Title: Stoical patients are more likely to have colorectal cancer

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Author's response to reviews: see over
Dear Prof Hampel

Re:    MS:  1537804626608917

Stoical patients are more likely to have colorectal cancer (title now changed to: Patients who take their symptoms less seriously are more likely to have colorectal cancer)

We thank the reviewers for their comments which have been helpful in improving our paper. We have addressed each of the comments below, and have made the changes referred to in our response, in the revised paper.

REVIEWER: ALICE SIMON

Major compulsory revisions

1. The authors propose that they have identified a single item measure of ‘stoicism’. I am not convinced that this item measures ‘stoicism’. In the existing literature ‘stoicism’ appears to refer to a stable personality trait describing a disposition related to the control of emotions. The item used in this study may be associated with this trait, but not measuring the trait itself. The item seems to be measuring a tendency to appraise symptoms in a particular way, and not some form of emotional processing. Therefore, I don’t think that it is entirely appropriate that the paper be framed around the term ‘stoicism’ - and re-writing with a different narrative is required.

Response:

We have removed all references in the paper to our question being a measure of stoicism. In addition, we have expanded the introduction to include more information about symptoms and health seeking behaviour.

2. The questions have been asked in the context of having a colonoscopy. Were the people in this study referred for colonoscopy on the basis of their symptoms rather than through some kind of screening programme? If so, then the scenario is retrospective i.e. after help-seeking has taken place. One might think that response to the symptom appraisal item will be somewhat coloured by how long each person actually took to seek help for their bowel symptoms. Can the authors comment on this and what effect it might have?

Response:

We agree that our findings are a function of being in a clinical population and we do not expect the finding to hold in a general population. We explain this in the discussion (page 12). We have clarified the population in which the study was undertaken, and have also added information about the cancer prevalence in our study.

3. The finding of an association between the symptom appraisal item and the presence of CRC is intriguing. However, there is a lack of clarity about what the underlying construct being measured is (see above) and also about what the underlying mechanism is for this association. The authors suggest that ‘stoics’ are simply more accurate. Might they also like to consider that stoics are ‘delayers’ ie. have taken a much longer time to seek help? Perhaps people who take symptoms more seriously seek help earlier and therefore do not ever get to the point of a CRC diagnosis e.g. maybe they have pre-cancerous polyps identified and removed ? This is purely speculative, but it seems that consideration of time to help seeking could be important in the observed relationship. Could the authors consider this - and perhaps also suggest other specific factors that may be mediators in the ‘discussion’?
Response:

We are delighted that the reviewer finds the association between how seriously people take their symptoms and CRC intriguing. We have added discussion about the uncertainty of the underlying constructs and mechanisms that may explain why a person takes their symptoms as they do (page 12). In addition, we have added the possibility that patients who take their symptoms more seriously may present for colonoscopy before their polyps have progressed to colorectal cancer in the discussion (page 13).

4. Overall this paper would be better if it was written in a more tentative manner with a view to encouraging some more detailed research – ie saying that this interesting relationship has been found, and encouraging future work that attempts to understand the underlying constructs and mechanisms. A short report or ‘letter’ format may be more appropriate. BMC Gast. may not support this type of submission – in which case an alternative publisher might be better.

Response:

We believe that our finding is an interesting one which may have potential clinical benefit, and which is certainly worthy of further research. It is therefore important that this question, its potential implications for future research and, if replicable, clinical implications are presented in full and this would not be possible in a shorter report.

In order to make our findings more tentative, we have changed the wording in the discussion (p 11, first paragraph of discussion) and our conclusion (p13, last paragraph). We have also suggested the need for additional research to assess if our finding using this question will be robust for different cancers and in different populations (page 11, and 13-the last paragraph of the paper).

Minor essential revisions:
5. The abstract cites ‘3.3’ times – it would be more accurate to report the adjusted model here instead.

Response:

We have added the adjusted estimate to the abstract (page 2).

Discretionary revisions:
6. The authors might like to explore de Nooijer and van Osch’s work on paying attention to symptoms e.g de Nooijer et al 2003 Soc Sci Med, van Osch et al 2007 EJ Cancer Prev.

Response:

We have added reference to these papers in our introduction (page 4).

REVIEWER: MAGDALENA ESTEVA

Reviewer comments
1.- Introduction
There are some weakness in the introduction that I think have to be afforded. The authors consider there is little research on the variability on how seriously people take their symptoms. However, there is considerable research from different disciplines as sociology and anthropology on symptom interpretation process, symptom seriousness and diagnosis delay, symptom seriousness and help seeking behaviour, how disruptive symptoms are perceived as more serious. A sounder literature review is needed.

Response:

We have reframed the background to our question, and have added to the literature review in the introduction. While there is literature exploring factors influencing people to seek
medical attention, and symptom interpretation, there is a dearth of literature linking these
to clinical outcomes; and in particular there is none on whether how seriously a person takes
their symptoms is associated with a finding of serious disease, such as colorectal cancer.

2. Methods:
The design of the study is not well defined in the methods sections but well
defined in the abstract. In the section 'Assessment of predictive validity', has to be added ' question
predictive validity for presence of colorectal cancer. Statistical analysis of predictive validity: Logistic
regression. Authors must explain why they have not considered other variables with univariate low p
values (<0.10 or <0.25) as recommends Lemeshow in order to explore confusion?. If symptom
perceptions is a new variable more variables of the previous study have to be included in the model
Nagerkele value of the model could be interesting

Response:

We have clarified the study design and methodology at the beginning of the methods
section (page 5).

We have amended the text to clarify and emphasise that the purpose of the multivariable
modelling in this paper is to assess the incremental gain (if any) when the study factor
variable (how seriously a patient takes their symptoms) is added to the previously published
multivariable model to predict the presence of cancer that was developed using these data
(page 5, 6-7).

Our previously published model investigated the association between socio-demographic
characteristics, family history, medical history and symptoms and a finding of colorectal
cancer on colonoscopy. Full details of the model development are given in a previous
publication [1] and we refer to this in the paper. In brief, backward elimination was used to
assess which interactions and variables should be retained in the model – all variables were
eligible for inclusion. This approach is more rigorous than the simple screen of P<0.25 based
on univariate analyses to assess which variables should be considered for inclusion as that
does not take into account correlations between covariates or possible effect modification
(interaction).

The relevant question in this paper is whether adding symptom perception to the
established model adds to (improves) the fit of that model. Hence, it would be inappropriate
to consider any of the variables in the established model for removal when symptom
perception is added as that could result in an overestimate of the importance of symptom
perception. Because variables in the existing model could be effect modifiers, we also looked
for evidence of interaction between symptom perception and the other variables. None
were found to be statistically significant.

We are adding variable(s) to an established model which means that the models we are
comparing are nested. In this situation, the conventional and appropriate method for
assessing whether there is an improvement to the fit of the model is to use the likelihood
ratio statistic, as we have done. When models that are being compared are not nested,
alternative approaches are required. In those circumstances, the Akaike Information
Criterion (AIC) is generally used rather than the Nagerkele R-square.

The area under the Receiver Operating Characteristic curve (AUC) is routinely used to assess
the discrimination of a diagnostic prediction model, in preference to a measure such as the
R-square for binary outcome data. Our previously published prediction model shows good
discrimination with an AUC of 0.85, this has now been stated in the text. Because the
already high AUC cannot show any more than a very minor increase on the addition of a single variable such as symptom perception the likelihood ratio test is the appropriate criterion to assess the contribution of this additional variable.

3. Statistical package used is needed.
   **Response:**
   All analyses were performed using SAS. This has been added to the text and references (page 6).

4. Results:
   Presentation of data is not sound. It will be much clear if all data is presented in tables together with results each statistical analysis. No figures in the manuscript as tables in this case are much more informative. Complete logistic regression model has to be presented in the correspondent table as it contains valuable information.
   **Response:**
   Based on this comment, it is not clear that the referee has accessed the supplementary tables that were submitted as supporting information for the paper. For instance, the table that is referred to relating to the full logistic model is in fact included in this supporting information. We are of the view that figures are more accessible to a general (and often non-statistical) readership in terms of conveying important associations and patterns in the results. The tables are also important in that they contain the details of the estimates, confidence intervals etc. Whilst we agree that the tables should be available to readers who require this level of detail (as we have done), we do not believe that the tables should replace the figures in the body of the text.

5. Discussion
   In the first paragraph authors declare a 2-fold increase in prevalence of colorectal cancer in those who take any symptom as less or lot less seriously compared with the same as others but adjusted OR IS 1.47 with a confidence interval that contains 1. The importance and dimension of these results have to be discussed more thoroughly and how this fact affects predictive validity. Consequently, last paragraph in pg 11 is too ambitious because authors have not built and obtained a robust predictive model. Moreover, if authors consider that comparison of those who take symptoms seriously vs less seriously is more relevant, reference category in adjusted and unadjusted analysis for this variable has to be changed.
   **Response:**
   We have amended the text to put more emphasis on the estimates relative to the referent group in the table. Both the comparison to the middle group and between the extremes are of interest, and this is now better reflected in the text (page 11). The confidence interval for the adjusted OR of 1.47 (95%CI: 1.00, 2.14) contains 1 reflecting the p-value of 0.04, however, when the extreme groups are compared there is a nearly 2-fold increase OR= 1.85 95%CI(1.11, 3.09). The confidence intervals and comparisons have been clarified in the text.

   Based on our comments above, we strongly disagree with the assertion that we “have not built and obtained a robust predictive model”

6. Discussion section is quite limited. Discuss very little about differences and similarities of others authors results. In fact there are only 3 references in the discussion section. Discuss how bowel symptoms considered by others as disrupting and often taken as serious like abdominal pain decreases in patients who take any symptom seriously.
   **Response:**
We have added to the discussion. However, there is very little research on the variability in how seriously people take their symptoms, and even less on how this is associated with clinical outcomes. Further, there are no studies that we are aware that explore symptom perception based on a single question.

7. Others points of interest in the discussion are:
Is the question explored a proxy of stoical?. Content or construct validity limitations. If the authors consider that those who take their symptoms more seriously than others access health services for minor symptoms that do not reflect organic pathology. How this fits with proven evidence that the main reason to visit a doctor is bad health?.

Response:
We have removed references in the paper to our question being a measure of stoicism. We acknowledge that there are many attributes that contribute to whether or when a person seeks medical advice, or indeed how they perceive their symptoms. We have also added comments about the clinical population in which the study was undertaken, as well as some plausible explanations for our findings such as the timing of colonoscopy in people who take their symptoms more seriously (page 13).

8. People waiting for colonoscopy are not general population, Most of them have experienced bowel symptoms and most of them could be expecting disappointing results. Would you expect different results from general population?

Response:
We agree that our results are applicable to a clinical population only, and have not claimed otherwise. We have clarified the population in which the study was undertaken in the discussion (page 12). We have also added information about cancer incidence in our study. We have strengthened reference to the population and the implications of this in the discussion.

We trust that this addresses all the issues raised by the reviewers, and look forward to a positive decision about publication.

Yours sincerely

Barbara-Ann Adelstein