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Practice effects and longitudinal cognitive change in normal aging vs. incident mild cognitive impairment and dementia in the Mayo Clinic Study of Aging

Mary M. Machulda¹, V. Shane Pankratz², Teresa J. Christianson², Robert J. Ivnik¹, Michelle M. Mielke², Rosebud O. Roberts^{2,3}, David S. Knopman³, Bradley F. Boeve³, and Ronald C. Petersen³

¹Department of Psychiatry and Psychology, College of Medicine, Mayo Clinic, Rochester, MN 55905

²Department of Health Sciences Research, College of Medicine, Mayo Clinic, Rochester, MN 55905

³Department of Neurology, College of Medicine, Mayo Clinic, Rochester, MN 55905

Abstract

The objective of this study was to examine practice effects and longitudinal cognitive change in a population based cohort classified as clinically normal at their initial evaluation. We examined 1390 individuals with a median age of 78.1 years and re-evaluated them up to four times at approximate 15 month intervals, with an average follow-up time of five years. Of the 1390 participants, 947 (69%) individuals remained cognitively normal, 397 (29%) progressed to mild cognitive impairment (MCI), and 46 (3%) to dementia. The stable normal group showed an initial practice effect in all domains which was sustained in memory and visuospatial reasoning. There was only a slight decline in attention and language after visit 3. We combined individuals with incident MCI and dementia to form one group representing those who declined. The incident MCI/dementia group showed an unexpected practice effect in memory from baseline to visit 2, with a significant decline thereafter. This group did not demonstrate practice effects in any other domain and showed a downward trajectory in all domains at each evaluation. Modeling cognitive change in an epidemiologic sample may serve as a useful benchmark for evaluating cognitive change in future intervention studies.

Keywords

Cognition; memory; practice effects; mild cognitive impairment; Alzheimer's disease

Introduction

With initial secondary prevention studies underway, the preclinical stage of Alzheimer's Disease is receiving intense interest and scrutiny (Sperling et al., 2011). The five to ten years prior to a diagnosis of mild cognitive impairment (MCI) may be a critical window of opportunity for targeted interventions that can slow or halt disease progression, before debilitating cognitive changes and significant neuronal loss occur. Because secondary prevention studies will use cognitive change as one of the outcome variables, it is crucial to

understand the cognitive changes associated with normal aging versus incident MCI/dementia.

Numerous longitudinal studies have reported on the cognitive changes and variability in practice effects observed in normal aging (Dodge, Wang, Chang, & Ganguli, 2011; Duff et al., 2010; Ivnik et al., 1999; Johnson, Storandt, Morris, & Galvin, 2009; Wilson, Beckett, Bennett, Albert, & Evans, 1999; Wilson, Li, Bienias, & Bennett, 2006) and MCI/dementia (Amieva et al., 2005; Bennett et al., 2002; Boyle, Wilson, Aggarwal, Tang, & Bennett, 2006; Cooper, Lacritz, Weiner, Rosenberg, & Cullum, 2004; Duff et al., 2011; Grober et al., 2008; Howieson et al., 2008; Johnson, et al., 2009; Small & Backman, 2007; Wilson et al., 2010; Wilson, Leurgans, Boyle, & Bennett, 2011; Yu et al., 2012; Zehnder, Blasi, Berres, Spiegel, & Monsch, 2007). Relatively few of these studies, however, focused specifically on the cognitive changes preceding the diagnosis of MCI (Howieson, et al., 2008; Wilson, et al., 2011; Yu, et al., 2012). Further, of those that focused on MCI, none have utilized a population-based sample. The objective of this study was to examine practice effects and longitudinal cognitive change in a population-based cohort of older adults, all of whom were clinically normal at their baseline evaluation. Based on the work of our group and others, we hypothesized that individuals who remained clinically normal would show a practice effect from visit 1 to visit 2 with relatively stable performance thereafter whereas individuals destined to develop MCI or dementia would not show a practice effect. To evaluate this, we compared change in four cognitive domains and a global index of cognition, over a five year period, between individuals who remained clinically normal vs. those who developed incident MCI or dementia.

METHOD

Study sample

Subjects were participants in the population-based Mayo Clinic Study of Aging (MCSA), which was designed to provide estimates on the incidence and prevalence of MCI in Olmsted County, MN. All subjects used in this study were 70 to 89 years old and classified as clinically normal at the time of enrollment. Baseline visits for the 2004 cohort took place between November 2004 and July 2007, while baseline visits for the 2008 cohort took place between April 2008 and January 2010. The Mayo Clinic and Olmsted Medical Center Institutional Review Boards approved this study which also followed Health Insurance Portability and Accountability Act (HIPAA) guidelines. Every subject provided written informed consent.

Evaluation

The present analysis included participants who were evaluated two to five times, at approximately 15 month intervals. At each visit, a study coordinator interviewed subjects and their informants. Subject interviews included questions about memory, and informant interviews obtained information for completing the Clinical Dementia Rating (CDR) Scale, (Morris, 1993) and the Functional Activities Questionnaire (FAQ) (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982). The neurologic evaluation included the Short Test of Mental Status (STMS), (Kokmen, Smith, Petersen, Tangalos, & Ivnik, 1991), a medical history review and administration of a questionnaire developed to elicit neurologic conditions that could influence cognition. The questionnaire assessed Parkinson's disease, depression, anxiety, alcoholism, problems with balance, tremor, speech, stroke or transient ischemic attack and sleep problems. The physician also performed a complete neurologic examination.

Neuropsychometric testing included the same nine measures at each evaluation. Delayed recall trials from three tasks [(Auditory Verbal Learning Test; (Rey, 1964), and the Wechsler Memory Scale-Revised (Wechsler, 1987) Logical Memory & Visual Reproduction subtests] assessed memory. The Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), and a category fluency task (Strauss, Sherman, & Spreen, 2006)] assessed language. Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981) Picture Completion and Block Design subtests examined visuospatial reasoning. The Trailmaking Test Part B (Reitan, 1958; Strauss, et al., 2006) and the WAIS-R Digit Symbol subtest assessed attention/executive ability. All raw neuropsychological test scores were standardized in the entire MCSA sample (Petersen et al., 2010). We obtained domain-specific scores by averaging the z scores of the individual tests included in each domain. Finally, we obtained a global z-score by averaging the four domain-specific z-scores. All subjects were test naive at their first study visit.

MCI was diagnosed according to published criteria: (1) cognitive concern by subject, informant (from CDR), study coordinator, or physician, (2) essentially normal functioning in activities of daily life (from CDR and FAQ), and (3) the absence of dementia (Petersen, 2004). Subjects with a CDR >1 were classified as demented if they met DSM-IV criteria for dementia (American Psychiatric Association, 2000). Subjects who received a CDR of 0.5 were carefully reviewed to determine whether they met criteria for MCI or dementia based on a critical review of information from the CDR, clinical examination and the STMS score to determine whether they met DSM-IV criteria for dementia.

Each evaluator (study coordinator, physician, and neuropsychologist) reached a preliminary impression of the subject's cognitive status that was independent of the impression of the other evaluators. Each evaluator was blind to the participant's previous classification, and the study coordinator and physician were blind to any cognitive data. To avoid circularity, we used only the ratings from the study coordinator and physician for the subject classification at each evaluation. We chose to be as conservative as possible when classifying subjects as normal given that we were not using neuropsychometric data as an indicator. Therefore, only one rater had to identify the participant as not being cognitively normal for that individual to receive a classification as MCI or dementia in the present study. This was an intentional deviation from our protocol.

APOE ϵ 4 Measurement

All subjects underwent a blood draw at their baseline visit. DNA extraction and apolipoprotein E (APOE) genotyping was performed for each subject using standard methods (Hixson & Vernier, 1990). The APOE carrier group included individuals with one or two copies of the ϵ 4 allele (i.e., ϵ 2 ϵ 4, ϵ 3 ϵ 4, ϵ 4 ϵ 4).

Statistics

We used linear mixed effects models to examine domain-specific and global cognitive changes (Laird & Ware, 1982). This allowed us to include all of the longitudinal data that was available for each subject. We performed a series of analyses for each of the four cognitive domains and the global score on the entire cohort. Our primary analyses tested for an overall difference in each of the domain and global scores across all assessments, with tests applied that compared the scores at one visit with the scores at the next visit. We first performed these comparisons on the entire cohort without adjustment for any covariates. Later analyses on the entire cohort were performed which adjusted for age, sex, years of education, and months between target and actual visit date [time offset]. In a final set of analyses, we tested whether there were differential effects on these cognitive test results across the multiple assessments by sex, education, and APOE ϵ 4 carrier status.

We then divided our sample into two groups defined by those who remained clinically normal through visit 5 (i.e., stable cognitively normal group) versus those who were classified as incident MCI or dementia at any point after the baseline visit (i.e., incident MCI/dementia group). We then performed the same series of analyses on each of these subgroups as were performed on the entire cohort. We used SAS for all statistical analyses (SAS Institute, Cary, NC, Version 9.3, 2011).

RESULTS

Demographics

This study included 1390 cognitively normal individuals at baseline who subsequently completed at least two, and up to five, evaluations with an average follow-up time of approximately five years. Table 1 provides participant demographics and clinical characteristics at enrollment. “(Table 1 about here)”. The median age was 78.1 years; 41% were 80 to 91 years old at baseline. Approximately 40% completed 12 years of education, 26% had some post-high school education, and 34% completed college or graduate level work. Consistent with estimates in the general population, roughly one-fourth of the sample were APOE ε4 carriers. Approximately 7% of the total sample had a Beck Depression Inventory-II (Beck & Steer, 2001) score of 13, and nearly 12% of all participants were taking an antidepressant. Only one individual was taking a medication for dementia at enrollment (i.e., memantine for approximately six months; this individual did not report using it for visits 2 – 4 and stayed cognitive normal for visits 2 – 4). No other individuals reported the use of donepezil, galantamine or rivastigmine.

Of the 1390 individuals classified as cognitively normal at baseline, 397 (29%) developed incident MCI and 46 (3%) developed incident dementia over the follow-up period. Thirty-one of the individuals who developed incident dementia received a classification of MCI before being diagnosed with dementia. Of the 15 that did not receive an MCI diagnosis before being classified with dementia, 6 had discordant ratings between the study coordinator vs. the physician (i.e., one rater classified the participant with MCI and one rater classified the participant with dementia), suggesting that the dementia was likely very mild. Overall, nearly half of all subjects classified as incident dementia at any time during the study had discordant ratings between the study coordinator vs. physician at the time of the first dementia rating, again suggesting that this group had very mild dementia. Table 2 includes information on the STMS scores and CDR Sum of Boxes for both stable normal and incident MCI/dementia groups. “(Table 2 about here)”. Table 3 provides a summary of number of evaluations completed in those who remained clinically normal and the number of individuals who developed incident MCI/dementia. “(Table 3 about here)”. Appendix 1 includes the z-scores for each cognitive domain for the stable normal and incident MCI/dementia groups at each visit.

Cognitive trajectories in entire cohort

We first evaluated the cognitive trajectories of our entire cohort in order to describe the natural history of elderly individuals initially classified as cognitively normal. We found significant changes in cognitive scores in each of the cognitive domains (see Table 4 and Figure 1). “(Table 4 about here)”. The memory domain displayed significant improvement from baseline (i.e., visit 1) to visit 2 ($p < .001$) and then plateaued. After visit 4, there was a significant decline ($p = .001$), though the group mean was still above the value observed at baseline. In contrast to memory, there was little change in performance on visuospatial reasoning tasks, with the exception of a significant decline between visits 4 and 5 ($p = .01$). The trajectories of change in attention and language domains and global score all followed the same pattern. Performance in these domains increased between the baseline and second

visit, but after the second visit, the average scores for attention, language and the global score significantly declined (all p -values <0.001), and the scores at visit 5 were significantly lower than the baseline values.

Adjusting for the covariates of interest did not have a large effect on these results. There was a trend towards sex ($p = .07$) and education ($p = .08$) being associated with differences in memory score trajectories, with women having a slightly greater tendency to continue learning after the baseline visit and those with higher education showing more persistent practice effects. There was no evidence for a significant modifying effect of either of these variables in the other domains. There was a significant effect of APOE $\epsilon 4$ status on memory across evaluations ($p = .02$). Both the APOE $\epsilon 4$ non-carriers and carriers showed a practice effect from baseline to visit 2. The APOE $\epsilon 4$ non-carriers maintained their level of performance through visit 5 while the APOE $\epsilon 4$ carriers' level of performance returned to baseline by visit 5. There was a trend for APOE $\epsilon 4$ differences in language ($p = .07$) and no differences in APOE $\epsilon 4$ carriers vs. non-carriers in attention ($p = .75$) or visuospatial reasoning ($p = .27$). (Cognitive trajectories of APOE $\epsilon 4$ carriers vs. non-carriers in the entire cohort are provided in Appendix 2.)

Cognitive trajectories for the stable normal group

The stable normal group showed significant improvements in memory from baseline to visit 2 and also from visit 2 to visit 3 ($p < .001$) followed by non-significant improvement from visit 3 to visit 4 and stable performance from visit 4 to visit 5. Attention similarly showed significant improvement from baseline to visit 2 ($p < .001$) that was maintained through visit 3 without additional improvement. This was followed by slight but significant declines from visit 3 to visit 4 ($p < .02$) and visit 4 to visit 5 ($p < .001$) though the overall group mean score at visit 5 was only slightly lower (.08 standard score units) than the baseline performance. Language also showed an improvement from baseline to visit 2 ($p < .05$) that was maintained at visit 3 and followed by significant declines from visit 3 to visit 4 ($p = .012$) and visit 4 to visit 5 ($p = .003$) though the standard score at Visit 5 was only 0.11 standard score units lower than the baseline score. There was a significant improvement in visuospatial reasoning from baseline to visit 2 ($p = .007$) whereas remaining means were essentially stable. The global score also showed an improvement from baseline to visit 2 ($p < .001$) that was stable through visit 4 after which there was a slight but significant decline ($p < .001$), though the group mean remained slightly above the value observed at baseline.

We further divided the stable normal group in those age 70 – 79 and 80+ and evaluated the memory trajectories in these two age groups. We found that older subjects started lower at enrollment by .28 standard score points ($p < .001$), but both groups improved by the same amount at visit 2 (.22 standard score points; $p = .92$). (See Figure 2). “(Figure 2 about here)”.

Cognitive trajectories for the incident MCI/dementia group

All cognitive domain and global z-scores for those who developed incident MCI/dementia were lower at baseline than the clinically normal group. The MCI/dementia group showed an improvement in memory from baseline to visit 2 ($p < .001$) followed by significant declines at each subsequent assessment. There was a slight decline in attention, language, and the global score from baseline to visit 2 which was followed by significant downward trajectories through visit 5 ($p = .007$ to $p < .001$). In contrast, there was a significant decline in visuospatial reasoning from baseline to visit 2 with only slight change through visit 4, followed by another decline at visit 5 ($p = .002$).

To further characterize the timing of the practice effect in relation to the diagnosis of incident MCI/dementia, we also plotted the cognitive trajectories separately for groups of

individuals who were classified as having declined at each visit [visit 2 (n=178), visit 3 (n=125), visit 4 (n=77), and visit 5 (n=63)] which are shown in Figure 3 and baseline standard scores are provided in Table 5. “(Table 5 about here)”. We were most interested in examining memory because of the unexpected practice effect observed in this domain. Those who declined at visit 2 showed a negligible practice effect from the baseline evaluation to visit 2 whereas those who declined at later visits started out incrementally higher at baseline and showed more notable improvements from baseline to visit 2. Those who declined at visit 3 did not sustain this practice effect. The group that declined by visit 4 showed a very slight decline at visit 3 followed by a decline at remaining time points. The group that declined at visit 5 sustained the practice effect through visit 3 before also declining in a stepwise fashion. The trajectories of the other cognitive domains and the global score vary slightly as a function of the visit at which decline was first noted.

DISCUSSION

We examined practice effects and cognitive changes in a population-based sample of adults, aged 70-89 at baseline, enrolled in the Mayo Clinic Study on Aging. Our main findings are: (1) Individuals who remained cognitively normal throughout the follow-up performed higher at baseline than those who developed incident MCI or dementia. They also showed different patterns of practice effects and cognitive trajectories according to cognitive domain; and (2) cognitively normal participants who developed incident MCI or dementia showed an initial practice effect in memory whereas all other cognitive domains show a downward trajectory. Further examination showed that those who developed incident MCI or dementia at visit 3 or later (or at least 30 months following baseline) showed the most practice effects suggesting that even in this group practice effects persist a few years before the onset of MCI/dementia.

We also examined whether demographic characteristics or the presence of the APOE $\epsilon 4$ allele influenced the practice effects and cognitive trajectories in the entire cohort. We found a significant effect for APOE $\epsilon 4$ on memory only, with APOE $\epsilon 4$ carriers failing to sustain their initial practice effect. An earlier study reported a diminished practice effect in APOE $\epsilon 4$ carriers relative to non-carriers in episodic memory, albeit in a slightly younger sample studied at only two time points (Zehnder et al., 2009).

The group who developed incident MCI/dementia differed from the clinically normal group in two important ways. First, while the incident MCI/dementia group mean score remained 0.86 standard score units below the clinically normal group at visit 2, this group showed an unexpected practice effect (i.e., improvement) in memory from baseline to visit 2. Further examination showed that the subtle practice effect at visit 2 for memory in the incident MCI/dementia group was driven by those who declined at visit 3 or later (i.e., not at their second visit) and may suggest essentially normal memory until a year or two before MCI-related decline becomes evident. This differs from two previous prospective longitudinal studies which did not find a practice effect in individuals who developed MCI (Howieson, et al., 2008; Wilson, et al., 2011). In contrast, another study found a practice effect in individuals with MCI over a 1 week period that was comparable to intact controls on all but the delayed recall trials on which they had a *larger* practice effect over a 1-week period (Duff, Callister, Dennett, & Tometich, 2012). These investigators also show practice effects in a subset of MCI patients over a 1 week interval who remained clinically stable one year later (Duff, et al., 2011). Our findings may partly reflect the phenomenon of reversion which demonstrates that individuals with MCI who revert to normal are still at increased risk for cognitive decline in the future (Koepsell & Monsell, 2012; Lopez et al., 2012; Roberts et al., 2013).

The second important way in which the incident MCI/dementia group differed from the clinically normal group was the longitudinal pattern of performance in attention, language, visuospatial reasoning and global cognition. In addition to starting out approximately one half of a standard score or more below the clinically normal group on each cognitive index, the incident MCI/dementia group did not show a practice effect in any of these domains or the global score, and declined at each subsequent evaluation. These results are consistent with other studies that show cognitive decline several years prior to the clinical diagnosis of MCI in multiple cognitive domains (Howieson, et al., 2008; Wilson, et al., 2011; Yu, et al., 2012). We did not find that one cognitive domain was preferentially more affected than another. This differs from a previous study showing that declines in semantic memory and working memory precede declines in other cognitive domains (Wilson, et al., 2011). However, our study did not specifically examine semantic memory and working memory. Further, about 13% of our participants were classified as either incident MCI or dementia at visit 2 (approximately 15 months after their baseline evaluation), which differs from studies that evaluated cognitive change for a longer period time prior to a diagnosis of incident MCI or dementia (Amieva, et al., 2005; Wilson, et al., 2011; Yu, et al., 2012).

Our clinically normal group showed a practice effect in all cognitive domains. These performance gains were sustained through visit 5 for both memory and visuospatial reasoning. Attention and language declined slightly after visit 3 though the mean group performance at the fifth evaluation was only slightly lower than at the baseline (i.e., attention = 0.08 standard score units; language = 0.11 standard score units.) We further examined the memory trajectories by age group (i.e., 70 – 79 and 80+). Although individuals in the older group started out slightly lower than their younger cohorts, they demonstrated a nearly identical practice effect at visit 2. Our results are consistent with a previous study from our group demonstrating that practice effects in multiple cognitive domains are most pronounced between visits 1 and 2 (Ivnik, et al., 1999) as well as several other studies showing that advanced aging in clinically normal individuals is not necessarily associated with dramatic cognitive decline (Amieva, et al., 2005; Johnson, et al., 2009; Wilson, et al., 1999; Wilson, et al., 2011).

Our findings have implications for future secondary preventions trials, both for identifying individuals at risk for future cognitive decline and evaluating the clinical effects of medications. Results from our study suggest that the absence of a practice effect could serve as an additional cognitive screen for enriching clinical trials with those who are in the pre-clinical stages of the disease process and most likely to benefit from disease-modifying therapy. Our longitudinal data could also serve as a benchmark against which to compare cognitive change in intervention trials. For example, the cognitive trajectory of a high risk group on a pharmacotherapeutic agent could be compared to the trajectories our clinical normal vs. incident MCI/dementia groups to determine whether there is a salutary effect. Both of these metrics could potentially reduce the number of participants needed to see a significant effect and therefore reduce the cost of secondary prevention studies.

This study has several considerable strengths. Our participants were randomly selected from the entire population in a geographically specific region (i.e., Olmsted County, Minnesota.) Our study design minimizes sample biases that may be present in volunteer samples recruited from advertisements or from patient samples recruited from referrals to specialized centers which enhances the generalizability of our findings. We modeled practice effects and longitudinal change in four cognitive domains and a global index of cognition over multiple evaluations spanning an average of five years, with every re-assessment performed without knowledge of the participants' earlier classifications.

Our study also has some limitations. Participants were 70 years or older at baseline so our results may not apply to younger ages. Our participants were predominantly Caucasian; therefore, our results may not apply to more racially diverse populations. It's also possible that our participants may be healthier than non-participants based on their ability to remain active in the study over several years.

In conclusion, our results show that the cognitive trajectories differed in four cognitive domains and a global index of cognition between those who remained clinically normal versus those who developed incident MCI or dementia. Our study highlights the importance of serial testing to monitor cognitive status as it relates to the development of clinical symptoms of disease. Modeling cognitive change in an epidemiologically specified sample may serve as a useful benchmark for evaluating cognitive change in future intervention studies. Future studies should examine practice effects in clinically normal individuals vs. those who develop incident MCI or AD as a function of biomarker status.

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Appendix 1

Domain score means and standard deviations at each visit

		All Baseline Normal Subjects	Stable Normal	Incident MCI/Dementia
		Mean ± SD	Mean ± SD	Mean ± SD
Memory	Visit 1	0.30 ± 0.90	0.53 ± 0.83	-0.19 ± 0.83
	Visit 2	0.49 ± 0.96	0.74 ± 0.87	-0.09 ± 0.92
	Visit 3	0.51 ± 1.07	0.88 ± 0.89	-0.20 ± 1.04
	Visit 4	0.54 ± 1.13	0.96 ± 0.93	-0.24 ± 1.06
	Visit 5	0.60 ± 1.19	1.02 ± 0.98	-0.28 ± 1.10
Attention	Visit 1	0.35 ± 0.84	0.55 ± 0.74	-0.08 ± 0.88
	Visit 2	0.38 ± 0.90	0.60 ± 0.78	-0.11 ± 0.98
	Visit 3	0.32 ± 0.96	0.62 ± 0.77	-0.26 ± 1.04
	Visit 4	0.30 ± 0.97	0.64 ± 0.73	-0.36 ± 1.03
	Visit 5	0.31 ± 1.00	0.56 ± 0.86	-0.27 ± 1.07
Language	Visit 1	0.29 ± 0.86	0.48 ± 0.79	-0.10 ± 0.86
	Visit 2	0.30 ± 0.88	0.50 ± 0.80	-0.15 ± 0.90
	Visit 3	0.27 ± 0.91	0.53 ± 0.77	-0.25 ± 0.94
	Visit 4	0.19 ± 0.97	0.53 ± 0.77	-0.43 ± 1.00
	Visit 5	0.21 ± 0.94	0.48 ± 0.78	-0.41 ± 0.98
Visuospatial	Visit 1	0.23 ± 0.91	0.38 ± 0.87	-0.10 ± 0.93

		All Baseline Normal Subjects	Stable Normal	Incident MCI/Dementia
		Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
	Visit 2	0.25 $\pm$ 0.95	0.43 $\pm$ 0.90	-0.18 $\pm$ 0.93
	Visit 3	0.27 $\pm$ 0.95	0.49 $\pm$ 0.86	-0.19 $\pm$ 0.97
	Visit 4	0.30 $\pm$ 0.94	0.56 $\pm$ 0.82	-0.21 $\pm$ 0.96
	Visit 5	0.35 $\pm$ 0.95	0.57 $\pm$ 0.84	-0.18 $\pm$ 0.99
Global	Visit 1	0.35 $\pm$ 0.84	0.59 $\pm$ 0.73	-0.17 $\pm$ 0.81
	Visit 2	0.44 $\pm$ 0.90	0.70 $\pm$ 0.76	-0.17 $\pm$ 0.90
	Visit 3	0.43 $\pm$ 0.95	0.78 $\pm$ 0.73	-0.28 $\pm$ 0.94
	Visit 4	0.43 $\pm$ 0.98	0.82 $\pm$ 0.74	-0.36 $\pm$ 0.93
	Visit 5	0.47 $\pm$ 0.98	0.80 $\pm$ 0.78	-0.32 $\pm$ 0.96

Appendix 2

Cognitive trajectories of APOE ϵ 4 non-carriers vs. carriers in the entire cohort

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CN = cognitively normal
MCI = mild cognitive impairment

Figure 1.

Cognitive trajectories in stable normal individuals, entire sample of subjects, and those who developed incident MCI/dementia by cognitive domain

Figure 2.
Memory trajectories for normal individuals by age group (< 80 and 80+)

CN = cognitively normal
MCI = mild cognitive impairment

Figure 3.
Cognitive trajectories of individuals who develop incident mild cognitive impairment/
dementia at Visits 2 – 5 by domain

Table 1

Demographic and clinical characteristics of study subjects

	Stable Normal (N=947)	Incident MCI/Dementia (N=443)	Total (N=1390)	p-value
Age (years)				<0.001
Mean (SD)	77.6 (4.7)	80.2 (5.1)	78.4 (5.0)	
Median [IQR]	76 [73, 81]	80 [75, 83]	78 [74, 82]	
Range	(70-90)	(70-91)	(70-91)	
80	326 (34.4%)	246 (55.5%)	572 (41.2%)	
Gender				0.094
Female	486 (51.3%)	206 (46.5%)	692 (49.8%)	
Male	461 (48.7%)	237 (53.5%)	698 (50.2%)	
Education				<0.001
Mean (SD)	14.4 (2.8)	13.6 (3.0)	14.1 (2.9)	
Median [IQR]	14 [12, 16]	13 [12, 16]	14 [12, 16]	
Range	(6-20)	(6-20)	(6-20)	
≤12	347 (36.6%)	213 (48.1%)	560 (40.3%)	
13-15	245 (25.9%)	113 (25.5%)	358 (25.8%)	
16-20	355 (37.5%)	117 (26.4%)	472 (34.0%)	
Marital Status				<0.001
Married	656 (69.3%)	254 (57.3%)	910 (65.5%)	
Previously Married	259 (27.3%)	168 (37.9%)	427 (30.7%)	
Never Married	32 (3.4%)	21 (4.7%)	53 (3.8%)	
Carrier of APOE ε4 allele^{<5>}	203 (21.5%)	136 (30.8%)	339 (24.5%)	<0.001
Population based, first selected year				
2004	725 (76.6%)	374 (84.4%)	1099 (79.1%)	
2008	222 (23.4%)	69 (15.6%)	291 (20.9%)	
BDI-II Total Score^{<30>}				<0.001
Mean (SD)	4.3 (4.0)	5.8 (5.1)	4.8 (4.4)	
Median [IQR]	4 [1,6]	5 [2, 8]	4 [1,7]	
Range	(0-26)	(0-30)	(0-30)	
Total 13, Depression, n (%)	44 (4.8%)	49 (11.3%)	93 (6.8%)	
Any Anti-Depressant	95 (10.0%)	66 (14.9%)	161 (11.6%)	0.008

Missing<N>

MCI = Mild Cognitive Impairment

BDI-II = Beck Depression Inventory-II

Table 2

Short Test of Mental Status and Clinical Dementia Rating Sum of Boxes for the stable normal and incident mild cognitive impairment/dementia groups.

		Stable Normal		Incident MCI/Dementia	
		Mean $\pm$ SD	Median [IQR]	Mean $\pm$ SD	Median [IQR]
STMS	Visit 1	34.9 $\pm$ 2.0	35 [34, 36]	33.2 $\pm$ 2.4	33 [31, 35]
	Visit 2	35.1 $\pm$ 2.1	35 [34, 37]	32.7 $\pm$ 2.9	33 [31, 35]
	Visit 3	35.2 $\pm$ 1.9	35 [34, 37]	31.9 $\pm$ 3.1	32 [30, 34]
	Visit 4	35.1 $\pm$ 2.0	35 [34, 37]	31.6 $\pm$ 3.6	32 [29, 34]
	Visit 5	35.0 $\pm$ 1.9	35 [34, 37]	30.9 $\pm$ 3.4	31 [29, 33]
CDR Sum of Boxes	Visit 1	0.0 $\pm$ 0.1	0 [0, 0.0]	0.0 $\pm$ 0.2	0 [0, 0.0]
	Visit 2	0.0 $\pm$ 0.1	0 [0, 0.0]	0.3 $\pm$ 0.7	0 [0, 0.5]
	Visit 3	0.0 $\pm$ 0.1	0 [0, 0.0]	0.6 $\pm$ 1.1	0 [0, 1.0]
	Visit 4	0.0 $\pm$ 0.1	0 [0, 0.0]	0.8 $\pm$ 1.4	0 [0, 1.0]
	Visit 5	0.0 $\pm$ 0.1	0 [0, 0.0]	1.1 $\pm$ 2.1	0 [0, 1.5]

STMS= Short Test of Mental Status

CDR = Clinical Dementia Rating

MCI = mild cognitive impairment

Table 3

Evaluation frequencies

Number of evaluations completed in individuals who remained clinically normal

		Number of Subjects	Percent
Completed	2 evaluations	947	100
Completed	3 evaluations	777	82.0
Completed	4 evaluations	558	58.9
Completed	5 evaluations	416	43.9

Clinically normal at enrollment who developed either incident MCI or dementia (N ==443)

	Number of Subjects	Percent	Cumulative Frequency	Cumulative Percent
Visit 2	178	40.2	178	40.2
Visit 3	125	28.2	303	68.4
Visit 4	77	17.4	380	85.8
Visit 5	63	14.2	443	100.0

Table 4

Results from linear mixed models analyses by cognitive domain

	All Baseline Normal Subjects				Stable Normal				Incident MCI/Dementia			
	LM Mean [*]	SE [*]	P-value		LM Mean [*]	SE [*]	P-value		LM Mean [*]	SE [*]	P-value	
Memory	Visit 1	0.25	0.03	<0.001 ^{**}	0.50	0.03	<0.001 ^{**}		-0.26	0.04	<0.001 ^{**}	
	Visit 2	0.46	0.02		0.74	0.03			-0.12	0.04		
	Visit 3	0.47	0.03		0.81	0.03			-0.22	0.05		
	Visit 4	0.46	0.03		0.86	0.03			-0.32	0.06		
	Visit 5	0.39	0.04		0.86	0.03			-0.54	0.07		
	2 vs 1	0.21	0.02	<0.001	0.23	0.02	<0.001		0.13	0.03	<0.001	
	3 vs 2	0.01	0.02	0.49	0.07	0.02	<0.001		-0.10	0.03	0.003	
	4 vs 3	-0.01	0.02	0.52	0.04	0.02	0.07		-0.10	0.04	0.006	
	5 vs 4	-0.07	0.02	0.001	0.00	0.02	0.89		-0.22	0.04	<0.001	
Attention	Visit 1	0.32	0.02	<0.001 ^{**}	0.53	0.02	<0.001 ^{**}		-0.13	0.04	<0.001 ^{**}	
	Visit 2	0.36	0.02		0.60	0.02			-0.16	0.04		
	Visit 3	0.29	0.02		0.58	0.02			-0.34	0.05		
	Visit 4	0.18	0.03		0.54	0.03			-0.55	0.06		
	Visit 5	0.08	0.04		0.45	0.04			-0.68	0.07		
	2 vs 1	0.04	0.01	0.006	0.07	0.02	<0.001		-0.03	0.03	0.28	
	3 vs 2	-0.07	0.02	<0.001	-0.01	0.02	0.41		-0.18	0.03	<0.001	
	4 vs 3	-0.11	0.02	<0.001	-0.04	0.02	0.023		-0.21	0.04	<0.001	
	5 vs 4	-0.10	0.02	<0.001	-0.09	0.02	<0.001		-0.13	0.05	0.007	
Language	Visit 1	0.28	0.02	<0.001 ^{**}	0.48	0.02	<0.001 ^{**}		-0.14	0.04	0.002 ^{**}	
	Visit 2	0.29	0.02		0.51	0.02			-0.19	0.04		
	Visit 3	0.23	0.02		0.48	0.02			-0.31	0.04		
	Visit 4	0.13	0.03		0.43	0.03			-0.49	0.05		
	Visit 5	0.05	0.03		0.37	0.03			-0.63	0.07		

	All Baseline Normal Subjects				Stable Normal				Incident MCI/Dementia			
	LM Mean [*]	SE [*]	P-value		LM Mean [*]	SE [*]	P-value		LM Mean [*]	SE [*]	P-value	
	2 vs 1	0.01	0.01	0.56	0.03	0.02	0.05		-0.05	0.03	0.06	
	3 vs 2	-0.06	0.02	<0.001	-0.03	0.02	0.15		-0.11	0.03	<0.001	
	4 vs 3	-0.10	0.02	<0.001	-0.05	0.02	0.012		-0.18	0.04	<0.001	
	5 vs 4	-0.08	0.02	<0.001	-0.07	0.02	0.003		-0.14	0.04	0.003	
Visual	Visit 1	0.22	0.02	0.07 ^{**}	0.38	0.03	0.024 ^{**}		-0.11	0.04	<0.001 ^{**}	
	Visit 2	0.23	0.02		0.43	0.03			-0.20	0.04		
	Visit 3	0.23	0.02		0.44	0.03			-0.23	0.04		
	Visit 4	0.22	0.03		0.46	0.03			-0.27	0.05		
	Visit 5	0.16	0.03		0.43	0.03			-0.42	0.06		
	2 vs 1	0.01	0.02	0.49	0.06	0.02	0.007		-0.09	0.03	0.005	
	3 vs 2	-0.01	0.02	0.64	0.01	0.02	0.72		-0.03	0.03	0.32	
	4 vs 3	-0.00	0.02	0.92	0.02	0.02	0.28		-0.04	0.04	0.30	
	5 vs 4	-0.06	0.02	0.010	-0.03	0.03	0.26		-0.14	0.05	0.002	
Global	Visit 1	0.33	0.02	<0.001 ^{**}	0.58	0.02	<0.001 ^{**}		-0.20	0.04	<0.001 ^{**}	
	Visit 2	0.41	0.02		0.71	0.02			-0.22	0.04		
	Visit 3	0.37	0.02		0.71	0.02			-0.35	0.04		
	Visit 4	0.29	0.03		0.70	0.02			-0.52	0.05		
	Visit 5	0.17	0.03		0.63	0.03			-0.75	0.06		
	2 vs 1	0.08	0.01	<0.001	0.12	0.01	<0.001		-0.02	0.02	0.44	
	3 vs 2	-0.04	0.01	<0.001	0.01	0.01	0.62		-0.13	0.02	<0.001	
	4 vs 3	-0.08	0.01	<0.001	-0.02	0.01	0.23		-0.17	0.03	<0.001	
	5 vs 4	-0.12	0.02	<0.001	-0.07	0.02	<0.001		-0.22	0.03	<0.001	

Models are adjusted for age/sex/education/time offset from expected follow-up times.

MCI = mild cognitive impairment

* LM Mean = estimated z-scores from the linear mixed model; SE = standard error of the LMM Mean estimate

** 4 df test for significance of Visit.

Table 5

Baseline standard scores for incident mild cognitive impairment/dementia group based on visit at which decline was noted.

	Declined			
	at Visit 2 N=178	at Visit 3 N=125	at Visit 4 N=77	at Visit 5 N=63
z Memory	-0.40 ± 0.81	-0.20 ± 0.80	-0.08 ± 0.79	0.24 ± 0.85
z Attention	-0.18 ± 0.93	-0.19 ± 0.81	0.03 ± 0.83	0.32 ± 0.83
z Language	-0.20 ± 0.86	-0.16 ± 0.86	-0.12 ± 0.84	0.30 ± 0.77
z Visuospatial	-0.14 ± 0.89	-0.22 ± 0.88	-0.12 ± 1.00	0.30 ± 0.95
z Global	-0.30 ± 0.81	-0.26 ± 0.73	-0.13 ± 0.84	0.35 ± 0.77

Mean ± SD