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Multiple markers contribute to risk of progression from normal to mild cognitive impairment

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ABSTRACT

Objective: To identify a parsimonious set of markers that optimally predicts subsequent clinical progression from normal to mild cognitive impairment (MCI).
Methods: 250 clinically normal adults (mean age = 73.6 years, SD = 6.0) from the Harvard Aging Brain Study were assessed at baseline on a wide set of markers, including magnetic resonance imaging markers of gray matter thickness and volume, white matter lesions, fractional anisotropy, resting state functional connectivity, positron emission tomography markers of glucose metabolism and β-amyloid (Aβ) burden, and a measure of vascular risk. Participants were also tested annually on a battery of clinical and cognitive tests (median follow-up = 5.0 years, SD = 1.66). We applied least absolute shrinkage and selection operator (LASSO) Cox models to determine the minimum set of non-redundant markers that predicts subsequent clinical progression from normal to MCI, adjusting for age, sex, and education.
Results: 23 participants (9.2%) progressed to MCI over the study period (mean years of follow-up to diagnosis = 3.96, SD = 1.89). Progression was predicted by several brain markers, including reduced entorhinal thickness (hazard ratio, HR = 1.73), greater Aβ burden (HR = 1.58), lower default network connectivity (HR = 1.42), and smaller hippocampal volume (HR = 1.30). When cognitive test scores were added to the model, the aforementioned neuroimaging markers remained significant and lower striatum volume as well as lower scores on baseline memory and processing speed tests additionally contributed to progression.
Conclusion: Among a large set of brain, vascular and cognitive markers, a subset of markers independently predicted progression from normal to MCI. These markers may enhance risk stratification by identifying clinically normal individuals who are most likely to develop clinical symptoms and would likely benefit most from therapeutic intervention.

1. Introduction

The pathophysiological process of Alzheimer's disease (AD) begins many years before clinical symptoms emerge (Jack et al., 2018; Sperling et al., 2014). This evidence prompted the shift of clinical trials to the preclinical stage of AD, where individuals harbor elevated β-amyloid (Aβ) burden in the absence of significant cognitive deficits (Sperling et al., 2014). Elevated Aβ burden alone, however, may not be

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sufficient to predict imminent clinical progression (Mormino et al., 2014; Burnham et al., 2016; Jagust, 2016). Therefore, there is a need for additional markers to be used along with Aβ burden to identify individuals at high risk of clinical progression who would likely benefit most from treatment.

Longitudinal studies in asymptomatic adults have identified a range of neuroimaging and clinical markers that predict cognitive decline and/or progression to mild cognitive impairment (MCI) or dementia. In addition to higher Aβ burden, these include greater tau deposition (Dumurgier et al., 2017; Sperling et al., 2019; Betthauser et al., 2020), reduced glucose metabolism (Hanseeuw et al., 2017; Ewers et al., 2014), poor vascular health (Rabin et al., 2018; Pase et al., 2016; Schneider et al., 2004; Arvanitakis et al., 2011), reduced cortical thickness/volume (Mormino et al., 2014; Bilgel et al., 2018; Fjell et al., 2010; Bangen et al., 2018), white matter hyperintensities (Bangen et al., 2018; Boyle et al., 2016; Debette and Markus, 2010), altered white matter microstructure (Rabin et al., 2019a, 2019b; Power et al., 2019), reduced functional connectivity (Buckley et al., 2017; Shaw et al., 2015), and subtle reductions in cognitive performance (Ewers et al., 2014; Rowe et al., 2013; Eckerström et al., 2013; Belleville et al., 2017; Blacker et al., 2007; Insel et al., 2016). However, the combination of measures that best captures subsequent clinical progression in asymptomatic individuals remains to be determined.

In the present study, participants from the Harvard Aging Brain Study (HABS) were assessed on a wide set of markers at baseline that captured multiple aspects of brain structure, brain function, and vascular health. The goal of the study was to identify a set of non-redundant markers that optimally predicted future clinical progression from normal to MCI. Secondary analyses examined a more subtle measure of clinical progression – a global clinical dementia rating (CDR) increase from 0 to 0.5.

2. Methods

2.1. Participants

Participants were 250 clinically normal adults recruited from HABS (Dagley et al., 2017). Study protocols were approved by the Partners HealthCare Institutional Review Board. All participants in HABS provided written informed consent prior to study procedures. At study entry, all participants were clinically normal, had a global CDR of 0 (Morris, 1993), Mini-Mental State Examination (MMSE) ≥ 27 with educational adjustment (Folstein et al., 1975), Geriatric Depression Scale < 11 (Yesavage et al., 1982), and performed within education-adjusted norms on Logical Memory delayed recall (Wechsler, 1987). All participants were screened for major neurological, psychiatric or unstable medical illnesses. Only participants with complete neuroimaging and clinical data from all modalities were included in the present study. The baseline demographic and clinical characteristics of the included sample are summarized in Table 1.

2.2. Clinical progression outcomes

The primary outcome measure was progression to MCI (i.e., progressor vs. non-progressor). MCI diagnosis was determined at consensus meetings comprising 6 or more clinicians (neuropsychologists, neurologists, and psychiatrists). Participants were brought to consensus if they had a global CDR of 0.5 or greater and/or performance fell 1.5 standard deviations below the sample mean on composite scores of episodic memory, executive function, or processing speed (Rabin et al., 2019; Orlovsky et al., 2017). In secondary analyses, we examined a more subtle measure of clinical progression, namely a global CDR increase from 0 to 0.5. The CDR is a widely used semi-structured interview for staging dementia severity (Morris, 1993; Berg, 1988). A global CDR of 0 corresponds to normal function; a score of 0.5 corresponds to very mild dementia; and scores of 1, 2, and 3 correspond to mild, moderate, and severe dementia, respectively. The CDR was administered to participants and reliable study partners by trained neuropsychologists and psychiatrists, and was rated independently from all other cognitive test results. All CDR raters were blind to participants' biomarker status.

2.3. Neuroimaging and clinical markers

All neuroimaging and clinical markers were selected *a priori* based on prior studies (Rabin et al., 2018; Hedden et al., 2016) and are presented in Table 2. All measures were obtained from participants' baseline visit. The measures are briefly described below.

2.3.1. β-amyloid positron emission tomography

As previously described (Johnson et al., 2016), baseline Aβ burden was measured with carbon 11–labeled Pittsburgh compound-B positron emission tomography (PET) using previously described protocols. Data were expressed as a distribution volume ratio using cerebellar gray matter as the reference region. As previously described (Hedden et al., 2016), a composite measure of cortical Aβ burden within frontal, lateral temporal and parietal, and retrosplenial cortices was computed ('FLR' regions) and a Gaussian mixture modeling approach was used to assign each participant a probability of belonging to the high or low Aβ distribution. The probability values ranged from 0 to 1, with higher values indicating greater likelihood of high Aβ burden.

2.3.2. Fludeoxyglucose PET

Baseline fludeoxyglucose F18–labeled (FDG) PET imaging was performed using previously described protocols (Hanseeuw et al., 2017). The mean FDG uptake was extracted from a previously published composite reflecting AD-vulnerable regions (lateral parietal, lateral inferior temporal, and posterior cingulate cortices) (Landau et al., 2011) and was normalized using a pons and vermis reference region.

2.3.3. Volume and cortical thickness analyses

Baseline magnetic resonance imaging (MRI) scans were conducted on a Siemens TrioTIM 3-Tesla scanner (Siemens, Erlangen, Germany)

Table 1
Participant demographic and clinical characteristics overall and by MCI progressor status.

	All (N = 250)	MCI Progressors (N = 23)	Non-Progressors (N = 227)	P Value
Baseline age, *M (SD)*	73.55 (6.0)	76.17 (6.1)	73.28 (5.94)	0.04
Years at diagnosis, *M (SD)*	–	3.96 (1.89)	–	–
Total years of follow-up, *M (SD)*	5.22 (1.66)	5.52 (1.73)	5.19 (1.66)	0.39
Education (years), *M (SD)*	15.80 (3.07)	15.74 (3.14)	15.81 (3.07)	0.92
Sex, no. of males (%)	105 (42)	8 (34.8)	97 (42.7)	0.61
MMSE, *M (SD)*	28.98 (1.11)	28.39 (1.53)	29.04 (1.05)	0.06
APOE genotype, no. of ε4 carriers (%)	68 (27.9)$^{+}$	10 (43.5)	58 (26.2)$^{++}$	0.13

APOE = Apolipoprotein E; MCI = mild cognitive impairment; MMSE = Mini Mental State Exam. $^{+}$*APOE* data were only available for 244 of 250 participants. $^{++}$*APOE* data were only available for 221 of 227 participants. The p values represent group differences between MCI progressors and non-progressors.

Table 2
Baseline values of the neuroimaging and clinical markers included in the LASSO Cox models.

Marker	Overall sample, mean (SD)	MCI Progressors, mean (SD)	MCI Non-progressors, mean (SD)	t value	p value
Aβ GMM Probability	0.26 (0.40)*	0.68 (0.43)	0.23 (0.37)	4.96	< 0.001
FDG PET uptake (SUVR)	1.31 (0.12)	1.26 (0.14)	1.32 (0.12)	−1.91	0.07
Default network connectivity	0.25 (0.07)	0.20 (0.07)	0.25 (0.07)	−3.75	< 0.001
Salience network connectivity	0.20 (0.05)	0.17 (0.05)	0.20 (0.05)	−3.16	0.004
Control network connectivity	0.27 (0.05)	0.24 (0.05)	0.27 (0.05)	−2.55	0.02
Dorsal attention network connectivity	0.23 (0.05)	0.22 (0.06)	0.23 (0.05)	−0.80	0.43
Entorhinal Thickness (mm)	3.35 (0.33)	2.98 (0.23)	3.39 (0.31)	−7.82	< 0.001
Parahippocampal thickness (mm)	2.55 (0.31)	2.42 (0.32)	2.57 (0.30)	−2.13	0.04
Average cortical thickness (mm)	2.34 (0.09)	2.31 (0.09)	2.35 (0.09)	−1.80	0.08
Hippocampal volume (mm^3)	3608 (433)	3246 (390)	3645 (420)	−4.64	< 0.001
Striatum volume (mm^3)	4104 (490)	3987 (568)	4116 (481)	−1.05	0.30
Log transformed WMH (mm^3)	7.63 (0.91)	7.99 (0.77)	7.59 (0.91)	2.35	0.03
DTI FA	0.511 (0.021)	0.506 (0.018)	0.512 (0.022)	−1.52	0.14
FHS-CVD risk score (%)	32.62 (18.03)	38.23 (15.29)	32.05 (18.21)	1.81	0.08
Memory factor score (z score)	−0.001 (0.76)	−0.43 (0.82)	0.04 (0.74)	−2.64	0.01
Executive function factor score (z score)	−0.02 (0.78)	−0.01 (0.84)	−0.02 (0.77)	0.03	0.98
Processing speed factor score (z score)	0.01 (0.89)	−0.34 (1.07)	0.05 (0.87)	−1.68	0.11

Baseline variables represent unstandardized (raw) values, with the exception of the factor scores, which represent z-score composites. GMM = Gaussian mixture modeling; FDG PET = 18F-fludeoxyglucose positron emission tomography; DTI FA = diffusion tensor imaging fractional anisotropy; FHS-CVD = Framingham Heart Study cardiovascular disease; MCI = mild cognitive impairment. SUVR = standard uptake value ratio, WMH = white matter hyperintensities. *For comparison purposes, the average Aβ distribution volume ratio across the whole sample is 1.16 (0.19).

with a 12-channel coil. High-resolution 3D T1-weighted multiecho magnetization prepared rapid acquisition gradient-echo anatomical images were collected with the following parameters: time repetition (TR) = 2200 ms, multiecho time echoes (TEs) = 1.54, 3.36, 5.18, and 7 ms, flip angle = 7°, 4x acceleration, 1.2 × 1.2 × 1.2 mm voxels and processed with FreeSurfer 5.1 (http://surfer.nmr.mgh.harvard.edu) using the default processing stream. As described previously (Hedden et al., 2016), volume measures were extracted from bilateral hippocampus and from bilateral striatum (average of caudate and putamen), and corrected for estimated total intracranial volume. Cortical thickness values were obtained from bilateral parahippocampal gyrus and from bilateral entorhinal cortex. As previously described (Hedden et al., 2016), average cortical thickness was computed across a broad set of cortical regions implicated in aging (Fjell et al., 2013).

2.3.4. Functional connectivity analyses

Baseline data for functional connectivity analysis were acquired using a gradient-echo echo-planar pulse sequence sensitive to blood oxygen level-dependent contrast using the following parameters: TR = 3000 ms, TE = 30 ms, flip angle = 85°, 3.0 × 3.0 × 3.0 mm voxels. Two runs of 124 volumes were acquired for 6 min 12sec each. During the scan participants were asked to remain awake and to focus on a cross-hair. We processed resting-state data using SPM8 (fil.ion.ucl.ac.uk/spm/). Functional connectivity estimates were derived using the Template Based Rotation method and have been described previously (Schultz et al., 2014). Following prior studies (Shaw et al., 2015), we focused on the following cognitive networks: default, salience, dorsal attention, and frontoparietal control.

2.3.5. Diffusion tensor imaging analyses

Baseline diffusion imaging data were collected with the following parameters: TR = 8040 ms, TE = 84 ms, time to inversion (TI) = 2100 ms, 2 × 2 × 2 mm voxels, 64 transverse slices, b-value = 700 s/mm^2, 30 diffusion directions, 2× acceleration. Diffusion tensor imaging (DTI) data were processed in FSL v5.0.9 (The Oxford Centre for Functional MRI of the Brain Software Library) and were corrected for eddy current and motion distortions using FSL's eddy tool (FMRIB Software Library) (Andersson and Sotiropoulos, 2016). Following tract-based spatial statistics procedures (Smith et al., 2006), we created a subject-specific template in Montreal Neurological Institute space (Montreal, Canada). This was then skeletonized and thresholded at 0.3 to exclude predominantly non-white matter voxels. After alignment to standard space, the average fractional anisotropy (FA) value was extracted from the full mask of the standard FSL FMRIB58 white matter skeleton.

2.3.6. White matter hyperintensity analyses

Baseline white matter hyperintensities (WMH) were assessed using fluid attenuation inversion recovery (FLAIR) images (TR = 6000 ms, TE = 454 ms, TI = 2100 ms, 1 × 1 × 1.5 mm voxels, 2x acceleration). All WMH were identified using an automated algorithm (Wu et al., 2006) and previously described methods (Hedden et al., 2012). Total WMH volume (mm^3) was estimated within a mask defined by the Johns Hopkins University White Matter Atlas (Wakana et al., 2004). Prior to analysis, WMH values were log-transformed to account for a positive skew.

2.3.7. Cardiovascular disease risk

As in previous studies from our group (Rabin et al., 2018, 2019), we quantified total cardiovascular risk using the office-based Framingham Heart Study cardiovascular disease (FHS-CVD) risk score at baseline (D'Agostino et al., 2008). The FHS-CVD risk score represents a weighted sum of age, sex, antihypertensive treatment (yes or no), systolic blood pressure, body mass index (calculated as weight in kilograms divided by height in meters squared), history of diabetes (yes or no), and current cigarette smoking status (yes or no). The FHS-CVD provides a 10-year probability of sustaining future cardiovascular events (defined as coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, and heart failure). Higher FHS-CVD scores represent greater risk.

2.3.8. Cognitive measures

Cognition was measured with a battery of neuropsychological and behavioral tasks selected primarily to represent domains of episodic memory, executive function, and processing speed. Episodic memory was assessed using the delayed recall score from the Wechsler Memory Scale-Revised Logical Memory subtest (Wechsler, 1987), the free recall score from the Free and Cued Selective Reminding Test (Grober et al., 2000), and the delayed recall score from Six-Trial Selective Reminding Test (Masur et al., 1990). Executive function was assessed by Letter-Number Sequencing from the Wechsler Adult Intelligence Scale-III (the number of trials correctly completed); (Wechsler, 1997) phonemic fluency (the sum of the words produced in response to the letters F, A,

Table 3
Coefficients and estimated hazard ratios of the significant markers selected from the LASSO Cox model predicting progression to MCI.

Marker	Coefficient	Estimated HR
Reduced entorhinal thickness	0.55	1.73
Higher Aβ burden	0.46	1.58
Lower default network connectivity	0.35	1.42
Smaller hippocampal volume	0.26	1.30

Estimated hazard ratios (HR) are computed as the inverse log of the coefficient. All non-significant variables had a coefficient of 0. MCI = mild cognitive impairment.

S, each over 60 s); (Spreen and Benton, 1977) and the Trail Making Test (time to complete Form B minus Form A) (Reitan, 1958). Processing speed was assessed by the Wechsler Adult Intelligence Scale-Revised Digit-Symbol Coding Test (number of items completed) (Wechsler, 1981) and the Trail Making Test (time to complete Form A) (Reitan, 1958). The derivation of factor scores have been previously published (Rabin et al., 2019; Orlovsky et al., 2017).

2.4. Statistical analyses

All statistical analyses were performed in R (version 3.4). In primary analyses, progression to MCI was used as the outcome of interest. Differences in demographic variables across individuals who progressed to MCI versus non-progressors were examined using a series of *t*-tests for continuous variables and χ^2 tests for dichotomous variables. Time to event was operationalized as the time in years from baseline to the first visit in which a participant received a diagnosis of MCI. For non-progressors (i.e., censored cases) time to (non-) event was defined as the last available study visit. In secondary analyses, we used a more subtle measure of clinical progression: a global CDR increase from 0 to 0.5. Because a global CDR increase from 0 to 0.5 can be a less stable measure of clinical progression compared to a diagnosis of MCI, we only classified participants as progressors if a global CDR of 0.5 was obtained at a minimum of any two follow-up visits. For these analyses, time to event was operationalized as time in years from baseline to the first visit in which a participant obtained a global CDR of 0.5. Participants were classified as non-progressors if a global CDR of 0 was obtained at all follow-up visits or if a global CDR of 0.5 was obtained at only one follow-up visit. Neuroimaging and clinical markers were z-transformed prior to model entry and some metrics were reversed, so that higher scores represented worse outcomes across all markers.

We used a series of least absolute shrinkage and selection operator (LASSO) Cox models to simultaneously evaluate the set of neuroimaging and clinical markers that optimally relate to clinical progression, adjusting for baseline age, sex, and years of education (implemented in the glmnet R package). A LASSO Cox model is well suited for datasets with correlated predictor variables and is designed for variable reduction (Tibshirani, 1997). We used a 5-fold cross-validation process, a resampling procedure that randomly splits the original sample into a training set to train the model and a test set to evaluate it. This process is repeated until each of the 5 folds serves as the test set. The variables that independently and significantly contribute to the outcome variable are given nonzero weights (the larger the weight, the larger the contribution to the outcome); all other variables are shrunk to zero. Standard errors and confidence intervals are not typically calculated for penalized regression approaches, since they are not very meaningful for strongly biased estimates, such as those from penalized estimation methods; this remains an open problem (Goeman, 2010). Predictive performance of all models was assessed using receiver operating characteristic (ROC) curves and area under the curve (AUC). Optimal cut-points from the ROC curves were identified using the Youden Index (using the OptimalCutpoints package in R) (López-Ratón et al., 2014). Nested models were compared with a likelihood ratio test (χ^2).

3. Results

Table 1 presents the baseline demographic characteristics of the overall study sample and by MCI progressor status. Of the 250 clinically normal adults included in the present study, 23 participants (9.2%) progressed to a diagnosis of MCI over an average of 3.96 years (SD = 1.89) of follow-up. Compared to non-progressors, participants who progressed to MCI were significantly older, however there were no significant differences in terms of total years of follow-up, proportion of males to females, years of education, baseline MMSE scores or Apolipoprotein E (*APOE*) ε4 status.

In the primary LASSO Cox model, the variables that significantly and substantially contributed to MCI progression included reduced entorhinal thickness, greater Aβ burden, lower default network connectivity, and smaller hippocampal volume. All non-significant variables had a coefficient of 0. The coefficients and estimated hazard ratios for each significant variable are summarized in Table 3. This model yielded an AUC of 0.90 (CI: 0.84–0.96) and a sensitivity and specificity of 73.9% and 90.3%, respectively. This model was an improvement upon a reference model that included Aβ burden alone (AUC of 0.77 [CI: 0.66–0.89]; sensitivity of 78.3%; specificity of 74.9%) and was significantly better fitting ($\chi^2 = 29.06$, $p < 0.001$). When we used a fully data-driven approach with an elastic net Cox model (resulting alpha = 0.65), the results were substantially similar to the LASSO Cox model. The same set of variables were identified as significant, with smaller striatum volume identified as an additional predictor by the elastic net Cox model, but with a very small coefficient (coefficient = 0.004; hazard ratio (HR) = 1.004).

Next, we added baseline cognitive test scores (episodic memory, executive function, and processing speed) to the LASSO Cox model to examine whether the above markers continued to predict progression to MCI beyond cognitive indicators . In this model, all of the previously identified markers continued to predict clinical progression, including reduced entorhinal thickness, greater Aβ burden, lower default network connectivity, and smaller hippocampal volume. We also found that smaller striatum volume (coefficient = 0.03; hazard ratio (HR) = 1.03) and lower performance on tests of episodic memory (coefficient = 0.50; HR = 1.65) and processing speed (coefficient = 0.09; HR = 1.09) significantly predicted MCI progression. This model had improved diagnostic accuracy (AUC of 0.92 [CI: 0.88–0.97], sensitivity of 91.3%, specificity of 84.6%) and significantly better model fit ($\chi^2 = 10.78$, $p = 0.01$) compared to the MCI model without cognition.

One potential concern regarding the present findings is that only a small number of participants progressed to MCI during the study period (n = 23/250), and predictive classifiers may perform poorly on imbalanced datasets. To examine the sensitivity of our results to class size, we simulated balanced classes by down-sampling the data to the smallest class size (n = 23) and then up-sampling the data to the largest class size (n = 227) (Datta et al., 2019). Using a downsampled LASSO Cox model (without cognition), we found that the same four markers reported in the LASSO Cox model above significantly contributed to MCI progression, including reduced entorhinal thickness, greater Aβ burden, lower default network connectivity, and smaller hippocampal volume. In the upsampled LASSO Cox model, we once again found that the same four markers significantly contributed to MCI progression. While several additional variables were also significant, these variables had smaller coefficients, and included lower frontoparietal control network connectivity, lower striatum volume, reduced parahippocampal thickness, fewer years of education, and counter-intuitively greater DTI FA. It was not unexpected that additional markers contributed to progression given the increased power with the larger simulated class size.

In secondary analyses, we repeated the LASSO Cox models and replaced the outcome of progression to MCI with a global CDR increase from 0 to 0.5 at more than one time point in order to capture more subtle clinical progression. Participants who only had a global CDR of

0.5 at their last available visit were not included as progressors (n = 18). A total of 37 of the 250 participants (14.8%) were considered progressors on the CDR. This secondary analysis largely replicated the results from the primary analyses where the outcome was progression to MCI. Specifically, we found that reduced entorhinal thickness (coefficient = 0.24; HR = 1.27), greater Aβ burden (coefficient = 0.19; HR = 1.21), lower default network connectivity (coefficient = 0.33; HR = 1.39), and smaller hippocampal volume (coefficient = 0.14; HR = 1.15) significantly discriminated between progressors and non-progressors. In this analysis, however, vascular risk also significantly contributed to progression (coefficient = 0.09; HR = 1.09). This model yielded an AUC of 0.76 (CI: 0.67–0.85) and a sensitivity and specificity of 56.8% and 85.0%, respectively. This model had improved diagnostic accuracy and significantly better model fit compared to a reference model that included Aβ burden alone (AUC of 0.65 [CI: 0.55 – 0.75], sensitivity of 67.6%, specificity of 67.1%, $\chi^2 = 20.87$, $p < 0.001$). As above, when this model was repeated as an elastic net model (alpha = 0.40), the results were substantially similar to the results from the LASSO Cox model, with no additional variables identified by the elastic net. We next added baseline cognitive test scores to the LASSO Cox model. We once again found that reduced entorhinal thickness, greater Aβ burden, lower default network connectivity, and smaller hippocampal volume significantly and substantially contributed to CDR progression as did lower episodic memory performance (coefficient = 0.71; HR = 2.03). Vascular risk no longer significantly contributed to progression, however we now observed a counterintuitive association of greater parahippocampal thickness with CDR progression (coefficient = −0.03; HR = 0.97). The CDR model that included cognition had improved diagnostic accuracy and significantly better model fit compared to the model without cognition (AUC of 0.83 (CI: 0.76–0.91), sensitivity of 73.0%, specificity of 78.9%, $\chi^2 = 28.54$, $p < 0.001$).

4. Discussion

The goal of the present study was to identify a parsimonious set of markers that optimally captures subsequent clinical progression in a well-characterized sample of adults who were clinically normal at baseline. This was accomplished using a LASSO Cox regression approach that identifies non-redundant variables that discriminate between progressors and non-progressors. We found that clinically normal adults were more likely to progress to MCI or a global CDR of 0.5 when they presented with greater Aβ burden, reduced entorhinal thickness, lower default network connectivity, and smaller hippocampal volume. In models that included cognitive tests scores, episodic memory consistently and substantially contributed to progression beyond the aforementioned markers. Pending replication in an independent sample, the aforementioned markers could help to improve enrichment strategies for clinical trials in preclinical AD by enrolling individuals who present with a combination of these markers.

Accumulating data suggest that elevated Aβ burden contributes, but is not sufficient, to predict imminent cognitive decline in asymptomatic adults (Sperling et al., 2014; Mormino et al., 2014; Burnham et al., 2016). Therefore, additional markers are needed to identify individuals in the earliest stage of AD who are most likely to progress to the symptomatic stage of the disease. Among a large set of neuroimaging and clinical variables, four markers consistently and robustly predicted clinical progression as measured by a diagnosis of MCI or a global CDR increase of 0 to 0.5. Consistent with prior work (Mormino et al., 2014; Bilgel et al., 2018; Buckley et al., 2017; Rowe et al., 2013), these markers included greater Aβ burden, reduced entorhinal thickness, lower default network connectivity, and smaller hippocampal volume. When cognitive test scores were added to the model, baseline memory performance also consistently and significantly contributed to clinical progression. Many of these markers (Aβ burden, hippocampal volume, entorhinal thickness, and memory performance) are in agreement with the staging of preclinical AD proposed by the National Institute on Aging—Alzheimer's Association (NIA-AA) workgroup (Sperling et al., 2011), which suggests that individuals with elevated Aβ burden, neurodegeneration, and subtle cognitive impairment (i.e., stage 3) are more likely to progress to MCI or dementia compared to those with only abnormal Aβ levels (i.e., stage 1). In addition to the variables recognized by the NIA-AA workgroup, lower default network connectivity consistently predicted clinical progression.

Lower default network connectivity predicted progression to MCI and a global CDR of 0.5 over and above other cognitive networks, including the salience, frontoparietal control, and dorsal attention networks. This finding is consistent with previous work showing preferential degradation of the default network in early stages of late-onset AD as well as in advanced autosomal-dominant AD (Chhatwal et al., 2018; Palmqvist et al., 2017; Hedden et al., 2009). It is also in line with studies showing strong associations between reduced default network connectivity and cognition in asymptomatic individuals (Buckley et al., 2017; Shaw et al., 2015). Taken together, these findings suggest that lower default network connectivity may complement standard AD biomarkers in predicting clinical progression.

When baseline cognitive test scores were included in the LASSO Cox models, memory performance consistently and robustly predicted clinical progression to MCI and a global CDR of 0.5. The models including cognition increased sensitivity at the expense of specificity relative to models that did not include cognition. One might reason that using cognitive performance as a predictor of MCI or global CDR progression is circular given that these outcomes take memory performance into account. However, in our diagnostic consensus meetings, greater weight is placed on longitudinal test scores compared to baseline scores and the CDR is rated independently of these cognitive test scores. The present findings are consistent with prior studies suggesting that clinically normal individuals performing at the lower end of the normal range on baseline memory or other cognitive tests are more likely to progress clinically (Ewers et al., 2014; Rowe et al., 2013; Eckerström et al., 2013; Belleville et al., 2017; Blacker et al., 2007; Insel et al., 2016). From a pragmatic standpoint, cognitive tests are inexpensive and can be administered relatively quickly, either in the clinic or at home.

Some of the significant markers discriminating progressors from non-progressors did not consistently predict clinical progression across models, such as lower striatum volume and greater vascular risk. Lower striatum volume explained minimal variance in its prediction of MCI progression, and was only significant when cognition was included in the LASSO Cox model and in the elastic net Cox model (HRs < 1.03). As such, this marker should be interpreted cautiously. With respect to vascular risk, it is notable that in a recent HABS study, vascular risk remained a significant predictor of longitudinal cognitive decline after adjusting for many of the same markers included in the present study, such as Aβ burden, hippocampal volume, FDG-PET uptake, and WMH (Rabin et al., 2018). Given that vascular risk was associated with cognitive decline in that study and predicted subtle progression (as measured by the CDR) in the present study suggests that vascular risk may be associated with a slower rate of clinical progression compared to the significant markers identified in the MCI LASSO Cox model.

Our study has several strengths. Most important, we had access to a wide set of neuroimaging and clinical variables at baseline in a well-characterized sample of clinically normal adults. In addition, study participants were followed longitudinally for up to 8 years (median years of follow-up = 5.0 years), with annual cognitive and clinical assessments. However, the study also has several limitations. First, because of our relatively small sample size (n = 250), only a small number of participants progressed to a diagnosis of MCI (n = 23) over the study period. This likely limited the predictive power of our models. However, simulated LASSO Cox models (using both down- and up-sampling) identified all of the significant predictors in the original model, indicating that the results are likely robust to the imbalanced

class size (assuming that the inputs to the simulated data adequately represent the true distribution of progression). Second, tau is an important biomarker to consider in the prediction of clinical progression (Jack et al., 2018; Krance et al., 2019; Dumurgier et al., 2017; Sperling et al., 2019; Betthauser et al., 2020), however tau PET was not available at baseline (it was collected several years after study entry). Cerebrospinal fluid collection was not a requirement for participation in HABS and was conducted on only a small subset of participants at baseline. For these reasons, tau was not included in the present study. It is possible that the significant contribution of entorhinal thickness or other variables may overlap with that of tauopathy. Third, other unmeasured variables, such as Lewy bodies, TDP-43 and hippocampal sclerosis, may contribute significant variance to clinical progression. Fourth, the connectivity network measures, although sampling multiple networks, were restricted to within-network connectivity measurements. Between-network or other measures of network dynamics (Schultz et al., 2017; Chan et al., 2014) may provide additional predictive value. Fifth, our relatively small sample size did not allow us to test the reproducibility of the results in our sample. While we did apply a 5-fold cross-validation procedure to increase model robustness, replication of the present findings should be examined in an independent sample. This is particularly important for validating whether the final multivariate models are superior to models that included Aβ burden alone. Finally, HABS participants are generally in good health, well-educated, and primarily Caucasian, and therefore future studies are needed to determine whether our findings generalize to more diverse samples.

5. Conclusion

As the field moves toward prevention at the preclinical stage of AD, there is a critical need to identify clinically normal individuals at high risk of clinical progression and most likely to benefit from therapeutic intervention. Although the present findings are preliminary and require replication, our results suggest that it is valuable to consider a set of biomarkers when screening asymptomatic individuals for inclusion in AD clinical trials. The set of clinical and neuroimaging markers that best captured clinical progression in our sample included reduced entorhinal thickness, higher Aβ burden, lower default network connectivity, and smaller hippocampal volume. Lower episodic memory scores could also be considered as a potential predictor of clinical progression. While additional work is needed to establish reliable cut-offs for these variables, the results here suggest that characterization on these markers may improve risk stratification.

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7. Search terms

Aging, Clinical Dementia Rating, Brain Markers, Alzheimer's Disease, Mild Cognitive Impairment, LASSO Cox models

8. Disclosure statement

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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