Title

Improved multimodal prediction of progression from MCI to Alzheimer's disease combining genetics with quantitative brain MRI and cognitive measures

Journal

Alzheimer's & Dementia, 19(11)

ISSN

1552-5260

Authors

Reas, Emilie T

Shadrin, Alexey

Frei, Oleksandr

et al.

Publication Date

2023-11-01

DOI

10.1002/alz.13112

Peer reviewed

HHS Public Access

Author manuscript

Alzheimers Dement. Author manuscript; available in PMC 2024 November 01.

Published in final edited form as:

Alzheimers Dement. 2023 November ; 19(11): 5151–5158. doi:10.1002/alz.13112.

Improved multimodal prediction of progression from MCI to Alzheimer's disease combining genetics with quantitative brain MRI and cognitive measures

Emilie T. Reas, (PhD)[1,*], **Alexey Shadrin, (PhD)**[2], **Oleksandr Frei, (PhD)**[2,3], **Ehsan Motazedi, (PhD)**[2], **Linda McEvoy, (PhD)**[6], **Shahram Bahrami, (PhD)**[2], **Dennis van der Meer, (PhD)**[2], **Carolina Makowski, (PhD)**[6], **Robert Loughnan, (MS)**[8], **Xin Wang, (MS)**[1], **Iris Broce, (PhD)**[1], **Sarah J. Banks, (PhD)**[1], **Vera Fominykh, (MD, PhD)**[2], **Weiqiu Cheng, (PhD)**[2], **Dominic Holland, (PhD)**[1], **Olav B. Smeland, (MD)**[2], **Tyler Seibert, (MD, PhD)**[6], **Geir Selbæk, (MD)**, **James B. Brewer, (MD, PhD)**[1], **Chun C. Fan, (MD)**[4,5,6], **Ole A. Andreassen, (MD)**[2], **Anders M. Dale, (PhD)**[1,4,6,7], **Alzheimer's Disease Neuroimaging Initiative**

[1]Department of Neurosciences, University of California San Diego, La Jolla, CA 92093, USA

[2]NORMENT Centre, Institute of Clinical Medicine, University of Oslo and Division of Mental Health and Addiction, Oslo University Hospital, 0407 Oslo, Norway

[3]Center for Bioinformatics, Department of Informatics, University of Oslo, PO box 1080, Blindern, 0316 Oslo, Norway

[4]Population Neuroscience and Genetics Lab, University of California, La Jolla, CA 92093, USA

[5]Center for Human Development, University of California, San Diego, La Jolla, CA 92093, USA

[6]Department of Radiology, University of California, San Diego, La Jolla, CA 92093, USA

[7]Department of Psychiatry, University of California, San Diego, La Jolla, CA 92093, USA

[8]University of California, San Diego, La Jolla, California, USA

Abstract

INTRODUCTION: There is pressing need for non-invasive, cost-effective tools for early detection of Alzheimer's disease.

METHODS: Using data from the Alzheimer's Disease Neuroimaging Initiative, Cox proportional models were conducted to develop a multimodal hazard score (MHS) combining age, a polygenic hazard score (PHS), brain atrophy, and memory to predict conversion from mild cognitive impairment to dementia. Power calculations estimated required clinical trial sample sizes after

*Address correspondence to Dr. Emilie T. Reas, Department of Neurosciences, Mail code 0841, UCSD, 9500 Gilman Dr., La Jolla, CA 92093-0841; ereas@ucsd.edu.

Consent statement

All ADNI sites acquired local institutional review board approval and informed subject consent for participation in the ADNI study.

hypothetical enrichment using the MHS. Cox regression determined predicted age of onset for Alzheimer's disease pathology from the PHS.

RESULTS: The MHS predicted conversion from mild cognitive impairment to dementia (hazards ratio for 80th versus 20th percentile: 27.03). Models suggest that application of the MHS could reduce clinical trial sample sizes by 67%. The PHS alone predicted age of onset of amyloid and tau.

DISCUSSION: The MHS may improve early detection of Alzheimer's disease for use in memory clinics or for clinical trial enrichment.

Keywords

Alzheimer's disease; Multimodal prediction; genetics; MRI; memory; amyloid; tau; mild cognitive impairment

1. Background

Alzheimer's disease (AD) is an age-dependent neurodegenerative disease hallmarked by the accumulation of extracellular amyloid-β plaques and intracellular neurofibrillary tau tangles that emerge decades before symptom onset [1]. This preclinical period is followed by a prodromal stage during which a diagnosis of amnestic mild cognitive impairment (MCI) indicates high probability of conversion to dementia within several years [2]. Because AD has a complex, multifactorial etiology with genetic and modifiable risk factors, diagnostic accuracy in preclinical periods is limited, which poses a particular challenge for clinical trial enrollment in which pre-screening precision is critical to minimize cost and subject burden. Thus, there is outstanding need to develop tools that can identify individuals with high probability of converting to AD for timely diagnosis and streamlined clinical trial screening.

Cerebrospinal fluid (CSF) or positron emission tomography (PET) measures of amyloid and tau pose obstacles to routine clinical use due to their cost, invasiveness, and radiation exposure. Inexpensive, non-invasive, and widely available approaches to quantify personalized AD risk will improve clinicians' ability to select patients with the greatest potential for therapeutic benefit, and to guide clinical trial enrichment to minimize trial cost and patient burden. To this end, accurate longitudinal prediction of disease progression in preclinical or prodromal stages, during which therapeutic interventions will be most effective [3], is urgently needed.

Late-onset AD has high genetic susceptibility, with *APOE4* conferring the strongest risk of any single gene [4]. Genome-wide association studies have identified a diversity of additional AD risk variants beyond *APOE* [5], which have been combined into polygenic risk scores (PRS) that estimate an individual's lifetime genetic risk. However, PRS models do not provide critical information about age of dementia onset, are limited in prognostic utility, and carry mixed accuracy at predicting amyloid and tau [6]. Using age-dependent survival analysis, we previously integrated common genetic variants into a polygenic hazard score (PHS) that accurately estimates age of AD onset, even among *APOE* ε3/ε3 individuals, who constitute the majority of AD cases [7, 8]. The Desikan AD PHS predicts CSF, PET, or post-mortem measures of neuropathological burden, rates of cognitive

decline, and conversion to AD [9–11], and may be useful for clinical trial enrichment [12]. Considering the time-sensitive nature of AD interventions, AD risk models using polygenic estimates such as the Desikan AD PHS will be of greatest clinical utility if they can precisely track the clinical time-course.

Because of the multi-etiological pathways that synergistically contribute to AD [13–15] and variable disease manifestations, multimodal tools for AD detection [16] and prognosis [17] are superior to single-modality methods. Thus, the sensitivity of genetic risk estimates may be maximized by integrating complementary markers of disease progression, such as neurodegeneration and memory decline, which are more proximal to clinical progression than amyloid or tau [18–20]. Our group developed a composite AD atrophy score that distinguishes individuals with MCI who convert to AD or demonstrate clinical decline from those who remain stable [21]. The ease of acquiring neuropsychological measures enhances their practical value in clinical and research settings. Whereas both AD atrophy scores and global cognition predict conversion from MCI to AD, combining the PHS with either measure improves prediction [10], suggesting that their integration may optimize prediction of AD progression.

Here, we evaluate the prognostic utility of the Desikan AD PHS in prodromal AD by integrating it with brain atrophy and cognitive scores into a Multimodal Hazard Score (MHS) to optimize precision of predicting time to conversion from MCI to dementia. By leveraging relatively cost-effective and non-invasive genetic, imaging, and cognitive biomarkers, multivariate predictive models such as the MHS could streamline clinical trial screening by reducing the number of participants required to undergo costly and burdensome pre-screening PET scans. The MHS may also be useful in memory clinics to target individuals with highest risk of progressing to AD and potential for therapeutic benefits, while minimizing concern among those experiencing memory complaints with low risk of developing AD.

2. Methods

2.1 Participants

Data were included from participants of the Alzheimer's Disease Neuroimaging Initiative (ADNI; adni.loni.usc.edu), a multicenter longitudinal observational study established in 2004 to validate clinical, imaging, genetic, and biospecimen barkers for prediction of progression to AD [22]. The present study analyzed data from 849 ADNI participants with a diagnosis of MCI or subjective memory complaints (SMC) at baseline and available genetic, MRI, and cognitive data. Follow-up assessments were conducted annually for up to 36 months. ADNI study procedures were approved by local institutional review boards, and all participants or their guardians provided written informed consent prior to participation.

2.2 Genotyping

Genotyping was conducted according to standard assays by Illumina and raw genetic data were downloaded from the ADNI website (https://adni.loni.usc.edu/). The Desikan AD PHS was computed based on a Cox proportional hazard regression model combining 31

AD-associated single nucleotide polymorphisms (SNPs) with two *APOE* variants (*ε2*/*ε4*), trained with genetic data from an independent cohort [7].

2.3 Magnetic resonance imaging

Details of image acquisition and analysis have been described previously [21]. Briefly, structural MRI data were acquired following strict standardization protocols, and raw baseline DICOM MRI data were downloaded from the ADNI web site (http://adni.loni.usc.edu/data-samples/mri/). Cortical thickness and subcortical volumes were measured from baseline structural T1 data using FreeSurfer v5.0 [23] to calculate quantitative morphometric measures from regions of interest (ROIs) for survival analysis. Automated volumetric segmentation and cortical surface reconstruction underwent quality review by trained technicians as described [24] and data with significant artifact were excluded from analysis. A previously validated brain atrophy score was computed as the sum of weighted measures from ROIs averaged across hemispheres, derived using linear discrimination analysis to distinguish AD patients from healthy controls [21]. Component measures of this atrophy score included volume of the hippocampus, and thickness of entorhinal cortex, middle temporal gyrus, bank of the superior temporal sulcus, isthmus cingulate (retrosplenial cortex), superior temporal gyrus, and medial and lateral orbitofrontal gyri.

2.4 Cognitive assessment

Memory performance was assessed at baseline using the learning (sum of trials 1–5) measure of the Rey Auditory Verbal Learning Test (RAVLT), a test of verbal episodic memory [25].

2.5 Measurement of amyloid-β and tau

Lumbar puncture was conducted as detailed in the ADNI manual (http://www.adni-info.org/). Amyloid-β 1–42 (Aβ42) and phosphorylated tau (p-tau) were measured from CSF samples using the Elecsys β-amyloid(1–42) CSF, and the Elecsys phosphotau (181P) CSF immunoassays at the Biomarker Research Laboratory, University of Pennsylvania, USA, as previously described [26]. Cutoffs for amyloid and tau positivity were Aβ42<977 pg/mL and p-tau>24 pg/mL, as deemed optimal for performance against visual PET read [26].

2.6 Statistical approach

2.6.1 Development of the MHS—The MHS was calculated to estimate age-specific risk of conversion from MCI to AD, based upon the combined contributions of genetics, brain morphometry, and memory performance. The Desikan AD PHS was used as an estimate of polygenic risk and RAVLT learning score was used as a measure of episodic memory. To quantify AD-specific atrophy patterns, sixty-four ROI volumetric measures [21] were combined into the imaging hazard score (HIS) by applying Cox regression to a training set of cross-sectional ADNI data. Age-specific proportional hazard scores were computed by applying time-invariant Cox proportion hazards regression with PHS, IHS and RAVLT scores as predictors, using the exponential baseline hazard function of [27]. Thus,

the PHS, IHS and RAVLT measures served as intermediaries to an aggregate risk estimate of conversion to AD, integrating complementary markers of genetic susceptibility, regional brain atrophy, and memory impairment.

2.6.2 Predicting conversion from MCI to AD using the MHS—All 849 participants with diagnoses of MCI or SMC at baseline were included for MHS model development, and time to first diagnosis to AD dementia was used at the outcome. The composite MHS model included predictors of age, the PHS, IHS, and RAVLT score. Model performance at predicting conversion from SMC or MCI to AD over a five-year period was assessed using age alone; age and the PHS; age with the PHS and IHS; and the aggregate MHS (age with PHS, IHS, and RAVLT) by testing on hold-out longitudinal data from the ADNI sample. All participants without an AD diagnosis at baseline were included for analysis. The outcome of interest was a diagnosis of AD five years after baseline.
To evaluate model performance according to risk stratification, hazard scores were ranked according to population percentile. Low and high-risk groups were identified as the lowest (20%) or highest (80%) of the population distribution. Hazard ratios (HRs) were computed between the lowest and highest risk groups (20% versus 80%; $HR_{80/20}$) for conversion from MCI to AD over the five-year follow-up, with higher HRs indicative of better model performance. To compare survival curves across risk groups and to obtain expected ages of onset from absolute hazards, we combined Cox proportional hazard scores with the exponential baseline hazard [28].

2.6.3 Optimizing clinical trial enrichment with the MHS—To assess the utility of the MHS at improving clinical trial enrichment strategies, power calculations were conducted to estimate sample sizes required for a hypothetical longitudinal clinical trial study. As the hypothetical trial outcome, models used annual percent rate (APR) of change on the Clinical Dementia Rating Scale - sum of boxes (CDR-SB), a measure of disease progression commonly used in AD clinical trials, computed per subject using linear regression across timepoints. To first assess the sensitivity of the MHS to longitudinal disease progression, Pearson's correlations were computed between each set of predictors in the MHS and CDR-SB change. Next, for each predictive model, participants were classified as high or low risk using a 50^{th} percentile cutoff, and the high-risk group was selected as the hypothetical trial enrichment group. Applying methods described by Fitzmaurice et al. [29], for each predictive model the necessary sample size to detect CDR-SB change, with β=0.80 and α=0.05, was computed using the full sample (both low and high risk groups) and within the high-risk subgroup. The difference in required sample size after enrichment with the MHS risk prescreening versus no enrichment was calculated as $(N_{\text{MHS high risk}} / N_{\text{low+high risk}})$.

2.6.4 Prediction of AD pathology—Using a partially overlapping dataset including 401 ADNI subjects (238 cognitively normal, 28 SMC, 109 MCI, 25 dementia, 1 unknown) with available CSF Aβ42 and p-tau data, Cox regression models were implemented to predict age of onset of CSF markers of AD pathology acquired from longitudinal ADNI data. Participants were followed up to over 8 years, with an average of 1.2±0.6 CSF measurements. Models used the Desikan AD PHS to determine age-dependent probabilities

of reaching threshold levels of Aβ42 and p-tau [26]. From the resulting model, we identified predicted age of onset for amyloid- and p-tau-positivity according to PHS risk stratification.

3. Results

3.1 Participant characteristics

Participant demographics and baseline diagnoses and cognitive data for the sample used in computation of the MHS are presented in Table 1. Subjects were diagnosed at baseline with either early or late MCI or SMC. Over the course of the five-year follow-up, 35% of subjects converted to AD dementia, including 1% (*N*=1) of SMC, 13% (*N*=36) of early MCI, and 54% (*N*=260) of late MCI.

3.2 MHS predicts conversion from MCI to AD

Prediction accuracy for conversion from MCI to AD dementia over the five-year follow-up period was computed for each combination of the four model components (age, PHS, IHS, and RAVLT, Supplemental Figure 1). Survival curves for models of interest are shown in Figure 1 with groups stratified by population risk from the 1st percentile to 99th risk percentile. Histograms of bootstrapped odds ratios$_{80/20}$ for each model are presented in Supplemental Figure 2 with 95% confidence intervals showing acceptable accuracy. There was a modestly increased likelihood of conversion to AD dementia with older age, with a $HR_{80/20}$ = 1.42 (95% confidence interval = 1.12, 1.97, Supplemental Figure 1). Adding PHS to the model significantly improved prediction (Figure 1A), evidenced by a greater separation of AD risk across PHS percentiles, with an $HR_{80/20}$ = 3.57 (2.63, 4.03). Model performance improved with addition of the IHS (Figure 1B), with $HR_{80/20}$ = 13.16 (8.93, 20.43). Finally, incorporating RAVLT scores into the MHS further improved model performance (Figure 1C), with $HR_{80/20}$ = 27.03 (17.46, 48.96), reflected by low conversion rates (10%) among those with a 20th percentile MHS risk in contrast to the high conversion rates (77%) among those in the 80th percentile risk group. The expected time to AD dementia onset significantly decreases with higher MHS; for example, as illustrated in Figure 1C, the time difference from baseline to a given probability of conversion to AD dementia can be five years or greater between the 80th and 20th percentile MHS groups.

3.3 Clinical trial enrichment with the MHS

To evaluate correspondence between predictive multivariate models and longitudinal disease progression, correlations were computed between each predictive model score and the CDR-SB APR. As shown in Table 2, correlations increased with each added predictor. The most pronounced improvement occurred with addition of the PHS to age, and again with addition of the IHS, whereas adding memory into the model marginally improved prediction. The strongest correlation with disease progression was observed for the full MHS (r=0.55 (0.50, 0.61)).

Given these findings that the MHS predicts time to conversion from MCI to dementia and correlates with clinical measures of AD progression, we next sought to evaluate the utility of the MHS for clinical trial enrichment. Table 2 illustrates the difference in required sample size after screening with each multivariate predictive model compared to no screening,

using change in the CDR-SB as the hypothetical trial outcome. Limiting trial enrollment to participants with the top 50% of MHS risk scores is expected to reduce the sample size necessary to detect significant clinical decline by 67%.

3.4 Predicting AD pathology with the PHS

Finally, to assess the use of the Desikan AD PHS at predicting age of onset of AD pathology, survival curves for Aβ42 positivity and p-tau positivity by age according to mean PHS risk are presented in Supplemental Figure 3. As expected, age strongly predicted the onset of pathology, with the probability of abnormal amyloid or p-tau increasing from zero at age 55 to greater than 90% by age 90 among those with a median PHS. PHS strongly modified survival curves, such that for a given probability, PHS shifted the age of onset for abnormal pathology by several years. For instance, an individual in the 1st PHS percentile has a 50% probability of amyloid positivity at age 82, whereas an individual in the 99th PHS percentile is predicted to reach 50% probability eight years prior, at age 74. Similarly, age for 50% probability of p-tau positivity for individuals in the 1st and 99th PHS percentiles is predicted at ages 83 and 75, respectively, again highlighting an eight-year shift in risk for p-tau abnormality related to PHS.

4. Discussion

In this study we demonstrate the utility of the Desikan AD PHS, both independently and integrated with complementary imaging and cognitive data, at predicting time to conversion from MCI to AD dementia and for enrichment of AD clinical trials. First, we leverage a multimodal approach to show that predicted time to conversion from MCI to AD can be optimized by integrating the PHS with an individual's brain atrophy signature and memory performance. Next, we demonstrate that this MHS predicts rates of disease progression and can thus be implemented to enrich clinical trials for participants who are most likely to exhibit clinical decline and demonstrate treatment effects. Thus, the MHS represents a conceptual advance in precision medicine over prior multimodal models by predicting age of disease onset, presenting a novel approach that could be extended to other disorders beyond AD.

Given the heterogeneity of MCI and the prognostic uncertainty of the diagnosis, tools for precision modeling of clinical trajectories from the MCI stage are needed. Because of the complexity of disease presentation in prodromal stages, multimodal tools that integrate complementary AD biomarkers demonstrate superior performance to single modality methods. Here, we present the MHS as an optimized predictive model that leverages economical and non-invasive biomarkers of genetics, neurodegeneration, and episodic memory impairment. This multifactorial tool provides a clinically meaningful separation of AD conversion risk, with a greater than five-year distance in predicted conversion time between those in the 20th versus 80th MHS percentiles. Prior integrative models that combine measures of pathology, neurodegeneration, cognition, or genetics, have also shown promise for cross-sectional discrimination of AD [16, 30] or prediction of cognitive decline or disease progression [17, 31, 32]. Whereas these multimodal tools relied upon either costly (e.g., PET) or invasive (e.g., CSF) biomarkers, measures used in computation

of the MHS would require relatively convenient and cost-effective tests that are readily accessible in clinical settings. Furthermore, in contrast to prior models of AD classification [30] or disease conversion [32] that included *APOE* genotype, the MHS captures a more comprehensive genetic risk profile with the PHS.

Recent advances in the development of disease-modifying therapies for AD indicate that novel pharmaceutical agents may soon be readily available in clinical settings [33]. Nevertheless, several critical issues remain to be addressed to maximize clinical utility, including heterogeneity of treatment efficacy according to genetics, sex, and ethnicity, potential for serious adverse events, and establishing long-term slowing of disease progression. Thus, the race for an effective treatment continues, with unprecedented failure rates of past trials partially attributed to imprecise selection of trial candidates [34]. Due to the high financial cost, participant burden, and risk of side effects of clinical trials, there has been an urgent call for strategies to reduce required sample sizes by enrichment with precision selection tools, particularly with multivariate measures that optimize power estimates [35]. Whereas PET-based amyloid-positivity is commonly used for pre-screening, alternative cost-effective methods that do not require radiation exposure will help to streamline enrollment pipelines. Here, we present the MHS as a candidate trial enrichment approach that, by integrating genetic, MRI, and cognitive data, obviates the need for invasive lumbar puncture for measurement of CSF biomarkers, or prohibitive cost and radiation exposure from PET scans. Our results suggest that incorporating the MHS for trial screening could lower required sample sizes to a third of those needed without pre-screening. Even a simpler model combining the Desikan AD PHS with age, requiring only a blood or saliva sample, would reduce target sample sizes by nearly half. The MHS provides a framework for minimizing clinical trial cost and participant exposure to drug side effects through multimodal enrichment strategies, warranting further investigation to both replicate our findings and optimize pre-screening predictive models. Finally, our results provide novel evidence that the Desikan AD PHS, a key component of the MHS, is a sensitive measure of accumulating AD pathology. Although cross-sectional studies have reported that PRS are associated with CSF tau but are only weakly associated with amyloid [36, 37], we previously observed strong associations of the Desikan AD PHS with both amyloid and tau [9]. Here, we extend these findings to demonstrate that the PHS can predict the age at which clinically significant amyloid and p-tau appear, with onset of pathology at increasingly younger ages for those with higher PHS. This pronounced separation of pathology risk by PHS stratification highlights its correspondence with the defining pathological features of AD, further supporting its potential value for enriching clinical trials with individuals carrying a specified burden of the neuropathological target, or in clinical settings to identify patients who are ideal candidates for disease-modifying therapies. While an effective clinical screening tool should at minimum be sensitive to the underlying pathological target of interest, pathological burden does not perfectly correspond with disease course, as has been highlighted by the disappointing effects on clinical progression by otherwise effective disease-modifying agents. Furthermore, the extended preclinical period of AD during which pathology may present below abnormality thresholds, argues for alternative predictive tools that are independent of current pathological burden. The MHS could fulfill this need by providing a biomarker-agnostic indicator of likely time to disease onset that is sensitive

to core AD pathologies but can be implemented during an earlier window of opportunity during which material pathological burden has yet to manifest.

This study has some limitations. AD research has suffered from limited representation of minority groups, some of whom are at elevated risk for dementia, which is particularly problematic for genome-wide association studies requiring exceptionally large datasets. The PHS and MHS are not immune to this deficiency and may not generalize to non-white populations, as they were developed using a sample of predominantly white participants of European ancestry. Thus, the multimodal predictive framework reported here should serve as a foundation for developing population-specific AD models as data from underrepresented groups become increasingly available. Despite their elevated risk for AD, women were also underrepresented in this sample. Furthermore, the data presented here reflect models that require validation in an independent sample. While polygenic tools are expected to provide substantial benefit in terms of cost and patient burden by reducing need for PET scanning and lumbar puncture, evaluation of these models in clinical trial settings will be critical to validate potential savings. This proof-of-concept study illustrates the potential of the MHS but warrants further investigation to establish clinical relevance, which we are pursuing in studies of real-world clinical samples to guide implementation in clinical practice. Finally, inclusion of AD biomarkers that are currently under development, such as plasma p-tau or other blood-based measures [38], may improve prognostic accuracy of the MHS as these measures become clinically available.

5. Conclusion

In conclusion, the PHS and the MHS are promising predictive tools for identifying individuals with high probability of transitioning from MCI to AD dementia and of demonstrating significant clinical decline. In memory clinic settings, these tools may improve precision medicine approaches to personalized risk assessment of AD and to identify candidates for therapeutic interventions. They may further minimize clinical trial expense and subject burden by providing cost-effective screening tools for targeted selection of patients at precise stages along the AD continuum.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding Sources

ETR was supported by the National Institute on Aging (R00 AG057797, R01 AG077202) and American Federation for Aging Research /McKnight Foundation (311122-00001). OAA was supported by Research Council of Norway (# 324499, 324252, 273291, 223273), Norwegian Health Association (# 22731), European Union's Horizon 2020 Research and Innovation Action Grant (#847776 CoMorMent). Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies;

Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Conflicts

AMD reports that he was a Founder of and holds equity in CorTechs Labs, Inc., and serves on its Scientific Advisory Board. He is a member of the Scientific Advisory Board of Human Longevity, Inc. He receives funding through research grants from GE Healthcare to UCSD. The terms of these arrangements have been reviewed by and approved by UCSD in accordance with its conflict of interest policies. Dr. Dale also reports that he has memberships with the following research consortia: Alzheimers Disease Genetics Consortium (ADGC); Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA); Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL); Psychiatric Genomics Consortium (PGC). OAA is a consultant to Cortechs.ai, and has received speaker's honoraria from Sunovion, Janssen and Lundbeck. He is also local PI of clinical trials in mental disorders (not dementia) sponsored by Boehringer Ingelheim, Janssen, Compass, MAPS. All other authors have no conflicts of interest.

Abbreviations:

AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
APR	annual percent rate
CSF	cerebrospinal fluid
CDR-SB	Clinical Dementia Rating Scale - sum of boxes
HR	hazard ratio
IHS	imaging hazard score
MRI	magnetic resonance imaging
MCI	mild cognitive impairment
MHS	multimodal hazard score
PHS	polygenic hazard score
PRS	polygenic risk score
PET	positron emission tomography
RAVLT	Rey Auditory Verbal Learning Test
SMC	subjective memory complaints

REFERENCES

[1]. Jack CR Jr., Holtzman DM. Biomarker modeling of Alzheimer's disease. Neuron. 2013;80:1347–58. [PubMed: 24360540]

[2]. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. Lancet. 2006;367:1262–70. [PubMed: 16631882]

[3]. Sperling RA, Jack CR, Aisen PS. Testing the Right Target and Right Drug at the Right Stage. Science Translational Medicine. 2011;3:111cm33–cm33.

[4]. Roses AD. Apolipoprotein E alleles as risk factors in Alzheimer's disease. Annu Rev Med. 1996;47:387–400. [PubMed: 8712790]

[5]. Wightman DP, Jansen IE, Savage JE, Shadrin AA, Bahrami S, Holland D, et al. A genome-wide association study with 1,126,563 individuals identifies new risk loci for Alzheimer's disease. Nat Genet. 2021;53:1276–82. [PubMed: 34493870]

[6]. Harrison JR, Mistry S, Muskett N, Escott-Price V. From Polygenic Scores to Precision Medicine in Alzheimer's Disease: A Systematic Review. J Alzheimers Dis. 2020;74:1271–83. [PubMed: 32250305]

[7]. Desikan RS, Fan CC, Wang Y, Schork AJ, Cabral HJ, Cupples LA, et al. Genetic assessment of age-associated Alzheimer disease risk: Development and validation of a polygenic hazard score. PLoS medicine. 2017;14:e1002258. [PubMed: 28323831]

[8]. Motazedi E, Cheng W, Thomassen JQ, Frei O, Rongve A, Athanasiu L, et al. Using Polygenic Hazard Scores to Predict Age at Onset of Alzheimer's Disease in Nordic Populations. Journal of Alzheimer's Disease. 2022:1–12.

[9]. Tan CH, Bonham LW, Fan CC, Mormino EC, Sugrue LP, Broce IJ, et al. Polygenic hazard score, amyloid deposition and Alzheimer's neurodegeneration. Brain. 2019;142:460–70. [PubMed: 30689776]

[10]. Kauppi K, Fan CC, McEvoy LK, Holland D, Tan CH, Chen CH, et al. Combining Polygenic Hazard Score With Volumetric MRI and Cognitive Measures Improves Prediction of Progression From Mild Cognitive Impairment to Alzheimer's Disease. Front Neurosci. 2018;12:260. [PubMed: 29760643]

[11]. Tan CH, Fan CC, Mormino EC, Sugrue LP, Broce IJ, Hess CP, et al. Polygenic hazard score: an enrichment marker for Alzheimer's associated amyloid and tau deposition. Acta Neuropathol. 2018;135:85–93. [PubMed: 29177679]

[12]. Banks SJ, Qiu Y, Fan CC, Dale AM, Zou J, Askew B, et al. Enriching the design of Alzheimer's disease clinical trials: Application of the polygenic hazard score and composite outcome measures. Alzheimers Dement (N Y). 2020;6:e12071. [PubMed: 32999917]

[13]. Sweeney MD, Montagne A, Sagare AP, Nation DA, Schneider LS, Chui HC, et al. Vascular dysfunction-The disregarded partner of Alzheimer's disease. Alzheimers Dement. 2019;15:158–67. [PubMed: 30642436]

[14]. Frost GR, Jonas LA, Li Y-M. Friend, foe or both? Immune activity in Alzheimer's disease. Frontiers in aging neuroscience. 2019;11:337. [PubMed: 31920620]

[15]. Clarke JR, Ribeiro FC, Frozza RL, De Felice FG, Lourenco MV. Metabolic dysfunction in Alzheimer's disease: from basic neurobiology to clinical approaches. Journal of Alzheimer's Disease. 2018;64:S405–S26.

[16]. Zhang D, Wang Y, Zhou L, Yuan H, Shen D. Multimodal classification of Alzheimer's disease and mild cognitive impairment. NeuroImage. 2011;55:856–67. [PubMed: 21236349]

[17]. Lee G, Nho K, Kang B, Sohn K-A, Kim D, Weiner MW, et al. Predicting Alzheimer's disease progression using multi-modal deep learning approach. Scientific Reports. 2019;9:1952. [PubMed: 30760848]

[18]. Whitwell JL, Shiung MM, Przybelski SA, Weigand SD, Knopman DS, Boeve BF, et al. MRI patterns of atrophy associated with progression to AD in amnestic mild cognitive impairment. Neurology. 2008;70:512–20. [PubMed: 17898323]

[19]. Killiany RJ, Gomez-Isla T, Moss M, Kikinis R, Sandor T, Jolesz F, et al. Use of structural magnetic resonance imaging to predict who will get Alzheimer's disease. Annals of Neurology. 2000;47:430–9. [PubMed: 10762153]

[20]. Belleville S, Fouquet C, Hudon C, Zomahoun HTV, Croteau J. Neuropsychological measures that predict progression from mild cognitive impairment to Alzheimer's type dementia in older adults: a systematic review and meta-analysis. Neuropsychology review. 2017;27:328–53. [PubMed: 29019061]

[21]. McEvoy LK, Fennema-Notestine C, Roddey JC, Hagler DJ Jr., Holland D, Karow DS, et al. Alzheimer disease: quantitative structural neuroimaging for detection and prediction of clinical

and structural changes in mild cognitive impairment. Radiology. 2009;251:195–205. [PubMed: 19201945]

[22]. Jack CR Jr., Bernstein MA, Fox NC, Thompson P, Alexander G, Harvey D, et al. The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. Journal of magnetic resonance imaging : JMRI. 2008;27:685–91. [PubMed: 18302232]

[23]. Dale AM. Optimal experimental design for event-related fMRI. Hum Brain Mapp. 1999;8:109–14. [PubMed: 10524601]

[24]. Hagler DJ Jr, Hatton S, Cornejo MD, Makowski C, Fair DA, Dick AS, et al. Image processing and analysis methods for the Adolescent Brain Cognitive Development Study. NeuroImage. 2019;202:116091. [PubMed: 31415884]

[25]. Schmidt M Rey auditory verbal learning test: A handbook: Western Psychological Services Los Angeles, CA; 1996.

[26]. Bittner T, Zetterberg H, Teunissen CE, Ostlund RE Jr., Militello M, Andreasson U, et al. Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of beta-amyloid (1–42) in human cerebrospinal fluid. Alzheimers Dement. 2016;12:517–26. [PubMed: 26555316]

[27]. Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. American journal of public health. 1998;88:1337–42. [PubMed: 9736873]

[28]. Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. Am J Public Health. 1998;88:1337–42. [PubMed: 9736873]

[29]. Fitzmaurice G, Laird N, Ware J. Applied Longitudinal Analysis. John Wiley & Sons. Inc, Haboken, NJ. 2004.

[30]. Tong T, Gray K, Gao Q, Chen L, Rueckert D. Multi-modal classification of Alzheimer's disease using nonlinear graph fusion. Pattern Recogn. 2017;63:171–81.

[31]. Ritter K, Schumacher J, Weygandt M, Buchert R, Allefeld C, Haynes J-D. Multimodal prediction of conversion to Alzheimer's disease based on incomplete biomarkers*This work was supported by the Bernstein Computational Program of the German Federal Ministry of Education and Research (01GQ1001C, 01GQ0851, GRK 1589/1), the European Regional Development Fund of the European Union (10153458 and 10153460), and Philips Research.*. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2015;1:206–15.

[32]. Lin W, Gao Q, Yuan J, Chen Z, Feng C, Chen W, et al. Predicting Alzheimer's Disease Conversion From Mild Cognitive Impairment Using an Extreme Learning Machine-Based Grading Method With Multimodal Data. Frontiers in aging neuroscience. 2020;12.

[33]. van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in Early Alzheimer's Disease. The New England journal of medicine. 2022.

[34]. Kim CK, Lee YR, Ong L, Gold M, Kalali A, Sarkar J. Alzheimer's Disease: Key Insights from Two Decades of Clinical Trial Failures. Journal of Alzheimer's Disease. 2022;87:83–100.

[35]. Veitch DP, Weiner MW, Aisen PS, Beckett LA, Cairns NJ, Green RC, et al. Understanding disease progression and improving Alzheimer's disease clinical trials: Recent highlights from the Alzheimer's Disease Neuroimaging Initiative. Alzheimer's & Dementia. 2019;15:106–52.

[36]. Altmann A, Scelsi MA, Shoai M, de Silva E, Aksman LM, Cash DM, et al. A comprehensive analysis of methods for assessing polygenic burden on Alzheimer's disease pathology and risk beyond APOE. Brain Communications. 2019;2.

[37]. Ge T, Sabuncu MR, Smoller JW, Sperling RA, Mormino EC, Initiative FtAsDN. Dissociable influences of APOE ε4 and polygenic risk of AD dementia on amyloid and cognition. Neurology. 2018;90:e1605–e12. [PubMed: 29592889]

[38]. Hansson O, Edelmayer RM, Boxer AL, Carrillo MC, Mielke MM, Rabinovici GD, et al. The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. Alzheimer's & Dementia. 2022.

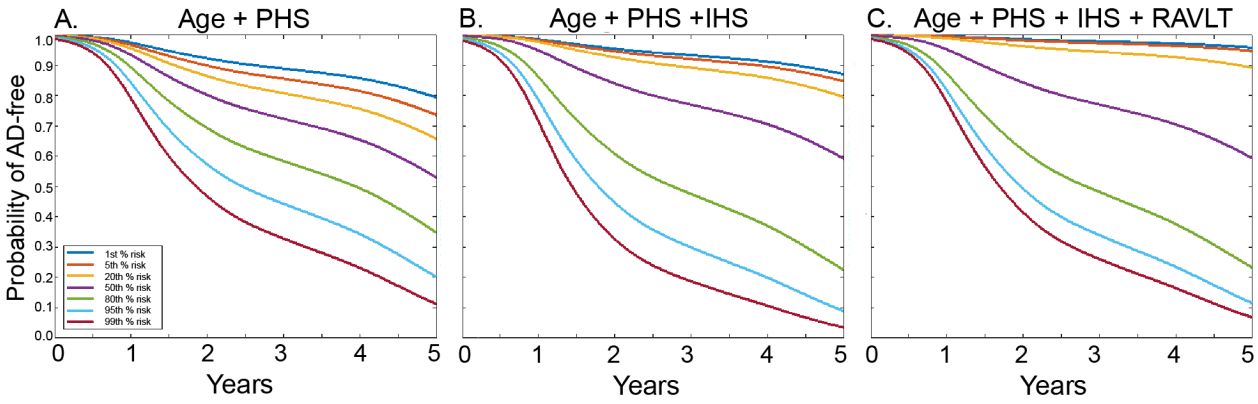

Figure 1. Multimodal prediction of conversion from MCI to AD dementia by PHS, brain atrophy, and memory.

Survival curves illustrate predicted probability of remaining free of AD dementia according to stratification by PHS models. Curves are shown for models using A) Age + PHS, B) Age + PHS + IHS, C) MHS (Age + PHS + IHS + RAVLT). IHS, imaging hazard score; MHS, multimodal hazard score; PHS, polygenic hazard score; RAVLT, Rey auditory verbal learning test

Table 1.

Baseline characteristics for all participants (*N*=849) used in computation of the MHS.

Characteristic	SMC *N*=90	Early MCI *N*=276	Late MCI *N*=483	All Subjects *N*=849
Age (mean, SD)	72.3 (5.8)	71.5 (7.3)	74.0 (7.5)	73.0 (7.4)
Women *N* (%)	55 (61.1%)	121 (43.8%)	182 (37.7%)	358 (42.2%)
MMSE score (mean, SD)	29.0 (1.2)	28.3 (1.6)	27.3 (1.8)	27.8 (1.8)
RAVLT score (scaled; mean, SD)	33.4 (37.1)	55.5 (34.2)	81.7 (29.5)	68.0 (36.2)
APOE4 carrier *N* (%)	30 (33.3%)	116 (42.0%)	259 (53.6%)	405 (47.7%)

MCI, mild cognitive impairment; MMSE, mini mental state exam; RAVLT, Rey auditory verbal learning test; SMC, subjective memory complaints

Table 2.

Pearson's correlation coefficients (95% confidence interval, CI) between scores from each predictive model and Clinical Dementia Rating – Sum of Boxes (CDR-SB) annual percent rate (APR) of change, and relative sample sizes needed for a hypothetical clinical trial after enrichment using the highest 50% risk from multivariate predictive models, with CDR-SB APR as the trial outcome.

Model	Correlation with CDR-SB APR (95% CI)	Relative sample size (95% CI)
Age	0.20 (0.12, 0.26)	0.71 (0.50, 0.72)
Age + PHS	0.35 (0.29, 0.41)	0.52 (0.42, 0.59)
Age + PHS + IHS	0.53 (0.48, 0.59)	0.36 (0.29, 0.38)
MHS: Age + PHS + IHS + RAVLT	0.55 (0.50, 0.61)	0.33 (0.29, 0.38)

IHS, imaging hazard score; MHS, multimodal hazard score; PHS, polygenic hazard score; RAVLT, Rey auditory verbal learning test