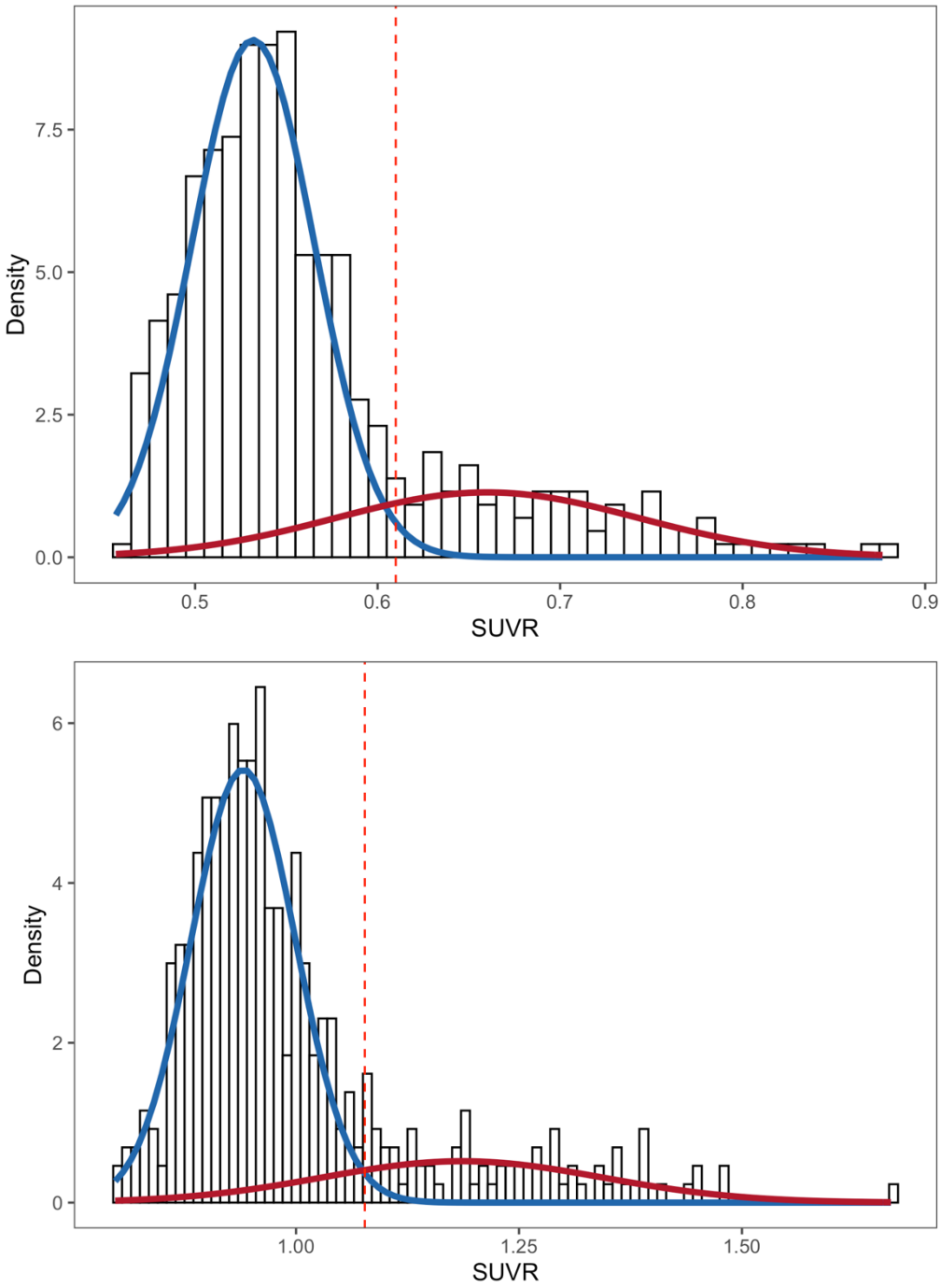
eMethods 1: Choice of reference region for amyloid-β PET quantification

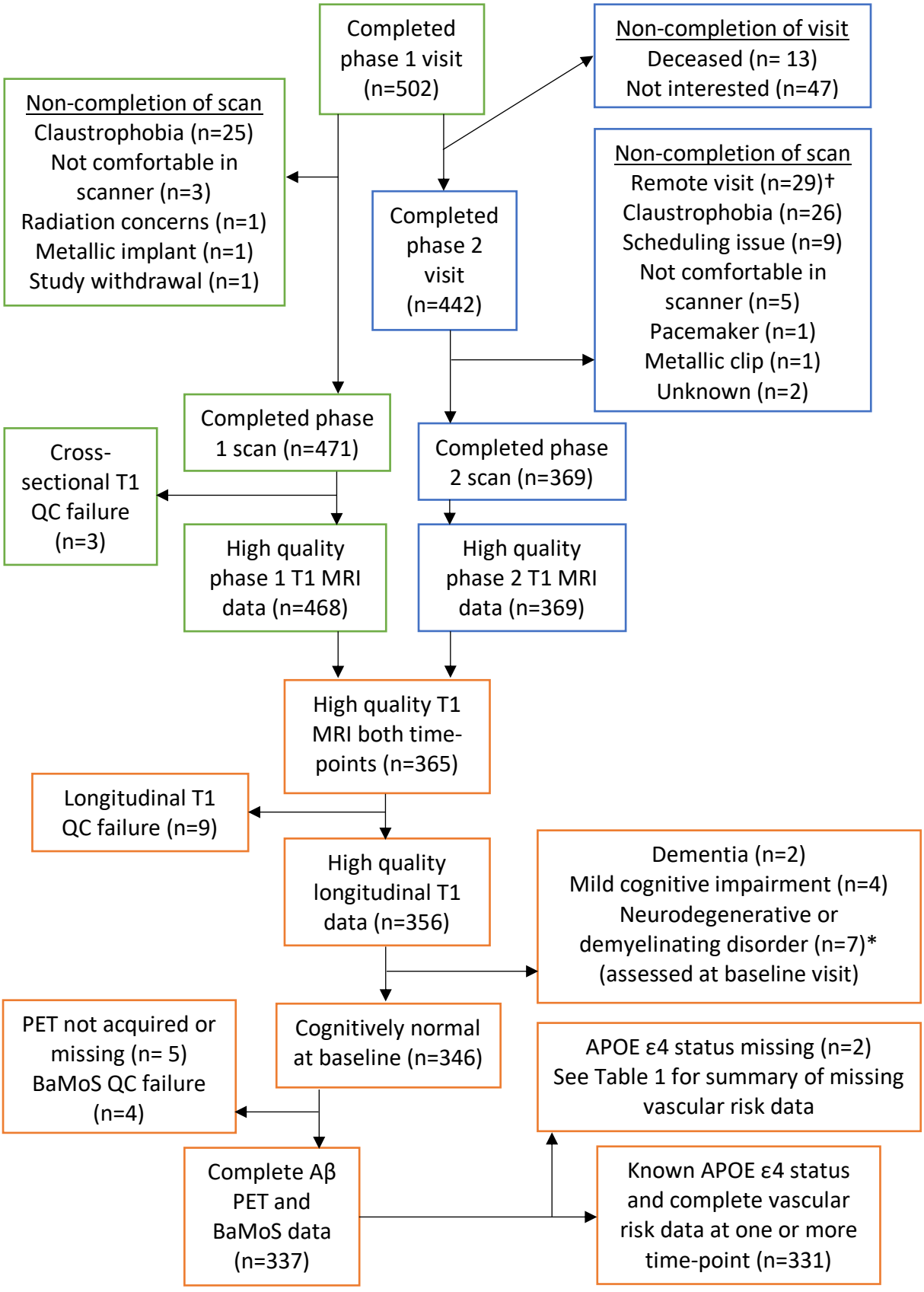
There is no consensus on methods of amyloid-β (Aβ) PET quantification in the literature. The cerebellum has often been chosen as a reference region for SUVR calculation since it is generally spared from Aβ.[1] However, concerns have been raised regarding the accuracy of cerebellar normalisation, particularly for assessment of longitudinal change, with several studies suggesting that an eroded subcortical white matter reference region may be superior in this regard.[2–4] The cerebellum is also affected by potential confounds, particularly when using a PET/MRI scanner, as is the case in the Insight 46 study. It can be more prone to attenuation correction artefacts due to its position near the bone, and it is also more susceptible to noise and small registration errors due to its proximity to the field of view edge and relatively small size. For these reasons, eroded subcortical white matter has been used as the primary reference region for all Insight 46 publications to date. Of particular relevance to analyses in the current study, however, emerging evidence suggests that Aβ PET tracer uptake in white matter may be affected by the presence of white matter hyperintensities.[5–8] An additional sensitivity analysis was therefore performed using SUVRs with a whole cerebellum reference region for comparison.

eFigure 1: Histograms showing SUVR distributions and mixture models for baseline β-amyloid PET quantification using eroded subcortical white matter (top) and whole cerebellum (bottom) reference regions



Solid red = amyloid positive; solid blue = amyloid negative; dashed red = cut-point for positivity

eFigure 2: Flow chart summarising missing and excluded data



* NB. 2 participants with a neurodegenerative or demyelinating disorder had dementia and 1 had mild cognitive impairment

† some participants had remote visits by telephone or video only due to restrictions related to the coronavirus pandemic

eMethods 2: Statistical methods

Linear regression model for atrophy

A multiple linear regression model relating an independent variable (*Y*) to *p* predictor variables (X_1,…, X_p) can be expressed as:

$$y_i = \alpha + \beta_1 x_{1i} + \beta_2 x_{2i} + \cdots + \beta_p x_{pi} + \varepsilon_i \quad (1)$$

In the multiple regression model for atrophy (Y) between two time points, all predictors act through their effects on the atrophy rate and so are included as a series of two-way interactions with duration between scans (t):

$$y_i = \left(\alpha + \beta_1 x_{1i} + \beta_2 x_{2i} + \cdots + \beta_p x_{pi}\right)t + \varepsilon_i \quad (2)$$

To fit an interaction in this model a three-way interaction is included between the two predictors of interest and time between scans. For example, the model including an interaction between predictors X1 and X2 is:

$$y_i = \left(\alpha + \beta_1 x_{1i} + \beta_2 x_{2i} + \beta_{(1*2)} x_{1i} x_{2i} \ldots + \beta_p x_{pi}\right)t + \varepsilon_i \quad (3)$$

Calculation of R^2 and semi-partial squared correlations for an atrophy model

For a linear regression model relating an independent variable (*Y*) to *p* predictor variables (X_1,…, X_p):

$$y_i = \alpha + \beta_1 x_{1i} + \beta_2 x_{2i} + \cdots + \beta_p x_{pi} + \varepsilon_i \quad (1)$$

The proportion of variance explained by the predictors in this model can be quantified by comparison to the below null model:

$$y_i = \alpha + \varepsilon_i \quad (4)$$

The comparison of the variance of Y explained by these two models is quantified by calculation of the coefficient of determination:

$$R^2 = \frac{\sum_{i=1}^{n}(\widehat{y_i} - \bar{y})^2}{\sum_{i=1}^{n}(y_i - \bar{y})^2} = 1 - \frac{\sum_{i=1}^{n}(y_i - \widehat{y_i})^2}{\sum_{i=1}^{n}(y_i - \bar{y})^2} \quad (5)$$

Where,

$\bar{y}$ is the mean of Y, which is equal to the fitted value from the null model

$\hat{y}_i$ is the fitted value of Y for the ith individual

y_i is the observed value of Y for the ith individual

The semi-partial R^2 for a predictor of interest captures the extra variance explained by that predictor, above that already explained by the other predictors in the model. It is calculated as the increase in R^2 between the full model (containing all predictors) and the reduced model excluding the predictor of interest but retaining all other variables:

$$R^2_{partial} = R^2_{full} - R^2_{reduced} \quad (6)$$

In the model for atrophy (*Y*), all predictors only act through effects on the atrophy rate:

$$y_i = \left(\alpha + \beta_1 x_{1i} + \beta_2 x_{2i} + \cdots + \beta_p x_{pi}\right)t + \varepsilon_i \quad (2)$$

Therefore, the proportion of variance explained by the predictors in this model can be quantified by comparison to the variance explained by below null model:

$$y_i = \alpha t + \varepsilon_i \quad (7)$$

The comparison of the variance of Y explained by these two atrophy models can quantified by calculation of a modified coefficient of determination:

$$R^{2*} = \frac{\sum_{i=1}^{n}(\hat{y}_i - \hat{y}_{0,i})^2}{\sum_{i=1}^{n}(y_i - \hat{y}_{0,i})^2} = 1 - \frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{\sum_{i=1}^{n}(y_i - \hat{y}_{0,i})^2} \quad (8)$$

Where,

$\hat{y}_{0,i}$ is the fitted value of Y for the ith individual from the null model in (7)

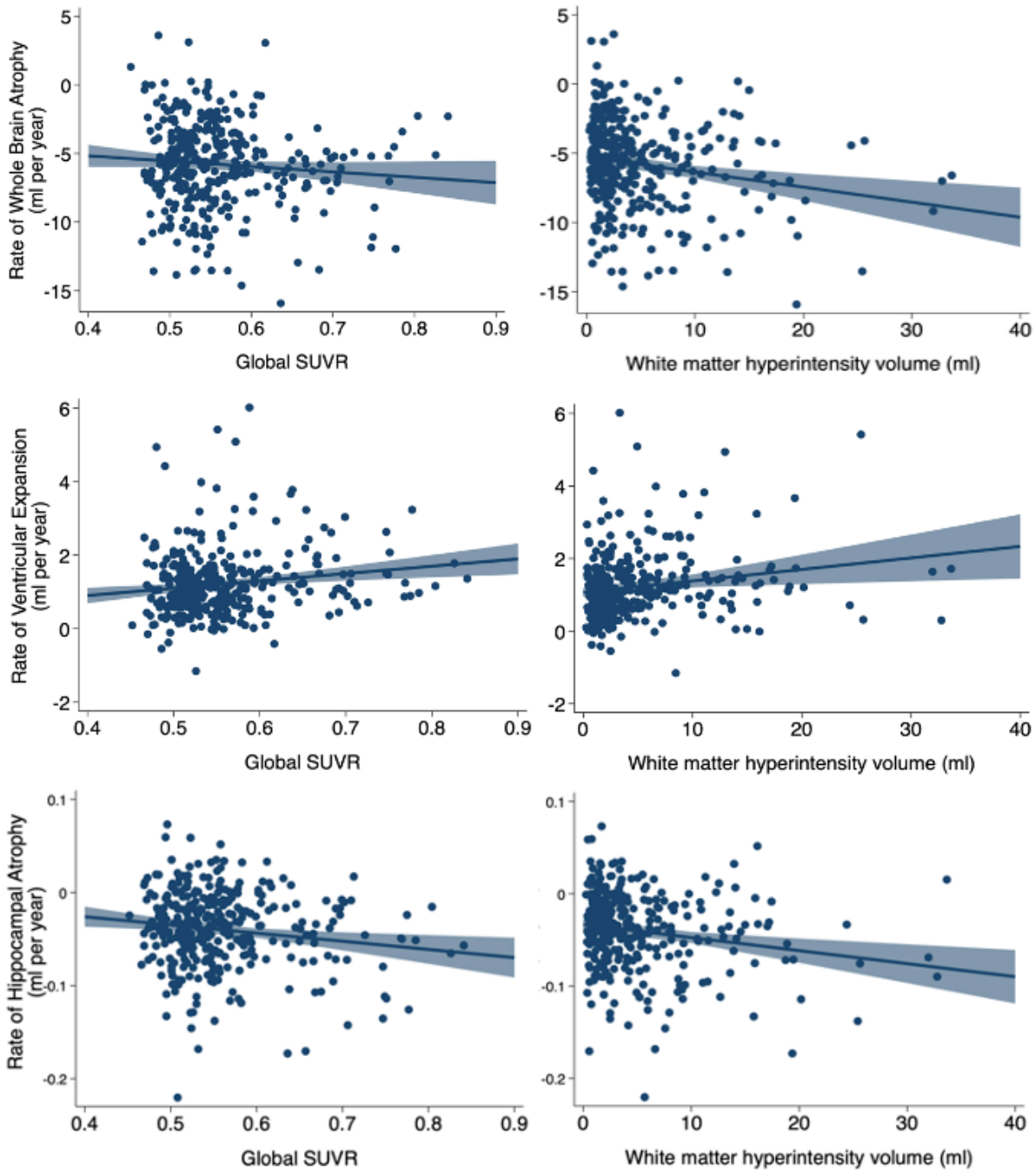
$\hat{y}_i$ is the fitted value of Y for the ith individual from the model in (2)

y_i is the observed value of Y for the ith individual

In this setting the semi-partial R^2 for a predictor of interest is calculated as the increase in the modified R^2 between the full model (containing all predictors) and the reduced model excluding the predictor of interest but retaining all other variables:

$$R^{2*}_{partial} = R^{2*}_{full} - R^{2*}_{reduced} \quad (9)$$

eFigure 3: Scatter plots showing relationships of baseline global β-amyloid SUVR and white matter hyperintensity volume with rate of neurodegeneration on MRI in cognitively normal participants



SUVR = standard uptake value ratio. Scatter plots show the raw data. The blue line is the line of best fit from the regression model (adjusted for sex, total intracranial volume and age at baseline scan) and the shaded area represents the 95% confidence intervals.

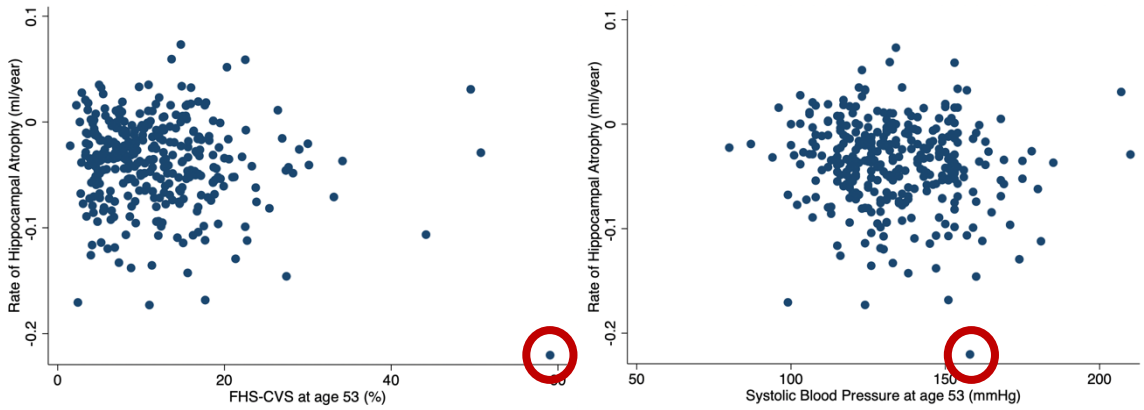
eTable 1: Interactive associations of predictors with rates of neurodegeneration on MRI in cognitively normal participants

Interaction	Difference in rate of change in BSI in ml/year (95% CIs)		
	Whole brain	Ventricles	Total hippocampus
WMHV x Aβ status	-0.17 (-1.68, 1.34)	0.01 (-0.51, 0.62)‡	0.007 (-0.013, 0.027)
WMHV x global Aβ SUVR	0.21 (-0.89, 1.32)	-0.12 (-0.49, 0.26)‡	0.006 (-0.009, 0.021)
Sex x Aβ status	-1.49* (-3.22, 0.25)	0.19 (-0.27, 0.66)‡	-0.013 (-0.037, 0.010)
Sex x global Aβ SUVR	-0.78* (-1.70, 0.15)	0.11 (-0.13, 0.36)‡	-0.006 (-0.018, 0.007)
Sex x WMHV	0.12 (-1.09, 1.33)	0.15 (-0.29, 0.68)‡	0.002 (-0.015, 0.018)
FHS-CVS age 69 x Aβ status	0.28* (-0.01, 0.58)	-0.07* (-0.15, 0.00)‡	0.006** (0.002, 0.010)
Systolic BP age 69 x Aβ status	0.27 (-0.26, 0.80)	-0.09 (-0.24, 0.07)‡	0.003 (-0.004, 0.010)

BSI = boundary shift integral; Aβ = β-amyloid; SUVR = standard uptake value ratio; WHMV = white matter hyperintensity volume; FHS-CVS = Framingham Heart Study Cardiovascular Risk Score; BP = blood pressure. All models were adjusted for sex, age at baseline scan and total intracranial volume. Models involving interactions with FHS-CVS or systolic BP were also adjusted for APOE ε4 status and adult socioeconomic position, and those involving interactions with systolic BP were additionally adjusted for smoking status, presence of diabetes and body mass index around time of baseline scan. *significant at p ≤0.1; **significant at p ≤0.01 ‡ bias-corrected and accelerated bootstrap 95% CIs. Interactions represent the following: WMHV x Aβ status is the effect of Aβ positive versus negative per 10ml additional WMHV; WMHV x global Aβ SUVR is the additional effect of 0.1 increment in global Aβ SUVR per 10ml additional WMHV; sex x Aβ status is the difference in effect of Aβ positive versus negative for females versus males; sex x global Aβ SUVR is the difference in effect of 0.1 increment in global Aβ SUVR for females versus males; sex x WMHV is the difference in effect of 10ml additional WMHV for females versus males; FHS-CVS x Aβ status is the effect of Aβ positive versus negative per 5% increment in FHS-CVS; systolic BP x Aβ status is the effect of Aβ positive versus negative per 10mmHg increment in BP.

eAppendix1: Associations of the Framingham Heart Study Cardiovascular Risk Score and systolic blood pressure at age 53 with rates of neurodegeneration on MRI in cognitively normal participants before and after exclusion of outlier

Scatter plots highlighting outlier (circled in red) in analyses of the effects of FHS-CVS and systolic blood pressure at age 53 on rates of hippocampal atrophy in later life



Summary of results before and after outlier was excluded

		Difference in rate of change in BSI in ml/year in later life (95% CIs) per 5% increment in the FHS-CVS at age 53 years		
		Whole Brain	Ventricles	Total Hippocampus
Before (n=327)	Model 1	-0.21 (-0.48, 0.07)	-0.01 (-0.08, 0.07)‡	-0.005* (-0.009, 0.001)
	Model 2	-0.18 (-0.46, 0.09)	-0.02 (-0.09, 0.05)‡	-0.005* (-0.008, -0.001)
After (n=326)	Model 1	-0.10 (-0.39, 0.20)	-0.01 (-0.09, 0.08)‡	-0.002 (-0.006, 0.002)
	Model 2	-0.07 (-0.36, 0.22)	-0.02 (-0.10, 0.06)‡	-0.002 (-0.006, 0.002)

BSI = boundary shift integral; FHS-CVS = Framingham Heart Study Cardiovascular Risk Score. Model 1 was adjusted for sex, total intracranial volume, age at baseline scan, APOE ε4 status, adult socioeconomic position and baseline amyloid-β status. Model 2 was further adjusted for baseline white matter hyperintensity volume. *significant at p ≤0.05; ‡ bias-corrected and accelerated bootstrap 95% CIs.

		Difference in rate of change in BSI in ml/year in later life (95% CIs) per 10mmHg increment in the systolic blood pressure at age 53 years		
		Whole Brain	Ventricles	Total Hippocampus
Before (n=326)	Model 1	-0.09 (-0.27, 0.09)	0.02 (-0.03, 0.08)‡	-0.003* (-0.005, -0.000)
	Model 2	-0.06 (-0.24, 0.12)	0.01 (-0.04, 0.06)‡	-0.002 (-0.005, 0.000)
After (n=325)	Model 1	-0.08 (-0.26, 0.10)	0.03 (-0.02, 0.08)‡	-0.002 (-0.005, 0.000)
	Model 2	-0.05 (-0.22, 0.13)	0.01 (-0.04, 0.06)‡	-0.002 (-0.004, 0.000)

BSI = boundary shift integral. Model 1 was adjusted for sex, total intracranial volume, age at baseline scan, APOE ε4 status, adult socioeconomic position, baseline amyloid-β status and smoking status, presence of diabetes and body mass index around time of baseline scan. Model 2 was further adjusted for baseline white matter hyperintensity volume. *significant at $p \leq 0.05$; ‡ bias-corrected and accelerated bootstrap 95% CIs.

eAppendix 2: Sensitivity analysis without adjustment for age at baseline scan

1. a) Effects of amyloid-β and white matter hyperintensity volume (assessed in separate models)

Predictor of interest	Difference in rate of change in BSI in ml/year (95% CIs)		
	Whole Brain	Ventricles	Total Hippocampus
Positive amyloid-β status (negative as reference)	-0.89* (-1.75, -0.03)	0.39** (0.17, 0.65)‡	-0.016** (-0.027, -0.004)
Global amyloid-β SUVR (per 0.1-unit increment)	-0.39 (-0.85, 0.07)	0.20** (0.08, 0.32)‡	-0.009** (-0.015, -0.002)
WMHV (per 10ml increment)	-1.10** (-1.70, -0.50)	0.32** (0.12, 0.62)‡	-0.014** (-0.023, -0.006)

1. b) Effects of amyloid-β status and white matter hyperintensity volume (assessed in same model)

Predictor of interest	Difference in rate of change in BSI in ml/year (95% CIs)		
	Whole Brain	Ventricles	Total Hippocampus
Positive amyloid-β status (negative as reference)	-0.84* (-1.69, 0.00)	0.38** (0.15, 0.64)‡	-0.015** (-0.027, -0.004)
WMHV (per 10ml increment)	-1.08** (-1.69, -0.48)	0.32** (0.13, 0.60)‡	-0.014** (-0.022, -0.006)

1. c) Effects of amyloid-β SUVR and white matter hyperintensity volume (assessed in same model)

Predictor of interest	Difference in rate of change in BSI in ml/year (95% CIs)		
	Whole Brain	Ventricles	Total Hippocampus
Global amyloid-β SUVR (per 0.1-unit increment)	-0.30 (-0.76, 0.15)	0.17** (0.05, 0.30)‡	-0.008* (-0.014, -0.001)
WMHV (per 10ml increment)	-1.06** (-1.66, -0.45)	0.30** (0.10, 0.59)‡	-0.013** (-0.022, -0.005)

SUVR = standard uptake value ratio; WMHV = white matter hyperintensity volume; BSI = boundary shift integral. All models were adjusted for sex and total intracranial volume. *significant at $p \leq 0.05$; **significant at $p \leq 0.01$; ‡ bias-corrected accelerated bootstrap 95% CIs.

2. Effects of APOE ε4 carrier status

Model	Difference in rate of change in BSI in ml/year (95% CIs) in APOE ε4 carriers compared to non-carriers		
	Whole brain	Ventricles	Total hippocampus
1	-0.61 (-1.32, 0.09)	0.11 (-0.08, 0.30)‡	-0.010* (-0.020, -0.001)
2	-0.42 (-1.17, 0.32)	0.00 (-0.18, 0.22)‡	-0.007 (-0.017, 0.003)
3	-0.51 (-1.20, 0.19)	0.07 (-0.12, 0.27)‡	-0.009 (-0.019, 0.001)
4	-0.32 (-1.05, 0.42)	-0.03 (-0.23, 0.18)‡	-0.005 (-0.015, 0.005)

BSI = boundary shift integral. Model 1 was adjusted for sex and total intracranial volume. Model 2 represents Model 1 plus adjustment for baseline β-amyloid status. Model 3 represents Model 1 plus adjustment for baseline white matter hyperintensity volume. Model 4 represents Model 1 plus adjustment for baseline β-amyloid status and white matter hyperintensity volume. *significant at p ≤0.05; ‡ bias-corrected and accelerated bootstrap 95% CIs.

3. Effects of the Framingham Heart Study Cardiovascular Risk Score at ages 36, 53 and 69

		Difference in rate of change in BSI in ml/year (95% CIs) per 5% increment in the FHS-CVS		
		Whole Brain	Ventricles	Total Hippocampus
Age 36 (n=301)	Model 1	-0.41 (-1.67, 0.85)	0.09 (-0.25, 0.47)‡	0.006 (-0.012, 0.024)
	Model 2	-0.27 (-1.52, 0.97)	0.05 (-0.30, 0.42)‡	0.008 (-0.009, 0.026)
Age 53 (n=326)	Model 1	-0.09 (-0.38, 0.21)	-0.01 (-0.10, 0.07)‡	-0.002 (-0.006, 0.002)
	Model 2	-0.06 (-0.35, 0.23)	-0.02 (-0.10, 0.06)‡	-0.002 (-0.005, 0.002)
Age 69 (n=330)	Model 1	-0.15 (-0.32, 0.02)	0.06* (0.00, 0.14)‡	-0.002 (-0.004, 0.000)
	Model 2	-0.12 (-0.29, 0.05)	0.05 (-0.01, 0.12)‡	-0.001 (-0.004, 0.001)

BSI = boundary shift integral; FHS-CVS = Framingham Heart Study Cardiovascular Risk Score. Model 1 was adjusted for sex, total intracranial volume, APOE ε4 status, adult socioeconomic position and baseline amyloid-β status. Model 2 was further adjusted for baseline white matter hyperintensity volume. Effects at age 53 refer to results after excluding an outlier (eAppendix 1). *significant at p ≤0.05; ‡ bias-corrected and accelerated bootstrap 95% CIs.

4. Effects of systolic blood pressure at ages 36, 53 and 69

		Difference in rate of change in BSI in ml/year (95% CIs) per 10mmHg increment in systolic blood pressure		
		Whole Brain	Ventricles	Total Hippocampus
Age 36 (m=301)	Model 1	-0.06 (-0.32, 0.20)	-0.01 (-0.09, 0.06)‡	-0.000 (-0.004, 0.003)
	Model 2	-0.06 (-0.32, 0.20)	-0.01 (-0.08, 0.06)‡	-0.000 (-0.004, 0.003)
Age 53 (n=325)	Model 1	-0.07 (-0.25, 0.11)	0.02 (-0.02, 0.08)‡	-0.002 (-0.005, 0.000)
	Model 2	-0.04 (-0.22, 0.14)	0.01 (-0.04, 0.05)‡	-0.002 (-0.004, 0.001)
Age 69 (n=333)	Model 1	-0.02 (-0.23, 0.19)	0.05 (-0.01, 0.14)‡	-0.001 (-0.004, 0.002)
	Model 2	0.02 (-0.18, 0.23)	0.03 (-0.03, 0.11)‡	-0.000 (-0.003, 0.003)

BSI = boundary shift integral. Model 1 was adjusted for sex, total intracranial volume, APOE ε4 status, adult socioeconomic position, baseline amyloid-β status, and smoking status, presence of diabetes and body mass index around time of baseline scan. Model 2 was further adjusted for baseline white matter hyperintensity volume. Effects at age 53 refer to results after excluding an outlier (eAppendix 1). ‡ bias-corrected and accelerated bootstrap 95% CIs.

eAppendix 3: Sensitivity analysis using SUVRs with cerebellar reference region

1. a) Effects of β-amyloid and white matter hyperintensity volume (assessed in separate models)

Predictor of interest	Difference in rate of change in BSI in ml/year (95% CIs)		
	Whole Brain	Ventricles	Total Hippocampus
Positive Aβ status (negative as reference)	-1.08* (-1.95, -0.20)	0.36** (0.16, 0.60)‡	-0.017** (-0.029, -0.005)
Global Aβ SUVR (per 0.1-unit increment)	-0.19 (-0.45, 0.06)	0.07 (-0.01, 0.13)‡	-0.004* (-0.007, -0.000)
WMHV (per 10ml increment)	-1.09** (-1.69, -0.49)	0.32** (0.12, 0.61)‡	-0.014** (-0.022, -0.006)

1. b) Effects of β-amyloid status and white matter hyperintensity volume (assessed in same model)

Predictor of interest	Difference in rate of change in BSI in ml/year (95% CIs)		
	Whole Brain	Ventricles	Total Hippocampus
Positive β-amyloid status (negative as reference)	-1.12* (-1.97, -0.26)	0.37** (0.17, 0.61)‡	-0.018** (-0.029, -0.006)
WMHV (per 10ml increment)	-1.11** (-1.71, -0.51)	0.32** (0.14, 0.65)‡	-0.014** (-0.023, -0.006)

1. c) Effects of β-amyloid SUVR and white matter hyperintensity volume (assessed in same model)

Predictor of interest	Difference in rate of change in BSI in ml/year (95% CIs)		
	Whole Brain	Ventricles	Total Hippocampus
Global β-amyloid SUVR (per 0.1-unit increment)	-0.20 (-0.46, 0.05)	0.07* (0.00, 0.14)‡	-0.004* (-0.007, -0.000)
WMHV (per 10ml increment)	1.10** (-1.70, -0.50)	0.32** (0.12, 0.62)‡	-0.014** (-0.022, -0.006)

SUVR = standard uptake value ratio; WMHV = white matter hyperintensity volume; BSI = boundary shift integral. Models were adjusted for sex, age at baseline scan and total intracranial volume. *significant at p ≤0.05; **significant at p ≤0.01; ‡ bias-corrected accelerated bootstrap 95% CIs.

2. Interactive effects of β-amyloid and other predictors

Interaction	Difference in rate of change in BSI in ml/year (95% CIs)		
	Whole brain	Ventricles	Total hippocampus
WMHV x β-amyloid status	0.35 (-1.55, 2.25)	-0.04 (-0.60, 0.78)‡	-0.014 (-0.040, 0.012)
WMHV x global β-amyloid SUVR	0.37 (-0.16, 0.89)	-0.16 (-0.44, 0.04)‡	0.002 (-0.005, 0.009)
Sex x β-amyloid status	-0.30 (-2.05, 1.45)	-0.08 (-0.49, 0.41)‡	0.011 (-0.013, 0.035)
Sex x global β-amyloid SUVR	-0.22 (-0.73, 0.29)	-0.00 (-0.15, 0.14)‡	-0.002 (-0.009, 0.005)
FHS-CVS age 69 x Aβ status	0.22 (-0.10, 0.53)	-0.04 (-0.13, 0.05)‡	0.000 (-0.004, 0.005)
Systolic BP age 69 x Aβ status	-0.16 (-0.68, 0.37)	0.06 (-0.09, 0.21)‡	-0.006 (-0.013, 0.001)

BSI = boundary shift integral; WHMV = white matter hyperintensity volume; SUVR = standard uptake value ratio; FHS-CVS = Framingham Heart Study Cardiovascular Risk Score; BP = blood pressure. All models were adjusted for sex, age at baseline scan and total intracranial volume. Models involving interactions with FHS-CVS or systolic BP were also adjusted for APOE ε4 status and adult socioeconomic position, and those involving interactions with systolic BP were additionally adjusted for smoking status, presence of diabetes and body mass index around time of baseline scan. ‡ bias-corrected and accelerated bootstrap 95% CIs. Interactions represent the following: WMHV x Aβ status is the effect of Aβ positive versus negative per 10ml additional WMHV; WMHV x global Aβ SUVR is the additional effect of 0.1 increment in global Aβ SUVR per 10ml additional WMHV; sex x Aβ status is the difference in effect of Aβ positive versus negative for females versus males; and sex x global Aβ SUVR is the difference in effect of 0.1 additional global Aβ SUVR for females versus males; FHS-CVS x Aβ status is the effect of Aβ positive versus negative per 5% increment in FHS-CVS; systolic BP x Aβ status is the effect of Aβ positive versus negative per 10mmHg increment in BP.

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