Author's response to reviews

Title: Co-morbidity and drug treatment in Alzheimer's disease. A cross sectional study of participants in the Dementia Study in Northern Norway.

Authors:

Fred Andersen (frea@online.no)
Matti Viitanen (matti.viitanen@ki.se)
Dag S Halvorsen (dag.seeger.halvorsen@unn.no)
Bjørn Straume (bjorn.straume@ism.uit.no)
Torgeir A Engstad (torgeir.a.engstad@unn.no)

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Author's response to reviews: see over
Dear Editor

Thank you for reviewing our paper “Co-morbidity and drug treatment in Alzheimer’s disease. A cross sectional study of participants in The Dementia Study in Northern Norway” (BMC Manuscript ID 1425928854549845).

Please find enclosed our response to the comments from the Editorial board and the referees answered point-by-point. All changes in the manuscript are underlined.

Referee 1 Graziano Onder

1. We have compared the study participants recruited by GPs and by postal screening, and find no differences with respect to co-morbidity or drug use. We have added the following sentence under Results, paragraph Medical history on page 10: “The differences in mean number of co-morbidities were non-significant between AD participants recruited by screening or by GPs (2.3 ± 1.5 and 2.0 ± 1.6 respectively, p=0.20)” and under Results, paragraph Drug treatment on page 11 “… or between AD participants recruited by screening or by GPs (5.0 ± 3.5 versus 5.2 ± 3.7 respectively, p=0.56 age and gender adjusted)”.

2. A more comprehensive description of the recruitment strategy, data collection and the training of the test technicians are implemented under Methods, paragraph Clinical examination session on page 7. All participants were tested by the two test technicians prior to inclusion. Unfortunately we cannot present data (kappa values) on intra- and inter observed variability between the two test technicians. The following sentences are included in the manuscript:
"Prior to study onset two test technicians were trained at the Geriatric Department, University Hospital in Northern Norway. To improve intra- and inter-rater reliability they observed and evaluated each other by testing a number of patients with Mini-Mental-State-Examination (MMSE), Alzheimer’s disease Assessment Scale, cognitive (ADAS-Cog) and Neuropsychiatric Inventory (NPI).”

3. Stratified analyses comparing AD participants living in nursing homes or at home are performed. We have extended the last sentence under Results, paragraph Medical history on page 10 like this: “------and between AD participants living at home compared to those living in nursing homes (2.4 ± 1.6 and 2.1 ± 1.5, respectively, p=0.20)”

4. The diagnostic criteria are included under Methods, paragraph Clinical examinations page 6 and 7: “Dementia and AD were diagnosed by GPs and geriatric specialists using the ICD-10 criteria and the Statistical Manual of Mental Disorders fourth edition (DSM-IV-TR). Diagnostic discrepancies were discussed with a geriatric colleague and solved by consensus advised by National Institute of Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders (NINCDS-ADRDA) criteria for probable AD. A third specialist (MV) was consulted if disagreement continued.”
5. We have included a co-morbidity score (Ref Schubert et al and McCarron et al) under Methods, paragraph Medical history on page 7. Under Results, paragraph Medical history on page 10, the following sentences are included: “The co-morbidity score was higher in AD participants compared to controls (2.1 ± 1.5 and 1.3 ± 1.2 respectively, p<0.001). AD participants had a higher frequency of cardiovascular diseases (i.e. angina pectoris, myocardial infarct, congestive heart failure and atrial fibrillation), stroke, diabetes mellitus, hypertension, chronic obstructive bronchitis and chronic pain but only chronic obstructive bronchitis (adjusted for age and gender) reached statistical significance (Table 2)”.

6. We have added a column of unadjusted p-values in table 2.

7. We have added a sentence in Statistics on page 10 explaining how CI was calculated. “The calculation of 95% confidence interval (CI) refers to age and gender adjusted differences between samples or groups according to the ANCOVA and to logistic regression analyses”. In addition we have added a new column of differences between groups in Table 3.

8. We agree that there is an inconsistency in this paper between the aims of the study and the presentation of blood pressure in the abstract, under results and in the discussion chapter. According to the referee we have omitted these data from the abstract and turned down the importance of this observation in the discussion.

Referee 2 Francesco Lapi

1. We agree that the description of drug interactions needs clarification. We have replaced the word “anticholinergic” with “drugs affecting the central nervous system” in the referred sentence from the background section on page 5: "Particularly, anxiolytic-hypnotic agents, antidepressants and antihistamines that often exhibit central nervous system effects are associated with increased cognitive impairment, sedation and confusion”. We have also extended the description of interactions by “Consequently, multiple drug prescriptions are leaving elderly vulnerable to adverse reactions and harmful interactions between psychotropic drugs and between psychotropic drugs and drugs aimed to treat co-morbidities, often classified as inappropriate drug prescriptions” on page 5.

2. The description of the data collection is extended under Methods, paragraph Medical history on page 7 and 8 by the following sentence: “The physicians had access to the medical record of AD participants confirming given information. In addition the caregiver or a next of kin was encouraged to extend the medical history”.

3. According to the referees, inappropriate drugs are now classified according to the STOPP criteria, and this is added under Methods, paragraph Drug treatment on page 8. “Inappropriate drugs were classified according to the “Screening Tool of Older Persons Prescription (STOPP) criteria which comprise a list of drugs at risk of interaction and adverse reactions when combined with common illnesses in geriatric practice.” Furthermore, we have replaced “Beers criteria” with “STOPP criteria” in the discussion on page 12 and in Table 3.
4. According to both referees, a co-morbidity score has been included. See our response to Referee 1 answer number 5. A description of the co-morbidity score under Methods, paragraph Medical history on page 7 has been included: “A co-morbidity score was calculated for each participant by adding the number of age related diseases identified as AD risk factors providing a sum score of chronic health conditions”. The Co-morbidity score variable has been used in multivariate analyses (See also our answer number 5 to Referee 1 and changes in the Abstract conclusion “..., even after adjustment for co-morbidity”).

The competing interest declaration is updated with information about Pfizer’s role in the project in accordance with the editorial request.

The figure will be uploaded separately

The reference list is adjusted according to the style of the journal.

We hope that the present revision of the manuscript and the point-by-point answers to the referees’ comments are in accordance with your expectations. Thank you for reconsidering our manuscript.

Yours sincerely

Fred Andersen