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FEATURED ARTICLE

Adverse driving behaviors increase over time as a function of preclinical Alzheimer's disease biomarkers

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Abstract

Introduction: We investigated the relationship between preclinical Alzheimer's disease (AD) biomarkers and adverse driving behaviors in a longitudinal analysis of naturalistic driving data.

Methods: Naturalistic driving data collected using in-vehicle dataloggers from 137 community-dwelling older adults (65+) were used to model driving behavior over time. Cerebrospinal fluid (CSF) biomarkers were used to identify individuals with preclinical AD. Additionally, hippocampal volume and cognitive biomarkers for AD were investigated in exploratory analyses.

Results: CSF biomarkers predicted the longitudinal trajectory of the incidence of adverse driving behavior. Abnormal amyloid beta ($A\beta_{42}/A\beta_{40}$) ratio was associated with an increase in adverse driving behaviors over time compared to ratios in the normal/lower range.

Discussion: Preclinical AD is associated with increased adverse driving behavior over time that cannot be explained by cognitive changes. Driving behavior as a functional, neurobehavioral marker may serve as an early detection for decline in preclinical AD. Screening may also help prolong safe driving as older drivers age.

KEYWORDS
Alzheimer's disease, cerebrospinal fluid biomarkers, driving, older adults

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using PubMed and Scopus, searching for relevant research published in peer-reviewed journals, meeting abstracts, and presentations. Research into driving and preclinical Alzheimer's disease (AD) using biomarkers was very limited, and an in-depth literature review helps put this new area of research in context.
2. **Interpretation**: Our findings build upon previous research into driving and preclinical AD, and add to the wider AD and driving literatures. We found that it is possible to detect changes in driving behavior associated with an increased risk of motor vehicle crashes in otherwise cognitively normal older adults who show signs of AD brain pathophysiology but do not have prodromal AD.
3. **Future directions**: The findings reported in the article represent an early step in detecting and assessing changes in high-risk driving behavior in those with preclinical AD. Awareness of this increased risk despite absence of cognitive symptoms of AD is important when considering early detection and interventions to prolong safe driving among aging drivers.

1 | INTRODUCTION

Alzheimer's disease (AD) is a risk factor for motor vehicle crashes, with up to five times higher crash risk in individuals with cognitive impairment compared to healthy controls.[1,2] Older age is also associated with increased risk of motor vehicle crashes.[3] The Centers for Disease Control and Prevention (CDC) reported 7480 deaths in the United States in 2020 due to crashes for those aged 65+ (the second leading cause of death by injury in that age range).[4] The CDC also reported 149,811 nonfatal injuries caused by motor vehicle accidents for the same age group, and such injuries have been linked with severe health outcomes in older adults compared to younger age groups.[5,6] Conversely, driving cessation is associated with depression,[7] increased mortality,[8] and loss of independence.[9] It is essential to understand how driving behavior is affected by age and AD to prolong driving ability while considering the safety of older drivers and others who share the road.

While the relationship between AD and motor vehicle crashes is established, crash risk in preclinical AD is an emerging area of research. An estimated 30% to 40% [10] of cognitively normal older adults are classified as having preclinical AD based on biomarkers that can sensitively detect AD brain pathology. Individuals with preclinical AD biomarkers have an annual conversion rate of 20% to 30%[11–13] to prodromal AD. Despite having apparently normal function, individuals with preclinical AD have a higher likelihood of failing a road test[14,15] and are at an increased risk of traffic violations and crashes.[16] However, studies on exactly *how* driving behavior changes over time are limited, and findings are predominantly based on data collected in a laboratory setting as opposed to observing naturalistic driving.

Certain driving behaviors like hard braking, hard acceleration, and speeding have been associated with increased risk of motor vehicle crashes.[17] Previous research has focused on mean differences in naturalistic driving metrics, and found that those with preclinical AD biomarkers take fewer trips, speed more often, but show fewer instances of hard braking and acceleration, which seems counterintuitive given the known risks associated with the disease.[18] Older adults may change their driving habits as they age,[19] but, whether these changes are due to conscious self-regulation is unclear.[20] Instead of cross-sectional group comparisons based on driving metrics, examining whether these driving behaviors change within an individual over time may provide appropriate insights.[21]

A better understanding of how preclinical AD affects the incidence of high-risk, or "adverse," driving behavior over time may inform clinicians on how early intervention can prolong safe driving in old age and maintain independence in both those who are at risk of developing AD and those wishing to age-in-place. A recent study into the effects of preclinical AD on adverse driving behaviors found an unexpected interaction between age and biomarker status.[22] Drivers with older age and preclinical AD biomarkers exhibited increased incidences of adverse driving compared to lower age ranges, whereas the opposite was true for biomarker-negative individuals for whom age was associated with decreased driving risk. In the current study, we expand upon these findings and analyzed adverse driving behaviors (hard braking, hard acceleration, and speeding) longitudinally in a sample of community-dwelling older adults. The aim is to replicate the pattern of data in the aforementioned cross-sectional analysis,[22] and investigate how incidences of adverse driving behavior change over time and how this is affected by preclinical AD. We hypothesized that drivers with preclinical AD, who can be identified by CSF biomarkers, will demonstrate an increase in adverse driving behaviors over time, and that drivers without preclinical AD biomarkers will demonstrate a decrease in these behaviors over time.

2 | METHODS

2.1 | Participants

The study sample consisted of 137 community-dwelling older adults aged > 65 years old who were enrolled in longitudinal studies of AD and driving behavior at the Washington University in St. Louis, Knight Alzheimer Disease Research Center (ADRC). Participants undergo annual clinical and cognitive assessments. Inclusion criteria were: (1) cognitively normal at baseline based on a Clinical Dementia Rating (CDR) [23] of "0," (2) drive at least once per week and have naturalistic driving data collected over at least 365 days, and (3) have completed lumbar puncture for the collection of cerebrospinal fluid (CSF) within 18 months of driving data. The study was approved by the Washington University Institutional Review Board, and each participant signed an informed consent.

2.2 | Cognition

Cognition was assessed using a composite score to assess whether participants differ by biomarker status. Although cognitive changes are not expected due to the inclusion criteria of CDR = "0", it is important to confirm whether the two groups differed in cognition. The composite score[24] was based on subtests measuring processing speed (Trail Making Test Part A),[25] executive function (Trail Making Test Part B),[25] episodic memory (Free and Cued Selective Reminding Test: Free recall score),[26] and semantic category naming (Animal Fluency).[27] The composite score was calculated by standardizing scores using the mean and standard deviation of each of the subtests and then calculating the mean of these standardized scores for each participant.

2.3 | Driving

Naturalistic driving data were captured using a GPS data logger ("G2 Tracking Device," Azuga Inc.). This device plugs into the onboard diagnostics-II (OBDII) port included in modern vehicles, requires 20 seconds to install, uses the vehicle's battery for power, and is minimally invasive. The variables collected during each vehicle's trip include date, time, latitude and longitude, and speed. In addition to whenever a notable driving event occurs, data are recorded at 30 second intervals. The Driving Real-World In-Vehicle Evaluation System (DRIVES) methodology has been described in detail in previous publications.[28-31]

To investigate adverse driving behaviors over time, a composite was created to include hard braking, sudden acceleration, and speeding. Hard braking and sudden acceleration were defined as deceleration/acceleration in excess of 8 miles per hour per second. Speeding was defined as speed $\geq$ 6 miles per hour over the posted speed limit. Posted speed limits are continuously obtained from each latitude and longitude of where the vehicle is driven and the difference in the vehicle speed versus the speed limit is automatically calculated by the vendor who supplies the dataloggers. These three measures were selected, as previous research has found differences in baseline measures of these behaviors between AD biomarker negative and biomarker positive groups,[18] and age-related differences in the incidence of these behaviors between negative and positive groups.[22] The variable was summarized and coded at a trip level, with "1" if there were any incidences of adverse driving behaviors, and "0" otherwise.

2.4 | CSF biomarkers

CSF was collected as previously described.[32] Levels of amyloid beta$_{42}$ (Aβ_{42}) and amyloid beta$_{40}$ (Aβ_{40}) were measured using automated electrochemiluminescence immunoassay (Lumipulse G1200, Fujirebio). The ratio Aβ_{42}/Aβ_{40} was used to classify preclinical AD: lower ratio values indicate greater pathology, and higher ratio values indicate lower pathology/absence of preclinical AD in an individual. Unless specified, analyses treated CSF Aβ_{42}/Aβ_{40} as continuous. For the analysis of hippocampal volume (due to issues with model convergence) and data summation in figures, participants were classified as being biomarker positive versus negative based on an established cut-off from an analysis of a large sample of ADRC participants to determine the highest concordance between CSF biomarkers and amyloid positron emission tomography (PET).[33] Participants with a Aβ_{42}/Aβ_{40} ratio below the cut-off of 0.0673 were classified as biomarker positive, and those at or above the cut-off were classified as biomarker. Similar models were analyzed substituting Aβ_{42}/Aβ_{40} with total tau (t-tau)/Aβ_{42} and phosphorylated tau (p-tau)/Aβ_{42}, and are included in the supporting information. The cut-off for preclinical AD biomarker positivity for t-tau/Aβ_{42}, was > 0.488 and for p-tau/Aβ_{42} was > 0.0649.

2.5 | Magnetic resonance imaging

Structural biomarkers via magnetic resonance imaging (MRI) imaging were captured using Siemens BioGraph mMR PET-MR 3T and Siemens Trio 3 T MRI scanners. MRI data were processed using the FreeSurfer 5.3 image analysis suite running on CentOS 5.5 Linux on Dell PowerEdge 1950 servers equipped with Intel Xeon processors. The technical details of the FreeSurfer analysis have been described previously.[34,35] Prior to analysis, hippocampal volume was normalized to account for differences in head size. The procedure consisted of computing the mean intracranial volume (ICV) for the sample, and then conducting a regression analysis with ICV as the sole independent variable and participants' hippocampal volume (the sum of right and left hippocampal volume) as the dependent variable. The β-weight was then used to compute participants' normalized hippocampal volume using the following equation: normalized hippocampal volume = raw hippocampal volume – (β-weight × [participant's ICV – sample mean ICV])[36]. MRI data were available for a subset of 106 participants.

2.6 | Statistical analysis

Analyses are separated into two sections: (1) the primary analysis of longitudinal change in participants' driving behavior and (2) exploratory analyses investigating potential explanations for the differences between AD biomarker positive and biomarker negative groups in adverse driving behavior.

Due to rolling enrollment in this longitudinal cohort, duration of naturalistic driving data collection varied across participants. Data for driving variables consisted of every trip taken by the participants for the dates in which they were enrolled in the study that were also within 18 months of a CSF biomarker collection. Exploratory MRI analyses were conducted on a smaller subset of participants (n = 106) due to missing data. All analyses controlled for age, sex, and education. Models also contained a random intercept for each participant to adjust for baseline variance in driving habits.

The primary analyses featured the same outcome variable, which was whether a trip had an incidence of adverse driving ("1") or not

("0"). The data were analyzed using binomial logistic regressions (binomial generalized linear mixed models [GLMMs]), which allow analysis of binary outcome data. GLMMs are a suitable analysis for these data because adverse driving events are rare and their incidences are highly variable between participants, such that Poisson regression is not appropriate due to zero inflation and overdispersion. The analysis investigated the change in driving behavior over time, that is, the number of days since naturalistic driving data capture started for each participant. Age at baseline was included as a fixed effect based on previous age-related findings[22] to control for those effects.

In analyses that included biomarkers, the closest biomarker data for each participant was selected and associated with each trip for analysis. CSF biomarker ratio was treated as a continuous variable in the primary driving analysis. For the analysis of hippocampal volume, biomarkers were dichotomized to positive ("1") and negative ("0") values based on the aforementioned cut-off due to issues with model convergence and also to aid interpretation of those models.

Age and education variables were centered by subtracting the sample means from each value to aid model convergence and interpretation of coefficient estimates. Time (number of days since data collection started) was scaled by subtracting the mean of the sample from each value and dividing by the standard deviation. This step was essential for model convergence because participants' time in the study varied. The composite cognition score and hippocampal volumes were also scaled prior to analysis to aid model convergence.

Analyses were conducted in R[37] using the lme4[38] (version 1.1-29) package, and plots were created using ggeffects[39] (version 1.1.3) and ggplot2[40] (version 3.3.6).

3 | RESULTS

3.1 | Participant characteristics

Table 1 summarizes participant characteristics. While the majority of analyses treated the CSF biomarker as a continuous variable, the sample has been grouped in biomarker positive and negative groups based on $A\beta_{42}/A\beta_{40}$ to summarize group differences. AD biomarker groups as defined by $A\beta_{42}/A\beta_{40}$ status (positive < 0.0673, negative ≥0.0673) did not vary in sex, race, or years of education. The biomarker positive group had a higher mean age at baseline ($P < 0.01$) and a larger proportion of apolipoprotein E ε4+ carriers ($P < 0.001$) compared to the biomarker negative group, which is expected given its association with AD risk. The biomarker groups did not differ in terms of the mean percentage of trips with speeding, hard braking, or hard acceleration, and also did not differ on the composite score of these behaviors. For cognition, the biomarker positive group performed worse on the Free and Cued Selective Reminding Test ($P < 0.01$) and had a lower composite score ($P < 0.05$).

3.2 | Analysis of driving variables

The primary analysis of longitudinal adverse driving is summarized in Table 2. The mean time in the study was 769.90 days (range = 372–1520). The regression analysis revealed a statistically significant effect of time on adverse driving, with an increase in the risk of adverse driving over time. There was also an interaction between time and $A\beta_{42}/A\beta_{40}$, indicating a different trajectory of adverse driving over time dependent on biomarker ratio. Figure 1 depicts model predictions of the probability of an adverse driving event during a trip, showing that older adults with normal biomarker ratios exhibit a decrease in adverse driving over time, while those at the other end of the ratio range demonstrate an increase in adverse behaviors. The analysis was repeated for t-tau/$A\beta_{42}$ ratio and p-tau/$A\beta_{42}$ ratios and the results were consistent with $A\beta_{42}/A\beta_{40}$ ratio (see supporting information). Notably, the negative intercept terms in these models indicate that trips are more likely to not feature an adverse driving event. In addition to investigating adverse driving, we ran additional analyses on more global driving behaviors (namely average distance travelled and speed, which could both indicate higher levels of highway driving) to check that other changes in driving behavior could not potentially explain incidence of adverse driving events. These analyses are summarized in the supporting information and did not provide evidence for alternative explanations for differences in adverse driving across the range of CSF biomarker values.

3.3 | Exploratory analyses

We conducted two exploratory analyses to examine the relationship between AD biomarkers and driving behavior. The first evaluated whether baseline cognition (as measured by the composite score summarized in Table 1) could explain the adverse driving effects in the primary analysis, while the second investigated whether hippocampal volume predicted changes in driving behavior.

The results for the analyses of baseline cognition are summarized in Table 3. The model contains the same interaction between time and biomarker ratio as observed in the previous analysis, but, crucially, the model does not contain a statistically significant three-way interaction among $A\beta_{42}/A\beta_{40}$, cognition, and time, suggesting that increase in driving risk over time could not be explained solely by baseline cognition. The assessment of cognition provided by the composite score does not appear to measure the same differences between the biomarker groups that leads to changes in driving behavior.

Table 4 summarizes analyses of participants' hippocampal volume at the closest date to the first driving date (mean interval = 282.77 days, range = 13–543). The model features a three-way interaction between time, biomarker status, and hippocampal volume. This interaction can be seen in Figure 2, which shows that hippocampal volume only appears to affect those in the biomarker positive group. In the left panel, it is clear that those biomarker positive participants with hippocampal volume one standard deviation below the sample

TABLE 1 Participant characteristics at baseline

	Total ($n = 137$)	$A\beta_{42}/A\beta_{40-}$ ($n = 83$)	$A\beta_{42}/A\beta_{40+}$ ($n = 54$)[a]	Test[a]
Age, years	73.80 ± 4.76	72.84 ± 4.51	75.28 ± 4.79	$P < 0.01$**
Sex, *N* = female, %	62 (45.26)	41 (49.40)	21 (38.89)	$P = 0.292$
Education, years	16.50 ± 2.27	16.25 ± 2.27	16.87 ± 2.25	$P = 0.120$
Race[b], *N* = White, %	120 (87.59)	69 (83.13)	51 (94.44)	$P = 0.064$
APOE ε4+ carrier, *N*, %	47 (34.31)	13 (15.66)	34 (62.96)	$P < 0.001$***
Biomarkers				
CSF: $A\beta_{42}/A\beta_{40}$	0.074 ± 0.023	0.091 ± 0.008	0.048 ± 0.010	$P < 0.001$***
CSF: t-tau	353.76 ± 179.72	295.30 ± 157.17	443.62 ± 176.31	$P < 0.001$***
CSF: p-tau	46.91 ± 22.82	36.28 ± 14.80	63.25 ± 23.42	$P < 0.001$***
MRI[c]: Hippocampal volume (normalized), cm^3	7.48 ± 0.95	7.47 ± 0.94	7.50 ± 0.96	$P = 0.874$
Driving				
Trips with speeding, %	9.02 ± 9.29	9.18 ± 8.69	8.80 ± 10.21	$P = 0.821$
Trips with hard braking, %	9.11 ± 7.28	9.79 ± 7.85	8.06 ± 6.22	$P = 0.153$
Trips with hard acceleration, %	4.11 ± 6.67	4.03 ± 6.82	4.24 ± 6.49	$P = 0.863$
Trips with any adverse driving events, %	18.53 ± 12.76	19.16 ± 12.43	17.57 ± 13.31	$P = 0.485$
Trips, *N*	2866.86 ± 1615.77	3033.22 ± 1656.63	2611.17 ± 1530.75	$P = 0.130$
Cognitive assessment				
Free & Cued Selective Reminding Task, Free recall score	30.28 ± 6.76	31.80 ± 6.21	27.94 ± 6.96	$P < 0.01$**
Animal Fluency, total animals named	21.09 ± 4.86	21.34 ± 4.97	20.72 ± 4.71	$P = 0.466$
Trail Making Test, Part A, seconds to complete	30.98 ± 9.72	29.96 ± 8.84	32.54 ± 10.83	$P = 0.148$
Trail Making Test, Part B, seconds to complete	75.93 ± 29.18	75.80 ± 30.11	76.15 ± 27.96	$P = 0.944$
Composite score	−0.15 ± 0.72	−0.05 ± 0.73	−0.31 ± 0.70	$P < 0.05$*

Note: Factors included in analyses are shown in bold.
Abbreviations: Aβ, amyloid beta; *APOE*, apolipoprotein E; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; p-tau, phosphorylated tau; t-tau, total tau.
[a]Means were compared using t-tests. Frequencies were compared using Fisher's exact test.
[b]The sample contains only Black and White races.
[c]Data only available for 106 participants. Biomarker negative = 65 (61.32%), biomarker positive = 41 (38.68%).
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

TABLE 2 Regression model investigating change in adverse driving over time

	Dependent variable
	Adverse driving
(Intercept)	−2.118 (0.120)***
Time (days)	0.116 (0.016)***
$A\beta_{42}/A\beta_{40}$	5.184 (0.666)***
Baseline age	−0.011 (0.017)
Sex (female vs. male)	0.012 (0.037)
Education (years)	−0.023 (0.037)
Time: $A\beta_{42}/A\beta_{40}$	−2.402 (0.202)***
Observations	392,760
Log likelihood	−169,455.500
AIC	338,927.000

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
Abbreviations: Aβ, amyloid beta; AIC, Akaike information criterion.

median demonstrate a decrease in adverse driving over time, whereas participants in all other groups do not.

4 | DISCUSSION

This study aimed to expand previous research into preclinical AD and driving, and investigate whether previously observed interactions between age and biomarker status[22] could be replicated in a longitudinal analysis of driving behavior. The relationship between preclinical AD and driving has been investigated in prior studies, but these investigations have focused on road tests,[14,15] or inclusion of a wide array of driving metrics to differentiate between biomarker positive and biomarker negative individuals.[18,41] These prior studies focused on using driving to differentiate between those with and without preclinical AD, rather than specifically which driving behaviors change over time, and how. This study adds to prior research by investigating longitudinal changes in driving behavior and how adverse driving

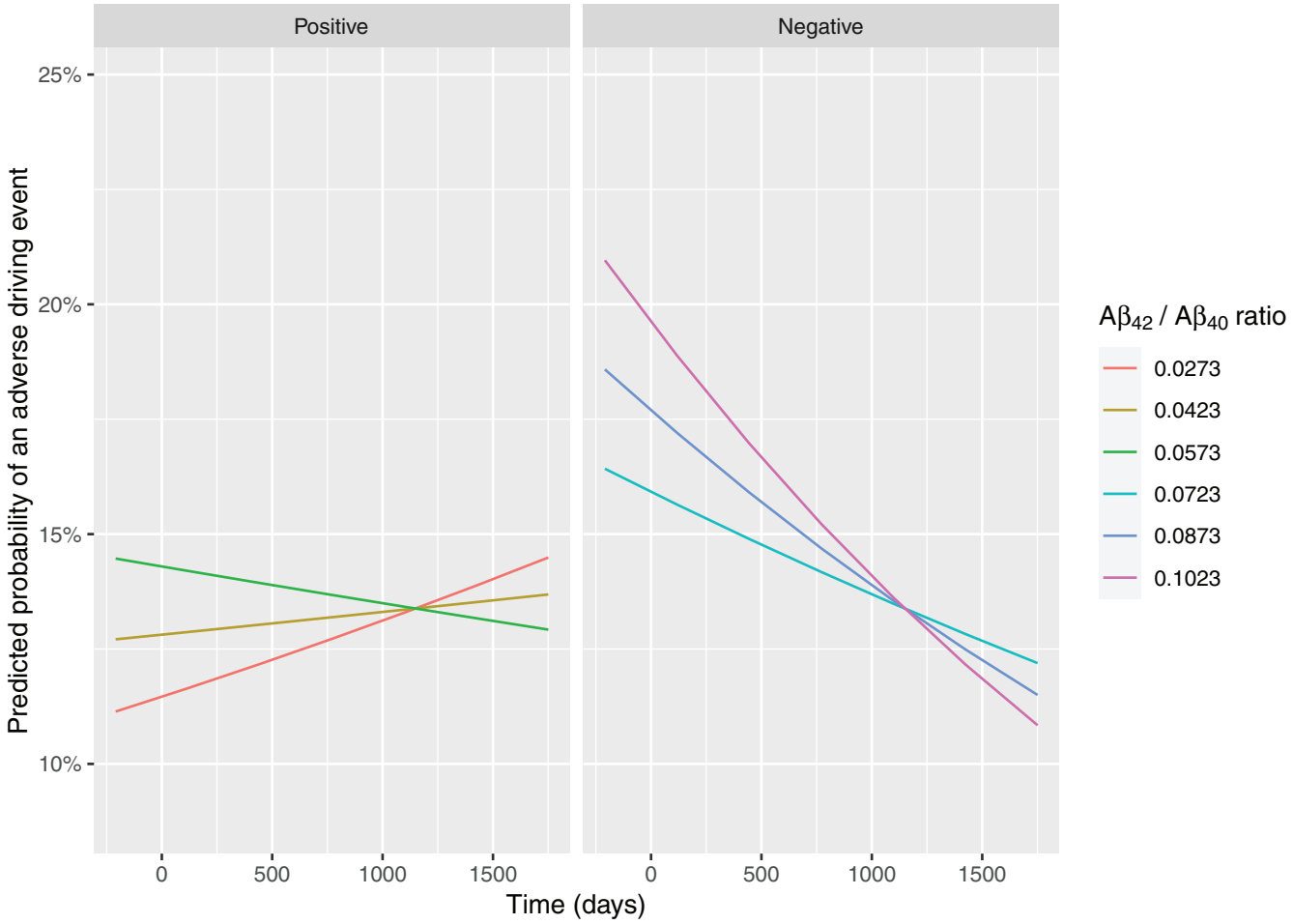

FIGURE 1 Predicted probability of an adverse driving event over time. Lines represent different amyloid beta ($A\beta)_{42}/A\beta_{40}$ ratios, and show a clear pattern of increasing pathology (lower ratios) affecting the trajectory of adverse driving behavior over time. Note: Although biomarkers are split into positive and negative groups, the analysis treated biomarkers as a continuous variable

risk is moderated by preclinical AD. We found that the trajectory of adverse driving behaviors over time could be predicted by preclinical AD biomarkers.

Our findings suggest that CSF biomarkers of AD predicted different patterns of change in driving behavior. Older drivers with biomarkers indicating AD brain pathology demonstrated an increase in adverse driving over time, while those with normal levels of AD biomarkers displayed a decrease in these behaviors. This finding complements the age-related findings reported in previous research,[22] expands and explains findings related to baseline differences in adverse driving behaviors,[18] and sheds some light on which behavioral changes may inform machine learning analyses to differentiate between biomarker groups based on a multitude of naturalistic driving variables.[42] Importantly, additional analyses of driving variables and cognition confirmed that these differences cannot be fully explained by other more global changes in driving behavior because none of these additional analyses revealed the same pattern of longitudinal interaction effects.

Despite inclusion criteria at baseline requiring a CDR of "0," we found that biomarker positive participants performed worse on cognitive testing compared to biomarker negative participants. However, this difference cannot explain the pattern of performance detected in the primary analysis. The pattern of main and interaction effects in the analysis of cognition indicates higher composite scores being associated with higher overall incidences of adverse driving in addition to higher incidences of these behaviors over time, counter to the main findings related to biomarkers and adverse driving. Coupled with the fact that the cognition models did not include statistically significant three-way interactions among time, biomarker status, and cognition, it is clear that cognition measures at baseline cannot fully explain changes in adverse driving behaviors.

These results are also supported by a recent study of the same cohort ($n = 161$) that examined whether baseline cognitive abilities like episodic memory, attentional control, processing speed, and working memory predicted change in driving space and behavior over 2 years.[43] Compared to older drivers with high attentional control (the ability to focus on relevant aspects of the environment while ignoring distracting or competing information), those with lower attentional control drove fewer trips per month and less at night, visited fewer unique locations, and drove in smaller spaces. Attentional control only explained ≈1% of the variance in change over time in the driving space score. None

TABLE 3 Regression models investigating baseline cognition and adverse driving

	Dependent variable Adverse driving
(Intercept)	−2.009 (0.117)***
Time (days)	0.133 (0.016)***
$A\beta_{42}/A\beta_{40}$	3.880 (0.663)***
Cognition (composite score)	−0.050 (0.091)
Baseline age	−0.008 (0.017)
Sex (female vs. male)	−0.045 (0.165)
Education (years)	−0.035 (0.036)
Time: $A\beta_{42}/A\beta_{40}$	−2.740 (0.204)***
Time: Cognition	0.021 (0.015)
$A\beta_{42}/A\beta_{40}$: Cognition	3.051 (0.514)***
Time: $A\beta_{42}/A\beta_{40}$: Cognition	0.098 (0.194)
Observation	392,760
Log Likelihood	−169,435
AIC	338,895

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
Abbreviations: Aβ, amyloid beta; AIC, Akaike information criterion.

TABLE 4 Regression models investigating baseline hippocampal volume and adverse driving

	Dependent variable Adverse driving
(Intercept)	−1.733 (0.135)***
Time (days)	−0.135 (0.007)***
$A\beta_{42}/A\beta_{40}$ +	−0.136 (0.128)
HV	0.005 (0.123)
Baseline age	−0.017 (0.024)
Sex (female vs. male)	0.010 (0.184)
Education (years)	−0.063 (0.043)
Time: $A\beta_{42}/A\beta_{40}$+	0.144 (0.013)***
Time: HV	−0.003 (0.007)
$A\beta_{42}/A\beta_{40}$ +: HV	−0.191 (0.181)
Time: $A\beta_{42}/A\beta_{40}$ +: HV	0.112 (0.017)***
Observations	300,313
Log likelihood	−127.324.000
AIC	252,672.000

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
Abbreviations: Aβ, amyloid beta; AIC, Akaike information criterion; HV, hippocampal volume.

of the cognitive abilities predicted change in performance metrics like hard braking, speeding, or sudden acceleration.[43] Driving behavior is a dynamic activity requiring rapid, sustained, and coordinated deployment of several conscious and subconscious systems (cognitive, motor, sensory, affective). As a result, cognitive abilities tested using a controlled condition via a single domain task are not scalable to an activity like driving in which the constraints and demands widely vary. Assessment of neuropsychological correlates with driving requires dynamic, multi-modal tasks.

The exploratory analysis of baseline hippocampal volume revealed a three-way interaction among volume, time, and biomarker status. This interaction reveals that those individuals in the biomarker positive group with lower baseline hippocampal volume demonstrated a decreased risk of adverse driving behavior over time, while those with volumes closer to the mean and above demonstrated an increase in adverse driving over time. Conversely, the biomarker negative group all demonstrate a decrease in adverse driving behavior over time regardless of hippocampal volume. It may be that decreased volume at baseline is associated with memory difficulties that the participant may be aware of, and so they consciously alter their driving behavior to avoid situations with increased risk. Those with less or no hippocampal volume atrophy may not be aware of changes in their cognition, and so are more prone to increases in aggressive driving that rely on other brain structures. The compounded effects of preclinical AD and hippocampal atrophy likely increase how much older drivers self-regulate their driving as a compensatory response to pathology and diminished structural capacity. Further investigation is needed to explore these effects, and the potential links among progression from preclinical to symptomatic AD, hippocampal volume, and driving.

4.1 | Limitations

This study is comprised of a fairly homogenous sample, consisting of highly educated and predominantly White individuals living in and around the St. Louis, Missouri area. Caution must be taken when generalizing these findings to other populations in terms of race, education, and geographical residence. Recruiting primarily from an urban environment prohibits an in-depth investigation of how the built environment, availability of other means of transportation besides personal vehicles, and the walkability of neighborhoods influences an older adult's self-regulation in relation to driving. There are ongoing efforts to expand the DRIVES methodology both nationally and internationally to recruit a wider sample to investigate how the links between preclinical AD and driving behavior may be moderated by other factors.

Due to rolling enrollment, participation time varied in the study. To maximize the sample size (which was essential due to the aforementioned rarity of adverse driving events) it was necessary to scale the time variable to model the data. A limitation of this approach is that it is not possible to draw conclusions on the exact time frame of the increases and decreases in adverse driving over time based on the coefficient estimate. We focused on differences in the trajectory of adverse driving behavior over time as a class. Continued data collection will allow future modeling in the rate of change in adverse driving behaviors and the specific type. Additionally, due to the relative rarity of adverse driving events, at this stage we are unable to separately investigate changes in the behaviors that make up the adverse behavior composite. Future studies aim to provide a more in-depth analysis of whether

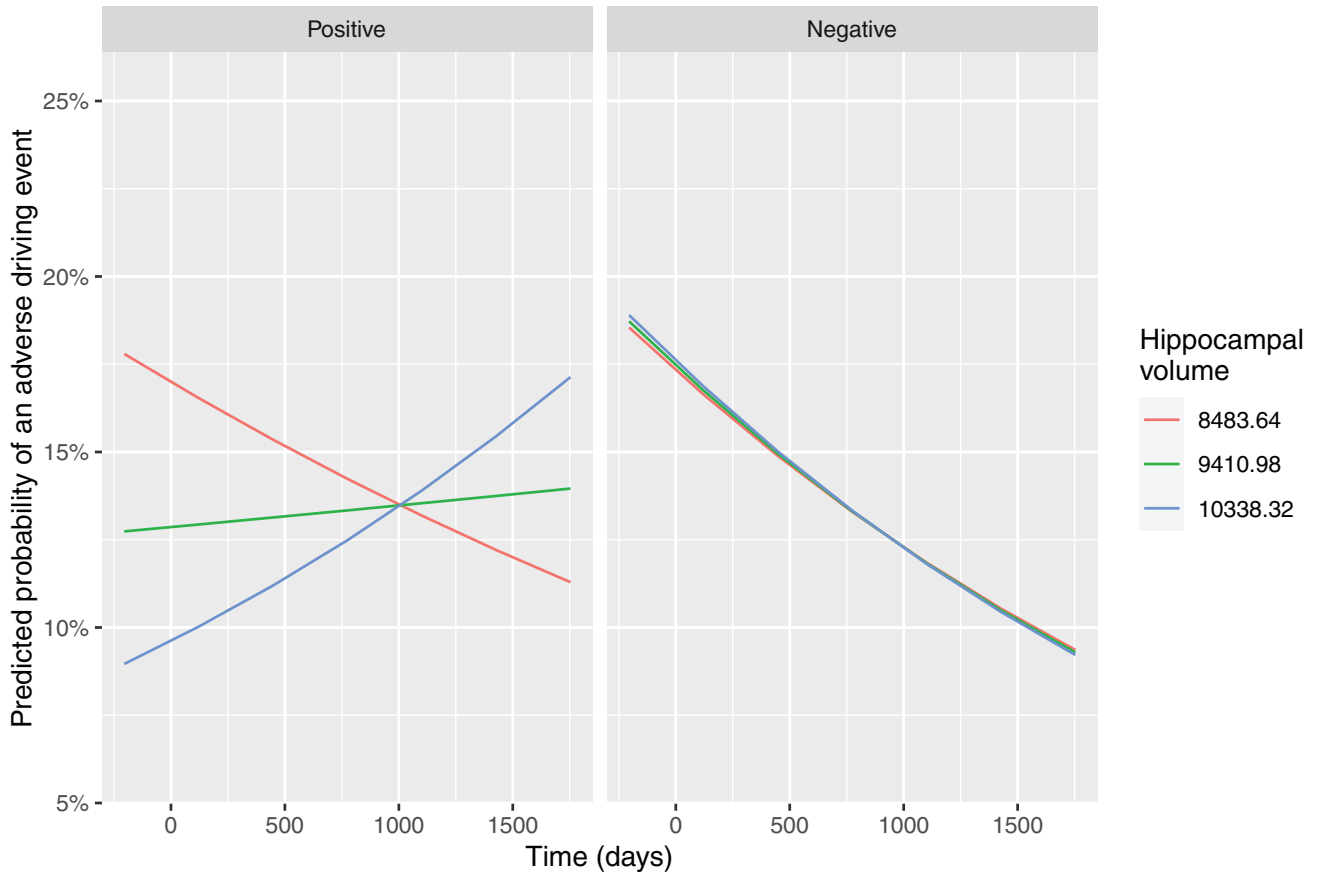

FIGURE 2 Driving aggression plotted by time, hippocampal volume, and biomarker status. The left panel includes predictions for participants with amyloid beta $(A\beta)_{42}/A\beta_{40}$ ratios indicating preclinical Alzheimer's disease, while the left panel refers to negative participants. Hippocampal groups represent mean and +/− 1 standard deviation volumes. Note: Although hippocampal volume is plotted in groups, it was treated as continuous in the analysis

incidences of hard braking, hard acceleration, and speeding individually change over time.

Another difficulty in investigating links between preclinical AD biomarkers and behaviors such as naturalistic driving is that the use of cut-offs for biomarker positivity are continually refined and updated. We elected to treat CSF biomarkers as continuous variables where the complexity of the statistical model is not so great that continuous variables complicate interpretation, and that the sample size is large enough to model such data. However, dichotomizing biomarker variables into positive and negative groups can allow convergence of models when the statistical power is not great enough to permit analysis of continuous variables, and to aid interpretation of complex interactions. A limitation of this approach is that conclusions based on biomarker positivity could change in the future as cut-offs continue to be researched and their confidence intervals shrink.

The focus of our research to date has been on those older adults who are without any overt cognitive symptoms of AD. Future research would benefit from an examination of a sample representing the full spectrum of AD ranging from cognitively normal biomarker negative and positive, and very mild and mild degrees of symptomatic AD for those who still drive. Additionally, we have observed in both prior research and the experiment reported here that those in the healthy CSF biomarker ranges demonstrate a *decrease* in adverse driving over time, but that baseline adverse driving rates were higher in this group. Future research aims to identify this pattern of behavior in individuals without preclinical AD biomarkers to understand why those with preclinical AD demonstrate the opposite pattern.

5 | CONCLUSION

This study shows that CSF biomarkers reflective of an increased risk of developing AD predict different longitudinal trajectories of adverse driving behavior. Specifically, those with more abnormal $A\beta_{42}/A\beta_{40}$ ratios that indicate preclinical AD exhibit an increase in driving risk over time, while the opposite pattern is true for those with biomarker ratios in the healthy range. These changes were not explained by other more global differences in driving behavior, nor by differences in cognition, and may be linked specifically with progression from preclinical to symptomatic AD based on links between driving and biomarker status. Further research is needed to fully explore when and why these changes in adverse driving behavior first present, and whether

they become markedly more common as individuals progress toward symptomatic AD. A more thorough understanding of the underlying mechanisms may help early screening efforts and inform clinicians evaluating patients at risk of AD to prolong driving while maintaining independence and autonomy.

AUTHOR CONTRIBUTIONS

Jason M. Doherty and Ganesh M. Babulal devised the study. Jason M. Doherty analyzed the data, drafted the tables, and generated figures. JMD and Ganesh M. Babulal drafted the manuscript. All authors contributed to interpretation of the data and reviewed the manuscript.

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CONFLICTS OF INTEREST

All authors declare no conflicts related to this work. S.E.S.: Analyzed data provided by C2N Diagnostics to Washington University at no cost. She has not received any research funding or personal compensation from C2N Diagnostics or any other for-profit organizations. Author disclosures are available in the supporting information.

REFERENCES

1. Marshall SC. The role of reduced fitness to drive due to medical impairments in explaining crashes involving older drivers. *Traffic Inj Prev*. 2008;9(4):291-298.
2. Charlton JL, Koppel S, O'Hare M, et al. Influence of chronic illness on crash involvement of motor vehicle drivers. *Monash University Accident Research Centre Reports*. 2004;(213):482.
3. Tefft B. Rates of motor vehicle crashes, injuries and deaths in relation to driver age, United States, 2014-2015. *AAA Foundation for Traffic Safety*. 2017.
4. WISQARS: Leading causes of death visualization tool. Center for Disease Control and Prevention (CDC). Accessed June 6, 2022. https://www.cdc.gov/injury/wisqars/
5. Cook LJ, Knight S, Olson LM, Nechodom PJ, Dean JM. Motor vehicle crash characteristics and medical outcomes among older drivers in Utah, 1992-1995. *Ann Emerg Med*. 2000;35(6):585-591.
6. Oskutis MQ, Lauerman MH, Kufera JA, et al. Are frailty markers associated with serious thoracic and spinal injuries among motor vehicle crash occupants? *J Trauma Acute Care Surg*. 2016;81(1):156-161.
7. Fonda SJ, Wallace RB, Herzog AR. Changes in driving patterns and worsening depressive symptoms among older adults. *J Gerontol B Psychol Sci Soc Sci*. 2001;56(6):S343-S351.
8. Edwards JD, Perkins M, Ross LA, Reynolds SL. Driving status and three-year mortality among community-dwelling older adults. *J Gerontol A Biol Sci Med Sci*. 2009;64(2):300-305.
9. Adler G, Rottunda S. Older adults' perspectives on driving cessation. *J Aging Stud*. 2006;20(3):227-235.
10. Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA*. 2015;313(19):1924-1938.
11. Morris JC, Roe CM, Grant EA, et al. Pittsburgh compound B imaging and prediction of progression from cognitive normality to symptomatic Alzheimer disease. *Arch Neurol*. 2009;66(12):1469-1475.
12. Jack Jr. CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010;9(1):119-128.
13. Schnknecht P, Pantel J, Kaiser E, Thomann P, Schrder J. Increased tau protein differentiates mild cognitive impairment from geriatric depression and predicts conversion to dementia. *Neurosci Lett*. 2007;416(1):39-42.
14. Roe CM, Babulal GM, Head DM, et al. Preclinical Alzheimer's disease and longitudinal driving decline. *Alzheimers Dement (N Y)*. 2017;3(1):74-82.
15. Roe CM, Barco PP, Head DM, et al. Amyloid imaging, cerebrospinal fluid biomarkers predict driving performance among cognitively normal individuals. *Alzheimer Dis Assoc Disord*. 2017;31(1):69.
16. Ott BR, Jones RN, Noto RB, et al. Brain amyloid in preclinical Alzheimer's disease is associated with increased driving risk. *Alzheimers Dement (N Y)*. 2017;6:136-142.
17. Klauer SG, Dingus TA, Neale VL, Sudweeks JD, Ramsey DJ. Comparing real-world behaviors of drivers with high versus low rates of crashes and near crashes. *U.S. Department of Transportation: National Highway Traffic Safety Administration DOT-HS-811-091*. 2009. https://trid.trb.org/view/894387
18. Roe CM, Stout SH, Rajasekar G, et al. A 2.5-year longitudinal assessment of naturalistic driving in preclinical Alzheimer's disease. *J Alzheimers Dis*. 2019;68(4):1625-1633.
19. Molnar LJ, Eby DW, Langford J, Charlton JL, Louis RMS, Roberts JS. Tactical, strategic, and life-goal self-regulation of driving by older adults: development and testing of a questionnaire. *J Saf Res*. 2013;46:107-117.
20. Molnar LJ, Eby DW, Charlton JL, et al. Reprint of Driving avoidance by older adults: is it always self-regulation? *Accid Anal Prev*. 2013;61:272-280.
21. Howcroft J, Wallace B, Goubran R, Marshall S, Porter MM, Knoefel F. Trip-based measures of naturalistic driving: considerations and connections with cognitive status in older adult drivers. *IEEE Trans Instrum Meas*. 2019;68(7):2451-2459.
22. Doherty JM, Roe CM, Murphy SA, et al. Adverse driving behaviors are associated with sleep apnea severity and age in cognitively normal older adults at risk for Alzheimer's disease. *Sleep*. 2022;45(6):zsac070.
23. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993;43(11):2412-2414.
24. Aschenbrenner AJ, Gordon BA, Benzinger TLS, Morris JC, Hassenstab JJ. Influence of tau PET, amyloid PET, and hippocampal volume on cognition in Alzheimer disease. *Neurology*. 2018;91(9):e859-e866.
25. Armitage SG. An analysis of certain psychological tests used for the evaluation of brain injury. *Psychol Monogr*. 1946;60(1):1-48.
26. Grober E, Buschke H, Crystal H, Bang S, Dresner R. Screening for dementia by memory testing. *Neurology*. 1988;38(6):900-900.
27. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Arch Clin Neuropsychol*. 1999;14(2):167-177.
28. Babulal GM, Stout SH, Benzinger TLS, et al. A naturalistic study of driving behavior in older adults and preclinical Alzheimer disease: a pilot study. *J Appl Gerontol*. 2019;38(2):277-289.
29. Babulal GM, Addison A, Ghoshal N, et al. Development and interval testing of a naturalistic driving methodology to evaluate driving behavior in clinical research. *F1000Res*. 2016;1:11.
30. Roe CM, Rosnick CB, Colletta A, Babulal GM. Reaction to a pandemic: social distancing and driving among older adults during COVID-19. *J Appl Gerontol*. 2021;40(3):263-267.
31. Bayat S, Babulal GM, Widener M, et al. COVID-19 and Preclinical Alzheimer Disease: driving, mobility, activity and experi-

ences of older adults in the United States. *Alzheimer's & Dementia*. 2021;17(S7):e057692.
32. Fagan AM, Mintun MA, Mach RH, et al. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid $A\beta_{42}$ in humans. *Ann Neurol*. 2006;59(3):512-519.
33. Volluz KE, Schindler SE, Henson RL, et al. Correspondence of CSF biomarkers measured by Lumipulse assays with amyloid PET. *Alzheimer's & Dementia*. 2021;17(S5):e051085.
34. Fischl B, Salat DH, Busa E, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002;33(3):341-355.
35. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis: II: inflation, flattening, and a surface-based coordinate system. *Neuroimage*. 1999;9(2):195-207.
36. Mathalon DH, Sullivan EV, Rawles JM, Pfefferbaum A. Correction for head size in brain-imaging measurements. *Psychiatry Res*. 1993;50(2):121-139.
37. R. Version 4.2.0. R Foundation for Statistical Computing. 2022.
38. MM DouglasBates, Bolker Ben, Walker S. Fitting linear mixed-effects models using *lme4*. *J Stat Softw*. 2015;67(1):1-48. 10.18637/jss.v067.i01
39. ggeffects LüdeckeD. Tidy data frames of marginal effects from regression models. *J Open Source Softw*. 2018;3(26):772. 10.21105/joss.00772
40. Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. Springer-Verlag; 2016.
41. Bayat S, Babulal GM, Schindler SE, et al. Identifying preclinical Alzheimer disease from driving patterns: a machine learning approach. Alzheimer's & Dementia. 2021;17(S5):e057316.
42. Bayat S, Babulal GM, Schindler SE, et al. GPS driving: a digital biomarker for preclinical Alzheimer disease. *Alzheimers Res Ther*. 2021;13(1):1-9.
43. Aschenbrenner AJ, Murphy SA, Doherty JM, et al. Neuropsychological correlates of changes in driving behavior among clinically healthy older adults. *J Gerontol Ser B*. 2022;77(10):1769-1778.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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