Author's response to reviews

Title: The influence of age, gender and socio-economic status on multimorbidity patterns in primary care. First results from the MultiCare Cohort Study

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Author's response to reviews: see over
Manuscript resubmission: The influence of age, gender and socio-economic status on multimorbidity patterns in primary care. First results from the MultiCare Cohort Study.

Dear Editor

Thank you very much for the report of the reviewers and for the opportunity to resubmit a revised version of this paper. We highly appreciate the constructive criticism and have revised the paper carefully. We hope to have met all the suggestions satisfactorily.

On the following pages you will find answers to each comment. To facilitate reading, the original comments of the reviewers were copied into this letter. Changes in the cited sections of the manuscript have been underlined.

A) Reviewer: Thomas O’Dowd

1) The authors divide their multi-morbidity findings into 2 patterns, that of “ADS” by which they seem to mean psychosomatic illnesses plus pain and those of cardiovascular / metabolic disorders. They show that ADS disorders and pain were more prominent in females while cardiovascular / metabolic disorder were commoner in males. While this finding is of interest to clinicians they are either ambivalent about the finding and seem anxious to downplay this in their conclusions by stating that there is no evidence that female gender is associated with higher morbidity burden. It seems gender analysis has revealed interesting patterns of multimorbidity disease but the authors are not sure about this in the end.
We appreciate that the reviewer points to a misleading formulation in the conclusions section (first paragraph). We clarified this: "We found that female gender is not generally associated with a higher morbidity load as many studies suggest – instead it seems to depend on the type of multimorbidity considered. Women seem to be more vulnerable to ADS and pain-related morbidity while men might more often suffer from cardiovascular and metabolic diseases."

2) They give the household adjusted income as €1,412 but do not state over what period of time this referred to. It seems to refer to per month later in the paper.

We clarified this:

a) in Table 2, 4th row, 1st column: "Household-size adjusted net income per month: mean ± sd",

b) in the methods/data collection section (final paragraph): "Income was reported as household-size adjusted net income per month, which is calculated as household total net income per month divided by the equivalised household size, which gives 1.0 to the householder, 0.5 to other household members aged 15 or over and 0.3 to each child aged less than 15 years old [16]. ",

c) in the results section (second paragraph): "The mean household-size adjusted net income per month at the present time was 1412 € [...]"

d) in the discussion/morbidity and multimorbidity patterns section (final paragraph): "Household-size adjusted morbidity also had an effect on the number of chronic conditions in general (0.3 diagnoses less for each step on the logarithmic scale, e.g. 1.100 to 3.000 Euros per month) [...]".

3) The introduction of household ownership is not discriminating as most people seem to be in private accommodation. Whether this is private rented or private owned is not clear but it does not seem to be a reliable measure of affluence or deprivation.

We would like to emphasize that "home ownership" (as one measure of deprivation) is discriminating as 40.3% of the patients own private homes (cf. table 2, row 5 and results, second paragraph) and 59.7% of the patients do not. The variable home ownership differs from the variable household type, which the reviewer probably refers to. Both variables are assessed with independent questions in the patient interview. We clarified the difference between both variables in the methods/data collection section (final paragraph): "The data collection of income was complemented by the assessment of home ownership (i.e. private owned homes in which the patients do not necessarily need to live themselves) serving as a measure of economic advantages or disadvantages accumulated over the life course [23]."
The variable household type describes the kind of household the patients live in (private home or protected institution) and their living arrangement (living alone or together with their spouse or family members). This information is assessed independent of the socioeconomic status of the patients (cf. table 2, row 8). It is analysed in our multilevel models in four groups: persons living at home alone (n=1,128; 35.4%; reference category), persons living at home with spouse (n=1,847; 57.9%), persons living at home with family members or others (n=153; 4.8%) and persons living in protected institutions (assisted living or retirement home) (n=61; 1.9%). We judge these groups as discriminating and in our opinion the number of cases is sufficient for our statistical models.

4) [...] The overall objective of this study is more complex than it appears as in order to analyse the influence of socio demographics on disease the authors will need to refer to the extensive deprivation literature and it does not appear that there are available national reference deprivation scores within the health services in their system.

We added some remarks on the association between social deprivation and morbidity among the aged including references (cf. introduction, 4th paragraph): "Many studies report a higher disease load in females and an increase in the number of chronic conditions with age [9]. In general, morbidity and mortality rates seem to be higher in elderly persons with low economic resources and low educational degree. [10-11] The Survey of Health, Aging and Retirement in Europe (SHARE) showed that older Europeans with a low educational level and wealth experience more cardiovascular disease, lung disease, arthritis, disability and higher mortality rates than their high socioeconomic status counterparts. [12] There also is evidence that multimorbidity is more common and more severe in persons with low socioeconomic status [9]."

We added the following references:

There is in fact no national reference deprivation score available in Germany. For this reason we discussed our findings regarding socioeconomic status with reference to other studies and German federal statistics if applicable (cf. discussion/socio-demographic data of multimorbid patients in primary care and their GPs sections, paragraphs 4-6).

5) To answer their objective requires more than descriptive statistics and will benefit from some simple modelling exercises.

We based our analyses on inferential statistics described in the methods/statistical analyses section (fourth paragraph): "We analysed the association of patient characteristics with the number of chronic conditions by multilevel mixed-effects linear regression allowing for random effects at the study centre and GP practice-within-study centre level. Age, gender, marital status, household type, education, degree of autonomy at former occupation, household-size adjusted net income and home ownership were used as independent variables."

6) They need to explain why they have chosen two particular multi-morbidity patterns or at least as it appears to me they have chosen cardiovascular / metabolic and ADS plus pain - this is a paper on its own.

We explained the choice of the multimorbidity patterns it in the methods/statistical analyses section (second paragraph): "Multimorbidity patterns were described according to the results of a factor analysis presented in another paper [15]. In short, these analyses were based on ambulatory data of insurants of the German statutory health insurance company Gmünder ErsatzKasse. Persons were included if they were aged 65 years and older and were permanently insured during the year 2006. The data set used for analyses consisted of 63,104 females and 86,176 males. In the above mentioned paper [15], correlations between diagnosis groups were analyzed by exploratory factor analysis based on a tetrachoric correlation matrix. We used an oblique (oblimin) rotation of factor loading matrices. The factors that result from this analysis can be interpreted as multimorbidity patterns (i.e. clusters of diagnosis groups frequently associated with each other) and each factor loading represents the association of the specific diagnosis group with a pattern. Factors were regarded as substantial if they had an eigenvalue ≥ 1.0. Diagnoses were assigned to a pattern if they had a factor loading of 0.25 or more on the pattern in charge. Additional file 1 shows the diagnosis groups assigned to the multimorbidity patterns of both genders including eigenvalues of the factors and factor loadings of diagnosis groups."

We gave reasons for the limitation to two of the three patterns in paragraph three and four of this section: "There were only very few patients with three or more conditions within the pattern of neuropsychiatric disorders, because we had to exclude patients with dementia at
baseline. For this reason we excluded the pattern of neuropsychiatric disorders from the figures showing the overlapping of multimorbidity patterns." – and – "Because of the low number of cases within the pattern of neuropsychiatric disorders we did not analyse the morbidity in this pattern separately."

7) There are 16 authors on this paper and there appears to be insufficient dialogue between the clinician members and the statistical / epidemiological members of the team. It will be useful for themselves if the authors can clarify their individual contributions to the paper. Cohort studies generally involve many people in the setting up and conduct of the work but not all need to be involved in each paper that ensues from the work.

The paper is a direct result of the work of all authors regardless of their discipline. They all had the opportunity to comment on the draft and approved the final draft of the manuscript. We did clarify the contribution of each author in the authors' contributions section: "HvdB, IS, HH, KW, MS and BW conceived and designed the study. BW and GS prepared the data for analysis. IS and GS analysed the data. IS drafted the manuscript. SH, AA, AD, JG, SRH, SW, WB, HHK, and OvdK participated in study design and implementation. All authors read and approved the final manuscript." The 16 persons authoring the manuscript are only a small part of the (scientific) study group of the project, which consists of 39 persons at the moment (cf. acknowledgements section).

8) The authors have requested publication in a clinical journal but the paper is as it stands it is overly statistical and insufficiently clinically oriented for the audience it has targeted.

In accordance with the reviewer we consider this paper to be mainly epidemiological in the first place, but it is still a long way until research in multimorbidity can be sufficiently clinically oriented. Until now there are only very few clinical studies and there are no guidelines for multimorbidity. Observational epidemiological studies can do some groundwork needed for both, intervention studies and clinical practice guidelines. However, we tried to extract some practical hints in terms of case finding issues related to everyday practice.

For example we still do not know exactly who are the multimorbid patients encountered in general practice. In our study we found some evidence regarding this matter – as maintained in the conclusions section (second paragraph): "[...] there seem to be at least two types of elderly multimorbid patients. First, there are patients with mainly cardiovascular and metabolic disorders, who are more often male, have an older age and a lower socio-economic status. Second, there are patients mainly with ADS and pain-related morbidity, who are more often female, but equally distributed across age and socio-economic groups."
These results can help setting priorities in daily routine care and can also be helpful for decisions regarding allocation of resources. However, we are aware of the need of further analysis in order to derive clinical implications from these results. For example, we need to analyse differences in risk factors and resources of our patients and observe how these differences influence the development of the patterns. There also is little known about long term outcomes of multimorbidity and multimorbidity patterns. And finally, there are also more analyses regarding the composition of the patterns to be done, e.g. the association between purely somatic diseases like joint arthrosis or rheumatoid arthritis and mental disorders like depression or anxiety in the ADS and pain pattern. The results described in our manuscript are the first step regarding these questions and we will conduct these further analyses when long-term longitudinal data from our project are available.

Besides, we considered our article as suitable for the journal as we did not understand BMC health services research as a purely clinical journal. Its scope is defined as "articles on all aspects of health services research, including delivery of care, management of health services, assessment of healthcare needs, measurement of outcomes, allocation of healthcare resources, evaluation of different health markets and health services organizations, international comparative analysis of health systems, health economics and the impact of health policies and regulations." The journal has also published a number of solely epidemiological articles, e.g.:

- Markos Minas, Nikolaos Koukosias, Elias Zintzaras, Konstantinos Kostikas, Konstantinos I Gourgoulianis
  Prevalence of chronic diseases and morbidity in primary health care in central Greece: An epidemiological study
  BMC Health Services Research 2010, 10:252 (28 August 2010)

- Martin Fortin, Catherine Hudon, Jeannie Haggerty, Marjan Akker, José Almirall
  Prevalence estimates of multimorbidity: a comparative study of two sources
  BMC Health Services Research 2010, 10:111 (6 May 2010)

- Gunter Laux, Thomas Kuehlein, Thomas Rosemann, Joachim Szecsenyi
  Co- and multimorbidity patterns in primary care based on episodes of care: results from the German CONTENT project
  BMC Health Services Research 2008, 8:14 (18 January 2008)

9) [...] They need to outline the rationale for their choice of multi-morbidity patterns and to attach appropriate significance to this along the gender lines they have applied. The rationale for the choice of the two multimorbidity patterns has been explicated in our response to comment 6. The patterns are not the result of a choice as they result from statistical testing and not from theoretical reasoning. The significance of the patterns with
regard to gender has been discussed in the corresponding paper (cf. reference 15). In our manuscript we found the same gender differences explicated in [15]. The patterns had been extracted for both genders separately. We found that there were slight differences in the composition of the patterns. A part of the differences between male and female patterns belongs to gender-specific morbidity. Gender differences in prevalence rates might to some extent also account for the different composition of the patterns.

B) Reviewer: Andrew W Murphy

I will now make comments in chronological order as the paper is read. I consider all these revisions to be minor discretionary revisions.

1) Abstract: It would be helpful, in the background section, if the multimorbidity patterns referred to in the paper were specified.
As suggested by the reviewer we referred to the patterns in the background section of the abstract: "[...] Our previous research has shown that multimorbidity can be divided into the multimorbidity patterns of 1) anxiety, depression, somatoform disorders (ADS) and pain, and 2) cardiovascular and metabolic disorders. [...]"

2) Introduction / Third Paragraph: ‘Recent Research’ includes reference to a paper from 2003 which does not appear so recent!
We replaced the reference from 2003 with a more recent one:

3) Methods: Data Collection: Reference is made to “ICD 10 Diagnoses, from patients’ charts, in the electronic documentation system of the GP”. Reliability information regarding this crucial aspect of the study needs to be provided.
We provided this information in the discussion/strengths and weaknesses section, paragraph 7: "The morbidity data were assessed in GP practices, which have been shown to be a less biased data source than patient self-reports [9]. But it also has been shown that the validity of claims-based diagnoses from German GP charts may be impaired by both, underreporting and overreporting. Underreporting mainly related to symptoms and less severe diagnoses frequently encountered in GP practice. Overreporting mostly applied to suspected, but not clinically confirmed diagnoses of chronic conditions. [63] The reliability of GP self-documentation (i.e. postal interviews) in cohort studies seems to be rather low. Over the
course of 4.5 years, 19% of the diagnoses of diabetes mellitus, 35% of coronary heart
disease, and 45% of stroke disappeared in the GP documentation of the AgeCoDe Study.
[64] To obtain a good data quality regarding morbidity, we decided to combine both data
sources – GP charts and GP interviews, use a standardized questionnaire as reminder and
conduct the interviews face-to-face. The reliability and validity of this approach could not be
assessed at baseline but will be examined and published when data from the first follow-up
are available."

4) Data Collection: Final Paragraph: Reference is made to CASMIN classification with
an associated reference. It would be helpful if some detail was provided on this for
readers, like myself, not familiar with this scale.
We provided these information in the manuscript: "The highest education grade was
described according to the international CASMIN classification in three groups: 1)
inadequately completed general education, general elementary education or basic vocational
qualification, 2) intermediate qualification or general maturity certificate, and 3) lower or
higher tertiary education [21]."

5) Discussion: Reference is made to ‘practice sharing’. Again this may not be familiar
to non-German readers and could be explained.
We are grateful to the reviewer for pointing this out, because we found that the terms "group
practice" and "practice-sharing" had been confused in table 1. The error has been corrected
in the manuscript.

We explained the practice types in the results section, first paragraph: "52.5% of the GPs
had a single practice. 12.7% conducted practice-sharing (i.e. share their practice with other
physicians, but have their own patient base) and 34.8% had a group practice (i.e. share
practice and patient base with other GPs)."

6) Discussion: Strengths and Weaknesses: It is noted that there was a statistically
significant increase in the proportion of patients with intestinal diverticulosis and
psoriasis who did not respond. It is perhaps not surprising that from 29 groups, two
comparisons would be significantly different. This could be noted.
We think that we have to accept the statistically tested results from our nonresponder
analysis. But we also agree that these differences might possibly result from chance. For this
reason we included the following sentence (discussion/strengths and weaknesses section,
3rd paragraph): "We also found a statistically significant and clinically relevant higher
proportion of patients with intestinal diverticulosis (with a 39% higher chance) and psoriasis
(with a 35% higher chance) although we have no definite medical explanation for these differences."

7) [...] Overall comments: This is a long and somewhat complex paper which is, at times, dense to read and comprehend. Consideration should be given to addressing this.

The manuscript is the first publication using data from the MultiCare Cohort study. For this reason many facts had to be introduced comprehensively (e.g. results from recruitment and response rate; imputation of missing values; description of GPs and patients at baseline; intercentre differences; extent of multimorbidity patterns; non-responder analysis) that are important for the interpretation of the study results and will be cited in future publications from this project. For this reason we kept most of the complexity of the manuscript.

Irrespective of this we shortened the manuscript regarding some additional information, e.g. regarding the influence of each indicator of socio-economic status alone on the number of chronic conditions (including one table). We also moved three tables into the additional files section.

8) [...] From a daily clinical perspective, the lack of strong association with age is surprising as is lack of protection from marital status.

We included a passage concerning marital status and living arrangements in our discussion/comparison with other studies section (6th paragraph): "We found no effect of marital status on the health status of our multimorbid cohort. This is contrary to many other studies which showed that married adults may have lower morbidity and better physical health than their unmarried counterparts [56]. There also was no difference in the morbidity load between persons living alone and persons living together with their spouse, which has been suggested by other studies. [57] It might be that both variables only play a minor role for the morbidity load of multimorbid patients."

9) Placing of the findings in the context of routine daily practice, would be helpful.

We clarified this in the conclusions section, 2nd paragraph: "In summary, there seem to be at least two types of elderly multimorbid patients. First, there are patients with mainly cardiovascular and metabolic disorders, who are more often male, have an older age and a lower socio-economic status. Second, there are patients mainly with ADS and pain-related morbidity, who are more often female, but equally distributed across age and socio-economic groups." and we also included this sentences in the abstract.

Yours sincerely