BMJ Open

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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2015-010357 |
| Article Type: | Research |
| Date Submitted by the Author: | 23-Oct-2015 |
| Complete List of Authors: | Rongve, Arvid; Haugesund Hospital, Department of Research and Innovation; University of Bergen, Department of Clinical Medicine<br>Soennesyn, Hogne; Stavanger University Hospital, Geriatric Medicine<br>Skogseth, Ragnhild; Haraldsplass Deaconess Hospital, Geriatric Medicine<br>Oesterhus, Ragnhild; Stavanger University Hospital, Pharmacology<br>Hortobágyi, Tibor; Kings College, Pathology<br>Ballard, Clive; King's College London, Wolfson Centre for Age-Related Diseases<br>Auestad, Bjorn; University of Stavanger, Department of Mathematics and Natural Sciences<br>Aarsland, Dag; Stavanger University Hospital |
| Primary Subject Heading: | Neurology |
| Secondary Subject Heading: | Geriatric medicine |
| Keywords: | Dementia < NEUROLOGY, Parkinson-s disease < NEUROLOGY, GERIATRIC MEDICINE |
| | |

**Title**

Cognitive decline in Dementia with Lewy Bodies - a five year prospective study

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**Key words**

Dementia with Lewy Bodies, Alzheimer's disease, longitudinal cohort study, prognosis.

**Word count**

Paper: 2763

Abstract: 258

Character count title: 66

**Statistical analyses**

Longitudinal analyses by Bjoern Henrik Auestad (PhD) and other statistics by Arvid Rongve (MD, PhD).

**Authors and their individual contributions to the manuscript**

Arvid Rongve: Concept and idea, collection of data, writing of the paper and statistical analyses.

Hogne Soennesyn: Collection of data and critically reviewing the whole content of the paper.

Ragnhild Skogseth: Collection of data and critically reviewing the whole content of the paper.

Ragnhild Oesterhus: Collection of data and critically reviewing the whole paper.

Tibor Hortobágyi: Neuropathological analysis and diagnosis, writing pathology parts and critically reviewing the whole paper.

Clive Ballard: Concept and idea, critically reviewing the whole paper.

Bjoern Henrik Auestad: Providing the longitudinal statistical analyses and writing the statistical methods section and critically reviewing the paper.

Dag Aarsland: Concept and idea, collection of data, writing the paper together with first author Arvid Rongve.

**Abstract**

**Objectives** We report the cognitive decline in persons diagnosed with mild Dementia with Lewy Bodies (DLB) and mild Alzheimer's disease (AD) during five years of annual follow ups.

**Methods** Patients were recruited into the study from geriatric, psychiatric and neurology clinics in Western Norway during 2005-2013. They were diagnosed according to clinical consensus criteria, based on standardized clinical rating scales. Autopsy-based diagnoses were available for 20 cases. Cognitive decline for up to five years was assessed using the Clinical Dementia Rating scale (CDR) and the Mini-Mental State Examination (MMSE). Survival analysis including Cox regression (time to reach severe dementia) and linear mixed effects (lme) modelling were used to model the decline on MMSE.

**Results** At least one follow-up assessment was available for 67 DLB and 107 AD patients, with a median follow-up time of 4.3 years. The time to reach severe dementia was significantly shorter in DLB (median 1793 days) compared to AD (1947 days) ($p=0.033$), and the difference remained significant in the multiple Cox regression analysis (Hazard ratio = 2.0, $p<0.02$. In the adjusted lme model, MMSE decline was faster in DLB (annual decline 4.4 points) compared to AD (3.2 points) ($p<0.008$).

**Conclusion** Our findings show that from the mild dementia stage patients with DLB have a more rapid cognitive decline than in AD. Such prognostic information is vital for patients and families and crucial for planning clinical trials and enabling health economic modelling.

**Funding and Disclosures** The project was funded by the Western Norway Regional Health Authority. None of the authors have any disclosures.

**Strengths and limitations**

- High attrition rate
- Annual follow ups
- Highly standardized diagnostic procedures including the MAYO fluctuation and MAYO sleep scales
- Autopsy-proven diagnosis for 9 % of cases
- Largest DLB cohort with longest follow up reported
- Most participants were clinically diagnosed

## Introduction

Few longitudinal cohort-studies of Dementia with Lewy bodies (DLB) exist compared to in other neurodegenerative diseases[1, 2]. Accordingly, the long-term course and prognostic factors in DLB are not known. Early observations suggested that DLB patients had a faster cognitive decline as compared to Alzheimer's disease[3], but subsequent studies have reported contradictory results. In a recent meta-analysis we found no significant difference in the rate of decline on Mini-Mental State Examination (MMSE) in DLB and Alzheimer's disease (AD)[4]. However, this conclusion was based on few studies with small sample sizes and short follow-up time. Understanding the disease course is vital to give patients and families a better understanding of prognosis and is also essential to underpin accurate design and powering of clinical trials and to enable health economic models for cost effectiveness. We therefore aimed to assess the rate of decline for up to 5 years in DLB in comparison to AD. In addition to the MMSE, which may be less sensitive to the cognitive changes in DLB compared to AD[5], we used a broader assessment of cognition and function, the Clinical Dementia Rating scale (CDR)[6], using time to reach severe dementia, CDR stage 3, as a co-primary outcome.

## Methods

### Design

We used a prospective design, and DLB patients, were diagnosed clinically using extensive and standardized diagnostic investigations and also recruiting for post-mortem confirmation. Our aim was to allow for long follow-up time from the time of diagnosis with annual assessment points. There is yet no consensus regarding the best cognitive scale to track cognitive decline in DLB, and thus we used CDR as our measure of cognitive functioning. The study was approved by the Regional Committees for Medical and Health Ethics, approval number 2010/ 633.

### Subjects and inclusion

In the Dementia Study of western Norway (DemVest-study) all referrals to geriatric and psychiatric clinics in Hordaland and Rogaland counties (with 448 343 (13.4% aged 67 or higher) and 393 104 (11.5% 67+) inhabitants, respectively) underwent a full medical examination for a first time diagnosis of mild dementia during 2005 – 2007, and consecutively invited to participate if inclusion and exclusion criteria were fulfilled. All neurology clinics in the region were invited to refer patients with suspected dementia to the study. The referral pattern varies among GPs, but most dementia patients are diagnosed by their local GP. To reduce risk for referral bias, GPs in the area were therefore contacted by letter prior to study start and invited to refer all patients with suspect dementia to one of the participating centers. Subsequently we included DLB cases selectively from 2007 until 2013 to increase sample size[7]. Patients were followed annually with a structured interview, caregiver interview and cognitive tests. Drug-treatment was provided as clinically indicated by the treating physician, but it was recommended that AD and DLB patients should receive treatment with cholinesterase inhibitor, and most patients were treated from inclusion in the study.

### Inclusion and exclusion criteria

To select patients with mild dementia only, a MMSE score of at least 20 or a CDR global score = 1 was required for inclusion. Patients without dementia or with acute delirium or confusion, terminal illness, recently diagnosed with a major somatic illness which according to the clinician would significantly impact on cognition, function or study participation, previous bipolar disorder or psychotic disorder were excluded. Patients were recruited for

brain donation and subsequent pathological diagnosis. Only patients with probable or definite DLB and AD were included in this study.

**Diagnostic and clinical baseline examination**

A research clinician performed a structured clinical interview of patients and caregivers regarding demographics, previous diseases, and drug history. The assessment procedure included a detailed history using a semi-structured interview, clinical examination including physical, neurological, psychiatric, and a detailed neuropsychological test battery, routine of blood and brain MRI. Dopamine transporter SPECT scans were available for 34 patients with DLB, and was clearly abnormal in 26 and borderline in 2 cases. The final clinical diagnosis was made by two of the study clinicians based on all available information, including pathological diagnosis when available, according to the consensus criteria for DLB and AD[8, 9]. The diagnoses were re-evaluated several times during the study period, and a final diagnosis was made in 2014. Please see reference [7] for further details of the inclusion and diagnostic and baseline procedures. A pathological diagnosis was available in a 20 patients (see below).

Structured rating scales for detecting the DLB core features were systematically administered to all patients by dedicated study physicians or research nurses. Annual meetings between study clinicians were held to maintain similar procedures. Fluctuating cognition was rated using the Clinician Assessment of Cognitive Fluctuations[10] or the Mayo Fluctuation Questionnaire[11]. RBD was diagnosed if there was a history of recurrent nocturnal dream enactment behavior recorded from the Mayo sleep questionnaire (MSQ)[12]. The unified Parkinson's rating scale item 3 (UPDRS-3)[13] was used to measure parkinsonian symptoms. Activities of daily living were assessed using the Rapid Disability Rating Scale-2[14]. The Neuropsychiatric Inventory (NPI) was applied to assess visual hallucinations and other psychiatric symptoms[15]. The Cumulative Illness Rating Scale (CIRS)[16] was applied to measure the total burden of all other diseases.

### Cognitive decline

Cognitive decline was measured using the CDR scale. The CDR examines 6 different areas in dementia: Memory, Orientation, Judgement and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. All 6 items are scored from 0 to 3, with 0 corresponding to no dementia, 0.5 mild cognitive impairment, 1 mild dementia, 2 moderately severe dementia and, 3 severe dementia. A global score 0-3 was calculated based on an available online algorithm. The time from baseline to the first assessment with an overall CDR score of 3, i.e. severe dementia, was recorded. The CDR was scored by a trained research physician, and the scoring was made independent of the other cognitive tests, by the same clinician at every occasion to the extent possible. In addition, cognition was also measured using the MMSE, administered by a trained research nurse. Decline was calculated from baseline to study end, death, or first assessment with MMSE score equal to zero.

### Pathological diagnosis and APOE genotyping

Brain dissection, regional sampling, and tissue processing and staining are done following standard protocols including BrainNet Europe and Brains for Dementia Research UK[17, 18]. Specific stain for identification of AD-type and LB pathologies (modified Bielschowsky), and immune histochemical procedures were used for detection of hyperphosphorylated tau (pretangles, tangles, dystrophic neurites and neuropil threads), amyloid beta (diffuse and classical plaques and amyloid angiopathy), and alpha-synuclein (Lewy bodies and Lewy neurites), according to standard immunohistochemical protocols. Each case was assessed by an experienced neuropathologist (T. H.) who was blinded to clinical data. Pathological diagnosis was made according to international consensus criteria for DLB[8], and AD[8, 17, 19-21]. The presence of possible co-existing TDP-43 proteinopathy was assessed according to guidelines[22], and microscopic vascular lesions considered and recorded[23]. A neuropathological diagnosis was available for a total 20 of the included patients. *APOE* genotyping was performed in 125 patients[24], and the proportion with at least one *e4* allele was 64% in both groups.

### Statistics

Baseline characteristics are presented and group comparisons made using t-test, Mann-Whitney or chi square tests as appropriate. We applied Kaplan-Meyer survival analysis and the Log-Rank test. Time to CDR = 3 was analyzed and compared between the groups using Cox regression analysis, and clinical predictors of course were identified. These data have

some indication of non-proportional hazards at about five years. To avoid problems caused by this, we partitioned the time axis by censoring at five years as suggested in[25]. This removed signs of possible non-proportional hazards. Results from cox regressions with and without time partitioning were comparable. We also analyzed time to CDR=3 or death as a clinically relevant outcome. Longitudinal analysis with linear mixed effects (lme) model, adjusting for age, sex, CIRS, duration and baseline MMSE and CDR was applied using random intercept and slope model. This produced a good fit to the data according to analyses of the residuals and random effects. Need for interaction terms in the model was checked with clear non-significant results. Possible nonlinear patterns in decline were checked by adding a time squared term to the model. This was also clearly insignificant. It may be argued that the more frequent drop out in the DLB group due to death as compared to the AD group occur at random[26] and thus the lme modelling approach adjusts for this in an appropriate way in this situation. To study the impact of different death rates on longitudinal outcome, we also tried joint modelling where the lme model is linked to a cox proportional hazards model for survival. This did not improve the results, but a significant correlation between death rates and longitudinal outcome was noted. All statistical analyses were done using the program packages SPSS and R[27].

**Results**

Follow-up data were available for 107 patients with probable or definite (n=12) AD and 67 with probable or definite (n=8) DLB. Demographic and clinical baseline characteristics are shown in Table 1. DLB patients were more commonly males, had slightly longer disease duration, and as expected higher NPI and UPDRS motor scores. DLB patients also had higher CIRS scores than the AD group. Duration of follow-up varied according to time of study inclusion and time of death. One hundred and eleven of the patients died, but there were no drop-outs for other reasons. Median follow up time was 1577 days (4.3 yrs.), and the number of person-years was 232 for DLB and 479 for AD. Seventy-one (40.8 %) patients reached a global CDR score of 3, 28 (41.8%) diagnosed with DLB and 43(40.2%) diagnosed with AD, p=0.834.

The median time to severe dementia, defined as CDR=3, was 1947 days in AD and 1793 days in DLB (p=0.033). (See figure 1) As can be seen in Figure 2, there were large variability in the cognitive decline, some having a short time to reach the severe dementia stage whereas others remained at the mild or moderate stage for several years. The unadjusted and adjusted

Cox models (Table 2) show that a diagnosis of DLB was associated with shorter time to severe dementia (HR 2.35, p<0.002 and 2.04, p=0.020). Median time until CDR=3 or death was1861 days in probable AD and 1210 days in probable DLB (p<0.0005). In the fully adjusted Cox regression model higher baseline age, longer duration of symptoms and higher CDR global scores predicted shorter time until CDR=3 or death in addition to having a DLB diagnosis. (p=0.039) (Table 4 in supplemental material online)

The progression of MMSE is shown in Figure 2. There is a significant decline in MMSE score over time. The diagnosis X time (years) interaction is significant (p=0.008) (Table 3), indicating that the decline over time differs between the two groups. In the adjusted linear mixed model, taking into account potential confounders (see Table 3), MMSE is reduced on average by 3.2 points per year in the AD group, whereas in the DLB group the decrease is more rapid; on average 4.4 points per year. The slope is also significantly affected by baseline MMSE level and baseline CDR global scores. The individual and mean group MMSE scores over the study period are shown in figure 2. Figure 2 also illustrates the variability in the rate of decline, which is slightly higher in DLB (SD of annual decline 2.2, range -5.9 to 4.1 vs) compared to AD (SD 1.6, range -4.1 to 3.3)

Among the 20 patients with neuropathological analysis, seven of the nine with a clinical diagnosis of DLB had their diagnosis confirmed neuropathologically, whereas two were changed to AD. In addition, one patient with a clinical diagnosis of AD was changed to DLB. Co-existing moderate or severe AD pathology was present in most of these cases. Ten of the 11 patients with clinical diagnosis of AD had their diagnosis confirmed with severe AD pathology (Braak tau stage 6), although some degree of coexisting DLB pathology was noted in 4, and three patients had mild TDP-43 pathology limited to the amygdala.

(Insert tables about here)

## Discussion

In the largest prospective longitudinal long-term cohort-study in DLB to date, the time to reach severe dementia was shorter, and the rate of cognitive decline was faster, in DLB than in AD. This adds to previous findings that DLB patients have a particularly severe prognosis, including more reduced quality of life[28], higher health-related costs[29], shorter time to nursing home admission[30], more severe caregiver burden[31], and shorter survival[32] than AD patients, all factors which are also crucial for health economic modelling. However, compared to these outcome measures, the difference in cognitive decline is less striking, suggesting that aspects other than the rate of cognitive decline are more important for clinical milestones such as

nursing home admission and death. Finally, unlike other studies, we used a different outcome (time to CDR=3) also in applying a more sophisticated statistical approach.

Previous studies comparing the cognitive course in DLB and AD have shown inconsistent results. In a recent systematic review we identified 18 longitudinal studies[4]. Some studies reported no difference in the rate of cognitive decline, whereas some reported faster decline in DLB and others a faster decline in AD. In addition, there seemed to be differential decline of the different cognitive domains, with more rapid memory decline in AD, and more rapid executive (verbal fluency) in DLB. In a meta-analysis including the six studies reporting decline on MMSE, no significant differences were found between AD and DLB. However, these 18 studies were based on small DLB groups and had a short follow-up period, which may lead to insecure estimates of decline. In addition, several studies included patients who were already at a moderate or severe degree of dementia, which may also influence the rate of subsequent decline.

Although our cohort is the largest prospectively studied DLB cohort, the number of patients is nevertheless small and thus statistical power to detect differences is limited. In addition, the relatively high mortality in DLB leads to few patients completing the full 5-year observation period. DLB is a heterogeneous disease and patients may thus be referred to clinics of different medical specialties, including psychiatry, neurology, geriatric medicine, and sleep medicine. Since it is possible that the symptom profile may be related to rate of decline, findings from different studies may vary according to recruitment procedures. The inclusion of referrals compared to community-based patients likely lead to more complex AD and DLB cases to be included which may have influenced the findings, and thus our conclusions may not be valid for community-based patients. Furthermore, we took care to include patients from a variety of specialist sources, the main recruitment was from old age psychiatry and geriatric medicine clinics. Neurology clinics were recommended to refer patients to the study, but patients with more severe motor symptoms may still be under-represented, and no patients were referred from internal medicine or sleep clinics. Thus, DLB patients with primary sleep or autonomous symptoms may not have been included.

We used time to severe dementia as measured by CDR in addition to MMSE as outcome measure. MMSE is less sensitive to the cognitive impairment associated with DLB[33], although may still be sensitive to the rate of change in these patients[34]. In contrast, the CDR

captures the full range of functional deficits due to cognition as judged by a trained clinician after interviewing patients and caregivers, and is likely a more accurate and comprehensive measure of severity. However, the CDR was developed for use in AD and has not yet been adequately tested in DLB.

Finally, for the majority of patients a clinical diagnosis was used, which is not 100% accurate. However, we used DaTSCAN/ CIT-SPECT to help in the differentiation between DLB and AD, as well as standardized rating scales for the core and suggestive clinical features of DLB. The longitudinal assessment by the same clinician also increases the diagnostic accuracy. In addition, neuropathological analysis was available for 20 (11 %) cases. which confirmed the clinical diagnosis in most cases. To conclude, we found that time to reach severe dementia is shorter in DLB compared to AD. This, together with the high mortality and institutionalization rate and caregiver burden in DLB, underlines the severe prognosis of this common disease. Future studies should explore the course of other key clinical symptoms, including motor and psychiatric symptoms. Detailed prognostic information is vital for patients and families and is essential to underpin accurate design and powering of clinical trials, and is also essential to enable the development of more accurate health economic models for cost effectiveness, which depend upon conversion between different stages of dementia severity.

**Table 1 Baseline characteristics of the cohort**

| | **Probable AD (n=107)** | **Probable DLB (n=67)** | **p-value** |
|---|---|---|---|
| Age | 75.1 (7·9) | 76.1 (7·2) | 0.598 |
| Female, N (%) | 80 (74.8%) | 32 (47.8%) | <0.0005 |
| Education, years, mean, SD | 9.8 (3.0) | 9.5 (2.7) | 0.512 |
| CDR global score, median, IQR | 1.00 (0.50) | 1.00 (0.50) | 0.217 |
| MMSE total score, mean, SD | 23.6 (2.3) | 23.5 (3.0) | 0.870 |
| Duration of symptoms before baseline, years, mean, SD | 2.0 (2.0) | 2.6 (1.9) | 0.011 |
| NPI-total scores, mean, SD | 15.7 (16.9) | 22.8 (19.1) | 0.006 |
| CIRS score, mean, SD | 5.1 (2.1) | 6.3 (2.6) | 0.004 |
| UPDRS III scores, mean, SD | 1.5 (2.3) | 14.2 (13.0) | <0.0005 |
| Anti-psychotics, N (%) | 4 (3.7) | 10 (14.9) | 0.008 |
| Anti-parkinsonian medication, N (%) | 0 (0) | 9 (13.4) | <0.005 |
| Anti-dementia medication, N (%) | 68 (63.6) | 38 (56.7) | 0.436 |
| Death during follow up, N (%) | 59 (55.1) | 52 (77.6) | 0.003 |

AD= Alzheimer's dementia, DLB=Dementia with Lewybodies, N=number, SD= standard deviation, CDR=Clinical Dementia Rating, IQR= Interquartile Range, MMSE= Mini-mental state examination, NPI= Neuropsychiatric Inventory, CIRS=Cumulative illness rating scale, UPDRS= Unified Parkinson's disease rating scale-motor subscale.

**Table 2 Factors associated with time to reach severe dementia**

| | Unadjusted hazard ratios | p-value | Adjusted hazard ratios | p-value |
|---|---|---|---|---|
| Age at baseline, years | 1.00 (0.97, 1.04) | 0.781 | | |
| Diagnoses, DLB vs. AD | 2.35 (1.39, 3.99) | 0.002 | 2.04 (1.12, 3.72) | 0.020 |
| Sex, females vs. males | 0.6 (0.35, 1.02) | 0.057 | 0.83 (0.45, 1.53) | 0.556 |
| Education in years | 1.01 (0.92, 1.10) | 0.907 | | |
| Duration of symptoms in years | 1.13 (1.00, 1.27) | 0.048 | 1.15 (1.01, 1.29) | 0.030 |
| MMSE total scores | 0.79 (0.71, 0.89) | <0.0005 | 0.82 (0.73, 0.93) | 0.002 |
| CIRS total scores | 1.02 (0.90, 1.16) | 0.745 | | |
| CDR global scores | 3.26 (1.80, 5.89) | <0.0005 | 2.42 (1.26, 4.65) | 0.008 |

Cox regression, time until CDR=3. Hazard ratios presented with 95% confidence interval. AD= Alzheimer's dementia, DLB=Dementia with Lewybodies, MMSE=Mini-mental state examination; CIRS=Cumulative illness rating scale.

**Table 3 Factors associated with the rate of decline on MMSE**

| | Coefficient | p-value |
|---|---|---|
| Follow up time in years | -3.20 (-3.69, -2.7) | <0.0005 |
| Diagnosis | 1.63 (0, 3.27) | 0.050 |
| Sex | 0.41 (-1.01, 1.83) | 0.571 |
| Age in years | 0.04 (-0.05, 0.13) | 0.402 |
| CIRS scores at baseline | -0.01 (-0.3, 0.29) | 0.957 |
| Duration of symptoms before baseline in years | -0.10 (-0.41, 0.21) | 0.524 |
| MMSE scores at baseline | 0.83 (0.58, 1.08) | <0.0005 |
| CDR at baseline | -2.48 (-4.16, -0.8) | 0.004 |
| Diagnosis x year | -1.24 (-2.15, -0.32) | 0.008 |

Linear mixed effects analysis, covariate adjusted. DLB=dementia with Lewybodies, AD= Alzheimer's dementia, MMSE=Mini-mental state examination; CIRS=Cumulative illness rating scale.



## Competing Interests

No, there are no competing interests

## Data Sharing Statement

Data collection is ongoing, and data sharing is currently limited to members of the study group

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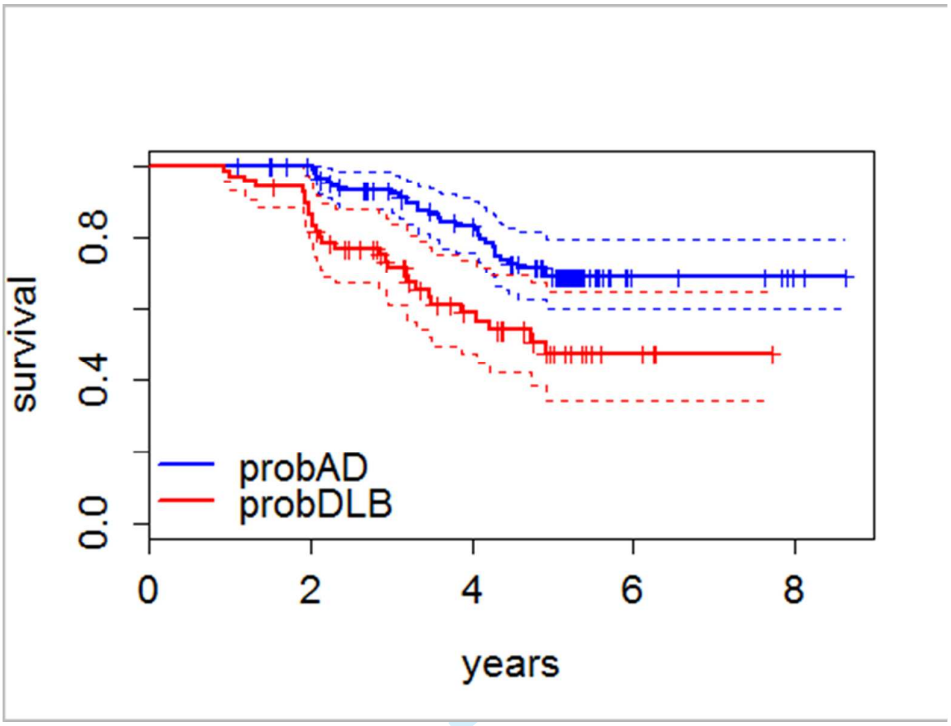
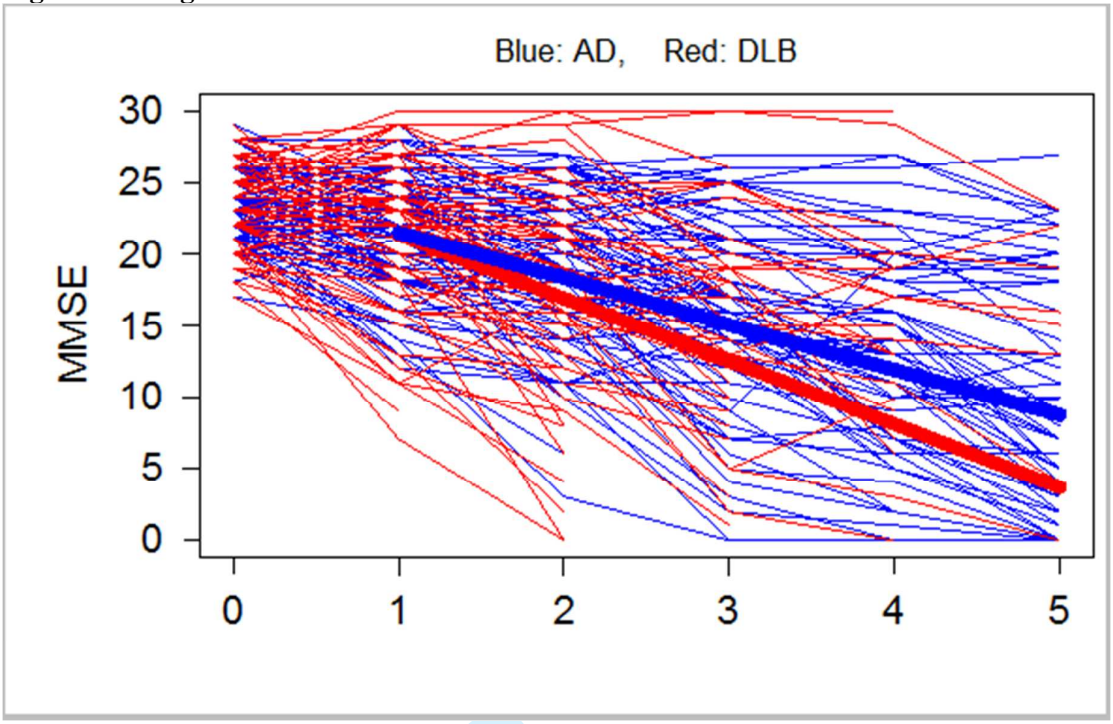
**Figure 1 Time until severe dementia in DLB and AD**



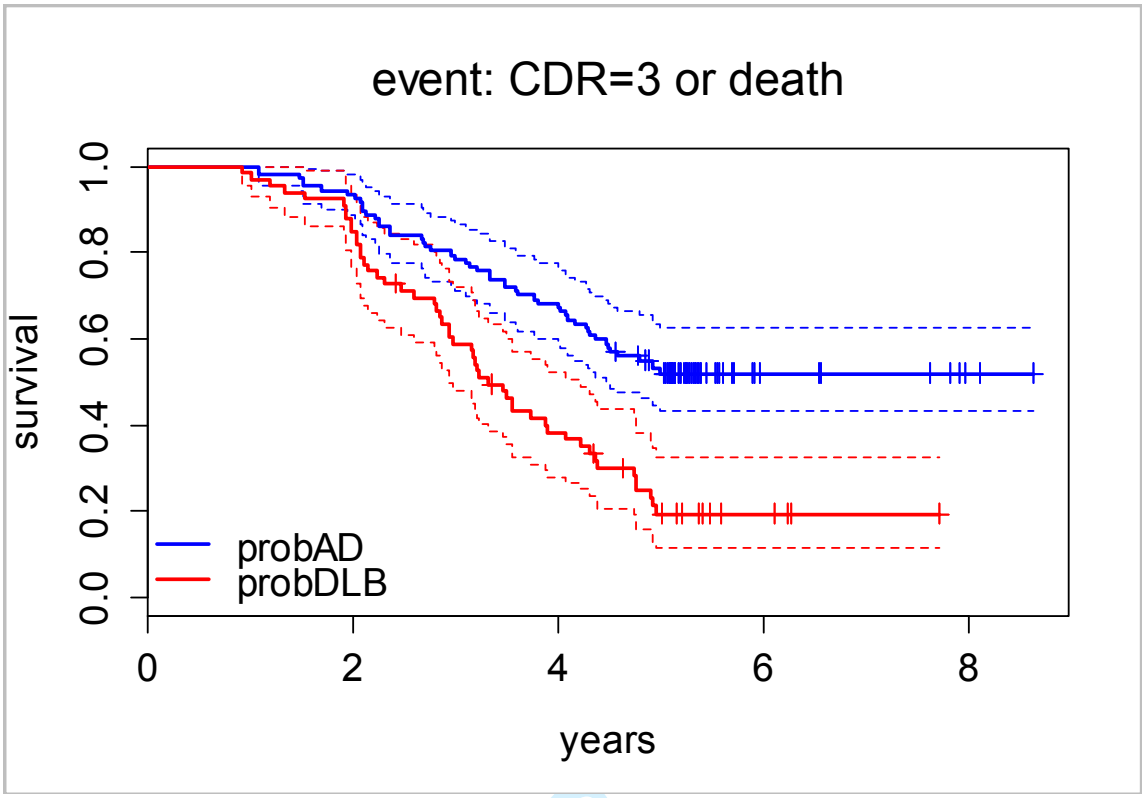

Time to severe dementia (CDR=3) is depicted by a survival (Kaplan-Meier) plot; blue: AD and red; DLB group. Additional censoring at five years has been used as explained in the text. There was significant difference between the groups both with and without the additional censoring (p=0.033 and 0.001, resp., log-rank tests)

**Figure 2: Longitudinal declines on individual MMSE scores and estimated lme-results**




Thin lines MMSE level for each individual at baseline (0) and follow ups 1 – 5; red: DLB group, blue: AD group. Thick lines: estimated level of MMSE for the DLB group (red) and AD group (blue). The MMSE levels at year 1 – 5 are adjusted for age, sex, CIRS, duration and baseline MMSE and CDR global. Estimates are based on lme model. The patient having 30 as the final score at the4th follow up had premorbid intelligence well above average and was highly educated (PhD). Baseline symptoms were symmetrical parkinsonism, apathy, frequent and severe visual hallucinations, and subtle cognitive problems predominantly calculation, working memory and planning. He had pathological DaTSCAN, as well as REM-sleep behavioural disorder and fluctuating cognition. CDR-SB was 2.5 at baseline, and worsened to 4.5 and 6 during the study period., and thus we concluded that the diagnostic criteria for probable DLB were fulfilled.

**Figure 3 Survival until severe dementia or death in AD and DLB**




Time to severe dementia (CDR=3) or death is depicted by a survival (Kaplan-Meier) plot; blue: AD amd red; DLB group. Additional censoring at five years has been used as explained in the text. There was significant difference between the groups both with and without the additional censoring ($p<0.0005$ both cases, log-rank tests).

**Table 4 Factors associated with time to reach severe dementia or death**

| | Unadjusted hazard ratios | p-value | Adjusted hazard ratios | p-value |
|---|---|---|---|---|
| Age at baseline, years | 1,05 (1.02, 1.08) | 0,0009 | 1.04 (1.00, 1.07) | 0.0293 |
| Diagnoses, DLB vs. AD | 2,37 (1.6, 3.5) | 0,0000 | 1.63 (1.03, 2.6) | 0.0389 |
| Sex, females vs. males | 0,66 (0.44, 0.97) | 0,0364 | 0.72 (0.44, 1.16) | 0.1745 |
| Education in years | 0,99 (0.93, 1.06) | 0,8493 | | |
| Duration of symptoms in years | 1,09 (0.99, 1.2) | 0,0731 | 1.12 (1.01, 1.24) | 0.0355 |
| MMSE total scores | 0,87 (0.8, 0.95) | 0,0011 | 0.93 (0.84, 1.02) | 0.106 |
| CIRS total scores | 1,14 (1.05, 1.24) | 0,0020 | 1.05 (0.95, 1.16) | 0.3375 |
| CDR global scores | 2,57 (1.6, 4.14) | 0,0001 | 2.02 (1.18, 3.44) | 0.0102 |

Cox regression, time until CDR=3 or death. Hazard ratios presented with 95% confidence interval. AD= Alzheimer's dementia, DLB=Dementia with Lewybodies, MMSE=Mini-mental state examination; CIRS=Cumulative illness rating scale.

BMJ Open

# Cognitive decline in Dementia with Lewy Bodies - a five year prospective cohort study

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|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2015-010357.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 25-Jan-2016 |
| Complete List of Authors: | Rongve, Arvid; Haugesund Hospital, Department of Research and Innovation; University of Bergen, Department of Clinical Medicine<br>Soennesyn, Hogne; Stavanger University Hospital, Geriatric Medicine<br>Skogseth, Ragnhild; Haraldsplass Deaconess Hospital, Geriatric Medicine<br>Oesterhus, Ragnhild; Stavanger University Hospital, Pharmacology<br>Hortobágyi, Tibor; Kings College, Pathology<br>Ballard, Clive; King's College London, Wolfson Centre for Age-Related Diseases<br>Auestad, Bjorn; University of Stavanger, Department of Mathematics and Natural Sciences<br>Aarsland, Dag; Stavanger University Hospital |
| Primary Subject Heading: | Neurology |
| Secondary Subject Heading: | Geriatric medicine |
| Keywords: | Dementia < NEUROLOGY, Parkinson-s disease < NEUROLOGY, GERIATRIC MEDICINE |
| | |

**Title**

Cognitive decline in Dementia with Lewy Bodies - a five year prospective cohort study

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**Key words**

Dementia with Lewy Bodies, Alzheimer's disease, longitudinal cohort study, prognosis.

**Word count**

Paper: 2763

Abstract: 258

Character count title: 66

**Statistical analyses**

Longitudinal analyses by Bjoern Henrik Auestad (PhD) and other statistics by Arvid Rongve (MD, PhD).

## Abstract

**Objectives** We report the cognitive decline in persons diagnosed with mild Dementia with Lewy Bodies (DLB) and mild Alzheimer's disease (AD) during five years of annual follow ups.

**Methods** Patients were recruited into the study from geriatric, psychiatric and neurology clinics in Western Norway during 2005-2013. They were diagnosed according to clinical consensus criteria, based on standardized clinical rating scales. Autopsy-based diagnoses were available for 20 cases. Cognitive decline for up to five years was assessed using the Clinical Dementia Rating scale (CDR) and the Mini-Mental State Examination (MMSE). Survival analysis including Cox regression (time to reach severe dementia) and linear mixed effects (lme) modelling were used to model the decline on MMSE.

**Results** At least one follow-up assessment was available for 67 DLB and 107 AD patients, with a median follow-up time of 4.3 years. The time to reach severe dementia was significantly shorter in DLB (median 1793 days) compared to AD (1947 days) (p=0.033), and the difference remained significant in the multiple Cox regression analysis (Hazard ratio = 2.0, p<0.02. In the adjusted lme model, MMSE decline was faster in DLB (annual decline 4.4 points) compared to AD (3.2 points) (p<0.008).

**Conclusion** Our findings show that from the mild dementia stage patients with DLB have a more rapid cognitive decline than in AD. Such prognostic information is vital for patients and families and crucial for planning clinical trials and enabling health economic modelling.

## Strengths and limitations

- We report the largest DLB cohort with the longest follow up to date
- We followed all included participants every 12 months until study end or death
- We applied highly standardized diagnostic procedures including the MAYO fluctuation and MAYO sleep scales to diagnose DLB
- We provide autopsy-proven diagnoses for 9 % of included cases
- Clinical dementia diagnoses were revised after 5 years of annual follow ups based on all available information.

## Introduction

Few longitudinal cohort-studies of Dementia with Lewy bodies (DLB) exist compared to in other neurodegenerative diseases[1, 2]. Accordingly, the long-term course and prognostic factors in DLB are not known. Early observations suggested that DLB patients had a faster cognitive decline as compared to Alzheimer's disease[3], but subsequent studies have reported contradictory results. In a recent meta-analysis we found no significant difference in the rate of decline on Mini-Mental State Examination (MMSE) in DLB and Alzheimer's disease (AD)[4]. However, this conclusion was based on few studies with small sample sizes and short follow-up time. Understanding the disease course is vital to give patients and families a better understanding of prognosis and is also essential to underpin accurate design and powering of clinical trials and to enable health economic models for cost effectiveness. We therefore aimed to assess the rate of decline for up to 5 years in DLB in comparison to AD. In addition to the MMSE, which may be less sensitive to the cognitive changes in DLB compared to AD[5], we used a broader assessment of cognition and function, the Clinical Dementia Rating scale (CDR)[6], using time to reach severe dementia, CDR stage 3, as a co-primary outcome.

## Methods

### Design

We used a prospective design, and DLB patients, were diagnosed clinically using extensive and standardized diagnostic investigations and also recruiting for post-mortem confirmation. Our aim was to allow for long follow-up time from the time of diagnosis with annual assessment points. There is yet no consensus regarding the best cognitive scale to track cognitive decline in DLB, and thus we used CDR as our measure of cognitive functioning. The study was approved by the Regional Committees for Medical and Health Ethics, approval number 2010/ 633.

### Subjects and inclusion

In the Dementia Study of western Norway (DemVest-study) all referrals to geriatric and psychiatric clinics in Hordaland and Rogaland counties (with 448 343 (13.4% aged 67 or higher) and 393 104 (11.5% 67+) inhabitants, respectively) underwent a full medical examination for a first time diagnosis of mild dementia during 2005 – 2007, and consecutively invited to participate if inclusion and exclusion criteria were fulfilled. All

neurology clinics in the region were invited to refer patients with suspected dementia to the study. The referral pattern varies among GPs, but most dementia patients are diagnosed by their local GP. To reduce risk for referral bias, GPs in the area were therefore contacted by letter prior to study start and invited to refer all patients with suspect dementia to one of the participating centers. Subsequently we included DLB cases selectively from 2007 until 2013 to increase sample size[7]. Patients were followed annually with a structured interview, caregiver interview and cognitive tests. Drug-treatment was provided as clinically indicated by the treating physician, but it was recommended that AD and DLB patients should receive treatment with cholinesterase inhibitor, and most patients were treated from inclusion in the study.

**Inclusion and exclusion criteria**

To select patients with mild dementia only, a MMSE score of at least 20 or a CDR global score = 1 was required for inclusion. Patients without dementia or with acute delirium or confusion, terminal illness, recently diagnosed with a major somatic illness which according to the clinician would significantly impact on cognition, function or study participation, previous bipolar disorder or psychotic disorder were excluded. Patients were recruited for brain donation and subsequent pathological diagnosis. Only patients with probable or definite DLB and AD were included in this study.

**Diagnostic and clinical baseline examination**

A research clinician performed a structured clinical interview of patients and caregivers regarding demographics, previous diseases, and drug history. The assessment procedure included a detailed history using a semi-structured interview, clinical examination including physical, neurological, psychiatric, and a detailed neuropsychological test battery, routine of blood and brain MRI. Dopamine transporter SPECT scans were available for 34 patients with DLB, and was clearly abnormal in 26 and borderline in 2 cases. The final clinical diagnosis was made by two of the study clinicians based on all available information, including pathological diagnosis when available, according to the consensus criteria for DLB and AD[8, 9]. The diagnoses were re-evaluated several times during the study period, and a final diagnosis

was made in 2014. Please see reference [7] for further details of the inclusion and diagnostic and baseline procedures. A pathological diagnosis was available in 20 patients (see below).

Structured rating scales for detecting the DLB core features were systematically administered to all patients by dedicated study physicians or research nurses. Annual meetings between study clinicians were held to maintain similar procedures. Fluctuating cognition was rated using the Clinician Assessment of Cognitive Fluctuations[10] or the Mayo Fluctuation Questionnaire[11]. RBD was diagnosed if there was a history of recurrent nocturnal dream enactment behavior recorded from the Mayo sleep questionnaire (MSQ)[12]. The unified Parkinson's rating scale item 3 (UPDRS-3)[13] was used to measure parkinsonian symptoms. Activities of daily living were assessed using the Rapid Disability Rating Scale-2[14]. The Neuropsychiatric Inventory (NPI) was applied to assess visual hallucinations and other psychiatric symptoms[15]. The Cumulative Illness Rating Scale (CIRS)[16] was applied to measure the total burden of all other diseases.

**Cognitive decline**

Cognitive decline was measured using the CDR scale. The CDR examines 6 different areas in dementia: Memory, Orientation, Judgement and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. All 6 items are scored from 0 to 3, with 0 corresponding to no dementia, 0.5 mild cognitive impairment, 1 mild dementia, 2 moderately severe dementia and, 3 severe dementia. A global score 0-3 was calculated based on an available online algorithm. The time from baseline to the first assessment with an overall CDR score of 3, i.e. severe dementia, was recorded. The CDR was scored by a trained research physician, and the scoring was made independent of the other cognitive tests, by the same clinician at every occasion to the extent possible. In addition, cognition was also measured using the MMSE, administered by a trained research nurse. Decline was calculated from baseline to study end, death, or first assessment with MMSE score equal to zero.

**Pathological diagnosis and APOE genotyping**

Brain dissection, regional sampling, and tissue processing and staining are done following standard protocols including BrainNet Europe and Brains for Dementia Research UK[17, 18]. Specific stain for identification of AD-type and LB pathologies (modified Bielschowsky), and

immune histochemical procedures were used for detection of hyperphosphorylated tau (pretangles, tangles, dystrophic neurites and neuropil threads), amyloid beta (diffuse and classical plaques and amyloid angiopathy), and alpha-synuclein (Lewy bodies and Lewy neurites), according to standard immunohistochemical protocols. Each case was assessed by an experienced neuropathologist (T. H.) who was blinded to clinical data. Pathological diagnosis was made according to international consensus criteria for DLB[8], and AD[8, 17, 19-21]. The presence of possible co-existing TDP-43 proteinopathy was assessed according to guidelines[22], and microscopic vascular lesions considered and recorded[23]. A neuropathological diagnosis was available for a total 20 of the included patients. *APOE* genotyping was performed in 125 patients[24], and the proportion with at least one *e4* allele was 64% in both groups.

**Statistics**

Baseline characteristics are presented and group comparisons made using t-test, Mann-Whitney or chi square tests as appropriate. We applied Kaplan-Meyer survival analysis and the Log-Rank test. Time to CDR = 3 was analyzed and compared between the groups using Cox regression analysis, and clinical predictors of course were identified. These data have some indication of non-proportional hazards at about five years which may lead to unreliable results. To avoid problems caused by this, we partitioned the time axis by censoring at five years as suggested in chapter 6 of Therneau et al.[25] The cox regression was performed using these extra censored data. This removed signs of possible non-proportional hazards according to tests based on scaled Schoenfeldt residuals. We also analyzed time to CDR=3 or death as a clinically relevant outcome. Longitudinal analysis with linear mixed effects (lme) model, adjusting for age, sex, CIRS, duration and baseline MMSE and CDR was applied using random intercept and slope model. This produced an adequate model for the data according to analyses of the residuals and random effects. Need for interaction terms in the model was checked with clear non-significant results. Possible nonlinear patterns in decline were checked by adding a time squared term to the model. This was also clearly insignificant. It may be argued that the more frequent drop out in the DLB group due to death as compared to the AD group occur at random[26] and thus the lme modelling approach adjusts for this in an appropriate way in this situation. To study the impact of different death rates on longitudinal outcome, we also tried joint modelling where the lme model is linked to a cox proportional hazards model for survival. Although a significant correlation between death rates and longitudinal outcome was registered, this death rate adjusted lme analysis showed practically

the same results as the ordinary lme analysis. All statistical analyses were done using the program packages SPSS and R[27].

**Results**

Follow-up data were available for 107 patients with probable or definite (n=12) AD and 67 with probable or definite (n=8) DLB (See flow chart Figure 4). Demographic and clinical baseline characteristics are shown in Table 1. DLB patients were more commonly males, had slightly longer disease duration, and as expected higher NPI and UPDRS motor scores. DLB patients also had higher CIRS scores than the AD group. Duration of follow-up varied according to time of study inclusion and time of death. One hundred and eleven of the patients died, but there were no drop-outs for other reasons. Median follow up time was 1577 days (4.3 yrs.), and the number of person-years was 232 for DLB and 479 for AD. Seventy-one (40.8 %) patients reached a global CDR score of 3, 28 (41.8%) diagnosed with DLB and 43(40.2%) diagnosed with AD, p=0.834.

The median time to severe dementia, defined as CDR=3, was 1947 days in AD and 1793 days in DLB (p=0.033). (See figure 1) The mortality rates were significantly higher in DLB than in AD. As can be seen in Figure 2, there were large variability in the cognitive decline, some having a short time to reach the severe dementia stage whereas others remained at the mild or moderate stage for several years. The unadjusted and adjusted Cox models (Table 2) show that a diagnosis of DLB was associated with shorter time to severe dementia (HR 2.35, p<0.002 and 2.04, p=0.020). Median time until CDR=3 or death was1861 days in probable AD and 1210 days in probable DLB (p<0.0005). (See figure 3) In the fully adjusted Cox regression model higher baseline age, longer duration of symptoms and higher CDR global scores predicted shorter time until CDR=3 or death in addition to having a DLB diagnosis. (p=0.039) (Table 4 in supplemental material online)

The progression of MMSE is shown in Figure 2. There is a significant decline in MMSE score over time. The diagnosis X time (years) interaction is significant (p=0.008) (Table 3), indicating that the decline over time differs between the two groups. In the adjusted linear mixed model, taking into account potential confounders (see Table 3), MMSE is reduced on average by 3.2 points per year in the AD group, whereas in the DLB group the decrease is more rapid; on average 4.4 points per year. The slope is also significantly affected by baseline MMSE level and baseline CDR global scores. The individual and mean group MMSE scores over the study period are shown in figure 2. Figure 2 also illustrates the variability in the rate

of decline, which is slightly higher in DLB (SD of annual decline 2.2, range -5.9 to 4.1 vs) compared to AD (SD 1.6, range -4.1 to 3.3). We conducted the lme-analysis also including antidementia drug-use in the model, which was not associated with decline and did not change the main findings (results not included).

Among the 20 patients with neuropathological analysis, seven of the nine with a clinical diagnosis of DLB had their diagnosis confirmed neuropathologically, whereas two were changed to AD. In addition, one patient with a clinical diagnosis of AD was changed to DLB. Co-existing moderate or severe AD pathology was present in most of these cases. Ten of the 11 patients with clinical diagnosis of AD had their diagnosis confirmed with severe AD pathology (Braak tau stage 6), although some degree of coexisting DLB pathology was noted in 4, and three patients had mild TDP-43 pathology limited to the amygdala.

(Insert tables about here)

## Discussion

In the largest prospective longitudinal long-term cohort-study in DLB to date, the time to reach severe dementia was shorter, and the rate of cognitive decline was faster, in DLB than in AD. This adds to previous findings that DLB patients have a particularly severe prognosis, including more reduced quality of life[28], higher health-related costs[29], shorter time to nursing home admission[30], more severe caregiver burden[31], and shorter survival[32] than AD patients, all factors which are also crucial for health economic modelling. However, compared to these outcome measures, the difference in cognitive decline is less striking, suggesting that aspects other than the rate of cognitive decline are more important for clinical milestones such as nursing home admission and death. Finally, unlike other studies, we used a different outcome (time to CDR=3) also in applying a more sophisticated statistical approach.

Previous studies comparing the cognitive course in DLB and AD have shown inconsistent results. In a recent systematic review we identified 18 longitudinal studies[4]. Some studies reported no difference in the rate of cognitive decline, whereas some reported faster decline in DLB and others a faster decline in AD. In addition, there seemed to be differential decline of the different cognitive domains, with more rapid memory decline in AD, and more rapid executive (verbal fluency) in DLB. In a meta-analysis including the six studies reporting decline on MMSE, no significant differences were found between AD and DLB. However, these 18 studies were based on small DLB groups and had a short follow-up period, which may lead to insecure estimates of decline. In addition, several studies included patients who

were already at a moderate or severe degree of dementia, which may also influence the rate of subsequent decline.

Although our cohort is the largest prospectively studied DLB cohort, the number of patients is nevertheless small and thus statistical power to detect differences is limited. In addition, the relatively high mortality in DLB leads to few patients completing the full 5-year observation period. DLB is a heterogeneous disease and patients may thus be referred to clinics of different medical specialties, including psychiatry, neurology, geriatric medicine, and sleep medicine. Since it is possible that the symptom profile may be related to rate of decline, findings from different studies may vary according to recruitment procedures. The inclusion of referrals compared to community-based patients likely lead to more complex AD and DLB cases to be included which may have influenced the findings, and thus our conclusions may not be valid for community-based patients. Furthermore, we took care to include patients from a variety of specialist sources, the main recruitment was from old age psychiatry and geriatric medicine clinics. Neurology clinics were recommended to refer patients to the study, but patients with more severe motor symptoms may still be under-represented, and no patients were referred from internal medicine or sleep clinics. Thus, DLB patients with primary sleep or autonomous symptoms may not have been included.

We used time to severe dementia as measured by CDR in addition to MMSE as outcome measure. MMSE is less sensitive to the cognitive impairment associated with DLB[33], although may still be sensitive to the rate of change in these patients[34]. In contrast, the CDR captures the full range of functional deficits due to cognition as judged by a trained clinician after interviewing patients and caregivers, and is likely a more accurate and comprehensive measure of severity. However, the CDR was developed for use in AD and has not yet been adequately tested in DLB.

Finally, for the majority of patients a clinical diagnosis was used, which is not 100% accurate. However, we used DaTSCAN/ CIT-SPECT to help in the differentiation between DLB and AD, as well as standardized rating scales for the core and suggestive clinical features of DLB. The longitudinal assessment by the same clinician also increases the diagnostic accuracy. In addition, neuropathological analysis was available for 20 (11 %) cases which confirmed the clinical diagnosis in most cases. Anti-dementia medications like choline esterase inhibitors and memantine improve cognition in both DLB and AD, but this effect may be longer lasting

in DLB as compared to in AD, and the cognitive decline in DLB therefor may be underestimated in our study[35]. Parkinsonism in DLB might influence the CDR scores and increase these scores independent of cognition. To conclude, we found that time to reach severe dementia is shorter in DLB compared to AD. This, together with the high mortality and institutionalization rate and caregiver burden in DLB, underlines the severe prognosis of this common disease. Future studies should explore the course of other key clinical symptoms, including motor and psychiatric symptoms. Detailed prognostic information is vital for patients and families and is essential to underpin accurate design and powering of clinical trials, and is also essential to enable the development of more accurate health economic models for cost effectiveness, which depend upon conversion between different stages of dementia severity.

**Table 1 Baseline characteristics of the cohort**

| | **Probable AD (n=107)** | **Probable DLB (n=67)** | **p-value** |
|---|---|---|---|
| Age | 75.1 (7·9) | 76.1 (7·2) | 0.598 |
| Female, N (%) | 80 (74.8%) | 32 (47.8%) | <0.0005 |
| Education, years, mean, SD | 9.8 (3.0) | 9.5 (2.7) | 0.512 |
| CDR global score, median, IQR | 1.00 (0.50) | 1.00 (0.50) | 0.217 |

| | | | |
|---|---|---|---|
| MMSE total score, mean, SD | 23.6 (2.3) | 23.5 (3.0) | 0.870 |
| Duration of symptoms before baseline, years, mean, SD | 2.0 (2.0) | 2.6 (1.9) | 0.011 |
| NPI-total scores, mean, SD | 15.7 (16.9) | 22.8 (19.1) | 0.006 |
| CIRS score, mean, SD | 5.1 (2.1) | 6.3 (2.6) | 0.004 |
| UPDRS III scores, mean, SD | 1.5 (2.3) | 14.2 (13.0) | <0.0005 |
| Anti-psychotics, N (%) | 4 (3.7) | 10 (14.9) | 0.008 |
| Anti-parkinsonian medication, N (%) | 0 (0) | 9 (13.4) | <0.005 |
| Anti-dementia medication, N (%) | 68 (63.6) | 38 (56.7) | 0.436 |
| Death during follow up, N (%) | 59 (55.1) | 52 (77.6) | 0.003 |

AD= Alzheimer's dementia, DLB=Dementia with Lewybodies, N=number, SD= standard deviation, CDR=Clinical Dementia Rating, IQR= Interquartile Range, MMSE= Mini-mental state examination, NPI= Neuropsychiatric Inventory, CIRS=Cumulative illness rating scale, UPDRS= Unified Parkinson's disease rating scale-motor subscale.

**Table 2 Factors associated with time to reach severe dementia**

| | Unadjusted hazard ratios | p-value | Adjusted hazard ratios | p-value |
|---|---|---|---|---|
| Age at baseline, years | 1.00 (0.97, 1.04) | 0.781 | | |
| Diagnoses, DLB vs. AD | 2.35 (1.39, 3.99) | 0.002 | 2.04 (1.12, 3.72) | 0.020 |
| Sex, females vs. males | 0.6 (0.35, 1.02) | 0.057 | 0.83 (0.45, 1.53) | 0.556 |
| Education in years | 1.01 (0.92, 1.10) | 0.907 | | |
| Duration of symptoms in years | 1.13 (1.00, 1.27) | 0.048 | 1.15 (1.01, 1.29) | 0.030 |
| MMSE total scores | 0.79 (0.71, 0.89) | <0.0005 | 0.82 (0.73, 0.93) | 0.002 |
| CIRS total scores | 1.02 (0.90, 1.16) | 0.745 | | |
| CDR global scores | 3.26 (1.80, 5.89) | <0.0005 | 2.42 (1.26, 4.65) | 0.008 |

Cox regression, time until CDR=3. Hazard ratios presented with 95% confidence interval. AD= Alzheimer's dementia, DLB=Dementia with Lewybodies, MMSE=Mini-mental state examination; CIRS=Cumulative illness rating scale.

**Table 3 Factors associated with the rate of decline on MMSE**

| | Coefficient | p-value |
|---|---|---|
| Follow up time in years | -3.20 (-3.69, -2.7) | <0.0005 |
| Diagnosis | 1.63 (0, 3.27) | 0.050 |

| | | |
|---|---|---|
| Sex | 0.41 (-1.01, 1.83) | 0.571 |
| Age in years | 0.04 (-0.05, 0.13) | 0.402 |
| CIRS scores at baseline | -0.01 (-0.3, 0.29) | 0.957 |
| Duration of symptoms before baseline in years | -0.10 (-0.41, 0.21) | 0.524 |
| MMSE scores at baseline | 0.83 (0.58, 1.08) | <0.0005 |
| CDR at baseline | -2.48 (-4.16, -0.8) | 0.004 |
| Diagnosis x year | -1.24 (-2.15, -0.32) | 0.008 |

Linear mixed effects analysis, covariate adjusted. DLB=dementia with Lewybodies, AD= Alzheimer's dementia, MMSE=Mini-mental state examination; CIRS=Cumulative illness rating scale.

**Contributorship statement**

Arvid Rongve: Concept and idea, collection of data, writing of the paper and statistical analyses.

Hogne Soennesyn: Collection of data and critically reviewing the whole content of the paper.

Ragnhild Skogseth: Collection of data and critically reviewing the whole content of the paper.

Ragnhild Oesterhus: Collection of data and critically reviewing the whole paper.

Tibor Hortobágyi: Neuropathological analysis and diagnosis, writing pathology parts and critically reviewing the whole paper.

Clive Ballard: Concept and idea, critically reviewing the whole paper.

Bjoern Henrik Auestad: Providing the longitudinal statistical analyses and writing the statistical methods section and critically reviewing the paper.

Dag Aarsland: Concept and idea, collection of data, writing the paper together with first author Arvid Rongve.

**Funding and Disclosures** The project was funded by the Western Norway Regional Health Authority. None of the authors have any disclosures.

**Competing interests**

None of the authors reported any competing interests.

**Funding**

This work was founded through a post doctoral grant to first author Arvid Rongve from the regional health authorities (Helse Vest )

**Data sharing statement**Data collection is ongoing, and data sharing is currently limited to members of the study group.

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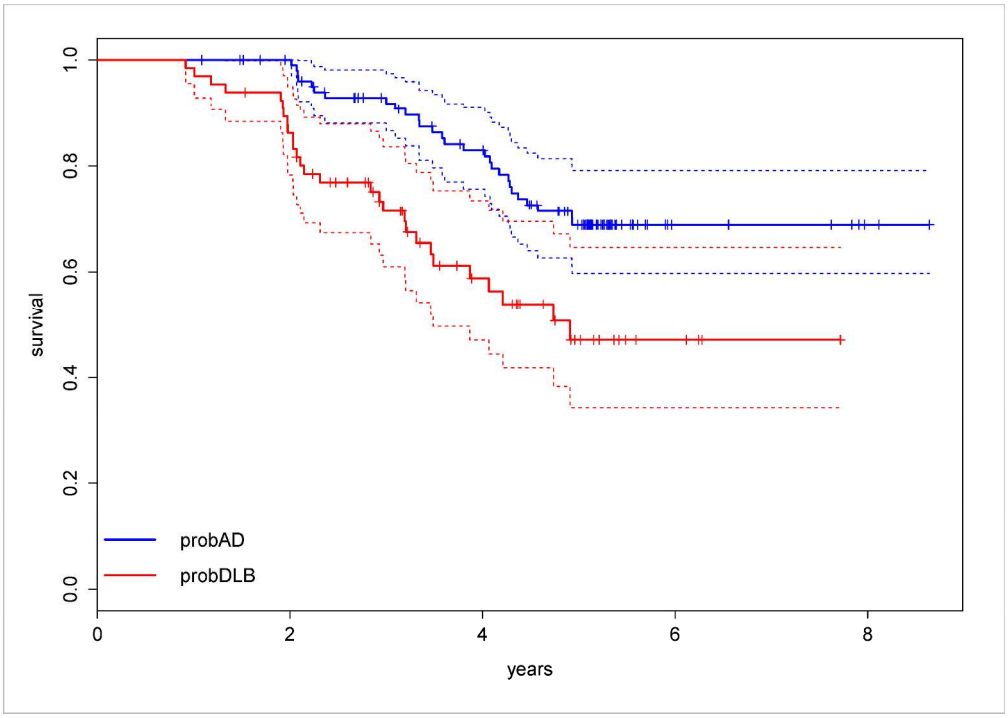



Figure 1 Survival until severe dementia in DLB and AD
296x209mm (300 x 300 DPI)

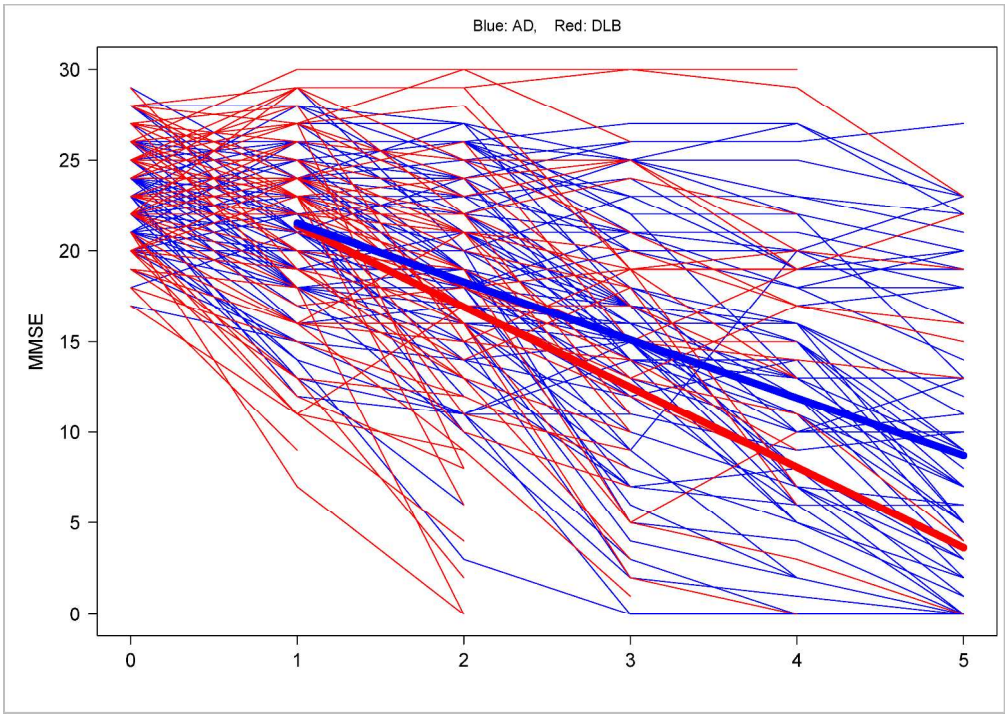



Figure 2: Longitudinal declines on individual MMSE scores and estimated lme-results
296x209mm (300 x 300 DPI)

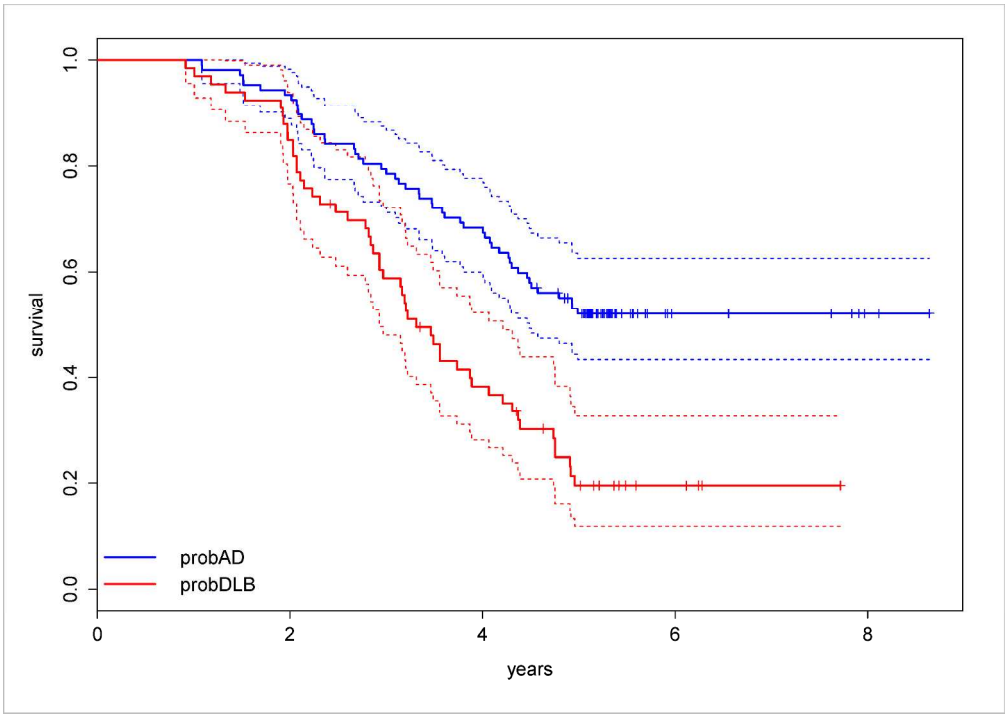
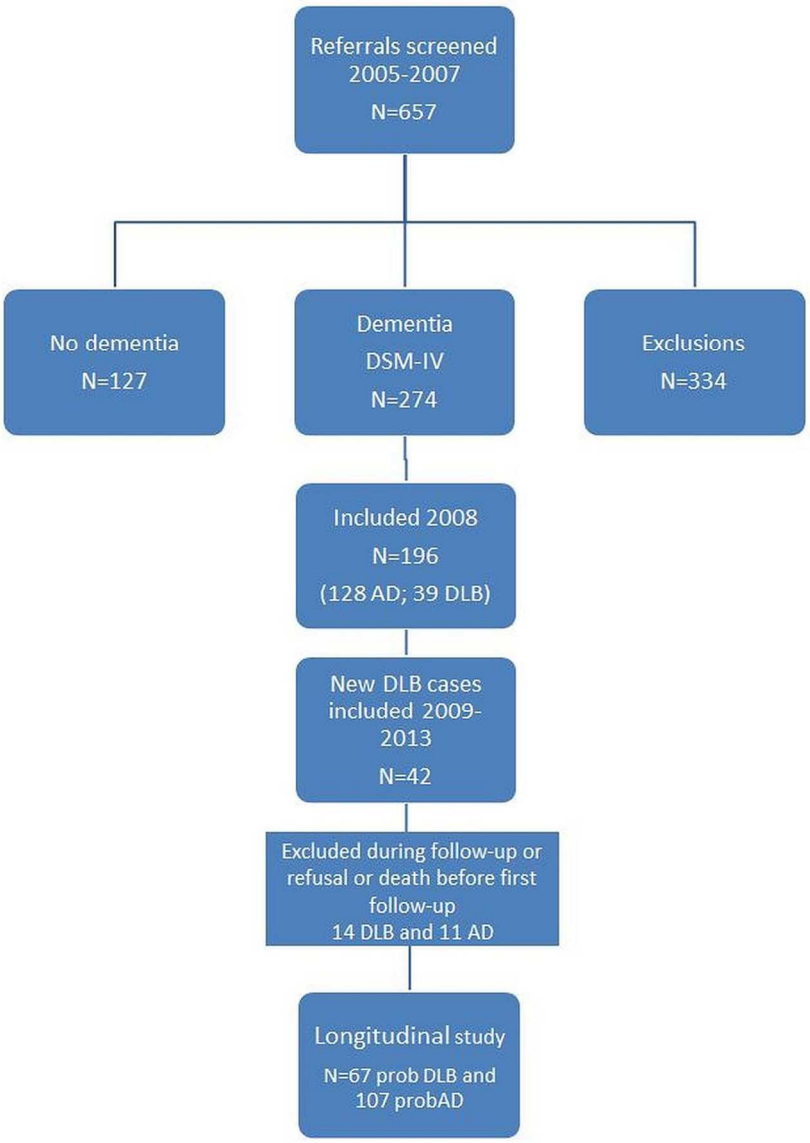



Figure 3 Survival until severe dementia or death in AD and DLB
296x209mm (300 x 300 DPI)




99x136mm (300 x 300 DPI)

**Factors associated with time to reach severe dementia or death**

| | Unadjusted hazard ratios | p-value | Adjusted hazard ratios | p-value |
|---|---|---|---|---|
| Age at baseline, years | 1,05 (1.02, 1.08) | 0,0009 | 1.04 (1.00, 1.07) | 0.0293 |
| Diagnoses, DLB vs. AD | 2,37 (1.6, 3.5) | 0,0000 | 1.63 (1.03, 2.6) | 0.0389 |
| Sex, females vs. males | 0,66 (0.44, 0.97) | 0,0364 | 0.72 (0.44, 1.16) | 0.1745 |
| Education in years | 0,99 (0.93, 1.06) | 0,8493 | | |
| Duration of symptoms in years | 1,09 (0.99, 1.2) | 0,0731 | 1.12 (1.01, 1.24) | 0.0355 |
| MMSE total scores | 0,87 (0.8, 0.95) | 0,0011 | 0.93 (0.84, 1.02) | 0.106 |
| CIRS total scores | 1,14 (1.05, 1.24) | 0,0020 | 1.05 (0.95, 1.16) | 0.3375 |
| CDR global scores | 2,57 (1.6, 4.14) | 0,0001 | 2.02 (1.18, 3.44) | 0.0102 |

Cox regression, time until CDR=3 or death. Hazard ratios presented with 95% confidence interval. AD= Alzheimer's dementia, DLB=Dementia with Lewybodies, MMSE=Mini-mental state examination; CIRS=Cumulative illness rating scale.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No | Recommendation |
|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract<br>*See "Title page"* |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found<br>*See "Abstract"* |
| **Introduction** | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported<br>*See "Introduction" page 3-4* |
| Objectives | 3 | State specific objectives, including any pre-specified hypotheses<br>*See "Introduction" page 3-4* |
| **Methods** | | |
| Study design | 4 | Present key elements of study design early in the paper<br>*See "Design" page 4* |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection<br>*See "Subjects and Inclusion" page 4* |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.<br>*See "Subjects and Inclusion" and "Inclusion and exclusion criteria" page 4-5.* |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed.<br>*Matching not applied.* |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.<br>*See "Diagnostic and baseline examination "page 5-6 and "Discussion" page 8-10.* |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.<br>*See "Diagnostic and baseline examination", "Cognitive decline" and "Pathological diagnosis and APOE genotyping" from page 5. See also "Reference" number 7.* |
| Bias | 9 | Describe any efforts to address potential sources of bias<br>*See " Subjects and Inclusion" and "Inclusion and exclusion criteria" and "Statistics" and "Results"* |
| Study size | 10 | Explain how the study size was arrived at<br>*See "Subjects and Inclusion" and "Flow Chart"* |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why<br>*See "Statistics" page 7.* |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding<br>*See "Statistics" page 7.* |
| | | (*b*) Describe any methods used to examine subgroups and interactions<br>*See "Statistics" page 7.* |
| | | (*c*) Explain how missing data were addressed<br>*See "Statistics" page 7.* |
| | | (*d*) If applicable, explain how loss to follow-up was addressed<br>*None of the included participants were lost to follow up.* |

| | | |
|---|---|---|
| | | (*e*) Describe any sensitivity analyses<br>*We analysed effects of anti-dementia drugs; see "Statistics" page 7 and "Results" page 8.* |
| **Results** | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed<br>*See "Flow chart"* |
| | | (b) Give reasons for non-participation at each stage<br>*See "Flow chart"* |
| | | (c) Consider use of a flow diagram<br>*"Flow chart" included* |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders<br>*See "Results" page 7 and "Table 1".* |
| | | (b) Indicate number of participants with missing data for each variable of interest<br>*Number of missing total MMSE scores at baseline; 0, at 1 year follow up (FU); 5(2.9%), at 2 y. FU; 3(2.0%), at 3 y. FU; 7(5.7%), at 4 y. FU; 12(13.0%) and at 5 y. FU; 11(15.9%). Missing CDR global scores at baseline; 12 (6.9%)* |
| | | (c) Summarise follow-up time (eg, average and total amount)<br>*See "Results"* |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>*See "Statistics" and "Results" and "Tables 2 & 3"* |
| | | (*b*) Report category boundaries when continuous variables were categorized<br>*Not relevant for this study.* |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses<br>*We analysed effects of drugs and potential confounders; Statistics p7, Results p8.* |
| **Discussion** | | |
| Key results | 18 | Summarise key results with reference to study objectives<br>*See "Discussion" page 9* |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias<br>*See "Discussion" page 9-10* |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence<br>*See "Discussion" page 10* |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results<br>*See "Discussion" page 9* |
| **Other information** | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based<br>*See "Funding and Disclosures"* |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.