SUPPLEMENTARY MATERIALS

METHODS

Alternative diagnostic criteria

Neuropsychological test scores (Rey Auditory Verbal Learning Test delayed memory recall, Rey Auditory Verbal Learning Test delayed memory recognition, Animal fluency, Boston Naming Test, Trail Making Test Parts A & B) covering three cognitive domains (memory, language, executive function) were entered into a cluster analysis to derive three previously documented subtypes of MCI (amnestic MCI, dysnomic MCI, and dysexecutive MCI), as well as a cluster-derived CU group.[1–3] The ADNI-defined CU and the cluster-derived CU were combined into one CU group, and the three cluster-derived MCI subtypes were combined into one MCI group, consistent with several recent studies using ADNI data.[4–6]

Bayesian linear growth models

Bayesian linear growth modeling using the brms package[7] in R[8] is a multilevel modeling approach using the probabilistic language Stan. Bayesian growth modelling handles missing participant data and thus boosts statistical power and accommodates varying time windows of measurement. This is an important feature of the present approach, as ADNI data is not collected uniformly across the entire study. Similar to interaction effects in regression models, the effect of an independent variable(s) (BPV, time), (or their interaction; BPV by time) on a dependent variable (CSF levels) changes depending on another independent variable (APOE ϵ4).

RESULTS

ADNI diagnostic criteria

CU

In the ADNI-defined CU group, elevated BPV was associated with increased Ptau levels (systolic: ß: 5.36 [95% CI 4.81, 5.83]; diastolic: ß: 10.77 [95% CI 10.65, 10.87]), increased total tau levels (systolic: ß: 2.66 [95% CI 2.31, 3.10]; diastolic: ß: 9.66 [95% CI 9.54, 9.74]), and decreased Aβ levels (systolic: ß: -1.79 [95% CI -3.75, -.48]; diastolic: ß: -1.51 [95% CI -2.70, -.40]).

MCI

Similarly, elevated BPV in the ADNI-defined MCI group was associated with increased Ptau levels (diastolic: ß: 3.03 [95% CI .70, 5.44]; systolic was not significant: ß: .18 [95% CI -.30, .67]), increased total tau levels (systolic: ß: 1.04 [95% CI .69, 1.39]; diastolic: ß: 3.95 [95% CI .73, 7.26]), and decreased Aβ levels (systolic: ß: -.65 [95% CI -.92, -.31]; diastolic: ß: -2.96 [95% CI -6.96, -.74) at follow-up.

Alternative diagnostic criteria

CU

In the alternative criteria-defined CU group, elevated BPV was associated with increased Ptau levels (systolic: ß: 4.94 [95% CI 3.44, 6.33]; diastolic: ß: 9.55 [95% CI 9.35, 9.77]), increased total tau levels (systolic: ß: 1.60 [95% CI .76, 2.44]; diastolic: ß: 1.77 [95% CI .77, 2.82]), and decreased Aβ levels (diastolic: ß: -2.33 [95% CI -5.48, -.75]; systolic was not significant: ß: -.39 [95% CI -.82, .11]).

MCI

In the alternative criteria-defined MCI group, elevated BPV was associated with increased Ptau levels for diastolic BPV (ß: .39 [95% CI .01, .77]), decreased Ptau levels for systolic BPV (ß: -3.56 [95% CI -5.90, -1.08]), decreased total tau levels for systolic BPV (ß: -2.56 [95% CI -4.74, -.36]), diastolic was not significant: ß: 3.35 [95% CI -.09, 6.80]), and decreased Aβ levels (systolic: ß: -.78 [95% CI -1.56, -.32]; diastolic: ß: -4.86 [95% CI -6.32, -2.08) at follow-up.

Supplementary Table 1.

Baseline clinical and demographic information of excluded participants.

	Total sample (*N* = 1858)
Age (years)	73.2 (7.4)
Sex (*n*, % female)	886 (47.7%)
Education (years)	16.0 (2.8)
APOE ϵ4 carriers (*n*, %)	830 (44.7%)

Supplementary Table 2.

Model estimates of systolic BPV, APOE predicting CSF AD biomarker levels with additional covariates

	ß (95% credible interval)					
	Ptau		Total tau		Aβ	
Added covariate	**BPV x time**	**BPV x time x APOE ϵ4**	**BPV x time**	**BPV x time x APOE ϵ4**	**BPV x time**	**BPV x time x APOE ϵ4**
History of smoking	.84 (.77, .95)	8.55 (.55, 14.97)	.83 (.71, 1.02)	-.33 (-1.22, .56)	-1.84 (-4.28, -.25)	--
History of dyslipidemia	.89 (.76, 1.06)	9.43 (.85, 17.30)	1.15 (.71, 1.63)	-.34 (-1.21, .52)	-1.94 (-5.31, -.22)	--
Antidementia medication use	.83 (.74, .97)	9.39 (2.33, 16.46)	.91 (.70, 1.16)	-.34 (-1.21, .54)	-1.82 (-4.54, -.34)	--
Clinical diagnosis (ADNI)	.51 (.21, .73)	15.23 (13.45, 17.04)	.94 (.71, 1.25)	-.34 (-1.21, .54)	-.88 (-2.38, -.08)	--
Clinical diagnosis (alt.)	.51 (.23, .73)	11.37 (5.62, 17.08)	.99 (.71, 1.33)	-.35 (-1.22, .53)	-1.78 (-2.41, -.09)	--
BMI	.51 (.21, .73)	9.99 (2.73, 17.15)	1.04 (.71, 1.44)	-.34 (-1.21, .53)	-1.43 (-2.26, -.11)	--
History of alcohol abuse	.51 (.26, .73)	12.81 (8.38, 17.09)	.98 (.71, 1.32)	-.35 (-1.22, .52)	-.89 (-2.32, -.08)	--

Models adjusted for age at lumbar puncture/CSF sample collection, sex, APOE ϵ4 carrier status, baseline MMSE score, years of education, average BP, baseline hypertension, antihypertensive medication use and vascular risk.

Abbreviations: BPV = blood pressure variability; APOE ϵ4 = apolipoprotein ϵ4; Ptau = phosphorylated tau; Aβ = amyloid-beta; BMI = body mass index; ADNI = Alzheimer's Disease Neuroimaging Initiative

Supplementary Table 3.

Model estimates of diastolic BPV, APOE predicting CSF AD biomarker levels with additional covariates

	ß (95% credible interval)					
	Ptau		Total tau		Aβ	
Added covariate	**BPV x time**	**BPV x time x APOE ϵ4**	**BPV x time**	**BPV x time x APOE ϵ4**	**BPV x time**	**BPV x time x APOE ϵ4**
History of smoking	3.71 (2.14, 5.27)	24.75 (18.85, 30.61)	1.85 (.82, 2.84)	-.25 (-1.20, .75)	-3.28 (-6.82, -.32)	--
History of dyslipidemia	3.75 (2.13, 5.31)	29.62 (28.73, 30.51)	1.96 (.84, 3.02)	-.26 (-1.18, .70)	-3.02 (-6.28, -.34)	--
Antidementia medication use	3.76 (2.15, 5.31)	25.13 (19.67, 30.52)	2.10 (1.21, 2.95)	-.26 (-1.19, .70)	-3.64 (-7.05, -.53)	--
Clinical diagnosis (ADNI)	3.94 (2.25, 5.62)	28.35 (27.24, 29.45)	1.92 (.91, 2.87)	-.27 (-1.18, .64)	-2.29 (-5.27, -.30)	--
Clinical diagnosis (alt.)	3.91 (2.26, 5.54)	23.47 (17.31, 29.38)	1.99 (1.08, 2.81)	-.28 (-1.20, .65)	-2.97 (-6.45, -.33)	--
BMI	3.82 (2.26, 5.38)	25.77 (22.14, 29.32)	1.86 (.77, 2.94)	-.28 (-1.20, .66)	-2.57 (-4.80, -.31)	--
History of alcohol abuse	3.82 (2.25, 5.38)	30.55 (29.93, 31.21)	1.86 (.85, 2.80)	-.23 (-1.19, .78)	-2.46 (-4.08, -.60)	--

Models adjusted for age at lumbar puncture/CSF sample collection, sex, APOE ϵ4 carrier status, baseline MMSE score, years of education, average BP, baseline hypertension, antihypertensive medication use and vascular risk.

Abbreviations: BPV = blood pressure variability; APOE ϵ4 = apolipoprotein ϵ4; Ptau = phosphorylated tau; Aβ = amyloid-beta; BMI = body mass index; ADNI = Alzheimer's Disease Neuroimaging Initiative

Supplementary Table 4.

Baseline clinical and demographic information by ADNI-defined clinical diagnosis

	Total sample (*N* = 466)	
	CU (*n* = 165)	**MCI (*n* = 301)**
Age (years)	74.7 (5.5)	72.0 (7.2)
Sex (*n*, % female)	77 (46.7%)	126 (41.9)
Education (years)	16.4 (2.7)	16.3 (2.6)
APOE ϵ4 carriers (*n*, %)	38 (23.0%)	146 (48.5)
MMSE score	29.2 (1.2)	27.7 (1.8)
BMI (kg/m^2)	27.3 (4.9)	27.2 (5.0)
Vascular risk* (*n*, % low)	156 (94.6%)	280 (93.0)
Vascular risk factors (*n*, %)		
Cardiovascular disease	12 (7.3%)	30 (10.0)
Diabetes mellitus type 2	10 (6.1%)	25 (8.3)
Atrial fibrillation	7 (4.2%)	5 (1.7)
Carotid artery disease	2 (1.2%)	2 (0.7)
TIA/subclinical stroke	6 (3.6%)	3 (1.0)
Medication use (*n*, %)		
Antihypertensive agents	68 (41.2%)	121 (40.2)
ACE inhibitors	25 (15.2%)	47 (15.6)
ARBs	9 (5.5%)	21 (7.0)
Alpha blockers	4 (2.4%)	6 (2.0)
Calcium channel blockers	16 (9.7%)	18 (6.0)
Diuretics	13 (7.9%)	26 (8.6)
Antidementia agents	0 (0.0%)	57 (18.9)
Systolic BP (mmHg)		
Baseline	135.5 (15.1)	134.2 (17.2)
Average	134.0 (12.1)	133.3 (13.3)
VIM	5.2 (3.3)	5.4 (3.3)
Diastolic BP (mmHg)		
Baseline	74.7 (11.2)	73.9 (9.7)
Average	74.0 (8.4)	73.5 (7.6)
VIM	6.0 (1.2)	5.9 (1.2)

Means and SDs shown unless otherwise indicated.

*Baseline vascular risk level determined from presence/absence of individual risk factors (history of cardiovascular disease, history of diabetes mellitus type 2, history of atrial fibrillation, history of carotid artery disease, history of TIA/subclinical stroke). Risk level is low (≤ 1 individual vascular risk factor) or high (≥ 2 individual vascular risk factors), as described elsewhere.[20,37,38]

Abbreviations: MMSE = Mini Mental State Exam; BP = blood pressure; BMI = body mass index: VIM = variability independent of mean; MCI = mild cognitive impairment; CDR-sb = Clinical Dementia Rating Scale sum of box score; ACE inhibitors = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; TIA = transient ischemic attack; CU = cognitively unimpaired

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