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Research Report

Associations Between Plasma, Imaging, and Cerebrospinal Fluid Biomarkers with Driving Behavior and Cognitive Tests: Implications for Biomarker Usefulness

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Abstract.
Background: Declines in instrumental activities of daily living like driving are hallmarks sequelae of Alzheimer's disease (AD). Although driving has been shown to be associated with traditional imaging and cerebrospinal fluid (CSF) biomarkers, it is possible that some biomarkers have stronger associations with specific aspects of driving behavior. Furthermore, associations between newer plasma biomarkers and driving behaviors are unknown.
Objective: This study assessed the extent to which individual plasma, imaging, and CSF biomarkers are related to specific driving behaviors and cognitive functions among cognitively normal older adults.
Methods: We analyzed naturalistic driving behavior from cognitively healthy older drivers (N = 167, 47% female, mean age = 73.3 years). All participants had driving, clinical, and demographic data and completed biomarker testing, including imaging, CSF, and/or plasma, within two years of study commencement.
Results: AD biomarkers were associated with different characteristics of driving and cognitive functioning within the same individuals. Elevated levels of plasma $A\beta_{40}$ were associated with more speeding incidents, higher levels of CSF tau were related to shorter duration of trips, and higher CSF neurofilament light chain values were associated with traveling shorter distances, smaller radius of gyration, and fewer trips at night. We demonstrated that plasma, like CSF and imaging biomarkers, were helpful in predicting everyday driving behaviors.
Conclusions: These findings suggest that different biomarkers offer complementary information with respect to driving behaviors. These distinct relationships may help in understanding how different biological changes that occur during the preclinical stage of AD can impact various sensorimotor and cognitive processes.

Keywords: Alzheimer's disease, biomarkers, cerebrospinal fluid, imaging, naturalistic driving

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INTRODUCTION

The ATN research framework of the National Institute on Aging – Alzheimer's Association (NIA-AA) depends upon "positivity" of markers of amyloid, tau, and neurodegeneration to operationalize the presence of biological Alzheimer's disease (AD), even among persons with normal cognition [1]. Cut-offs to determine biomarker positivity were originally developed by finding the numerical point that best distinguishes a group with clinical dementia from one with normal cognition [2]. Validation and cut-offs for newer biomarkers, such as those derived from blood plasma, have also relied on their strength of association with older molecular biomarkers such as amyloid imaging [3, 4]. In addition to being able to distinguish clinical groups, these established cut-offs can successfully predict time to incident dementia among persons who are cognitively normal [5, 6].

The predictive utility of AD biomarkers, and their associated cut-off values, likely depends on what is being predicted. AD impacts widespread functional activities of daily living, such as driving [7, 8], which incorporates cognitive functioning. Driving is important for maintaining mobility and independence among older adults, and 83% of those aged 70 and above have current driver's licenses [9–11]. However, traffic crashes are among the leading causes of accidental disability and death in this age group, with almost 700 persons aged 65+ years being injured and over 20 being killed every day in the US [12]. Being able to identify who is likely to be an unsafe driver, and who is at risk for future driving problems, will enable early intervention and reduce disability and death among older adults.

The relationship between AD biomarkers and cognition differs based on both the specific biomarker used and the domain of cognition examined [13, 14]. Although driving behavior has been shown to be associated with traditional imaging and CSF biomarkers [8, 15, 16], it is possible that, as with cognition, some biomarkers have stronger associations with particular aspects of driving behavior than others. Further, associations between newer plasma biomarkers and driving behaviors are currently unknown. Blood-based biomarkers are expected to play an important clinical role in the future, as they are likely to be more accessible, affordable, and acceptable to patients compared to biomarkers derived from CSF and imaging [17].

As a necessary first step in optimizing identification and prediction of AD-related driving difficulties, we examined the extent to which individual plasma, imaging, and CSF biomarkers are related to specific driving behaviors among cognitively normal older drivers. We also compared these associations to those of the biomarkers with selected cognitive tests.

MATERIALS AND METHODS

Participants

Data from cognitively normal participants (Clinical Dementia Rating® [CDR] = 0) aged 65 years and older who provided informed consent and were enrolled in naturalistic driving studies were used. Participants had a data logger installed in their personal vehicles and drove at their discretion for at least six months between June 2, 2015 and February 29, 2020. The end date for driving data collection was chosen because driving behavior for this group began to change due to the COVID-19 pandemic (e.g., social distancing, business and workplace shutdowns) around March/April 2020 [18].

Participants provided written informed consent, and all study procedures were approved by the Washington University Human Research Protection Office. The study was conducted in accordance with the Declaration of Helsinki.

Driving data collection and outcomes

The data logger (Azuga, Inc.) plugs into the OBDII port of the participant's vehicle and is powered by the vehicle's battery. Within 1 min after installation, the data logger accesses available satellites for orientation and synchronization and begins transmitting data via cell phone towers, to the vendor's servers for initial storage. Data on date, time, vehicle latitude and longitude, speed, and time are collected every 30 s while ignition is on. The data are aggregated daily by the vendor, and then downloaded to local, encrypted data storage on secured servers for use by our laboratory. Based on our prior research [8, 16, 19, 20], we used the following driving outcomes: total number of trips, number of unique locations visited, average distance travelled, average duration of a trip, average jerk, average acceleration, number of hard braking events per mile, number of rapid accelerations per mile, proportion of trips with over speeding, proportion of trips with under speeding, number of trips

taken at night, radius of gyration, and straightness index.

Biomarkers and cognitive assessments

Within two years of data logger installation, participants completed biomarker testing. Imaging, CSF, and plasma procedures have been described previously [21, 22]. Amyloid pathology was assessed using positron emission tomography (PET) with Pittsburgh Compound B or florbetapir (F-AV-45) tracers. Mean standardized uptake value ratio with partial volume correction via regional spread function was estimated using 30 to 60 min post-injection as the time window using the cerebellum cortex as the default reference region. Amyloid burden was expressed using centiloids across the tracers.

Tau pathology was assessed using PET and ^{18}F-AV-1451 (previously known as T807). Data were examined for the 80–100 min post-injection window and were converted to standardized uptake value ratios using the whole cerebellum as a reference. A tauopathy value was obtained by averaging the binding potential values from the amygdala, entorhinal cortex, interior temporal, and lateral occipital cortex regions of interest.

Structural imaging was obtained from an MRI based upon the Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol. High-resolution T1 MPRAGE was used for the assessment of brain structures to produce normalized whole brain volume and hippocampal volume (HV) measurements. HV was normalized to account for differences in head size. Then the mean intracranial volume (ICV) was calculated for the sample, followed by conducting a regression analysis with ICV as the sole independent variable and participants' HV (the sum of right and left HV) as the dependent variable. The β-weight was then used to compute participants' normalized HV using the following equation: normalized HV = raw HV – (β-weight × (participant's ICV – sample mean ICV))

For the lumbar puncture/CSF collection, approximately two tablespoons (20–35 ml) of CSF were collected at 8:00 AM following an overnight fasting period by an experienced neurologist utilizing a 22-gauge Sprotte spinal needle. Samples were free from blood contamination, inverted to avoid gradient effects, centrifuged at low speed, aliquoted into polypropylene tubes, and frozen at –80°C. Samples were ($A\beta_{42}$, $A\beta_{40}$, tau, $ptau_{181}$, $tau/A\beta_{42}$, $ptau_{181}/A\beta_{42}$, neurofilament light chain [NfL]) utilizing automated electrochemiluminescence immunoassay (Lumipulse G1200, Fujirebio) in the same lot to eliminate drift or batch effects.

Blood samples from each participant were collected at a single session at approximately 8 AM following overnight fasting. Plasma $A\beta_{42}$, $A\beta_{40}$, NfL were measured at C_2 N Diagnostics, a CLIA commercial laboratory with immunoprecipitation–mass spectrometry. All assays were performed by personnel who were blinded to the participant's demographic data.

Annually, participants were given a CDR and completed the Montreal Cognitive Assessment (MoCA) screen [23], along with a brief neuropsychological battery that included the Selective Reminding Test (SRT) – Free Recall portion [24], Animal naming [25], and Trailmaking A and B [26].

Statistical analyses

To compare the strength of associations, the mean on each of the biomarker and driving variables across the study period was computed for each participant and then standardized such that the distribution of each variable had a mean of 0 and a standard deviation of 1. Pearson product-moment correlations were used to examine the unadjusted Pearson correlations between the biomarker variables and the driving and cognitive measures. General linear models (GLM) were used to test the biomarker-driving/cognitive associations after adjusting for age, gender, race, and education. The natural log of NfL was used in these analyses because its distribution was less skewed than raw NfL values.

RESULTS

There were 167 participants that met the inclusion criteria for analyses. Each participant received a CDR = 0 at their clinical assessment closest to data logger installation (mean ± standard deviation [SD] = 156.1 ± 125.5 days). Participants' ages ranged from 65.6 to 90.8 with a mean ± SD of 73.3 ± 4.9 years, a mean ± SD of 16.6 ± 2.2 years of education, 47.3% were women, and 13.8% were Black or African American (all other participants were White). Driving time with the data logger installed ranged from 0.6 to 4.7 (mean ± SD = 2.2 ± 0.9) years.

All participants had complete driving, clinical, and demographic data available, but the number with each biomarker type varied as follows: N = 139

with amyloid imaging; 103 with tau imaging; 144 with normalized hippocampal volume; 125 with CSF $A\beta_{42}$, $A\beta_{40}$, tau, and $ptau_{181}$; 118 with CSF NfL; and 116 with plasma $A\beta_{42}$, $A\beta_{40}$, and NfL. Table 1 shows the magnitude and direction of the Pearson correlation coefficients with each of the driving and cognitive variables. When analyses adjusted for age, gender, race, and education, the relative strength and direction of associations was similar, although fewer pairings were significant at the 0.05 or 0.01 alpha level (Table 2). This was expected, given the decrease in statistical power with greater numbers of independent variables in the models. Unless otherwise specified, the findings reported going forward refer to the adjusted analyses (Table 2).

Plasma

Both plasma $A\beta_{40}$ and $A\beta_{42}$, but not the ratio of $A\beta_{42}/A\beta_{40}$, were associated with fewer trips taken and trips of shorter distance and duration. Additionally, higher levels of plasma $A\beta_{40}$ were related to fewer trips taken at night, and higher values of $A\beta_{42}$ to more overspeeding. Plasma $A\beta_{42}/A\beta_{40}$ was associated with SRT Free Recall scores, but not to any of the driving metrics. Plasma NfL was unrelated to any of the driving and cognitive variables examined.

Imaging

The imaging data showed that participants with higher PET amyloid levels went to fewer unique destinations, took fewer trips at night, had worse performance on the MoCA, and had marginally worse performance on SRT Free Recall ($p = 0.06$). Neither PET tauopathy nor normalized hippocampal volume were associated with any of the driving or clinical measures.

CSF

Higher levels of $A\beta_{40}$, and lower levels of $A\beta_{42}$, were related to larger radius of gyration driving values. Greater $A\beta_{40}$ values were additionally associated with shorter distances. Higher ratios of $A\beta_{42}/A\beta_{40}$ predicted greater acceleration, higher SRT Free Recall scores, and lower straightness values (i.e., the ratio between the distance from the starting point to the destination and the distance travelled to reach the destination, ranging from 0 to 1). Straightness was related to $A\beta_{42}/A\beta_{40}$, tau, $ptau_{181}$, tau/$A\beta_{42}$ and $ptau_{181}/A\beta_{42}$. Tau and $ptau_{181}$ were also related to shorter duration of trips. Higher NfL values were associated with traveling shorter distances, smaller radius of gyration and fewer trips at night.

DISCUSSION

The current study is a first attempt at understanding the interconnectedness between traditional and novel AD biomarkers, driving behaviors and cognition. A key finding of the study is that plasma biomarkers, like CSF and imaging biomarkers, are useful in predicting everyday behaviors on complex functional tasks such as driving. More specifically, these results show that elevated levels of plasma $A\beta_{40}$ and/or $A\beta_{42}$ are associated with fewer total trips and night trips, decreased trip distance and duration, as well as more speeding incidents. Taking a closer look at this interconnectivity, our findings further suggest that the associations between plasma biomarkers and driving behaviors differ from the relationship between these biomarkers and cognition. In fact, it can be observed that plasma $A\beta_{42}/A\beta_{40}$, though an effective predictor of cognition [21], may not be strongly associated with driving behaviors.

Another key finding of this study is that different AD biomarkers are associated with different dimensions of driving and cognitive functioning. It has long been shown that different AD biomarkers have varying associations with cognitive domains and specific domains (e.g., memory, attention, and executive function) [14]. Our results align with the broader observation that there is not always a strong association between cognitive performance and fluid markers of preclinical AD. Notably, this is consistent with observations from our earlier investigations [16, 27]. As the understanding of these dynamics expands, it could provide valuable insights into the nuanced progression of Alzheimer's disease and its broader clinical manifestations. On the other hand, our findings provide evidence that different biomarkers are related to different everyday driving behaviors. For instance, elevated levels of CSF tau and NfL (reflecting neurodegeneration) are associated with more self-regulating driving behaviors. More specifically, higher levels of CSF tau were related to shorter duration of trips, while higher CSF NfL values were associated with traveling shorter distances, smaller radius of gyration and fewer trips at night. Furthermore, CSF and plasma $A\beta_{42}$ and $A\beta_{40}$ behave differently with respect to driving within the same individuals and may therefore yield complemen-

Table 1
Pearson correlation coefficients (r^2) for the relation of imaging, CSF, and plasma biomarkers with driving variables and cognitive test scores. The darker cell colors represent stronger correlations (i.e., the darker the color the higher the correlation between the two variables)

		Imaging			CSF							Plasma				
		PET amyloid	PET tau	nHV	$A\beta_{42}$	$A\beta_{40}$	$A\beta_{42}/A\beta_{40}$	tau	ptau181	tau/ $A\beta_{42}$	ptau181/ $A\beta_{42}$	NfL	$A\beta_{40}$	$A\beta_{42}$	$A\beta_{42}/A\beta_{40}$	NfL
Driving Variables	Number of trips	–0.18	0.09	0.06	0.10	0.09	0.09	0.00	0.00	0.10	–0.13	–0.06	–0.24	0.23	0.05	0.01
	Number of unique destinations	0.25	0.14	0.06	0.08	0.01	0.17	–0.05	0.10	0.16	0.17	–0.18	0.14	–0.09	0.13	0.00
	Average distance	–0.07	–0.15	0.11	0.11	0.23	0.10	0.19	–0.19	–0.09	–0.06	0.24	0.24	0.30	0.10	0.01
	Average duration	0.12	0.15	0.01	0.00	0.26	0.15	–0.22	0.22	0.17	0.15	–0.16	0.22	0.32	0.15	0.06
	Average acceleration	–0.14	0.04	0.12	0.09	0.04	0.20	–0.13	0.15	0.19	0.18	0.18	0.04	0.10	0.14	–0.07
	Average jerk	–0.19	0.04	0.10	0.11	–0.02	0.21	–0.14	0.16	0.13	–0.20	–0.17	0.00	0.00	0.17	–0.08
	Number of hard braking instances per mile	–0.08	0.02	0.04	0.02	0.00	0.05	–0.10	–0.09	0.11	–0.09	–0.13	–0.04	0.00	0.00	0.01
	Number of rapid accelerations per mile	0.00	–0.06	0.00	0.00	–0.05	–0.06	–0.07	0.01	0.01	0.04	–0.02	0.03	0.00	–0.05	0.02
	Proportion of trips with over speeding	0.10	0.20	0.06	0.04	–0.12	0.11	0.15	0.15	0.12	–0.12	–0.11	0.17	0.23	0.10	–0.08
	Proportion of trips with under speeding	0.07	0.00	0.19	–0.07	0.00	–0.13	0.13	0.10	0.18	0.14	0.16	0.11	0.00	–0.15	0.00
	Number of trips taken at night	0.25	0.12	0.00	0.10	–0.02	0.18	–0.08	–0.12	0.16	0.16	–0.20	0.21	0.14	0.10	0.01
	Radius of gyration	–0.02	0.17	0.06	0.20	0.27	–0.01	–0.14	–0.13	0.02	0.02	–0.25	0.00	0.06	0.12	–0.04
	Straightness index	–0.02	0.06	0.13	0.09	0.09	–0.14	0.24	0.30	0.25	0.25	–0.12	0.01	0.00	0.00	0.01
Cognitive Tests	MoCA total score	0.19	0.00	0.18	0.13	0.06	0.18	–0.04	–0.05	0.14	–0.13	–0.03	–0.14	–0.04	0.20	0.00
	SRT Free Recall	0.19	–0.01	0.13	0.20	0.03	0.29	–0.04	–0.10	0.19	0.21	–0.17	–0.13	0.05	0.29	0.00
	Animal naming	–0.04	0.03	0.11	0.05	0.02	0.00	0.05	–0.04	0.04	0.06	–0.04	–0.12	–0.09	0.06	0.05
	Trailmaking A	–0.01	0.07	–0.09	0.04	0.01	–0.05	–0.05	0.00	–0.06	–0.06	–0.06	–0.06	0.00	–0.02	–0.07
	Trailmaking B	0.07	–0.06	0.00	0.07	0.09	0.00	0.00	0.02	0.00	–0.03	0.02	–0.01	0.00	0.02	–0.05

nHV, normalized hippocampal volume.

Table 2
p-values from the general linear models (GLM) of biomarker-driving/cognitive associations after adjusting for age, gender, race, and education

		Imaging			CSF							Plasma			
		PET amyloid	PET tau	nHV	$A\beta_{42}$	$A\beta_{40}$	$A\beta_{42}/A\beta_{40}$	tau	ptau181	tau/ $A\beta_{42}$	ptau181/ $A\beta_{42}$	NfL	$A\beta_{40}$	$A\beta_{42}$	$A\beta_{42}/A\beta_{40}$	NfL
Driving Variables	Number of trips	0.139	0.540	0.624	0.254	0.139	0.540	0.472	0.869	0.415	0.155	0.732	**0.009****	**0.008****	0.956	0.720
	Number of unique destinations	**0.031***	0.353	0.811	0.509	0.589	0.244	0.889	0.571	0.214	0.152	0.099	0.306	0.209	0.601	0.394
	Average distance	0.922	0.358	0.535	0.115	**0.016***	0.785	0.081	0.104	0.612	0.700	**0.012***	**0.000****	**0.001****	0.894	0.495
	Average duration	0.941	0.080	0.892	0.599	0.081	0.352	**0.036***	**0.031***	0.177	0.234	0.282	**0.001****	**0.001****	0.928	0.315
	Average acceleration	0.370	0.921	0.855	0.420	0.835	**0.028***	0.240	0.994	0.072	0.105	0.084	0.172	0.314	0.255	0.886
	Average jerk	0.183	0.989	0.921	0.317	0.954	0.083	0.205	0.176	**0.038***	0.061	0.146	0.301	0.545	0.209	0.827
	Number of hard braking instances per mile	0.306	0.983	0.994	0.826	0.528	0.609	0.120	0.112	0.170	0.208	0.169	0.365	0.328	0.923	0.838
	Number of rapid accelerations per mile	0.963	0.666	0.964	0.481	0.545	0.767	0.301	0.691	0.786	0.859	0.436	0.694	70.620	0.707	0.942
	Proportion of trips with over speeding	0.390	0.132	0.648	0.515	0.154	0.501	0.164	0.104	0.338	0.337	0.072	**0.027***	0.077	0.285	0.157
	Proportion of trips with under speeding	0.979	0.753	0.084	0.601	0.667	0.553	0.362	0.760	0.147	0.266	0.348	0.658	0.501	0.578	0.553
	Number of trips taken at night	**0.013***	0.248	0.864	0.475	0.783	0.109	0.425	0.208	0.127	0.106	**0.029***	0.067	**0.028***	0.654	0.887
	Radius of gyration	0.804	0.190	0.878	**0.011***	**0.007****	0.328	0.320	0.434	0.427	0.394	**0.015***	0.432	0.503	0.637	0.752
	Straightness index	0.640	0.243	0.462	0.170	0.396	**–0.038***	**0.006****	**0.000****	**0.003****	**0.003****	0.206	0.988	0.907	0.831	0.921
Cognitive Tests	MoCA	**0.001****	0.270	0.112	0.285	0.772	0.770	0.615	0.637	0.199	0.219	0.391	0.615	0.155	0.134	0.380
	SRT Free Recall	0.059	0.324	0.252	0.104	0.991	**0.007****	0.699	0.287	0.850	**0.042***	0.359	0.978	0.228	**0.024***	0.706
	Animal naming	0.297	0.729	0.427	0.380	0.762	0.600	0.482	0.811	0.659	0.393	0.962	0.602	0.307	0.371	0.170
	Trailmaking A	0.814	0.753	0.871	0.997	0.331	0.504	0.998	0.843	0.645	0.662	0.945	0.597	0.738	0.726	0.520
	Trailmaking B	0.209	0.624	0.373	0.297	0.099	0.784	0.467	0.551	0.882	0.835	0.936	0.680	0.793	0.944	0.243

*significant at 0.05 level; **significant at 0.01 level. nHV, normalized hippocampal volume.

tary information. Overall, these distinct relationships may help in understanding how different biological changes that occur during the preclinical stage of AD can impact various sensorimotor and cognitive processes.

Our findings have implications for models of AD development, as they may help in establishing the timeline of the appearance of functional changes relative to changes in biomarkers and cognition. Additionally, biomarker cut-offs have been established because they are best at discriminating persons with symptomatic AD from those with normal cognition. However, these results indicate that the optimal cut-off points for biomarker positivity and negativity must be tailored to the specific outcome being monitored and predicted. Similar to impairment in cognitive processes, functional impairment is also a defining characteristic of AD as the disease progresses. Future AD research should work to determine the most effective cut-off values for using biomarkers to identify and predict functional outcomes such as driving, in order to provide a more nuanced understanding of the AD's impact on daily living.

Though more work lies ahead before we can monitor, detect, or predict AD in the preclinical phase on an individual basis, the findings of this study open up other interesting directions for further research in the field. One future research direction is to investigate how AD pathologies, as reflected in different biomarkers, affect other daily activities such as falls and gait patterns. With appropriate techniques and devices, we can create a novel scheme for behavioral staging of AD across its entire spectrum.

Finally, the findings should be considered in light of a few limitations. First, testing these relationships in additional samples are required to establish the reliability of these findings. Second, the sample lacks generalizability since the participants in this study are almost all non-Hispanic White and primarily reside in the St. Louis Area. Similar studies should be conducted in more geographically and racially diverse samples to establish the generalizability of these findings. Additionally, although our small sample size was effective for demonstrating that individual AD biomarkers (plasma, CSF, and imaging) are differentially related to naturalistic driving behaviors and cognitive test scores, the application of larger sample sizes, with increased statistical power, might uncover associations that were not deemed significant in our final models. For example, CSF NfL was significantly correlated with acceleration in the unadjusted analyses, but not in the GLMs.

Conclusion

The current study demonstrates that individual AD biomarkers (plasma, CSF, and imaging) are differentially related to naturalistic driving behaviors and cognitive test scores, with some biomarkers highly related to driving but not cognitive outcomes (e.g., plasma and $CSF_{A\beta 1\text{-}40}$, CSF NfL), and others related to cognitive test scores but not driving behaviors (e.g., plasma $A\beta_{42}/A\beta_{40}$ ratio). The findings highlight the need for targeted research into understanding how different processes in AD pathology, as characterized by different biomarkers, are associated with complex activities of daily living and behavioral staging of AD.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

[1] Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman DM, Jagust W, Jessen F, Karlawish J, Liu E, Molinuevo JL, Montine T, Phelps C, Rankin KP, Rowe CC, Scheltens P, Siemers E, Snyder HM, Sperling R, Elliott C, Masliah E, Ryan L, Silverberg N (2018) NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement* **14**, 535-562.

[2] Villemagne VL, Burnham S, Bourgeat P, Brown B, Ellis KA, Salvado O, Szoeke C, Macaulay SL, Martins R, Maruff P, Ames D, Rowe CC, Masters CL (2013) Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: A prospective cohort study. *Lancet Neurol* **12**, 357-367.

[3] Li Y, Schindler SE, Bollinger JG, Ovod V, Mawuenyega KG, Weiner MW, Shaw LM, Masters CL, Fowler CJ, Trojanowski JQ, Korecka M, Martins RN, Janelidze S, Hansson O, Bateman RJ (2022) Validation of plasma amyloid-β 42/40 for detecting Alzheimer disease amyloid plaques. *Neurology* **98**, e688-e699.

[4] Mattsson N, Andreasson U, Zetterberg H, Blennow K, for the Alzheimer's Disease Neuroimaging Initiative (2017) Association of plasma neurofilament light with neurodegeneration in patients with Alzheimer disease. *JAMA Neurol* **74**, 557-566.

[5] Weinstein G, Seshadri S (2014) Circulating biomarkers that predict incident dementia. *Alzheimers Res Ther* **6**, 6.

[6] Locascio JJ, Fukumoto H, Yap L, Bottiglieri T, Growdon JH, Hyman BT, Irizarry MC (2008) Plasma amyloid β-protein and c-reactive protein in relation to the rate of progression of Alzheimer disease. *Arch Neurol* **65**, 776-785.

[7] Marshall GA, Amariglio RE, Sperling RA, Rentz DM (2012) Activities of daily living: Where do they fit in the diagnosis of Alzheimer's disease? *Neurodegener Dis Manag* **2**, 483-491.

[8] Bayat S, Babulal GM, Schindler SE, Fagan AM, Morris JC, Mihailidis A, Roe CM (2021) GPS driving: A digital biomarker for preclinical Alzheimer disease. *Alzheimers Res Ther* **13**, 115.

[9] Ragland DR, Satariano WA, MacLeod KE (2005) Driving cessation and increased depressive symptoms. *J Gerontol Ser A* **60**, 399-403.

[10] Dickerson AE, Reistetter T, Davis ES, Monahan M (2011) Evaluating driving as a valued instrumental activity of daily living. *Am J Occup Ther* **65**, 64-75.

[11] IIHS-HLDI crash testing and highway safety, Older drivers. https://www.iihs.org/topics/older-drivers

[12] Centers for Disease Control and Prevention (2022) Older adult drivers. https://www.cdc.gov/transportation safety/older_adult_drivers/index.html

[13] Tsoy E, Strom A, Iaccarino L, Erlhoff SJ, Goode CA, Rodriguez A-M, Rabinovici GD, Miller BL, Kramer JH, Rankin KP, La Joie R, Possin KL (2021) Detecting Alzheimer's disease biomarkers with a brief tablet-based cognitive battery: Sensitivity to Aβ and tau PET. *Alzheimers Res Ther* **13**, 36.

[14] Aschenbrenner AJ, Gordon BA, Fagan AM, Schindler SE, Balota DA, Morris JC, Hassenstab JJ, Tales A (2020) Neurofilament light predicts decline in attention but not episodic memory in preclinical Alzheimer's disease. *J Alzheimers Dis* **74**, 1119-1129.

[15] Roe CM, Barco PP, Head DM, Ghoshal N, Selsor N, Babulal GM, Fierberg R, Vernon EK, Shulman N, Johnson A, Fague S, Xiong C, Grant EA, Campbell A, Ott BR, Holtzman DM, Benzinger TL, Fagan AM, Carr DB, Morris JC (2017) Amyloid imaging, cerebrospinal fluid biomarkers predict driving performance among cognitively normal individuals. *Alzheimer Assoc Disord* **31**, 69-72.

[16] Roe CM, Babulal GM, Head DM, Stout SH, Vernon EK, Ghoshal N, Garland B, Barco PP, Williams MM, Johnson A, Fierberg R, Fague MS, Xiong C, Mormino E, Grant EA, Holtzman DM, Benzinger TLS, Fagan AM, Ott BR, Carr DB, Morris JC (2017) Preclinical Alzheimer's disease and longitudinal driving decline. *Alzheimers Dement Transl Res Clin Interv* **3**, 74-82.

[17] Leuzy A, Mattsson-Carlgren N, Palmqvist S, Janelidze S, Dage JL, Hansson O (2022) Blood-based biomarkers for Alzheimer's disease. *EMBO Mol Med* **14**, e14408.

[18] Roe CM, Rosnick CB, Colletta A, Babulal GM (2021) Reaction to a pandemic: Social distancing and driving among older adults during COVID-19. *J Appl Gerontol* **40**, 263-267.

[19] Wisch JK, Roe CM, Babulal GM, Metcalf N, Johnson AM, Murphy S, Hicks J, Doherty JM, Morris JC, Ances BM (2022) Naturalistic driving measures of route selection associate with resting state networks in older adults. *Sci Rep* **12**, 6486.

[20] Babulal GM, Stout SH, Benzinger TLS, Ott BR, Carr DB, Webb M, Traub CM, Addison A, Morris JC, Warren DK, Roe CM (2019) A naturalistic study of driving behavior in older adults and preclinical Alzheimer disease: A pilot study. *J Appl Gerontol* **38**, 277-289.

[21] Schindler SE, Bollinger JG, Ovod V, Mawuenyega KG, Li Y, Gordon BA, Holtzman DM, Morris JC, Benzinger TLS, Xiong C, Fagan AM, Bateman RJ (2019) High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis. *Neurology* **93**, e1647-e1659.

[22] Schultz SA, Gordon BA, Mishra S, Su Y, Morris JC, Ances BM, Duchek JM, Balota DA, Benzinger TLS (2020) Association between personality and tau-PET binding in cognitively normal older adults. *Brain Imaging Behav* **14**, 2122-2131.

[23] Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* **53**, 695-699.

[24] Grober E, Lipton RB, Hall C, Crystal H (2000) Memory impairment on free and cued selective reminding predicts dementia. *Neurology* **54**, 827-832.

[25] Goodglass H, Kaplan E (1983) *The assessment of aphasia and related disorders*, Lea & Febiger, Philadelphia.

[26] Armitage SG (1946) An analysis of certain psychological tests used in the evaluation of brain injury. *Psychol Monogr* **60**, 1-48.

[27] Roe CM, Stout SH, Rajasekar G, Ances BM, Jones JM, Head D, Benzinger TLS, Williams MM, Davis JD, Ott BR, Warren DK, Babulal GM (2019) A 2.5-year longitudinal assessment of naturalistic driving in preclinical Alzheimer's disease. *J Alzheimers Dis* **68**, 1625-1633.