

RESEARCH ARTICLE

Latent change-on-change between amyloid accumulation and cognitive decline

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Abstract

INTRODUCTION: While the influence of cross-sectional β -amyloid ($A\beta$) on longitudinal changes in cognition is well established, longitudinal change-on-change between $A\beta$ and cognition is less explored.

METHODS: A series of bivariate latent change score models (LCSM) examined the relationship between changes in ¹¹C-Pittsburgh Compound-B (PiB) positron emission tomography (PET) and the Preclinical Alzheimer's Cognitive Composite-5 (PACC-5) while adjusting for covariates, including cross-sectional medial temporal lobe (MTL) tau-PET burden. We selected 352 clinically normal older participants with up to 9 years of PiB-PET and PACC-5 data from the Harvard Aging Brain Study (HABS).

RESULTS: $A\beta$ accumulation was associated with subsequent cognitive decline beyond the effects of cross-sectional $A\beta$ burden. Within this model including covariates such as age, sex, and apolipoprotein ϵ 4 (APOE ϵ 4) status, we found no evidence supporting previously published associations between cross-sectional tau-PET and cognitive intercept/slope.

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DISCUSSION: Short-term $A\beta$ changes are significantly associated with cognitive decline in clinically normal older adults and may eclipse the effect of cross-sectional $A\beta$ and MTL tau.

KEYWORDS

Alzheimer's disease, amyloid accumulation, change-on-change, cognitive decline, latent change score models, structural equation models

Highlights

- $A\beta$ accumulation is associated with subsequent cognitive decline.
- High $A\beta$ burden is not the sole metric signaling impending cognitive decline.
- Contrary to prior work, MTL tau-PET and cognition were not associated in our models.
- Models of bivariate latent $A\beta$ and cognitive change may eclipse the effects of MTL tau.

1 | BACKGROUND

A critical question for understanding the natural history of preclinical Alzheimer's disease (AD) is the relationship between changes in pathology and changes in cognitive manifestations of the disease. Elevated levels of β -amyloid ($A\beta$) plaques are one of the earliest pathological markers of subsequent cognitive symptoms of the disease.¹ While the influence of cross-sectional $A\beta$ on longitudinal changes in cognition is well established,^{2–4} the effect of longitudinal changes in $A\beta$ pathology on longitudinal changes in cognition is less explored.

Existing studies that examine clinicopathological change-on-change associations suggest an association between longitudinal $A\beta$ accumulation and cognitive decline.^{5–9} Many of these studies, however, have limiting factors. Sample sizes and the length of longitudinal $A\beta$ and cognitive follow-up are relatively small. Statistical approaches used to analyze change-on-change are often limited to the correlation of extracted slopes or employing linear models including a raw $A\beta$ change score calculated from the difference between two timepoints. These methods can obscure measurement and model error and induce artefactual associations between variables.¹⁰ Further, these approaches to modeling change-on-change restrict the capabilities of addressing more complex questions, such as the direction and magnitude of the effect during the study, as well as the appropriate adjustment of covariates on both variables in the change-on-change model, because they are purely correlational. Advanced statistical methods, such as latent change score models (LCSM),¹¹ can simultaneously examine individual changes in $A\beta$ and cognition as well as their relationship to each other and in combination with covariates. LCSM has been applied in previous studies to examine changes between brain structure and memory changes,^{12,13} vocabulary knowledge and reading comprehension,¹⁴ and depressive symptoms and memory.¹⁵ An additional advantage of

these models is their ability to explore serial directionality to help us understand the extent to which dynamic $A\beta$ accumulation, rather than a lifetime-accumulated presence of $A\beta$ burden, is driving cognitive change.

Our objective was to employ an extension of LCSM,¹² a class of structural equation models, to examine the bidirectional relationship between changing $A\beta$ and cognition while also adjusting for covariates. The bidirectionality of these models allowed us to infer the sequence of effects and examine changes in $A\beta$ on subsequent changes in cognition and vice versa.¹² We hypothesize that $A\beta$ accumulation will have a significant influence on subsequent cognitive decline, even after adjusting for important covariate effects that influence change in both variables, such as age, sex, years of education, apolipoprotein $\epsilon 4$ (APOE $\epsilon 4$) status, glucose metabolism, and medial temporal lobe (MTL) tau burden, but there will be no evidence of cognitive decline impacting subsequent $A\beta$ changes. Given that we presume pathology should have an acting effect on cognition, any evidence of the alternative pattern of effects might indicate a lack of temporality to the AD clinicopathological trajectory in our data.

2 | METHODS

2.1 | Participants

Data were obtained from the Harvard Aging Brain Study (HABS), a longitudinal observational study of aging and preclinical AD.¹⁶ We identified 352 HABS participants who were considered clinically normal at baseline based on neuropsychological testing and a clinical consensus panel that included behavioral neurologists, clinical neuropsychologists, and geriatric psychiatrists. These participants had up to nine timepoints of annual neuropsychological assessment (years of follow-up_{mean(sd) [min, max]} = 6.33 (2.54)^{1,11}) and up to four timepoints

RESEARCH IN CONTEXT

- 1. Systematic review:** The authors reviewed the literature for the association between changes in A β pathology and changes in cognition. Evidence suggests that A β accumulation is associated with subsequent cognitive decline, but the current research is limited by small sample sizes, short follow-up periods, and less sophisticated statistical methods.
- 2. Interpretation:** Our results support previous findings of a negative impact of A β accumulation on changes in cognition. Our unique contribution to the literature is the finding that A β accumulation is associated with subsequent cognitive decline and has a stronger influence on decline than an individual's A β burden at a single timepoint after adjusting for multiple covariates. Employing advanced methods such as latent change score models allows us to simultaneously test the influence of cross-sectional and accumulating A β on cognitive changes within the same model.
- 3. Future directions:** Further work is needed to determine the influence of changing biomarkers other than A β on cognitive decline.

of global A β -positron emission tomography (PET) (years of follow-up_{mean(sd) [min, max]} = 5.30 (2.27)^{2,10}) collected at visits one, four, six, and nine. Sample sizes for each year are reported in Supplementary Table 1. Participant demographics are displayed in Table 1. At baseline, 82 participants start as ¹¹C-Pittsburgh Compound-B positive (PiB+) (defined

by a 1.186 DVR cutoff), and an additional 33 participants progress to PiB+ over the follow-up time. The frequency of PiB positivity at each visit is additionally reported in Table S1. Study procedures for HABS were approved by the Partners Human Research Committee, the Institutional Review Board for Massachusetts General Brigham hospitals. The study was carried out by the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2 | Neuropsychological evaluation

Global cognition was assessed using the Preclinical Alzheimer's Cognitive Composite-5 (PACC-5), which is a z-scored and averaged composite of five neuropsychological tests: the Mini-Mental State Examination, Logical Memory Delayed Recall, Digit-Symbol Substitution Test, Free and Cued Selective Reminding Test (both cued and free recall), and Category Fluency (Animals, Fruit, Furniture).^{17,18}

2.3 | Positron emission tomography (PET)

PET images were acquired using a Siemens HR+ scanner, and all acquisition parameters followed previously published protocols.¹⁶ A β -PET imaging was acquired with a bolus injection of ¹¹C-Pittsburgh Compound-B (PiB)-PET¹⁹ and a subsequent 1-h dynamic acquisition over 39 volumes (8 $\times$ 15 s, 4 $\times$ 60 s, 27 $\times$ 120 s). PET data underwent reconstruction and attenuation correction, were evaluated for head motion, and were co-registered to a contemporaneous parcellated T1 MRI (using FreeSurfer version 6.0). Distribution volume ratios (DVRs) were calculated using the Logan graphical method (40–60 min) with a cerebellar gray reference tissue. PiB-PET was analyzed as a neocortical (NEO) aggregate region of interest (ROI) of the frontal,

TABLE 1 Participant demographics

Characteristic	Overall N = 352 ^a	PIB– N = 270 ^a	PIB+ ^b N = 82 ^a
Sex [female]	211 (59.94%)	162 (60.00%)	49 (59.76%)
Baseline age (years)	71.80 (8.02) [50, 90]	70.82 (8.24) [50, 89]	75.00 (6.32) [60, 90]
Years of education	15.86 (2.96) [6, 20]	15.78 (2.97) [6, 20]	16.11 (2.91) [8, 20]
APOE ϵ 4 [ϵ 4+]	96 (27.59%)	46 (17.29%)	50 (60.98%)
Baseline PACC-5	0.06 (0.68) [–2.39, 2.06]	0.07 (0.68) [–2.15, 2.06]	0.01 (0.69) [–2.39, 1.30]
Baseline PiB	1.16 (0.19) [0.92, 1.98]	1.08 (0.05) [0.92, 1.19]	1.45 (0.18) [1.19, 1.98]
MTL composite	1.19 (0.12) [0.87, 1.76]	1.16 (0.09) [0.87, 1.44]	1.28 (0.15) [0.91, 1.76]
FDG composite	1.06 (0.08) [0.88, 1.29]	1.07 (0.08) [0.90, 1.29]	1.04 (0.08) [0.88, 1.25]

Abbreviations: APOE ϵ 4, apolipoprotein ϵ 4; FDG, ¹⁸F fluorodeoxyglucose; MTL, medial temporal lobe; PACC-5, Preclinical Alzheimer's Cognitive Composite-5; PiB, ¹¹C-Pittsburgh Compound-B.

^aMean (SD) [range], n (%).

^bPiB+ threshold = 1.186 DVR.

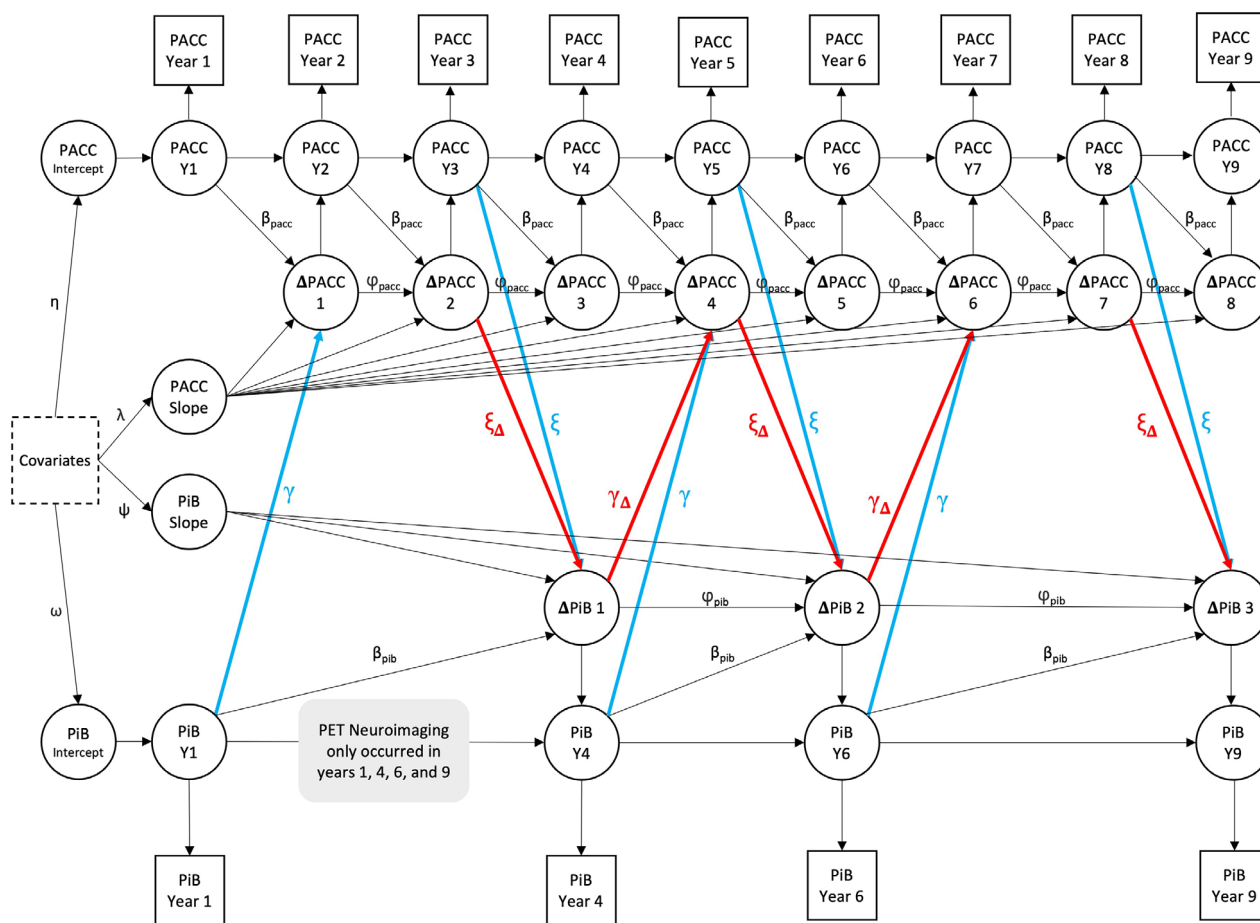


FIGURE 1 Path diagrams of latent change score model. Squares represent observed variables and circles represent latent variables. γ denotes regressions predicting PACC-5, and ξ denotes regressions predicting PiB-PET. The delta subscript refers to relationships between two change parameters (γ_{Δ} and ξ_{Δ}). η , λ , ψ , and ω denote multiple regression between covariates and PiB-PET/PACC-5 intercept and slopes. β and ϕ denote within-variable change patterns. Unlabeled paths are fixed to 1. PACC-5, Preclinical Alzheimer's cognitive composite-5; PiB-PET, ^{11}C -Pittsburgh Compound-B positron emission tomography; Y, year

lateral temporal parietal, and retrosplenial (FLR) cortices, which were defined by FreeSurfer using the Desikan-Killiany atlas. Due to the longitudinal nature of the models, we did not employ partial volume correction.²⁰

Tau-PET imaging was acquired for 264 participants approximately 80–110 min postinjection with ^{18}F -Flortaucipir (FTP)-PET (formerly AV1451 or T807). PET data were co-registered to each participant's T1 image and segmented with FreeSurfer version 6.0. Tau-PET signal was computed using standard uptake volume ratios (SUVRs) and referenced to cerebellar grey. We created a cross-sectional MTL tau-PET composite comprised of bilateral amygdala, entorhinal, and parahippocampal regions collected at the participants final timepoint (collected on average 5.95 [2.63] years post-baseline). We used MTL tau-PET collected at participants most recent visit rather than baseline to account for later tau accumulation that contributes to cognitive decline.

^{18}F Fluorodeoxyglucose (FDG)-PET was acquired for 244 participants from 45 to 75 min after a 5 to 10 mCi bolus injection in 6 × 5-min frames. FDG was represented with SUVR and referenced to cerebellar grey. The target region we investigated involved a cross-sectional

composite of regions sensitive to AD-related glucose hypometabolism, including bilateral hippocampal, inferior parietal, and posterior cingulate regions²¹ collected at A β baseline.

2.4 | Statistical analyses

All analyses were performed in R 4.3.2 using the lavaan package.²² R scripts and model syntax discussed in this section can be found in the following GitHub repository: <https://github.com/klinger-hm/lcsm>.

A series of bivariate changes to changes LCSM¹² were used to examine the relationship between changes in PiB-PET and changes in PACC. Full information maximum likelihood was used to account for missing data.^{23,24} All data were z-scored. We denote all coefficients in regressions within our LCSM predicting PACC-5 by γ and those predicting PiB-PET by ξ . The delta subscript refers to relationships between two change parameters (γ_{Δ} and ξ_{Δ}). We examined the impact of only PiB-PET on PACC-5 change, and the impact of only PACC-5 on PiB-PET change, and then explored these effects at the same time. These models include:

1. Model 1: A no-coupling model where PiB-PET and PACC-5 are independent ($\gamma = \gamma_{\Delta} = \xi = \xi_{\Delta} = 0$; see Figure 1).
2. Model 2: Cross-sectional PiB-PET solely predicting changes in PACC-5 ($\gamma_{\Delta} = \xi = \xi_{\Delta} = 0$).
3. Model 3: Cross-sectional and changes in PiB-PET predicting changes in PACC-5 ($\xi = \xi_{\Delta} = 0$).
4. Model 4: Cross-sectional PACC-5 solely predicting changes in PiB-PET ($\gamma = \gamma_{\Delta} = \xi_{\Delta} = 0$).
5. Model 5: Cross-sectional and changes in PACC-5 predicting changes in PiB-PET ($\gamma = \gamma_{\Delta} = 0$).
6. Model 6: Cross-sectional PiB-PET predicting change in PACC-5 and cross-sectional PACC-5 predicting change in PiB-PET ($\gamma_{\Delta} = \xi_{\Delta} = 0$).
7. Model 7: Cross-sectional and changes in PiB-PET predicting changes in PACC, as well as cross-sectional and changes in PACC-5 predicting changes in PiB-PET.

Within each model, change in PiB-PET is represented through three parameters. The constant change parameter (PiB_{slope}, also referred to as latent PiB-PET slope) estimates the linear trend of change that has the same effect on all latent PiB-PET change score parameters. The proportional change parameter (β) determines if prior cross-sectional PiB-PET influences subsequent change in PiB-PET. An autoregressive change parameter (φ) that is unique to the changes to changes LCSM determines if prior PiB-PET change scores influence the subsequent PiB-PET change score.²⁵ The combination of these three parameters (PiB_{slope}, β , φ) dictate the pattern of change in PiB-PET. Comparable parameters are also estimated to parameterize the change in PACC-5. In addition to the different change components, a latent intercept is estimated for both PiB-PET and PACC-5. Correlations were calculated between all the latent slopes and intercepts.

Baseline age, sex, years of education, APOE ϵ 4 status, a cross-sectional MTL tau-PET composite, and a baseline FDG-PET composite were included as covariates as these variables are known associates of changes in PiB-PET and/or PACC-5 change. This was done within the model by regressing the latent PiB-PET and PACC-5 intercept (ω and η , respectively) and slopes (ψ and λ , respectively) onto each covariate in a multiple regression (see Figure 1).

To ensure convergence to an optimal model, a variety of equality constraints were applied to the parameters. Within each model, the mean of both observed and latent PiB-PET and PACC-5 structures and the variance of latent PiB-PET and PACC-5 structures were set equal to zero and the residual variance of the observed PiB-PET and PACC-5 were constrained to be equal,¹² as these parameters were not of interest, we did not require their estimation. Regression coefficients (γ , γ_{Δ} , ξ , ξ_{Δ} , β , and φ) were also specified to be invariant over time to reduce model complexity. This equality constraint does not represent constant or linear change over time, rather it refers to the dynamics accumulating systematically.¹² That is, changes that occur earlier are continuously expressed in later occasions.¹¹

Likelihood ratio tests (LRT) were used to determine if more complex models were an improvement of a simpler version of the model.²³ Model fit was additionally examined using -2 log-likelihood (-2LL), Akaike's information criterion (AIC), Bayesian information criterion

(BIC), comparative fit index (CFI), Tucker Lewis index (TLI), and root mean square error of approximation (RMSEA).^{12,26} A better fitting model is indicated by smaller AIC and BIC values, CFI or TLI values closer to 1, and an RMSEA closer to zero. Cut-offs of CFI ≥ 0.95 and TLI ≥ 0.95 were used as criteria to indicate a good fit while an RMSEA ≤ 0.08 was considered acceptable and an RMSEA ≤ 0.05 was considered good.^{27,28}

3 | RESULTS

3.1 | Associations between PiB-PET and PACC-5 decline

Before examining the relationship between PiB-PET and PACC-5, we first ran a model with no coupling parameters between PiB-PET and PACC-5 (Model 1). We then compared all the following models to this model using LRT to determine if adding coupling parameters improved the model.

Examining only the effect of cross-sectional PiB-PET on change in PACC-5 (γ) was an improvement of Model 1 (LRT p -value < 0.001) and we found that cross-sectional PiB-PET was significantly associated with subsequent cognitive decline (Model 2; Table S2). This association remained when additionally including the effect of changes in PiB-PET (γ_{Δ}) in the same model (Model 3, Figure S1). This latter model was an improvement of Model 2 (LRT p -value < 0.001), and we found that greater PiB-PET accumulation was associated with faster subsequent decline (Table 2) and exhibited a larger effect on PACC-5 decline than cross-sectional PiB-PET burden. Individual trajectories of PACC-5 and PiB-PET were extracted from Model 3, our overall best-fitting model, and are displayed in Figure 2 by age from baseline and in Figure S2 by time from baseline.

3.2 | Associations between PACC-5 and PiB-PET accumulation

By contrast, estimating the effect of cross-sectional PACC-5 on change in PiB-PET (ξ ; Model 4) was not an improvement of Model 1 (LRT p -value = 0.45) and, therefore, was not further explored. Including the effect of change in PACC-5 on change in PiB-PET in the same model (ξ_{Δ} ; Model 5) was an improvement of Model 1 (LRT p -value < 0.001), but we found no evidence that cross-sectional or changing PACC-5 had an impact on changing PiB-PET (Table S2).

3.3 | Bidirectional associations between PiB-PET and PACC

We additionally examined the effect of both cross-sectional PiB-PET on change in PACC-5 (γ) and cross-sectional PACC-5 on change in PiB-PET (ξ) within the same model (Model 6). The pattern of effects was the same as the previous models, but Model 6 was not an improvement

TABLE 2 Model fit statistics and select model parameter standardized estimates and significance.

	Model 1 (no coupling)	Model 2 ^a	Model 3 ^{a,b}	Model 4	Model 5 ^a	Model 6 ^a	Model 7 ^a
Fit Statistics							
AIC	11,712.74	11,659.91	11,642.09	11,714.18	11,700.58	11,661.06	11,644.26
BIC	11,990.92	11,941.96	11,927.99	11,996.23	11,986.49	11,946.97	11,937.90
−2LL	11,568.74	11,513.91	11,494.09	11,568.18	11,552.58	11,513.06	11,492.26
CFI	0.9403	0.9522	0.9564	0.9402	0.9425	0.9522	0.9564
TLI	0.9321	0.9452	0.9496	0.9314	0.9347	0.9448	0.9488
RMSEA	0.0748	0.0671	0.0644	0.0751	0.0733	0.0674	0.0649
Parameters							
γ	0	−0.25***	−0.15***	0	0	−0.26***	−0.15***
γ_{Δ}	0	0	−0.43***	0	0	0	−0.44***
ξ	0	0	0	−0.02	0.02	−0.04	−0.11
ξ_{Δ}	0	0	0	0	−0.09	0	0.29

Abbreviations: γ_{Δ} , effect of PiB-PET change on PACC-5 change; γ , effect of cross-sectional PiB-PET on PACC-5 change; ξ_{Δ} , effect of PACC-5 change on PiB-PET change; ξ , effect of cross-sectional PACC-5 on PiB-PET change; −2LL, 2 log-likelihood, AIC, Akaike's information criterion, BIC, Bayesian information criterion, CFI, comparative fit index, RMSEA, root mean square error of approximation; TL, Tucker Lewis index.

^aModel achieves a significantly better fit than Model 1 determined by a likelihood ratio test.

^bOverall best fitting model.

*** < 0.001

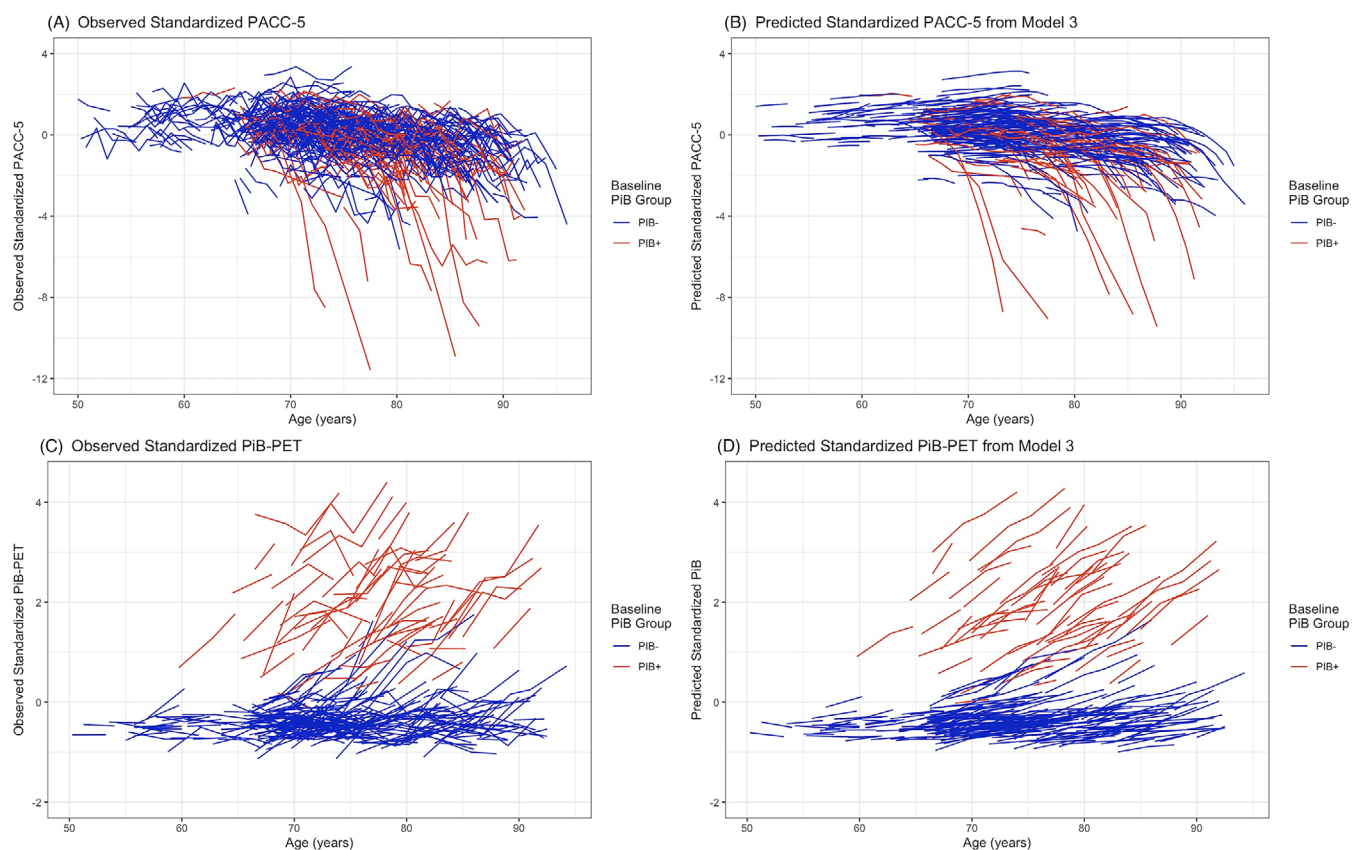


FIGURE 2 (A) Longitudinal standardized observed PACC-5 scores over age from the HABS data set. (B) Longitudinal predicted standardized PACC-5 scores over the age from Model 3. (C) Longitudinal observed standardized PiB-PET levels over the age from the HABS data set. (D) Longitudinal predicted standardized PiB-PET levels over the age from Model 3. HABS, Harvard Aging Brain Study; PACC-5, Preclinical Alzheimer's cognitive composite-5; PiB-PET, ¹¹C-Pittsburgh Compound-B positron emission tomography.

TABLE 3 Significant covariate parameter standardized estimates and significance of the best fitting model.

Parameter	Model 1 (no coupling)	Model 3
PACC _{intercept} ~ Age	−0.04***	−0.04***
PACC _{slope} ~ Age	0.02*	−0.01*
PiB _{intercept} ~ Age	0.01*	0.01*
PiB _{slope} ~ Age	0.01**	0.01*
PACC _{intercept} ~ Sex [M]	−0.39***	−0.42***
PACC _{slope} ~ Sex [M]	0.23*	−0.08**
PACC _{intercept} ~ YrsEd	0.31***	0.32***
PACC _{slope} ~ YrsEd	−0.18**	0.07***
PiB _{intercept} ~ YrsEd	0.09*	0.10*
PACC _{slope} ~ APOEε4 [ε4+]	−0.6	0.06*
PiB _{intercept} ~ APOEε4 [ε4+]	0.62***	0.62***
PiB _{intercept} ~ MTL	0.36***	0.36***

Abbreviations: APOEε4, apolipoprotein ε4; M, males; MTL, medial temporal lobe tau composite; PACC, Preclinical Alzheimer's Cognitive Composite-5; YrsEd, years of education.

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$.

on Model 2 (LRT p -value = 0.35) and so was not investigated further. In our most complicated model, we merged Models 3 and 5 to examine the impact of both PiB-PET on PACC-5 and PACC-5 on PiB-PET. This model included the effect of both cross-sectional and changes in PiB-PET (γ and γ_{Δ}) on changes in PACC-5 in addition to cross-sectional and changes in PACC-5 (ξ and ξ_{Δ}) on changes in PiB-PET within the same model (Model 7). This model also mirrored our previous findings but was not an improvement of Model 3 (LRT p -value = 0.40) where only the effect of cross-sectional and changes in PiB-PET on PACC-5 were included (γ and γ_{Δ} , respectively). As such, we did not explore this model further.

3.4 | Covariate associations

Table 3 displays the significant covariate associations with the estimated latent PiB-PET and PACC-5 intercept and slope for select models. Covariate associations across all models are reported in Table S3. In our overall best fitting model, Model 3, we found that older age was associated with a lower PACC-5 intercept and faster PACC-5 decline, as well as a greater PiB-PET intercept and faster PiB-PET accumulation. Men had a lower PACC-5 intercept and faster PACC-5 decline relative to women. Greater years of education was associated with a higher PACC-5 intercept, slower PACC-5 decline, and a higher PiB-PET intercept. APOEε4 positive carrier status was associated with an increased PACC-5 slope and a greater PiB-PET intercept. We did not find evidence of any significant associations with FDG-PET. Finally, we found that greater MTL tau-PET burden was associated with a greater PiB-PET intercept but was not associated with the latent PACC-5 inter-

cept or slope. To better understand the lack of association between MTL tau-PET and PACC-5, Figure 3 displays the associations found within the model (facets B and D) relative to what we found within our data set (facets A and C). Given the lack of MTL tau association with cognition, which is a well-established association in the literature,²⁹ we were also curious about our model associations when instead including a NEO tau-PET composite (using an average of the fusiform, inferior temporal, middle temporal, and inferior parietal regions). Similar to MTL tau burden, we did not find evidence of a significant relationship between NEO tau burden and PACC-5 intercept or slope.

3.5 | Sensitivity analyses

Our time intervals are not perfect even across all participants which can be a limiting factor in LCSM. As a sensitivity analysis, we restricted our sample to only include participant time points within a 6-month window of their expected visit date ($n_{\text{observations_full}} = 3325$ PACC-5 and 3094 PiB-PET vs $n_{\text{observations_restricted}} = 3006$ PACC-5 and 2910 PiB-PET). Time intervals between visits in our full sample and restricted sample are reported in Table S4. In these sensitivity analyses, we recapitulated the same pattern of results as in our full sample.

While it is common practice for regression estimates to be invariant over time in LCSM, we ran a version of Model 3 allowing the γ_{Δ} estimates (PiB-PET change predicting subsequent PACC-5 change) to be freely estimated (i.e., not constrained over time). Allowing γ_{Δ} to be freely estimated demonstrated no improvement over Model 3 (LRT p -value = 0.1691).

Our long period of longitudinal PiB-PET and PACC-5 follow-up allowed us to also consider the question of temporality. That is, rather than just investigate the change-on-change relationship between PiB-PET and PACC-5 in the immediate subsequent timepoint (i.e., one visit later), we could examine the time-lagged effect (i.e., changes two visits later). In these sensitivity analyses examining the lagged relationship, few models were an improvement of Model 1, and none were an improvement of their corresponding immediate-change model; therefore, we did not further explore this time-lagged relationship.

4 | DISCUSSION

In this longitudinal study of clinically normal older adults followed up to 9 years, we observed that Aβ accumulation was more strongly associated with subsequent cognitive decline than cross-sectional Aβ. We found no evidence that prior change in cognition was associated with subsequent Aβ accumulation. This supports the consistent findings that show elevated levels of Aβ precede subsequent cognitive symptoms of AD.¹ Rates of Aβ accumulation are relatively slow and insidious over many years; however, these models support the notion that the chronicity—or time to abnormal Aβ levels—of high Aβ burden (macro-level)³⁰ is not a sole marker of impending cognitive decline, but that short-term Aβ changes (micro-level) also contribute to decline. We observed these changes after adjusting for multiple covariates, includ-

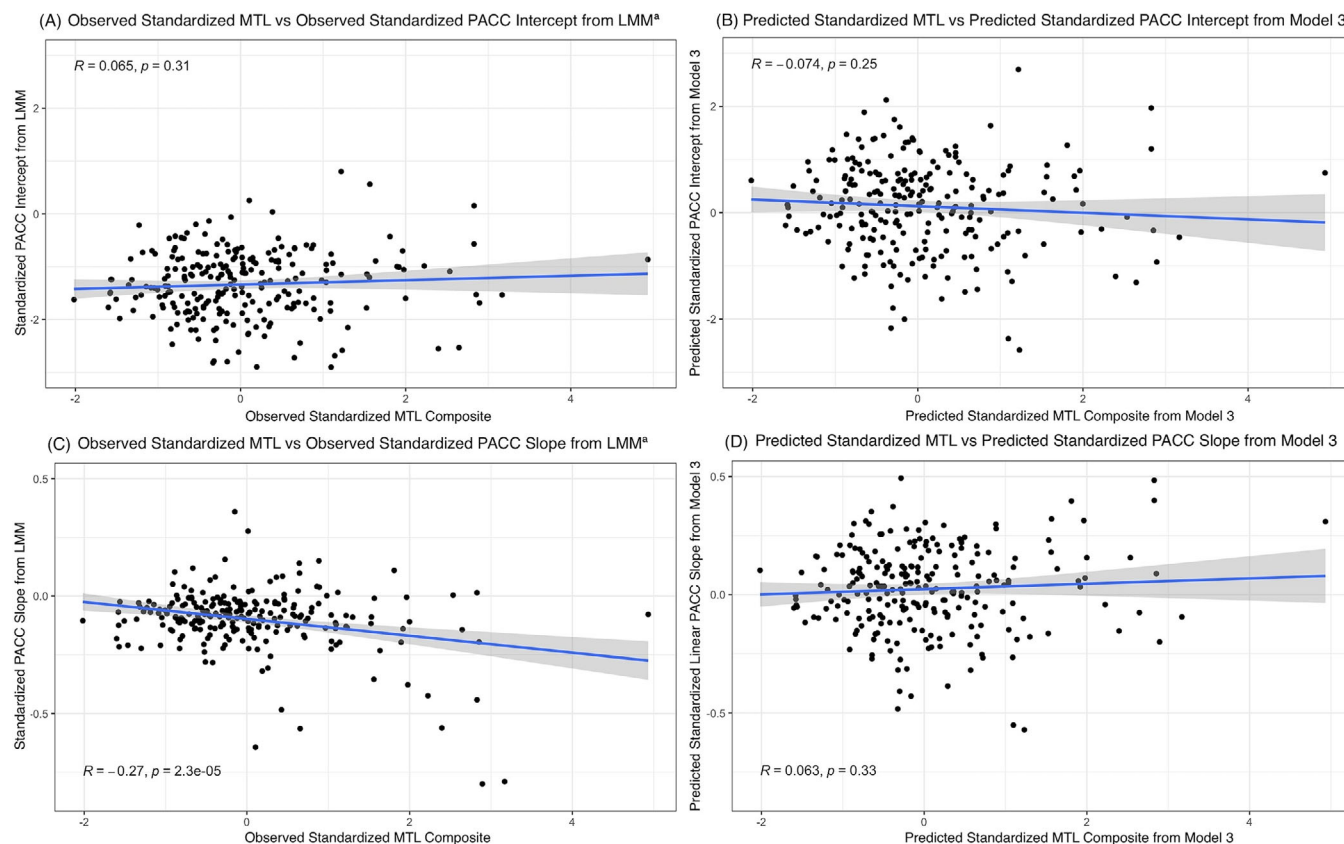


FIGURE 3 (A) Observed standardized MTL composite versus standardized PACC-5 intercept from LMM^a (B) Predicted standardized MTL composite versus predicted standardized PACC-5 intercept from Model 3 (C) Observed standardized MTL composite versus standardized PACC-5 slope from LMM^a. (D) Predicted standardized MTL composite versus predicted standardized PACC-5 slope from Model 3. ^a indicates Random intercept/slope from a linear mixed-effects model of time predicting standardized PACC-5, adjusted for standardized baseline age, sex, years of education, APOEε4 status, cross-sectional FDG composite, and baseline PiB-PET. APOEε4, apolipoprotein ε4; FDG, ¹⁸F fluorodeoxyglucose; LMM, linear mixed-effects model; MTL, medial temporal lobe; PACC-5, Preclinical Alzheimer's cognitive composite-5; PiB-PET, ¹¹C-Pittsburgh Compound-B positron emission tomography.

ing age, sex, education, APOEε4 status, MTL tau burden, and glucose metabolism.

Our results support those demonstrating the impact of Aβ accumulation on changes in cognition. Our team previously revealed the serial impact of change in Aβ-PET on change in cognitive decline via changes in tau-PET.⁶ Another study revealed the relationship between Aβ accumulation and cognitive decline was strongest in posterior cortical regions of Aβ load.⁷ These findings, and others,^{5,8,9} provide a glimpse into the temporality of changes in Aβ biomarkers to subsequently influence cognitive trajectories. Studies are currently limited by either their sample size or the length of follow-up, with some having as low as 60 participants or only following participants across 3 years. Additionally, the statistical methods of these studies focus on simpler approaches, such as extracting and correlating time-demarcated slopes,^{6,8,9} or calculating a raw Aβ change score from the difference in Aβ levels between two timepoints.⁷ By implementing LCSM with our large cohort across a large period of follow-up, we have more power to explore the relationship between Aβ accumulation and cognitive decline, which allows us to investigate the temporal intricacies between the two.

We found that Aβ accumulation had a much larger effect size than cross-sectional Aβ. In previous models of autosomal dominant AD (ADAD), the opposite has been found, with cross-sectional Aβ providing more explained variance than rates of Aβ accumulation on cognitive decline. In the aforementioned study, the only longitudinal biomarkers that contributed significantly explained variance to cognitive decline were changes in glucose metabolism and hippocampal atrophy.⁹ Our study only examined changes in two variables (Aβ and cognition), so we would need to extend our models to include more sophisticated changes across many biomarkers to align more directly with the previous analytic design. Another difference with this study is the focus on ADAD, which involves predominately younger participants with genetic mutations of the *PSEN1*, *PSEN2*, or *APP* genes.³¹ These genes all directly impact Aβ development and aggregation, with much more aggressive early Aβ accumulation, which may contribute to some differences that we see in this work relative to our study.

We considered many covariates in our model and their association with a cognitive global intercept and slope and an Aβ global intercept and slope. The term global here refers to the overall linear slopes estimated in the model. Of greatest interest to us was a lack of association

between MTL tau burden and cognitive slope, which sits in opposition to previous findings, including our own.³² One possibility for this disconnect is the modeling approach, in which we estimate all variance from cross-sectional and longitudinal data within one model. In the model-building process, as we led up to our final bivariate models, we found that in an initial univariate PACC-5 constant change model¹² covarying for MTL tau-PET, greater cross-sectional MTL tau burden was associated with a lower PACC-5 slope. In addition to the previous work from our team consistently publishing an association between MTL tau and declining cognition in the HABS, we had current and prior evidence to suggest an association. However, as we built off this basic model, this association became attenuated, supporting our assumption that the lack of association is due to the variance calculated from other parameters within our models. An interpretation of these models is that the direct association between MTL tau burden and cognitive decline may represent multiple indirect associations that are poorly accounted for in other models, and as such may not be as strong. Expected tau associations may be eclipsed by the relationship between A β and cognitive changes in combination with cross-sectional A β and cognition, as well as other covariates. Our future directions will be to include changes in MTL or NEO tau burden in these LCSMs; however, this will greatly increase the complexity of the interpretation of estimates.

The most consistent findings across all models were the effect of age, education, and sex on PACC-5 intercept (older age, lower education, and male sex were associated with lower PACC-5 scores), APOE ϵ 4 status on A β intercept (APOE ϵ 4 carriers had a higher A β intercept), and cross-sectional MTL tau burden on A β intercept (higher MTL tau was associated with higher A β intercept). These covariate associations largely followed previous findings in the literature; however, there is some disagreement about sex differences in patterns of cognitive decline.³³ The lack of association between PACC-5 and A β intercept and slope and baseline levels of glucose metabolism in our models is perhaps in line with the notion that these are all clinically normal individuals at the outset and any associations with FDG-PET are unlikely to appear until later in the disease. We also found that greater years of education were associated with a greater A β intercept and that APOE ϵ 4 carriers had a greater PACC-5 slope, both of which sit in the opposite direction of what we would expect and may arise due to the complexity of the models, similar to our MTL tau findings. However, it should be noted that two-thirds of our APOE ϵ 4 carrier group are women ($N = 65$ [67.71%]), and there is robust literature showing that clinically normal women outperform men on most neuropsychological tests.^{34–36} In our models, men were performing significantly worse at the baseline and over time. As such, it is possible that this obscured any APOE ϵ 4 effects. It is important to point out; however, that there is also some literature to suggest a faster cognitive decline in APOE ϵ 4 carrying women^{37,38} so this needs to be explored further.

This longitudinal study is strengthened by a large well-characterized cohort of preclinical AD participants with a large amount of follow-up spanning 9 years. However, there are some limitations to consider. Our cohort of participants selected from the HABS is predominately non-Hispanic white, highly educated, and has low cardiovascular burden.

As such, it is less representative of the general population. Within our models, we focused on the impact of change in A β on immediate subsequent cognitive decline. We explored temporality within our models and the impact of “downstream” changes to cognition from changes in A β two visits earlier in our sensitivity analyses. We are, however, limited in the duration of follow-up, and as such, are restricted in our ability to interpret the enduring effects of A β accumulation on cognition up to decades later. Longer follow-up periods and increased A β timepoints would also help us address more questions about time, such as how many years after A β accumulation is cognitive decline occurring. Finally, LCSM are complex models. Larger sample sizes, along with greater longitudinal time points, are preferred to increase power and liability. These restrictions make it difficult to implement LCSM in all cohorts; therefore, this study and our results are difficult to replicate.

In this longitudinal study, we observed that prior A β accumulation is associated with faster subsequent cognitive decline and has a stronger influence on cognitive decline than cross-sectional A β burden. Further work is needed to fully understand the relationship between changes in A β and changes in cognition. Future directions of this project include replicating this analysis in other cohorts and looking at changes in biomarkers other than A β , such as tau or hippocampal volume. Examining the relationship between MTL tau-PET change and cognitive change in a bivariate LCSM will help us better understand the intricate associations between MTL tau-PET and cognitive decline. While our study uses PET imaging, it would be insightful to examine this relationship using biofluids, given their increasing clinical salience. In conclusion, the findings from this study show that LCSMs are a powerful technique to better understand the intricacies of the relationship between A β accumulation and cognitive decline.

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CONFLICT OF INTEREST STATEMENT

None of the authors report any disclosures relevant to this manuscript. Author disclosures are available in the [supporting information](#).

CONSENT STATEMENT

Study procedures for HABS were approved by the Partners Human Research Committee, the Institutional Review Board for Massachusetts General Brigham hospitals. The study was carried out

by the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants.

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