



Published in final edited form as:

J Alzheimers Dis. 2021 ; 79(3): 1009–1014. doi:10.3233/JAD-201294.

Identifying Preclinical Alzheimer's Disease Using Everyday Driving Behavior: Proof of Concept

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Abstract

We examined whether driving behavior can predict preclinical Alzheimer's disease (AD). Data from 131 cognitively normal older adults with cerebrospinal fluid (CSF) and/or positron emission tomography (PET) biomarkers were examined with naturalistic driving behavior. Receiver operating characteristic curves were used to predict the highest 10%, 25%, and 50% of values for CSF tau/A β ₄₂, ptau₁₈₁/A β ₄₂, or amyloid PET. Six *in vivo* driving variables alone yielded area under the curves (AUC) from 0.64–0.82. Addition of age, Apolipoprotein ϵ 4, and neuropsychological measures to the models improved the AUC (0.81 to 0.90). Driving can be used as novel neurobehavioral marker to identify presence of preclinical AD.

Keywords

Aging drivers; Alzheimer's disease; biomarkers; driving decline; preclinical

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia and cognitive impairment and is associated with impaired driving performance [1, 2]. Preclinical AD is the

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asymptomatic stage (~15–20 years), when early AD pathology is present, but the individual remains cognitively normal. Identifying the biological presence of AD at its earliest stage is currently accomplished using molecular biomarkers obtained via imaging and lumbar puncture [3, 4]. However, these methods present challenges in widespread use due to cost, acceptability, and availability.

Driving behavior, a widespread everyday activity, may provide a neurobehavioral marker of preclinical AD. Driving is the prevalent means of transportation for adults aged 65 and above, and the number of older drivers will continue to grow as the older adult population rapidly increases, along with the number of persons with symptomatic AD. By 2050, 88 million United States citizens are expected to be 65 years or older and 25% of all drivers will be in this age group [5]. Among cognitively normal older adults, elevated cerebrospinal fluid (CSF) tau/A β ₄₂ and ptau₁₈₁/A β ₄₂ levels and widespread amyloid plaques on PET imaging are associated with increased numbers of driving errors on a road test [6]. Additionally, higher CSF tau/A β ₄₂ and ptau₁₈₁/A β ₄₂ levels predict which participants will be the earliest to fail or to receive a “Marginal” or “Pass” rating on the road test when retested in the future [7]. Notably, this research found no baseline differences in cognitive functioning between persons with and without preclinical AD, suggesting that the preclinical stage of AD may have a subtle functional impact on complex behaviors such as driving which go unnoticed or undetected using traditional neuropsychological measures [6, 7].

Validation of new biomarkers typically includes determining the degree to which the candidate biomarker predicts AD neuropathology as reflected in molecular biomarkers. For example, the usefulness of plasma A β ₄₂/40 has been tested by examining its concordance with traditional CSF and PET biomarkers [8, 9]. We therefore sought to determine whether driving behavior discriminates older adults with and without preclinical AD. We also examined whether adding measures of age, Apolipoprotein E (*APOE*) genotype, and neuropsychological test scores improved the ability of the driving-based models to identify preclinical AD.

METHODS

Participants

Participants were enrolled in longitudinal studies on aging and dementia conducted at the Washington University Knight Alzheimer’s Disease Research Center and in a longitudinal driving study (R01AG056466). All participants were cognitively normal as determined by a score of 0 on the Clinical Dementia Rating (CDR®), were 65 years old or older, had a valid driver’s license, drove at least once per week, and had *in vivo* CSF collection and/or amyloid imaging. The study protocol was approved by the Washington University Human Research Protection Office, and written informed consent was obtained.

CSF biomarkers

A β ₄₂, tau, and phosphorylated tau₁₈₁ (ptau₁₈₁) analytes were measured using enzyme linked immunosorbant assay (ELISA) (INNOTEST; Fujirebio [formerly Innogenetics], Ghent, Belgium). Sample acquisition, processing, and storage have been described elsewhere [9].

Values of $A\beta_{42}$ were adjusted using assay- and date-specific cutoffs that accounted for upward drift in INNOTEST immunoassay $A\beta_{42}$ values over time [9]. Ratios were computed for $A\beta_{42}$ with tau and ptau_{181} ($\text{tau}/A\beta_{42}$; $\text{ptau}_{181}/A\beta_{42}$) and used for analyses, given our prior work supporting their strong associations with driving [7].

Imaging biomarker

Participants completed PET imaging [10] to determine amyloid burden using either Pittsburgh Compound B (PiB) or florbetapir (F-AV-45) radiotracers in a Siemens 962 HR +ECAT PET or Biograph 40 scanner (Siemens/CTI, Knoxville, KY). Amyloid burden was expressed in centiloids based on the mean cortical standardized uptake value ratio with partial volume correction via regional spread function [PIB MCSUVR RSF = 16.4 and AV45 MCSUVR RSF = 20.6] [11–13].

Clinical and neuropsychological tests

Participants completed annual clinical assessments which included the CDR, Mini-Mental State Examination, *APOE* genotyping, and neuropsychological measures (Animal Naming, Trail Making Test A and B, and the Selective Reminding Free Recall Test).

Naturalistic driving

A GPS data logger (G2 Tracking Device™, Azuga Inc, San Jose, CA) was plugged into the vehicle's onboard diagnostics-II port and data collected every 30 seconds. This methodology, the Driving Real World In-Vehicle Evaluation System (DRIVES), collected data each time a vehicle was driven [14]. An aggressive action was triggered after surpassing a set threshold for hard braking (decrease of 8 miles per hour in one second), sudden acceleration (increase of 8 miles per hour in one second), or speeding (driving more than 6 miles per hour above posted speed limit). Aggressive actions (hard braking, sudden acceleration, and speeding) were recorded anytime they occurred during a trip, regardless of standard sampling. Data were collected between 7/1/15 and 4/30/19. A 'trip' was defined as data gathered from the period of 'ignition on' to 'ignition off'. The date and distance of each trip, the time spent traveling, and the route were recorded. The mean value per month was calculated for each driving variable for each participant.

Statistical analysis

Data from participants with CSF and/or PET biomarkers within two years before or six months after the installation date of DRIVES were selected for analysis. Clinical data from the assessment date closest to date of DRIVES installation were used. Logistic regression was employed to generate receiver operating characteristic (ROC) curves to determine the ability of the DRIVES variables to identify preclinical AD as reflected by CSF $\text{tau}/A\beta_{42}$, $\text{ptau}_{181}/A\beta_{42}$, or amyloid PET. To address multi-collinearity concerns, six DRIVES variables with a $r < 0.65$ were selected (trips per month, miles per trip and average trips with: hard braking, speeding, sudden acceleration, night driving). For each biomarker, three sets of models were run identifying participants with the highest 10%, highest 25%, and highest 50% of values for that biomarker.

The modeling strategy was similar to that used by others when testing the ability of a novel biomarker to distinguish between clinical groups [8, 15]. First, the discriminant ability of the novel biomarker(s) alone is tested to discover whether it is significantly greater than chance (AUC = 0.50), and if so, the point estimate of discrimination (AUCs range from 0 to 1, with higher AUCs reflecting better discriminant ability). Later modeling steps examine whether the predictive ability of the novel biomarkers(s) alone can be enhanced by adding additional variables, such as age and *APOE4* [8, 15]. In each model, the DRIVES variables were entered first, then age (midpoint taken across driving period), then *APOE4* positivity, and then the neuropsychological test scores. Since preliminary modeling indicated no effects of sex and education on identification of biomarker positivity, they were not included in the final models. Statistical analyses were conducted in SAS version 9.4 (SAS Institute Inc.).

RESULTS

Participants ($n = 131$) were older (Mean = 72.2), highly educated (Mean = 16.5), and the majority were male (52.7%) and white (84.7%) (Table 1). The AUC (95% confidence interval [CI]) for predicting “high” molecular biomarker values from DRIVES variables alone ranged from 0.64 (0.53–0.75) to 0.82 (0.71–0.94) (Fig. 1); and improved significantly with the addition of age alone (Fig. 1D and E, $p < 0.010$), age and *APOE4* (Fig. 1F-I, $p < 0.022$), and age, *APOE4*, and the neuropsychological test scores (Fig. 1A, B), depending on the specific biomarkers and cutoff used. In the final models including all variables, the AUCs (95% CI) ranged from 0.81 (0.74–0.88) to 0.90 (0.81–0.99) (Fig. 1).

DISCUSSION

Our findings suggest that driving behaviors may ultimately serve as neurobehavioral markers for identifying preclinical AD. We found that the predictive value of driving behavior can be improved by including characteristics of the individual such as age, *APOE4* status, and neuropsychological test scores. As with previous work testing conventional biomarkers as predictors of cognitive status [8, 9], the ability of driving behavior to identify preclinical AD is dependent on the cutoff used to determine preclinical AD. However, for all biomarkers and all cutoffs, the driving variables together with age alone resulted in an acceptable (AUC 0.70–0.80) level of accuracy in identifying preclinical AD [16]. With the addition of *APOE* status and neuropsychological test scores, the predictive ability of all models increased to the excellent range (AUCs 0.80–0.90) [16].

Despite the technophilic enthusiasm of automated/driverless vehicles, widespread adoption and implementation are weighed down by cost, security, trust, privacy, reliability, and liability—human driving will continue to be the prevailing means for decades [17]. Our prior work suggests that changes in driving performance and behavior precede changes in cognitive functioning during preclinical AD [7, 18]. Since cognitive impairment symptoms may occur up to 12 years prior to an AD diagnosis [19], identifying changes in driving behavior may also move up the time to a clinical diagnosis. Further, it is possible that driving behaviors could be used to track changes in AD progression as an older adult converts to symptomatic AD.

Future research aimed at using everyday driving as a behavioral marker of AD should explore additional statistical modeling techniques to determine optimal combinations of variables, and examine additional easily-obtained variables not studied here, that may further enhance identification accuracy. Longitudinal studies should also test whether driving behaviors can predict the time to an incident dementia diagnosis. Our study participants were predominantly white and well-educated, and future work should examine the generalizability of these results to other samples. In addition to its potential use as a biomarker of preclinical AD, measurement of driving behavior among older adults has other protective benefits. Alerts indicating unsafe driving behaviors can be transmitted to the driver and/or their family member in real-time, likely increasing safety and decreasing crash risk. Drivers with AD who become disoriented or lost can be found quickly and returned home safely.

In conclusion, this proof-of-concept study indicates that the biological presence of AD can be identified by unobtrusively measuring driving behavior, a common, but complex daily activity. These findings provide a foundation for the development of novel neurobehavioral biomarkers of AD. Additional studies are needed to examine how driving behavior predicts time to a future dementia diagnosis.

ACKNOWLEDGMENTS

This research was funded by the National Institute on Aging [NIA, R01AG043434, R01AG056466, R01AG067428, R01AG068183, P50AG005681, P01AG003991, P01AG026276]; Fred Simmons and Olga Mohan, the Farrell Family Research Fund and the Charles and Joanne Knight Alzheimer Research Initiative of the Washington University Knight Alzheimer Disease Research Center (ADRC). The authors would like to express their gratitude to the research volunteers who participated in the studies from which these data were obtained and their supportive families. The authors would like to thank the Clinical, Biomarker and Imaging Cores at the Knight Alzheimer Disease Research Center for sample and data collection.

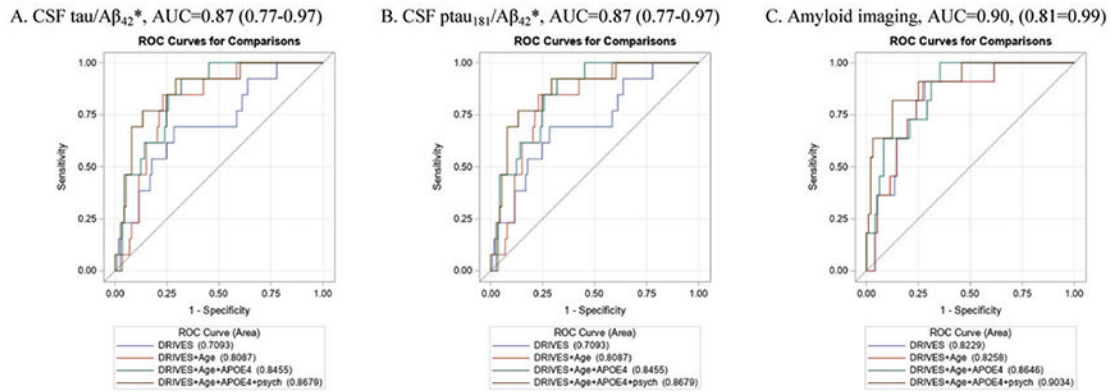
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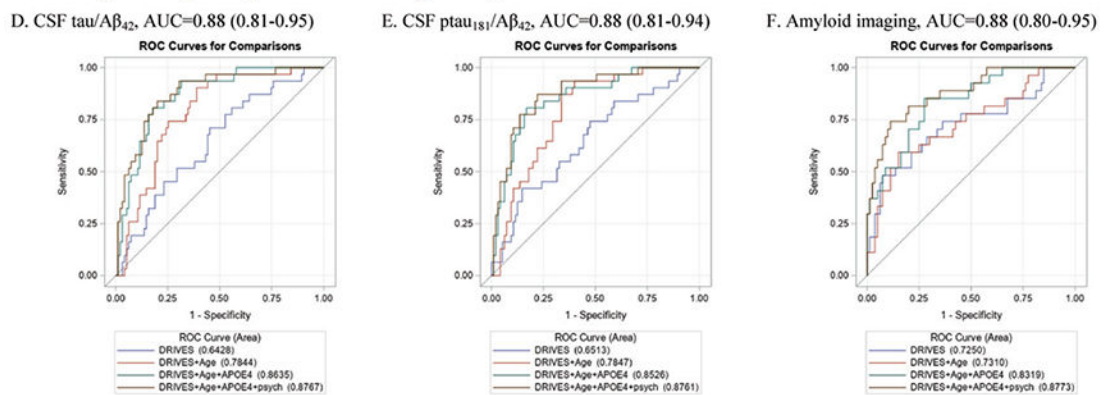
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Predicting which participants have the highest 10% of biomarker values.



Predicting which participants have the highest top 25% of biomarker values.



Predicting which participants have the top 50% of biomarker values.

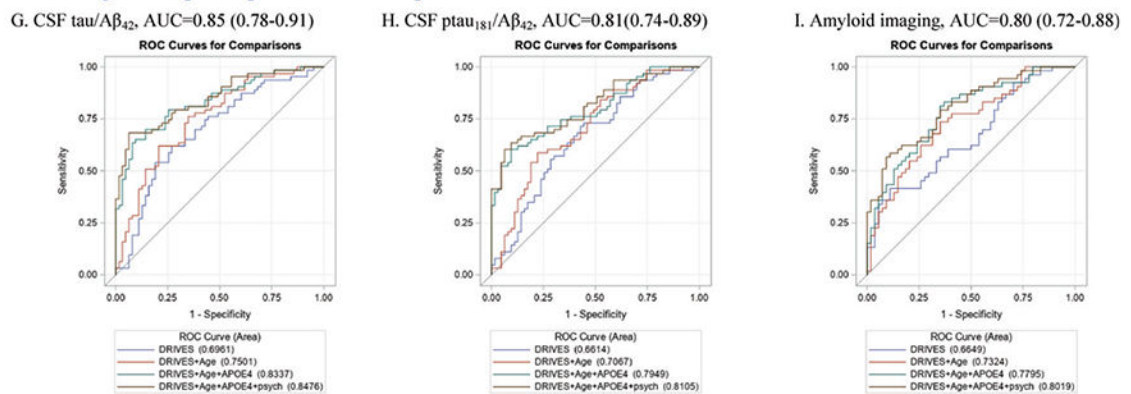


Fig. 1. Final area under the receiver operating curves (AUC) and 95% confidence intervals for each biomarker and each cutoff examined. Legends show the AUC as each variable type is added to the model: blue = driving variables, red = age, cyan = apolipoprotein $\epsilon 4$ status, brown = psychometric test scores. *This cutoff resulted in the same participants being assigned to each group for the CSF tau/A β_{42} and ptau₁₈₁/A β_{42} biomarkers.

Table 1

Demographics (N = 131) *

Age (y)	74.2 ± 4.8
Education (y)	16.5 ± 2.3
Women, N (%)	62 (47.3%)
Race, Caucasian, N (%)	111 (84.7%)
<i>APOE</i> ε4+, N	44 (33.6%)
MMSE (out of 30)	29.2 ± 1.0
Neuropsychological tests	
Selective Reminding Test – Free Recall Subtest	31.3 ± 6.1
Animal Naming	21.1 ± 4.8
Trailmaking A (s)	31.3 ± 9.2
Trailmaking B (s)	80.0 ± 33.3
DRIVES variables	
Number of trips per month	109.7 ± 43.0
Miles per trip (miles)	7.2 ± 3.5
Percentage of trips at night	5.6 ± 4.8
Percentage of trips with any hard braking	8.7 ± 6.3
Percentage of trips with any speeding	9.2 ± 9.6
Percentage of trips with any sudden acceleration	4.4 ± 7.1

APOE ε4, Apolipoprotein E ε4; MMSE, Mini-Mental State Examination.

* Mean ± Standard Deviation or count (percentage).