatment and engaging in preventive strategies. Advanced magnetic resonance imaging (MRI) techniques and machine learning methods offer promising tools for detecting early brain changes and identifying new predictors for dementia. Despite the development of dementia prediction models, their implementation in clinical practice has been limited. Therefore, the aim of this thesis was to investigate the role of MRI in identifying individuals at high risk of dementia, to assess how neuroimaging can enhance the performance of dementia prediction models, and to explore strategies for the implementation of such models in clinical practice.

The aim of **Chapter 2** was to study the role of white matter imaging markers in assessing and predicting brain health in elderly adults. **Chapter 2.1** shows that machine learning can be applied to unravel distinct white matter patterns using multimodal brain MRI. Patterns with poor brain structure showed to have a higher prevalence of cardiovascular risk factors, lacunes, and microbleeds. Additionally, I showed that these patterns are associated with different risks for dementia, stroke, and mortality. Models with these patterns also outperformed models with only a single imaging marker for dementia and mortality.

In **Chapter 2.2**, I compared predictive value of multiple diffusion MRI markers of the brain for cognitive decline and dementia risk. I showed that peak-width skeletonized mean diffusivity (PSMD) and mean diffusivity (MD) had a superior model fit and discriminatory value for dementia risk, compared to other measures. For cognitive decline, PSMD was the optimal predictor, indicating that PSMD is the preferred measure of structural white matter integrity in prediction of cognitive decline and dementia.

Chapter 3 dives into the realm of grey matter as indicator of dementia risk. In **Chapter 3.1**, I focused on the size of different subcortical grey matter structures and their association with 5-year dementia risk. Participants with subjective cognitive decline

or mild cognitive impairment from two memory clinic-based cohorts and one population-based cohort were included in this study. I showed that smaller hippocampal volume and amygdalar volume were consistently associated with increased dementia risk in individuals with subjective cognitive decline or mild cognitive impairment, independent of other subcortical grey matter structures. This underscores the potential of these structures for dementia prediction in a clinical practice.

While **Chapter 3.1** focusses on subcortical grey matter, **Chapter 3.2** revolves around the thickness of specific cortical grey matter regions and its association with dementia risk. This novel neuroimaging marker showed strong associations with dementia risk in a previous study and I assessed this association within the population-based Rotterdam Study. Although the imaging marker was associated with dementia risk, it did not outperform hippocampal volume for dementia risk stratification. This highlights the importance of replication studies in establishing robust biomarkers for dementia prediction.

Chapter 4 sheds light on the perspectives of the public towards dementia prediction and on the development of these prediction models. In **Chapter 4.1**, I combined qualitative and quantitative research methods to determine the different views on dementia prediction in the general population. I showed that there is a substantial group of individuals who have the desire of wanting to know their dementia risk. Additionally, I showed that a family history of dementia was one of the primary factors driving individuals' desire to know their dementia risk, while fear and the lack of effective interventions were the main reasons for those who preferred not to know their dementia risk. Furthermore, while there was a wide variety in how individuals perceive their dementia risk, most people tended to perceive their risk as relatively high.

These insights formed the foundation for the development of the dementia prediction models in **Chapter 4.2**. Therefore, this study included dementia-free individuals over 60 years of age, who had either subjective memory complaints or a family history of dementia. I developed two prediction models: a basic model with easily accessible predictors suitable for primary care settings, and an extended model incorporating advanced predictors, including neuropsychological assessment, genetics, and brain imaging, designed for use in a memory clinic setting. Both models achieved good discrimination for 5-year and 10-year dementia prediction, compared to age-only

models. Calibration showed an underestimation of absolute risks. The incorporation of cognitive, genetic, and imaging data did not substantially improve discrimination overall, but did lead to somewhat better calibration within 5 years, compared to the basic model. Moreover, it may contribute in further refining risk estimation within high-risk groups.

To conclude, in **Chapter 5**, I summarized my key findings within a broader context and discussed important methodological considerations. I also discussed the implications of my findings and provided directions for future research to further improve our knowledge on imaging markers for dementia prediction. Additionally, this chapter reflects on how dementia prediction models can be successfully implemented in clinical practice, and how they may contribute to the development of prevention strategies and targeted treatment for dementia.

Samenvatting

Dementie is een complex syndroom dat wordt gekarakteriseerd door een progressieve cognitieve achteruitgang die het dagelijks leven van een individu beïnvloedt. Door de vele mogelijke oorzaken en trajecten van de ziekte is voorspelling van dementie een uitdaging. Daarnaast wordt dementie vaak niet opgemerkt in de vroege stadia. Het aantal mensen met dementie neemt toe, met wereldwijd 57 miljoen mensen met dementie, waaronder 310.000 in Nederland.

Vroege identificatie van individuen met een hoog risico op dementie is cruciaal voor het verbeteren van behandelingen en het aangaan van preventieve strategieën. Geavanceerde magnetische resonantiebeeldvorming (MRI) technieken en machine learning-methoden bieden veelbelovende handvatten voor het detecteren van vroege hersenveranderingen en het identificeren van nieuwe voorspellers voor dementie. Ondanks de ontwikkeling van dementievoorspellingsmodellen, is hun implementatie in de klinische praktijk beperkt. Het doel van dit proefschrift was daarom het onderzoeken van de rol van MRI in het identificeren van individuen met een hoog risico op dementie, het beoordelen van hoe neuro-beeldvorming de prestaties van dementievoorspellingsmodellen kan verbeteren, en het verkennen van strategieën voor de implementatie van dergelijke modellen in de klinische praktijk.

Het doel van **Hoofdstuk 2** was het bestuderen van de rol van witte stof beeldvorming markers in het beoordelen en voorspellen van de hersengezondheid bij oudere volwassenen. **Hoofdstuk 2.1** toont aan dat machine learning kan worden toegepast om verschillende witte stof patronen te ontrafelen met behulp van multimodale hersen-MRI. Patronen met een slechte hersenstructuur vertoonden een hogere prevalentie van cardiovasculaire risicofactoren, lacunes en microbloedingen. Daarnaast heb ik aangetoond dat deze patronen geassocieerd zijn met verschillende risico's voor dementie, beroerte en mortaliteit. Modellen met deze patronen presteerden ook beter dan modellen die slechts één beeldvorming marker voor dementie en mortaliteit gebruikten.

In **Hoofdstuk 2.2** vergeleek ik de voorspellende waarde van meerdere diffusie-MRI markers van de hersenen voor cognitieve achteruitgang en het risico op dementie. Ik liet zien dat de peak-width skeletonized mean diffusivity (PSMD) en mean diffusivity (MD) een betere model fit en discriminerende waarde hadden voor het risico op dementie, vergeleken met andere diffusiematen. Voor cognitieve achteruitgang bleek PSMD de optimale voorspeller te zijn, wat aangeeft dat PSMD de voorkeur heeft als

maat voor de structurele integriteit van witte stof bij de voorspelling van cognitieve achteruitgang en dementie.

Hoofdstuk 3 richt zich op grijze stof als indicator voor het risico op dementie. In **Hoofdstuk 3.1** focuste ik op de grootte van verschillende subcorticale grijze stof structuren en hun associatie met het vijfjarige dementierisico. Deelnemers met subjectieve cognitieve achteruitgang of milde cognitieve stoornissen uit twee geheugenpoli cohorten en één populatie cohort werden in deze studie opgenomen. Ik toonde aan dat een kleinere hippocampus en amygdala consistent geassocieerd waren met een verhoogd risico op dementie bij mensen met subjectieve cognitieve achteruitgang of milde cognitieve stoornissen, onafhankelijk van andere subcorticale grijze stof structuren. Dit onderstreept het potentieel van deze structuren voor dementievoorspelling in de klinische praktijk.

Terwijl **Hoofdstuk 3.1** zich richt op subcorticale grijze stof, draait **Hoofdstuk 3.2** om de dikte van specifieke corticale grijze stof regio's en de associatie met het risico op dementie. Deze nieuwe neuro-beeldvorming marker vertoonde sterke associaties met het risico op dementie in een eerdere studie en ik onderzocht deze associatie binnen het Erasmus Rijnmond Gezondheids Onderzoek (ERGO). Hoewel de beeldvorming marker werd geassocieerd met het risico op dementie, overtrof het niet het hippocampale volume voor het stratificeren van het dementierisico. Dit benadrukt het belang van replicatiestudies bij het vaststellen van robuuste biomarkers voor dementievoorspelling.

Hoofdstuk 4 belicht de perspectieven van het publiek ten aanzien van dementievoorspelling en de ontwikkeling van deze voorspellingsmodellen. In **Hoofdstuk 4.1** combineerde ik kwalitatieve en kwantitatieve onderzoeksmethoden om de verschillende opvattingen over dementievoorspelling in de algemene bevolking te bepalen. Ik toonde aan dat er een aanzienlijke groep mensen is die hun dementierisico wil weten. Daarnaast bleek dat een familiegeschiedenis van dementie een van de belangrijkste factoren was voor het wel willen weten van hun dementierisico, terwijl angst en het ontbreken van effectieve interventies de belangrijkste redenen waren voor degenen die liever niet hun dementierisico wilden weten. Bovendien, hoewel er een grote variëteit was in hoe individuen hun dementierisico waarnamen, gaven de meeste mensen aan dat ze hun risico relatief hoog inschatten.

Deze inzichten vormden de basis voor de ontwikkeling van de dementievoorspellingsmodellen in **Hoofdstuk 4.2**. Dit onderzoek includeerde individuen ouder dan 60 jaar zonder dementie, die ofwel subjectieve geheugenklachten of een familiegeschiedenis van dementie hadden. Ik ontwikkelde twee voorspellingsmodellen: een basismodel met gemakkelijk toegankelijke voorspellers, geschikt voor eerstelijnszorg, en een uitgebreid model met geavanceerde voorspellers, waaronder neuropsychologische beoordeling, genetica en hersenbeeldvorming, ontworpen voor gebruik in een geheugenkliniek. Beide modellen behaalden een goede discriminatie voor de voorspelling van dementie op 5 jaar en 10 jaar, vergeleken met modellen die alleen op leeftijd waren gebaseerd. De kalibratie toonde een onderschatting van de absolute risico's. De toevoeging van cognitieve, genetische en beeldvormingsgegevens verbeterde de discriminatie niet substantieel, maar leidde wel tot een iets betere kalibratie binnen 5 jaar, in vergelijking met het basismodel. Bovendien kunnen deze geavanceerde voorspellers bijdragen aan het verder verfijnen van risicoschattingen binnen risicogroepen.

Tot slot, in **Hoofdstuk 5**, heb ik mijn belangrijkste bevindingen samengevat binnen een bredere context en belangrijke methodologische overwegingen besproken. Ik heb ook de implicaties van mijn bevindingen besproken en richtingen voor toekomstig onderzoek gepresenteerd om onze kennis over imaging markers voor dementievoorspelling verder te verbeteren. Daarnaast reflecteert dit hoofdstuk op hoe dementievoorspellingsmodellen succesvol kunnen worden geïmplementeerd in de klinische praktijk, en hoe ze bij zouden kunnen dragen aan de ontwikkeling van preventiestrategieën en gerichte behandelingen voor dementie.

CHAPTER 7

APPENDICES



PhD portfolio

Name:	Mathijs Thomas Rosbergen
Erasmus MC department:	Epidemiology | Radiology and Nuclear Medicine
Research school:	Netherlands institute for Health Sciences
PhD period:	2021-2025
Promotors:	Prof. dr. Meike W. Vernooij
	Prof. dr. M. Arfan Ikram
Co-promotor:	Dr. Frank J. Wolters

PhD training	**Year**	**ECTS***
Master of Science – Epidemiology	2021-2023	70
General courses	2021-2023	
Review of Mathematics and Introduction to Statistics		1.0
Study Design		4.0
Biostatistics I		4.5
Biostatistics II		4.5
Principles of Public Health		3.0
Clinical Epidemiology		3.0
Selected Topics in Epidemiology		3.0
Core Competences Exam		1.0
Portfolio		0.2
Intercultural communication		0.2
Intervision		0.4
Scientific Writing in English for Publication		2.0
Erasmus Summer Program	2021-2022	
Social Epidemiology		0.7
Fundamentals of Medical Decision Making		0.7
Methods of Public Health Research		0.7
The Practice of Epidemiologic Analysis		0.7
Principles of Genetic Epidemiology		0.7
Principles of Research in Medicine and Epidemiology		0.7
Elective courses	2022-2023	
Repeated Measurements in Clinical Studies		1.7
Implementation Science		1.4
Topics in Medical Decision-making		1.4
Quality of Life Measurement		0.9
Psychiatric Epidemiology		1.1
Advanced Analysis of Prognosis Studies		0.9
Competing Risks and Multi-state Models		0.9
Clinical Translation of Epidemiology		2.0

PhD training	Year	ECTS*
Scientific Integrity course	2022	0.3
Departmental research seminars	2021-2025	2.0
2020 meetings	2021-2025	2.0
Conferences		
Alzheimers's Assocation International Conference (AAIC), Amsterdam, the Netherlands: poster presentation	2023	1.2
Erasmus MC Dementia Day: poster presentation	2024	1.2
Alzheimers's Assocation International Conference (AAIC), Philadelphia, United States of America: poster presentation	2024	1.2
Dutch Dementia Researchers Conference: poster presentation	2024	1.2
Teaching activities		
Supervision BSc student Medicine	2023-2024	1.0
Supervision Bachelor of Applied Sciences student Biomedische Technologie	2024-2025	1.0
Supervision MSc student Health, Ageing & Society	2025	1.0
Other activities		
Peer review	2022-2025	1.0
Imaging management Rotterdam Study	2021-2025	2.0
Scan appraisal for incidental findings in population imaging	2021-2025	2.0
Actigraphy data collection	2021-2025	2.0
Organization "Year in Review"	2024	0.2
Organization ABOARD JOB visits and retreat	2024	0.5

*1 ETCS *European Credit Transfer System) equals a workload of 28 hours.

List of Publications

Manuscripts that form the basis of this thesis:

Rosbergen MT, Wolters FJ, Vinke EJ, Mattace-Raso FUS, Roshchupkin GV, Ikram MA, Vernooij, MW. "Cluster-Based White Matter Signatures and the Risk of Dementia, Stroke, and Mortality in Community-Dwelling Adults." Neurology 103.7 (2024): e209864.

Rosbergen MT, Wolters FJ, Ikram MA, Vernooij MW. Head-to-head comparison of structural connectivity measures for cognitive decline and risk of dementia: the population-based Rotterdam Study. *Submitted*

Rosbergen MT, Van der Veere P, Claus JJ, Evans TE, Venkatraghavan V, Barkhof F, van Harten AC, Ikram MA, van der Flier WM, Vernooij MW, Wolters FJ. (2025). Subcortical gray matter volumes and 5-year dementia risk in individuals with subjective cognitive decline or mild cognitive impairment: A multi-cohort analysis. Alzheimer's & Dementia, 21(7), e70413.

Claus JJ*, **Rosbergen MT***, Roshchupkin GV, Ikram MA, Vernooij MW, Wolters FJ. (2025). Validation of a novel neuroimaging signature for dementia and clinical Alzheimer's disease in the population-based Rotterdam study. Journal of Alzheimer's Disease, 13872877251315044.

Claus JJ, **Rosbergen MT**, Splinter MJ, van Heemst J, Ikram MA, Vernooij MW, Wolters FJ. (2025). Public attitudes toward dementia risk prediction: A mixed-methods study. Alzheimer's & Dementia, 21(5), e14615.

Rosbergen MT, Claus JJ, Andrinopoulou E, Mattace-Raso FUS, Roshchupkin GV, Ikram MA, Vernooij MW, Wolters FJ. Development of a dementia prediction model for individuals with cognitive complaints or familial history. *In preparation*.

**contributed equally*

Other publications:

Claus JJ, **Rosbergen MT**, Labrecque JA, Vernooij MW, Wolters FJ, Ikram MA. (2025) Mediation of the Association Between APOE ε4 Genotype, Cognition, and Dementia by Neuropathology Imaging Markers in the Rotterdam Study. Neurology, 104(11), e213679.

Claus JJ, Box CV, Vinke EJ, **Rosbergen MT**, Berghout BP, Vernooij MW, Ikram MA, Ikram MK, Wolters FJ. (2026) Incidence and prognostic indicators of dementia in patients with covert brain infarction, transient ischemic attack, and stroke: the population-based Rotterdam study. Journal of the American Heart Association, e041316.

Yua J, **Rosbergen MT**, Wolters FJ, Bron EE, Vernooij MW, Ikram MA, Roshchupkin GV, for the Alzheimer's Disease Neuroimaging Initiative. Imaging-genetics-based dementia risk prediction using deep survival neural networks in the Rotterdam Study. *Accepted in Scientific Reports*.

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About the author



Mathijs Thomas Rosbergen was born on August 24th in Capelle aan den IJssel, the Netherlands. After graduating high school, he started a joint bachelor's degree in Clinical Technology at the Erasmus University Rotterdam, Delft University of Technology, and Leiden University Medical Center. In 2018, he continued with a master's degree in Technical Medicine at the same three universities. As part of this program, he completed a 9-month research internship at the Department of Radiology at Erasmus University Medical Center. Subsequently, he started a PhD at the Departments of Epidemiology and Radiology at Erasmus University Medical Center under the supervision of Meike Vernooij, Arfan Ikram, and Frank Wolters. His research focused on the role of magnetic resonance imaging (MRI) in predicting dementia, with the ultimate goal of enhancing dementia prediction models, which lead to the work presented in this thesis. During his PhD, he also completed a second master's degree in Epidemiology. After finishing his PhD, he pursued a postdoctoral research position within the Medical Delta program. He currently lives in Rotterdam with his partner and continues his work as a postdoctoral researcher within the ALIVE flagship at the Department of Epidemiology at the Erasmus University Medical Center. Outside of academia, he is enthusiastic about travelling, sports like running and swimming, and enjoys activities such as board games and escape rooms.

Imagine attempting to look into a black hole: a mysterious phenomenon, whose inner workings remain largely hidden from view.

Similarly, predicting dementia is like trying to look into the unknown. While some clinical signs suggest the onset of neurodegeneration, dementia often hides its early stages. Dementia is one of the largest health problems and absolute numbers are increasing. Early identification of individuals at high risk for dementia is crucial for improving treatment and engaging in preventive strategies.

Advanced magnetic resonance imaging (MRI) techniques and machine learning methods offer promising tools for detecting early brain changes and identifying new predictors for dementia. This thesis investigates the role of MRI in identifying individuals at high risk of dementia and presents newly developed dementia prediction models that incorporate patient and clinical considerations.

