Author’s response to reviews

Title: Does diagnosed comorbidity differ between elderly patients with and without dementia? Results from an analysis based on German insurance claims data.

Authors:

Kathrin Bauer (mail@kathrinbauer.net)
Larissa Schwarzkopf (L.schwarzkopf@helmholtz-muenchen.de)
Elmar Gräßel (Elmar.Graessel@uk-erlangen.de)
Rolf Holle (holle@helmholtz-muenchen.de)

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Author’s response to reviews: see over
Dear Ms Olino,

enclosed please find the revised version of the manuscript **MS 1123258197102077**

“Does diagnosed comorbidity differ between elderly patients with and without dementia?
Results from an analysis based on German insurance claims data”

We thank our reviewers for their valuable comments and suggestions which significantly improved both clarity and precision compared with the initial version. In order to ensure an easy traceability of the modifications made, please kindly note the attached point-to-point response.

Since we felt, that some of the amendments suggested by the reviewers would overload the manuscript text itself, we now provide two additional files. Would you please be good enough to take care of an online publication of the additional information as some kind of appendix.

Also, as recommended by the journal editors, we carefully adapted the entire manuscript according to the guidelines of “BMC Geriatrics” and sought the assistance of an English language editor.

We are convinced that the reworked manuscript addresses all previous points of concern in a satisfying manner and thus resubmit our paper for your kind consideration for publication in “BMC Geriatrics”.

We would be glad if you consider the manuscript for publication.

Yours sincerely,

Larissa Schwarzkopf

Enclosed:
- Manuscript tracked version (BMG_Geriatrics_MS1123258197102077_tracked.doc)
- Manuscript clean version (BMG_Geriatrics_MS1123258197102077_clean.doc)
- Point-to-point Response (point_to_point_response_MS1123258197102077.doc)
- Additional file 1: Sources of origin for considered comorbidity complexes
- Additional file 2: Table 6 Diagnosed comorbidity complexes of community-living dementia patients and control subjects stratified by gender

Please address correspondence to
Larissa Schwarzkopf
Helmholtz Zentrum München/ Institute of Health Economics and Health Care Management
Ingolstaedter Landstrasse 1
85764 Neuherberg
Germany

Phone.: ++49-89-3187-3994
Fax: ++48-89-3187-3375
Email: l.schwarzkopf@helmholtz-muenchen.de
Comments Reviewer Giovanni Zuliani:

1. Database analysis might have some intrinsic limitations, and this aspect has to be underlined by the Authors

- Within the strength and weakness section on page 16 we now reflect database-related limitations in more detail. In this context particularly the fact that insurants of AOK Bavaria SHI Fund might not be representative for the elder population as a whole was discussed more thoroughly (as a reference see Hoffmann/Icks, Gesundheitswesen, 2012).

First, the distinct SHI funds cover due to historic reason different clienteles. Our data analyses used data of AOK Bavaria SHI Fund, which is the market leading fund in the study region. However, it is known that AOK SHI Fund has a comparatively high share of insurants with low-income, low educational level and poor health status. Thus, the observed prevalence rates most likely overestimate the real prevalence within the entire population aged 65 and older. However, it has to be assumed, that the effect of overestimation affects the various comparison groups in a similar way, thus the presented ORs seem to be better transferable than the prevalence rates themselves.

2. The phenomenon of “under-diagnosis” in dementia patients has been already reported by some Authors; thus the conclusions are not really original.

- We are aware of the fact that our conclusion is not per se original but corresponding conclusions have not yet been drawn for Germany. Moreover, the phenomenon of under-diagnosis has so far scarcely been researched based on claims data but mostly based on hospital admission/discharge data or clinical examinations which means restricting to a rather selective subpopulation of dementia patients. With regard to the gender-stratified and the care setting-specific analyses our research picks out two aspects of comorbidity in dementia patients that have as per our knowledge not been investigated in such detail before.

3. I wonder whether the possible treatment of dyslipidemias in older patients with dementia would be useful; no evidences are available over 80 years of age.

- The analysis of treating dyslipidemias in older patients with dementia is for sure an interesting research topic. However, the intention of our study was describing common comorbid conditions in dementia patients and not to
evaluate treatment options for common comorbid conditions. These issues are beyond the scope of our paper.

4. Are the findings about severe vision or hearing loss in dementia and controls in line with current Literature? I would expect both these conditions being associated with an increase in the prevalence of cognitive impairment.

Unfortunately, only few studies investigate the association of dementia with vision and hearing problems. Thus, it is difficult to assess their association with dementia comprehensively. For vision loss, Holroyd et al. reported that corresponding symptoms might accompany dementia disorders (Holroyd et al., Survey of ophthalmology, 2001), and Rogers et al. found that visual problems might precede the symptoms of cognitive decline (Rogers MA et al., American journal of epidemiology 2010). From our point of view a negative association seems more likely.

In a quite recent study Lin et al. described an inverse association between hearing loss and incident dementia (Lin FR, et al. Archives of neurology, 2011) without being able to name a definite explanation. Instead, a range of explanations is discussed, e.g. neurobiological processes, a link through the exhaustion of cognitive reserve and social isolation.

Keeping the still inconclusive findings in mind, we would like to point the reviewer's attention to the fact that „documented morbidity” might to some extent not reflect „existing morbidity” as pointed out within the discussion section on page 12. We indeed believe that the prevalence of vision respectively hearing impairment of individuals with dementia is not lower than in individuals without dementia. However, these impairments are very likely to remain undiagnosed because a) patients might have reduced capabilities to communicate their problem, b) family members and physicians might misinterpret non-reaction on verbal communication or disorientation/not finding things as symptoms of dementia instead as a result of hearing and vision loss and c) physician might not consider a treatment of vision and hearing loss (for example by prescribing glasses or hearing aids) as worthwhile in dementia patients. As a consequence, ICD 10 codes for vision and hearing impairment do not appear in line with the epidemiological prevalence of these conditions within the claims data. Corresponding information was added on page 12:

"Deficits in communication seem also to be a possible explanation for the lower prevalence of diagnosed vision and hearing impairment in individuals with dementia."

5. I suspect that the lower prevalence of hypertension in demented individuals might be related to another phenomenon other than under-diagnosis that is the “normalization” of blood pressure with progression of dementia (see Skoog I et al. Lancet 1996).

We thank the reviewer for bringing up this alternative explanation of our finding. We added a few sentences dealing with this issue on Page 11 of the manuscript.
"Except for hypertension, the chance of being affected by these comorbidity complexes was higher for dementia patients in our study as well. Our finding of an inverse association of hypertension and dementia might be explained by the importance of age at hypertension exposure: midlife blood pressure eventually is the more relevant predictor of dementia development compared to hypertension in late life. The decline of blood pressure in late-life might be secondary to the brain lesions and may give the impression of a "normalization" of blood pressure values in course of dementia progression, which might contribute to a lower prevalence of documented hypertension in individuals with dementia. This alternate explanatory approach is supported by our finding that the gap between dementia patients and non-demented control subjects is reduced when only community-living individuals are looked at (OR = 0.90; vs OR = 0.76) and nursing home residents – who are older and most probably in a more advanced stage of dementia – are disregarded."

In addition, we also adapted the corresponding paragraph on page 13.

"In this context, some comorbidity complexes from our analysis stand out. Hypertension is the most surprising example, as one would expect a similar occurrence of hypertension in the case and control group. Yet, the odds of having a documented hypertension ICD-10 code were lower for people with dementia in our analysis. We already provided explanations in a previous paragraph, yet those are unconfirmed hypotheses. Therefore, we also want to bring up the potential under-diagnosis of hypertension."

6. Muscular skeletal: the most important difference between the 2 groups is the lower prevalence of low back pain (59% vs 49%). How the Author read this data? Deficit of communication?

Regarding the different prevalence rates of low back pain we would like to refer to the general discussion on diseases of the musculoskeletal system and the connective tissue on page 12, which also applies to low back pain as a more specific case of musculoskeletal diseases. Basically there are at least two possible explanatory approaches: One is pathophysiological and refers to altered pain processing in individuals with dementia (for details see citation, Schreder et al 2009). The other one is that individuals with dementia face difficulties to make their environment aware of pain and discomfort. Schreder et al conclude that the available literature on pain in dementia is sparse, but suggests that pain may not be adequately treated in patients with dementia. This accordingly applies to back pain. The aspect of insufficient communication might be especially pronounced in more advanced stages of dementia where interpersonal verbal communication is almost impossible. Within the reworked manuscript we put more emphasis on the second aspect by modifying the discussion on page 12 as follows:

"An exception might be diseases of the musculoskeletal system and connective tissue. They usually manifest in pain, and thus could be negatively associated with dementia because of altered pain processing. The inappropriate communication of pain is another likely reason which may contribute to the negative association. With progressing dementia the capabilities to express and especially to verbalize pain decrease step by
Step. Thus, individuals with dementia might face difficulties in raising awareness for their physical pain.”

7. No differences were found in cancer prevalence between demented and controls. This data do not agree with previous results from Roe CM et al. (Neurology 2010). Could the Authors make some comments on it

First, even though there is only a small difference in cancer prevalence (25.0% case vs. 27.5% control), the OR suggests a negative association between dementia and cancer (OR 0.89 (0.85–0.94) p<0.001), which also applies to the stratified analysis. Therefore we would like to disagree that we found no differences in documented prevalence. Second, Roe et al distinguished several dementia subtypes and tested a) whether prevalent dementia is associated with future hospitalizations for cancer and b) whether a history of cancer at baseline is associated with a future diagnosis of dementia. This is basically another research objective than to assess cancer prevalence in individuals with dementia. However, they only found a significant association between dementia and cancer hospitalization for individuals with Alzheimer’s dementia (who have a lower rate of future cancer hospitalizations) but not for vascular forms. As we do not account for dementia subtypes, there might be opposing effects in different types of dementia that cancel out each other in our analysis.

Besides the mixed findings of Roe et al., other studies by trend suggest a negative association which is partly explained by common biological mechanisms [1,2], but also by the assumption that physicians might less thoroughly look for cancer among individuals with dementia, indicating a bias due to underdiagnosis [4]. Survival bias (cancer patients die before dementia onset) seems to be an additional contributing factor [1].

References for the answer of this question:
1) Page 2, first full paragraph, line 4 – What is meant by “pathophysiological variances”?

- By using the term “pathophysiological variances” we intended to express that the dementia syndrome is associated with a change in pathophysiological mechanisms (compared to individuals without dementia). This means that individuals with dementia face a particular risk for developing certain comorbid conditions which differs from the risk of non-demented individuals due to purely medical (dementia-related) reasons. To avoid confusion we reworded the phrase on page 4 as follows:

“Different prevalence rates of diagnosed comorbidity might to some extent be explained by a (dementia-related) change in pathophysiological mechanisms which eventually results in different risks for individuals with and without dementia to develop a distinct comorbid condition.”

2) Were any of the earlier studies comparing persons with and without dementia done with health insurance (administrative) data? The introduction should include a sentence that mentions the data source(s) for each of these (references 4-10 and 12).

- We now mention explicitly the data sources of the reference studies on page 4:

“Cross-sectional population-based studies can be considered as some kind of gold standard to assess the prevalence of comorbidity in individuals with and without dementia since they include a representative sample of individuals at risk. However, this comprehensive research approach is rarely chosen [12]. Instead, most previous studies drew conclusions on comorbidity based on hospital admission respectively discharge data [4, 7, 9, 10, 13] which does not reflect true prevalence rates, owing to the fact that only a small share of all patients undergoes hospital treatment. In this end, insurance claims data [6, 8] which include all individuals who seek any kind of inpatient or outpatient treatment seem to be a less selective approach, since less severe treatment occasions (which do not require hospitalization) are also accounted for.”

3) Page 5, first full paragraph, line 4 - Do the “nursing homes” mentioned here differ from the “care homes” in Table 1?

- We are grateful for the reviewer’s detailed look at our labeling. Indeed, within table 1 the term “care home” was used as a synonym for “nursing home”. To avoid confusion we now consequently use the term “nursing home” to describe the institutional setting. Moreover, we reworded the term “living at home” in table 1 by “living in community setting” to further emphasize the different care settings.
The LTCI domain “institutional care” exclusively addresses individuals with “Heimpflegebedürftigkeit” (i.e. need for institutional care). These individuals are either cared for in nursing homes or in special wards within residential homes for the elderly. These wards are run in a comparable manner as nursing homes. Thus, it can be concluded that all individuals who receive payments for “institutional care” are basically nursing home residents – either in “real” nursing homes or in nursing home-like wards of residential homes for the elderly. We did not account for institutional care in homes for the handicapped which is pointed out in the reworked manuscript on page 6. However, since homes for the handicapped are expected to play a minor role we believe that our selection strategy describes the institutional setting quite well.

"For the living environment-specific analysis, the institutional and the community setting were distinguished, based on payments for a component of long-term care insurance (LTCI) called 'institutional care', which is the only parameter within German claims data to conclude on an individual’s care setting. This service domain is only available for individuals who are institutionalized within nursing homes respectively special wards of residential homes for the elderly. Assuming that institutional care is only affordable with LTCI coverage, individuals receiving no LTCI support at all respectively no LTCI support for ‘institutional care’ fall into the community setting. Subjects with an uninterrupted sequence of LTCI support for ‘institutional care’ in 2006 were allocated to the institutional setting and subjects for whom the starting date of payments for institutional care was in 2006 were classified as transferring to a nursing home. Details about the allocation to settings are available elsewhere. After excluding institutionalized individuals as well as transferring individuals, 5,524 cases and 27,595 control subjects were suitable for the community-setting analysis. However, our approach does not allocate residents of homes for the handicapped to the institutional setting."

Dementia (ICD 10-codes F00, F01, F02, F03) is one of the 17 conditions considered for calculating the Charlson Index. As a consequence, when comparing the Charlson Index of individuals with and without dementia, the dementia patients have a disadvantage. Compared to non-demented control subjects they have at least one additional comorbid condition contributing to the Charlson Index, which is dementia itself. To allow a fair comparison of disease burden apart from dementia we calculated the Charlson Index for both groups including all Charlson conditions except of dementia. This modified version of the Charlson Index hence only includes 16 conditions and in individuals with dementia its score is lower than the score of the
original Charlson Index due to the disregard of dementia. The reason beyond calculating a modified Charlson Index is now referred to in more detail on page 7.

"The original version of the CI includes 17 disease categories with dementia being one of them. Thus, dementia patients with an equal comorbidity profile as non-demented control subjects would have a higher CI due to the fact that dementia contributes to calculating the index score. To reflect disease burden apart from dementia we calculated a modified version of the CI which consists of only 16 disease categories and does not include dementia in calculating the index score."

Moreover, within the reworked manuscript we now always refer to the "Modified Charlson Index".

6) The Results should begin with a paragraph describing the entire population – its average age (standard deviation and range), percent male and female, etc. Either a new table should be included or a column presenting these data should be added to the right hand side of Table 1.

- As suggested by the reviewer, the reworked results section starts with some baseline information on the entire study population on page 8, which is also included within a new column in Table 1. To avoid information overload, we split Table 1 into two new tables, the first describing the case and the control group as a whole and the second containing a gender-stratified description.

"The study population included 37,753 individuals aged between 65 and 103. 27,012 (71.6%) individuals within the study population were female and 33,119 individuals (87.7%) lived within a community setting during the entire observation period."

7) Information describing the male and female populations should be added to the beginning of the paragraph on Gender-stratified case-control comparison.

- The gender-stratified comparison on page 9 starts now with a brief description of the male and the female population as suggested by the reviewer.

"As pointed out within table 3, female individuals with and without dementia were older than their male counterparts (p <.0001, both) and in both groups fewer women than men stayed in a domestic environment (p <.0001, both)"

8) Second paragraph, first sentence – Different “aspects” of what?

- The finding that different prevalence rates for documented comorbidity were found in dementia patients and non-demented controls is supposedly
explainable via different approaches, which are a) differences in real prevalence, b) differences in health seeking behaviour and c) differences in diagnosis and treatment patterns. The term “different aspects” was intended to refer to these different explanatory approaches. To ensure an unambiguous reading the first paragraph on page 11 starts with a reworded sentence:

“To comprehensively judge our findings different explanatory approaches regarding the observed prevalence rates of documented comorbidity have to be considered.”

9) Page 10, first full paragraph, line 4 – Not “feasible” but “reasonable” or “logical.”

• We thank the reviewer for this linguistic remark and chose the term “reasonable” instead of “feasible” within the reworked manuscript.

10) Page 10, first full paragraph, line 6 - “overlooking or simply ignoring less severe diseases” – Or making the conscious decision that because of the patient’s condition, these are of lower priority for diagnosis or treatment.

• As per our view the reviewer raises an important issue disregarded so far. To account for this alternative interpretation we added the following sentence on page 13 of the manuscript.

"Moreover, physicians might come to the conscious decision not to treat these comorbidity complexes based on the assumption that therapeutic interventions for these not per se life-threatening conditions reduce the dementia patients’ remaining quality of life disproportionately compared to the beneficial effects of treatment. However, some kind of therapeutic nihilism based on the thinking that guideline-conform therapy of these conditions is not worthwhile in a cognitively impaired population can also not be fully excluded."

11) To me the most interesting finding of this study is the higher prevalence (odds ratio) of many conditions of men with dementia versus men without dementia in comparison to the lower prevalence for women with dementia versus women without dementia. Unfortunately, the paragraph in the Discussion on Comorbidity and Gender is incomplete. It does not cite any other studies with similar findings. (...). The authors should provide a more complete discussion of the literature in this paragraph. Perhaps a more fundamental issue that needs to be better addressed is what would explain the finding of more multimorbidity among older demented men than women.

a) Is there something different in the physiology of men with dementia versus women?
b) Could this difference be due to differential case-finding between the two genders?

c) Specifically, is there something about the Bavarian healthcare system or this particular health plan that would result in more thorough medical examinations of men with dementia than women?

d) Further, all of the men in this study were born before 1941. Presumably a high proportion of them would have been in the military during World War II. Would they qualify for any military veterans’ benefits that require in-depth medical evaluations?

e) Could there be a selection effect relating to gender and when in the course of dementia men versus women are diagnosed (this, case-finding)? Male dementia patients living with a spouse should be diagnosed earlier in the course of the disease because their spouse will notice dementia symptoms and motivate them to visit the doctor, leading to the identification of more co-morbidities. Females living alone may be diagnosed later in the course and therefore have fewer diagnoses.

Within the discussion section the paragraph on gender and comorbidity was fundamentally reworked and more emphasis was dedicated to relating to the current body of evidence. Basically following issues were addressed:

- When looking at the prevalence of the different disease groups in men compared to women similar comorbidity patterns emerged for cases and controls and in the end men suffered from different comorbidities than women but not necessarily from a greater amount of comorbidity. To stress this, within the reworked manuscript the discussion on comorbidity and gender on page 14 starts as follows:

  "Basically, men with and without dementia do not have a higher comorbidity burden than females with and without dementia, but there is a gender-specific comorbidity profile. The comorbidity patterns of male and female individuals observed in our study are similar to patterns found by other authors who assessed gender-specific multimorbidity. Both, women with and without dementia suffer more frequently from osteoporosis and thyroid dysfunction as well as from mental health problems, but less frequently from cancer and cardiovascular diseases."

- Unfortunately, we could not identify another study that compared comorbidity of male and female individuals with and without dementia. The papers investigating multimorbidity (like Schäfer and Rizza) do not report separate results of the number of chronic conditions of male/female dementia subpopulations, which is clarified within the discussion section on page 14.

To our knowledge, other studies investigating dementia and comorbidity did not focus on gender differences rendering our finding even harder to explain. We did not find sound literature providing explanations for comorbidity differences based on different physiology of men and women with dementia, but dementia research is far from being complete. Hence, the effect of dementia on the development of other
medical conditions might indeed differ for men and women, despite corresponding evidence is lacking.

- We thank the reviewer for drawing our attention to the multimorbidity risk ratios for male and female dementia patients reported by van den Bussche et al. and included this information in our discussion on page 14.

"Yet, the effect of gender on the case-control comparison was striking. When comparing cases and controls for the male and female population separately, gender did have a significant influence on the ORs for half of the comorbidity complexes. Also, except for four conditions (fractures/injuries, purine/pyrimidine metabolism disorders, cancer, anemia) the ORs of the male sample exceeded the corresponding ORs of the female sample for the respective comorbidity complex. This implies that the documented prevalence of comorbidity complexes is more similar between female cases and controls. For example, women with dementia had a OR of 3.01 of being diagnosed with incontinence, whereas the OR of a male dementia patient of being diagnosed with incontinence was even 4.19. Van den Bussche et al. also found that compared to subjects without dementia men with dementia have a higher relative risk of multimorbidity than women with dementia (RR 4.9 vs. 3.4)."

Regarding the possible explanatory factors for different comorbidity patterns of men and women raised by the reviewer we would like to comment on:

Ad a)
With regard to different pathophysiological processes we would like to refer to the previous paragraph and the amendment on page 14 of the reworked manuscript.

"We did not find sound literature providing explanations for comorbidity differences based on different physiology of men and women with dementia, but dementia research is far from being complete. Hence, the effect of dementia on the development of other medical conditions might indeed differ for men and women, despite corresponding evidence is lacking.

Ad b)
As per our view, different case finding is the most probable explanation for the observed differences. Potentials for differences in personal interaction between male respectively female patients and their physicians - which results in different diagnoses – are addressed on page 15 within the reworked manuscript:

"We assume that the personal interaction between male patients and their physicians differs in comparison to female patients. One factor might be that the majority of physicians are males themselves which might ease talking about sensitive issues. Moreover, symptoms for diseases (e.g. cardiac infarction) have mainly been deduced from male patients, thus physicians might be more aware of the symptom profile in male patients than in female ones. As an additional factor one might argue, that men might communicate their interests with more impetus
than women. However, as far as we are able to judge these effects apply to both, men with and without dementia and might more rather explain different prevalence rates between men and women than different ORs in the gender-stratified case control comparison.”

Ad c)
Within the German SHI system, all funds are legally obliged to offer the same range of services. These services are available to all insurants irrespective of age, gender or income. We strongly believe that there is no health care system-specific or health plan-specific explanation that would result in more thoroughly medical examinations of men with dementia compared to women with dementia.

Ad d)
The German health care system does not provide special health care benefits for veterans of World War II but there are some specific pension claims. However, medical examinations that might have been required to benefit from these pension claims would have been conducted long before 2006. (In Germany the statutory retirement age is 65 and the youngest veterans of World War II are born in the late 1920ies. Hence, they would have reached the statutory retirement age about ten years previous to the year of observation). Altogether, we are convinced that eligibility for veterans’ pension claims does not lead to a more thoroughly medical examination of aged men compared to aged women in the case of Germany.

Ad e)
Concerning other case-finding related explanations, we already mentioned within the original version of the manuscript that living together with a spouse might contribute to more regularly physician visits of male dementia patients. The situation described by the reviewer fits perfectly well with our own thoughts. However, within the previous version of the manuscript we might not have put sufficient emphasis on this explanatory approach. Within the reworked manuscript we now dedicate more attention to the role of spousal instigation of medical examination and treatment on page 15.

“The fact that male dementia patients probably still live with a spouse who is vigilant about regular physician’s visits whereas elder women are more often single-living and have no advocacy caring for their health care seeking behaviour very likely adds to the effect, too.”

12) There is a large difference in the proportion of males versus females living in a care home. It would be interesting to see how the ORs of males and females compared for the community sample, that is, the sample from which the institutionalized patients were removed. 3.

We are grateful for the valuable comment of our reviewer and had a closer look at the gender-specific odds ratios for the community-living population only. Compared to the gender-stratified analysis which also
included transferring and institutionalized individuals the relative change of ORs was in general more pronounced in women than in men except for CAD, cardiac insufficiency and insomnia. However, the ORs almost all changed in the same direction. The only exceptions were renal insufficiency (increase in men, decrease in women) and psychotic/neurotic disorders (no change in men, increase in women). For both genders we observed a particularly strong decrease of ORs regarding Parkinson's, pneumonia, incontinence, fluid/electrolyte disorders and fractures/injuries as well as a particularly strong increase of ORs regarding low back pain, dyslipidemia, fall risks/dizziness and lower limb varicosis. In addition, there was a strong percentaged increase of diagnosed cancer in men and of diagnosed vision reduction in females.

We added a corresponding paragraph to the results section which deals with the gender-specific aspects of the community-based analyses. In this regard we consciously decided against providing an additional set of corresponding ORs. Since we already present a comprehensive and complex insight into comorbidity patterns of individuals with dementia we felt that adding the suggested information within a separate table would be more confusing than enlightening for the audience. However, corresponding information is made available for the interested readership as an additional file as pointed out on page 10.

"In the community setting, the likelihood of a dementia patient of being diagnosed with a comorbidity complex was higher than in the main analysis, except for Parkinson’s, pneumonia, incontinence, fluids/electrolyte disorders, fractures and injuries, stroke and cardiac insufficiency. A gender-stratified analysis of the community-living population revealed a particularly strong decrease of ORs regarding the first five of these comorbidity complexes for both genders and particularly strong increase of ORs regarding low back pain, dyslipidemia, fall risks/dizziness and lower limb varicosis. Altogether, the percentaged change in ORs was in general more pronounced in women than in men. Further information on this gender-stratified analysis is made available as additional file 2.”

13) Table 1 should have columns for the p values of the comparisons between males and females in the case and control groups.

- Within the reworked manuscript table 1 was split into two separate tables. The first describes case and control group as a whole inclusive of p-values. The second contrasts male individuals with and without dementia as well as female individuals with and without dementia, whereupon p-values are reported for both comparisons.
Comments Reviewer Daniel Malone:

1. The study has many thousands of patients and therefore even trivial differences between the two groups will be statistically significant. (…) Furthermore multiple tests are conducted on the same data thus increasingly the likelihood of spurious findings.

   - We thank the reviewer for pointing our attention to this methodological aspect. We agree that in large sample sizes a statistically significant difference might not per se be clinically relevant. For the reworked manuscript we performed a Bonferroni adjustment resulting in a new significance threshold of 0.0017.

   Since we tested 30 comorbidity complexes we addressed multiple testing by setting a Bonferroni adjusted significance level of \( p < 0.0017 \) (0.05/30).

   Moreover, all tables contain information on prevalence rates, ORs and 95%-confidence intervals in addition to \( p \)-values. This additional information seems well suited to judge our findings more comprehensively.

   However, we felt that aspect needed to be emphasized a little more and refer to the issue within the discussion section as a methodological limitation on page 17.

   "Besides these more content related aspects it has to be mentioned that owing to the large sample sizes even small differences in documented prevalence of comorbidity become statistically significant despite they might not per se be clinically relevant. We tried to address this issue by reporting adjusted prevalence rates, ORs and 95% CIs in addition to \( p \)-values in order to allow a more comprehensive judgment of our findings."

2. What is meant by the statement: "what extent do discrepancies in health care provision contribute?"

   - Our interest was to highlight, that different prevalence rates of diagnosed comorbidities might be the result of different factors, which are 1) a real difference in disease prevalence and 2) a seemingly difference due to under-diagnosis respectively under-treatment. The term “discrepancies in health care provision” was intended to express, that dementia patients and non-demented controls might have different attitudes within their health care seeking behaviour (i.e. given a certain condition there are different probabilities within both groups to visit a doctor) and even physicians might have different attitudes to treat a certain condition. To avoid misunderstanding the sentence on page 4 was reworded as follows:

   “Different prevalence rates of diagnosed comorbidity might to some extent be explained by a (dementia-related) change in pathophysiological mechanisms which eventually results in different risks for individuals with and without dementia to develop a distinct comorbid condition. In this case, different prevalence rates of documented comorbidity reflect a really existing- and medically reasonable - difference regarding the occurrence of..."
a comorbid condition. However, differences in documented prevalence might also to some extent be explained by a different health care seeking behaviour of respectively a different attitude towards health care service provision for individuals with and without dementia and hence more likely reflect under-diagnosis and under-treatment of conditions with a comparable real prevalence rate.”

3. What is the purpose of creating “dementia quarters”? Does quarter refer to a time period – such as a quarter of a year (it appears this is the case), or something else? This terminology (“dementia quarters”) is unconventional and it is recommended to be stricken from the paper.

- Within the German SHI system physicians report their diagnoses not on a daily base, but the point of reference is a distinct quarter of a year. Therefore, we decided to base our selection process on this three months period. The detailed concept of dementia quarters is described in Schwarzkopf L, et al:

  Excess costs of dementia disorders and the role of age and gender an analysis of German health and long-term care insurance.

  In brief, dementia patients were identified by means of physician diagnoses, hospital diagnoses and anti-dementia drug prescriptions by constructing ‘dementia quarters’. These represent quarters with at least one documented dementia-specific ICD-10 code or with at least one filled prescription for a dementia-specific drug. To avoid misinterpretation of the term ‘dementia quarter’ the paragraph on page 5 was reworded as follows:

  “Since in the German SHI system physician diagnoses always refer to a distinct quarter of the year, each quarter of the years 2005 and 2006 was screened for the documentation of dementia-specific diagnoses (ICD-10 codes ‘F00’, ‘F01’, ‘F02’, ‘F03’ and ‘G30’) or anti-dementia drugs ((ATC codes N06DA (cholinesterase inhibitors) and N06DX01 (memantine)). To improve the validity of diagnoses the analyses accounted only for those individuals who had at least one corresponding dementia indicator during three out of four consecutive quarters. Non-demented control subjects were randomly selected from the remaining insurants without any dementia indicator in 2005 and 2006.”

4. What age matched on nearest year? Please be more specific.

- As supposed correctly matching was performed based on year of birth which is now mentioned explicitly in the text on page 5

  “They were matched by age based on year of birth and gender in a 4:1 ratio”

5. Don’t report matching results in the methods. This belongs in the results section.
• We totally agree with the reviewer that result should not occur within the methods part of a manuscript. However, since the matching procedure was an essential part of the sample selection procedure we do not feel that reporting the matching results is a break of this general rule. Therefore, we kept the information in the methods section within the reworked manuscript, too.

6. The authors should provide references for the “other studies” mentioned in this sentence regarding identification of chronic conditions. “The choice of the 30 final diagnosis groups was on account of their prevalence, their frequent mention in other studies”

The reference studies have already been mentioned on page 7 when the baseline set of 52 comorbidity complexes out of which the final set of 30 complexes have been selected was introduced. However we no put stronger emphasize on clarifying the selection process itself on page 7:

“The choice of comorbidity complexes is based on a list of 46 chronic conditions compiled by Schäfer et al.(...) Additionally, single ICD-10 codes disregarded by Schäfer et al., but highly prevalent (prevalence >10%) in our sample, were assessed. Some of these were added to existing complexes, and some formed new complexes and were added to the list of conditions, as well as some groups that were added after a review of disease groups commonly chosen by other authors [5-10, 12, 17-24]. As a result, 52 comorbidity complexes were assembled and reviewed. For our analyses, we included all complexes which had a) a prevalence of at least 15% within the case or the control group of our study population or which were b) accounted for within at least five of the reference studies [5-10, 12, 17-24]or which were c) considered as being of high medical interest within a thoroughly appraisal by the authors. Multiple mentioning of conditions was allowed (e.g. highly prevalent, and frequently mentioned in previous studies). By this approach 30 comorbidity complexes were finally considered. Their source of origin is accessible as additional file 1.”

7. Every statement in the results that infers the groups are similar or alike should have the result from a statistical test also reported. For example, the authors state in the 1st paragraph of the results that the case group had a “slightly higher” value of the Charlson score than controls. What does slightly higher mean? Is this difference statistically significant? Avoid terms such as “slightly” – either it is or it isn’t higher.

• We share the reviewers opinion that a difference is either statistically significant or not. Therefore we dropped the meaningless term “slightly” and report the corresponding p-value and information on statistical significance instead.
8. The authors should state the results represent the “prevalence of comorbid conditions.” The study only examines the prevalence on condition, not the incidence. This should be made more explicit in the reporting of the study results.

- We now explicitly mention that prevalence in 2006 was our point of reference on page 6 of the manuscript.

"We analysed the prevalence of comorbid conditions based on 2006 inpatient and outpatient diagnoses, which were grouped to 30 comorbidity complexes."

9. Table 1 needs to contain p-values. Are there significant differences between the groups with respect to age, environment, care level?

- Table 1 was now split into two tables (case and control group as table 1, gender aspects as table 2). Corresponding p-values have been amended.