

Alzheimer disease biomarkers may aid in the prognosis of MCI cases initially reverted to normal

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Abstract

Objective

To identify potential predictors for outcome in individuals with mild cognitive impairment (MCI) who have reverted to normal cognition (NC).

Methods

We selected individuals with MCI, who reverted at follow-up to NC, with follow-up after reversion from Alzheimer's Disease Neuroimaging Initiative. Common clinical markers, Alzheimer disease (AD) biomarkers, and neurodegeneration imaging markers were used to compare MCI reverters based on subsequent clinical outcome (i.e., subsequent decline or stable reversion). For independent comparison, findings of the clinical Amsterdam Dementia Cohort are presented.

Results

Seventy-seven (10%) out of 757 individuals with MCI reverted to NC and 61 of these individuals had follow-up data available. After 3.2 ± 2.2 years, 16 (24%) progressed to MCI, and 3 (5%) to dementia. Those who declined were older and had a higher amyloid PET burden and higher CSF tau levels.

Conclusion

In MCI reverters, abnormal biomarkers for AD pathology are associated with subsequent decline. AD biomarkers may aid in the prognosis of reverting MCI.

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A complete listing of ADNI investigators can be found in the appendix at adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (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 analysis or writing of this report.

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Glossary

$A\beta_{1-42}$ = β -amyloid 1–42; AD = Alzheimer disease; ADC = Amsterdam Dementia Cohort; ADNI = Alzheimer's Disease Neuroimaging Initiative; GDS = Geriatric Depression Scale; HV = hippocampal volume; MCI = mild cognitive impairment; NC = normal cognition; PiB = Pittsburgh compound B; SUVr = standard uptake value ratio; t-tau = total tau.

Individuals with mild cognitive impairment (MCI) are at increased risk to develop dementia.¹ Yet, up to 25% of individuals with MCI revert to normal cognition (NC).^{2,3} Although improved cognition seems to be a positive event, individuals reverting from MCI remain at increased risk to develop dementia compared to NC individuals.^{1,4,5} Timely identification of individuals with a higher risk will increase prognostic certainty for patients and be useful for health care planning.

In individuals with NC and MCI, low memory function, abnormal biomarkers for Alzheimer disease (AD), and neurodegeneration predict dementia.^{6,7} While MCI reverters deviate from the common clinical trajectory, the same disease processes may be underlying. Our aim was to investigate whether MCI reverters who subsequently showed clinical decline have more abnormal AD markers than MCI reverters who remain stable.

Methods

Participants

Data analyzed were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu, downloaded on August 9, 2017). From the individuals with at least 2 years clinical follow-up, we selected all individuals with prevalent and incident MCI reverting to NC with additional follow-up after reversion.⁸ The ADNI was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. The goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can measure progression to MCI and early AD. Next to the primary analyses in ADNI, we selected from the Amsterdam Dementia Cohort (ADC) all MCI reverters with follow-up after reversion. Similar clinical and biomarker assessments are presented for this small, independent clinical sample for illustration purposes only (for cohort and biomarker methods⁹).

Standard protocol approvals, registrations, and participant consents

All protocols were approved by an ethical review board and participants signed informed consent.

Clinical markers and APOE

All individuals had baseline data on age, sex, and education. APOE genotype was dichotomized into $\epsilon 4$ carriers and non-carriers. Overall cognitive status was assessed by the Mini-Mental State Examination, memory by the Rey Auditory Verbal Learning Test immediate (0–75) and delayed total

recall (0–15), executive function by the Trial-Making Test A and B (seconds), and depressive symptoms by the Geriatric Depression Scale (GDS) (0–15). Subthreshold depression was classified as GDS >4.¹⁰

Biomarkers of AD and neurodegeneration

We studied CSF β -amyloid 1–42 ($A\beta_{1-42}$) and total tau (t-tau) (Luminex in ADNI¹¹; Innostest in ADC¹²) and amyloid PET (florbetapir and Pittsburgh compound B [PiB]) as markers for AD pathology. PiB scans were harmonized to florbetapir by new value = PiB standard uptake value ratio (SUVr) * 0.67 + 0.15.¹³ For imaging markers of neurodegeneration, we studied FDG-PET, hippocampal volume (HV; UCSF in Freesurfer v4.4/v5.1), normalized to total intracranial volume, and white matter hyperintensity volume.¹⁴ Cut points for abnormality for dichotomized analysis in ADNI were as follows: CSF $A\beta_{1-42}$ < 192 pg/mL, CSF t-tau > 93 pg/mL, amyloid PET SUVr > 1.10, FDG-PET SUVr METAROI < 1.21, and raw HV < 6,732 mm³ (see references 11, 12, 15, and 16 for procedures and processing). Data collected within 1 year before or after MCI diagnosis were included.

Statistical analysis

MCI reverters with NC at last follow-up and MCI reverters with subsequent decline were compared on clinical and biomarkers using χ^2 , Wilcoxon, and *t* tests when appropriate. We report results unadjusted and adjusted for age, sex, education, and APOE $\epsilon 4$ genotype with univariate linear regression models, and scaling of continuous outcomes, to facilitate comparability of effects.

Data-sharing statement

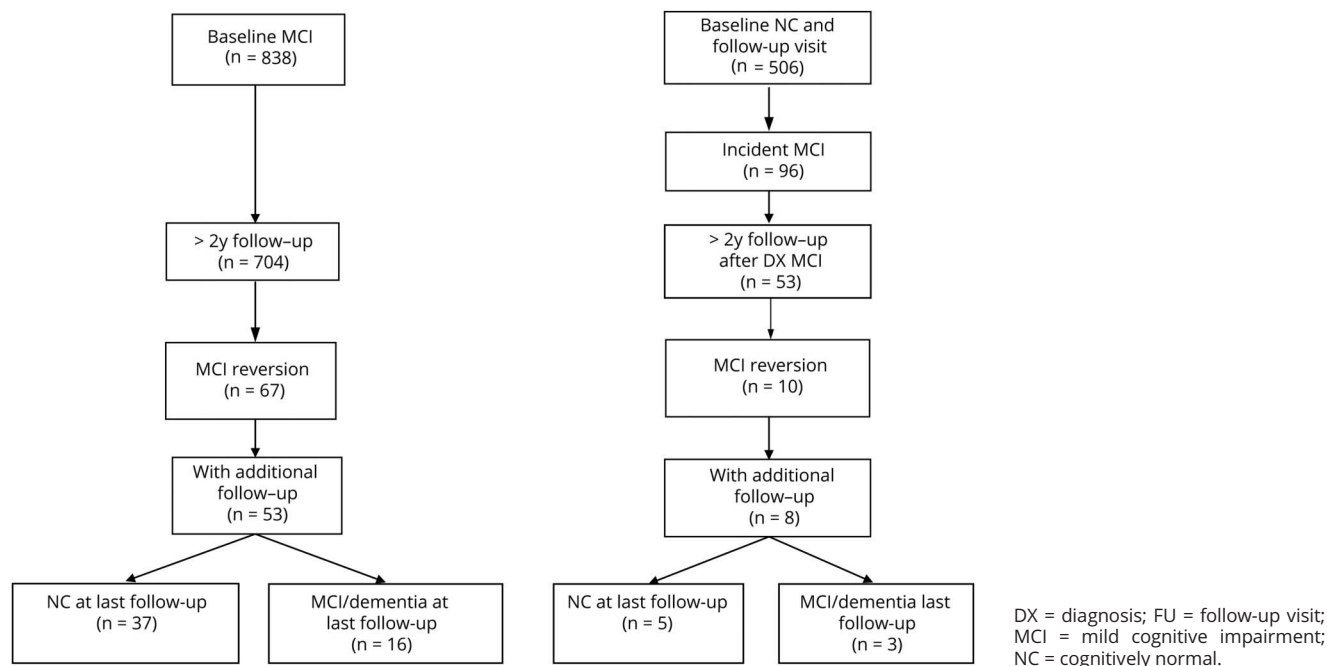
Data used for this study are available from the corresponding author, upon reasonable request.

Results

In ADNI, 757 individuals with prevalent or incident MCI had been followed for at least 2 years (figure 1). Of these, 77 (10%) reverted to NC, and 61 (79%) had additional follow-up available. After 3.2 ± 2.2 years (mean \pm SD), 16 (24%) had converted to MCI, and 3 (5%) to dementia. One individual was excluded, due to missing data.

MCI reverters who showed subsequent clinical decline were on average 5 years older than reverters remaining NC, and had, adjusted for age, sex, education, and APOE, higher and more often abnormal AD biomarkers (amyloid PET and CSF t-tau), less impaired memory, and higher GDS scores

Figure 1 Flow diagram: Sample selection, Alzheimer's Disease Neuroimaging Initiative



(table and figure 2). Follow-up after reversion seemed slightly shorter for stable MCI reverters ($p = 0.11$). Repeating analyses including this covariate did not essentially change the results (table e-1, doi.org/10.5061/dryad.04n8502).

Post hoc analyses further showed that biomarkers of MCI reverters were on average more similar to NC than non-reverting MCI, except for amyloid, which was more often abnormal in MCI reverters than in NC (table e-2, doi.org/10.5061/dryad.04n8502). Still, MCI reverters showed higher clinical progression rates (110/1,000 person-years) compared to baseline NC (52/1,000 person-years, hazard ratio [95% confidence interval] 2.3 [1.4–4.0], $p = 0.002$) (table e-3 and figure e-1, doi.org/10.5061/dryad.04n8502). The biomarker associations with progression were similar for NC and MCI reverters, whereas associations with progression and cognitive test scores were less consistent (table e-4 and figure e-2, doi.org/10.5061/dryad.04n8502).

Outcome of MCI reverters in clinical ADC cohort

In the ADC, of 735 patients with MCI and a follow-up visit, 75 (10%) reverted to NC. Twenty-six (35%) patients had 1.6 ± 0.8 years (mean \pm SD) follow-up available after reversion, after which 24 (92%) remained NC and 2 (8%) had dementia. Small group size precluded formal statistical testing. The 2 decliners had abnormal CSF $A\beta_{1-42}$ and t-tau (table). The majority of individuals remaining NC had normal CSF $A\beta_{1-42}$ (80%) and t-tau (85%). Thirty-two percent of the stable reverters showed baseline subthreshold depression.

Discussion

Age and AD biomarkers are associated with decline in patients with MCI who initially reverted to normal cognition. MCI reverters showed higher clinical progression rates than NC individuals, which is in line with previous reports.^{1,4} MCI reverters with subsequent decline had an increased amyloid PET burden and CSF tau compared to reverters remaining normal. Between amyloid markers, amyloid PET showed a significant association with the subsequent decline group in MCI reverters, while this association was significant for CSF $A\beta_{1-42}$ in NC. Although previous research suggests that CSF amyloid becomes abnormal before PET,^{17,18} the findings are in line with other reports that this may not apply to all individuals,^{19,20} which contributes to the notion that CSF $A\beta_{1-42}$ and amyloid PET may represent different AD-related processes.

An outstanding question is why individuals with underlying AD temporarily improved. Our results suggest that at baseline, MCI reverters were more similar to NC than non-reverting MCI. Furthermore, biomarker values associated with subsequent decline were similar for reverting MCI and NC, while cognitive measures were less consistent. Possibly, reverters with decline received an MCI diagnosis very early in their clinical disease course, as their biomarker profiles were like the nonreverting MCI. A modest improvement, for example, due to learning effects, resolving of (subthreshold) depressive symptoms, or measurement error, may have contributed to reclassification as normal. Here we observed that when AD is present, such improvement is often not lasting.

Table Mild cognitive impairment (MCI) reverters with follow-up of Alzheimer's Disease Neuroimaging Initiative (ADNI) and Amsterdam Dementia Cohort (ADC)

	ADNI MCI reverters				ADC MCI reverters	
	Persistent normal cognition (n = 42)	Decline to MCI or dementia (n = 19)	p Value ADNI group comparison	p Value adjusted for age, sex, education, APOE ε4	Persistent normal cognition (n = 24)	Decline to MCI or dementia (n = 2)
Baseline characteristics						
Age, y	69 (8)	74 (8)	0.016 ^a	NA	65 (7)	71 (7)
Female, %	50	26	0.146	NA	29	100
Education, ADNI, y; ADC, Verhage scale	17.2 (2.6)	16.3 (2.0)	0.095 ^b	NA	5 (1.4)	5 (1.4)
APOE ε4 carrier, %	38	32	0.839	NA	46	50
Follow-up						
Total follow-up, y, median (IQR)	4 (2.3)	5 (2.5)	0.109	NA	3.0 (1.8)	5.3 (1.6)
Time to reversion, y, median (IQR)	1 (1.8)	2 (2)	0.462	NA	1.3 (1.0)	1.8 (0.7)
Follow-up after reversion, y, median (IQR)	2 (1.8)	3 (2)	0.265	NA	1.4 (0.9)	3.6 (1.0)
Time to progression after reversion, y, median (IQR)	NA	1 (1)	NA	NA	NA	1 (0)
N with > 1 reversion	4	2	>0.99	NA	2	1
Clinical						
MMSE	28.7 (1.4)	28.3 (1.8)	0.573	0.904	27.5 (1.6)	29
RAVLT immediate total recall	43 (11)	47 (12)	0.262	0.002 ^a	36 (10)	19
RAVLT delayed total recall	6.6 (4.2)	8.3 (4.6)	0.185	0.002 ^a	5.6 (1.6)	3
Trail-Making Test A	31 (10)	34 (11)	0.496	0.700	38 (11)	44 (1)
Trail-Making Test B	72 (24)	80 (31)	0.362	0.973	90 (36)	94 (30)
GDS	1.1 (1)	1.6 (2)	0.138	0.018 ^a	3.7 (3)	3.5 (2)
GDS >4, n (%)	2 (5)	1 (5)	>0.99	0.508	7 (32)	1 (50)
AD biomarkers						
Amyloid PET, SUVR	1.08 (0.15)	1.21 (0.21)	0.026 ^a	0.016 ^a	—	—
Amyloid PET, n SUVR > 1.10 (%)	10 (30)	9 (64)	0.065 ^b	0.018 ^a	—	—
Luminex CSF Aβ ₁₋₄₂ , pg/mL ^c	218 (45) ^b	190 (65) ^b	0.214	0.213	—	—
Innotest CSF Aβ ₁₋₄₂ , pg/mL ^c	—	—	—	—	1,047 (243) ^c	780 (5) ^c
Abnormal CSF Aβ ₁₋₄₂ , n (%) ^c	9 (31)	5 (45)	0.629	0.455	4 (20)	2 (100)
Luminex CSF t-tau, pg/mL ^c	53 (17) ^b	84 (42) ^b	0.042 ^a	0.020 ^a	—	—
Innotest CSF t-tau, pg/mL ^c	—	—	—	—	284 (140) ^c	955 (24)
Abnormal CSF t-tau, n (%) ^c	0 (0)	3 (27)	0.024 ^a	0.009 ^a	3 (15)	2 (100)

Continued

Table Mild cognitive impairment (MCI) reverters with follow-up of Alzheimer's Disease Neuroimaging Initiative (ADNI) and Amsterdam Dementia Cohort (ADC) (continued)

	ADNI MCI reverters				ADC MCI reverters	
	Persistent normal cognition (n = 42)	Decline to MCI or dementia (n = 19)	p Value ADNI group comparison	p Value adjusted for age, sex, education, APOE ε4	Persistent normal cognition (n = 24)	Decline to MCI or dementia (n = 2)
Imaging markers of neurodegeneration						
FDG-PET METAROI, SUVr	1.34 (0.11)	1.27 (0.14)	0.051 ^b	0.458	—	—
FDG-PET METAROI, SUVr < 1.21, n (%)	5 (13)	6 (35)	0.126	0.627	—	—
Hippocampus/intracranial volume, cm³	0.48 (0.07)	0.42 (0.09)	0.092	0.591	—	—
Hippocampus volume < 6,673 mm³, n (%)	6 (27)	5 (56)	0.280	0.731	—	—
White matter hyperintensities volume, cm³	1.80 (2.69)	4.29 (6.24)	0.263	0.054 ^b	—	—

Abbreviations: Aβ₁₋₄₂ = β-amyloid 1-42; GDS = Geriatric Depression Scale; IQR = interquartile range; MMSE = Mini-Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; SUVr = standard uptake value ratio.

Sample sizes in ADNI: amyloid PET: n = 47; FDG-PET: n = 55; MRI hippocampal volume: n = 31; white matter hyperintensities: n = 58; CSF: n = 40. Sample sizes in ADC: RAVLT: n = 24; GDS: n = 24; CSF: n = 22. Data are mean (SD) unless otherwise specified.

^a p < 0.05.

^b p < 0.10.

^c For ADNI: Luminex assay abnormality threshold: CSF Aβ₁₋₄₂ < 192 pg/mL, total tau >93 pg/mL; in ADC Innotest values corrected for upwards drift with abnormality thresholds CSF Aβ₁₋₄₂ < 813 pg/mL; total tau >375 pg/mL.

Verhage scale ranges from 1 to 7.

Furthermore, it remains unclear as to why individuals who reverted and remained NC over time were initially diagnosed with MCI. Aside neurodegenerative diseases, depressive symptoms are a common cause of MCI. Low depressive symptoms scores in ADNI reflect inclusion criteria. In the ADC, subthreshold depression was more common. Another possibility is that distress or insecurity led to a suboptimal performance. The question remains how to deal with the classification of these individuals in the context of AD progression research, when MCI is often regarded as an intermediate disease stage. A practical implementation could be to classify reverting MCI with normal biomarkers as NC. Alternatively, including stability of the diagnosis in the classification has been suggested.⁴

A limitation of this study is the relatively short follow-up time, and so we cannot exclude the possibility that some individuals in the stable group may progress again. Compared to population-based studies, reversion rates in both cohorts were low.³ Possibly, this reflects that clinicians will not easily reverse a known diagnosis. Reversion rates may even be lower, because we based reversion rates on individuals with MCI who met our inclusion criteria. Individuals with MCI excluded from these analyses as they were lost to follow-up were somewhat older and more cognitively impaired, which are characteristics that associate with decline¹ (table e-5, doi.org/10.5061/dryad.04n8502). Although further replication in large population-based studies is necessary, our results suggest that AD biomarkers aid in the prognosis of

MCI reverters, and could help to identify those with a good short term prognosis and those likely to decline again in the longer term.

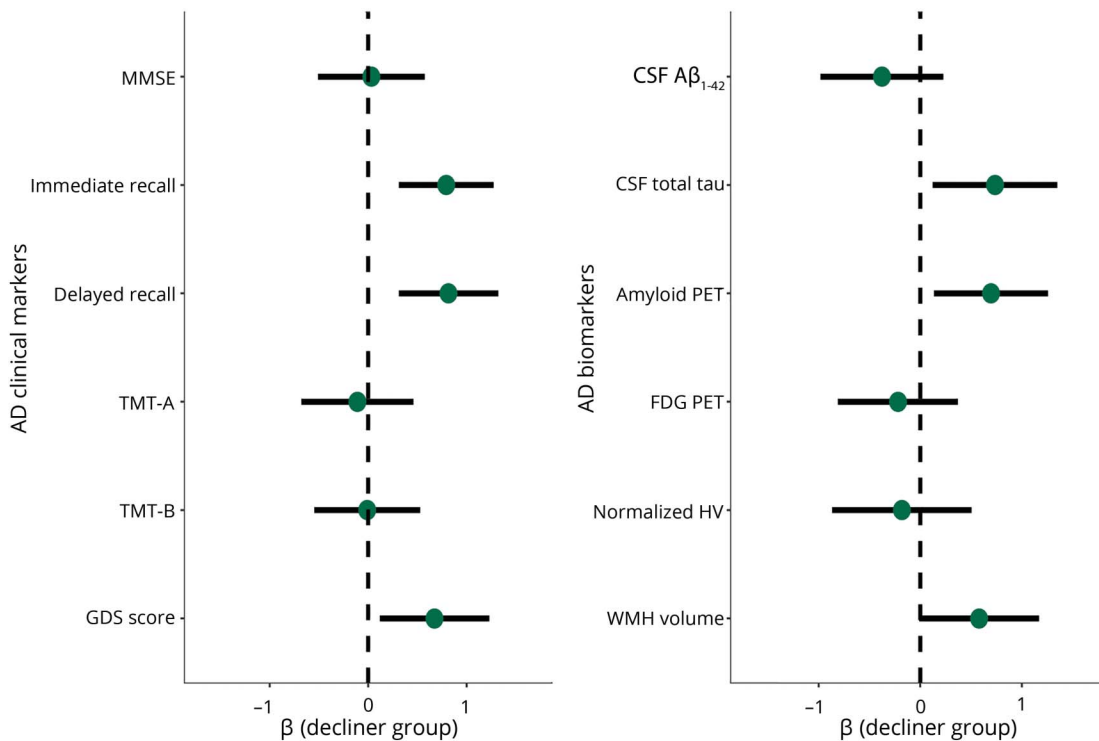
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Figure 2 Standardized β s: Alzheimer disease (AD) clinical markers and biomarkers for decliner group



Immediate and delayed recall of the Rey Auditory Verbal Learning Test, Trail-Making Test (TMT), Geriatric Depression Scale (GDS), white matter hyperintensities (WMH), and hippocampal volume (HV). Models were adjusted for age, sex, education, and *APOE* $\epsilon 4$.

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Disclosure

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Appendix Authors

Name	Location	Role	Contribution
L. Vermunt, MD	Amsterdam UMC, the Netherlands	Author	Designed and conceptualized study, analyzed the data, drafted and revised the manuscript for intellectual content

Appendix (continued)

Name	Location	Role	Contribution
A.J.L. van Paasen, BSc	Amsterdam UMC, the Netherlands	Coauthor	Interpreted the data, revised the manuscript for intellectual content
C.E. Teunissen, PhD	Amsterdam UMC, the Netherlands	Coauthor	Interpreted the data, analyzed the data, revised the manuscript for intellectual content
P. Scheitens, MD, PhD	Amsterdam UMC, the Netherlands	Coauthor	Interpreted the data, revised the manuscript for intellectual content
P.J. Visser, MD, PhD	Amsterdam UMC, the Netherlands	Coauthor	Interpreted the data, revised the manuscript for intellectual content
B.M. Tijms, PhD	Amsterdam UMC, the Netherlands	Senior author	Designed and conceptualized study, analyzed the data, interpreted the data, writing, revised the manuscript for intellectual content

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