8 Supplementary Material

8.1 Imputation for the date of reaching abnormal Aβ-amyloid levels:

For individuals presenting with Aβ-amyloid levels at baseline between the cut-off for abnormality and median values observed in mild AD participants, the date at which their Aβ-amyloid level became abnormal was imputed (AIBL: cut-off=1.40, μ_{AD}=2.03, N=95; ADNI: cut-off=0.61, μ_{AD}=0.91, N=85). Amyloid deposition was assumed to occur at a constant rate between the cut-off for abnormality and the median level seen in mild AD, in line with the sigmoidal trajectory observed in models of Aβ-amyloid deposition (Budgeon et al., 2017; Jack et al., 2013a; Villemagne et al., 2013). Given the stable nature of the rates of deposition over this region, the timeframe an individual would have been considered to have abnormal Aβ-amyloid levels was calculated as the result of dividing the difference between 1.4 SUVR (0.61 for ADNI participants) and their mean SUVR (of all their evaluations) by their individual rate of deposition. This timeframe was then subtracted from the median date of their evaluations to provide the imputed date at which they would have presented with abnormal Aβ-amyloid levels. Participants presenting with baseline Aβ-amyloid levels above the median level seen in mild AD were removed from this aspect of the study (AIBL: N=21; ADNI: N=35). Case resampling bootstrapping for estimating the rates of deposition, as previously described (Budgeon et al., 2017), was undertaken to provide confidence intervals around the survival estimates.

11 Supplementary Figure Legends

Supplementary Figure 1A. Boxplots detailing the rates of Aβ-amyloid deposition for cognitively normal AIBL participants above the abnormal threshold for Aβ-amyloid at baseline (^{11}C-PiB PET SUVR≥1.4) stratified by *APOE*-ε4 carriage

Supplementary Figure 1B. Boxplots detailing the rates of Aβ-amyloid deposition for cognitively normal AIBL participants below the abnormal threshold for Aβ-amyloid at baseline (^{11}C-PiB PET SUVR≥1.4) stratified by *APOE*-ε4 carriage

Supplementary Figure 1C. Boxplots detailing the rates of Aβ-amyloid deposition for cognitively normal ADNI participants above the abnormal threshold for Aβ-amyloid at baseline (^{18}F- Florbetapir SUVR≥0.61) stratified by *APOE*-ε4 carriage

Supplementary Figure 1D. Boxplots detailing the rates of Aβ-amyloid deposition for cognitively normal ADNI participants below the abnormal threshold for Aβ-amyloid at baseline (^{18}F- Florbetapir SUVR≥0.61) stratified by *APOE*-ε4 carriage

Supplementary Figure 2A. Boxplots detailing the rates of Aβ-amyloid deposition for AIBL participants, including the non-accumulators, above the abnormal threshold for Aβ-amyloid at baseline (^{11}C-PiB PET SUVR≥1.4) stratified by *APOE*-ε4 carriage

Supplementary Figure 2B. Boxplots detailing the rates of Aβ-amyloid deposition for AIBL participants, including the non-accumulators, below the abnormal threshold for Aβ-amyloid at baseline (^{11}C-PiB PET SUVR≥1.4) stratified by *APOE*-ε4 carriage

Supplementary Figure 2C. Boxplots detailing the rates of Aβ-amyloid deposition for ADNI participants, including the non-accumulators, above the abnormal threshold for Aβ-amyloid at baseline (^{18}F- Florbetapir SUVR≥0.61) stratified by *APOE*-ε4 carriage

Supplementary Figure 2D. Boxplots detailing the rates of Aβ-amyloid deposition for ADNI participants, including the non-accumulators, below the abnormal threshold for Aβ-amyloid at baseline (^{18}F- Florbetapir SUVR≥0.61) stratified by *APOE*-ε4 carriage

Supplementary Figure 3A: The raw data and fitted linear models for each AIBL *APOE*-ε4 carrier, step one from the method. Green represents NC, blue represents MCI and red represents AD.

Supplementary Figure 3B: Plots of the AIBL *APOE*-ε4 carriers' slopes vs their mean observed values and the fitted cubic polynomial to this data, step two from the method. Green represents NC, blue represents MCI and red represents AD.

Supplementary Figure 3C: The raw data and fitted linear models for each AIBL *APOE*-ε4 non-carrier, step one from the method. Green represents NC, blue represents MCI and red represents AD.

Supplementary Figure 3D: plots of the AIBL *APOE*-ε4 non-carriers' slopes vs their mean observed values and the fitted cubic polynomial to this data, step two from the method. Green represents NC, blue represents MCI and red represents AD.

Supplementary Figure 4A: The raw data and fitted linear models for each ADNI *APOE*-ε4 carrier, step one from the method. Green represents NC, blue represents MCI and red represents AD.

Supplementary Figure 4B: plots of the ADNI *APOE*-ε4 carriers' slopes vs their mean observed values and the fitted cubic polynomial to this data, step two from the method. Green represents NC, blue represents MCI and red represents AD.

Supplementary Figure 4C: The raw data and fitted linear models for each ADNI *APOE*-ε4 non-carrier, step one from the method. Green represents NC, blue represents MCI and red represents AD.

Supplementary Figure 4D: plots of the ADNI *APOE*-ε4 non-carriers' slopes vs their mean observed values and the fitted cubic polynomial to this data, step two from the method. Green represents NC, blue represents MCI and red represents AD.

Supplementary Figure 5. The natural history of deposition of neocortical Aβ-amyloid in cognitively normal AIBL participants stratified by *APOE*-ε4 carriage. Shaded areas indicate 95% confidence intervals.

Supplementary Figure 6A. Kaplan-Meier plot detailing, by age, the prevalence of cognitively normal AIBL participants with high levels of Aβ-amyloid at baseline (^{11}C-PiB PET SUVR≥1.4) stratified by *APOE*-ε4 carriage. Shaded areas indicate 95% confidence intervals.

Supplementary Figure 6B. Kaplan-Meier plot detailing, by age, the prevalence of cognitively normal ADNI participants with high levels of Aβ-amyloid at baseline (^{18}F-Florbetapir SUVR≥0.61) stratified by *APOE*-ε4 carriage. Shaded areas indicate 95% confidence intervals.

Supplementary Table 1: Demographics table for AIBL and ADNI participants excluded from the study as non-accumulators stratified by *APOE*-ε4 carriage

	APOE-ε4 carriage in AIBL		p-value	*APOE*-ε4 carriage in ADNI	
	No	Yes		No	Yes
Number of Participants [N]	29	17		13	1
Clinical Classification NC/MCI/AD [N]	23/4/2	8/5/4	0.055	7/6/0	0/1/0
Gender: Males [N (%)]	16 (55.17)	12 (70.59)	0.471	8 (61.54)	0 (0.00)
Age (years) [mean (sd)]	71.26 (6.41)	67.85 (7.80)	0.110	72.82 (6.83)	70.33 (6.87)
Years of Follow-up [Mean (sd)]	4.59 (1.51)	4.17 (1.06)	0.612	3.54 (0.52)	3.00 (0.00)