



Cerebral Amyloid- β Burden and White Matter Injury: Associations, Clues for Underlying Mechanisms, and Implication on Cognitive Trajectory after Lecanemab Therapy

Ke Shi^{1, #}, Xin-Yu Luo^{1, #}, Tong-Tong Liu², Wen-Zhe Liu¹, Yuan-Fei Dong³, Fei-Bo Zheng³, Xin Zhou⁴, Jing-Song Xing⁴, Zhi-Hua Sun¹, Qiong-Qiong Chen¹, Li Jiang¹, Chen-Chen Tan¹, for the Alzheimer's Disease Neuroimaging Initiative, Lan Tan^{1, *}, Wei Xu^{1, *}

¹ Department of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China; ² Shandong University of Traditional Chinese Medicine, School of Rehabilitation Medicine; ³ Department of Nuclear Medicine, Qingdao Municipal Hospital, Qingdao, China; ⁴ Department of Sports Rehabilitation, Qingdao Municipal Hospital, Qingdao, China

Introduction

- White matter hyperintensity (WMH) is linked to cognitive decline and risk of Alzheimer's disease (AD).

Objectives

- To test whether amyloid- β (A β) deposition contributes to white matter injury and whether WMH dynamics can modulate the clinical efficacy of the anti-A β therapy.

Methods

- Twenty patients with early AD who are receiving lecanemab and a matched cohort of 110 untreated AD patients were followed. Linear mixed-effects models were used to examine the interplay between WMH trajectories and lecanemab on cognitive decline. The roles of A β burden in predicting baseline severity and progression rates of WMH were evaluated in a larger cohort of 1,031 adults. Finally, cerebrospinal fluid (CSF) proteomic and bioinformatic analyses were performed to identify potential candidate mediators and pathways linking A β to WMH progression.

Results

- Baseline data are shown in Table1, 2.

Table 1. Demographic and clinical characteristics between the Lecanemab and ADNI cohorts at baseline.

Characteristics	Lecanemab cohort (n=20)	Reference cohort (n=110)	p-value
Age, Years, (median [IQR])	72.5 (64.5, 81)	72 (67, 81)	0.905
Female, n (%)	17 (85.00)	87 (79.09)	0.543
MCI, n(%)	11 (55.00)	55 (50)	1.000
APOE ϵ 4, n (%)	14/19 (73.68)	76/110 (69.09)	0.687
History of stroke, n (%)	1 (5.00)	2 (1.82)	0.383
Hypertension, n (%)	8 (40.00)	47 (42.73)	0.820
Hyperlipidemia, n (%)	6 (30.00)	26(24.64)	0.543
Diabetes, n (%)	3 (15.00)	8 (7.27)	0.253
Coronary heart disease, n (%)	3 (15.00)	7 (6.36)	0.182
Depression, n (%)	3 (15.00)	32 (29.09)	0.191
Anxiety, n (%)	1 (5.00)	11 (10.00)	0.477
Cancer, n (%)	0 (0.00)	19 (17.27)	0.044
Sleep apnea, n (%)	1 (5.00)	16 (14.55)	0.244
Insomnia, n (%)	0 (0.00)	9 (8.18)	0.185
WMH (ml), (median [IQR])	11.40 (4.33, 18.71)	5.67 (2.18, 11.95)	0.024
MMSE scores, (median [IQR])	18 (11, 24)	25 (23, 28)	< 0.001
MoCA scores, (median [IQR])	11 (5.25, 18)	20 (17, 23)	< 0.001

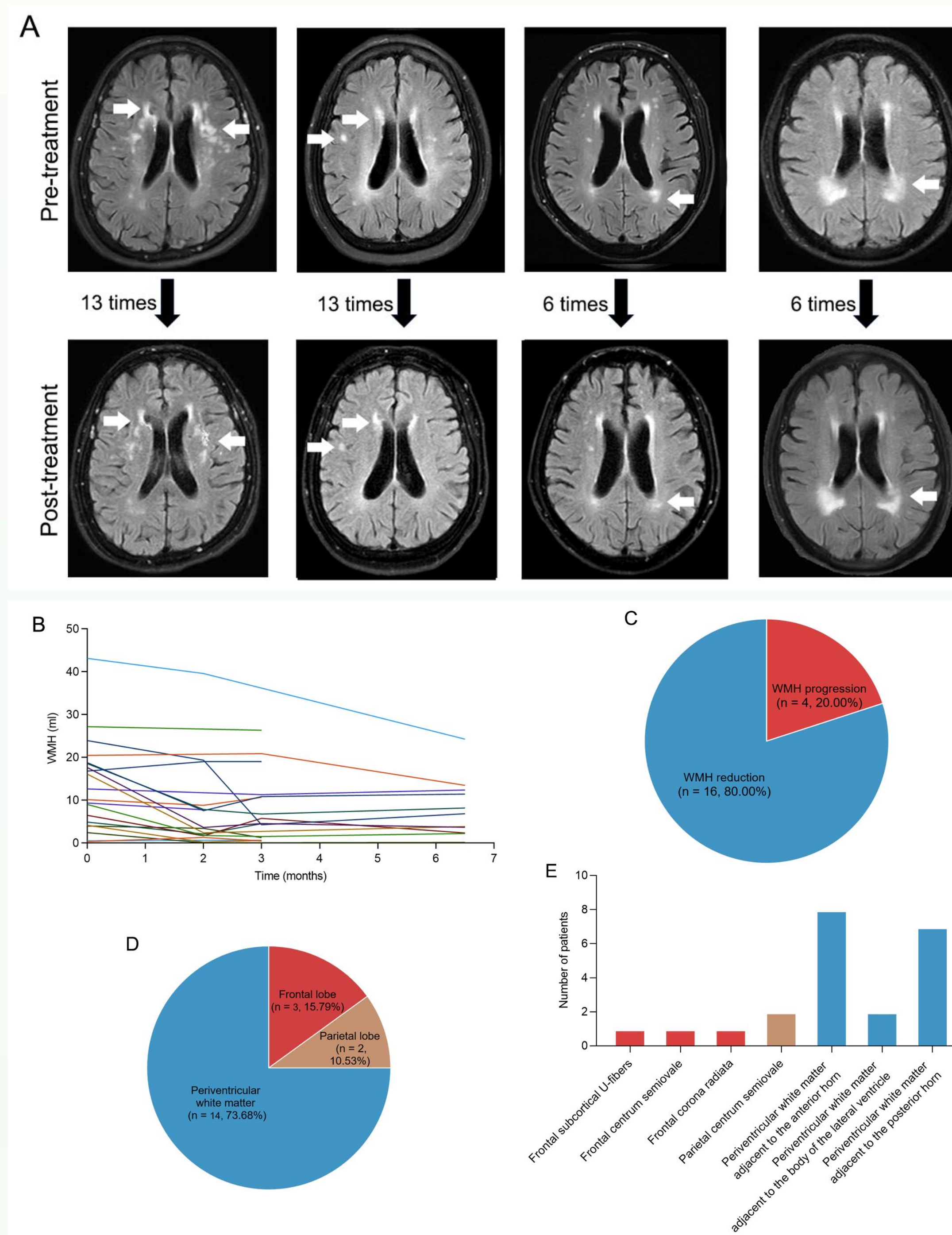
Abbreviations: MCI, Mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; WMH, white matter hyperintensity. Data are presented as median (interquartile range) for continuous variables and number (percentage) for categorical variables. P values were calculated using the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

Table 2. Baseline demographic and clinical characteristics in the ADNI cohort.

Characteristics	Total (n=1031)	High A β burden (n=60)	Low A β burden (n=971)	p-value
Age, Years, (median [IQR])	72 (67, 77)	72 (66.75, 75.25)	72 (67, 78)	0.166
Female, n (%)	531 (51.50)	29 (48.33)	502 (51.70)	0.709
BMI, kg/m ² , mean (SD)	26.38 (24.08, 29.51)	26.75 (23.42, 30.17)	26.35 (24.11, 29.50)	0.851
AD, n(%)	145 (14.06)	28 (46.67)	117 (12.05)	< 0.001
APOE ϵ 4, n (%)	460 (44.62)	46 (76.66)	414 (42.63)	< 0.001
History of stroke, n (%)	34 (3.30)	1 (1.67)	33 (3.40)	0.716
Hypertension, n (%)	462 (44.81)	30 (50.00)	432 (44.49)	0.485
Hyperlipidemia, n (%)	189 (18.33)	9 (15.00)	180 (18.54)	0.606
Diabetes, n (%)	96 (9.31)	8 (13.33)	88 (9.06)	0.381
Coronary heart disease, n (%)	73 (7.08)	2 (3.33)	71 (7.31)	0.431
Depression, n (%)	234 (22.70)	20 (33.33)	214 (22.04)	0.062
Anxiety, n (%)	81 (7.86)	10 (16.67)	71 (7.31)	0.018
Cancer, n (%)	146 (14.16)	1 (1.67)	145 (14.93)	0.002
Sleep apnea, n (%)	98 (9.51)	8 (13.33)	90 (9.27)	0.415
Insomnia, n (%)	95 (9.21)	3 (5.00)	92 (9.47)	1.000
Smoking, n (%)	199 (19.30)	11 (18.33)	188 (19.36)	0.978

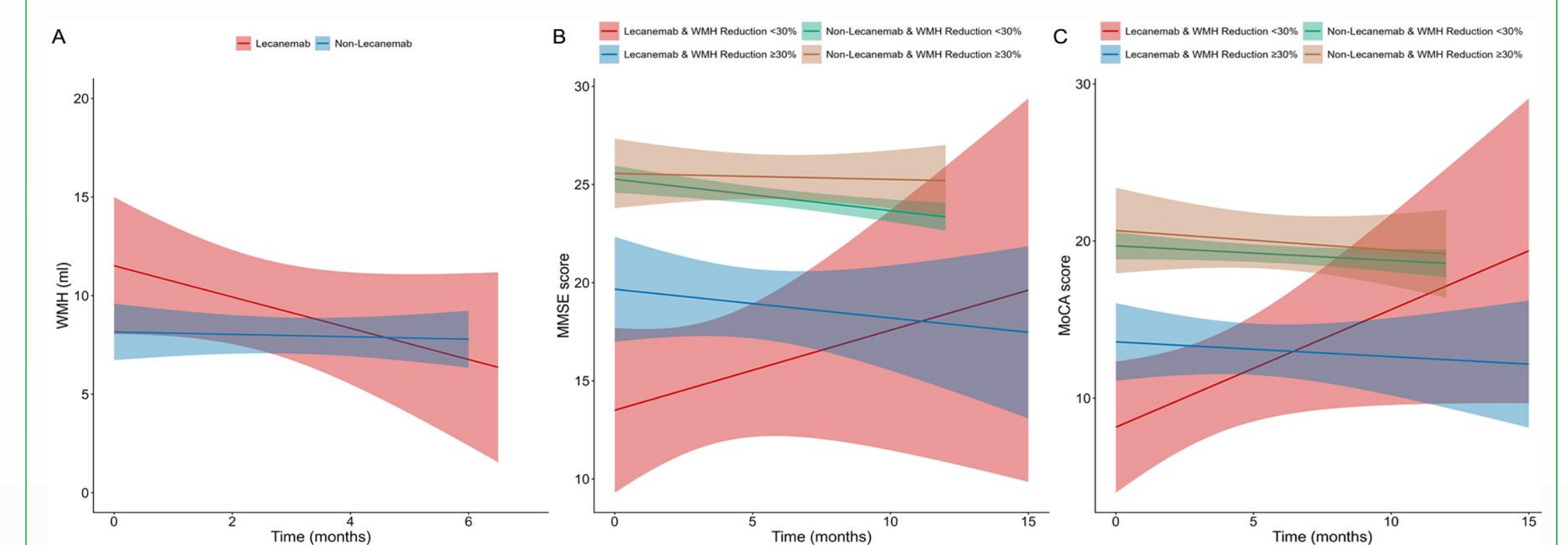
Data are presented as median (interquartile range) for continuous variables and number (percentage) for categorical variables. P values were calculated using the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

- Following lecanemab treatment (median = 13 times), 80% of patients showed WMH reductions, predominantly in periventricular and frontoparietal regions .

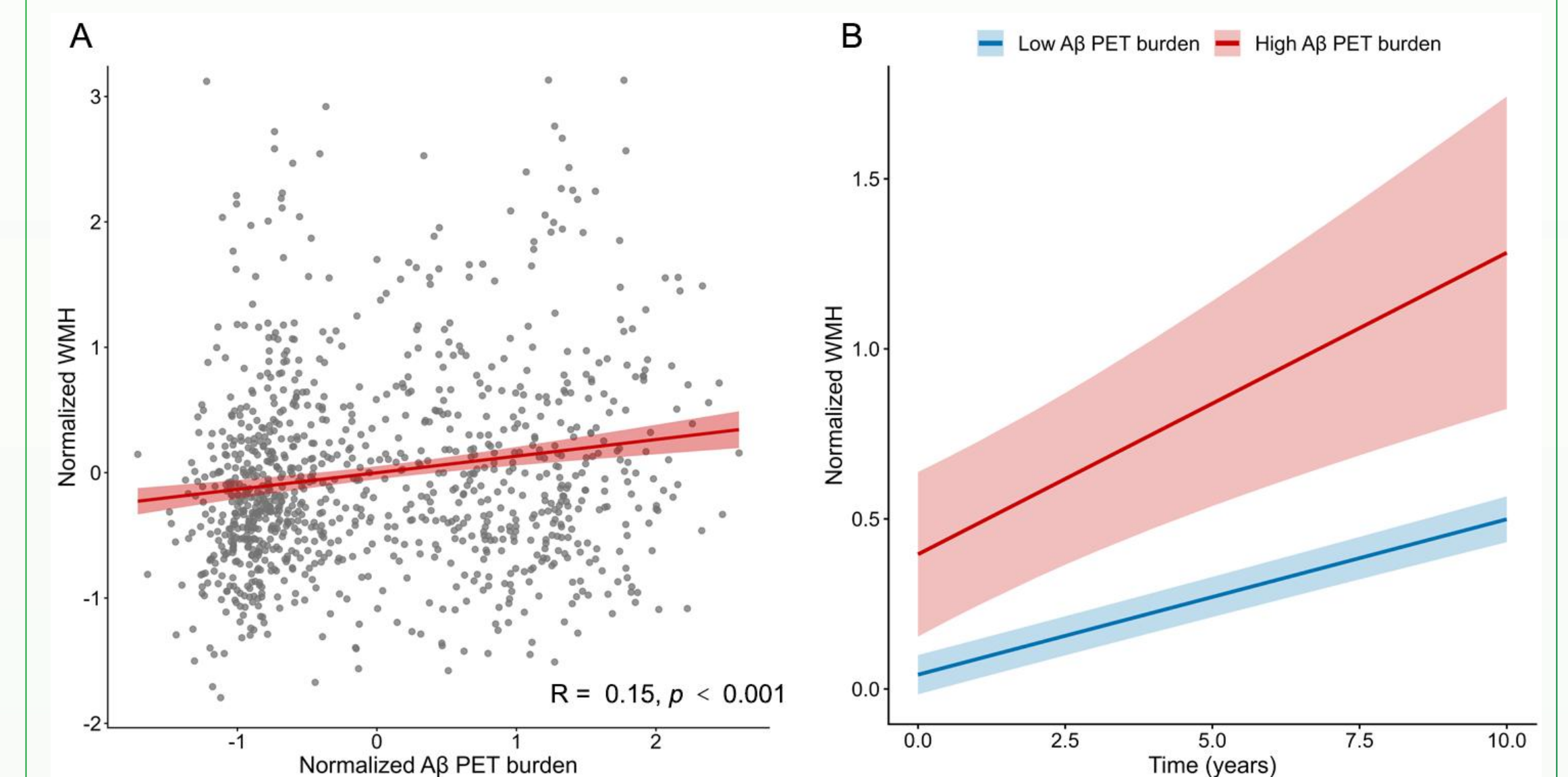


- Compared to the reference cohort, WMH progression is significantly slower among those with anti-A β therapy.

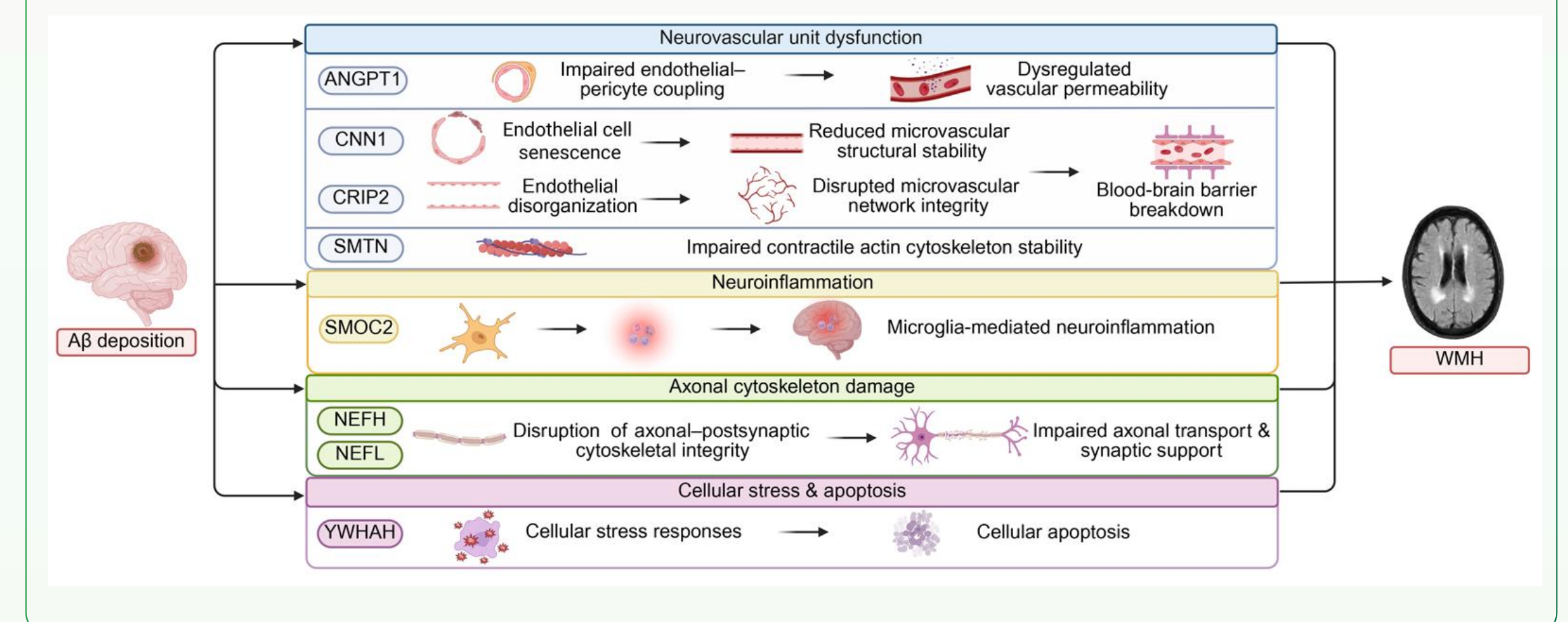
- WMH trajectory significantly modified the relationship between anti-A β therapy and cognitive decline, with greater cognitive improvement observed among those with smaller WMH reductions .



- The levels of A β burden were correlated with higher burden and accelerated rates of WMH.



- Eight proteins in CSF were found to mediate the association of A β with WMH. They were enriched in vascular-endothelial, neuro-cytoskeletal, and neuroinflammation pathways .



Conclusion

- The interplay of A β with white matter integrity contribute to cognitive decline in the context of Alzheimer's disease.

These authors contribute to this work equally.

* Correspondence to: Prof. Wei Xu & Prof. Lan Tan, Department of Neurology, Qingdao Municipal Hospital, Qingdao, China, Donghai Middle Road, No.5, Qingdao, China.

E-mail address: dr_xuwei@qdu.edu.cn (Wei Xu) & dr.tanlan@163.com (Lan Tan)

Tel: +86 0532 15610091257