Cognitive and behavioural predictors of survival in Alzheimer disease

Cognitive and behavioural predictors of survival in Alzheimer disease: results from a sample of treated patients in a tertiary-referral memory clinic

Running head: Predictors of survival in AD

Keywords: Survival, Prognosis, Alzheimer disease, Cognitive factors, Neuropsychiatric Symptoms, Cause of death

Key Point:

- In addition, to age and being female, CANTAB Paired Associate Learning score and the presence of psychotic symptoms were significant predictors of survival in Alzheimer Disease

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Competing Interests

TCR's post is funded by Alzheimer Scotland and he is employed in the NHS by the Scottish Dementia Clinical Research Network, which is funded by the Chief Scientist Office (part of the Scottish Government Health Directorates).

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Submission elsewhere

None of this manuscript has been submitted for publication anywhere else but the results have been accepted for presentation as a poster at the Alzheimer's Association ICAD in Paris in July 2011. The organisers have requested the results be embargoed until the conference.

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Abstract

Objective: This study examined the influence of cognitive and non-cognitive factors at the time of diagnosis on the survival of patients with treated probable Alzheimer Disease (AD).

Methods: Consecutive patients seen at a regional, tertiary-referral clinic completed a battery of cognitive tests and assessments of activities of daily living and neuropsychiatric symptoms. These clinic data were linked with death certificate data for all individuals and survival from diagnosis was calculated. Cox regression models were constructed using the baseline covariates.

Results: The sample comprised 653 patients (459 women), mean age 77.1 years (SD 7.6, range 48–94 years), diagnosed with probable AD and treated with a cholinesterase inhibitor. In the survival analysis, age was a consistently significant predictor of survival with a gender-adjusted hazard ratio of 1.35 (95% CI 1.23, 1.48) for one standard deviation increase in age. Men were at greater risk of death than women (age-adjusted HR 1.44, 95% CI 1.19, 1.73). In a model adjusted for all study variables, Paired Associate Learning (CANTAB) and the psychotic factor of the NPI were significant predictors of survival.

Conclusions: At diagnosis, in addition to the anticipated impact of age and gender, the presence of psychotic symptoms and poor performance on PAL are also indicators of poor prognosis.

[206 words]

Introduction

The notion that capturing a series of patient characteristics will aid in estimating prognosis is appealing for clinicians, patients and their relatives as they plan their future. With the number of cases of dementia increasing rapidly (Ferri, et al. 2005), there is an obvious need to understand prognosis in people with this condition. While it is known that mortality in dementia increases with the severity of disease (e.g. Andersen et al. 2010), there is a general paucity of data about other predictors of survival and conclusions are limited by the difficulties in extrapolating from populations to individuals. Apart from the more general effect of delirium on survival in all patients (Inouye, et al. 1993), co-morbid medical conditions (Van Dijk, et al. 1996)—particularly cerebrovascular and respiratory diseases (Helmer, et al. 2001; Hicks, et al. 2010) but also falls, diabetes and cardiovascular disease (Larson, et al. 2004; Mielke, et al. 2007)—and socio-economic factors, such as education (Musicco, et al. 2009) have been shown to affect survival in dementia. Further potential candidates for predictors of survival in people with dementia have included baseline cognitive function (Andersen et al. 2010; Hötte, et al. 2010; Landi, et al. 1999), pre-morbid cognitive ability (cognitive reserve; Scarmeas, et al. 2006; Stern, et al. 1999), difficulties with activities of daily living (ADLs; Agüero-Torres, et al. 1998; Newcomer, et al. 2003) and the presence of behavioural and psychological symptoms of dementia (BPSDs; Tun, et al. 2007), particularly psychotic symptoms (Scarmeas, et al. 2005).

Therefore, the aim of this study was to examine the influence of cognitive status, ADLs and the presence of BPSDs at the time of diagnosis on the survival of patients with treated probable Alzheimer disease (AD) seen in a tertiary-referral clinic. The objectives were to identify any predictors of survival from the above-mentioned factors.

Methods

Sample

As described in detail by Starr (2007) and Starr and Lonie (2007a, 2007b, 2008), the sample comprises consecutive patients seen at a tertiary-referral memory treatment centre covering the Lothian region (Lothian Memory Treatment Centre; LMTC) between February 2000 and July 2001. Routine assessment data were collected as part of a service evaluation approved by the Director of Public Health. Patients were included if they were diagnosed with probable AD—diagnosis was consensus-based involving two old age psychiatrists, a geriatrician and a neuropsychologist using NINCDS-ADRDA criteria (McKhann, et al. 1984)—and commenced on a cholinesterase inhibitor (either donepezil or rivastigmine).

Measures

Patients attending the LMTC completed a battery of seven cognitive tests, shown in box 1. ADLs were measured using the instrumental activities of daily living (IADL) and the physical self-maintenance scales (PSMS; both Lawton and Brody 1969). Patients and carers also completed the Neuropsychiatric Inventory (NPI; Cummings, et al. 1994).

Data Linkage

Permission for data linkage was obtained from the NHS Lothian Caldicott Guardian. The Information and Services Division of NHS National Services Scotland linked the data with death certificate data from the General Register Office for Scotland, providing date of death and all causes mentioned on the death certificate for those who had died. The data supplied did not distinguish between immediate, underlying or contributory causes of death.

Prior to the merging of the anonymised dataset with the linked data, Scottish Index of Multiple Deprivation (SIMD) ranks were obtained for each individual using their postcode (Scottish

Government National Statistics 2009).

Calculation of survival times

Survival was calculated in months from an estimated assessment date using the patient's date of birth and age when assessed. The earliest and latest possible dates of assessment were calculated, giving longest and shortest possible survival times respectively. A middle survival using the midpoint of the year or the patient's date of death, whichever was earlier, was also calculated.

Sensitivity analyses

In order to test the robustness of conclusions, a number of sensitivity analyses were carried out. The younger half of the cohort were assigned the shortest survival (i.e. worst prognosis) and compared to the older half who were assigned the longest survival. Similarly, *post-hoc*, the half with lower scores on PAL were compared with the half with higher scores and the half with lower scores on the NPI psychotic factor were compared to the half with higher scores. Furthermore age x gender interaction was examined in all univariate models.

Confounding

A potential confounder of survival in dementia is antipsychotic medication use, data for which were not available for this cohort, since patients with more BPSD (and therefore higher NPI scores) might be more likely to be prescribed antipsychotic medications which might affect their survival (Schneider, et al. 2005; Wang, et al. 2005). Therefore, the NPI scores for the cases who had cerebrovascular disease mentioned on any part of their death certificate (n=87, 17.3%) were compared with those without.

Statistical Analysis

Data were analysed with the statistical package PASW Statistics version 18.0 (SPSS Inc 2010). All

covariates, apart from gender and drugs administered, were continuously scored. Age-adjusted univariate hazard ratios for men and women were similar, so data were pooled and gender-adjusted. The combined sample size was sufficient to detect hazard ratios of 1.31 at 80% power or 1.37 at 90% power (both with alpha at 0.05). Median survival times were calculated using the Kaplan-Meier method (Kaplan and Meier 1958). Cox regression (Cox 1972) was performed using stepwise entry of independent variables at $p<0.05$ with age and gender forced into all models. The predictive capacity of each variable was examined separately. Next, multivariate models with the following variables were examined because they capture similar domains: MMSE and NART-IQ; the standard bedside battery of MMSE and tests of frontal lobe function; PAL and DMTS; PSMS and IADL; NPI (patient) and NPI (carer). The three NPI factors were also examined in a multivariate model. Subsequently the best predictive model was constructed. Study members with missing data were excluded from individual models but all models were re-run with using only cases with no missing data and hazard ratios were compared to those using the complete dataset.

Results

The analysis included 653 patients (459 women), mean age 77.1 years (SD 7.6, range 48–94 years). All patients were treated with either donepezil (429, 66%) or rivastigmine (224, 34%). By the date of record linkage on 8th June 2010 502 patients (77%) had died and data from death certificates were available for all of these. Baseline characteristics of the sample are shown in table 1. All cognitive tests correlated strongly with each other, as did IADL and PSMS scores. NPI scores for patient and carer correlated significantly with each other and with the three factors but these factors did not correlate with each other.

Effect estimates did not vary with survival time used (longest, middle or shortest) and so the middle survival was used.

Median survival was 65 months (IQR 69). Women survived significantly longer than men (71 months, IQR not calculable, vs 52 months, IQR 63; Log Rank p=0.001) as did those treated with donepezil rather than rivastigmine (71 months, IQR 74, vs 54 months, IQR 67; Log Rank p=0.021).

There were significant differences in survival between decade age groups (Log Rank p<0.001). Median survival was 91 months for those aged 50-59 (IQR not calculable), 85 months for those aged 60-69 (IQR not calculable), 66 months for those aged 70-79 (IQR 65), 53 months for those aged 80-89 (IQR 61) and 33 months for those aged 90 or over (IQR 55).

Results of Cox regression models for each variable are shown in table 2. Poorer performance on all cognitive tests—apart from DMTS which showed a non-significant trend—was significantly associated with worse survival. Higher NPI scores for the patient and carer were associated with poorer survival. Of the NPI factors, only the psychotic factor was significantly associated with worse survival but the hazard ratio for the mood factor was also elevated. Choice of cholinesterase inhibitor did not significantly affect survival but greater deprivation was significantly associated with worse survival.

Table 3 shows the results of the multivariate Cox regression models. Age had a consistently significant effect on survival with a hazard ratio of 1.33–1.42 in all models per standard deviation increase. Gender was significantly associated with survival but became non-significant with an attenuated effect in the more-adjusted models.

Both MMSE and NART-IQ were significantly associated with survival but only MMSE remained significant when both were included in the model. Entering the standard bedside battery of the MMSE and tests of frontal function (Animals and FAS), as recommended by the Mental Welfare

Commission for Scotland (2007) for the assessment of dementia, resulted in both MMSE and Animals being significant covariates—i.e. higher cognitive function and, specifically, better frontal lobe function, were associated with better survival. PAL remained a significant predictor of survival in a model with PAL and DMTS entered into it. Entering the three significant cognitive tests (MMSE, Animals and PAL) or indeed all the cognitive tests conducted identified PAL as a consistently significant covariate, i.e. a higher PAL score was associated with better survival.

Of the measures of ADLs, IADL was significantly associated with survival but became non-significant when the patient's NPI score was included in a model. The patient's NPI score was significantly associated with survival but the carer's NPI score was not. Deprivation, measured by SIMD, was a significant predictor of survival in a univariate model but not in any multivariate model. Examining individual NPI factors (mood, psychotic, frontal) identified the psychotic factor as the only significant covariate. In a fully-adjusted model the PAL and NPI psychotic factor remained significant predictors of survival.

The sensitivity analyses did not affect the results. There was little evidence of age x gender interaction following formal testing. Re-running all models using only cases with no missing data (n=235) gave similar results but the effect of gender was attenuated (age-adjusted HR male gender 1.17, 95% CI 0.84, 1.62, p=0.35). Characteristics of individuals with missing data and the non-missing dataset are shown in table 4.

Table 5 shows the causes of death recorded on the patient's death certificates classified into categories adapted from Thomas et al. (1997). There were no differences between men and women apart from the general categories of 'other disease' (t=-2.0, df=333.5, p=0.05) and 'senility' (t=-3.1, df=603.3, p=0.002) but the former is a heterogeneous category and there were

very few instances of men dying with 'senility' recorded on their death certificate (n=4, 2.5%). Therefore cause of death data for men and women were analysed together. 159 patients (31.7% deceased individuals) had pneumonia recorded as a cause of death and 36 (7.2%) senility or a similar non-specific category. 111 patients (22.2%) had cardiac disease and 45 (9.0%) had other vascular disease recorded on their death certificates.

Rates of all recorded categories of causes of death are higher than the rates for all deaths in 2009 in Lothian apart from neoplasms (rates for dementia, 'other vascular disease' and 'senility' were not available from data from the General Register Office for Scotland, 2009; similarly it was not possible to calculate a meaningful category of 'other disease' from available data). Hospital discharge data (SMR 01) estimate the crude prevalence of coronary heart disease in the over-75s to be 16.1% in Lothian (22.3% M, 12.3% F; ISD Scotland 2011) suggesting a slightly higher rate of cardiovascular disease in the females in this cohort with probable AD than the general female population.

Comparing individuals who died with cerebrovascular disease mentioned on their death certificate (n=87, 17.3%) revealed no significant differences in mean overall NPI scores, factor scores or relevant individual items (agitation, aggression, hallucinations or delusions) for which antipsychotics might be prescribed. This suggests that antipsychotic-related mortality has not confounded the results.

Discussion

The main finding of this study was that, in addition to increasing age and male gender, a lower score on PAL and the presence of psychotic symptoms at baseline were associated with significantly worse survival. Survival was consistently approximately 33-42% worse per standard deviation increase in age at baseline in all models. Women survived longer in this study, as has

been often shown in dementia (e.g. Doody, et al. 2005; Sinforiani, et al. 2010; Stern, et al. 1997) but not Brookmeyer et al. 2002), but the effect of gender became non-significant in models including more variables. Gambassi et al. (1999) have suggested that their observed gender-differences in mortality might result from different levels of comorbidity but, few gender-differences in causes of death were observed.

Predictors of survival

In this highly selected, tertiary-referral clinic sample, median overall survival was 65 months (5.4 years) and median survival by age-group was: 50-59—91 months (7.6 years), 60-69—85 months (7.1 years), 70-79—66 months (5.5 years), 80-89—53 months (4.4 years) and over 89—33 months (2.8 years).

Overall survival in this sample was slightly longer than the 4.9 years reported by Doody et al. (2005)—despite the wide recruitment strategy used in that study—and much longer than the 3.1 years reported from the Canadian Study of Health and Aging (Wolfson, et al. 2001), even though they estimated survival from onset of symptoms. Tsai et al. (2007) found a mean survival of 4.5 years in their memory clinic sample in China, though their AD death rate was only 28.9% compared to 77% in the current sample.

Rait et al. (2010) reported a comparable median survival for 60-69 year olds of 6.7 years (vs 7.1 years in this study) despite using a primary care sample rather than a tertiary-referral sample. However, excluding untreated patients from our analysis would be expected to bias the results towards prolonged survival. Furthermore, treatment itself is unlikely to be associated with poorer survival.

In the present study baseline cognitive function, measured by MMSE, categorical verbal fluency

(Animals) and PAL, predicted survival in this clinic sample of people with AD. However in a model containing all the cognitive tests, PAL was the only significant predictor of survival. Prospective (Andersen et al. 2010; Hötte et al. 2010; Tsai et al. 2007) and retrospective studies (Landi et al. 1999) have found that baseline cognitive function—either measured by MMSE or severity of dementia—was significantly associated with increased mortality. However Reisberg et al. (1996) found that mortality was not related to baseline dementia severity.

NART-IQ has been shown by McGurn et al. (2004), using a sample from this treatment centre, to be a reliable measure of pre-morbid full scale IQ in patients with dementia and therefore serves as a putative index of cognitive reserve (Richards and Deary 2005; Stern 2006; Stern 2009; Whalley, et al. 2004). NART-IQ was significantly associated with survival in a model including age and gender—in this study individuals with lower estimated premorbid IQ declined more rapidly after diagnosis in contrast to the cognitive reserve hypothesis (Scarmeas et al. 2006; Stern et al. 1999). However NART-IQ did not remain significant when MMSE was included in the model.

Both IADL and the patient's NPI score predicted survival in this sample. However IADL became non-significant when further variables were included and the NPI psychotic factor was the only element which significantly predicted survival. Newcomer et al. (2003) found that requiring maximum help in ADLs was associated with worse survival; this effect increased with the numbers of activities requiring assistance. Agüero-Torres et al. (1998) found that those who functioned worse declined faster. Miller et al. (2011), in the CATIE-AD trial, found that preserved ADLs were protective for nursing home admission, though they did not report predictors of survival.

Tun et al. (2007) found that survival was significantly lower in AD patients with more BPSD.

Sinforiani et al. (2010) also found that higher NPI score at baseline was associated with earlier loss of autonomy. Scarmeas et al. (2005) reported that delusions and hallucinations were associated with faster decline, both in cognition and function, and that hallucinations were associated with increased mortality.

Causes of death

Bronchopneumonia is commonly reported in people dying with dementia (Morgan and Clarke 1995), up to 70.9% in presenile AD (Thomas et al. 1997). Table 5 shows a lower rate of pneumonia at death suggesting that other age-related causes of death might be more important in a late-onset dementia sample compared with patients with early-onset disease.

High rates of cerebrovascular disease and diabetes at death confirm the importance of cardiovascular risk factors, particularly diabetes, in the natural history of AD (Knopman, et al. 2001; Luchsinger, et al. 2005; Solfrizzi, et al. 2004; Whitmer, et al. 2005). The high rate of falls suggests that impaired mobility may be an important factor in the later stages of the disease. Indeed Buchner and Larson (1987) found a very high fracture rate (15%) in a sample of patients with AD.

Limitations

The assessment battery used in this clinic is likely to be more extensive than that used elsewhere in the UK though the treatment protocol will have been similar. Lothian has less of an ethnic mix than average in the UK but there it provides a stable population, with migration particularly low in this age group.

Since the data were collected for a service evaluation—and not for research purposes—they do present limitations and the date of assessment had to be estimated from the patient's date of

birth and their age when assessed, as described above. However there were no differences in effect estimates when the longest or shortest possible survival times were used so a midpoint date of assessment was used to calculate survival.

Sensitivity analyses examining the effects of assigning worse survival to younger individuals, those with higher PAL scores and fewer psychotic symptoms did not alter the results. Furthermore there was no evidence of age x gender interaction.

Details of prescribed medication were not available but increased mortality related to antipsychotic medication (Schneider et al. 2005; Wang et al. 2005), as mentioned above, does not seem to have confounded the results. However individuals with higher NPI scores—for whom these medications might be prescribed—did not have an excess of cerebrovascular disease.

Cardiovascular disease and other risk factors, such as smoking, obesity and individual socio-economic status (as opposed to the area-based measure used here) are extremely important in dementia survival. The absence of these variables is a limitation of this study but since the clinic served the whole region of Lothian, there is likely to have been a wide spread of these risk factors, as shown by the range of SIMD ranks, and so confounding can be assumed to be minimal.

While the sample is specific for patients with treated probable AD it has, by definition, excluded patients with other dementias and patients with untreated AD. The implications for survival of using a treated sample have been discussed above. In addition, it should be mentioned that this study does not allow us to comment on severe dementia since few patients had a baseline MMSE of lower than 12 (n=54, 12.9%), in line with trial data and guidelines at the time.

Recording of causes of death on death certificates is widely acknowledged to be less than completely accurate, particularly for dementia (Martyn and Pippard 1988; Morgan and Clarke 1995). This is confirmed in this study since only 359 (71.5% of deceased) patients had dementia entered onto their death certificate. It is likely that other diseases are also under-reported, perhaps not to the same extent, but this is impossible to estimate.

The comparison data are based on all deaths—since this was the only data available—but 79.5% deaths in Scotland in 2009 were over-65s (General Register Office for Scotland 2009) and the majority of the outcomes are age-related diseases. Proportions of over-65s in death data were similar for all areas covered by the LMTC.

Conclusion

In addition to the anticipated impact of age and gender, the presence of psychotic symptoms and poor performance on PAL at baseline are also indicators of poor prognosis.

These clinic-based data indicate that at diagnosis, clinicians should not be optimistic or pessimistic about prognosis according to most measures of current cognitive status, pre-morbid mental ability, or current functional abilities, or the presence of other BPSDs. Age is a useful predictor of survival, with those over 90 years surviving less than three years on average. Common causes of death in people with AD were cardiovascular disease (in women) and falls: these represent opportunities at diagnosis for prevention to improve survival.

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Text Box 1: Cognitive Battery in the present sample[1]

Cognitive Test	*Reference*	*Comments*
National Adult Reading Test *(NART-IQ)*	(Nelson, 1982)	The patient is asked to read aloud a list of fifty irregularly-pronounced words. McGurn et al. (2004) validated this test as an estimate of premorbid full-scale IQ in a subgroup of this cohort. Higher score = more able.
Mini-Mental State Examination *(MMSE)*	(Folstein, et al. 1975)	Tests a broad range of cognitive domains and scored out of 30. Higher score = more able.
Hopkins Verbal Learning Test *(Hopkins)*	(Brandt 1991)	The total score of three trials of free recall were used from this test of recent verbal memory/new learning ability. Higher score = more able.
Category (Semantic) Fluency *(Animals)*	(Lezak 2004)	This common test of executive function also tests semantic memory. The patient is asked to name as many animals (or fruit or vegetables or any other category) as possible in a minute. Higher score = more able.
Lexical Verbal Fluency *(FAS)*	(Lezak 2004)	Similar to category fluency but with the extra demand of set-shifting. The patient is asked to name as many words as possible beginning with the letter F (and then A and then S) in one minute. Higher score = more able.
Paired Associate Learning *(PAL)*	(Robbins, et al. 1994)	Subtest from the Cambridge Automated Neuropsychological Test Assessment Battery (CANTAB) of visual and working memory. Higher score = more able.
Delayed Matching to Sample *(DMTS)*	(Robbins et al. 1994)	Subtest from the CANTAB visual and working memory battery. Higher score = more able.

[1] previously described in Starr (2007) and Starr and Lonie (2007b)

Table 1: Baseline characteristics of the present sample

Test[1]	n	median	IQR	Range
MMSE	621	20	8	0–30
NART-IQ	351	107	15	0–128
Hopkins	596	9	6	0–32
Animals	599	7	5	0–24
FAS	599	20	18	0–67
PAL	456	4	3	0–17
DMTS	443	11	4	0–19
IADL	546	16	10	0–30
PSMS	543	7	3	0–23
NPI (patient)	551	11	14	0–67
NPI (carer)	550	5	9	0–56
SIMD Rank	613	4306	3944	51–6504

[1] *MMSE,* Mini-Mental State Examination; *NART-IQ,* Estimated IQ using the National Adult Reading Test; *Hopkins,* Hopkins Verbal Learning Test; *Animals,* Category (Semantic) Fluency—naming animals; *FAS,* Lexical Verbal Fluency using the letters F, A & S; *PAL,* Paired Associate Learning from CANTAB; *DMTS,* Delayed Match to Sample from CANTAB; *IADL,* Instrumental Activities of Daily Living scale; *PSMS,* Personal Self-maintenance scale; *NPI,* Neuropsychiatric Inventory; *SIMD,* Scottish Index of Multiple Deprivation

Table 2: Age- and gender-adjusted univariate hazard ratios for the relation between study participant characteristics and mortality

Model[1]	Deaths	N	HR[3]	95% CI	*P*
MMSE	471	621	1.32	1.21, 1.44	<0.001
NART-IQ	264	351	1.13	1.01, 1.28	0.038
Hopkins	449	596	1.31	1.19, 1.45	<0.001
Animals	454	599	1.30	1.18, 1.44	<0.001
FAS	454	599	1.26	1.14, 1.39	<0.001
PAL	339	456	1.34	1.19, 1.50	<0.001
DMTS	328	443	1.11	1.00, 1.23	0.062
IADL	422	546	1.17	1.06, 1.30	0.002
PSMS	421	543	1.17	1.06, 1.28	0.002
NPI (patient)	430	551	1.20	1.09, 1.32	<0.001
NPI (carer)	428	550	1.12	1.03, 1.23	0.013
NPI mood factor	225	358	1.07	0.93, 1.22	0.38
NPI psychotic factor	225	358	1.18	1.04, 1.34	0.010
NPI frontal factor	225	358	0.99	0.86, 1.13	0.84
Drug[2]	502	653	1.09	0.90, 1.32	0.39
SIMD rank	472	613	1.11	1.01, 1.21	0.028

[1] *MMSE,* Mini-Mental State Examination; *NART-IQ,* Estimated IQ using the National Adult Reading Test; *Hopkins,* Hopkins Verbal Learning Test; *Animals,* Category (Semantic) Fluency—naming animals; *FAS,* Lexical Verbal Fluency using the letters F, A & S; *PAL,* Paired Associate Learning from CANTAB; *DMTS,* Delayed Match to Sample from CANTAB; *IADL,* Instrumental Activities of Daily Living scale; *PSMS,* Personal Self-maintenance scale; *NPI,* Neuropsychiatric Inventory; *SIMD,* Scottish Index of Multiple Deprivation

[2] Categorical variable: whether patient received donepezil (reference) or rivastigmine

[3] Hazard ratios, computed using Cox regression analysis, are for one standard deviation disadvantage, apart from drug given

Table 3: Hazard ratios for the relation of study participant characteristics with mortality (analyses are stepwise conditional entry with age and gender forced into the models as established risk factors for survival in dementia)

Model[1]	Deaths	N	*p*	HR[2] (95% CI)	Variables included in the model but statistically non-significant ($p > 0.05$)
Age	502	653	<0.001	1.35 (1.23, 1.48)	—
Male Gender			<0.001	1.44 (1.19, 1.73)	
Age	471	621	<0.001	1.37 (1.24, 1.51)	
Male Gender			<0.001	1.43 (1.18, 1.74)	—
MMSE			<0.001	1.32 (1.21, 1.44)	
Age	264	351	<0.001	1.42 (1.24, 1.63)	
Male Gender			0.059	1.29 (0.99, 1.68)	—
NART-IQ			0.038	1.13 (1.01, 1.28)	
Age	263	350	<0.001	1.38 (1.20, 1.58)	
Male Gender			0.098	1.25 (0.96, 1.63)	NART-IQ (p=0.39)
MMSE			<0.001	1.32 (1.17, 1.48)	
Age	453	598	<0.001	1.33 (1.21, 1.48)	
Male Gender			<0.001	1.42 (1.17, 1.74)	
MMSE			0.008	1.17 (1.04, 1.32)	—
Animals			0.004	1.19 (1.06, 1.35)	
Age	453	598	<0.001	1.36 (1.23, 1.50)	
Male Gender			<0.001	1.46 (1.19, 1.78)	
MMSE			0.002	1.21 (1.07, 1.36)	—
FAS			0.042	1.13 (1.00, 1.27)	
Age	450	592	<0.001	1.32 (1.20, 1.46)	
Male Gender			<0.001	1.45 (1.19, 1.77)	
MMSE			0.005	1.18 (1.05, 1.33)	FAS (p=0.30)
Animals			0.004	1.19 (1.06, 1.34)	
Age	308	419	<0.001	1.33 (1.18, 1.51)	
Male Gender			0.024	1.32 (1.04, 1.69)	DMTS (p=0.23)
PAL			<0.001	1.36 (1.20, 1.53)	
Age	335	451	<0.001	1.35 (1.20, 1.52)	
Male Gender			0.014	1.34 (1.06, 1.69)	MMSE (p=0.11)
PAL			<0.001	1.34 (1.19, 1.50)	Animals (p=0.055)
Age	338	455	<0.001	1.33 (1.18, 1.49)	
Male Gender			0.013	1.34 (1.06, 1.69)	MMSE (p=0.056)
PAL			<0.001	1.34 (1.20, 1.51)	

Table 3 continues on the next page

Table 3 continued

Age	205	278	<0.001	1.39 (1.19, 1.62)	MMSE (p=0.12), NART-IQ (p=0.69), Animals (p=0.12), FAS (p=0.18), Hopkins (p=0.11), DMTS (p=0.60)
Male Gender			0.28	1.18 (0.87, 1.60)	
PAL			<0.001	1.35 (1.17, 1.57)	
Age	421	543	<0.001	1.39 (1.25, 1.55)	
Male Gender			<0.001	1.51 (1.23, 1.86)	PSMS (p=0.26)
IADL			<0.001	1.18 (1.07, 1.30)	
Age	428	549	<0.001	1.42 (1.28, 1.58)	
Male Gender			0.001	1.42 (1.16, 1.74)	NPI (carer) (p=0.50)
NPI (patient)			<0.001	1.20 (1.09, 1.32)	
Age	472	613	<0.001	1.39 (1.26, 1.53)	
Male Gender			<0.001	1.43 (1.18, 1.74)	—
SIMD			0.028	1.11 (1.01, 1.21)	
Age	270	353	<0.001	1.42 (1.23, 1.63)	
Male Gender			0.038	1.32 (1.02, 1.71)	IADL (p=0.83)
NPI (patient)			0.003	1.21 (1.07, 1.36)	SIMD (p=0.66)
PAL			<0.001	1.35 (1.18, 1.54)	
Age	225	295	<0.001	1.37 (1.17, 1.61)	
Male Gender			0.16	1.23 (0.92, 1.63)	NPI mood factor (p=0.42)
NPI psychotic factor			0.010	1.18 (1.04, 1.34)	NPI frontal factor (p=0.83)
Age	175	236	0.001	1.39 (1.15, 1.67)	
Male Gender			0.39	1.15 (0.83, 1.60)	Animals (p=0.14)
PAL			0.007	1.25 (1.06, 1.47)	IADL (p=0.88)
NPI psychotic factor			0.012	1.21 (1.04, 1.40)	NPI (patient) (p=0.25)

[1] *MMSE,* Mini-Mental State Examination; *NART-IQ,* Estimated IQ using the National Adult Reading Test; *Hopkins,* Hopkins Verbal Learning Test; *Animals,* Category (Semantic) Fluency—naming animals; *FAS,* Lexical Verbal Fluency using the letters F, A & S; *PAL,* Paired Associate Learning from CANTAB; *DMTS,* Delayed Match to Sample from CANTAB; *IADL,* Instrumental Activities of Daily Living scale; *PSMS,* Personal Self-maintenance scale; *NPI,* Neuropsychiatric Inventory; *SIMD,* Scottish Index of Multiple Deprivation

Table 4: Comparison of the characteristics of patients with complete data and those with missing data

Variable[1]	No missing data (N=235)	Missing data (N=418)	*p*
Age (mean, sd)	78.0 (6.6)	76.6 (8.1)	0.023
Female (%)	70.2	70.3	0.97
Donepezil use (%)	64.7	66.3	0.68
MMSE (mean, sd)	20.6 (4.7)	18.5 (6.3)	<0.001
NART-IQ (mean, sd)	106.9 (10.2)	99.9 (28.4)	0.011
Hopkins (mean, sd)	10.2 (5.0)	8.7 (4.7)	<0.001
Animals (mean, sd)	8.8 (4.4)	7.2 (4.1)	<0.001
FAS (mean, sd)	24.7 (13.7)	20.4 (12.4)	<0.001
PAL (mean, sd)	4.4 (1.8)	4.1 (1.8)	0.024
DMTS (mean, sd)	11.4 (2.6)	10.8 (3.5)	0.024
IADL (mean, sd)	14.8 (6.3)	16.6 (6.5)	0.001
PSMS (mean, sd)	7.4 (2.7)	8.3 (3.3)	0.001
NPI (patient) (mean, sd)	12.6 (11.7)	13.9 (11.3)	0.173
NPI (carer) (mean, sd)	6.1 (6.6)	7.4 (7.4)	0.033
NPI mood factor (mean, sd)	-0.2 (0.98)	0.11 (1.10)	0.39
NPI psychotic factor (mean, sd)	0.01 (1.02)	-0.01 (0.96)	0.89
NPI frontal factor (mean, sd)	0.02 (1.07)	-0.05 (0.69)	0.62
SIMD Rank (mean, sd)	4067.0 (1965.8)	3984.7 (2006.4)	0.62

[1] *MMSE,* Mini-Mental State Examination; *NART-IQ,* Estimated IQ using the National Adult Reading Test; *Hopkins,* Hopkins Verbal Learning Test; *Animals,* Category (Semantic) Fluency—naming animals; *FAS,* Lexical Verbal Fluency using the letters F, A & S; *PAL,* Paired Associate Learning from CANTAB; *DMTS,* Delayed Match to Sample from CANTAB; *IADL,* Instrumental Activities of Daily Living scale; *PSMS,* Personal Self-maintenance scale; *NPI,* Neuropsychiatric Inventory; *SIMD,* Scottish Index of Multiple Deprivation

Table 5: Causes of death recorded on death certificates in the present sample by gender

	Male (n=160, 82.5%)			*Female (n=342, 74.5%)*		
Cause	n[1]	%[2]	% Lothian deaths (2009)[3]	n[1]	%[2]	% Lothian deaths (2009)[3]
Dementia	116	72.5	–	243	71.1	–
Pneumonia	54	33.8	2.8	105	30.1	4.0
Cardiac disease	35	21.9	20.9	76	22.2	15.9
Cerebrovascular disease	31	19.4	7.4	73	21.3	11.0
Neoplasms	21	13.1	31.7	37	10.8	27.6
Other vascular disease	15	9.4	–	30	8.8	–
'Senility' or other general term	4	2.5	–	32	9.4	–
Falls	7	4.4	1.0	19	5.6	1.8
Diabetes	7	4.4	0.9	15	4.4	1.1
Hip fracture	4	2.5	–	18	5.3	–
Other disease	58	36.3	–	102	29.8	–

[1] Number of deceased individuals from present sample with each cause mentioned on their death certificate

[2] Percentages of causes of death for all deceased individuals add up to more than 100 because multiple causes were recorded for each individual

[3] Lothian data are for all 2009 deaths from General Register Office for Scotland (2009)—data only available for routinely reported categories