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MILD COGNITIVE IMPAIRMENT THAT DOES NOT PROGRESS TO DEMENTIA: A POPULATION-BASED STUDY

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Abstract

Background/Objective: In population studies, most individuals with mild cognitive impairment (MCI) do not progress to dementia in the near term, but rather remain stable MCI or revert to normal cognition. Here, we characterized MCI subgroups with different outcomes over 5 years.

Setting/Participants: A population-based cohort (N=1603).

Measurements: Clinical Dementia Rating (CDR); self-reported medical conditions, subjective cognitive concerns, self-rated health, depressive symptoms, blood pressure, medications, blood pressure, *APOE* genotype, cognitive domain composite scores.

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AUTHOR CONTRIBUTIONS. Dr. Ganguli was responsible for study concept and design, study supervision, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. Ms. Jia was responsible for analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. Dr. Hughes was responsible for interpretation of data, and critical revision of the manuscript for important intellectual content. Dr. Snitz was responsible for interpretation of data, and critical revision of the manuscript for important intellectual content. Dr. Chang was responsible for study supervision, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. Dr. Berman was responsible for interpretation of data, and critical revision of the manuscript for important intellectual content. Dr. Sullivan was responsible for critical revision of the manuscript for important intellectual content. Dr. Kamboh was responsible for data acquisition and critical revision of the manuscript for important intellectual content. **SPONSOR'S ROLE.** The National Institute on Aging funded the research grant under which this work was completed. The sponsor had no other role in the design, methods, participant recruitment, data collection, analysis, and preparation of the manuscript.

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SUPPLEMENTAL TEXT FILE S1

This online file includes details of the assessment and statistical methods that are not included in the main body of the manuscript.

Design: We compared 3 MCI subgroups who progressed to dementia (n=86), stabilized at MCI (n=384), or reverted to normal (n=252), to those who remained consistently normal (n=881), defining MCI as CDR = 0.5 and dementia as CDR $\geq$ 1. Using multinomial logistic regression models adjusted for demographics, we examined the associations of each group with selected baseline characteristics.

Results.—With the normal group for reference, worse subjective cognitive concerns, functional impairments, self-rated health, and depressive symptoms were associated with being in any MCI group. Taking more prescription medications was associated with being in the stable MCI and reverter groups; diabetes and low diastolic blood pressure were associated with stable MCI. The *APOE4* genotype was associated with stable and progressive MCI; stroke was associated with progressive MCI. All MCI subgroups had lower mean composite scores in all cognitive domains and more operationally defined impairments in attention, language, and executive function; reverts lacked memory and visuospatial impairments.

Conclusions: MCI subgroups with different 5-year outcomes had some distinct characteristics suggesting different underlying causes. The progressors, unlike the reverts, had a profile broadly typical of Alzheimer's disease; the stable MCIs had other, including vascular, morbidity. These data shed light on the heterogeneity of MCI in the population.

Keywords

Aging; Epidemiology; Cognition

INTRODUCTION

Mild cognitive impairment (MCI) is an intermediate, but not necessarily transitional, cognitive state between normal cognition and dementia.^{1–3} In specialty clinics, the majority of individuals meeting diagnostic criteria for MCI progress to dementia within a relatively short time. In the community setting, MCI is more heterogeneous; the majority remains stable at the MCI level, a minority progresses to dementia, while another minority reverts to normal.^{4–8} Previous studies addressed the characteristics of those MCI progressed to dementia, with features typically resembling the Alzheimer's disease (AD) profile: older age, prominent memory loss, and the *APOE4* genotype.^{9–12} Those whose MCI reverts to normal cognition lack these characteristics^{10, 12} although in some studies they too eventually progress to dementia.⁹ However, the largest group of people with MCI, those who remain stably mildly impaired, have received less attention.¹³ Knowing the characteristics associated with likelihood of MCI progression can be helpful to clinicians in treatment planning.

We investigated, at the community level, the five-year outcomes of MCI: what proportions of people with MCI progressed to dementia, remained at stable MCI, and reverted to normal, and what baseline characteristics distinguished the MCI subgroups from one another and from those who remained consistently normal. Specifically, we identified their distinctive demographic, health, and cognitive characteristics, and their eventual dementia and mortality rates, compared to the normal group.

METHODS

The Monongahela-Youghiogheny Healthy Aging Team (MYHAT) is a cohort participating in a population-based, prospective study of cognitive impairment and dementia. It comprised 1982 individuals recruited from 2006–2008 by age-stratified random sampling from the publicly available voter registration list for a group of contiguous small towns in southwestern Pennsylvania. Eligibility criteria included age 65+ years, non-institutionalized, lacking severe sensory impairment, and having decisional capacity. Details of sampling, recruitment, and assessment have been reported previously.^{14–16} Participants were reassessed annually. All study procedures were approved by the University of Pittsburgh Institutional Review Board. All participants provided written informed consent.

Exposure variables.

The assessments included, but were not limited to, demographic characteristics (age, sex), education (high school graduate HSG, < HSG, >HSG), self-report of diagnoses by a health care provider, prescription and nonprescription drug intake, self-rated general health, subjective cognitive concerns,¹⁷ depression symptoms,^{18, 19} independence in instrumental activities of daily living (IADLs), lifestyle factors (exercise, smoking, alcohol use) and *APOE* genotype, as well as a brief focused physical and neurological examination.^{14, 16, 20}

The neuropsychological assessment comprised tests tapping the cognitive domains of attention/processing speed, memory, executive, language, and visuospatial functions. For each participant we created a standardized composite score for each domain by first standardizing each individual test score and then calculating the mean of all the standardized scores in that domain.¹⁵

Classification and Outcome variables.

We rated participants on their everyday independent cognitively-driven activity using the Clinical Dementia Rating (CDR)²¹ where CDR=0 is normal, CDR=0.5 is mild cognitive impairment, and CDR=1, 2, and 3 represent mild, moderate, and severe dementia. We used the CDR definition of MCI, which is independent of neuropsychological data, so that we could evaluate baseline cognitive data as predictors of different MCI outcomes. We assigned participants CDR ratings at study entry and each annual assessment. Excluding individuals with prevalent dementia (CDR ≥ 1) at study entry, we identified four groups: consistently normal (CDR=0 at up to 10 annual visits), stable MCI (CDR=0.5 for five consecutive visits), reverting/fluctuating MCI (CDR reverts from 0.5 to 0, including any who then return to 0.5, within five visits), and progressed to dementia (CDR=0.5 progresses to CDR ≥ 1 within five visits).

For each MCI participant, we designated as the “index visit” the first visit at which the CDR was 0.5. We then measured outcomes over the subsequent 5-year observation period (5 annual visits). Thus, different MCI participants were followed for different 5-year calendar periods, depending on the dates of their index visits. MCI participants’ index visits serve as their “baseline;” the normal group’s baseline visits were their initial (study entry) visits. We compared the baseline characteristics of 3 MCI subgroups with those of the normal group

and with one another. We also compared the reverters who remained at CDR=0 with those who returned to CDR=0.5 (fluctuators). In *post-hoc* analyses, we addressed attrition during the observation period, incident dementia after the observation period, and mortality.

Statistical Methods

Descriptive statistics.—To compare baseline characteristics, overall and across groups, we created indicator variables for self-rated health (poor or fair *vs.* good or excellent), IADL impairment (any *vs.* none), depressive symptoms (>3 *vs.* ≤ 3 , the 90th percentile of the MYHAT cohort), subjective cognitive concerns (any *vs.* none), prescription medicines (>3 *vs.* ≤ 3 , a median split), *APOE4* genotype (*E*4* carrier *vs.* non-carrier); history of stroke/TIA, heart disease, and diabetes; current smoking, alcohol consumption, and physical exercise, systolic (>130 *vs.* ≤ 130 mm Hg) and diastolic (>70 *vs.* ≤ 70 mm Hg) blood pressures. We examined cognitive domain composite scores, both as continuous variables (standardized z scores), and categorized as impaired/unimpaired at the threshold of 1.5 standard deviations (SD) below the appropriate mean.

Multivariable Models.—We fit multinomial logistic regression models treating membership in all four groups as the outcome variables, with the normal group as reference, to assess the effect of each baseline characteristic on the likelihood of belonging to each group, adjusting for demographics.

Attrition: We examined the proportions lost to follow-up in each group during 5-year followup, and the average ages at which individuals left the study. We fit Cox proportional hazard models with time to dropout as the outcome, adjusting for demographics. As sensitivity analyses, we repeated the multinomial logistic regression models excluding those who were lost before completing 5 followup years.

Fluctuation: We compared the reverters who remained at CDR=0 with those reverters (fluctuators) who returned to CDR= 0.5 during the 5 years.

Subsequent outcomes: In *post-hoc* analyses, we examined the occurrence of incident dementia ($\text{CDR} \geq 1$) and mortality beyond 5 years.

We used Stata 15.0 and R 3.4.3 for all analyses.

Additional methodological details are provided in Supplemental Text S1.

RESULTS

Of the 1982 individuals who met all eligibility criteria at study entry, 1413 (71.3%) were rated CDR=0; 546 (27.6%) were rated CDR=0.5. We excluded the following individuals: 23 with prevalent dementia; 258 with only initial assessments; 93 with no follow-up assessments after the index visit; and 5 who progressed directly from CDR=0 to CDR ≥ 1 without being observed at a 0.5 stage. We report here the data from the remaining 1603 individuals.

We identified four groups: *Consistently normal* (n=881); *Reverter /fluctuator MCI* (n=252; of these, 81 individuals fluctuated back to CDR=0.5 during the 5 years); *Stable MCI* (n=384); *Progressed to dementia* (n=86).

Participants were followed on average for 6.93 years; normal, reverter, stable MCI, and progressor groups were followed on average for 7.05, 8.02, 6.05, and 6.43 years. For all analyses reported in this section, except for the pairwise comparisons, all reported results compare each MCI subgroup to the consistently normal group.

Sample description (Unadjusted comparisons)

We found significant overall differences across the 4 groups in several variables in unadjusted analyses of baseline characteristics (Table 1). We followed up the significant overall differences with pairwise unadjusted comparisons (Supplemental Table S1).

In unadjusted analyses of baseline cognitive functioning, all 3 MCI groups had significantly lower average composite scores in all domains than the normals and were significantly less likely to meet operational criteria for cognitive impairment in most domains (Supplemental Table S2).

Demographic, Health, and Lifestyle Comparisons Adjusted for Demographics (multivariable models)

In multinomial logistic regression models, for each independent variable (covariate), we fit a single model for all three MCI groups simultaneously, adjusting for demographics. Each relative risk ratio (RRR) indicates the effect size for a given covariate's association with each MCI group compared to the normal group.

For example, in Table 2, all three MCI groups had significantly more subjective cognitive concerns than the normals, with RRRs of 22.58, 16.32, and 12.79 for the reverters, stable MCI, and progressors; i.e., the reverters had the strongest association with subjective concerns, followed by stable MCIs and progressors.

In contrast, IADL impairment was most strongly associated with the progressor group, followed by the stable and reverter groups, all compared to the normal group.

Fair or poor self-rated health and >3 depression symptoms were about equally associated with all MCI groups; number of prescription medications was associated only with stable MCI and reverter (but not progressor) groups.

*APOE*4* carrier status was associated with stable and progressor but not reverter groups. Diabetes and diastolic blood pressure (DBP) <70 mm Hg were associated only with stable MCI.

Alcohol use was negatively associated with all 3 MCI groups; smoking and exercise were associated with none.

Cognitive Characteristics of Groups, adjusted for Demographics.

In multinomial models (Table 3), we found associations with lower composite scores in all cognitive domains with all 3 MCI subgroups, with the RRRs indicating progressively stronger effects from reverter through stable to progressor groups.

Comparing proportions with operationally defined impairments in attention, language, and executive functions, we found increasingly strong effects in reverter, stable MCI, and progressor groups. In the memory and visuospatial domains, the progressors had the strongest effect followed by the stable MCIs; we found no association among reverters. The executive function domain showed the largest effect sizes in all MCI groups.

Attrition.—During the 5-year observational period, in the normal, reverter, stable MCI, and progressor groups, the proportions lost to follow-up were 29.06%, 29.76%, 70.83%, and 56.98%; the corresponding mean ages at leaving the study were 80.3, 85.4, 86.8, and 87.3 years. In Cox proportional hazard models with time to dropout as the outcome, adjusting for demographics, the stable MCI and progressor groups, but not the reverters, were significantly more likely than normals (hazard ratio 2.7, 95% confidence interval 2.3–3.3 and HR 1.5, 95% CI 1.1 – 2.0) to be lost to follow-up.

In the sensitivity analysis, (models excluding those who dropped out before 5 years of follow-up), some power was lost. Effects which were attenuated and became non-significant were: the associations of *APOE4* genotype, DBP, smoking, diabetes, and memory impairment with stable MCI; alcohol consumption, language impairment and attention impairment with MCI reverters; and stroke/TIA with MCI progressors. We could not assess the effect of executive function impairment as none of the normals had executive function impairment (data not shown).

Fluctuation.—Compared with the 171 reverters who remained at CDR=0, the 81 fluctuators who returned to CDR= 0.5 during the 5 years were significantly older ($p=0.022$), reported more subjective cognitive concerns ($p=0.039$), and were more likely to report history of stroke/TIA ($p=0.027$). They had lower scores in executive ($p=0.003$), memory ($p=0.014$), and visuospatial ($p=0.003$) domains, but were more likely to have impairment only in attention ($p = 0.023$).

Outcomes beyond 5 years.—By definition, 100% of progressors developed dementia, and 0% of the normals have as yet developed dementia. Of the 171 reverters who remained at CDR=0 during the 5 years, 19 (11%) subsequently returned to CDR=0.5. Incident dementia was eventually observed in 3 (1.19%) reverters and 15 (3.91%) stable MCI cases. (Figure 1).

Mortality beyond 5 years.—Progressors have the highest proportion (44.19%) who have died thus far, with the stable, reverter, and normal groups experiencing 30.47%, 27.38%, and 21.91% mortality.

DISCUSSION

In a population-based aging cohort followed over at least 5 years, we identified a relatively small subgroup of individuals with MCI who progressed to dementia, and larger subgroups that remained stably impaired or reverted to normal. This pattern, typical of community samples in contrast to clinic samples,^{4, 5, 9, 13, 22–24} has been attributed to selection factors.⁶ More fundamentally, it reflects different distributions of underlying morbidities and risk factors, i.e., the heterogeneity of MCI at the population level. We identified shared as well as distinct baseline features among the three MCI groups compared with those who remained consistently normal.

As in previous studies,^{9, 24} all three MCI groups were older and less well-educated than the normals, with no sex differences. The educational gradient across the four groups is consistent with lower education being an established risk factor for cognitive decline and dementia. Not unexpectedly, all three MCI groups had lower mean composite scores in all cognitive domains, and were more likely to report subjective cognitive concerns and IADL impairments. Although all MCI groups had lower mean baseline cognitive performance than normals, the reverters had the highest scores among the MCI groups, followed by the stable group and the progressors. Higher proportions of the progressor and stable MCI groups had operationally defined impairment in all domains.

The progressors' characteristics broadly match the typical prodromal AD profile of memory impairment and *APOE4* genotype, as in previous community^{9, 22} and clinical studies.^{10–12} They were also the only group more likely than normals to report history of stroke, consistent with evidence that combined neurodegenerative and cerebrovascular disease increases likelihood of dementia.^{25, 26}

In contrast, reverters resembled normals in operationally defined memory and visuospatial impairments, *APOE4* genotype, and previous strokes, and had the weakest associations with cognitive and IADL impairments. However, they were the most likely to report at least one subjective cognitive concern, although the average number of concerns was fairly similar across MCI groups. Notably, the reverters who remained at CDR=0 (unlike the fluctuators who then returned to CDR=0.5) were more likely to have impaired attention, possibly reflecting transient or reversible medically or pharmaceutically derived effects.^{27–31} Reverters were also more likely to take >3 prescription drugs, which might themselves contribute to reversible impairments, or reflect the presence of underlying reversible morbidities. In effect, these individuals represent potentially reversible MCI.

The stable MCI group was more likely than the normals to take prescription medications and to have diabetes and low DBP. We speculate that stable cardiovascular and metabolic abnormalities might underlie static cognitive impairment. Diabetes is a known risk factor for dementia³² and MCI.³³ Low DBP could be attributed to factors such as medication effects, but is characteristic of heart failure which could lead to chronic hypoxemia and cerebral hypoperfusion. We found low DBP was significantly associated with history of heart failure, both overall ($p=0.007$) and in the stable MCI group ($p=0.0001$). Hypoxemia is implicated in the associations of heart failure with cognitive impairment,³⁴ and of chronic obstructive

lung disease with MCI.^{35, 36} The stable MCI group was also more likely to have the *APOE4* genotype which is associated not only with AD but also with hypercholesterolemia and heart disease.³⁷ However, unlike the progressors, those with stable MCI were not more likely than normals to report stroke, i.e., their cardiovascular disease had not led to cerebrovascular events. Notably, they experienced the highest 5-year attrition rate; in all groups, an unknown proportion of the dropouts might have evidenced dementia had they remained in the study.

With regard to established risk factors or markers of AD dementia, our results validate those of several previous community-based studies. Older age, amnesic MCI, poor memory performance, worse overall cognitive function, *APOE4* genotype, and stroke are consistent predictors of MCI progression to dementia.^{9, 11, 22, 24, 38, 39} In neuroimaging studies, medial temporal and global cortical atrophy, and rate of volume loss, predict progression to dementia.⁴⁰ Studies of reverters show the converse.^{9–12, 22, 38}

However, we also investigated predictors of non-progression, and the potential roles played by factors reflecting other morbidities and lifestyle factors. The majority of individuals with MCI who remain mildly impaired, and the minority who revert to normal, may not have underlying progressive neurodegenerative or cerebrovascular processes. Yet, non-progressive impairments also have clinical and public health significance, interfering with everyday functioning, productivity, and quality of life.⁴¹ Our data suggest that these cases of mild impairment may have causes such as diabetes and heart failure. Further, all MCI groups were significantly more likely to report depressive symptoms than normals, reflecting the well-documented relationship between depression and cognitive impairment.^{42–44} Here, depressive symptoms did not seem to distinguish among MCI groups, although in another study they predicted progression to dementia.⁴⁵ The cognitive impairments related to these chronic conditions may not be progressive, particularly if the underlying conditions are adequately controlled.

Our study extends the literature in comparing three distinct MCI subgroups to normal individuals over at least 5 years, and in examining variables besides neuropsychological performance and *APOE* genotype. Our findings regarding depression symptoms, self-rated health, prescription medications, health history, and DBP appear to be novel. While our finding of greater IADL impairment and subjective concerns in all MCI groups is as expected, the gradient of effect sizes across MCI groups is informative.

As regards strengths and limitations, our community-based assessments are less intensive than those in clinical research settings and lack neuroimaging; however, our ability to compare people with MCI to cognitively normal individuals from the same population is an advantage over research clinics that rely on highly selected volunteer or referred subjects. Variations in findings - for example, only about 1% of the reverters and 4 % of the stable MCI have as yet developed incident dementia in our study - can result from varying MCI definitions^{9, 22, 24} and statistical approaches.¹³ The large size and population-based nature of our study cohort, and 5-year follow-up, longer than others,⁴⁶ reinforce both external and internal validity. Our study cohort, representing the older population of this study area, is largely of European descent; it should be replicated in other racial/ethnic groups.

MCI subgroups with different 5-year outcomes have some shared and some distinct characteristics. Knowing these relationships can help clinicians with early identification of prognostic subgroups so that the likely progressors and non-progressors can be targeted for appropriate interventions. All individuals with MCI need not assume that they will progress to dementia, nor should they all be subjected to the same therapeutic strategies. Despite our field's current understandable focus on early detection of progressive dementing diseases, we should not ignore the clinical and public health significance of potentially reversible or stable MCI, which together make up a substantial proportion of mild impairment at the population level.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Impact Statement: We certify that this work is both novel and confirmatory of recent novel research.^{9,11} The potential impact of this research on clinical care is that it describes the characteristics of individuals with mild cognitive impairment who do not progress to dementia. Clinicians need to recognize and care for these individuals understanding that their impairment may have treatable causes other than underlying neurodegenerative diseases.

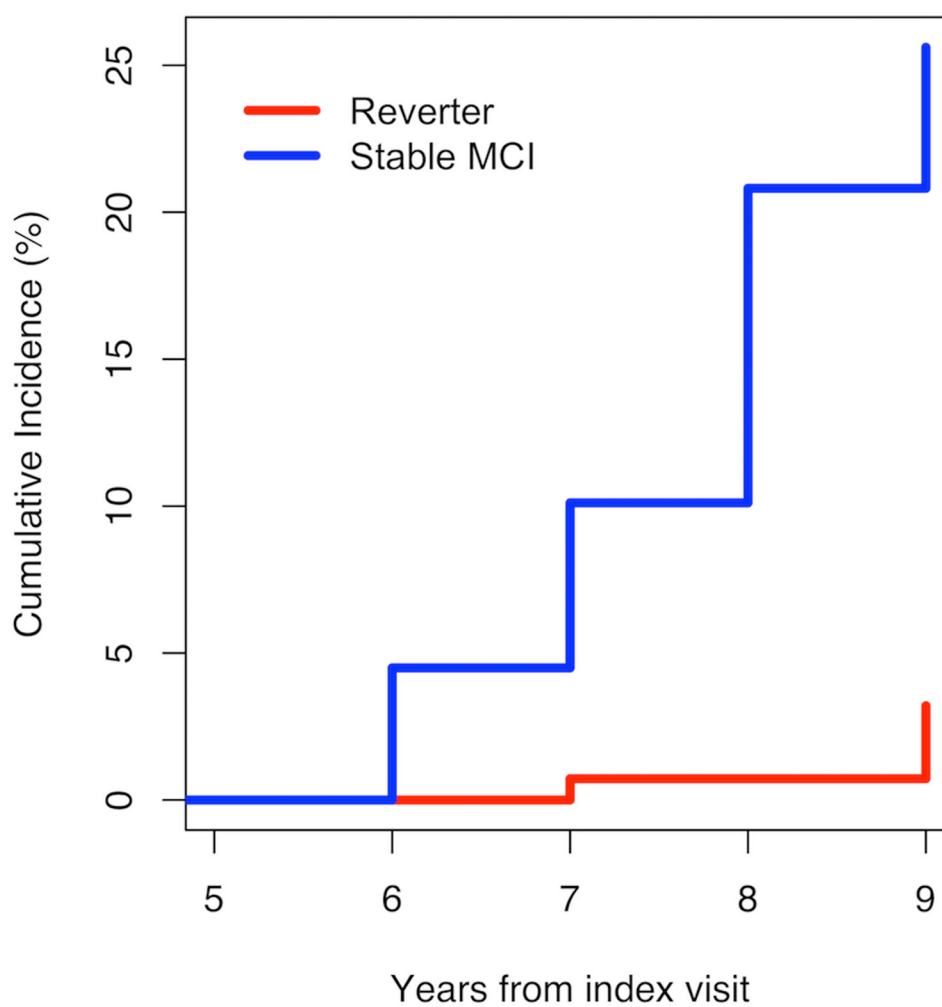


Figure 1. Cumulative Incidence of Dementia In Stable MCI and Reverter Groups , Years 06–09 after Index Visit.

Table 1.

Characteristics of entire sample and of MCI subgroups

Characteristic at "baseline" *	Total N	All participants N=1603	Consistently normal participants N=881	Reverters from MCI to normal N=252	Stable MCI N=384	Progressors from MCI to dementia N=86	Overall Kruskal-Wallis, chi-square or Fisher's exact test: P value
Age	1603	77.7 (7.6)	75.2 (7.0)	77.5 (7.0)	82.3 (6.9)	83.6 (5.7)	0.0001
Sex	1603	62.0	62.1	58.7	64.1	61.6	0.605
Education	1603	13.0	8.3	12.7	20.3	29.1	
		44.8	44.6	45.2	47.40	33.7	<0.001
		42.2	47.1	42.1	32.3	37.2	
Any subjective memory concerns (SMC)	1600	70.8	51.4	96.0	94.5	93.0	<0.001
Number of SMC	1600	2 (4)	1 (2)	4 (2)	4 (3)	5 (4)	0.0001
Self-rated health	1603	17.1	11.8	23.4	24.2	20.9	<0.001
Any IADL impairments	1603	19.6	8.2	21.0	38.3	48.	<0.001
Depressive symptoms (>3)	1603	8.1	4.7	12.3	11.5	15.1	<0.001
APOE *4 genotype	1478	20.9	19.2	21.4	21.9	34.2	0.1
Systolic blood pressure (SBP)	1603	51.1	51.8	48.0	51.0	53.5	0.727
Diastolic blood pressure (DBP)	1603	59.6	64.7	61.9	49.0	47.7	<0.001
H/o Stroke/TIA	1603	11.8	8.5	12.3	18.2	22.1	<0.001
H/o Heart attack	1603	36.6	35.3	39.3	37.8	36.1	0.646
H/o Diabetes	1603	22.2	20.4	20.2	27.3	23.3	0.044
Current Smoking	1603	6.9	8.5	6.4	3.4	7.0	0.011
Current Alcohol consumption	1603	80.4	88.3	79.4	66.7	62.8	<0.001
Number of prescription medications	1603	4 (4)	3 (4)	5 (4)	5 (5)	4 (3)	0.0001
Exercise	1603	59.6	63.2	56.8	55.5	48.8	0.006

* Baseline for Stable Normal group is study entry (assessment 1). Baseline for MCI groups is the "index visit" at which the participant was first classified as MCI (CDR=0.5)

SMC: Subjective Memory Concerns

IADL: Instrumental Activities of Daily Living

Mean and SD, or median and interquartile range, were compared for continuous variables, and percentages for categorical variables. To detect overall group differences, Kruskal-Wallis rank tests were performed for continuous predictors when the assumptions for one-way ANOVA were not met. Chi-square tests were performed for categorical predictors, and Fisher's Exact Tests were conducted when sample size was small.

Table 2.

Multinomial Logistic regression comparing MCI subgroups to normal group, adjusting for demographics

	Reverters vs. Consistently Normal			Stable MCI vs. Consistently Normal			Progressor vs. Consistently Normal		
	RRR	SE	p-value	RRR	SE	p-value	RRR	SE	p-value
>0 Subjective cognitive concerns	22.58	7.46	<0.001	16.33	4.02	<0.001	12.79	5.64	<0.001
Number of subjective concerns	2.52	0.13	<0.001	2.73	0.14	<0.001	3.02	0.19	<0.001
Self-rated health – good/very good/excellent (ref: poor/fair)	0.417	0.77	<0.001	0.364	0.064	<0.001	0.424	0.128	0.004
>0 IADL impairments	2.629	0.540	<0.001	4.174	0.732	<0.001	6.150	1.656	<0.001
≥ 3 depressive symptoms	2.872	0.728	<0.001	2.557	0.627	<0.001	3.55	1.283	<0.001
<i>APOE</i> *4 genotype	1.221	0.226	0.28	1.535	0.263	0.012	3.062	0.833	<0.001
Systolic blood pressure (SBP)	0.844	0.122	0.242	0.925	0.123	0.558	0.976	0.231	0.919
Diastolic blood pressure (DBP)	0.993	0.15	0.96	0.74	0.1	0.026	0.757	0.181	0.245
Reported Stroke/TIA	1.518	0.347	0.068	2.556	0.502	<0.001	1.967	0.671	0.047
Reported Heart attack	1.088	0.163	0.573	0.924	0.128	0.568	0.826	0.204	0.438
Reported Diabetes	1.002	0.18	0.99	1.605	0.25	0.002	1.312	0.369	0.334
Smoking	0.846	0.244	0.561	0.615	0.199	0.133	1.575	0.731	0.327
Alcohol	0.543	0.105	0.002	0.362	0.06	<0.001	0.306	0.082	<0.001
Number of Prescription medications	1.13	0.03	<0.001	1.15	0.02	<0.001	1.02	0.04	0.656
Exercise (any)	0.807	0.119	0.146	0.884	0.12	0.366	0.676	0.161	0.1

Table 3.

Multinomial Logistic regression for baseline * cognitive characteristics, adjusting for demographics

	Reverter vs. Consistently Normal			Stable MCI vs. Consistently Normal			Progressor vs. Consistently Normal		
	RRR	SE	p-value	RRR	SE	p-value	RRR	SE	p-value
Cognitive Domain Composite Scores									
Attention [†]	0.657 [†]	0.069	<0.001	0.563 [†]	0.056	<0.001	0.375 [†]	0.065	<0.001
Executive	0.576	0.067	<0.001	0.344	0.038	<0.001	0.236	0.04	<0.001
Language	0.587	0.071	<0.001	0.274	0.031	<0.001	0.200	0.031	<0.001
Memory	0.558	0.065	<0.001	0.236	0.027	<0.001	0.1	0.019	<0.001
Visuospatial	0.783	0.064	0.004	0.543	0.048	<0.001	0.421	0.068	<0.001
% with Cognitive Impairment by Domain									
Attention	3.309	1.885	0.036	3.713	1.874	0.009	7.954	4.565	<0.001
Executive	13.243	10.465	0.001	19.052	14.339	<0.001	45.407	35.655	<0.001
Language	2.946	1.297	0.014	6.049	2.193	<0.001	12.167	5.199	<0.001
Memory	2.215	2.033	0.386	2.619	0.744	0.001	5.473	2.043	<0.001
Visuospatial	1.459	0.518	0.288	2.074	0.591	0.001	4.885	1.774	<0.001

* Baseline for Stable Normal group is study entry (assessment 1). Baseline for MCI groups is the assessment at which the participant was first classified as MCI (CDR=0.5)

[†] For example, a one-unit change in the composite attention domain score multiplied the risk of reversion by 0.657, of stable MCI by 0.563, and of progression by 0.375, compared to remaining stably normal.