

PAPER

Mild cognitive impairment in different functional domains and incident Alzheimer's disease

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Background: Little is known about factors that predict transition from mild cognitive impairment to Alzheimer's disease (AD).

Objective: To examine the relation of impairment in different cognitive systems to risk of developing AD in persons with mild cognitive impairment.

Methods: Participants are 218 older Catholic clergy members from the Religious Orders Study. At baseline, they met criteria for mild cognitive impairment based on a uniform clinical evaluation that included detailed cognitive testing. Evaluations were repeated annually for up to 10 years. Analyses were controlled for age, sex, and education.

Results: Eighty two persons (37.6%) developed AD. In separate analyses, episodic memory, semantic memory, working memory, and perceptual speed, but not visuospatial ability, were associated with risk of AD, but when analysed together only episodic memory and perceptual speed were associated with AD incidence, with the effect for episodic memory especially strong. Overall, those with impaired episodic memory were more than twice as likely to develop AD as those with impairment in other cognitive domains (relative risk (RR) = 2.45; 95% confidence interval (CI): 1.53 to 3.92), and they experienced more rapid cognitive decline. Lower episodic memory performance was associated with increased risk of AD throughout the observation period, whereas impairment in other cognitive domains was primarily associated with risk during the following year but not thereafter.

Conclusion: Among persons with mild cognitive impairment, episodic memory impairment is associated with a substantial and persistent elevation in risk of developing AD compared to impairment in other cognitive systems.

Among older persons, those with mild cognitive impairment are known to be at increased risk of developing Alzheimer's disease (AD) compared to older persons without discernable cognitive impairment.^{1–3} Older persons with mild cognitive impairment, variously defined,^{1–5} are a heterogeneous group; however, some subsequently develop dementia, but a substantial proportion do not. The factors contributing to these different outcomes are not well understood.

Several prospective studies of people with mild cognitive impairment have examined the relation of level and type of cognitive impairment to risk of developing dementia and AD, with mixed results. Thus, severity of impairment in global cognition, as measured by the Mini-Mental State Examination⁶ or Dementia Rating Scale,⁷ has been associated with risk of AD in some studies,^{8–9} but the effect has been limited to a subset of items^{10–11} or been absent^{12–13} in other studies. Because impaired episodic memory is an early and defining feature of AD, some definitions of mild cognitive impairment are based primarily or exclusively on memory impairment.^{4–12–14–15} Whether impairment in memory predicts subsequent dementia better than impairment in some other form of cognition is uncertain, however. In persons with mild cognitive impairment, memory test performance has been inversely associated with risk of developing AD in some studies^{9–10–14–16–17} but not in others.^{12–13–18} One reason for these inconsistent findings may be that the ability of level of cognition to predict disease risk declines with the passage of time, but prior studies have not examined this issue to our knowledge. In addition, knowledge of the relation of cognitive function in domains other than episodic memory to risk of AD is limited because few large prospective studies have assessed

multiple cognitive systems in people with mild cognitive impairment.

In this paper, we use data from the Religious Orders Study¹⁹ to examine how impairment in different cognitive domains is related to incident AD. Participants are older Catholic nuns, priests, and brothers with mild cognitive impairment who had structured annual clinical evaluations for up to 10 years. At baseline, they completed a battery of cognitive tests from which previously established summary measures of episodic memory and four other cognitive domains were derived. We first examined the differential association of level of function in several cognitive domains with risk of developing AD at any follow up point in a series of accelerated failure models. We then assessed the persistence of the risk associated with function in each cognitive domain in a series of logistic regression models with disease incidence at varying follow up durations as the outcomes.

METHODS

Participants

All participants are from the Religious Orders Study which involves annual clinical evaluations and brain donation at death. It was approved by the Institutional Review Board of Rush University Medical Center.

Clinical evaluations began in January of 1994 and are continuing. At the time of these analyses, 995 persons had completed the baseline clinical evaluation. Of these, 79 met criteria for dementia, 674 had no cognitive impairment, and

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; NINCDS/ADRDA, National Institute of Neurological Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

242 met criteria for mild cognitive impairment, as described below. Of those with mild cognitive impairment, eight died before the first follow up evaluation and 11 had not yet reached their first follow up date at the time of these analyses. Of the remaining 223 persons, 218 (97.8%) participated in at least one follow up evaluation, with a mean of 6.1 evaluations per individual (because the study has ongoing enrolment, the number of evaluations ranged from 2 to 10). All analyses are based on this group. They had a mean (SD) age of 78.0 (7.1) years, a mean (SD) of 17.7 (3.2) years of education, and a mean (SD) Mini-Mental State Examination score of 27.4 (1.9) at baseline; 70.6% were women and 80.3% were white and non-Hispanic.

Clinical evaluation

At baseline, each participant underwent a uniform clinical evaluation that included a medical history, neurological examination, cognitive function assessment (see below), and review of brain scan if available. Clinical classification of cognitive impairment, dementia, and AD was accomplished in a three step process, as previously described.¹ First, neuropsychological tests were administered by trained technicians and scored by a computer. Second, a board certified clinical neuropsychologist, blinded to the person's age, sex, and race, reviewed the results of all cognitive tests and data on education, occupation, sensory and motor deficits, and effort. Based on review of these data, the neuropsychologist rendered a clinical judgment regarding the presence of impairment in episodic memory and other cognitive domains. To maximise the consistency of these judgments, the neuropsychologist was provided with educationally adjusted cut off scores for determining impairment on 11 of the tests, as previously reported.¹ Third, an experienced physician evaluated each participant and, based on review of all available data, classified each one with respect to AD and other common conditions of old age. The diagnosis of AD followed the criteria of the joint working group of the National Institute of Neurological Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA).²⁰ These criteria require a history of cognitive decline and impairment in at least two cognitive domains, one of which must be memory, to meet AD criteria.

There are no consensus criteria for the clinical classification of mild cognitive impairment. In this study, persons were designated as having mild cognitive impairment who were judged to have cognitive impairment by the neuropsychologist, but did not meet NINCDS/ADRDA criteria for dementia. These criteria for mild cognitive impairment have been used in many previous studies.^{1 21–24} In some analyses, we subdivided persons with mild cognitive impairment into those judged by the neuropsychologist to have episodic memory impairment, as described above, and those without impaired episodic memory.

Assessment of cognitive function

A total of 20 cognitive performance tests were administered as part of each evaluation. One test, the Mini-Mental State Examination,⁶ a measure of global cognition, was used for descriptive purposes, but not in analyses. Seven tests assessed episodic memory: immediate and delayed recall of the East Boston Story^{25 26} and Story A from Logical Memory,²⁷ and Word List Memory, Recall and Recognition.²⁸ Semantic memory was assessed with a 20 item version of the Boston Naming Test,²⁹ a 15 item form of Extended Range Vocabulary,³⁰ and a 20 item form of the National Adult Reading Test.³¹ There were four tests of working memory: Digit Ordering,³² Alpha Span,³³ and Digit Span Forward and Digit Span Backward.²⁷ Perceptual speed was assessed with

the oral version of the Symbol Digit Modalities Test³⁴ and Number Comparison,³⁰ and visuospatial ability was evaluated with a 15 item version of Judgment of Line Orientation³⁵ and a 17 item version of Standard Progressive Matrices.³⁶

Composites of two or more tests were used in analyses to reduce measurement error in general and floor and ceiling artefacts in particular. Based in part on a factor analysis of the tests at baseline,²⁶ we formed measures of episodic memory (based on seven tests), semantic memory (four tests), working memory (four tests), perceptual speed (two tests), and visuospatial ability (two tests). Raw scores on each component test were converted to z scores, using the baseline mean and standard deviation from all participants in the Religious Orders Study, and averaged to form the composite measures. Further information on the individual tests and on the derivation and psychometric properties of these composite measures is contained in previous publications.^{26 37 38}

Data analysis

To assess the differential association of level of function in various cognitive systems with overall disease risk, we constructed a series of accelerated failure time models³⁹ adjusted for age, sex, and education. The Weibull accelerated failure time model allows characterisation of relative risk ratios when the assumption of proportional hazards is not tenable, which was the situation with our data. We first constructed separate models for each composite cognitive measure and then analysed all five measures together, followed by a model contrasting those with and without impaired episodic memory.

We used mixed effects models⁴⁰ to test whether rate of decline in each cognitive domain differed between persons with versus without episodic memory impairment. Each model had terms for time, the presence of episodic memory impairment, and their interaction plus terms to control for age, sex, and education. The interaction term indicates the additional decline per year associated with having impaired episodic memory at baseline. Further information on the use of mixed effects models with longitudinal cognitive data is published elsewhere.^{26 41}

To examine how the association of level of cognition with risk of AD changed with time, we divided those who developed AD into five subgroups of approximately equal size based on how soon the diagnosis was made following the baseline evaluation. Using these time categories, we then tested the association of each baseline cognitive measure with risk of developing AD within a given follow up period (for example, during the first year, during the second year, after 6 or more years) in a set of five separate logistic regression models adjusted for age, sex, and education.

Model assumptions were examined graphically and analytically, and found to be adequately met. Programming was done in SAS.⁴²

RESULTS

Level of function in different cognitive systems and incidence of Alzheimer's disease

At baseline, the composite measure of episodic memory had a mean of -0.43 (SD 0.64, interquartile range 0.83); mean semantic memory score was -0.33 (SD 0.66, interquartile range 0.84); mean working memory score was -0.26 (SD 0.65, interquartile range 0.78); mean perceptual speed score was -0.35 (SD 0.79, interquartile range 1.02); and mean visuospatial ability score was -0.53 (SD 0.75, interquartile range 1.11).

During a mean of 5.1 years of follow up, 82 persons developed AD, a rate of about 8% per year which is roughly consistent with previous research.^{43 44} Three persons who

developed other forms of dementia (that is, stroke, Parkinson's Disease, depression) were excluded from further analyses. We first examined the association of baseline level of function in each cognitive domain to disease incidence in separate accelerated failure models adjusted for age, sex, and education. In these analyses (left side of table 1), lower level of each function except visuospatial ability was related to increased risk of developing AD, although the effect appeared considerably stronger for episodic memory compared to other functions.

We visually examined these associations by plotting the model based estimate of the cumulative hazard of developing AD for persons with high (75th percentile) and low (25th percentile) levels of function in each cognitive domain (fig 1). The figure suggests that the risk of developing AD associated with a low episodic memory score was about twice the risk associated with having a low score in other cognitive domains.

To assess the independent contribution of each domain, we repeated the analysis with all five cognitive measures in the same model (right side of table 1). In this analysis, episodic memory and perceptual speed, but not the other cognitive measures, were related to disease incidence.

To further examine the differential risk associated with impairment of episodic memory compared to other cognitive domains, we divided participants into those with ($n = 126$) and without ($n = 116$) episodic memory impairment, based on review of all test data by a boarded clinical neuropsychologist, as described above. As shown in fig 2, which was based on this analysis, persons with episodic memory impairment were more than twice as likely to develop AD as persons with impairment in other cognitive domains (relative risk (RR) = 2.45; 95% confidence interval (CI): 1.53 to 3.92).

Because clinical classification of AD can be difficult, we examined rate of cognitive decline, the primary clinical manifestation of the disease, in those with and without episodic memory impairment. In separate mixed effects models controlled for age, sex, and education, those with baseline episodic memory impairment declined more rapidly in semantic memory ($p = 0.027$) and visuospatial ability ($p = 0.007$) than those with impairment in other cognitive systems, with no differences in the other cognitive domains (all $p > 0.150$).

Persistence of AD risk associated with level of function in different cognitive systems

To evaluate how the relation of cognitive function to disease incidence changed with the passage of time, we divided those who developed AD into five subgroups: 26 people diagnosed at the first year follow up, 15 at year 2, 16 at year 3, 13 in years 4 and 5 combined, and 12 in year 6 or later. We then examined the relation of baseline score on each summary cognitive measure to disease incidence at each of these five follow up points in separate logistic regression models adjusted for age, sex, and education. The results of these analyses for episodic memory are shown at the top of table 2.

Lower baseline episodic memory was associated with an increased risk of developing AD at the first and second year follow up evaluations and after 6 or more years of follow up, with similar trends at the intermediate follow up points. By contrast, lower levels of semantic memory, working memory, and perceptual speed were each associated with a higher risk of AD at the first year follow up point but relatively rarely thereafter, and visuospatial ability was unrelated to disease incidence at any follow up point.

DISCUSSION

We annually examined a group of more than 200 older persons with mild cognitive impairment for a mean of about 5 years. Among those with episodic memory impairment, risk of developing AD was stronger and more persistent, and cognition declined more rapidly, compared to those with impairment in other cognitive domains. The results suggest that risk of AD in mild cognitive impairment depends strongly on level of episodic memory.

The association between cognitive test performance in persons with mild cognitive impairment and subsequent risk of dementia and AD has been difficult to establish, as noted above. One issue is that sample sizes have often been small, with few studies of more than 100 participants,^{10 14 17 18} limiting the power to detect the associations of interest and the ability to control potentially confounding variables like age and education. In larger prospective studies that controlled for demographic variables, measures of episodic memory,^{14 17} semantic memory,^{10 17} working memory,¹⁴ and perceptual speed¹⁰ have been associated with disease risk, consistent with the results of this study.

Another uncertainty has been whether impairment in some cognitive domains predicts AD better than impairment in other domains among those with mild cognitive impairment. In this cohort, we found that the presence and severity of episodic memory impairment was generally more robustly related to risk of disease than the presence or severity of impairment in other cognitive domains. This effect may be due in part to memory impairment being a diagnostic criterion for AD.^{20 45} However, persons with impaired episodic memory experienced more rapid cognitive decline than those with impairment in domains other than episodic memory. This observation plus neuroimaging evidence of structural⁴⁶ and functional⁴⁷ abnormalities in the medial region of the temporal lobe of persons with mild cognitive impairment suggest that the effect has a biological basis.

A novel feature of this study is that we examined predictive accuracy as a function of the time between cognitive testing and clinical classification of disease incidence. As expected, predictive accuracy tended to decline with the passage of time, likely reflecting the modest correlation between cognition measured at a single point in time and subsequent rate of change in cognition.^{26 48} Of interest, the association of episodic memory with AD risk attenuated relatively little during the observation period, whereas the association of semantic memory, working memory, and perceptual speed

Table 1 Relation of baseline level of function in different cognitive domains to risk of incident AD*

Cognitive domain	Separate models				Single model			
	Estimate (SE)	χ^2	p	RR (95% CI)	Estimate (SE)	χ^2	p	RR (95% CI)
Episodic memory	0.72 (0.13)	33.2	<0.001	0.39 (0.28 to 0.54)	1.12 (0.15)	55.6	<0.001	0.18 (0.11 to 0.28)
Semantic memory	0.38 (0.14)	7.0	0.008	0.62 (0.43 to 0.88)	0.13 (0.15)	0.8	0.370	0.81 (0.52 to 1.28)
Working memory	0.42 (0.15)	8.0	0.005	0.59 (0.41 to 0.85)	0.07 (0.15)	0.2	0.651	0.90 (0.57 to 1.42)
Perceptual memory	0.43 (0.12)	12.2	<0.001	0.57 (0.42 to 0.78)	0.36 (0.12)	8.3	0.004	0.58 (0.40 to 0.84)
Visuospatial ability	-0.16 (0.12)	1.7	0.198	1.22 (0.90 to 1.66)	0.07 (0.11)	0.4	0.536	0.90 (0.63 to 1.27)

*Estimated from accelerated failure models adjusted for age, sex, and education.
CI, confidence interval; RR, relative risk.

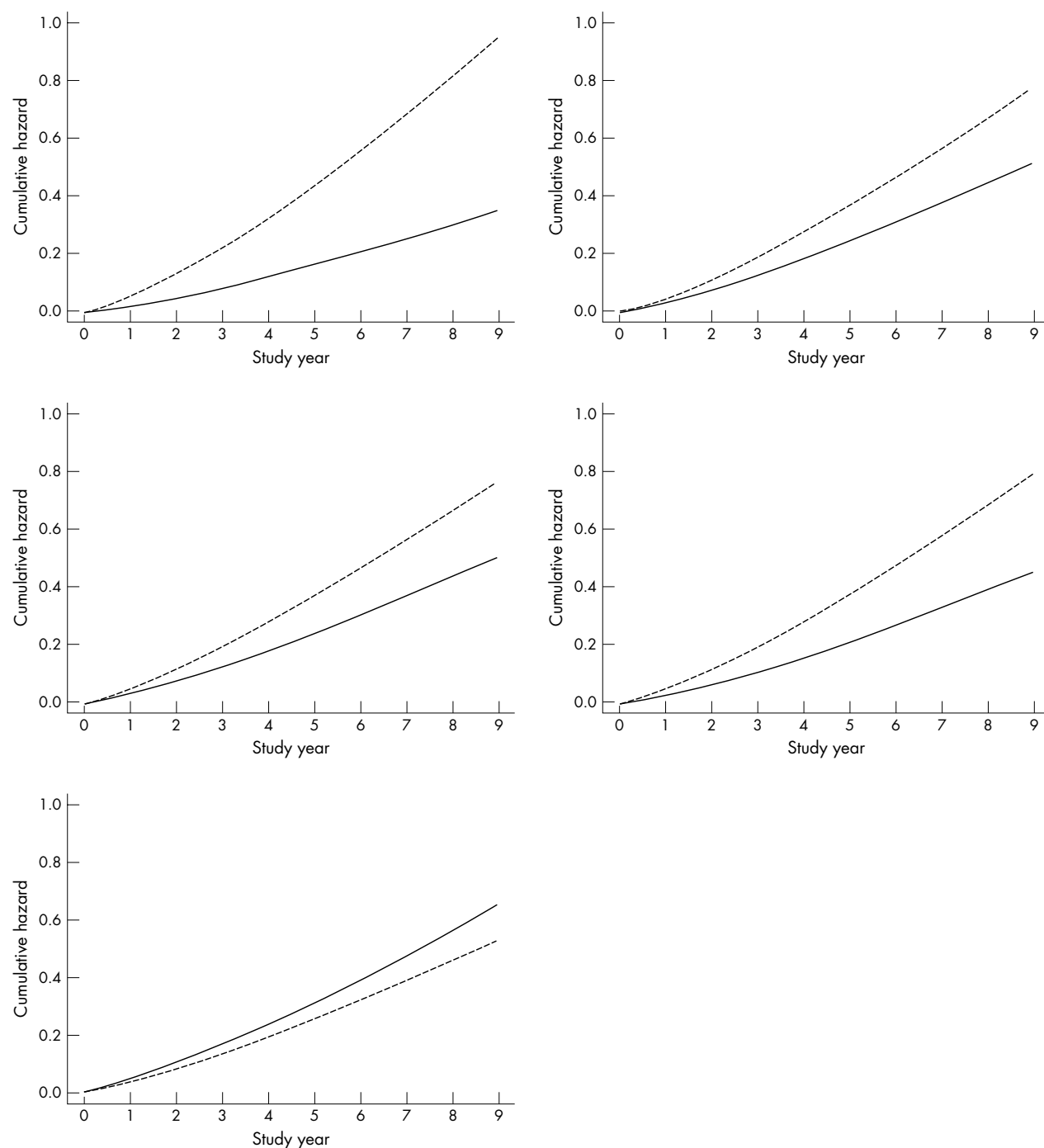


Figure 1 Cumulative hazard of developing AD in those with cognitive scores at the 25th (dotted line) versus 75th (solid line) percentile in episodic memory (upper left), semantic memory (upper right), working memory (middle left), perceptual speed (middle right), and visuospatial ability (lower left).

with disease incidence was mainly confined to the first year or two of follow up, suggesting that low episodic memory performance is more likely to reflect functional decline than is low performance in other cognitive domains. An unexpected finding was that visuospatial ability, which has not been extensively studied in mild cognitive impairment, had no association with AD risk at any follow up point.

An obstacle to research progress in this area is the lack of agreement on what constitutes mild cognitive impairment. Classification of mild cognitive impairment in this study was based on criteria that have been widely used in previous research.^{1 21–24} These criteria have several important features.

First, they require evidence of cognitive impairment on performance testing so that persons with reported cognitive dysfunction or difficulty with activities of daily living in the absence of cognitive impairment are not included. Second, the criteria allow all older people to be classified as having dementia, mild cognitive impairment, or no cognitive impairment. Third, they do not assume that particular subtypes or dimensions of mild cognitive impairment are more important than others.

Confidence in these finding is strengthened by several factors. Clinical classification of mild cognitive impairment and AD was based on a uniform clinical evaluation and

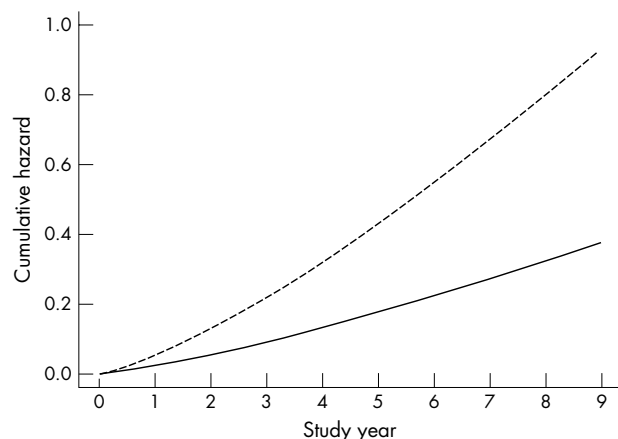


Figure 2 Cumulative hazard of developing AD in those with impairment in episodic memory (dotted line) or in some other cognitive domain (solid line).

application of widely used criteria by experienced clinicians, and the effect of episodic memory impairment was observed for both clinically diagnosed AD and rate of cognitive decline, reducing the likelihood that diagnostic bias or imprecision affected results. The availability of more than 200 people with mild cognitive impairment with a mean of 5–6 years of follow up and high follow up participation enhanced our power to detect associations between cognitive test performance and disease incidence. Use of previously established composite measures of different cognitive systems allowed us to examine whether the association of cognition with disease risk varied across functional domains.

The main limitation of these findings is that they are based on a selected group of participants who differ in education and lifestyle from older persons in the United States population. Similar studies of more diverse groups of older people are needed. In addition, episodic memory was assessed exclusively with verbal tests. Whether these results will apply to episodic memory for non-verbal information is uncertain.

These findings have practical implications for clinicians who have older patients with mild cognitive impairment. Given evidence of episodic memory impairment, suspicion that the underlying condition is AD should remain high even if function in other cognitive domains is relatively preserved. Conversely, in the absence of impaired episodic memory, impairment in other cognitive domains is less likely to be an early sign of AD.

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Table 2 Relation of baseline level of function in different cognitive domains to risk of developing incident AD at different follow up periods*

Year AD diagnosed	Cognitive domain	Odds ratio	95% CI
1	Episodic memory	0.199	0.093 to 0.425
2		0.152	0.053 to 0.436
3		0.430	0.166 to 1.115
4, 5		0.401	0.139 to 1.158
6 or later		0.206	0.048 to 0.888
1	Semantic memory	0.488	0.245 to 0.971
2		0.330	0.125 to 0.873
3		1.054	0.402 to 2.765
4, 5		1.122	0.393 to 3.203
6 or later		0.244	0.054 to 1.098
1	Working memory	0.399	0.184 to 0.864
2		0.858	0.350 to 2.106
3		0.778	0.303 to 1.996
4, 5		0.170	0.047 to 0.620
6 or later		0.606	0.195 to 1.886
1	Perceptual speed	0.402	0.217 to 0.745
2		0.561	0.254 to 1.238
3		0.747	0.303 to 1.845
4, 5		0.549	0.228 to 1.324
6 or later		0.602	0.193 to 1.881
1	Visuospatial ability	1.054	0.584 to 1.903
2		1.323	0.639 to 2.740
3		1.450	0.636 to 3.307
4, 5		1.005	0.418 to 2.417
6 or later		1.177	0.394 to 3.518

*From logistic regression models adjusted for age, sex, and education.

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