Predicting the time of conversion to MCI in the elderly

Role of verbal expression and learning

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ABSTRACT

Background: Increasing awareness that minimal or mild cognitive impairment (MCI) in the elderly may be a precursor of dementia has led to an increase in the number of people attending memory clinics. We aimed to develop a way of predicting the period of time before cognitive impairment occurs in community-dwelling elderly. The method is illustrated by the use of simple tests of different cognitive domains.

Methods: A cohort of 241 normal elderly volunteers was followed for up to 20 years with regular assessments of cognitive abilities using the Cambridge Cognitive Examination (CAMCOG); 91 participants developed MCI. We used interval-censored survival analysis statistical methods to model which baseline cognitive tests best predicted the time to convert to MCI.

Results: Out of several baseline variables, only age and CAMCOG subscores for expression and learning/memory were predictors of the time to conversion. The time to conversion was 14% shorter for each 5 years of age, 17% shorter for each point lower in the expression score, and 15% shorter for each point lower in the learning score. We present in tabular form the probability of converting to MCI over intervals between 2 and 10 years for different combinations of expression and learning scores.

Conclusion: In apparently normal elderly people, subtle measurable cognitive deficits that occur within the normal range on standard testing protocols reliably predict the time to clinically relevant cognitive impairment long before clinical symptoms are reported. *Neurology*® 2009;73:1436–1442

GLOSSARY

AD = Alzheimer disease; **AFT** = accelerated failure time; **aMCI** = amnestic mild cognitive impairment; **CAMCOG** = Cambridge Cognitive Examination; **CAMDEX** = Cambridge Examination for Disorders of the Elderly; **CI** = confidence interval; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **NINCDS** = National Institute of Neurological and Communicative Disorders and Stroke; **OPTIMA** = Oxford Project to Investigate Memory and Ageing; **OR** = odds ratio.

Mild cognitive impairment (MCI), as operationally defined, often represents the predementia stage of a neurodegenerative disorder in elderly subjects, including Alzheimer disease (AD), vascular dementia, or other dementia.[1,2] Amnestic MCI (aMCI), with a predominant impairment in episodic memory, may be a precursor of AD.[3-5]

Several studies have shown that deficits in memory retention and abstract reasoning are the most important cognitive predictors of AD, problems being evident more than 10 years before diagnosis.[6-9] However, little is known about the factors that predict when normal subjects, or those with minimally impaired cognition, will develop aMCI.[10-12] Sensitive neuropsychological tests have been shown to detect cognitive dysfunction in elderly who show no signs of dementia.[13,14] The Cambridge NeuropsychologicalTest Automated Battery Paired Associates Learning Test was shown to have improved specificity and positive predictive value for conversion to MCI in 4 years when used at 2 consecutive time points in a cohort considered cognitively

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healthy at baseline.[11] Impairments in other cognitive domains are also associated with conversion to MCI,[15] as well as early life linguistic ability.[16]

The focus of this study was the probability of developing future cognitive impairment in the cognitively healthy elderly. Instead of simply identifying risk factors for cognitive decline, we aimed to develop a method of estimating the duration of time before conversion to aMCI, based on an initial cognitive score or a combination of test scores, in subjects initially classified as cognitively healthy.

METHODS

Study participants. The Oxford Project to Investigate Memory and Ageing (OPTIMA) study began in 1988 as a case-control study of subjects with probable and possible AD (http://www.medsci.ox.ac.uk/optima). At study entry, participants were classified as being control, probable/possible AD,[17] or other dementia syndrome according to clinical diagnostic procedures current at the time. For this study, all participants enrolled in OPTIMA as cognitively healthy controls from 1988 until the end of 2008 with a record of at least 2 visits were included in the selection procedure. At their first episode, all participants were given the Cambridge Examination for Disorders of the Elderly (CAMDEX),[18] which consists of an informant interview and a patient interview that includes a cognitive assessment, the Cambridge Cognitive Examination (CAMCOG). The CAMCOG is comprised of subtests including orientation, comprehension, expression, recent memory, remote memory, learning, abstract thinking, perception, praxis, attention, and calculation as well as a derived Mini-Mental State Examination (MMSE) score (appendix e-1 on the *Neurology*® Web site at www.neurology.org).

Control subjects (n = 241) were defined as those fulfilling all of the following criteria: "National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) negative," no dementia present, MMSE score ≥24, and CAMCOG learning subscore ≥13 out of 17 points.

Standard protocol approvals, registrations, and patient consents. The study was approved by the local ethics committee (COREC C1656), and all subjects gave written consent for their participation.

Measures used to identify subjects who converted to MCI after their first visit. Diagnosis (control or MCI) was checked at each visit for each participant to determine the date when conversion to aMCI (if it occurred) was first identified. Conversion to aMCI was defined when a participant was found to have fulfilled all of the following criteria[1] by a neuropsychologist (C.A.d.J.) who examined the clinical notes recorded by physicians:

- Subjective memory complaints, either by the subject or as reported by the informant in the CAMDEX questionnaire.
- Objective memory impairment, assessed from available memory test scores, with a value of <1.5 SD below the cutoff. Predetermined cutoffs for aMCI were based on a normal control sample of healthy elderly volunteers in OPTIMA at study entry,[19] unless there were published norms available (appendix e-1).
- No dementia present and NINCDS negative.
- MMSE (≥24) and no significant problems reported with activities of daily living as assessed by questions in the CAMDEX.

Statistical analysis. The important property that characterizes conversion data is that the conversion to MCI (or to any other state), if it happens, always occurs between visits. The exact date of conversion is usually not known, only the interval during which the conversion has occurred. This property defines the interval-censored data framework.[20] We defined the main outcome measure as the duration of time (in years) between the first visit and the date conversion to MCI was first identified, if the subject converted, or until the last visit recorded, if the subject had not converted. For those subjects who converted to MCI, the date of conversion is interval-censored because the conversion took place between visits. Subjects who did not convert were right-censored; these included 21 who withdrew and 49 who died. The nature of the outcome variable suggested that survival analysis would be the best method for data analysis. The standard Cox proportional hazard model, in which the interval is replaced by its midpoint, could have been used. However, to avoid the approximations and potential biases of using the midpoint of the interval, we adopted different approaches that accommodate the interval-censored survival data (appendix e-1).

Primary method. The smoothing accelerated failure time (AFT) procedure, using G-splines,[21] was selected. This method is a trade-off between parametric and semiparametric AFT models. It is naturally adapted to interval-censored data, can handle many predictors (in contrast to its semiparametric version), and also profits from the advantages of parametric methods leaving the baseline distribution, in practice, largely unspecified. In this statistical model, all CAMCOG subscores were tested as potential predictors of the duration of conversion to MCI. The following covariates were also included in the model: age, years of school education, further education, gender, and ApoE4 status.

Secondary methods. *Extended Cox proportional hazard model using the iterative convex minorant algorithm.* This version of the Cox model[22] is adapted to interval-censored data. The *p* values and confidence intervals (CIs) were calculated using the bootstrap methodology, but no estimated curve could be plotted. This method was used just to confirm the results of the primary method.

Fixed study period approach. We used logistic regression to investigate which cognitive subscores significantly predict the conversion to MCI when the study period was fixed, and also to identify those subscores that are always significant whatever the duration of the study period (details in appendix e-1).

RESULTS

Descriptive statistics. Two hundred forty-one control subjects (at first visit) from the OPTIMA database were eligible for inclusion in this study. During follow-up between 1988 and 2008, 91 controls (37.8%) converted to MCI and their conversion durations were thus interval-censored, whereas the remaining 150 were still control subjects at their last recorded episode and their conversion durations were thus right-censored (table 1). At baseline, the mean (SD) age was 71.85 (8.83) years, years of school education was 11.46 (1.49), years of further education was 2.31 (2.29),

Table 1 Conversion to MCI over a 20-year period

Study period	Converters to MCI	Nonconverters	Right-censored
Baseline	0	241	0
0–2 y	13	206	22
0–4 y	19	176	46
0–5 y	38	143	60
0–6 y	39	130	72
0–7 y	49	110	82
0–8 y	53	101	87
0–9 y	65	87	89
0–10 y	76	42	123
0–20 y	91	0	150

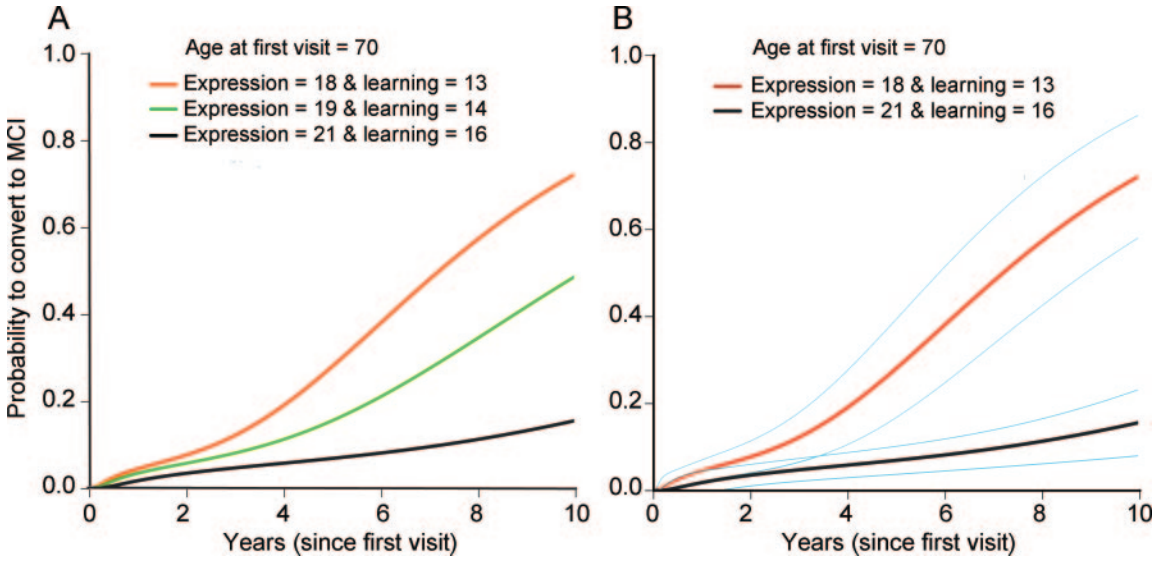
Converters: Those converting to mild cognitive impairment (MCI) during the study period. Nonconverters: Those who did not convert to MCI during the study period and for whom the follow-up is greater than the study period. Right-censored: Those who did not convert during the study period but for whom the follow-up is less than the study period. This includes all controls that withdrew during the study period (21), those who died (49), and/or controls still in the study but with follow-up less than the study period.

plasma total homocysteine was 12.6 (3.9) μmol/L, blood pressure was 153.5 (22.5) mm Hg systolic and 83.8 (11.2) mm Hg diastolic, 53.1% of subjects were male, and 27.4% were ApoE4 positive.

The cognitive scales used in the analysis as potential predictors of the duration of time to convert to MCI were the subscores from the CAMCOG. All subscores at episode 1 (when all subjects were controls) were entered and tested in the model. Table e-1 (appendix e-1) shows the scores at baseline for the whole study cohort. We show below that the only significant predictors of the duration of time to conversion to MCI with all the statistical models used were the CAMCOG expression and learning subscores, and age. The normal range of scores was between 15 and 21 for expression and between 13 and 17 for learning.

Primary statistical method. The AFT model showed that among all CAMCOG subscores, only expression and learning were significant predictors of the time to conversion to MCI. Among the demographic data, only age at first visit was significant. From the model, the duration of time to convert to MCI was 0.83 ($p = 0.0001$) times shorter (−17%) when the expression score decreased by 1 point, 0.85 ($p = 0.001$) times shorter (−15%) when the learning score decreased by 1 point, and 0.86 ($p = 0.0001$) times shorter (−14%) when age increased by 5 years. To graphically depict these significant effects, we have plotted the model-estimated cumulative distributions (figure 1A). The figure shows the cumulative probabilities of conversion according to 3 combinations of expression and learning scores at baseline. The age at baseline was fixed at 70 years. From the curves, it can be seen that the probability to convert to MCI in less than 5 years was only 7% for the group with the highest scores, whereas it was 4 times greater (28%) for those with the lowest scores. CI curves for these cumulative probabilities of conver-

Figure 1 Conversion to MCI according to the AFT model



(A) Estimated cumulative probabilities of conversion to mild cognitive impairment (MCI) according to the accelerated failure time (AFT) model. The figure shows the cumulative probabilities of conversion according to 3 combinations of expression and learning scores at baseline for subjects aged 70 years. The curve is exactly the inverse of the well-known survival curve. (B) Ninety-five percent confidence intervals of the cumulative probabilities of conversion to MCI by the AFT model. Ninety-five percent confidence intervals (blue lines) of the cumulative probabilities of conversion for 2 combinations of expression and learning scores at baseline for subjects aged 70 years. The R code for the determination of confidence intervals is given in appendix e-2.

Table 2 Estimated probabilities of conversion to MCI in 3 different groups, age = 70 years

	Expression = 18, Learning = 13		Expression = 19, Learning = 14		Expression = 21, Learning = 16	
	Estimated probability, %	95% CI, %	Estimated probability, %	95% CI, %	Estimated probability, %	95% CI, %
2 y	7.78	4.10-11.45	5.88	3.12-8.63	3.56	1.07-6.05
4 y	19.21	10.64-27.77	11.37	7.22-15.52	5.88	2.98-8.78
6 y	38.23	24.88-51.58	21.22	15.50-26.95	8.22	4.52-11.91
8 y	57.46	42.62-72.31	34.73	27.77-41.69	11.36	6.17-16.56
10 y	72.39	58.32-86.45	48.91	40.75-57.07	15.69	8.04-23.34

MCI = mild cognitive impairment; CI = confidence interval.

sion according to 2 combinations of expression and learning are given in figure 1B.

Table 2 gives the estimated cumulative probabilities of conversion in these 3 groups at 2, 4, 6, 8, and 10 years after the initial assessment along with 95% CIs. From this table, a subject aged 70 years with an expression score of 18 and a learning score of 13 has a risk of 38.2% to convert to MCI during the next 6 years. In comparison, another subject with the same age but with an expression score of 21 and a learning score of 16 has a risk of only 8.2% to convert to MCI during this period.

Furthermore, from the fitted model, the probability of conversion can be estimated during any period of time for any combination of age, expression, and learning at baseline. Table 3 shows these predictions when age was fixed at 70 years and also shows a comparison with the average risk for subjects without dementia. The average probability is estimated from the model using average scores for expression and learning at baseline, but leaving age fixed at 70 years.

An example from table 3 based on the 4 years conversion column is as follows. On average, there is a risk of 10% to convert to MCI during the first 4 years for control subjects aged 70 years. A subject with the same age but with an expression score of 15 and a learning score of 13 (first row) has instead a risk of 49% to convert to MCI during this period of time; thus, the odds ratio (OR) (relative to the average population) is 8.65. In contrast, a subject with the same age but with an expression score of 21 and a learning score of 17 (last row) has a risk of 5% to convert to MCI within 4 years; thus, the OR (relative to the average population) is 0.47.

Goodness-of-fit of the AFT model. To illustrate graphically how well the AFT model fits the observed data, a plot is shown (figure 2) that depicts the observed cumulative proportions of subjects converting to MCI for 2 different groups of subjects: those with expression scores between 20 and 21 (n = 114) vs those with scores between 15 and 19 (n = 127); these represent approximate median splits. The empirical curves in figure 2 are descriptive in the sense that no statistical model has been used to generate them. The curves were calculated using an extended version of the Kaplan-Meier nonparametric estimator to take into account interval-censored data.[23] Figure 2 confirms our finding, first, by showing a significant difference in the observed cumulative proportions of subjects converting to MCI between the 2 groups, and second, by showing how well the curves estimated from the AFT model (red lines) fitted the data.

Secondary statistical methods. ***Extended Cox proportional hazard model.*** The extended Cox model using bootstrap (10,000 replications) confirmed the results of the AFT model given above. Indeed, the effects of expression, learning, and age on the risk of conversion (or on the hazard) at any time were highly significant. From the Cox model, the instantaneous risk (or the hazard) of conversion to MCI is 1.37-fold higher ($p = 0.001$) when age increases by 5 years, 1.52-fold higher ($p = 0.001$) when expression decreases by 1 point, and 1.47-fold higher ($p = 0.001$) when learning decreases by 1 point. If both the expression and learning scores each decrease by 1 point, the risk of conversion is 2.2-fold higher, i.e., the risks are multiplicative.

Logistic regression to study fixed endpoint data. Table e-2 (appendix e-1) shows that for all 9 study periods, between 2 and 12 years, the best logistic model always included expression and learning. Age was also a good predictor once the study period exceeded 4 years, but other covariates, such as perception, ApoE4, and gender, were less consistent predictors. Using the logistic regression approach allowed us to draw receiver operating characteristic curves for the prediction of conversion (figure e-1, appendix e-1); these had areas under the curve ranging from 85% to 90%, showing a high degree of accuracy in the predictions.

Overall, the results for age, expression, and learning were not significantly changed when additional covariates (systolic blood pressure, education, stroke, homocysteine, ApoE4) were included in the models, except that now the presence of ApoE4 exerted a negative effect, i.e., carriers of this allele converted more rapidly than noncarriers (table e-3, appendix e-1).

Thus, the 3 different statistical approaches each show that the 2 subscores, expression and learning, are robust for predicting the conversion to MCI. We prefer to use survival analysis rather than logistic regression as used previously,[6] first, because the study period does not need to be fixed; second, because it allows the use of the right- and interval-censored data, which is not the case for logistic regression; and finally, because survival analysis answers some additional questions and most importantly directly models the duration of the period before conversion.

Table 3 Predictive probabilities of conversion to MCI

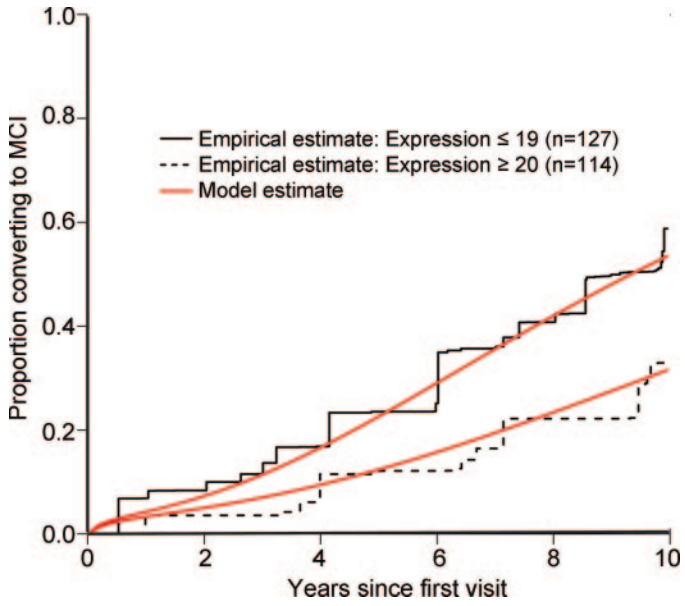
Predictors		Conversion in 2 y		Conversion in 4 y		Conversion in 6 y		Conversion in 8 y		Conversion in 10 y	
Expr	Learn	Prob (average 0.05)	OR	Prob (average 0.1)	OR	Prob (average 0.18)	OR	Prob (average 0.29)	OR	Prob (average 0.42)	OR
15	13	0.16	3.62	0.49	8.65	0.76	14.43	0.9	22.03	0.95	26.24
15	14	0.12	2.59	0.39	5.75	0.66	8.84	0.83	11.95	0.92	15.88
15	15	0.1	2.11	0.3	3.86	0.55	5.57	0.74	6.97	0.86	8.48
15	16	0.09	1.88	0.23	2.69	0.45	3.73	0.64	4.35	0.78	4.9
15	17	0.07	1.43	0.17	1.84	0.35	2.45	0.53	2.76	0.69	3.07
16	13	0.12	2.59	0.37	5.29	0.64	8.1	0.81	10.44	0.91	13.96
16	14	0.1	2.11	0.28	3.5	0.53	5.14	0.72	6.3	0.85	7.83
16	15	0.08	1.65	0.22	2.54	0.42	3.3	0.62	3.99	0.76	4.37
16	16	0.07	1.43	0.17	1.84	0.33	2.24	0.51	2.55	0.67	2.8
16	17	0.06	1.21	0.13	1.34	0.25	1.52	0.41	1.7	0.56	1.76
17	13	0.09	1.88	0.27	3.33	0.51	4.74	0.7	5.71	0.83	6.74
17	14	0.08	1.65	0.2	2.25	0.4	3.04	0.6	3.67	0.74	3.93
17	15	0.07	1.43	0.16	1.71	0.31	2.05	0.49	2.35	0.64	2.46
17	16	0.06	1.21	0.12	1.23	0.24	1.44	0.39	1.57	0.53	1.56
17	17	0.06	1.21	0.1	1	0.18	1	0.3	1.05	0.43	1.04
18	13	0.08	1.65	0.19	2.11	0.38	2.79	0.57	3.25	0.72	3.55
18	14	0.07	1.43	0.15	1.59	0.29	1.86	0.47	2.17	0.62	2.25
18	15	0.06	1.21	0.12	1.23	0.22	1.28	0.37	1.44	0.51	1.44
18	16	0.05	1	0.1	1	0.17	0.93	0.28	0.95	0.41	0.96
18	17	0.05	1	0.08	0.78	0.14	0.74	0.21	0.65	0.32	0.65
19	13	0.07	1.43	0.14	1.47	0.28	1.77	0.44	1.92	0.6	2.07
19	14	0.06	1.21	0.11	1.11	0.21	1.21	0.35	1.32	0.49	1.33
19	15	0.05	1	0.09	0.89	0.16	0.87	0.27	0.91	0.39	0.88
19	16	0.05	1	0.08	0.78	0.13	0.68	0.2	0.61	0.3	0.59
19	17	0.04	0.79	0.07	0.68	0.1	0.51	0.16	0.47	0.23	0.41
20	13	0.06	1.21	0.11	1.11	0.2	1.14	0.33	1.21	0.47	1.22
20	14	0.05	1	0.09	0.89	0.16	0.87	0.25	0.82	0.37	0.81
20	15	0.05	1	0.08	0.78	0.12	0.62	0.19	0.57	0.28	0.54
20	16	0.04	0.79	0.07	0.68	0.1	0.51	0.15	0.43	0.21	0.37
20	17	0.04	0.79	0.06	0.57	0.08	0.4	0.12	0.33	0.17	0.28
21	13	0.05	1	0.09	0.89	0.15	0.8	0.24	0.77	0.35	0.74
21	14	0.04	0.79	0.08	0.78	0.12	0.62	0.18	0.54	0.27	0.51
21	15	0.04	0.79	0.07	0.68	0.1	0.51	0.14	0.4	0.2	0.35
21	16	0.04	0.79	0.06	0.57	0.08	0.4	0.11	0.3	0.16	0.26
21	17	0.03	0.59	0.05	0.47	0.07	0.34	0.09	0.24	0.12	0.19

Fractional probabilities (Prob) and odds ratios (OR) of conversion to mild cognitive impairment (MCI) for normal subjects aged 70 years at baseline with different combinations of scores for expression (Expr) and learning (Learn). The average probability of conversion is estimated from the model using average scores for expression and learning at baseline, but leaving age fixed at 70 years.

DISCUSSION This study showed significant effects of a combination of the CAMCOG expression and learning subscores and age on the duration of time to convert to MCI in elderly subjects who seem to have normal cognitive function at the time of assessment. The period before conversion shortened with increasing age as well as with lower baseline cognitive scores, singly or combined. These effects were independent of other factors known to increase the risk of developing cognitive impairment, such as low education, stroke, blood pressure, and homocysteine, none of which influenced the duration of time to cognitive impairment.

In survival analysis, 2 families of models are broadly used in the statistical literature. The first

Figure 2 Empirical and model-estimated cumulative proportions converting to MCI in 2 groups formed from the median split of the expression score



Black lines show the empirically observed cumulative proportions converting to mild cognitive impairment (MCI). Red lines show the proportions converting estimated by the accelerated failure time model.

family is the accelerated failure time models. In this family, the duration of time to conversion to MCI (the "event" in our study) is directly modeled as a function of the potential predictors or covariates. The effect of a given predictor, if found significant, either shortens or lengthens the duration of time to conversion. The second family is that of proportional hazard models usually known as the Cox proportional hazard model when the baseline hazard function is nonparametrically specified. In this family, the hazard function (or the risk of conversion) at any time is modeled as a function of the potential predictors or covariates. The effect of a given predictor, if found significant, then increases or decreases the risk of conversion. Usually in practice, these 2 models need not confirm each other because they are based on different assumptions. In our study, we used both families of models by adapting the second one (the Cox model) to interval-censored data. We found that these 2 independent models both produced the same result, showing significant effects of the same predictors on the period of conversion from control to MCI status in our cohort. This confirmation makes our results robust and consistent.

Although memory impairment was the hallmark of the first criteria for aMCI[24] and is also the recommended domain to measure for assessing predementia AD,[25] we found that "expression" or language ability was a stronger predictor of duration to conversion to aMCI than "learning" or memory. The importance of expression as a predictor was shown not only in the survival analyses, but also using logistic regression to study fixed time periods.

The CAMCOG expression subtest comprises tasks of verbal fluency, comprehension, spoken language descriptions, and definitions (appendix e-1). It has been recognized previously that the early stages of dementia are associated with linguistic problems, such as word-finding difficulties. Evidence from the Nun Study[16,26] on archived autobiographical essays at the time of entry into the order showed that nuns who developed MCI or AD decades later composed simpler narratives (in terms of both content and grammar) than those who died with normal brains. It has also been reported that linguistic changes analogous to those seen in established AD emerged in the later writings of a novelist some time before the clinical signs of AD.[27] These studies document some form of change in spontaneously produced language either early in or before the diagnosis of a neurodegenerative disorder and, as in the Nun Study, long before any awareness of cognitive decline.

The present findings have implications in the clinical context. Increasing awareness of the significance of memory impairment has resulted in an increase in the number of referrals of elderly subjects for assessment in memory clinics, which will probably increase with the emphasis on early diagnosis that is a major part of the National Dementia Strategy currently being implemented in England. In many instances, a diagnosis of MCI, AD, or another dementia will be made, but many others referred will seem to have normal cognitive function on existing routine testing paradigms, despite their or their families' perception of a change. Our approach could have a valuable role in guiding those conducting the assessment, e.g., about relative risk for medical management planning, especially in conjunction with levels of biomarkers if these become established, and what information to give their patient and his or her carers. It may also have potential as an outcome measure in clinical trials of treatment to reduce the rate of disease progression, when therapeutic strategies designed for use early in the disease become available, or to enrich trial cohorts with subjects who have a higher risk of conversion in a shorter time span.

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Appendix e-1 to paper by Oulhaj et al.: Predicting the time of conversion to MCI in the elderly: role of verbal expression and learning

Criteria for conversion to aMCI

As well as the criteria described in the paper, we used the following cut-off values for scores in several tests: including CAMCOG learning scores (≤12), the HVLT (total recall ≤18/36),[1] The Placing Test (≤13/20),[2] the CERAD wordlist delayed recall (≤4/10),[3] and The Doors (≤8/12) and Shapes Test (≤18/36).[4]

'Learning' and 'expression' subtests in the CAMCOG[5] and their reliability

Objective episodic memory was assessed from the '*learning*' subtest. The score is comprised of separate scores for delayed recall (visual and verbal) and visual recognition. The visual memory test consists of an encoding phase where subjects are asked to name 6 items presented as photographs on separate pages. Any incorrect answers are corrected and recall is tested after a delay. To obtain the recognition score, the subject is asked to identify the correct item seen before from a choice of 3 similar items. Verbal recall is based on memory for a name and address previously written on an envelope.
The '*expression*' subtest comprises a combination of scores from tests of naming two items presented and 6 objects from colour photographs; category fluency for animals (1 minute); definitions of 4 words (concrete and abstract); sentence repetition; and a spontaneous description of the 'cookie theft' picture. As some responses to the expression items are spontaneous in nature, the scoring is categorical for these items and there are guidelines for correct responses in the manual. These tests were all recorded on tape for scoring after the test session to ensure accuracy and standardisation.
Some examples of expression item guidelines for scoring responses are:
Definitions:
What is an opinion? Incorrect (0); a good opinion of someone (1); a person's ideas about something (2);
Cookie theft description:
No response, response irrelevant (0); Names objects only, no complete sentences (1); Some appropriate sentences (2); Adequate description (3).

The reliability (on retest) and validity (against other cognitive tests and for discrimination of dementia and non-dementia cases) of the CAMCOG and its subtests has been shown to be very good.[6-8] Because performance on most subscales is modified by age and education level,[7] stratified norms are desirable rather than absolute cut-off scores for assessing cognitive impairment.[9] However, in our study we have controlled for these confounders in the model.

Statistical appendix

Interval-censored approach[10]

For those subjects who converted to MCI the date of conversion occurs in an interval, defined as [*LD_c , FD_mci]* where LD_c is the last date where they were still determined to be a control subject, and FD_mci is the first date at which they were diagnosed as having aMCI. The duration of time to convert to MCI in such cases lies in an interval with the lower bound defined as the period since first visit until LD_c and the upper bound as the period since first visit until FD_mci. In such a scenario the data is called interval-censored.[11] In the second scenario, the subjects have not converted to MCI by the time of their last recorded episode. This means that they remained as control subjects during their follow-up. In such cases, the data is called right-censored.[11]

The standard Cox-proportional hazard model would be a candidate analysis method if the conversion data were right-censored rather than interval-censored. For this method, the duration of the interval could be approximated from the midpoint between two visits and used to produce a Cox proportional hazards model. However the disadvantages of this simplified approach have been described in many statistical papers, for example Lessafre et al. (2005) wrote: "…..Therefore, in practice, modelling with interval-censored data is often mimicked by methods developed for right-censored data. For this, the interval needs to be replaced by an exact time. The most common assumption is that the event occurred at the midpoint of the interval. However, applying methods for right-censored data on these artificial fixed points can lead to biased and misleading results."[11] For this reason, we preferred to use the methods described in the paper.

Logistic regression

A common approach is to study survival until a fixed end-point, such as the end of the study period. Logistic regression is a powerful method for analysis of such data. But in order to use logistic regression it is necessary to ensure that the outcome variable is binary. In other words, data at a given fixed study period should contain only subjects who converted during that period and those who completed the study with no conversion. Subjects who were right-censored during the study period (e.g. died etc…) should be removed from the data. For example, if in the present data set we fix the study period to 0-2 years, then among the 241 controls at baseline, 13 converted during the first 2 years, 206 remained controls and 22 were right-censored. The logistic regression then uses 219 subjects (13 + 206) instead of 241. Similarly if we fix the study period to 0-5 years then among the 241 controls at baseline, 38 converted during the first 5 years, 143 remained controls and 60 were right-censored. The logistic regression then uses 181 subjects (38 + 143) instead of 241. Table e-1 shows the sample size used at some fixed study periods. For each study period in table e-1, we performed a stepwise model selection by the Akaike's information criterion (AIC), using the R package stepAIC, to find the optimal combination of subscores and other covariates in the logistic regression model, that significantly affect the probability of conversion to MCI . ROC curves were generated from the data (Figure e-1) and show the accuracy of prediction of conversion to MCI using the identified covariates.
In further analyses we found that parametric AFT models such as the Weibul, the lognormal and loglogistic distributions also confirmed the results.

Bias and missing data

Bias: There was no systematic bias of selection of the participants since all OPTIMA controls that had available data and who satisfied the inclusion criteria were included in the analysis.
In relation to potential statistical bias of the estimators, since the model used is survival analysis with the AFT model, then the estimators of the effects of the covariates (the unknown parameters of the model) are known to be statistically unbiased and consistent.

Missing data: The model we used is survival analysis. In this type of model, the missing true durations, caused by either drop-out or death or anything else, were considered as right-censored observations and were used in the model. That is the strength of this type of analysis in contrast to any other statistical analysis that models the probability of conversion up to a pre-defined time, such as the logistic regression analysis. In the latter model, missing observations (i.e. right-censored observations) are usually simply removed.

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Table e-1. Descriptive statistics: CAMCOG subscores and MMSE at baseline for the entire cohort (n = 241)

	Mean	SD	Min	Max	2·5% centile	97·5% centile
CAMCOG	99·1	3·7	85	106	91	105
MMSE	28·7	1·4	24	30	25	30
expression	19·3	1·3	15	21	17	21
attention	6·4	1	2	7	3	7
abstract thinking	7·3	1·1	2	8	4	8
learning	14·3	1	13	17	13	16
praxis	11·4	0·8	8	12	9	12
perception	10·2	0·9	6	11	8	11
comprehension	8·8	0·5	7	9	7	9
remote	5·5	0·7	2	6	4	6
orientation	9·9	0·4	8	10	9	10
recent	3·9	0·3	2	4	3	4
calculation	2	0·2	0	2	1	2

Table e-2. Significant predictors of conversion to MCI at different study periods using logistic regression

Study period	Sample size	Best significant logistic model	Odds ratio estimates (Per 1SD change)	Odds ratio 95% CI (Per 1SD change)	P values
0-2 years	219	Expression	2	[1.1 , 3.6]	0.022
		Learning	4.5	[1.9 , 13.7]	0.002
0-4 years	195	Expression	3.2	[1.8 , 6.2]	<0.0001
		Learning	3.7	[1.8 , 8.6]	<0.0001
		Perception	2.3	[1.5 , 4]	<0.0001
0-5 years	181	Expression	2.6	[1.6 , 4.6]	<0.0001
		Perception	2.3	[1.5 , 3.7]	<0.0001
		Age	2.6	[1.6 , 4.8]	<0.0001
		Apoe4+	3.9	[1.5 , 10.8]	0.006
0-6 years	169	Expression	2.7	[1.7 , 5.0]	<0.0001
		Learning	1.8	[1.03 , 3.2]	0.045
		Perception	2.2	[1.4 , 3.8]	0.001
		Age	2.8	[1.6 , 5.4]	<0.0001
		Apoe4+	4.4	[1.5 , 13.8]	0.007
0-7 years	159	Expression	2.2	[1.4 , 3.8]	0.001
		Learning	2.1	[1.3 , 3.8]	0.006
		Perception	1.9	[1.2 , 3.2]	0.008
		MMSE	1.7	[1.03 , 2.7]	0.038
		Age	2.5	[1.5 , 4.5]	0.000
		Apoe4+	2.8	[1.01 , 7.8]	0.050
0-8 years	154	Expression	2.5	[1.6 , 4.1]	<0.0001
		Learning	2.8	[1.7 , 5.1]	<0.0001
		Perception	1.6	[1.03 , 2.6]	0.045
		Age	2	[1.2 , 3.4]	0.006
0-9 years	152	Expression	3	[1.9 , 5.2]	<0.0001
		Learning	2.3	[1.4 , 4.0]	0.001
		Recent	2.1	[1.3 , 4.0]	0.006
		Age	3.1	[1.9 , 5.3]	<0.0001
		Apoe4+	3.7	[1.3 , 10.9]	0.015
0-10 years	118	Expression	2.5	[1.5 , 4.5]	<0.0001
		Learning	1.7	[1.05 , 2.8]	0.037
		Age	3	[1.8 , 5.3]	<0.0001
0-12 years	105	Expression	2.9	[1.5 , 6.4]	0.003
		Learning	2.2	[1.2 , 4.2]	0.014
		Age	4.1	[2.1 , 9.3]	<0.0001
		Gender	5.2	[1.3 , 25.3]	0.026

Table e-3. Comparison of effects of covariates according to stroke

	Stroke included (n = 241) Effect (p-value)	Stroke excluded (n = 223) Effect (p-value)
Expression	0.83 (0.0001)	0.82 (0.0001)
Learning	0.85 (0.001)	0.86 (0.002)
Age	0.86 (0.0001)	0.85 (0.0001)
Apoe4+	Not significant	0.77 (0.036)
Education	Not significant	Not significant
BP systolic	Not significant	Not significant
Homocysteine	Not significant	Not significant

Figure e-1: **ROC curves, for the prediction of conversion to MCI, according to different study periods**

The figure shows the ROC curves for 9 study periods, between 2 and 12 y. For each study period, the ROC curve (red line) is generated from the best significant logistic model as described in table e-1. auc, area under the curve.

Figure e-1