PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The association between perceived stress, multimorbidity, and primary care health services – a Danish population-based cohort study
AUTHORS	Prior, Anders Vestergaard, Mogens Larsen, Karen Fenger-Gron, Morten

VERSION 1 – REVIEW

REVIEWER	Amaia Calderón-Larrañaga Aging Research Center, Karolinska Institutet
REVIEW RETURNED	13-Jul-2017

GENERAL COMMENTS	This is a well written and interesting study on perceived stress, multimorbidity and use of primary care services. The increasing number of people with multimorbidity who will be using primary care services in the near future justifies the need to investigate the profiles of those patients who are likely to make the highest utilization of these services. This manuscript would benefit from some minor changes/clarifications detailed below: - There is no justification in the introduction as to why the role of multimorbdity needs to be analyzed in the association between perceived stress and primary care services use. There is neither a work hypothesis regarding the expected findings. - I have doubts whether this could be called a population-based cohort study, since what the authors do is to collect administrative one-year long data for a transversally selected population (i.e. that from the 2010 Danish Health Survey). - Please clarify the reason for categorizing the stress score into quintiles (and not medians, tertiles or quartiles). - Please explain how all covariates are operationalized in the analyses within the “Other covariates” section. - Please justify the need to perform each of the three sensitivity analyses within the “Sensitivity analyses” section. It may not be clear for all readers. - Please clarify for Tables 2 and 3 that the study outcomes are operationalized as “at least one spirometry, blood sugar measure, etc.” - In the discussion, the authors state that: “these treatment choices may be in contrast to the more general approach to mental health problems: Danish and international treatment guidelines recommend stepped care, where psychoeducation and psychosocial or psychological interventions are the first steps of choice before

	pharmacological treatment". I find this good practice difficult to be ruled out in this study since it is unknown for how long patients have been suffering from stress. It could be the case that people with multimorbidity have also suffered from stress for a longer period of time, and therefore other non-pharmacological interventions have already been tried out.

REVIEWER	Peter Bower University of Manchester
REVIEW RETURNED	21-Jul-2017

GENERAL COMMENTS	Overall, this is a well written paper on stress, multimorbidity and health care utilisation. The study draws on the strengths of routine data in Denmark, complemented by self-reported data. The analysis uses a variety of multivariate statistical techniques to assess associations. The writing is clear and the interpretation suitably measured The hypotheses could perhaps be stated more clearly. The introduction implies that the paper seeks to assess the link between stress and utilisation, and between multimorbidity and utilisation – at least that was how I read it. However, the main analyses seems to focus on stress as a main effect, and to consider multimorbidity as a covariate (in the first instance) and as a moderator of the effect of stress (in the second). I think the exact analyses could be usefully clarified in the introduction and then perhaps more effectively structured in the results section (possibly through the use of subheadings). The discussion 'comparison with existing literature' could then more clearly link this data with the various studies exploring multimorbidity as a main effect and as a moderator. Although 'stress' has a very significant 'track record', and currency with both patients and professionals, its status within primary care practice (such as guidelines) and research is much more ambiguous, compared to conventional psychiatric issues such as anxiety and depression. The advantages and disadvantages of a focus on stress might be outlined in the introduction and discussion, as well as giving some indication of the empirical relationship between stress and measures of depression and anxiety. The study used indicators of mental health utilisation. There is a large literature on identification of mental health, which highlights under-recognition in primary care. I think this literature could be briefly referred to in the paper. The description of the methodology was accessible, with the strengths and weaknesses of the various measures clearly described. The rationale for the particular sensitivity analyses chosen (especially analysis 1 and 2) could be usefully summarised. What is the meaning of the PSS score of 11? Does it have a useful clinical or psychological referent? It would be important to put this in some clinical context so as to make the results more interpretable. There is a really interesting finding about stress reducing use of elective chronic care services and increasing out of hours use. This

	seems really important, but it was not clear to me whether this was a very new finding. What is the literature on this finding more generally? As noted by the author, this could account for the poor outcomes demonstrated by these patients and would be particularly important for health service managers in terms of managing patient demand more effectively. The author has usefully outlined the implications of the findings in terms of clinical practice, and it would be useful to explore thoughts about the future research programme required to place the concept of stress into a clinical and policy context, especially the role of other methods to complement the impressive database studies presented here.

REVIEWER	Margret Tomasdottir Department of Family Medicine, University of Iceland, and Department of Public Health and Nursing, General Practice Research Unit, NTNU, Trondheim, Norway
REVIEW RETURNED	29-Sep-2017

GENERAL COMMENTS	Abstract: Objectives are a litte bit confusing. Firstly you state that mental stress is associated with multimorbidity, suboptimal care and increased mortality, which is correct. However your focus is on metnal stress for those already having multimorbidity – so the association there is the other way than for suboptimal care and mortality. Although mental stress can lead to multimorbidity that is not what you are focusing on so the sentence becomes confusing. Suggest: mental stress is often caused by multimorbdity and causes s. care and mortality. Again similar confusion regarding aim: association between perceived stress and primary care services sounds strange – the effect off perceived stress on services rather (it doesnt sound good to use associate for a personal condition and then point of care) mental health related activites is also a confusing concept which is difficult to understand and is not made clearer later in the text, and what are markers of elective/acute care? I don´t see them mentioned again either. In participants better to say „with one year follow up“ rahter then followed for one year. In results it is strange to compare in line: GP talk therapy, consult with psychologist, antidepressant prescription, annual chronic care and then use of out-of-hours service. Use of service must be another factor than the form of treatment chosen and cannot be compared in line. “talk therapy” is not an official English word to describe this form of therapy, suggest using more formal wording. In general the article is very short, both the introduction and discussion, not really going into depth regarding the importance of perceived stress, perceived vs objective evaluation of stress, possible importance of addressing stress etc - or in drawing deeper ideas or hypotheses from the work, neither regarding aims nor discussion. Methods: Perceived stress: Sounds like the scale is named “Cohen´s widely used and validated Perceived Stress Scale” – better wording suggested. Would be useful to see the 10 item Danish scale used as a supplementary file.

	Multimorbidity: Seems from eTable1 that mood, stress-related and anxiety disorders were seen as one conditions – as the article mainly focuses on stress – wouldn´t it be possible – and more clear to take stress-related conditions out of the multimorbidity definition? Wouldn´t it highly confound all further estimations to include stress-related conditions – both with multimorbidity included and excluded? Again in outcomes – if mental health related activity (as used in abstract) means going to the doctor to get help regarding mental health related to main outcome group 1 that must be stated or explained as the meaning for that phrase. The same must be said regarding "markers of care" if they mean the form of contact with the gp. Cohabitation status – are you referring to marital status (single, married, divorced, widowed) or cohabitation as in who do you live with (parents, friends, spouse etc…) What is vital status? Working status?? I suggest help with language. Statistical analyses: CIPs and IRRs must be further explained for the reader to understand what the porpose of the test is and what they were aimed to show. Nr 2 of sensitivity analyses is very hard to understand – what were you doing there? Which primary care outcomes? Register based-information as a proxy for stress??? This chapter needs further work. Results: Number of primary care services – does that mean number of contacts or number of different service outcome? What does it mean to receive primary care service? This concept is not defined in the text. Are you meaning doctor appointments or solutions to problems provided after meeting the doctor? If you mean appointments or contact with primary care – you seek that yourself, the primary care service does not come for you to receive. Again mental health related acitivities – ambiguous and not defined. Then in 20-27 pg 9 again this strange list defined between getting help for mental health problems and seeking out of hours service (are you not able to get help for mental health problems out of hours in Denmark?? – does one exclude the other?) IRR for receiving mental health service was stable across PSS quintiles is a very interesting result and should be discussed and contemplated –? Does it contradict the main aim of the paper? The same is to say about MM patients – as higher stress levels were not associated with more elective chronic care service, and tended to decrease. Summary of results: Sentence in line 47-49 on page 10 is confusing – what did you define as mental health services if not medication and "talk therapy"? Discussion is rather shallow and does not really go into describing the main hypotheses (which were?) or trying to find possible answers to the results. It merely describes the results again in context with the literature. Any possible solutions or implications of the research for general practice?

REVIEWER	Olaf v.d. Knesebeck University Medical Center Hamburg-Eppendorf, Germany
REVIEW RETURNED	12-Oct-2017

GENERAL COMMENTS	This is an interesting, well written paper on a relevant topic. I have a couple of points the authors should consider: - The Introduction is a bit short and lacks information on the conceptual background. The authors may think about considering Andersen's behavioral model of health services use. - The relevance of multimorbidity for the research question/the analyses is unclear. Is it an indicator for need? Do you consider it as a moderator variable and/or as a covariate? The above mentioned model may help to find a rationale for the inclusion of multimorbidity. - Could you clarify what kind of indicators of primary care services you are using? Are they all measuring utilization as suggested in the conclusion (e.g. Abstract)? In my view, utilization is a patient behavior. - The figures are quite small and hard to read. - Please check the references (e.g. number 4 2016, in press).

REVIEWER	Andrew Wister Simon Fraser University, BC, Canada
REVIEW RETURNED	14-Oct-2017

GENERAL COMMENTS	This is a well-organized and interesting paper on an important topic. The authors provide evidence that perceived stress is associated with higher utilization of health services, especially GPs. The authors need to stress the limitation of the timing of the stress and multimorbidity, as well as interactions. Support for the multimorbidity measure needs to be strengthened. (See Wister, A., Levasseur, M., Griffiths, L., & Fyffe, I. 2015. Multiple morbidity disease burden among older persons: A convergent construct validity study to discriminate between six chronic illness measures, CCHS 2008/09. Biomedical Central (BMC) Geriatrics, 15(12), DOI 10.1186/s12877-015-0001-8. Also, the authors should discuss future research that examines cluters of multimorbidity (osteo, vascular, etc.), since groups of specific illnesses may be synergistic. Lack of GP records on patients also makes it difficult to understand the context in which stress and multimorbidity interact to affect health care utilization. The Tables are informative, and analyses appropriate given limitaitons above.

VERSION 1 – AUTHOR RESPONSE

Editorial Requirements:
- Please revise your title to state the research question, study design, and setting (location). This is the preferred format for the journal.
- Please revise the Strengths and Limitations section (after the abstract) to focus on the methodological strengths and limitations of your study.

The title has been revised to:
The association between perceived stress, multimorbidity, and primary care health services – a Danish population-based cohort study

The Strengths and Limitations section has been revised according to your directions:

• This is the first population-based cohort study to investigate the association between stress perception and primary healthcare utilization while taking multimorbidity into account.
• A major strength of the study was the large cohort of 118,410 participants in the Danish National Health Survey 2010 who answered questions on stress, lifestyle and socioeconomic factors.
• The participants' self-reported data were linked at the individual level with national health register information on multimorbidity status, vital status, and primary care daytime and out-of-hours services, which ensured virtually no loss to follow-up.
• Multimorbidity was assessed by prospectively recorded register-based data on diagnoses and medication prescriptions for 39 mental and physical conditions.
• The limitations of this study include the lack of data on stress in non-respondents, the lack of data on private practicing psychologists, and no access to primary care medical records with details on the provided services and diagnoses.

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Amaia Calderón-Larrañaga
Institution and Country: Aging Research Center, Karolinska Institutet
Please state any competing interests: Non declared

Please leave your comments for the authors below

This is a well written and interesting study on perceived stress, multimorbidity and use of primary care services. The increasing number of people with multimorbidity who will be using primary care services in the near future justifies the need to investigate the profiles of those patients who are likely to make the highest utilization of these services. This manuscript would benefit from some minor changes/clarifications detailed below:

1. There is no justification in the introduction as to why the role of multimorbdity needs to be analyzed in the association between perceived stress and primary care services use. There is neither a work hypothesis regarding the expected findings.
Thank you for your comments. We agree that the introduction could be expanded to explain the background for the study in more detail. The section has been rewritten in order to include the theoretical framework, the work hypothesis, and more references on the link between multimorbidity and mental stress.

2. I have doubts whether this could be called a population-based cohort study, since what the authors do is to collect administrative one-year long data for a transversally selected population (i.e. that from the 2010 Danish Health Survey).
The cohort consisting of National Health Survey 2010 participants is from a nationally representative sample. These cross-sectional data describe the population at the baseline of the study period. The cohort is followed over time for one year with prospectively recorded health service data and exact data on drop-out (death or emigration) which means that there are precise recordings of person-time at risk. Thus, we believe that the term 'population-based cohort study' is justified.

3. Please clarify the reason for categorizing the stress score into quintiles (and not medians, tertiles or quartiles).
There is no consensus of subdivision of this scale, but some previous studies have concluded that the top-20% in a population with the PSS score is at particular risk. Studies on mortality and hospitalization for ambulatory care sensitive conditions in this cohort has been performed using quintiles of the PSS score as well. We chose to stay in line with these studies, but still wanted to be

able to analyze a potential non-linear relationship between the PSS score and the outcomes, and therefore the use of quintiles was suited for the study. A clarification has been added to the Methods section under "Perceived stress" with references:
"The PSS has no predefined cut-off values,34 but fifth quintile values are often considered abnormal.1 The stress score was, therefore, divided into quintiles to assess potential non-linear relations with outcomes."

4. Please explain how all covariates are operationalized in the analyses within the "Other covariates" section.
The "Other covariates" paragraph has been elaborated and the operationalization of the categorical variables added:
"Information on the highest achieved education level according to the UNESCO classification system (<10 years, 10-15 years, >15 years of education),41 cohabitation status (single or cohabiting), and ethnicity (Danish, other western background, other) was obtained from Statistics Denmark.42 The Danish Civil Registration System provided information on sex, age (10-year age bands), and vital status (alive, dead, or emigrated).28 Information on working status (currently employed or unemployed, students, and retirees) and lifestyle factors (physical activity [light or no weekly activity, moderate activity ≥4 hours weekly, hard activity ≥4 hours weekly], body mass index [underweight < 18, normal weight 18-25, overweight 25-30, obese > 30], and alcohol [drinks per week for men and women], smoking [never smoker, former smoker, current smoker], and dietary habits [unhealthy, medium, healthy]) was obtained from the survey."

5. Please justify the need to perform each of the three sensitivity analyses within the "Sensitivity analyses" section. It may not be clear for all readers.
The rationale for the three sensitivity analyses has been added to the Statistical analyses section:
"Three sensitivity analyses were performed to test the robustness of our results. Firstly, we included in our analysis only persons without diagnosed psychiatric illness to separate the effect of perceived stress and symptoms related to psychiatric illness. Secondly, we performed a non-response analysis to test the generalisability of our findings; analyses of general primary care outcomes were carried out using register-based information on both survey respondents and non-respondents for which psychiatric illness acted as a proxy for stress (because the PSS score was unobtainable for non-respondents). Thirdly, a complete-case analysis, which excluded persons with missing data, was performed to validate the use of multiple imputations on missing values."

6. Please clarify for Tables 2 and 3 that the study outcomes are operationalized as "at least one spirometry, blood sugar measure, etc."
For all primary care activity outcomes, we report both a cumulative incidence proportion at one year and the incidence rate (CIP1y and IR in Tables 2 and 3); the CIP value should be interpreted as "at least one service during a year", but the incidence rate incorporates the total number of reported services during the year of the study. This count measure is used in the Poisson regression of the incidence rate ratios (IRR). The operationalization and interpretation are therefore inherent to the analysis as added to the Statistical analyses section:
"Cumulative incidence proportions (CIPs), which reflect the proportion of persons with at least one contact at one year after the index date, and incidence rates (IRs), which reflect the total number of contacts during follow-up were calculated for all investigated primary care activities."

7. In the discussion, the authors state that: "these treatment choices may be in contrast to the more general approach to mental health problems: Danish and international treatment guidelines recommend stepped care, where psychoeducation and psychosocial or psychological interventions are the first steps of choice before pharmacological treatment". I find this good practice difficult to be ruled out in this study since it is unknown for how long patients have been suffering from stress. It

could be the case that people with multimorbidity have also suffered from stress for a longer period of time, and therefore other non-pharmacological interventions have already been tried out.
We agree with the Reviewer that there is a limitation regarding the disease and treatment history before the year of the study. The timing of the stress measure has been discussed in the strength and limitation section, and to the above mentioned sentence we have added this limitation:
"However, we had no means to assess the exact treatment history and the duration of the appraised level of stress in this study. Therefore, patients with multimorbidity may already have tried a number of treatment options if they have had stress for a longer period of time."

Reviewer: 2
Reviewer Name: Peter Bower
Institution and Country: University of Manchester
Please state any competing interests: I am reviewing a PhD viva linked to this work later in the year

Please leave your comments for the authors below

1. Overall, this is a well written paper on stress, multimorbidity and health care utilisation. The study draws on the strengths of routine data in Denmark, complemented by self-reported data. The analysis uses a variety of multivariate statistical techniques to assess associations. The writing is clear and the interpretation suitably measured
Thank you for your general comments.

2. The hypotheses could perhaps be stated more clearly. The introduction implies that the paper seeks to assess the link between stress and utilisation, and between multimorbidity and utilisation – at least that was how I read it. However, the main analyses seems to focus on stress as a main effect, and to consider multimorbidity as a covariate (in the first instance) and as a moderator of the effect of stress (in the second). I think the exact analyses could be usefully clarified in the introduction and then perhaps more effectively structured in the results section (possibly through the use of subheadings). The discussion 'comparison with existing literature' could then more clearly link this data with the various studies exploring multimorbidity as a main effect and as a moderator.
We acknowledge the suggestions and have rewritten the Introduction section with a stronger focus on the interplay between stress and multimorbidity and a clearer hypothesis. Please see the answer to Reviewer 1, comment 1. Subheadings have been added to the Results section for better structure. The Discussion section has also been revised, please see comment to Reviewer 3, answer 4 and Reviewer 2, comment 6 below.

3. Although 'stress' has a very significant 'track record', and currency with both patients and professionals, its status within primary care practice (such as guidelines) and research is much more ambiguous, compared to conventional psychiatric issues such as anxiety and depression. The advantages and disadvantages of a focus on stress might be outlined in the introduction and discussion, as well as giving some indication of the empirical relationship between stress and measures of depression and anxiety.
The focus on mental stress that does not fulfil the criteria for psychiatric disorders (such as major depression and anxiety disorders) in this paper has been emphasized in the Introduction section. Previous studies conducted by us and others have shown that stress is common and that the morbidity and mortality tend to increase with increasing stress level. Although stress has major public health implications, it is our impression that it does not get much clinical attention. We acknowledge that stress is difficult to measure in epidemiological studies and have expanded our discussion about the measurement of stress in the Discussion. Please see comment 6.

4. The study used indicators of mental health utilisation. There is a large literature on identification of mental health, which highlights under-recognition in primary care. I think this literature could be briefly referred to in the paper.
We agree on the issue of under-recognition of mental disorders in general practice, and we have added a reference to this in the Discussion section. This underlines the importance of studying the association between self-reported stress and mental-health related health utilization in primary care. The lack of a primary care register for our research meant that we did not have direct access to the GPs' assessments, but we relied on secondary care diagnoses and prescriptions of psychotropic drugs (Discussion section):
"Psychiatric diagnoses were based on contacts to the psychiatric hospitals and out-patient clinics combined with prescriptions of psychotropic drugs; there may be a general under-recognition of psychiatric conditions in primary care, and the distinction between e.g. stress and depression may vary among GPs.48"

5. The description of the methodology was accessible, with the strengths and weaknesses of the various measures clearly described. The rationale for the particular sensitivity analyses chosen (especially analysis 1 and 2) could be usefully summarised.
The rationale for the sensitivity analyses has been elaborated; please see our answer to Reviewer 1, comment 5.

6. What is the meaning of the PSS score of 11? Does it have a useful clinical or psychological referent? It would be important to put this in some clinical context so as to make the results more interpretable.
The Perceived Stress Scale measures an independent stress construct, but because the scale is not validated as a clinical instrument with a predefined cut-off value, a value of 11 has no easily interpretable clinical meaning. The near-linear dose-response relationship between the PSS value and the health service outcomes speaks against the use of a cut-off, and the scale was not originally designed with cut-offs. However, there are well-documented construct overlaps between the PSS and the Hospital Anxiety and Depression Scale (r=0.72) and the Beck Depression Inventory r=0.67). The following has been added to the Discussion section:
"The PSS measures an independent stress construct and was originally intended as a one-dimensional scale without predefined cut-off values.34 The value of the score may not be easily interpretable in a clinical setting, and caseness is difficult to operationalise. Stress symptoms are common in psychiatric disorders and overlaps exist, which is also reflected in the correlation between measurements of stress, depression, and anxiety.36,68,69 However, directing the focus away from diagnoses has important strengths, e.g. less stigmatization and reduced focus on pharmacological treatment."

7. There is a really interesting finding about stress reducing use of elective chronic care services and increasing out of hours use. This seems really important, but it was not clear to me whether this was a very new finding. What is the literature on this finding more generally? As noted by the author, this could account for the poor outcomes demonstrated by these patients and would be particularly important for health service managers in terms of managing patient demand more effectively.
To the best of our knowledge, the reported associations between perceived stress and use of specific primary healthcare service consumptions are new. Evidence suggests that psychosocial factors and psychiatric conditions predict high use of out-of-hours service and poor chronic care, and our findings are discussed in this light in the Discussion section:
"Existing evidence on the association between mental health and primary healthcare use is generally in line with our findings: psychosocial factors,50 mental health problems,51-53 and illness perception54 are associated with frequent GP attendance even after accounting for the strong association between mental illness and physical health.55-57 Multimorbidity is expected to increase both the number of primary care consultations and the general prescription rate,58-60 which is also

confirmed by our study. The effect of multimorbidity on healthcare consumption may be modified by personal factors that are known to be associated with appraised stress level, e.g. gender, age, and continuity of care.61
The finding that stress may lead to less timely chronic care is supported by the literature on mental-physical multimorbidity; a combination of psychiatric and physical conditions seems to hinder sufficient consultation time, impose errors, and impair the general quality of chronic care in primary care.62,63 High utilization of out-of-hours services and unscheduled care have been described in patients with mental health problems including stress,20 specifically in patients with chronic conditions, although disease burden or severity may confound the association.19,64 In our study, we had the statistical power to take into account the confounding factor of multimorbidity to counter this."

8. The author has usefully outlined the implications of the findings in terms of clinical practice, and it would be useful to explore thoughts about the future research programme required to place the concept of stress into a clinical and policy context, especially the role of other methods to complement the impressive database studies presented here.
This is a relevant topic to cover and may put the research in context. We have added some thoughts on the topic in the end of the manuscript:
"Mental stress and multimorbidity are common problems that often coexist in the general population. Therefore, even a small impact of stress on the prognosis and general healthcare utilization may be relevant in public health. Future research should explore potential management strategies and preventive interventions aimed at patients with mental stress. Patient-centred care research and qualitative research conducted in primary care may provide some new answers to these questions."

Reviewer: 3
Reviewer Name: Margret Tomasdottir
Institution and Country: Department of Family Medicine, University of Iceland, and Department of Public Health and Nursing, General Practice Research Unit, NTNU, Trondheim, Norway
Please state any competing interests: None declared

Please leave your comments for the authors below
Abstract:
1. Objectives are a litte bit confusing. Firstly you state that mental stress is associated with multimorbidity, suboptimal care and increased mortality, which is correct. However your focus is on metnal stress for those already having multimorbidity – so the association there is the other way than for suboptimal care and mortality. Although mental stress can lead to multimorbidity that is not what you are focusing on so the sentence becomes confusing. Suggest: mental stress is often caused by multimorbdity and causes s. care and mortality.
Thank you for the comment. We have revised the Introduction section to elaborate more on the objective and rationale for the study. We wanted to focus on all persons with stress, including persons without multimorbidity (the majority), but we aim to investigate the impact of multimorbidity in relation to stress, because of the well-documented association between mental and physical health. We agree with your suggestion that mental stress is often caused by multimorbidity and causes suboptimal care and mortality, but this is not always the case, and the referenced studies do not unambiguously support this causal pathway. We draw no conclusion on whether multimorbidity caused the stress or vice versa; our data cannot conclude on this (cross-sectional survey data on PSS). However, we do have strong data to adjust the association between perceived stress and health service outcomes for the confounding effects of multimorbidity.

2. Again similar confusion regarding aim: association between perceived stress and primary care services sounds strange – the effect off perceived stress on services rather (it doesnt sound good to use associate for a personal condition and then point of care) mental health related activites is also a

confusing concept which is difficult to understand and is not made clearer later in the text, and what are markers of elective/acute care? I don´t see them mentioned again either.
The hypothesis and aims in the Introduction section have been revised. The term “association between perceived stress and health service outcomes” may sound strange, and we agree that the most obvious interpretation of our observed statistical association is that stress has an impact on care utilization. However, epidemiologists have strong opinions on the words “impact” and “effect” as they imply convincing causal pathways without confounding. In this case, “association” is the most correct term in an observational cohort study to underline that this is a statistical association and not necessarily a causal relationship. We have clarified what “mental health related activities” and “markers of elective chronic care” means in the Methods section in the “Outcomes” paragraph.

3. In participants better to say „with one year follow up“ rahter then followed for one year.
In results it is strange to compare in line: GP talk therapy, consult with psychologist, antidepressant prescription, annual chronic care and then use of out-of-hours service. Use of service must be another factor than the form of treatment chosen and cannot be compared in line. “talk therapy” is not an official English word to describe this form of therapy, suggest using more formal wording.

We have changed the above-mentioned sentence to: “We conducted a population-based cohort study with up to one year follow-up until death, emigration, or end-of-study (1 May 2011), whichever came first.”
Overall, we aimed to assess treatment in primary care on a nationwide-level. For this purpose, we used available register data on reimbursed services in primary care. There is no reimbursement for writing a prescription, which could be a very relevant treatment action taken by the GP. However, redeemed drug prescriptions are registered at the pharmacy so we used this data for a more complete assessment of the GP treatment preferences.
In the tables and graphs, all outcome estimates are principally comparable, but we agree that they are of different nature and hence different groupings are possible depending on the chosen logic (place of contact, consultation type, time of day, general or specific service, data source, etc.). We chose to place the results in two tables/graph (one for mental-health related services and one for more general services including out-of-hours contacts) to avoid too large tables/figures and poor overview.
Talk therapy or conversational therapy are often used to describe psychotherapy with health care professionals in a less formal form compared with e.g. cognitive behavioral therapy and with an emphasis on the conversation; for instance, the National Institute of Mental Health uses the term (https://www.nimh.nih.gov/index.shtml) and it is recognized by the Merriam-Webster dictionary. There is a specific service code for this type of therapy in Danish general practice.

4. In general the article is very short, both the introduction and discussion, not really going into depth regarding the importance of perceived stress, perceived vs objective evaluation of stress, possible importance of addressing stress etc - or in drawing deeper ideas or hypotheses from the work, neither regarding aims nor discussion.
We agree with the Reviewer that some parts of the manuscript were less accessible to general readers. We have rewritten the introduction and added paragraphs in the Discussion section regarding the theoretical stress paradigms and clinical importance of stress:
“Both definition and measurement of stress depend on the chosen recognised stress paradigm of which several exist. Stress can be seen as a fairly objective external factor and measured as the perceived magnitude and duration of a specific stressor, such as a stressful life event or long-term work stress exposure.44 Another approach is to assess stress through stress hormone levels and physiological responses to stress in the body.11 In this study, we approached mental stress as a subjective self-reported state reflecting the balance between perceived stressful events and individual coping mechanisms.45 This paradigm recognises that adaptation to stress is subject to numerous individual factors, including genetic predisposition and social context. The allostatic load theory synthesises the above mentioned stress paradigms in a theoretical framework focusing on the

dynamic adaptation to stress over time.46 Assessing perceived stress through a survey at one point in time has an important limitation; we do not know for how long the observed stress level has been present, but the PSS seems to remain fairly stable over time.47" …
"The PSS measures an independent stress construct and was originally intended as a one-dimensional scale without predefined cut-off values.34 The value of the score may not be easily interpretable in a clinical setting, and caseness is difficult to operationalise. Stress symptoms are common in psychiatric disorders and overlaps exist, which is also reflected in the correlation between measurements of stress, depression, and anxiety.36,68,69 However, directing the focus away from diagnoses has important strengths, e.g. less stigmatization and reduced focus on pharmacological treatment."

5. Methods: Perceived stress: Sounds like the scale is named "Cohen´s widely used and validated Perceived Stress Scale" – better wording suggested. Would be useful to see the 10 item Danish scale used as a supplementary file.
We agree that the wording about the PSS could be better. This has been changed in the "Perceived stress" paragraph:
"In the survey questionnaire, we measured perceived stress by Cohen's Perceived Stress Scale (PSS).34-36 The PSS has been widely used and psychometrically validated as a reliable measure of psychological stress.35,36"
We do not have the copyright to the Danish version of the survey questionnaire and the PSS, but it is available for download at http://www.danskernessundhed.dk/Spoergeskema

6. Multimorbidity: Seems from eTable1 that mood, stress-related and anxiety disorders were seen as one conditions – as the article mainly focuses on stress – wouldn´t it be possible – and more clear to take stress-related conditions out of the multimorbidity definition? Wouldn´t it highly confound all further estimations to include stress-related conditions – both with multimorbidity included and excluded?
We agree that, from a clinical point of view, the merged diseases are different in nature, but for the analyses, certain groupings were required. The reason for merging mood, stress-related, and anxiety disorders was that they are collected in the same ICD-10 chapters of diseases (F30-F48) as described in the original paper on the Danish multimorbidity index (Prior et al, Am J Epi, 2016). In this context, the stress-related disorders are based on secondary care psychiatric diagnoses so only persons submitted to a psychiatric hospital for their stress-related disorders, e.g. PTSD, are affected. This is different from the self-reported stress levels measured by the PSS, but overlaps are natural and expected; this has been added to the Discussion section (please see answer to Reviewer 2, comment 6). We adjusted our estimates using the knowledge on psychiatric illnesses to avoid confounding from psychiatric symptoms on perceived stress. Still, your argument is actually the reason for doing the first sensitivity analysis in which we exclude persons with psychiatric diagnoses to test whether the association between perceived stress and outcomes was still significant, and it was. The background for the sensitivity analyses has been elaborated in the Statistical analyses section. Please see answer to Reviewer 1, comment 5.

7. Again in outcomes – if mental health related activity (as used in abstract) means going to the doctor to get help regarding mental health related to main outcome group 1 that must be stated or explained as the meaning for that phrase. The same must be said regarding "markers of care" if they mean the form of contact with the gp.
We have elaborated on the concepts of Danish primary care and the services as registered by Danish GPs in the Methods section:
"Danish GPs are contractors in a partly per capita, partly fee-for-service remuneration system.31 The contract with the public healthcare system defines reimbursement fees for daytime consultations and out-of-hours services (typically from 4 pm to 8 am). Most medical work is covered by an unspecific base fee, but some specific services performed during the consultation, e.g. talk therapy or

psychometric testing, are additionally reimbursed. Annual chronic care consultations can be performed once a year for each chronic condition and are remunerated by a special fee. Invoices from the contractors are recorded in the Danish National Health Service Register, which provided us with data on all contacts and publicly reimbursed services performed by Danish GPs, psychologists, and psychiatrists.32
Drug prescriptions are not recorded in the Danish National Health Service Register, but the Danish National Prescription Registry provided data on redeemed drug prescriptions based on data from all Danish pharmacies.33 " …
"Our main outcomes of interest were selected from the list of reimbursed services and redeemed drug prescriptions. These were categorised into three groups: 1) services related to mental health (GP talk therapy, GP psychometric tests, and sessions with a publicly reimbursed private practicing psychologist or psychiatrist) and redemption of psychotropic medication, 2) services in general practice related to elective chronic care (spirometry test for lung disease, blood sugar sampling for diabetes, electrocardiograms (ECGs), home blood pressure monitoring for cardiovascular disease, and annual chronic care consultations [one annual review meeting per chronic disease per patient]), and 3) the overall rate of consultations based on the time of day, i.e. daytime face-to-face consultations with GPs and out-of-hours services (telephone or face-to-face consultations with GP)."

8. Cohabitation status – are you referring to marital status (single, married, divorced, widowed) or cohabitation as in who do you live with (parents, friends, spouse etc…) What is vital status? Working status?? I suggest help with language.
The cohabitation status is whether you are living alone or with someone on the same address. It is not necessarily the same as the marital status because many couples live together without formally being married. The categorization of the covariates has been added to the Methods section; please see the answer to Reviewer 1, comment 4.
Vital status is whether you are alive, dead, or emigrated as registered in the Danish Civil Registration System. This has been clarified in the Methods section. The term is standard and used e.g. by the National Cancer Institute (www.cancer.gov) and in research, please see https://www.ncbi.nlm.nih.gov/pubmed/10068251.

9. Statistical analyses: CIPs and IRRs must be further explained for the reader to understand what the porpose of the test is and what they were aimed to show.
The statistical meaning in more common language of the CIPs and IRRs has been added to the Statistical analysis section. Please see answer to Reviewer 1, comment 6.

10. Nr 2 of sensitivity analyses is very hard to understand – what were you doing there? Which primary care outcomes? Register based-information as a proxy for stress???
This chapter needs further work.
We have elaborated on the rationale and the methods behind the sensitivity analyses in the Statistical analyses section, please see answer to Reviewer 1, comment 5.

11. Results: Number of primary care services – does that mean number of contacts or number of different service outcome?
What does it mean to receive primary care service? This concept is not defined in the text. Are you meaning doctor appointments or solutions to problems provided after meeting the doctor? If you mean appointments or contact with primary care – you seek that yourself, the primary care service does not come for you to receive.
In general, we report the total number of contacts during follow-up for each service. We have elaborated on the concepts of primary care services as registered by Danish GPs in the Methods section. The wording regarding the GP provided services has been changed from "receive" to "attended" or "used".

12. Again mental health related acitivities – ambiguous and not defined.
Then in 20-27 pg 9 again this strange list defined between getting help for mental health problems and seeking out of hours service (are you not able to get help for mental health problems out of hours in Denmark?? – does one exclude the other?)
We have elaborated on the concepts of primary care services as registered by Danish GPs in the Methods section. The distinctions are based on registration practice in the registers in which out-of-hours contacts do not include e.g. talk therapy. Mental health services are available 24/7, but most are recorded in secondary care registers (e.g. psychiatric emergency room contacts). A full description of this is outside the scope of this article.

13. IRR for receiving mental health service was stable across PSS quintiles is a very interesting result and should be discussed and contemplated –? Does it contradict the main aim of the paper? The same is to say about MM patients – as higher stress levels were not associated with more elective chronic care service, and tended to decrease.
In our view, the IRRs for the provided services increased across PSS quintiles in a dose-response manner, but this pattern of increase seemed stable for all the investigated outcomes (except home blood pressure measures) even after various adjustments. It is difficult to interpret whether a general increase in care utilization with stress level is appropriate as an answer to increased medical demand or not. When stratifying by the number of physical conditions, this pattern remained for all but the chronic care related services. This suggests that perceived stress affects the overall contact and treatment pattern, but suboptimal chronic care is provided for those with multimorbidity and high perceived stress levels. This has been further discussed in the Discussion section:
"Patients with more severe or complicated chronic disease may be followed in outpatient clinics and have fewer GP chronic care visits. If stress level was a marker of disease severity, this may explain the lack of association between stress and chronic care services among persons with multimorbidity."…
"In the literature, high stress levels in patients with multimorbidity are associated with suboptimal care and adverse outcomes, e.g. more potentially preventable hospitalisations and high mortality.2,18 In our study, high stress levels were not associated with higher use of preventive chronic care services for those with severe multimorbidity; more chronic care services than observed would be expected and considered appropriate in those with high stress levels. This potential undertreatment or lack of timely chronic disease management in persons with mental-physical multimorbidity may play a role in the explanation of adverse outcomes. Conversely, highly stressed persons requested acute out-of-hours services more often than the less stressed, which is generally seen as a less desirable contact pattern for chronic disease management.67"

14. Summary of results:
Sentence in line 47-49 on page 10 is confusing – what did you define as mental health services if not medication and "talk therapy"?
Services related to mental health are defined in the Methods section as GP talk therapy, GP psychometric tests, sessions with a publicly reimbursed private practicing psychologist or psychiatrist, and redemption of psychotropic medication. For the summary, we compare a psychotherapeutic with a pharmacological treatment, but we have now emphasized that we conclude on absolute number of services and have revised the sentence to:

"However, in absolute numbers few persons with high levels of perceived stress used mental health services, and more persons received psychotropic medication prescriptions than talk therapy."

15. Discussion is rather shallow and does not really go into describing the main hypotheses (which were?) or trying to find possible answers to the results. It merely describes the results again in context with the literature.
Any possible solutions or implications of the research for general practice?

Overall, the Discussion section has been elaborated and put into context of the introduction and theoretical background. Also, the implications for clinical practice and future research have been strengthened. Please see our answer to Reviewer 2, comment 8.

Reviewer: 4
Reviewer Name: Olaf v.d. Knesebeck
Institution and Country: University Medical Center Hamburg-Eppendorf, Germany
Please state any competing interests: None declared.

Please leave your comments for the authors below

This is an interesting, well written paper on a relevant topic. I have a couple of points the authors should consider:
1. The Introduction is a bit short and lacks information on the conceptual background. The authors may think about considering Andersen's behavioral model of health services use.

Thank you for your comments and for pointing out Andersen's behavioral model that suits our study well. We have elaborated on the Introduction section to better explain the rationale and background for our study.

2. The relevance of multimorbidity for the research question/the analyses is unclear. Is it an indicator for need? Do you consider it as a moderator variable and/or as a covariate? The above mentioned model may help to find a rationale for the inclusion of multimorbidity.

The Introduction section has been rewritten to describe the interplay between stress and multimorbidity in more detail. Please also see our answers to Reviewer 1, comment 1, and Reviewer 2, comment 2.

3. Could you clarify what kind of indicators of primary care services you are using? Are they all measuring utilization as suggested in the conclusion (e.g. Abstract)? In my view, utilization is a patient behavior.

We agree that some measures of service utilization in this study are mainly driven by patient behavior, e.g. general daytime and out-of-hours consultations, but some are more related to doctor behavior once the consultation takes place, e.g. psychometric testing and prescribing. The indicators of primary care services are obtained from administrative registers of reimbursed GP services and drug prescriptions. The Danish primary healthcare system and the data on the services available to us are now explained in more detail in the Methods section. Please see answer to Reviewer 3, comment 7.

4. The figures are quite small and hard to read.

The figures contain much information owing to the number of outcomes, but seem to be resized for the combined pdf-version of the manuscript. However, the real figures are in high resolution with good detail and should be easily readable in the final version of the paper.

5. Please check the references (e.g. number 4 2016, in press).

Thank you for pointing this out. The references have been updated.

Reviewer: 5
Reviewer Name: Andrew Wister
Institution and Country: Simon Fraser University, BC, Canada
Please state any competing interests: none

Please leave your comments for the authors below
This is a well-organized and interesting paper on an important topic. The authors provide evidence that perceived stress is associated with higher utilization of health services, especially GPs.

1. The authors need to stress the limitation of the timing of the stress and multimorbidity, as well as interactions.

Thank you for your comments. We have described the timing of the stress and multimorbidity measures in more detail in the Discussion section. Interactions or effect modification between perceived stress level and level of multimorbidity have been reported using stratified analyses in Figures 1 and 2. The sample size of the study did not allow for meaningful analysis of formal multiplicative or additive statistical interactions.

“Assessing perceived stress through a survey at one point in time has an important limitation; we do not know for how long the observed stress level has been present, but the PSS seems to remain fairly stable over time.47”
“Multimorbidity status was assessed at the time of the survey by using an algorithm of prospectively collected register data for up to 15 years before baseline.2”

2. Support for the multimorbidity measure needs to be strengthened. (See Wister, A., Levasseur, M., Griffiths, L., & Fyffe, I. 2015. Multiple morbidity disease burden among older persons: A convergent construct validity study to discriminate between six chronic illness measures, CCHS 2008/09. Biomedical Central (BMC) Geriatrics, 15(12), DOI 10.1186/s12877-015-0001-8.

The multimorbidity measure was developed for Danish register-based research and combines the strengths of numerous Danish registers, which are all considered to be of high quality and validity (see references for description and validation studies in the original reference). It is largely based on the 2012 Lancet study by Barnett et al for international comparability. More details supporting the use of the multimorbidity index has been added to the Methods section:

“The algorithm combined data on diagnoses from all Danish hospitals and out-patient clinics with redeemed drug prescriptions from all Danish pharmacies. This approach is in line with recognised international measures of multimorbidity.37 No international consensus on the choice of multimorbidity indices exists, apart from some key diseases that are always included.38,39”

3. Also, the authors should discuss future research that examines cluters of multimorbidity (osteo, vascular, etc.), since groups of specific illnesses may be synergistic.

Thank you for your suggestion. It could be interesting to examine clusters of multimorbidity, especially mental-physical multimorbidity in relation to care utilization. The literature on multimorbidity clusters is large and may be outside the scope of this study. To avoid oversimplification of the multimorbidity concept, we individually adjusting for each of the 39 diseases in the overall estimation of the association between the PSS score and the health service outcomes instead of adjusting using a raw disease count. This has been clarified in the Statistical analysis paragraph.

4. Lack of GP records on patients also makes it difficult to understand the context in which stress and multimorbidity interact to affect health care utilization.
The Tables are informative, and analyses appropriate given limitaitons above.

We concur with the Reviewer that we lack GP records data in this kind of epidemiological study to examine the context of the treatment and conclude on what specific factors in the patient, the doctor, and the healthcare system are most likely to cause the observed findings. However, GP records review or interviews in more than 100,000 patients are not feasible and must be supplemented by other research methods for a more full understanding of the associations. This has been emphasized in the Discussion section:

“For this type of epidemiological study, we lacked detailed GP records data to examine the context of the treatment and to conclude which specific factors in the patient, the doctor, and the healthcare system are most likely to cause the observed findings.”

VERSION 2 – REVIEW

REVIEWER	Andrew Wister Simon Fraser University Canada
REVIEW RETURNED	12-Dec-2017

GENERAL COMMENTS	The authors have addressed all of the reviewers' comments to my satisfaction.

REVIEWER	Peter Bower University of Manchester UKq
REVIEW RETURNED	15-Dec-2017

GENERAL COMMENTS	I am happy with the revised manuscript and think this is now ready for publication

REVIEWER	Olaf v.d. Knesebeck University Medical Center Hamburg-Eppendorf, Germany
REVIEW RETURNED	18-Dec-2017

GENERAL COMMENTS	Thank you for considering my comments.

REVIEWER	Amaia Calderón-Larrañaga Aging Research Center, Karolinska Institutet
REVIEW RETURNED	22-Dec-2017

GENERAL COMMENTS	The authors adequately responded to all of my previous comments.