Clinical and demographic predictors of mild cognitive impairment for converting to Alzheimer's disease and reverting to normal cognition

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Author's key words: Alzheimer's disease, Mild cognitive impairment, Reverter, Converter, Clinical and demographic predictors

Abbreviation: AD, Alzheimer's disease; ADNI, Alzheimer's disease neuroimaging initiative; APOE, apolipoprotein E; CDR, clinical dementia rating; DWMH, deep white matter hyperintensity; FLAIR, fluid attenuated inversion recovery; MCI, mild cognitive impairment; MMSE, mini-mental state examination; MRI, magnetic resonance imaging; NINCDS / ADRDA, national institute of neurological and communicative disorders and stroke and Alzheimer's disease and related disorders association; PGA, parahippocampal gyrus atrophy; PVH, periventricular hyperintensity; VRFs, vascular risk factors; VSRAD, voxel-based specific regional analysis system for Alzheimer's disease; WMLs, white matter lesions.

Abstract

Objective: To identify clinical and demographic predictors for converting to Alzheimer's disease (AD), sustaining mild cognitive impairment (MCI), or reverting to normal cognition from MCI.

Methods: We retrospectively investigated 74 baseline MCI subjects who were categorized into three subgroups those who converted to AD, sustained with MCI, or reverted to normal cognition in one year. The clinical and demographic characteristics assessed were age, gender, educational attainment, vascular risk factors (VRFs), white matter lesions (WMLs), and parahippocampal gyrus atrophy (PGA) on magnetic resonance imaging (MRI). PGA was analyzed using the Voxel-based Specific Regional analysis system for AD (VSRAD).

Results: Out of 74 MCI subjects, 29 (39.2%) were classified as "converters", 39 (52.7%) as "sustained MCI", and 6 (8.1%) as "reverters". Among the three subgroups, there were significant differences in educational attainment (years) (*p=0.03), baseline mini-mental state examination (MMSE) scores (***p<0.001), and periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH) grades (*p=0.02 and *p=0.03, respectively). Baseline PGA showed a significant increasing trend among the three subgroups (reverters < sustained MCI < converters, $^{###}$p<0.001). MCI subjects with higher educational attainment and a low VSRAD Z-score without WMLs were related to the reverter-to-normal cognitive function.

Conclusions: Risk factors of MCI for AD converters were a low educational attainment, a low baseline MMSE score, high grade WMLs, and a high VSRAD Z-score, while a high educational attainment, a low VSRAD Z-score, and no WMLs characterized reverters.

Keywords: Alzheimer's disease, Mild cognitive impairment, reverter, converter, Clinical and demographic predictors

Introduction

Mild cognitive impairment (MCI) has been defined as a transition state between healthy aging and dementia, such as Alzheimer's disease (AD)[1]. The annual rate of conversion from MCI to AD was from 8.3% to 33.6%[2, 3] with a high rate of MCI subjects with sustained MCI (64%)[4] and the reversion to normal cognition varying from 2.0% to 53.0%[5-7]. Detecting predictors of MCI for converting to AD or for reverting to normal cognition is important to prevent or delay further cognitive decline and to promote reversion.

Previous studies have implicated a number of clinical and demographic predictive factors to AD or back to normal cognition: age, gender, educational attainment, the apolipoprotein E (APOE) ε4 allele, cognitive status, vascular risk factors (VRFs), white matter lesions (WMLs), medial temporal lobe atrophy, and biomarkers of AD neuropathology[7-11]. Risk factors converting to AD were inversely associated with those reverting to normal cognition[4]. However, those previous reports studied only one direction of MCI for converting to AD or reverting to normal cognition.

Here, we investigated MCI subjects with clinical and demographic predictors in both directions of MCI for converting to AD and reverting to normal cognition as well as with sustained MCI.

Patients and Methods

To carry out this observational study, we used the computerized database of the Okayama University Hospital, Japan. We retrospectively investigated 74 patients (age range 58-89 years old) with MCI based on the Alzheimer's disease neuroimaging initiative (ADNI) criteria, which consists of mini-mental state examination (MMSE) scores between 24-30 (inclusive), a memory complaint, a clinical dementia rating (CDR) of 0.5, essentially preserved activities of daily living, and the absence of dementia[12]. At the follow-up about one year later, cognitive status was reassessed and categorized into three types, i.e., converters to mild AD, sustained MCI, and reverters to normal cognition. There were three inclusion criteria for patients with mild AD: (1) an MMSE score between 20-26 (inclusive), (2) a CDR of 0.5 or 1.0, (3) National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS / ADRDA) criteria for probable AD[13]. Normal cognition met the following criteria: (1) MMSE scores between 24-30 (inclusive), (2) CDR of 0, (3) no MCI and no dementia.

The clinical and demographic characteristics assessed were age, gender, educational attainment, WMLs by magnetic resonance imaging (MRI),

parahippocampal gyrus atrophy (PGA) by MRI, and vascular risk factors (VRFs) such as hypertension, hyperlipidemia, diabetes mellitus, and smoking history. PGA was analyzed using the Voxel-based Specific Regional analysis system for Alzheimer's disease (VSRAD) [14]. With this program, the T1 weighted image of the entire brain was taken with a 1.5 Tesla MRI device.

The location and severity of WMLs were estimated on T2 and fluid attenuated inversion recovery (FLAIR) scans by a trained neurologist using the Fazekas scale[15]. The Fazekas scale provides two different scores (periventricular hyperintensity, PVH, and deep white matter hyperintensity, DWMH), rated on a 0 to 3 point scale of increasing severity. Participants were classified as having no WMLs, mild, moderate, or severe (grade 0, 1, 2, or 3, respectively) in each location. We dichotomized our sample into low grade WMLs (participants with no or mild lesions) and high grade WMLs (participants with moderate or severe lesions). High grade PVH was thus defined as PVH $\geqq$ 2 and high grade DWMH as DWMH $\geqq$ 2.

Exclusion criteria

Participants were excluded if they had a previous diagnosis of psychotic symptoms, multiple sclerosis, motor neuron disease, Parkinson’s disease, other major neurological diseases, or if they had medical or psychological conditions that prevented their assessment tasks.

Statistical analysis

Comparisons were performed using the Kruskal-Wallis test (post hoc test; Steel-Dwass test) and the Fisher's exact test, as appropriate. In addition, trends were analyzed with the Cochran-Armitage and Jonckheere-Terpstra tests. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing)[16]. More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. We selected $p< 0.05$ as the threshold of significance.

This study was approved by the Ethics Committee on Epidemiological Studies of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences No. 694. Written informed consent was obtained from all participants.

Results

The clinical and demographic characteristics of this study follow. As the data

did not show a normal distribution, statistical significance was assessed using nonparametric tests and thus the data are presented as median values. Seventy-four subjects with a median age of 79.0 years were enrolled in the present study. Of 74 subjects, 29 were male and 45 female. The median of years of education was 12.0 years, the median of test intervals was 371.0 days and the median MMSE score of all MCI subjects was 26.0 points.

As shown in Table 1, 29 subjects (39.2%) were classified as subgroup "converters", 39 subjects (52.7%) as sustained MCI, and 6 subjects (8.1%) as "reverters". The three subgroups were well matched for age (converters 79.0 years, sustained MCI 79.0 years, and reverters 78.5 years), gender, and test intervals (392.0, 371.0, and 358.0 days, respectively). However, educational attainment (12.0, 12.0, and 14.0 years, respectively, *p=0.03) and MMSE (baseline MMSE; 26.0, 27.0, and 28.0 points, respectively, ***p<0.001; follow-up MMSE; 23.0, 27.0, and 29.0 points, respectively, ***p<0.001) were significantly different among these three subgroups.

As shown in Table 2, there were no significant differences in VRFs among the three subgroups. However, the proportion of high grade PVH was 19/29 (65.5%) in the converters, 15/39 (38.5%) in the sustained MCI, and 1/6 (16.7%) in the reverters, in descending order. Similarly, the proportion of high grade DWMH was 20/29 (69.0%) in the "converters", 18/39 (46.2%) in the sustained MCI, and 1/6 (16.7%) in the "reverters", in descending order. There were significant differences between high grade PVH and DWMH proportions among the three subgroups (*p=0.02 and *p=0.03, respectively). The proportion of subjects with high grade PVH and DWMH increased gradually with a linear trend ($^{###}$p<0.001 for the trend in both cases).

There was significant difference in educational attainment among the three subgroups (Table 1, *p=0.03). Compared with the reverters, the median period of education was significantly shorter in the converters (Fig. 1, 12.0 vs 14.0 years, *p=0.02), while that in sustained MCI was not significantly different. Furthermore, there was no significant difference between converters and sustained MCI (Fig. 1, 12.0 vs 12.0 years). Trend analysis showed a statistically significant decreasing trend among the three subgroups (Fig. 1, reverters > sustained MCI > converters, $^{###}$p<0.001 for the trend).

There were differences in baseline and follow-up MMSE scores among the three subgroups (Table 1, baseline MMSE; converters 26.0 points, sustained MCI 27.0 points, and reverters 28.0 points, ***p<0.001; follow-up MMSE; 23.0, 27.0, and 29.0 points, respectively, ***p<0.001). The scores of converters became significantly worse than those of the reverters (Fig. 2, 26.0 vs 28.0 points, **p<0.01 and 23.0 vs 29.0 points,

***p<0.001, respectively). Moreover, the follow-up MMSE score of converters was significantly lower than that of sustained MCI (Fig. 2, 23.0 vs 27.0 points, ***p<0.001). Trend analysis showed a statistically significant decreasing trend among the three subgroups (Fig. 2, reverters > sustained MCI > converters, ###p<0.001 for the trend).

The results of Z scores by VSRAD are presented in Fig. 3. Z scores did not differ among the three subgroups. However, trend analysis showed a statistically significant increasing trend of the VSRAD value among the three subgroups (reverters < sustained MCI < converters, ###p<0.001 for the trend).

Discussion

Our study showed that the level of progression to dementia (converters) was 39.2%, and that of reverters to normal cognition was 8.1% (Table 1). The present age- and gender- matched study showed that lower educational attainment, lower baseline MMSE score, high grade WML and high Z-score of VSRAD were the risk factors for conversion to AD (Tables 1-2, Fig. 1-3). In contrast, higher educational attainment, higher baseline MMSE score, low grade WMLs and a low Z-score of VSRAD were the factors that characterized reverters (Tables 1-2, Fig. 1-3). Previous reports described an annual level of conversion that ranged from 8.3% to 33.6%[2, 3], and a level of reversion that varied from 2.0% to 53.0%[5, 6]. Thus, compared to the literature, our study showed a slightly higher level of AD conversion and average reversion.

MMSE is a widely used and well validated assessment for global cognitive function[17, 18], and a simple clinical tool for quantifying the risk of future cognitive decline in MCI[19]. As poorer cognitive performance is associated with converters[20], a low MMSE score is a substantial predictor of AD[21]. In the present study, we found a significant difference in the baseline MMSE and follow-up MMSE scores among the three subgroups (Table 1). Similar to an epidemiologic study in which low educational attainment was significantly associated with an increasing risk of AD[22], our present study also confirmed that a short educational period was also a risk of MCI to AD conversion (Fig. 1, Table 1), and that a cognitive reserve with high educational attainment could prevent the conversion to AD and promote the reversion of cognitive function.

Some reports showed that the severity of WMLs significantly affected cognitive performance in AD[23, 24], while others did not[25, 26]. The present study showed a high grade WMLs (Fazekas grades 2 and 3) tended to be associated with AD converters than low grade WMLs (Table 2). WMLs may affect cognitive performance by disconnecting the cortex from subcortical nuclei or distant cortical territories. VRFs

may be risk factors of incident AD, and treatment of VRFs reduced both the risk of dementia[10, 27] and the cognitive decline of AD[28]. However, the present study showed no difference among the three subgroups with regards to VRFs (Table 2), suggesting that it does not reflect a true effect of VRFs in conversion or reversion in a short study period such as one year. Previous studies of VRFs and AD followed up more than a period of 2 years time between the onset and diagnosis of AD[10, 29]. In addition, a systematic review and meta-analysis reported that VRFs in midlife increased the risk of AD in later life, but in our study was latelife[30].Cognitive decline is particularly related to medial temporal lobe atrophy[31-34]. In the present study, there was a significant increasing trend of the VSRAD value among the three subgroups (Fig. 3), suggesting the impact of PGA conversion to AD. A recent meta-analysis found that MCI subjects consistently showed a small hippocampus and amygdala than healthy controls[35], but did not show a relation with hippocampal size between MCI subjects and AD.

In summary, the present study showed that educational attainment, baseline MMSE score, WMLs, and the baseline Z-score of VSRAD in MCI subjects were significantly associated with AD conversion or reversion, suggesting that they could be suitable clinical and demographic predictors of MCI conversion to subsequent AD or reversion to normal cognition.

Acknowledgment

This work was partly supported by a Grant-in-Aid for Scientific Research (B) 21390267 from the Ministry of Education, Science, Culture, and Sports of Japan and by Grants-in Aid from the Research Committee of CNS Degenerative Diseases (I. Nakano) and grants (H. Mizusawa, M. Nishizawa, H.Sasaki, G. Sobue) from the Ministry of Health, Labour and Welfare of Japan.

Footnotes

The authors have declared no conflicts of interest.

References

1. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999; 56: 303-308. doi:10.1001/archneur.56.3.303
2. Larrieu S, Letenneur L, Orgogozo JM, et al. Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. Neurology 2002; 59: 1594-1599. doi:10.1212/01.WNL.0000034176.07159

3. Rozzini L, Chilovi BV, Conti M, et al. Conversion of amnestic Mild Cognitive Impairment to dementia of Alzheimer type is independent to memory deterioration. Int J Geriatr Psychiatry 2007; 22: 1217-1222. doi: 10.1002/gps.1816
4. Koepsell TD, Monsell SE. Reversion from mild cognitive impairment to normal or near-normal cognition: risk factors and prognosis. Neurology 2012; 79: 1591-1598. doi: 10.1212/WNL.0b013e31826e26b7
5. Petersen RC, Aisen PS, Beckett LA, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. Neurology 2010; 74: 201-209. doi: 10.1212/WNL.0b013e3181cb3e25
6. Ganguli M, Snitz BE, Saxton JA, et al. Outcomes of mild cognitive impairment by definition: a population study. Arch Neurol 2011; 68: 761-767. doi: 10.1001/archneurol.2011.101
7. Sachdev PS, Lipnicki DM, Crawford J, et al. Factors predicting reversion from mild cognitive impairment to normal cognitive functioning: a population-based study. PLoS One 2013; 8: e59649. doi: 10.1371/journal.pone.0059649
8. Maioli F, Coveri M, Pagni P, et al. Conversion of mild cognitive impairment to dementia in elderly subjects: a preliminary study in a memory and cognitive disorder unit. Arch Gerontol Geriatr 2007; 44: 233-241. doi: 10.1016/j.archger.2007.01.032
9. Landau SM, Harvey D, Madison CM, et al. Comparing predictors of conversion and decline in mild cognitive impairment. Neurology 2010; 75: 230-238. doi: 10.1212/WNL.0b013e3181e8e8b8
10. Li J, Wang YJ, Zhang M, et al. Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. Neurology 2011; 76: 1485-1491. doi: 10.1212/WNL.0b013e318217e7a4
11. Roberts RO, Knopman DS, Mielke MM, et al. Higher risk of progression to dementia in mild cognitive impairment cases who revert to normal. Neurology 2014; 82: 1-9. doi: 10.1212/WNL.0000000000000055
12. Petersen RC, Roberts RO, Knopman DS, et al. Mild cognitive impairment: ten years later. Arch Neurol 2009; 66: 1447-1455. doi: 10.1001/archneurol.2009.266
13. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. 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 1984; 34: 939-944. http://www.neurology.org/
14. Hirata Y, Matsuda H, Nemoto K, et al. Voxel-based morphometry to discriminate

early Alzheimer's disease from controls. Neuroscience Letters 2005; 382: 269-274. doi: 10.1016/j.neulet.2005.03.038

15. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol 1987; 149: 351-356. doi:10.2214/ajr.149.2.351
16. Kanda Y. Investigation of the freely-available easy-to-use software “EZR” (Easy R) for medical statistics. Bone Marrow Transplant 2013; 48: 452-458. doi: 10.1038/bmt.2012.244
17. Xu G, Meyer JS, Thornby J, Chowdhury M, Quach M. Screening for mild cognitive impairment (MCI) utilizing combined mini-mental-cognitive capacity examinations for identifying dementia prodromes. Int J Geriatr Psychiatry 2002; 17: 1027-1033. doi: 10.1002/gps.744
18. Abe K, Ikeda Y, Kurata T, et al. Cognitive and affective impairments of a novel SCA/MND crossroad mutation Asidan. Eur J Neurol 2012; 19: 1070-1078. doi: 10.1111/j.1468-1331.2012.03669.x
19. Xie H, Mayo N, Koski L. Predictors of future cognitive decline in persons with mild cognitive impairment. Dement Geriatr Cogn Disord 2011; 32: 308-317. doi: 10.1159/000334996
20. Gallassi R, Oppi F, Poda R, et al. Are subjective cognitive complaints a risk factor for dementia? Neurol Sci 2010; 31: 327-336. doi: 10.1007/s10072-010-0224-6
21. Mauri M, Sinforiani E, Zucchella C, Cuzzoni MG, Bono G. Progression to dementia in a population with amnestic mild cognitive impairment: clinical variables associated with conversion. Funct Neurol 2012; 27: 49-54. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3812753/
22. Lindsay J, Laurin D, Verreault R, et al. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol. 2002; 156: 445-453. doi: 10.1093/aje/kwf074
23. Bracco L, Piccini C, Moretti M, et al. Alzheimer's disease: role of size and location of white matter changes in determining cognitive deficits. Dement Geriatr Cogn Disord 2005; 20: 358-366. doi:10.1159/000088562
24. Burns JM, Church JA, Johnson DK, et al. White matter lesions are prevalent but differentially related with cognition in aging and early Alzheimer disease. Arch Neurol 2005; 62: 1870-1876. doi:10.1001/archneur.62.12.1870
25. Hirono N, Kitagaki H, Kazui H, Hashimoto M, Mori E. Impact of white matter changes on clinical manifestation of Alzheimer's disease: A quantitative study. Stroke 2000; 31: 2182-2188. doi: 10.1161/01.STR.31.9.2182

26. Kono I, Mori S, Nakajima K, et al. Do white matter changes have clinical significance in Alzheimer's disease? Gerontology 2004; 50: 242-246. doi:10.1159/000078353
27. de la Torre JC. Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. Lancet Neurol 2004; 3: 184-190. doi: 10.1016/S1474-4422(04)00683-0
28. Deschaintre Y, Richard F, Leys D, Pasquier F. Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. Neurology 2009; 73: 674-680. doi: 10.1212/WNL.0b013e3181b59bf3
29. Solfrizzi V, Panza F, Colacicco AM, et al. Vascular risk factors, incidence of MCI, and rates of progression to dementia. Neurology 2004; 63: 1882-1891. http://www.neurology.org/
30. Meng XF, Yu JT, Wang HF, et al. Midlife Vascular Risk Factors and the Risk of Alzheimer's Disease: A Systematic Review and Meta-Analysis. J Alzheimers Dis 2014; [Epub ahead of print]. doi: 10.3233/JAD-140954
31. Jack CR Jr, Shiung MM, Gunter JL, et al. Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. Neurology 2004; 62: 591-600. doi: 10.1212/01.WNL.0000110315.26026.EF
32. Staekenborg SS, Koedam EL, Henneman WJ, et al. Progression of mild cognitive impairment to dementia: contribution of cerebrovascular disease compared with medial temporal lobe atrophy. Stroke 2009; 40: 1269-1274. doi: 10.1161/STROKEAHA.108.531343
33. Shim YS, Youn YC, Na DL, et al. Effects of medial temporal atrophy and white matter hyperintensities on the cognitive functions in patients with Alzheimer's disease. Eur Neurol 2011; 66: 75-82. doi: 10.1159/000329277
34. Tokuchi R, Deguchi K, Yamashita T, Abe K. Impact of combined medial temporal atrophy and white matter lesion for cognitive function and emotional function in Alzheimer's disease patients. Nihon Ronen Igakkai Zasshi 2014; 51: 342-349
35. Nickl-Jockschat T, Kleiman A, Schulz JB, et al. Neuroanatomic changes and their association with cognitive decline in mild cognitive impairment: a meta-analysis. Brain Struct Funct 2012; 217: 115-125. doi: 10.1007/s00429-011-0333-x

Table 1. Clinical and demographic characteristics of MCI subgroups.

Characteristics	Reverters (n=6)	Sustained MCI (n=39)	Converters (n=29)	p-value
n, (%)	6 (8.1)	39 (52.7)	29 (39.2)	
Gender, M / F	2 / 4	18 / 21	9 / 20	0.42 [b]
Age, y	74.3 ± 8.8 (78.5)	75.8 ± 8.3 (79.0)	77.2 ± 7.0 (79.0)	0.64 [a]
Educational attainment, y	14.0 ± 2.2 (14.0)	12.1 ± 2.3 (12.0)	11.3 ± 1.1 (12.0)	**0.03** [a]
Test interval, d	372.8 ± 84.5 (358.0)	364.4 ± 72.1 (371.0)	364.2 ± 87.4 (392.0)	0.96 [a]
PVH grade 0 / 1 / 2 / 3	1 / 4 / 1 / 0	4 / 20 / 13 / 2	1 / 9 / 15 / 4	0.20 [b]
DWMH grade 0 / 1 / 2 / 3	1 / 4 / 1 / 0	4 / 17 / 13 / 5	1 / 8 / 13 / 7	0.26 [b]
VSRAD	1.3 ± 0.9 (1.3)	2.2 ± 1.1 (2.0)	2.7 ± 1.2 (2.8)	0.13 [a]
Baseline MMSE	28.3 ± 1.0 (28.0)	26.7 ± 2.1 (27.0)	25.8 ± 1.6 (26.0)	**<0.001** [a]
Follow-up MMSE	28.5 ± 1.8 (29.0)	26.7 ± 1.9 (27.0)	22.7 ± 1.9 (23.0)	**<0.001** [a]
Baseline CDR	0.5	0.5	0.5	
Follow-up CDR	0 ± 0	0.5 ± 0	0.7 ± 0.3	

y, year; d, day.

[a] Kruskal–Wallis test. [b] Fisher's exact test

Data are presented as mean ± SD (median)

PVH, periventricular hyperintensity; DWMH, deep white matter hyperintensity

VSRAD, voxel-based specific regional analysis system for Alzheimer's disease

MMSE, mini-mental state examination; CDR, clinical dementia rating

Table 2. Number of subjects with vascular risk factors and white matter lesions within MCI subgroups.

			Reverters (n=6)	Sustained MCI (n=39)	Converters (n=29)	p-value Fisher's exact test	p-value Cochran-Armitage test
Vascular risk factors	Hypertension	(-)	4	16	13	0.52	0.63
		(+)	2	23	16		
	Hyperlipemia	(-)	3	23	18	0.88	0.60
		(+)	3	16	11		
	Diabetes mellitus	(-)	6	31	21	0.42	0.16
		(+)	0	8	8		
	Smoking history	(-)	3	30	23	0.32	0.25
		(+)	3	9	6		
White matter lesion (Fazekas scale)	PVH grade	0 and 1	5	24	10	**0.02**	**<0.001**
		2 and 3	1	15	19		
	DWMH grade	0 and 1	5	21	9	**0.03**	**<0.001**
		2 and 3	1	18	20		

Data are presented as numbers.

Fig. 1. Educational attainment (years) in MCI subgroups. Reverters (white box), sustained MCI (gray box), and converters (black box).

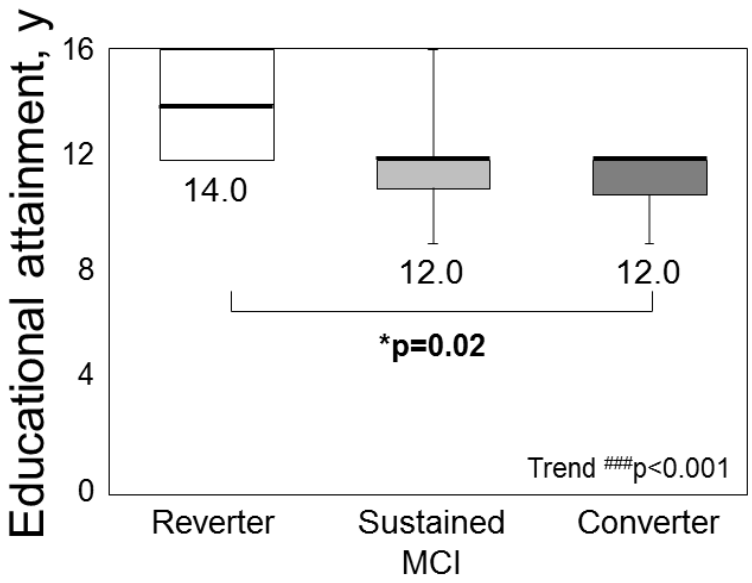

Fig. 2. Baseline and follow-up MMSE in MCI subgroups. Reverters (white box), sustained MCI (gray box), and converters (black box).

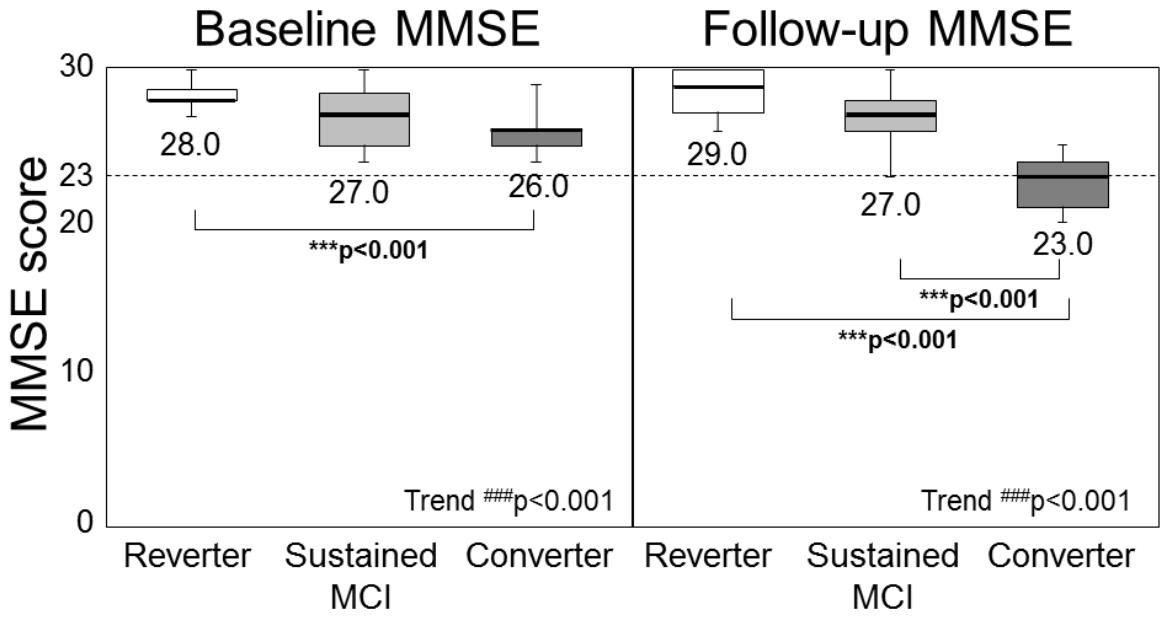

Fig. 3. VSRAD *Z* scores in MCI subgroups. Reverters (white box), sustained MCI (gray box), and converters (black box).