Received: 5 April 2022 | Revised: 27 July 2022 | Accepted: 29 August 2022

DOI: 10.1002/dad2.12360

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Trajectory of clinical symptoms in relation to amyloid chronicity

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Funding information
National Institute on Aging, Grant/Award Numbers: NIH R01AG021155, R01AG027161, P30 AG062715, S10 OD025245

Abstract

Introduction: While it is generally appreciated that amyloid precedes symptomatic Alzheimer's disease (AD) by decades, a greater understanding of this timeline may increase prognostic accuracy, planning, and care of persons who are on the AD continuum.

Methods: We examined trajectories of Clinical Dementia Rating–Sum of Boxes (CDR-SB) relative to estimated years of amyloid positivity (A+) in $n = 123$ participants who were all A+ based on [C-11]Pittsburgh compound B positron emission tomography.

Results: The average amyloid chronicity at CDR-SB of 2.5 was 20.1 years. The average trajectory of CDR-SB accelerated after 10 years of elevated amyloid and varied greatly between 10 and 30 years. Exploratory analyses suggested that older age and higher volume of white matter hyperintensities shortened the interval between amyloid onset and cognitive impairment.

Discussion: The recontextualization of amyloid burden into the time domain will facilitate studies of disease progression, the influence of co-pathology, and factors that hasten or slow cognitive impairment.

KEYWORDS
Alzheimer's disease, amyloid imaging, biomarkers, dementia, white matter hyperintensities

1 | INTRODUCTION

The duration of the presymptomatic stage of Alzheimer's disease (AD) has largely been surmised through joining observations from multiple sources rather than person-specific trajectories in amyloidosis and cognitive decline.[1,2] Previous studies have suggested an average duration of 15 to 24 years of amyloid positivity (A+), as detected by amyloid positron emission tomography (PET) imaging, before the onset of AD

dementia syndrome.[1,3–5] Together these studies represent a major advance: they demonstrate the window of presymptomatic amyloidosis is often 20+ years wide, implying a time window for secondary prevention and opportunity for slowing the disease prior to symptoms. Although these prior studies infer an extended duration of amyloid exposure before clinical onset, they do not track individual trajectories of clinical symptoms nor do they address individual variability in clinical onset with respect to amyloid onset.

A major barrier to individual trajectory estimates has been the inability to define *when the disease starts within an individual*. Using a decade of longitudinal Pittsburgh compound B (PiB) positron emission tomography (PET) data from the Wisconsin PiB series and growth curve modeling,[6] we recently demonstrated that person-level estimates of amyloid onset age are possible from a single positive scan. We further showed that longer A+ chronicity was associated with tau PET accumulation and faster cognitive decline on a preclinical AD composite in a sample that was unimpaired at baseline cognitive assessment. Other groups have recently demonstrated the ability to get person-level estimates of amyloid onset or A+ age using different mathematical approaches,[7–11] and in turn, use these estimates to characterize clinical decline or development of other biomarkers. For example, Schindler et al.[10] showed that the onset of clinical symptoms, as measured by the Clinical Dementia Rating (CDR),[12] was highly correlated with the age of amyloid onset.

In this report, we describe variability in the time relationship between years since amyloid onset and the ensuing trajectories of cognitive and functional symptoms as measured by the CDR, or analogous scores from the Quick Dementia Rating System (QDRS), which are widely used, validated informant dementia staging systems. The sample included A+ individuals enrolled in either the Wisconsin Registry for Alzheimer's Prevention (WRAP), the Wisconsin Alzheimer's Disease Research Center (ADRC), or associated studies. In exploratory analyses, we examined factors that may be different between individuals who appear more or less susceptible to cognitive and functional changes for a given level of amyloid.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the body of literature estimating the temporal progression of Alzheimer's disease (AD) pathology and clinical onset using traditional sources (e.g., PubMed). In particular, evidence and updates to the model of AD pathological cascade and several recent publications on the estimation of amyloid onset were reviewed and are appropriately cited.
2. **Interpretation**: Our findings provide an estimation of the individual variability that exists in symptom onset in relation to the duration of amyloid positivity and initial evidence that age and cerebrovascular disease may impact the timing of symptom onset.
3. **Future Directions**: First, the study provides a framework for evaluating the potential role of factors to hasten or slow cognitive impairment. We anticipate future studies will examine whether other factors hasten or slow cognitive impairment in relation to amyloid chronicity. Second, we anticipate that similar analyses will be conducted to validate these results in other cohorts and using other in vivo measures of amyloid, such as other positron emission tomography tracers, cerebrospinal fluid markers, and plasma markers.

2 | METHODS

2.1 | Participants

The sample included 123 participants who were amyloid positive (see the Neuroimaging section for details) from WRAP (n = 67),[13] the Wisconsin ADRC (n = 39), and a linked study (n = 17). Participants from all studies were recruited from memory clinics, community advertisements, and word of mouth. Inclusion criteria included: English fluency; adequate visual and auditory acuity to complete neuropsychological testing; and the absence of major neurological, psychiatric, or health conditions that would interfere with study participation over time. All human subjects provided informed consent and study procedures were approved by the University of Wisconsin–Madison Institutional Review Board and are in concordance with the Declaration of Helsinki.

2.2 | Dementia staging ratings

All three study protocols included administration of either the CDR only (ADRC and linked study; collected from baseline) or either CDR or CDR-harmonized QDRS scores (WRAP; details below). The CDR is completed based on a semi-structured interview with the participant and an informant (family member or friend who knows the participant well) and consisted of impairment ratings (0 = none, 0.5 = questionable, 1 = mild, 2 = moderate, 3 = severe) within six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The QDRS is a 10-item informant questionnaire including ratings for these same domains. For each, the sum of boxes ("SB") was calculated by adding the ratings for each domain represented in the CDR (range possible = 0–18). The four domains in the QDRS that are not represented in the CDR were excluded from the SB calculation. The CDR is a "gold standard" measure in dementia staging[12] and the QDRS has been shown to have excellent concordance with the CDR.[14,15] In the ADRC and linked study, CDR was completed annually or biennially, depending on age and cognitive status of the participant. In WRAP, informant reports were administered at 2-year intervals beginning in 2012 when the CDR was added to the assessment protocol. In 2015, the protocol was modified such that the QDRS was administered as a screener and followed by the CDR when the QDRS global score was > 0 (see Berman et al.[15] for supporting

analyses). CDRs were also administered for a subset of those with QDRS = 0 (approximately 1:1 balance with QDRS > 0). When both CDR and QDRS data were available, CDR scores were used. Of all the dementia staging ratings used from the sample, 24.9% consisted of the QDRS.

2.3 | Neuroimaging

Radioligand synthesis, PET, and magnetic resonance imaging (MRI) acquisition, processing, and analysis methods have been described elsewhere.[16] All participants underwent 3D T1-weighted and 3D fluid attenuated inversion recovery (FLAIR) MRI, and [11C]PiB ([11C]6-OH-BTA-1) PET. Amyloid positivity was defined as the average cortical PiB distribution volume ratio (DVR) > 1.19 using a global composite region of interest comprising bilateral anterior and posterior cingulate cortex, the precuneus, the angular gyrus, supramarginal gyrus, middle and superior temporal gyrus, and medial orbital gyrus. The DVR A+ cut-point was derived with reference to a visual rating[16] and corresponds to 22 centiloids.[7]

For secondary analysis, tau PET imaging and analysis of white matter hyperintensity (WMH) volumes were available for a subset of participants. Tau PET data were obtained with [F-18]MK-6240 (also known as florquinitau) and available for 97 participants.[17] Tau positivity was determined by a rater (SCJ) blind to amyloid features. The rating was comprised of six general regions corresponding to (1) the entorhinal area, (2) amygdala and hippocampus, (3) fusiform, (4) ventral and lateral temporal lobe and cingulate, (5) fronto-parietal association cortex, and (6) primary cortex of the temporal or occipital lobe. These regions corresponded broadly to those used for neuropathological staging of neurofibrillary tangles described by Braak and Braak.[18]

WMH volumes were available for 100 (81.3%) of the participants. WMH lesion volume was measured using the lesion prediction algorithm from the Lesion Segmentation Tool.[19] Briefly, the method used a FLAIR scan (with co-registration and resampling to the resolution of a T1-weighted reference image) to estimate the lesion probability at each voxel, outputting a lesion probability map. In the quantification step, the lesion volume was summed for voxels where the probability was ≥0.5. The output underwent visual quality assessment by trained reviewers including a neuroradiologist (LBE).

2.4 | Amyloid chronicity

Amyloid chronicity was calculated using a previously published method.[6] Briefly, group-based trajectory modeling (GBTM) was used to identify functions that characterized four age-related accumulation patterns and to classify individuals with longitudinal PiB PET data into one of these trajectory groups. GBTM is a finite mixture modeling approach that has been widely used in clinical research to identify latent classes.[20] Bayes' theorem was then used to determine the probability of group membership of each group based on the most recent PiB PET scan. For each participant, individualized amyloid onset age was calculated as the sum of the probability weighted averages of estimated amyloid onset age for each of the four trajectory groups. Last, amyloid chronicity was calculated as the age at CDR assessment minus estimated amyloid onset age.[6] GBTM-based chronicity estimates were replicated recently using two additional methods.[7]

2.5 | Statistical methods

Statistical analyses were conducted in R, SPSS (v26), and SAS (v9.4). Descriptive statistics are reported as mean (standard deviation [SD]) for normally distributed continuous variables, median (quartile 1 [Q1[–quartile 3 [Q3]) for non-normally distributed continuous variables, and *n* (%) for categorical or ordinal variables. For the primary analysis examining whether amyloid chronicity predicted longitudinal CDR-SB scores, a mixed effects model was used to evaluate the association between chronicity and CDR-SB (covariates sex and baseline CDR age; random slope and intercept). To investigate and characterize potential non-linearity in chronicity's association with CDR-SB, the model included a chronicity-by-baseline chronicity category (< 0, 0–5, 5–10, 10–15, 15–20, and > 20 years) interaction term (< 0 = reference range). After a significant interaction (i.e., $\alpha = 0.05$), simple slopes were compared between the reference group (baseline chronicity < 0) and each other group.

2.6 | Secondary/exploratory analyses

Visual inspection of spaghetti plots with overlaid locally estimated scatterplot smoothing (LOESS) regression line (Figure 1) showed subgroups of people whose CDR-SB scores worsened earlier and reached incident dementia earlier (i.e., with less amyloid chronicity) relative to others. Therefore, in exploratory analyses, we sought to categorize and investigate characteristics of early versus later incident dementia subgroups as follows. Because CDR-SB of 2.5 has been validated as a threshold of very mild dementia,[21] we used 2.5 as the

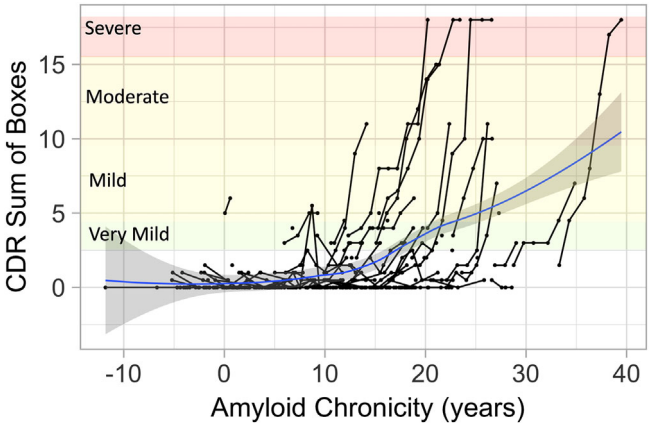

FIGURE 1 Spaghetti plots display individual trajectories of Clinical Dementia Rating (CDR) Sum of Boxes in relation to amyloid chronicity years. The blue trend line uses a locally estimated scatterplot smoothing function with the standard error shaded in gray. The colored shading displays the range of clinical severity guidelines

indicator of incident clinical dementia. We estimated amyloid chronicity at first impairment (average amyloid chronicity of 20.1 years at CDR-SB = 2.5) in a subset of participants ($n = 16$) who either reached a CDR-SB of 2.5 ($n = 7$) or linear interpolation was used for participants who surpassed a CDR-SB 2.5 between visits ($n = 9$). For participants who had always had CDR-SB scores > 2.5 ($n = 18$), we estimated chronicity at first CDR-SB = 2.5 using regression based on the average trajectories observed within different levels of clinical severity. We then categorized impaired participants ($n = 34$) into either "more susceptible" ($n = 23$) or "less susceptible" ($n = 11$), depending on whether their observed or estimated chronicity at CDR-SB = 2.5 was less than or greater than the average chronicity at CDR-SB = 2.5. In addition, participants with an amyloid chronicity greater than 20.1 years who remained unimpaired at their last CDR were included in the less susceptible group ($n = 10$). Based on regression estimates indicating it would take 2.9 years on average to progress from 0.5 to 2.5 CDR-SB (slope of 0.69 CDR-SB/year), the less susceptible group also included unimpaired participants (CDR-SB < 2.5) with an amyloid chronicity of 17.2 or higher and therefore unlikely to become impaired before 20.1 years of chronicity ($n = 12$). In summation, the less susceptible group included 33 participants: 11 who became impaired after 20.1 years of amyloid chronicity, 10 who remained unimpaired after 20.1 years of amyloid chronicity, and 12 who were unimpaired with a chronicity between 17.2 and 21.1 and unlikely to become impaired before 20.1 years of amyloid. Individuals who were unimpaired at last CDR with last amyloid chronicity < 17.2 years were excluded from the exploratory analysis as it is unknown if they will decline before or after 20.1 years of amyloid chronicity ($n = 67$). For those who never reached a CDR-SB = 2.5, last age and chronicity were saved for descriptive statistics. To compare the more and less susceptible groups, we used one-way analysis of variance for normally distributed variables and Mann–Whitney *U* tests for variables with non-normal distributions. Chi-square tests were used for nominal variables.

TABLE 1 Participant demographics ($N = 123$)

	Mean	Std. dev	Range
Age at first CDR	68.94	6.44	49.9–84.6
Age at first PiB	69.78	6.96	46.9–84.65
Amyloid chronicity at first CDR	9.58	9.11	−11.82–33.30
	Median	**IQR**	**Range**
Estimated age of PiB positivity	61.6	17.9	50.6–84.6
Years of follow-up	2.78	5.12	0–13.2
Years of education	17	3	9–22
Number of CDR assessments	3	9	1–10
CDR-SB at baseline	0.5	1.5	0–5
	n	**%**	
Female	74	60.2%	
Race			
White	117	95.1%	
Black	4	3.3%	
American Indian	2	1.6%	
APOE genotype			
ε2/ε3	2	1.6%	
ε2/ε4	3	2.4%	
ε3/ε3	30	24.4%	
ε3/ε4	47	38.2%	
ε4/ε4	18	14.6%	
Missing	23	18.7%	
Baseline CDR global			
0	67	54.5%	
0.5	52	42.3%	
1	4	3.3%	

Abbreviations: *APOE*, apolipoprotein E; CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating-Sum of Boxes; PiB, Pittsburgh compound B.

3 | RESULTS

3.1 | Demographics/sample characteristics

Details on participant characteristics are presented in Table 1. Briefly, the predominantly non-Hispanic White sample included more women than men, had average ages of first CDR and PiB scans in the late 60s, and showed a 30-year range of amyloid chronicity at first CDR and a range of ≈50 to 85 for ages of amyloid onset. More than half of the sample carried at least one apolipoprotein E (*APOE*) ε4 risk allele and had an unimpaired CDR at baseline. Most participants had three or more CDR measurements, while 28 (22.8%) had only one CDR measurement.

3.2 | Primary analysis

A spaghetti plot of individual trajectories of CDR-SB in relation to amyloid chronicity is displayed in Figure 1. The LOESS curve in the figure indicates that the threshold of very mild impairment is reached around an amyloid chronicity of 17 years when all subjects are included in the curve calculation. The LOESS curve also indicates that CDR-SB of 4.5, which is comparable to a global CDR of 1, which is reached around 21 years of A+. When limited to only those subjects who reached CDR-SB of 2.5 during the course of follow-up ($n = 16$), the average chronicity of amyloid at the time this CDR-SB threshold was reached was 20.1 years.

We next examined CDR-SB and rate of change as a function of amyloid duration groupings. A mixed effects model indicated that on average, the trajectory of CDR-SB begins to accelerate after 10 years of amyloid. Specifically, among those with negative amyloid chronicity at baseline, annual change in CDR-SB did not differ from zero (chronicity beta and 95% confidence interval [CI] = −0.02 [−0.17, 0.13]). Compared to this reference group, the A+ 10- to 15-years group, 15- to 20-years group, and the > 20 years group had a significantly greater

TABLE 2 Mixed-effects model with random intercept and random slope predicting CDR-SB

Predictor	B Estimate	Std. Error	Confidence interval[a] 2.5%	97.5%
(Intercept)	1.48	2.64	−4.18	6.84
Amyloid chronicity	−0.02	0.08	−0.17	0.13
Age at baseline CDR-SB	−0.03	0.04	−0.11	0.05
Male sex	0.79	0.48	−0.17	1.83
Baseline chronicity groups				
0–5 years group	0.72	0.88	−0.99	2.51
5–10 years group	0.45	1.17	−1.71	2.71
10–15 years group	−3.32	1.34	−5.86	−0.66
15–20 years group	−24.31	2.12	−28.38	−20.13
>20 years group	−18.43	2.84	−24.04	−12.92
Chronicity by baseline chronicity groups (interaction)				
0–5 years group	0.00	0.12	−0.23	0.25
5–10 years group	0.09	0.12	−0.13	0.32
10–15 years group	0.37	0.11	0.16	0.59
15–20 years group	1.49	0.13	1.24	1.76
>20 years group	0.88	0.13	0.63	1.16

[a]Statistical significance was determined by estimating the 95% confidence intervals with bootstrapping ($k = 1000$).
Abbreviation: CDR-SB, Clinical Dementia Rating-Sum of Boxes.

slope of CDR-SB, interaction beta and 95% CI = 0.37 (0.16, 0.59), 1.49 (1.24, 1.76), 0.88 (0.63, 1.16), respectively (Table 2).

3.3 | Secondary/exploratory analysis

Figure 1 also reveals variability around the mean LOESS fit line such that some individuals reach impairment with a short A+ duration, and others a much longer duration relative to the mean fit. Some do not reach impairment despite a seemingly sufficient amount of time for impairment to declare itself, while still others have not been followed for a sufficient duration of time. To examine this heterogeneity further, as described in the Methods section, we created two groups that represented participants who were more or less susceptible to clinical decline relative to their estimated amyloid chronicity. Participants who were unimpaired and have yet to be followed long enough to determine whether they will remain unimpaired after 20.1 years of amyloid chronicity were excluded from the comparisons ($n = 67$). The more susceptible group had a higher CDR-SB and global CDR at baseline (Table 3). Groups did not differ on age at first PiB PET scan. However, the more susceptible group had a shorter amyloid chronicity at their first CDR measurement (Mean = 12.59 years) compared to the less susceptible group (Mean = 19.97 years). The more susceptible group had an older estimated age of amyloid onset (Mdn = 61.4 years) compared to the less susceptible group (Mdn = 50.6 years). *APOE* ε4 carriage did not significantly differ between groups.

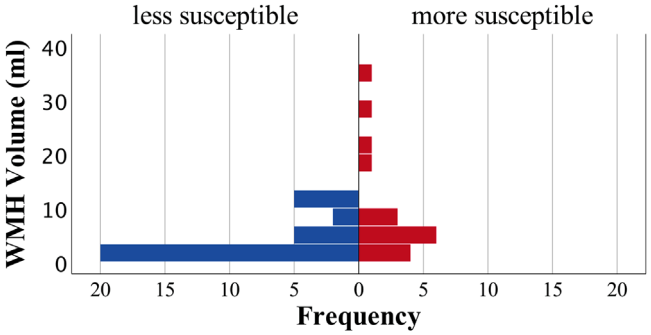

FIGURE 2 Split histograms display the distribution of white matter hyperintensity (WMH) volumes (mL) among those who are less susceptible to amyloid chronicity (blue) and those who are more susceptible to amyloid chronicity (red)

There was no difference in years of education between the susceptibility groups. In the subset with available WMH volume measurements, the more susceptible group had significantly greater WMH volumes (Mdn = 5.14 mL; n = 17) than the less susceptible group (Mdn = 1.5 mL; $n = 32$; Figure 2).

Tau PET imaging was available for 13 participants in the more susceptible group and 23 participants in the less susceptible group. Overall, both susceptibility groups appeared to have similar distributions of tau (Table 4). The vast majority of participants in both groups were tau positive in the entorhinal cortex, with progressively lower percentages of tau positivity in the cortical regions examined. Slightly less than half of participants in both groups were tau positive in the primary temporal or occipital cortex. In contrast, tau was less extensive in the excluded group, with 47.5% rated as not having any detectable tau, possibly reflecting the shorter amyloid chronicity at the time of the tau PET scan ($M = 8.38$ years) compared to the more susceptible group ($M = 12.77$ years) and less susceptible group ($M = 22.26$ years).

4 | DISCUSSION

Expanding the application of amyloid biomarkers in the preclinical stage of AD, before cognitive and functional symptoms, could potentially offer an opportune window of time for implementing prevention strategies and prognostic information to inform treatment and life planning decisions. The primary aim of the current study was to determine the duration between the onset of amyloid positivity and the onset of clinical symptoms as indicated by CDR-SB scores. Consistent with previous studies, the current results suggested that after becoming amyloid positive on PiB PET, the slope of cognitive decline—on average—begins to worsen after 10 years and clinical impairment is reached after 20 years.[1,3–5,10] By modeling individual trajectories, this study illustrates the wide range of decline onset relative to amyloid duration and identifies potential contributors to this variability.

TABLE 3 Characteristics of secondary groups

	More susceptible			Less susceptible					Excluded		
	n	Mean	Std. dev	*n*	Mean	Std. dev	*t*	*P*	*n*	Mean	Std. dev
Age at first CDR	23	70.48	6.29	33	72.24	5.71	−1.09	0.28	67	66.79	6.06
Age at first PiB	23	71.50	6.42	33	72.65	6.67	−0.64	0.52	67	67.78	6.71
Age at tau PET	13	73.47	5.91	23	73.93	4.40	−0.27	0.79	61	71.44	5.38
Amyloid chronicity at tau PET	13	12.77	5.53	23	22.26	3.36	−6.43	<0.01	61	8.38	5.69
Amyloid chronicity at first CDR	23	12.59	4.52	33	19.97	5.54	−5.27	<0.01	67	3.44	6.01
	n	Median	IQR	*n*	Median	IQR	*U*	*P*	*n*	Median	IQR
Estimated age of A+ onset	23	61.38	11.00	33	50.6	0.31	254.0	0.03	67	61.65	9.97
Years of follow-up	23	2.48	5.43	33	2.45	5.11	379	0.99	67	4.41	3.49
Years of education	23	17.00	4	33	17.00	4	370.5	0.88	67	16.00	2
Number of CDR assessments	23	2	3	33	3	4	364.5	0.80	67	3	1
CDR-SB at baseline	23	3	2.0	33	0.5	1.75	126.5	<0.01	67	0	.50
WMH volume (mL)	17	5.14	11.63	32	1.5	5.67	153	0.01	54	0.84	1.62
		n	%		*n*	%	X^2	*P*		*n*	%
Female		12	52.2		22	66.7	1.19	0.28		40	59.7
APOE genotype							0.38	0.95			
ε2/ε3		1	6.3		1	4.3				3	4.9
ε2/ε34		0	0		0	0				0	0
ε3/ε3		3	18.8		6	26.1				21	34.4
ε3/ε4		7	43.8		10	43.5				30	49.2
ε4/ε4		5	31.3		6	26.1				7	11.5
Missing		7			10						
Baseline CDR global							15.68	<0.01			
0		1	4.3		18	54.5				48	71.6
0.5		19	82.6		14	42.4				19	28.4
1		3	13.0		1	3.0					

Note: To compare the more and less susceptible groups, one-way analysis of variance, Mann–Whitney *U* tests and chi-square tests were used.
Abbreviations: CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating–Sum of Boxes; IQR, interquartile range; PET, positron emission tomography; PiB, Pittsburgh compound B; WMH, white matter hyperintensity.

TABLE 4 Regional tau positivity by visual assessment

	More susceptible (*n* = 13)	Less susceptible (*n* = 23)	Excluded (*n* = 61)
None	1 (7.7%)	1 (4.3%)	29 (47.5%)
Entorhinal	12 (92.3%)	22 (95.7%)	32 (52.5%)
Amygdala, hippocampus	10 (76.9%)	20 (87.0%)	21 (34.4%)
Fusiform	10 (76.9%)	19 (82.6%)	19 (31.1%)
Ventral & lateral temporal, cingulate	8 (61.5%)	18 (78.3%)	21 (34.4%)
Fronto-parietal association cortex	8 (61.5%)	16 (70.0%)	14 (23.0%)
Primary temporal or occipital cortex	6 (46.2%)	11 (47.8%)	3 (4.9%)

Note: Regional MK-6240 tau PET positivity was determined visually by a rater (SCJ) blind to amyloid features. Tau PET scans were available for 13/23 participants in the more susceptible group, 23/33 in the less susceptible group, and 61/67 in the excluded group.
Abbreviation: PET, positron emission tomography.

Exploratory analyses aimed to identify factors that may make individuals susceptible to cognitive decline in the presence of amyloid. These results provide preliminary evidence that in the context of accumulating amyloid, greater WMH volume, suggestive of vascular copathology, was associated with faster decline. This finding has support from the neuropathology literature.[22] Furthermore, in agreement with recent studies, we found that passing the threshold of amyloid positivity at an older age was associated with a shorter period before the emergence of cognitive symtpoms.[7,10] PET tau sample sizes for susceptibility groups were insufficient to detect differences in tau positivity between groups. However, the low amount of tau distribution in the excluded group (mean amyloid chronicity = 8.34 years) relative to the more susceptible group (mean amyloid chronicity = 12.77 years) suggests that more years of amyloid chronicity and more tau are associated with greater cognitive decline. Therneau et al.[11] reported an average of 13.3 years between amyloid positivity and tau positivity and it may be meaningful that the less susceptible group had similar rates of tau distribution compared to the more susceptible group despite having a longer period of amyloid chronicity (mean amyloid chronicity = 22.26 years). The results of these secondary analyses suggest hypotheses to be examined in future research with larger sample sizes and longer CDR follow-up duration. These results also provide a framework for future research in larger samples to investigate the role of additional lifestyle factors that have been implicated in the onset of AD.[23]

To understand the preclinical course of AD, it is critical to know when the disease begins on a person level. Amyloid proteinopathy may develop sporadically at any age in older life.[7] Modeling clinical symptoms in relation to when amyloid began on a person level provides a better understanding of the variability in the preclinical disease course, which is critical to providing clinical prognosis. For instance, one participant presented with clinical decline at baseline and was determined to be amyloid positive, suggesting a diagnosis of AD. However, with temporal modeling, it was estimated that the participant had only recently become amyloid positive, indicating amyloid was not the plausible cause of impairment. Clinical follow-ups revealed progressive infarcts, suggesting that cerebrovascular disease was likely the primary factor driving impairment. Determining the relative contribution of various factors that influence cognitive decline is often clinically challenging and knowing amyloid chronicity—and not only the binary amyloid status—may better inform clinical diagnosis and management.

In addition, temporal biomarker methodology such as shown here will be key to understanding the impact of the many putative health behaviors or resilience characteristics that have been proposed[24] to speed or slow the onset of cognitive symptoms due to AD and other causes of dementia. Indeed, results of the current study revealed a large amount of variation in symptom onset relative to amyloid chronicity. Secondary analyses provided evidence that amyloid onset at an older age was associated with a shorter duration of amyloid before the onset of clinical symptoms. Health comorbidities are common in older age and are associated with neurodegeneration that may increase susceptibility to cognitive decline.[25] The secondary analyses presented preliminary evidence that WMH, reflecting co-occurring vascular disease, may confer additional susceptibility to early decline in the context of accumulating amyloid. In typical aging, WMH are considered markers of cerebrovascular disease, yet there is some controversy in the literature regarding the role of WMH in AD. Some studies have found that WMH may be due to vascular disease independent of amyloid pathology[26,27] while others have suggested that WMH may be a core feature of the disease.[28–32] A recent very large community-based *post mortem* study demonstrated strong associations between WMH and vascular pathology, but associations with amyloid pathology were driven by clinical stage such that WMH were more common in people with dementia. There were no associations with neurofibrillary tangles.[33]

In conclusion, these results suggest that examining cognitive decline in the context of amyloid chronicity is a useful framework for understanding contributors to cognitive decline. Currently, determining amyloid status through one of the several amyloid radioligands is considered appropriate only in those who are cognitively impaired, and the information obtained from amyloid PET has demonstrated value improving diagnostic accuracy and clinical management.[34–37] However, in cognitively healthy individuals, amyloid PET is not recommended because evidence for predictive utility or time to any specific clinical outcome is lacking. Many cognitively healthy adults have amyloid and it is unknown when—or if—they may experience clinical decline.[1] We demonstrated that estimating amyloid duration can provide valuable information regarding prognosis. The clinical outlook of an unimpaired adult with an amyloid chronicity of less than 10 years is likely different than someone with an amyloid chronicity of >20 years. Our analysis of contributing factors (albeit incomplete), provided preliminary evidence that older age at A+ onset, presence of WMH and tau, in addition to duration of amyloid itself are all associated with the time to onset of clinical symptoms. Future work will need to incorporate additional risk and disease factors beyond the few that were explored here. The integration of several biomarkers of AD and other proteinopathies, together with temporal modeling, will likely be needed to accurately predict symptoms onset at the individual level.

The current study has several limitations. We defined impairment using the CDR but this may be too coarse of an instrument to identify more subtle symptoms. Future work should examine cognitive change in specific cognitive domains such as episodic memory and executive function. The time period of amyloid chronicity before clinical symptoms is dependent on biomarker sensitivity. Observations reported here with PiB need to be replicated with other amyloid PET tracers and fluid biomarkers. We used the GBTM method, which is not commonly used in biomarker research, for estimating amyloid onset age and duration; our findings should be replicated with other scalable modeling methods. Because onset of amyloid was retrospectively estimated, we did not follow all participants from an amyloid onset baseline. Further, we excluded a portion of the sample from secondary analyses who remained cognitively unimpaired and it is unknown when they may become impaired. Additional follow-up is necessary and ongoing to understand the course of imaging biomarkers and the several factors that hasten or slow cognitive decline relative to amyloid duration. In addition, these results, which were obtained on a convenience

sample, may differ in other populations and cohorts. The limited ethnocultural diversity in the sample limits the generalizability of the findings and efforts are under way to increase representation in biomarker research. Last, we did not use multiple comparisons correction and the sample sizes were small for some of the secondary analyses, which limited power to detect differences. The hypotheses generated from these results need to be assessed in larger samples before informing clinical practice.

ACKNOWLEDGMENTS

The authors would like to thank participants and study personnel who made this work possible. Funding for this research was provided by the National Institute on Aging (NIH R01AG021155, R01AG027161, P30 AG062715, S10 OD025245) and Alzheimer's Association AARF-19-614533. Funding sources had no role in the design or conduct of the study or the content of this manuscript.

CONFLICTS OF INTEREST

Sterling C. Johnson has served on advisory boards for Roche Diagnostics and Eisai. Robert J. Przybelski has served on a speaking panel for Biogen. The remaining authors have no relevant disclosures. Author disclosures are available in the supporting information.

REFERENCES

1. 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. doi:10.1001/jama.2015.4668
2. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):280-292. doi:10.1016/j.jalz.2011.03.003
3. Jack CR Jr, Lowe VJ, Weigand SD, et al. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. *Brain*. 2009;132(Pt 5):1355-1365. doi:10.1093/brain/awp062
4. Jagust WJ, Landau SM. Alzheimer's Disease Neuroimaging I. Temporal dynamics of beta-amyloid accumulation in aging and Alzheimer disease. *Neurology*. 2021;96(9):e1347-e1357. doi:10.1212/WNL.0000000000011524
5. Villemagne VL, Burnham S, Bourgeat P, et al. Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurol*. 2013;12(4):357-367. doi:10.1016/S1474-4422(13)70044-9
6. Koscik RL, Betthauser TJ, Jonaitis EM, et al. Amyloid duration is associated with preclinical cognitive decline and tau PET. *Alzheimers Dement (Amst)*. 2020;12(1):e12007. doi:10.1002/dad2.12007
7. Betthauser TJ, Bilgel M, Koscik RL, et al. Multi-method investigation of factors influencing amyloid onset and impairment in three cohorts. *Brain*. 2022. doi:10.1093/brain/awac213
8. Bilgel M, An Y, Zhou Y, et al. Individual estimates of age at detectable amyloid onset for risk factor assessment. *Alzheimers Dement*. 2016;12(4):373-379. doi:10.1016/j.jalz.2015.08.166
9. Insel PS, Donohue MC, Berron D, Hansson O, Mattsson-Carlgren N. Time between milestone events in the Alzheimer's disease amyloid cascade. *Neuroimage*. 2021;227:117676. doi:10.1016/j.neuroimage.2020.117676
10. Schindler SE, Li Y, Buckles VD, et al. Predicting symptom onset in sporadic Alzheimer disease with amyloid PET. *Neurology*. 2021;97(18):e1823-e1834. doi:10.1212/WNL.0000000000012775
11. Therneau TM, Knopman DS, Lowe VJ, et al. Relationships between beta-amyloid and tau in an elderly population: an accelerated failure time model. *Neuroimage*. 2021;242:118440. doi:10.1016/j.neuroimage.2021.118440
12. Morris JC, Ernesto C, Schafer K, et al. Clinical dementia rating training and reliability in multicenter studies: the Alzheimer's Disease Cooperative Study experience. *Neurology*. 1997;48(6):1508-1510. doi:10.1212/wnl.48.6.1508
13. Johnson SC, Koscik RL, Jonaitis EM, et al. The Wisconsin Registry for Alzheimer's Prevention: a review of findings and current directions. *Alzheimers Dement (Amst)*. 2018;10:130-142. doi:10.1016/j.dadm.2017.11.007
14. Galvin JE. The Quick Dementia Rating System (Qdrs): a rapid dementia staging tool. *Alzheimers Dement (Amst)*. 2015;1(2):249-259. doi:10.1016/j.dadm.2015.03.003
15. Berman SE, Koscik RL, Clark LR, et al. Use of the Quick Dementia Rating System (QDRS) as an initial screening measure in a longitudinal cohort at risk for Alzheimer's disease. *J Alzheimers Dis Rep*. 2017;1(1):9-13. doi:10.3233/ADR-170004
16. Johnson SC, Christian BT, Okonkwo OC, et al. Amyloid burden and neural function in people at risk for Alzheimer's Disease. *Neurobiol Aging*. 2014;35(3):576-584. doi:10.1016/j.neurobiolaging.2013.09.028
17. Betthauser TJ, Cody KA, Zammit MD, et al. In vivo characterization and quantification of neurofibrillary tau PET radioligand (18)F-MK-6240 in humans from Alzheimer disease dementia to young controls. *J Nucl Med*. 2019;60(1):93-99. doi:10.2967/jnumed.118.209650
18. Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathol*. 2006;112(4):389-404. doi:10.1007/s00401-006-0127-z
19. Schmidt P, Gaser C, Arsic M, et al. An automated tool for detection of FLAIR-hyperintense white-matter lesions in Multiple Sclerosis. Research Support, Non-U.S. Gov't. *NeuroImage*. 2012;59(4):3774-3783. doi:10.1016/j.neuroimage.2011.11.032
20. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol*. 2010;6:109-138. doi:10.1146/annurev.clinpsy.121208.131413
21. O'Bryant SE, Lacritz LH, Hall J, et al. Validation of the new interpretive guidelines for the clinical dementia rating scale sum of boxes score in the national Alzheimer's coordinating center database. *Arch Neurol*. 2010;67(6):746-749. doi:10.1001/archneurol.2010.115
22. Frank B, Ally M, Tripodis Y, et al. Trajectories of cognitive decline in brain donors with autopsy-confirmed Alzheimer disease and cerebrovascular disease. *Neurology*. 2022;98(24):e2454-e2464. doi:10.1212/WNL.0000000000200304
23. Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. *Nat Rev Neurol*. 2018;14(11):653-666. doi:10.1038/s41582-018-0070-3
24. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413-446. doi:10.1016/S0140-6736(20)30367-6
25. Vassilaki M, Aakre JA, Kremers WK, et al. The association of multimorbidity with preclinical AD Stages and SNAP in cognitively unimpaired persons. *J Gerontol A Biol Sci Med Sci*. 2019;74(6):877-883. doi:10.1093/gerona/gly149
26. Vemuri P, Lesnick TG, Przybelski SA, et al. Vascular and amyloid pathologies are independent predictors of cognitive decline in normal elderly. *Brain*. 2015;138(Pt 3):761-771. doi:10.1093/brain/awu393
27. Bilgel M, Bannerjee A, Shafer A, An Y, Resnick SM, Vascular risk is not associated with PET measures of Alzheimer's disease neuropathology among cognitively normal older adults. *Neuroimage Rep*. 2021;1(4):100068. doi:10.1016/j.ynirp.2021.100068

28. Brickman AM, Zahodne LB, Guzman VA, et al. Reconsidering harbingers of dementia: progression of parietal lobe white matter hyperintensities predicts Alzheimer's disease incidence. *Neurobiol Aging*. 2015;36(1):27-32. doi:10.1016/j.neurobiolaging.2014.07.019
29. Lee S, Viqar F, Zimmerman ME, et al. White matter hyperintensities are a core feature of Alzheimer's disease: evidence from the dominantly inherited Alzheimer network. *Ann Neurol*. 2016;79(6):929-939. doi:10.1002/ana.24647
30. Alosco ML, Sugarman MA, Besser LM, et al. A clinicopathological investigation of white matter hyperintensities and Alzheimer's disease neuropathology. *J Alzheimers Dis*. 2018;63(4):1347-1360. doi:10.3233/JAD-180017
31. Grimmer T, Faust M, Auer F, et al. White matter hyperintensities predict amyloid increase in Alzheimer's disease. *Neurobiol Aging*. 2012;33(12):2766-2773. doi:10.1016/j.neurobiolaging.2012.01.016
32. Walsh P, Sudre CH, Fiford CM, et al. CSF amyloid is a consistent predictor of white matter hyperintensities across the disease course from aging to Alzheimer's disease. *Neurobiol Aging*. 2020;91:5-14. doi:10.1016/j.neurobiolaging.2020.03.008
33. Arfanakis K, Evia AM, Leurgans SE, et al. Neuropathologic correlates of white matter hyperintensities in a community-based cohort of older adults. *J Alzheimers Dis*. 2020;73(1):333-345. doi:10.3233/JAD-190687
34. Boccardi M, Altomare D, Ferrari C, et al. Assessment of the incremental diagnostic value of florbetapir F 18 imaging in patients with cognitive impairment: the incremental diagnostic value of amyloid PET with [18F]-Florbetapir (INDIA-FBP) study. *JAMA Neurol*. 2016;73(12):1417-1424. doi:10.1001/jamaneurol.2016.3751
35. Johnson KA, Minoshima S, Bohnen NI, et al. Appropriate use criteria for amyloid PET: a report of the amyloid imaging task force, the society of nuclear medicine and molecular imaging, and the Alzheimer's association. *J Nucl Med*. 2013;54(3):476-490. doi:10.2967/jnumed.113.120618
36. Rabinovici GD, Gatsonis C, Apgar C, et al. Association of amyloid positron emission tomography with subsequent change in clinical management among medicare beneficiaries with mild cognitive impairment or dementia. *JAMA*. 2019;321(13):1286-1294. doi:10.1001/jama.2019.2000
37. Apostolova LG, Haider JM, Goukasian N, et al. Critical review of the appropriate use criteria for amyloid imaging: effect on diagnosis and patient care. *Alzheimers Dement (Amst)*. 2016;5:15-22. doi:10.1016/j.dadm.2016.12.001

SUPPORTING INFORMATION

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

How to cite this article: Birdsill AC, Koscik RL, Cody KA, et al. Trajectory of clinical symptoms in relation to amyloid chronicity. *Alzheimer's Dement*. 2022;14:e12360. https://doi.org/10.1002/dad2.12360