Author’s response to reviews

Title: Neuropsychiatric symptoms in patients with dementia in primary care: a study protocol

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Author’s response to reviews: see over
To the editorial office
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Dear members of the BMC editorial team,

We would like to thank you for the valuable review of our manuscript "Neuropsychiatric symptoms in patients with dementia in primary care: a study protocol". Please find our itemized, point-to-point response to the comments of the reviewers below.

Yours sincerely,
Also on behalf of the co-authors,

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Paper entitled: Neuropsychiatric symptoms in patients with dementia in primary care: a study protocol

Authors: Petra Borsje, Roland B Wetzels, Peter LBJ Lucassen, Anne-Margriet Pot and Raymond TCM Koopmans

Referee 1:

1. The background needs to be reworked. The gap in the current literature needs to be explained more clearly. The authors seems to be arguing that the profile of NPS may be different in primary care compared with memory clinics/clinical settings – but there is no explanation as to why they would be different. There are a large number of studies described in the background that examine NPS. If the setting is critical, then this needs to be reported for each of the studies described. Some of the studies don’t have a setting identified, and there appears to be a mix of community and clinical settings. It seems that the bigger contribution that this study will make is the prospective examination of the relationship between caregiver characteristics and NPS.

Author’s reaction:
In line with the request of the referee, we reworked the background. We not only changed the text, but also added some new text.

Changes made to the text:
“High (cumulative) prevalence and (cumulative) incidence rates of NPS were found in these studies. In the multicenter PHRC REAL-FR cohort, a prevalence of 66% at baseline increased to 88% after 4 years [13]. In the MAASBED study, a prevalence of 80.9% at baseline increased to a cumulative prevalence of 88.9% after 2 years, and the cumulative incidence after 6-12 months was 74% in ambulatory patients of memory clinics or psychiatric services [15]. In the LASER-AD study, 33% of the participants were recruited from 24-hour care settings and 67% were living at home. The prevalence rates of NPS at baseline were 93.8% for at least one NPS, and 88.4% of the participants had a NPI score ≥ 4 in at least one domain. At 6-month follow-up, 96.2% had at least one NPS in any domain. Of these participants 80.3% had a persistent NPI score ≥ 4 in at least one domain [12].” (page 5,6).

“In Cache County, 62% of the participants with dementia had at least one NPS at baseline and 23% had a NPI score ≥ 4 in at least one domain. After 18 months, 95% of the participants had at least one NPS at baseline and 49% had a NPI score ≥ 4 in at least one domain. However, of the 5092 individuals who were enrolled in this study, 265 resided in nursing homes. Information was not provided on the percentage of the 329 participants with dementia who
resided in nursing homes [16]. In the Medical Research Council Cognitive Function and Aging Study, prevalence rates of 5.8% for confabulation to 50.3% for apathy were found in dementia patients. Incidence rates of 2% for anxiety to 61% for apathy were found after 2 years. Furthermore, persistence rates were 13% for confabulation and 66% for apathy. The percentage of participants who lived in institutions was 38% at baseline and 66% after 2-year follow-up. It appears as though the prevalence and incidence rates of NPS in community-dwelling patients with dementia are lower (23% to 50% and 49% to 60% respectively) than those of ambulatory patients of memory clinics or clinical centers and ambulatory patients of psychiatric services (66% to 96.2% and 74% respectively). Finally, the relationship between caregiver characteristics and caregiver distress and NPS was unclear in these studies.” (page 5,6).

2. The method does not appear to address the hypotheses. The hypotheses indicate that there will be differences in NPS between primary care compared with memory clinics/clinical settings – but only primary care participants are included in the study. If comparisons will be made with data from other studies, the method for doing this needs to be described. Which studies will be selected and how will comparisons be made? Also, the hypotheses should be directional. Rather than stating there will be differences you need to indicate which way you expect the differences to be – eg do you expect that NPS will be lower in primary care compared with memory clinics/clinical settings?

Author’s reaction:
We agree with referee that the method section does not address the hypotheses. The referee noticed an important omission in our manuscript. We actually do not plan to do a head to head comparison between ambulatory patients with dementia and those form memory clinics of clinical centres. The methods are not suitable to answer such a research question. Therefore we deleted that hypothesis.

Changes made to the text:
We deleted the following sentences: “We hypothesize that patients with dementia in primary care represent a heterogeneous group and will show a different course of NPS compared to ambulatory patients with dementia in memory clinics or clinical centres. In addition, we hypothesize that informal caregiver distress in primary care is different compared to informal caregiver distress in memory clinics or clinical centres.” (page 7).

3. The predictor variables for the univariate analyses need to be listed in the data analysis section.

Author’s reaction:
We agree with referee that the predictor variables (independent determinants) for the univariate analyses need to be listed in the data analysis section.

**Changes made to the text:**

“Independent determinants will be multicomponent collaborative care (CONCERN), single component dementia CM, NPS at baseline, cognition and use of health care services (home care: nursing and domestic; use of day care services).” (page 17).

4. Will the predictor variables include whether the participant has had access to a specialised dementia service (eg. single component dementia case management)?

**Author’s reaction:**

Yes, the predictor variables (independent determinants) include whether the participant has had access to a specialised dementia service.

**Changes made to the text:**

“Independent determinants will be multicomponent collaborative care (CONCERN), single component dementia CM, NPS at baseline, cognition and use of health care services (home care: nursing and domestic; use of day care services).” (page 17).

5. Need to explain how drop-outs will be managed in the analyses.

**Author’s reaction:**

In line with the request of the referee we explain how drop-outs will be managed in the analyses.

**Changes made to the text:**

“Only data of patients and caregivers with complete follow-up of 18 months will be used for data analysis. Patient and caregiver characteristics of withdrawals (subjects included, but no data received) and losses to follow-up/drop-outs will be described and compared with the patients and caregivers who will complete follow-up.” (page 16).

6. Need to explain whether a participant who becomes institutionalized will still be followed up in a facility.

**Author’s reaction:**

We agree with referee that we need to explain whether a participant who becomes institutionalized will still be followed up in a facility.

**Changes made to the text:**

“If patients become institutionalized during follow-up, data collection will be continued with the same informant/informal caregiver. Patient and caregiver characteristics, baseline MMSE and
baseline NPI total scores will be compared to the non-institutionalized subjects. If these data are comparable, then they will be used for data analysis.” (page 16).

7. Reduce abstract – don’t need details of baseline demographic variables, secondary analyses or use of SPSS.

**Author’s reaction:**

We agree with referee that the abstract can be reduced by deleting detailed information of baseline demographic variables and secondary analyses or use of SPSS.

**Changes made to the text:**

We deleted the following (parts of) sentences: “age, gender, marital state, socio-economic status/educational level and profession”, “Secondary outcomes for patients with dementia are agitation, depression, cognition and quality of life; For the caregivers: depression, general health and quality of life. Data will be analyzed using SPSS 20.0.” (page 2).

8. In the background you refer to NPI total scores of 4 or more as being clinically significant. Given the NPI total score ranges from 0-144 – a score of 4 seems quite low. Is this correct?

**Author’s reaction:**

We agree with referee that a score of 4 or more on a total score seems quite low. However, a score on one symptom of the NPI can be clinically very relevant. In line with previous studies [8, 13, 14, 15, 16] we used the same definition of a clinically relevant symptom, a NPI score of 4 or more.

**Changes made to the text:**

“For each positive symptom, the severity and frequency are scored on the basis of structured questions administered to the patients’ caregiver. The continuous score for each symptom is obtained by multiplying severity (1-3) by frequency (1-4). In line with previous studies [8, 13, 14, 15, 16], a score of 4 or more on one symptom will be taken to indicate the presence of specific ‘clinically relevant’ symptoms. Caregiver distress is also assessed (0-5), but is not calculated in the NPI total score. Frequency and severity scores of individual symptoms can be multiplied (FxS score) and summed over 12 items, yielding a total NPI score that ranges from 0 to 144.” (page 11).

9. Language throughout needs to be improved. Eg “We will retrieve patients with dementia from the electronic medical files of these general practices.” Replace with “We will retrieve electronic medical files of patients with dementia from these general practices.” Page 8 – “The CMO judged that this project is NOT subject..”

**Author’s reaction:**
We agree with referee that the language throughout needs to be improved. This new version of the study protocol was edited for proper English language, grammar, punctuation, spelling and overall style by two of the native English speaking editors at American Journal Experts.

Changes made to the text:
“Adjustments have been made throughout the manuscript following the suggestions of the editors of American Journal Experts”.

10. Review the use of present tense throughout.
Author’s reaction:
We reviewed the manuscript to use a consistent verb tense.
Changes made to the text:
“Appropriate adjustments have been made throughout the manuscript”.

11. Replace periods in numbers with commas – ie 35.6 million rather than 35,6 million (page 3)
Author’s reaction:
In line with the request of the referee we replaced periods in numbers with commas
Changes made to the text:
“35.6 million people” (page 3), “7.3%, 5.8% and 5.7% respectively” (page 3), “Prevalence of agitation increased from 17.9% to 29.1%, apathy from 43.0% to 62.9%, disinhibition from 2.6% to 14.6%, hallucination from 2% to 4.6% and aberrant motor behavior from 13.9% to 29.1%” (page 5).

12. Provide more details on how patients are recruited – does their GP ring them and ask them if they are happy for their details to be sent to the researchers?
Author’s reaction:
We agree with referee that more details of patient recruitment should be given.
Changes made to the text:
“Patients and informal caregivers will be approached by letter. Informal caregivers are persons who are listed in the electronic medical files of the GP as the main informal caregiver and contact person. There will be no restriction in the amount of time that the informal caregiver spends with the patient. After the letter is mailed to the patient and informal caregiver, the GP will contact the patient or informal caregiver by telephone to stimulate participation in the study. The assessment interviews will take place at the patients home by a trained interviewer.” (page 8).
13. It would be good to include in the background a section describing the Dutch context of dementia services (i.e., a lot of the information on page 7 could be moved forward).

**Author’s reaction:**

We can imagine that the referee would like to move information about the Dutch context of dementia services on page 7 forward to the background. However, the description of the Dutch context is part of the definition of single component dementia CM and of CONCERN and therefore we decided to write this information in the method section.

14. Describe how caregivers are identified—do they need to spend a certain amount of time with the patient, etc.

**Author’s reaction:**

We agree with referee that there is no description of how caregivers are identified.

**Changes made to the text:**

“Informal caregivers are persons who are listed in the electronic medical files of the GP as the main informal caregiver and contact person. There will be no restriction in the amount of time that the informal caregiver spends with the patient.” (page 8).

15. The discussion could be moved around so that the section “The data will help GPs and other professionals....better treatment opportunities” could be moved to the end of the discussion as a better concluding comment.

**Author’s reaction:**

In line with the suggestion of referee that the discussion could be moved around and that the section “The data will help GPs and other professionals....better treatment opportunities” will be a more powerful concluding comment we reworked the discussion.

**Changes made to the text:**

The section “The current study will provide more detailed information about consequences of NPS for the quality of life of both patients and informal caregivers as well as the influence of NPS on depressive symptoms and experienced health state of the caregiver, which is clinically important. The data will help GPs and other professionals in planning follow-up visits and in the timing of offering psycho-education, psychosocial interventions and the provision of care. It will enlarge their awareness of NPS in their patients with dementia. An individually tailored approach for patients with dementia and their informal caregivers may offer more and better treatment opportunities.” is moved to the end of the discussion. (page 19).
Referee 3:

1. Some of the aims and hypotheses are not actually going to be accomplished in the study, for instance the comparison of the prevalence NPS in this population compared to other populations will only be indirectly compared as there is no memory clinic group in the present study.

   Author’s reaction:
   We agree with referee that the comparison of the prevalence of NPS in this population compared to other populations will only be indirectly compared as there is no memory clinic or psychiatric service group in the present study. The referee noticed an important omission in our manuscript. We actually do not plan to do a head to head comparison between ambulatory patients with dementia and those form memory clinics of clinical centres. The methods are not suitable to answer such a research question. Therefore we deleted that hypothesis.

   Changes made to the text:
   We deleted the following sentences: “We hypothesize that patients with dementia in primary care represent a heterogeneous group and will show a different course of NPS compared to ambulatory patients with dementia in memory clinics or clinical centres. In addition, we hypothesize that informal caregiver distress in primary care is different compared to informal caregiver distress in memory clinics or clinical centres.” (page 7).

2. More detail on how the general practitioners were approached to participate would be useful to understand potential selection biases.

   Author’s reaction:
   We agree with referee that more detail on how the GP’s were approached to participate should be given.

   Changes made to the text:
   “For this study, all 192 known general practitioners (GPs) in 114 general practices in the region West- and Middle-Brabant in the southern part of the Netherlands were invited to participate. All GPs of the 114 practices individually received a letter with information on the study and were invited to attend a meeting about NPS and the study. Announcements of this study were also posted on the websites of the regional GP corporations.” (page 7)

3. Could the authors provide some information on the accuracy of these codes for identifying people with dementia (P70, P20). One of the most challenging problems with dementia in primary care is that it is underdetected and this method of identifying patients may bias the sample towards a more severe spectrum of illness.

   Author’s reaction:
To our knowledge there is no information on the accuracy of these codes for identifying people with dementia. The ICPC is not a method to diagnose dementia, but a method for classification. GPs indeed will not be able to recognize all of the dementia patients in their practice. In the group of patients with a code for dementia, there will not be many patients who will not have dementia. On the other hand there will be more patients with dementia who are not identified and do not have a code for dementia in the electronic medical file. Referee is rightly pointing out that this may bias the sample towards a more severe spectrum of illness.

**Changes made to the text:**

“On the other hand, this may bias the sample towards a more severe spectrum of illness.” (page 18)

4. Additional information on how patients and caregivers will be approached to participate would be helpful.

**Author's reaction:**
We agree with referee that additional information about the approach of patients and caregivers should be given.

**Changes made to the text:**

“Patients and informal caregivers will be approached by letter. (page 8) After the letter is mailed to the patient and informal caregiver, the GP will contact the patient or informal caregiver by telephone to stimulate to participation in the study.” (page 8).

5. With only 3 assessments over 18 months I am concerned that the utility of the NPS measures will be limited given that important changes in NPS are likely to occur over shorter time periods which would be helpful to know. I would suggest increasing the frequency of measurement to every 3 months.

**Author's reaction:**
We agree with referee that important changes in NPS can occur over shorter time periods. We mentioned in the discussion that variations in course between two successive assessments will be unknown and this is one of the weaknesses in this study. As there is limited funding for this study we decided to choose a study design with a length of 1.5 years and 3 measurements (baseline, 9 months and 18 months) and not 1 year and 3 measurements (baseline, 6 months and 12 months). Despite this we are convinced that the data will provide valuable information on the frequency of NPS and on the long-term course of NPS in community dwelling patients with dementia.
6. The Charlson index may not be the best measure of medical comorbidity in a geriatric population, perhaps that authors could consider using the cumulative illness rating for geriatrics in its place.

**Author's reaction:**
Both Charlson Index and Geriatric Cumulative Illness Rating Scale show good interrater reliability: CI: 0.78 (95% CI: 0.67-0.86); CIRS-G (score): 0.66 (95% CI: 0.53-0.78) [Rodriguez MA Rev Esp Geriatr Gerontol 2012;47(2):67-70]. The comorbidity is assessed in an interview by the research assistant with both the patient and informal caregiver. To our opinion there is no advantage in using the Geriatric Cumulative Illness Rating Scale (CIRS-G) instead of the Charlson index.

7. There are no measures of the severity of dementia, the MMSE only measures cognition and has significant limitations. Perhaps an instrument such as the Global Deterioration Scale would be useful to include.

**Author's reaction:**
As we are studying patients with a diagnosis of dementia and living in their own homes and not in residential care facilities or nursing homes only few stages of the Global Deterioration Scale would be useful and thus not allow us to detect changes.

8. Although the authors state that the impact of service utilization will be assessed it is not described in any detail in the methods section.

**Author's reaction:**
We agree with referee that the use of health care services is not prescribed in detail in the methods section.

**Changes made to the text:**
“use of health care services (psychiatric services; home care: nursing, domestic; day care services; on waiting list for residential care facility or nursing home)” (page 10).

9. There is no sample size calculation presented or anticipated drop-out rate for this study, it is difficult to tell if the study is feasible without this information.

**Author's reaction:**
Referee is rightly pointing out that there is no sample size calculation or anticipated drop-out rate given for this study. We totally reworked the data analysis section and included information on the anticipated study population.

**Changes made to the text:**
According to the National Public Health Compass, developed and co-ordinated at the Dutch National Institute of Public Health and the Environment, absolute prevalence of patients with dementia in registrations of general practices is 20 per general practice per year. Based on their interest in participating 18 practices were selected. With an assumed response rate of 50% and loss to follow-up rate of 30% after 18 months, the expected study population will be 126 patients with dementia. In analysis of causal influences in observational data, as a rule of thumb 1 candidate predictor can be studied for every 10 patients. For logistic regression this rule can be relaxed to 5-9 events per candidate predictor [64]. The assumed prevalence rate of NPS in primary care is 60% [16,17]. The number of independent variables in this study will be 7. Therefore 126 patients with dementia will suffice for the regression analyses [64].

10. The statistical analysis is presented in a very superficial manner and would benefit from further detail. How are the authors going to account for the clustering of participants within primary care practices as observations from within a practice are not going to be independent of each other.

**Author’s reaction:**

In line with the request of referee We totally revised the data analysis section.

**Changes made to the text:**

“All data will be analyzed using the Statistical Package for Social Science 20.0 (SPSS 20.0). Descriptive analysis will be used for general patient and caregiver characteristics, disease characteristics and time to death or time to institutionalization. Only data of patients and caregivers with complete follow-up of 18 months will be used for data analysis. Patient and caregiver characteristics of withdrawals (subjects included, but no data received) and losses to follow-up/ drop-outs will be described and compared with the patients and caregivers who will complete follow-up. If patients become institutionalized during follow-up, data collection will be continued with the same informant/informal caregiver. Patient and caregiver characteristics, baseline MMSE and baseline NPI total scores will be compared to the non- institutionalized subjects. If these data are comparable, then they will be used for data analysis.

The frequency (point and cumulative prevalence), cumulative incidence, and persistence of symptoms are expressed as the percentage of patients with scores greater than 3 on any item of the NPI, at study onset and/or at any follow-up evaluations. Point prevalence will be defined as the proportion of patients with specific symptoms at each assessment. The accumulative prevalence will be defined as the proportion of patients developing a specific symptom on at least one assessment over the 18-month study period. The cumulative incidence will be rated as the proportion of patients who are symptom-free at baseline but
develop the specific symptom at subsequent assessments. A symptom will be considered as persistent if it was present on at least two subsequent assessments, regardless of time of first manifestation of the symptom. In addition, the proportion of patients with persistence of symptoms during all 3 assessments will be calculated.

Univariate analysis will be performed to identify determinants of NPS in patients with dementia in primary care as dependent variable for each assessment. Univariate analysis will also be performed to identify determinants of caregiver distress as dependent variable. Independent determinants will be multicomponent collaborative care (CONCERN), single component dementia CM, NPS at baseline, cognition and use of health care services (home care; nursing and domestic; use of day care services).

All determinants will then be tested in a multivariate regression analysis to determine their unique contribution to the course of NPS and informal caregiver distress. To take into account the clustering of patients with dementia/informal caregivers in general practices and the repeated measurements within patients random coefficient analyses will be used.

According to the National Public Health Compass, developed and co-ordinated at the Dutch National Institute of Public Health and the Environment, absolute prevalence of patients with dementia in registrations of general practices is 20 per general practice per year. Based on their interest in participating 18 practices were selected. With an assumed response rate of 50% and loss to follow-up rate of 30% after 18 months, the expected study population will be 126 patients with dementia. In analysis of causal influences in observational data, as a rule of thumb 1 candidate predictor can be studied for every 10 patients. For logistic regression this rule can be relaxed to 5-9 events per candidate predictor [64]. The assumed prevalence rate of NPS in primary care is 60% [16,17]. The number of independent variables in this study will be 7. Therefore 126 patients with dementia will suffice for the regression analyses.

Proportions (prevalence, incidence, persistence) can be estimated with absolute precision of 10% and a confidence level of 95% taking into account design effect of 1.25 based on an ICC of 0.05 and a mean clustersize of 6, assuming a conservative estimate of anticipated proportion of 50%. “(page 16,17).
“Adjustments have been made throughout the manuscript following the suggestions of the editors of American Journal Experts.”