Journal of Alzheimer's Disease 73 (2020) 759–768
DOI 10.3233/JAD-191005
IOS Press

Associations of White Matter Hyperintensities with Cognitive Decline: A Longitudinal Study

Yan-Li Wang[a,1], Wei Chen[a,1], Wen-Jie Cai[c,1], Hao Hu[a], Wei Xu[a], Zuo-Teng Wang[a], Xi-Peng Cao[b], Lan Tan[a,*] and Jin-Tai Yu[c,*] Alzheimer's Disease Neuroimaging Initiative[2]
[a]*Department of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China*
[b]*Clinical Research Center, Qingdao Municipal Hospital, Qingdao University, Qingdao, China*
[c]*Department of Neurology and Institute of Neurology, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China*

Handling Associate Editor: Yong Liu

Accepted 10 November 2019

Abstract. White matter hyperintensities (WMHs), mainly caused by cerebrovascular injury, may lead to cognitive impairment. In order to identify whether the volume of WMHs is associated with cognitive decline over years, this longitudinal study involved 818 individuals from the ADNI-2 dataset from August 2010 to May 2017. Cross-sectional and longitudinal associations of WMHs with 8 cognitive domains were explored, using Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Clinical Dementia Rating Sum of Boxes (CDRSB), Alzheimer Disease Assessment Scale-Cognitive (ADAS-Cog13), Rey Auditory Verbal Learning Test (RAVLT), Functional Assessment Questionnaire (FAQ), executive function (ADNI-EF), and memory function (ADNI-Mem). The association analyses were performed using multiple linear regression models, linear mixed models, Spearman rank correlation, and Kaplan-Meier survival curves. The volumes of WMHs were greater in patients with Alzheimer's disease (AD) dementia compared with controls ($p < 0.001$) and mild cognitive impairment ($p = 0.006$) patients at baseline. The bigger volumes of WMHs correlated with worse performances on ADAS-Cog13 and ADNI-EF ($p = 0.029$; $p = 0.003$) at baseline and MMSE, MoCA, CDRSB, ADAS-Cog13, FAQ, and ADNI-Mem (overall $p < 0.05$) longitudinally, after adjusting for age, sex, educational level, apolipoprotein E $\varepsilon 4$ genotype, hypertension, hyperlipidemia, diabetes, smoking, infarction, and diagnosis. Additionally, the correlations between the change rate of WMHs and change rates of MMSE, MoCA, CDRSB, FAQ, ADNI-EF, and ADNI-Mem were statistically significant. Furthermore, patients with high WMH volumes showed an increased likelihood of dementia. The results of the study suggest that WMH volume is associated with cognitive decline, and it contributes to the conversion to AD.

Keywords: Alzheimer's disease, Alzheimer's Disease Neuroimaging Initiative, cognition, white matter hyperintensities

[1]These authors contributed equally to this work.

[2]Data used in preparation for this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

*Correspondence to: Dr. Jin-Tai Yu, Department of Neurology, Huashan Hospital, Fudan University, No. 12 Wulumuqi Road, Shanghai, China. E-mail: yu-jintai@163.com.; Dr. Lan Tan, Department of Neurology, Qingdao Municipal Hospital, Qingdao University, No. 5 Donghai Middle Road, Qingdao, China. E-mail: dr.tanlan@163.com.

ISSN 1387-2877/20/$35.00

INTRODUCTION

White matter hyperintensities (WMHs) are areas of increased signal in brain white matter visualized by magnetic resonance imaging (MRI). WMHs, which are common in older adults, are a major manifestation of cerebral small vessel disease [1]. The results of previous studies revealed that increased WMH volumes were associated with increased risk of late onset cognitive impairment and dementia, and the severity of WMHs could alter the risk and progression of Alzheimer's disease (AD) [2, 3]. Pathological studies showed that WMHs were usually considered to represent ischemic-associated demyelination and axonal degeneration [4]. Besides, patients with AD are characterized by demyelination and axonal loss [5]. WMHs are also a result of vascular amyloidosis, and cerebral amyloid-β protein deposition is an important pathophysiological process underlying AD [6]. Therefore, whether the occurrence of WMHs could facilitate the diagnosis of AD needs to be discussed [3].

Generally, several biomarkers could be used to monitor the progression of AD, including cerebrospinal fluid amyloid and tau, as well as positron emission tomography (PET) of brain amyloid and tau [7, 8]. In consideration of invasiveness or expensiveness, these biomarkers are unsuitable for clinical application. However, MRI, a noninvasive and inexpensive marker, plays an important part in diagnosing AD and monitoring AD process. Previous studies focused on structural imaging findings, such as hippocampus volume, and ignored subcortical MRI changes related to AD which included WMHs. The progression of WMHs may be a promising biomarker to predict cognitive outcomes [9].

However, whether WMHs are associated with dementia is inconsistent. A longitudinal cohort aging study revealed that periventricular WMHs were not correlated with dementia [10], possibly due to interference with specific cholinergic projections. Due to the insufficient previous research, our study aimed to detect associations of WMHs with cognitive decline. To prove the hypothesis that WMH progression is associated with cognitive decline, we longitudinally measured the volume of WMHs among participants with normal cognition, mild cognitive impairment (MCI), and AD dementia in the Alzheimer Disease Neuroimaging Initiative (ADNI).

METHODS

ADNI dataset

Data used in this study were obtained from the ADNI database (http://adni.loni.usc.edu) in May 2019. The ADNI database was established in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and non-profit organizations as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, as well as clinical and neuropsychological assessments can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments, monitor their effectiveness, as well as shorten the time and cost of clinical trials.

The principal investigator of this initiative is Michael W. Weiner, MD, the VA Medical Center and the University of California-San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the United States and Canada. For up-to-date information, see http://www.adni-info.org. The ADNI was approved by medical ethics committees of all participating institutions. Written informed consent was obtained from all participants.

Participants

From August 2010 to May 2017, our cohort recruited cognitively normal adults, patients clinically diagnosed with MCI and those with AD dementia with baseline and follow-up data on WMHs. The inclusive and exclusive criteria for participants were described in a previous study [11]. The healthy controls had a Mini-Mental State Examination (MMSE) score of 24 to 30 and a Clinical Dementia Rating Sum of Boxes (CDR-SB) score of 0, without memory complaints. The MCI subjects had memory complaints, abnormal memory tested by education adjusted scores on the Wechsler Memory Scale Logical Memory II, a MMSE score of 24 to 30, a CDR-SB score of 0.5, and absence of dementia. The AD patients had a MMSE score of 20 to 26 and a CDR-SB score of 0.5 or 1, and met the

National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for probable AD [12].

A total of 818 ADNI participants were included in the present study, including 259 with normal cognition, 448 with MCI, and 111 with AD dementia. In the cohort, the mean (standard deviation, SD) age was 72.4 (7.1) years; 386 (47.2%) were women; mean (SD) years of education was 16.3 (2.6) years; and 372 (45.5%) were apolipoprotein E (*APOE*) ε4 allele carriers. All tests in the analysis were administered at baseline, 6 months, 1 year, and every year thereafter.

Measurement of WMHs

The process of MRI scan was described in a previous publication [13]. Briefly, ADNI participants from 2004 to 2009 had a 1.5-Tesla MRI, while from 2010 onward brain images were acquired using 3.0-Tesla MRI (http://adni.loni.usc.edu/methods/mri-tool/mri-analysis/). And in this study, all participants were scanned using 3.0T T1-weighted and fluid-attenuation inversion recovery (FLAIR) sequences. The WMH measurement approach has been described in detail on the ADNI site (http://adni.loni.usc.edu). Images were processed to 1) remove non-brain tissues from T1-weighted and FLAIR images; 2) spatially align the image pair; and 3) remove artifacts in MRI. Next images were warped to a standard template space in which the prior probability of WMH occurrence and the FLAIR signal characteristics of WMHs were modeled at every location in the cerebral white matter. This prior information, together with the signal intensities of the FLAIR image in question, was used to identify WMHs. The numbers of participants for different measures at each visit are shown in Supplementary Table 1, and the mean (SD) follow-up time was 28.6 (16.2) months. For analysis, WMHs volumes were power transformed to meet normal distribution. Infarctions were defined as presence or absence on T2-weighted images.

Cognitive assessments

Participants in this analysis had single-factor cognitive assessments and composite measures. The single-factor cognitive tests included MMSE [14], Montreal Cognitive Assessment (MoCA) [15], CDR-SB [16], Alzheimer Disease Assessment Scale-Cognitive (ADAS-Cog13) [17], Rey Auditory Verbal Learning Test (RAVLT) [18], and Functional Assessment Questionnaire (FAQ) [19]. The composite scores referred to test results of executive function (ADNI-EF) [20] and memory function (ADNI-Mem) [21] using psychometrically optimized approaches with items from ADNI neuropsychological assessments. Briefly, item-level data from the Trail Making Test (A and B), digit span backward, digit symbol, animal naming, vegetable naming, and the clock drawing test were used in the calculation of the ADNI-EF score. Single-factor models based on item-level data from the RAVLT, the ADAS-Cog, the MMSE, and the Logical Memory test were used in the calculation of the ADNI-Mem score. Finally, the analyses of baseline cognitive scores and longitudinal change rates over 4 years were conducted.

Statistical analysis

All statistical analyses were performed with R version 1.1.383. A two-tailed p-value<0.05 was considered statistically significant. Associations between the volume of WMHs and demographic characteristics were assessed using the Kruskal-Wallis test and Spearman rank correlation. Multiple linear regression models were used to investigate associations between the volume of WMHs at baseline and cognition. Linear mixed models with random effects were employed to determine longitudinal associations between the volume of WMHs and cognition. All models were adjusted for age, sex, educational level, *APOE* ε4 genotype, hypertension, hyperlipidemia, diabetes, smoking, infarction, and diagnosis, and all dependent variables in the models were transformed into z scores. Besides, Spearman rank correlation was used to evaluate correlations between the slope for WMHs and the slopes for cognition. Slopes were calculated in separate liner mixed-effects models controlled for age, sex, educational level, *APOE* ε4 genotype, hypertension, hyperlipidemia, diabetes, smoking, infarction, and diagnosis. Kaplan-Meier survival curves were plotted with log-rank test to compare the probabilities of conversion to AD dementia between low and high WMH groups. And the median WMH volume was chosen as cutoff to classify participants as high WMH group ($n = 1367$) or low WMH group ($n = 1367$).

Table 1
Subject characteristics at baseline

Characteristics	CN ($n=259$)	MCI ($n=448$)	AD ($n=111$)	p
Age, mean ± SD, y	72.96 ± 6.06	71.45 ± 7.35	74.66 ± 7.93	<0.001
Female, No. (%)	138 (53.28)	203 (45.31)	45 (40.54)	0.04
Educational level, mean ± SD, y	16.64 ± 2.54	16.19 ± 2.64	15.95 ± 2.60	0.029
≥1 *APOE* ε4 allele, No. (%)	79 (30.50)	214 (47.77)	79 (71.17)	<0.001
Hypertension (yes/no) ($n=707$)	124/96	210/184	47/46	0.602
Hyperlipidemia (yes/no) ($n=707$)	123/97	232/162	63/30	0.149
DM2 (yes/no) ($n=707$)	27/193	45/349	11/82	0.951
Smoking (yes/no) ($n=707$)	4/216	5/389	3/90	0.416
WMH volume, mean ± SD, cm^3	5.42 ± 6.05	6.67 ± 7.29	7.81 ± 7.07	<0.001
Infarction (yes/no) ($n=771$)	11/210	36/404	2/108	0.031
Cognitive score				
MMSE, mean ± SD	29.03 ± 1.22	28.09 ± 1.69	23.09 ± 2.04	<0.001
MoCA, mean ± SD	25.76 ± 2.42	23.45 ± 3.18	17.31 ± 4.49	<0.001
CDR-SB, mean ± SD	0.04 ± 0.15	1.44 ± 0.87	4.58 ± 1.60	<0.001
ADAS-Cog13, mean ± SD	8.92 ± 4.33	14.7 ± 6.60	30.81 ± 8.17	<0.001
RAVLT, mean ± SD	45.87 ± 10.35	37.2 ± 11.08	21.87 ± 6.67	<0.001
FAQ, mean ± SD	0.23 ± 0.73	2.51 ± 3.67	13.41 ± 6.90	<0.001
ADNI-EF, mean ± SD	0.83 ± 0.81	0.39 ± 0.85	–0.82 ± 0.86	<0.001
ADNI-Mem, mean ± SD	1.07 ± 0.59	0.37 ± 0.69	–0.91 ± 0.48	<0.001

CN, cognitively normal; *APOE*, apolipoprotein E; DM2, diabetes mellitus type 2; WMHs, white matter hyperintensities; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CDR-SB, Clinical Dementia Rating Sum of Boxes; ADAS-Cog13, Alzheimer Disease Assessment Scale-Cognitive; RAVLT, Rey Auditory Verbal Learning Test; FAQ, Functional Assessment Questionnaire; ADNI-EF, executive function; ADNI-Mem, memory.

RESULTS

Baseline characteristics

Characteristics of the study participants are shown in Table 1. In the whole cohort, WMHs were associated with age (Spearman $\rho=0.45$, $p<0.001$) and sex ($\rho=-0.10$, $p=0.005$), but not with educational level ($p=0.071$) or *APOE* ε4 genotype ($p=0.752$). Similarly, WMHs were associated with age ($\rho=0.52$, $p<0.001$) and sex ($\rho=-0.10$, $p=0.042$), but not with educational level ($p=0.051$) or *APOE* ε4 genotype ($p=0.992$) in the MCI group. However, WMHs were only associated with age ($\rho=0.31$, $p<0.001$) in the controls and were associated with age ($\rho=0.35$, $p<0.001$) and *APOE* ε4 genotype ($\rho=-0.21$, $p=0.024$) in AD dementia group.

Correlations between WMHs and diagnostic groups

Baseline WMH volumes of the AD group (7.81 cm^3) were bigger than those of controls (5.42 cm^3; $p<0.001$) and MCI group (6.67 cm^3; $p=0.006$), but the differences were not significant between controls and MCI group ($p=0.111$; Fig. 1a). Over time, the WMH volume increased in all diagnostic groups, and the rates of increase were not significantly different among groups (Fig. 1b).

Baseline associations of WMHs with cognition

Table 2 shows the baseline associations between WMHs volume and cognitive measurements. At baseline, bigger WMH volumes correlated with lower ADNI-EF score ($\beta=-0.096$, $p=0.003$) and higher ADAS-Cog13 score ($\beta=0.059$, $p=0.029$) in the whole cohort. WMH volume was significantly associated with MoCA ($\beta=-0.126$, $p=0.022$), ADAS-Cog13 ($\beta=0.126$, $p=0.019$) and EF ($\beta=-0.127$, $p=0.015$) scores in the MCI group and with FAQ ($\beta=0.247$, $p=0.037$) in the AD group.

Longitudinal associations of WMHs with cognition

Longitudinal associations of WMH volume with cognition are shown in Fig. 2. Over time, increased WMH volumes were associated with all measurements. Table 3 shows the associations of longitudinal cognitive measurements with baseline WMH volume and change rate of WMHs. In the whole cohort, CDRSB score showed the strongest association

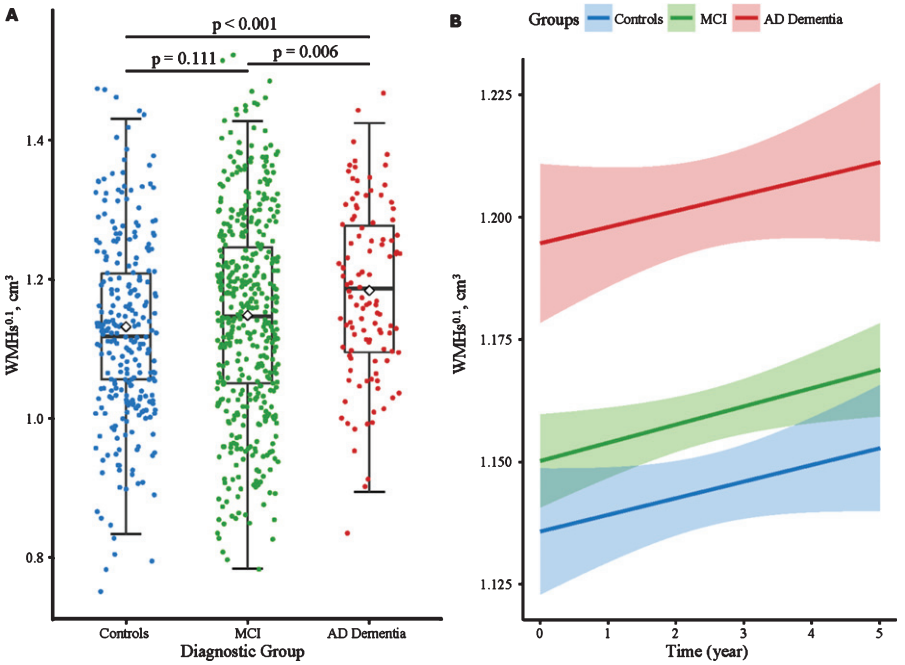

Fig. 1. White matter hyperintensities (WMHs) volume by diagnosis. A) WMHs in patients with normal cognition, MCI, and AD at baseline. B) WMHs in different diagnostic group longitudinally. MCI, mild cognitive impairment; AD, Alzheimer's disease.

Table 2
Associations of WMHs with cognitive measurements at baseline

	All subjects		Controls		MCI		AD dementia	
	β	p	β	p	β	p	β	p
MMSE	–0.0406	0.1273	–0.0284	0.7002	–0.0664	0.2357	–0.1846	0.1095
MoCA	–0.0569	0.0669	–0.0287	0.6644	–0.1263	0.0217	–0.0890	0.4247
CDRSB	0.0072	0.7217	–0.0373	0.6082	0.0368	0.5345	0.0913	0.4340
ADAS-Cog13	0.0591	0.0292	0.0079	0.9037	0.1257	0.0194	0.1128	0.3455
RAVLT	–0.0066	0.8283	0.0638	0.3287	–0.0418	0.4104	–0.0474	0.6712
FAQ	0.0531	0.0654	–0.0074	0.9160	0.0635	0.2897	0.2474	0.0368
ADNI-Mem	–0.0184	0.5009	0.0267	0.6833	–0.0589	0.2512	–0.0361	0.7639
ADNI-EF	–0.0958	0.0032	–0.1039	0.1031	–0.1273	0.0152	–0.0610	0.5990

WMHs, white matter hyperintensities; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CDR-SB, Clinical Dementia Rating Sum of Boxes; ADAS-Cog13, Alzheimer Disease Assessment Scale-Cognitive; RAVLT, Rey Auditory Verbal Learning Test; FAQ, Functional Assessment Questionnaire; ADNI-EF, executive function; ADNI-Mem, memory.

with baseline WMH volume (β= 0.058, $p = 0.001$), and MoCA score showed the strongest association with the change rate of WMH volume (β=–0.063, $p < 0.001$). Over time, bigger baseline WMHs volume was associated with lower ADNI-Mem score (β=–0.039, $p = 0.024$) in the MCI group and lower MMSE score (β=–0.247, $p = 0.023$) in the AD group (Supplementary Table 2). A higher rate of increase in WMHs was associated with lower MoCA (β=–0.147, $p = 0.020$) in the controls, as well as with higher CDRSB (β=0.0546, $p = 0.041$) and higher FAQ (β= 0.050, $p = 0.049$) in the MCI group (Supplementary Table 3).

Correlations between change rates of WMHs and cognitive measurements

For all patients, increased change rate of WMHs was associated with decreases in MMSE, MoCA, ADNI-Mem, and ADNI-EF scores and increases in CDRSB and FAQ scores. Furthermore, the rate of increase in WMHs was positively associated the rates of increase in FAQ score in controls, and negatively associated with the rates of increase in MMSE and MoCA scores in patients with MCI and with the rates of increase in RAVLT and ADNI-EF scores in patients with AD (Table 4).

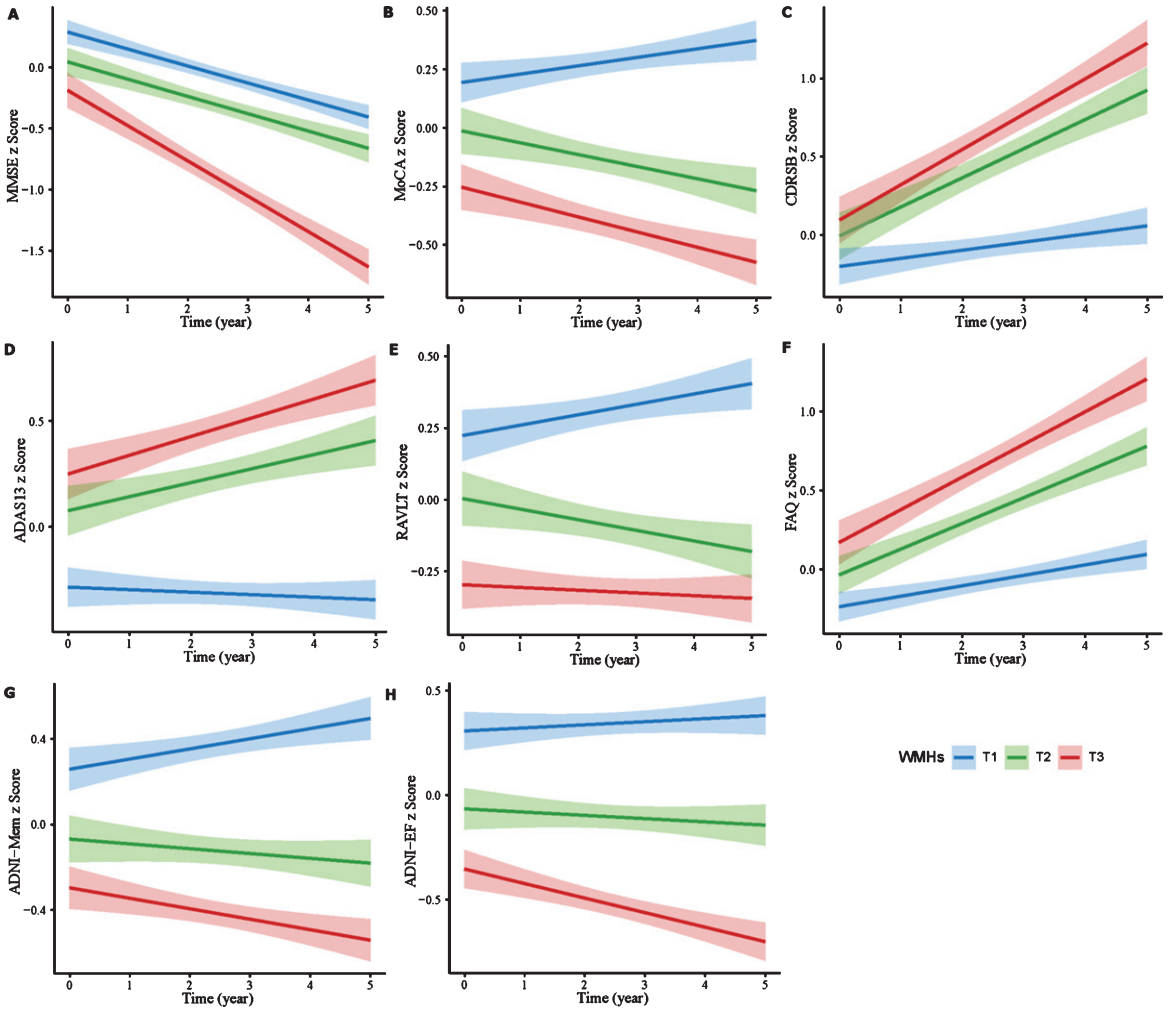

Fig. 2. Longitudinal associations between white matter hyperintensities (WMHs) and cognition decline. Estimated means and 95% CIs from linear mixed-effects models adjusted for age, sex, educational level, *APOE* ε4 genotype, infarction, hypertension, hyperlipidemia, diabetes, smoking and diagnosis. MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CDR-SB, Clinical Dementia Rating Sum of Boxes; ADAS-Cog13, Alzheimer Disease Assessment Scale-Cognitive; RAVLT, Rey Auditory Verbal Learning Test; FAQ, Functional Assessment Questionnaire; ANDI-Mem, memory function; ADNI-EF, executive function.

Probability of conversion to AD dementia

Kaplan-Meier survival curve showed that patients with high WMH volumes are at a higher risk of progression to AD (Log-rank $p = 0.004$; Fig. 3).

DISCUSSION

The present study aimed to investigate the relationships of WMHs with cognitive decline and AD dementia. The primary results showed that an increased WMH volume was linked to a faster cognitive decline at baseline and follow-up. For all patients, WMH volume was significantly associated with ADAS-Cog13 and ADNI-EF scores at baseline and with MMSE, MoCA, CDRSB, ADAS-Cog13, FAQ, and ADNI-Mem scores longitudinally. In addition, the change rate of WMHs volume was statistically significantly correlated with the change rates of MMSE, MoCA, CDRSB, FAQ, ADNI-Mem, and ADNI-EF scores. The different associations between WMHs and various cognitive measurements may cause by one-off tests of intricate cognitive components.

AD is a degenerative disorder of the brain accompanied by cognitive decline. Most prior studies on AD pathogenesis focused on the amyloid hypothesis but ignored small cerebral vessel disease-related

Table 3
Correlations between WMHs and longitudinal cognitive measurements of all patients

	Baseline WMH level		WMH rate	
	β	*p*	β	*p*
MMSE	–0.0459	0.0286	–0.0619	0.0049
MoCA	–0.0437	0.0119	–0.0631	0.0007
CDRSB	0.0577	0.0012	0.0559	0.0026
ADAS-Cog13	0.0402	0.0057	0.0364	0.0172
RAVLT	–0.0183	0.2317	–0.0085	0.6000
FAQ	0.0417	0.0166	0.0517	0.0043
ADNI-Mem	–0.0340	0.0036	–0.0309	0.0123
ADNI-EF	–0.0201	0.1633	–0.0401	0.0087

WMHs, white matter hyperintensities; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CDR-SB, Clinical Dementia Rating Sum of Boxes; ADAS-Cog13, Alzheimer Disease Assessment Scale-Cognitive; RAVLT, Rey Auditory Verbal Learning Test; FAQ, Functional Assessment Questionnaire; ADNI-EF, executive function; ADNI-Mem, memory.

pathological changes, like WMHs. A study found that WMHs may play an important role at the early phase of AD [22]. Correlations between WMHs and cognition may vary according to different clinical stages. For example, baseline WMH volume was significantly correlated with MoCA, ADAS-Cog13, and ADNI-EF scores in MCI stage but not in cognitive normal or AD stage. The changes in WMH volume and cognition may not be obvious in stage dementia, so most cognitive measurements were related to WMHs in the cognitive normal and MCI stage. Consistent with previous studies, our study showed WMH volume had a statistically significant association with cognitive decline in MCI patients [23, 24]. Meanwhile, a prior study showed that WMHs were associated with the risk of conversion from normal cognition to MCI [25]. Subjects with greater WMHs volumes may develop cognitive impairment earlier due to small vessel ischemia and gliosis [26]. In addition, WMHs volume was only associated with two tests (FAQ baseline; MMSE longitudinally) in the AD dementia phase, which may be explained by the short-time follow-up of the AD dementia group. Besides, the correlations of baseline WMHs or the increase rate of WMHs with the rate of cognitive decline were also confirmed in our study.

WMHs were not a specific marker of AD and they also increased in patients with vascular dementia, Lewy body disease, and depression [26, 27]. Previous studies have demonstrated that WMHs were associated with atherosclerosis, leading to hemadostenosis, ischemia, and hypoxia of distal small vessels and vascular endothelial injury, and further resulting in white matter damage [28]. Interestingly, there was a different opinion that white matter changes were not due to vascular disease [22]. Several mechanisms have linked WMHs with cognitive decline. Small vessel disease could damage prefrontal subcortical loops or result in stroke, which explains its possible association with cognitive impairment [29]. WMHs may interfere in projection pathways of modulating neurotransmitters, for example the cholinergic system. Acetylcholine may be a transmitter associated with attention, learning, and memory functions [30]. Various vascular risk factors could also have associations with cognitive decline via other mechanisms [29]. In addition, cerebrovascular damage could lead to AD-typical amyloid deposition and diffuse plaques [31]. Taken together, WMHs were significantly associated with cognitive decline.

The major strength of our study is that it is a longitudinal study assessing the changes in WMHs and multiple cognitive functions. And these results were based on the latest ADNI-2 cohort. The first limitation is that this study was restricted to participants with smaller WMH burden, which excluded patients with > 4 Hachniski score, resulting in a rel-

Table 4
Correlations between WMHs rate and change rate of cognitive measurements

	All subjects		Controls		MCI		AD dementia	
	ρ	*p*	*ρ*	*p*	*ρ*	*p*	*ρ*	*p*
MMSE	–0.0779	0.0435	0.0434	0.5524	–0.1293	0.0105	–0.1707	0.1019
MoCA	–0.1173	0.0024	0.0188	0.7969	–0.1463	0.0038	–0.1392	0.1879
CDRSB	0.0774	0.0446	0.0689	0.3460	0.0465	0.3588	0.1656	0.1126
ADAS-Cog13	0.0713	0.0646	0.0065	0.9297	0.0915	0.0709	0.1470	0.1619
RAVLT	–0.0382	0.3228	0.0462	0.5273	–0.0185	0.7146	–0.2284	0.0287
FAQ	0.0983	0.0108	0.2054	0.0047	0.0804	0.1124	0.1935	0.0648
ADNI-Mem	–0.0761	0.0485	0.0063	0.9311	–0.0750	0.1385	–0.1756	0.0922
ADNI-EF	–0.0953	0.0134	–0.0732	0.3164	–0.0883	0.0813	–0.2659	0.0102

WMHs, white matter hyperintensities; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CDR-SB, Clinical Dementia Rating Sum of Boxes; ADAS-Cog13, Alzheimer Disease Assessment Scale-Cognitive; RAVLT, Rey Auditory Verbal Learning Test; FAQ, Functional Assessment Questionnaire; ADNI-EF, executive function; ADNI-Mem, memory.

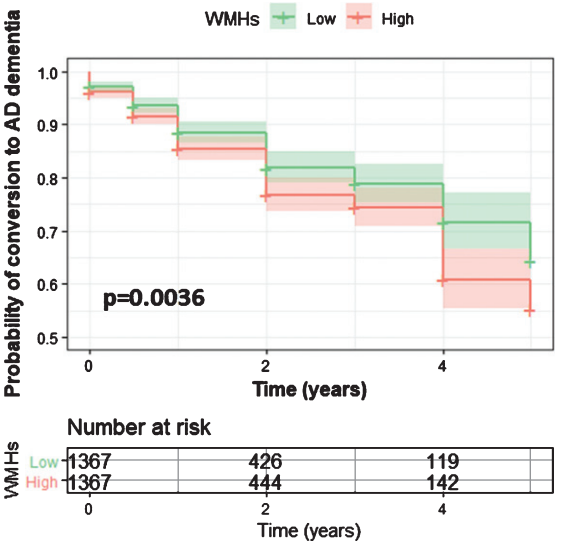

Fig. 3. Kaplan-Meier survival curves for white matter hyperintensities (WMHs) volume. Kaplan-Meier curves displayed conversion from cognitive normal or MCI to AD dementia. Seagreen: low WMHs; Salmon: high WMHs.

atively low correlation. The second limitation is that the cohort included those with non-AD neurodegenerative diseases, which prevented our testing for WMHs diagnostic specificity. The third limitation is that because the 2-year follow-up of AD dementia patients was short, the longitudinal associations between WMHs volume and cognition in the AD phase were not significant. Furthermore, we did not conduct a subanalysis stratified by the severity of WMHs according to Fazekas and Scheltens scales. These rating scales are time-consuming and not proper for assessing the progression of WMHs. In addition, future studies are also needed to explore the longitudinal associations of WMHs with cerebrospinal fluid or serum biomarkers, genetic markers, and neuroimaging markers.

Conclusion

This large longitudinal study suggests that WMHs have a significant impact on cognitive impairment and elevate the risk of conversion to dementia. Therefore, WMHs volume can be regarded as a noninvasive marker of cognitive degeneration.

ACKNOWLEDGMENTS

This study was supported by grants from the National Natural Science Foundation of China (81771148, 91849126), Shanghai Municipal Science and Technology Major Project (No.2018SHZDZX01) and ZHANGJIANG LAB, Tianqiao and Chrissy Chen Institute, and the State Key Laboratory of Neurobiology and Frontiers Center for Brain Science of Ministry of Education, Fudan University.

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (http://www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/19-1005r1).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-191005.

REFERENCES

[1] Rizvi B, Narkhede A, Last BS, Budge M, Tosto G, Manly JJ, Schupf N, Mayeux R, Brickman AM (2018) The effect of white matter hyperintensities on cognition is mediated by cortical atrophy. *Neurobiol Aging* **64**, 25-32.

[2] Lee S, Viqar F, Zimmerman ME, Narkhede A, Tosto G, Benzinger TL, Marcus DS, Fagan AM, Goate A, Fox NC, Cairns NJ, Holtzman DM, Buckles V, Ghetti B, McDade E, Martins RN, Saykin AJ, Masters CL, Ringman JM, Ryan NS, Forster S, Laske C, Schofield PR, Sperling RA, Salloway S, Correia S, Jack C, Jr., Weiner M, Bateman RJ, Morris JC, Mayeux R, Brickman AM, Dominantly Inherited Alzheimer Network (2016) White matter hyperintensities are a core feature of Alzheimer's disease: Evidence from the dominantly inherited Alzheimer network. *Ann Neurol* **79**, 929-939.

[3] Bos D, Wolters FJ, Darweesh SKL, Vernooij MW, de Wolf F, Ikram MA, Hofman A (2018) Cerebral small vessel disease and the risk of dementia: A systematic review and meta-analysis of population-based evidence. *Alzheimers Dement* **14**, 1482-1492.

[4] McAleese KE, Walker L, Graham S, Moya ELJ, Johnson M, Erskine D, Colloby SJ, Dey M, Martin-Ruiz C, Taylor JP, Thomas AJ, McKeith IG, De Carli C, Attems J (2017) Parietal white matter lesions in Alzheimer's disease are associated with cortical neurodegenerative pathology, but not with small vessel disease. *Acta Neuropathol* **134**, 459-473.

[5] Englund E (1998) Neuropathology of white matter changes in Alzheimer's disease and vascular dementia. *Dement Geriatr Cogn Disord* **9 Suppl 1**, 6-12.

[6] Sarro L, Tosakulwong N, Schwarz CG, Graff-Radford J, Przybelski SA, Lesnick TG, Zuk SM, Reid RI, Raman MR, Boeve BF, Ferman TJ, Knopman DS, Comi G, Filippi M, Murray ME, Parisi JE, Dickson DW, Petersen RC, Jack CR, Jr., Kantarci K (2017) An investigation of cerebrovascular lesions in dementia with Lewy bodies compared to Alzheimer's disease. *Alzheimers Dement* **13**, 257-266.

[7] Blennow K, Zetterberg H, Perry G, Avila J, Tabaton M, Zhu X (2018) The past and the future of Alzheimer's disease fluid biomarkers. *J Alzheimers Dis* **62**, 1125-1140.

[8] Laforce R, Jr., Soucy JP, Sellami L, Dallaire-Theroux C, Brunet F, Bergeron D, Miller BL, Ossenkoppele R (2018) Molecular imaging in dementia: Past, present, and future. *Alzheimers Dement* **14**, 1522-1552.

[9] Prabhakaran S (2019) Blood pressure, brain volume and white matter hyperintensities, and dementia risk. *JAMA* **322**, 512-513.

[10] Smith CD, Snowdon DA, Wang H, Markesbery WR (2000) White matter volumes and periventricular white matter hyperintensities in aging and dementia. *Neurology* **54**, 838-842.

[11] Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, Jack CR, Jr., Jagust WJ, Shaw LM, Toga AW, Trojanowski JQ, Weiner MW (2010) Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. *Neurology* **74**, 201-209.

[12] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-944.

[13] Jack CR, Jr., Bernstein MA, Fox NC, Thompson P, Alexander G, Harvey D, Borowski B, Britson PJ, J LW, Ward C, Dale AM, Felmlee JP, Gunter JL, Hill DL, Killiany R, Schuff N, Fox-Bosetti S, Lin C, Studholme C, DeCarli CS, Krueger G, Ward HA, Metzger GJ, Scott KT, Mallozzi R, Blezek D, Levy J, Debbins JP, Fleisher AS, Albert M, Green R, Bartzokis G, Glover G, Mugler J, Weiner MW (2008) The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. *J Magn Reson Imaging* **27**, 685-691.

[14] Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.

[15] Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* **53**, 695-699.

[16] Morris JC (1993) The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* **43**, 2412-2414.

[17] Rosen WG, Mohs RC, Davis KL (1984) A new rating scale for Alzheimer's disease. *Am J Psychiatry* **141**, 1356-1364.

[18] Schmidt M (1996) *Rey Auditory Verbal Learning Test: A Handbook*. Western Psychological Services, Los Angeles, CA.

[19] Pfeffer RI, Kurosaki TT, Harrah CH, Jr., Chance JM, Filos S (1982) Measurement of functional activities in older adults in the community. *J Gerontol* **37**, 323-329.

[20] Gibbons LE, Carle AC, Mackin RS, Harvey D, Mukherjee S, Insel P, Curtis SM, Mungas D, Crane PK, Alzheimer's Disease Neuroimaging Initiative (2012) A composite score for executive functioning, validated in Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with baseline mild cognitive impairment. *Brain Imaging Behav* **6**, 517-527.

[21] Crane PK, Carle A, Gibbons LE, Insel P, Mackin RS, Gross A, Jones RN, Mukherjee S, Curtis SM, Harvey D, Weiner M, Mungas D, Alzheimer's Disease Neuroimaging Initiative (2012) Development and assessment of a composite score for memory in the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Brain Imaging Behav* **6**, 502-516.

[22] Sachdev PS, Zhuang L, Braidy N, Wen W (2013) Is Alzheimer's a disease of the white matter? *Curr Opin Psychiatry* **26**, 244-251.

[23] Silbert LC, Dodge HH, Perkins LG, Sherbakov L, Lahna D, Erten-Lyons D, Woltjer R, Shinto L, Kaye JA (2012) Trajectory of white matter hyperintensity burden preceding mild cognitive impairment. *Neurology* **79**, 741-747.

[24] Vipin A, Foo HJL, Lim JKW, Chander RJ, Yong TT, Ng ASL, Hameed S, Ting SKS, Zhou J, Kandiah N (2018) Regional white matter hyperintensity influences grey matter atrophy in mild cognitive impairment. *J Alzheimers Dis* **66**, 533-549.

[25] Smith EE, Egorova S, Blacker D, Killiany RJ, Muzikansky A, Dickerson BC, Tanzi RE, Albert MS, Greenberg SM, Guttmann CR (2008) Magnetic resonance imaging white matter hyperintensities and brain volume in the prediction of mild cognitive impairment and dementia. *Arch Neurol* **65**, 94-100.

[26] Boyle PA, Yu L, Fleischman DA, Leurgans S, Yang J, Wilson RS, Schneider JA, Arvanitakis Z, Arfanakis K, Bennett DA (2016) White matter hyperintensities, incident mild cognitive impairment, and cognitive decline in old age. *Ann Clin Transl Neurol* **3**, 791-800.

[27] Prins ND, van Straaten EC, van Dijk EJ, Simoni M, van Schijndel RA, Vrooman HA, Koudstaal PJ, Scheltens P, Breteler MM, Barkhof F (2004) Measuring progression of

cerebral white matter lesions on MRI: visual rating and volumetrics. *Neurology* **62**, 1533-1539.

[28] Liu Y, Zhang M, Bao H, Zhang Z, Mei Y, Yun W, Zhou X (2018) The efficacy of intravenous thrombolysis in acute ischemic stroke patients with white matter hyperintensity. *Brain Behav* **8**, e01149.

[29] Prins ND, Scheltens P (2015) White matter hyperintensities, cognitive impairment and dementia: an update. *Nat Rev Neurol* **11**, 157-165.

[30] Bocti C, Swartz RH, Gao FQ, Sahlas DJ, Behl P, Black SE (2005) A new visual rating scale to assess strategic white matter hyperintensities within cholinergic pathways in dementia. *Stroke* **36**, 2126-2131.

[31] Cox SR, Lyall DM, Ritchie SJ, Bastin ME, Harris MA, Buchanan CR, Fawns-Ritchie C, Barbu MC, de Nooij L, Reus LM, Alloza C, Shen X, Neilson E, Alderson HL, Hunter S, Liewald DC, Whalley HC, McIntosh AM, Lawrie SJ, Pell JP, Tucker-Drob EM, Wardlaw JM, Gale CR, Deary IJ (2019) Associations between vascular risk factors and brain MRI indices in UK Biobank. *Eur Heart J* **40**, 2290-2300.