Author's response to reviews

Title: Fecal pancreatic elastase-1 levels in older individuals without known gastrointestinal diseases or diabetes

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Author's response to reviews: see over
Dear Editor

enclosed we would like to re-submit our revised version of manuscript entitled

“Fecal pancreatic elastase-1 levels in older individuals without known gastrointestinal diseases or diabetes mellitus.”

We thank the referees for the kind comments and changed the manuscript accordingly.

We hope that our manuscript is now acceptable for publication in *BMC Geriatrics*.

With kind regards.

Sincerely,

Karl-Heinz Herzig

For the authors
Point to point response to

MS: 1165766712424979 Fecal pancreatic elastase-1 levels in older individuals without known gastrointestinal diseases or diabetes

Karl-Heinz Herzig, Anna-Kaisa Purhonen, Kati M Räsänen, Joanna Idziak, Petri Juvonen, Ryszard Phillips and Jaroslaw Walkowiak

We thank the referees for their kind comments. Enclosed please find our point-to-point response.

Reviewer 1

1) Herzig et. al must give data on body weight and/or composition of the study subjects. At least BMI (Min/Max/Mean/Range) of the study subjects and the control group must be given. This is important since
a) there has been no testing for diabetes mellitus (persons with obesity or elevated BMI might be more likely to suffer from diabetes mellitus)
b) there might be a correlation between exocrine pancreatic function and BMI which would be very interesting to know. The authors should than state if there are any statistical correlations between BMI and exocrine pancreatic function. This would additionally improve the quality of the study!
Do the authors have data on malnutrition in those with a decreased exocrine function? This would be very interesting to know.

Comment: We do not have data on weight and height since the patients where were recruited from local elderly homes, health care centers from the Eastern Finland and from the ophthalmology outpatient clinic a the time of the study.
Pancreatic insufficiency should clearly be negative related to BMI since of the maldigestion and adsorption of fat. It is used therapeutically via the lipase inhibitor orlistat.
There were no extreme forms of obesity and a history of diabetes mellitus was an exclusion criterion, but increased fasting glucose or impaired glucose tolerance cannot of course be excluded. There are not data in the literature that this prediabetic condition would affect pancreatic exocrine function. None of the individuals had a special diet or any known gastrointestinal disease or prior gastrointestinal surgery. None of the subjects had been diagnosed with exocrine pancreatic insufficiency or had been treated with pancreatic enzymes before the study. The later sentence has been added to the method section.

2) Do the authors have any data on qualitative nutritional state (especially vitamin D levels) of the study subjects? Is there a correlation of exocrine pancreatic insufficiency with decreased levels of vitamin D? Is there a correlation with bone fractures?
If the study group does not have any data on this, this would be a very interesting topic for a follow up study. The problem of potential qualitative malnutrition (especially on vitamin D – please see available studies) in the elderly must be adequately addressed before being published.

Comment: We did not measure vitamin D levels in this study, but we agree with the reviewer that it would definitely be a very interesting topic for a follow up study.
3) It would be very interesting to know how many of the study subjects with exocrine pancreatic insufficiency had been diagnosed with „exocrine pancreatic insufficiency“ before inclusion into the study. Had even one general physician thought of testing these patients before? Do the authors have the impression the problem is well known among general physicians in care of the elderly? Maybe there could be a short comment about this in the „discussion“ section. Additionally, how many of the patients had been treated with pancreatic enzyme because of exocrine insufficiency before the study?

*Comment:* None of the subjects had been diagnosed with exocrine pancreatic insufficiency or had been treated with pancreatic enzymes before the study. The purpose of the study was to increase awareness of this problem in normal elderly population in health care providers. We believe that the exocrine pancreatic insufficiency is not recognized enough among general physicians and more attention should be paid on the issue and most of the elderly individuals are not being examined thoroughly.

4) If the authors do find a prevalence of 21.7% and none of the subjects has been screened or treated for exocrine pancreatic insufficiency before by the general practitioner or other physicians, that is quite a result suggesting that there is no awareness of this disease among physicians. This is an important point that should also be discussed in the discussion section and since it helps to stress the importance of the study by Herzig et al.

*Comment:* We agree with the referee and have added this issue to the discussion section.

5) Do the authors have data on signs and symptoms of exocrine pancreatic dysfunction (e.g. flatulence, pain, diarrhhoea, etc.) of the study subjects. This would help to improve the study further (yet it is not mandatory).

*Comment:* The included subjects have been considered healthy and there were not signs of diarrhea or obvious symptoms associated with pancreatic insufficiency – otherwise the general physician would have been investigating it.

**Discretionary Revisions**

1) Please change the title of the study from „diabetes“ to „diabetes mellitus“. Otherwise one might also think of „diabetes insipidus“.

*Comment:* The title has been changed accordingly.

2) Unfortunately no laboratory test on blood glucose have been performed in the study subjects. Therefore it is likely that there are some diabetics in the study population. This of course, influences the quality of the study negatively. Yet the authors frankly state this in the discussion section which is important and reflects good research practice. Furthermore, concerning the main conclusion (exocrine pancreatic insufficiency in the elderly is more often then expected) it is after all not very important whether all subjects have been screened for diabetes mellitus or pathological glucose tolerance.

*Comment:* A history of diabetes mellitus was an exclusion criterion, but increased fasting glucose or impaired glucose tolerance cannot of course be excluded. There are not data in the literature that this prediabetic condition would affect pancreatic exocrine function.
Reviewer 2

Major compulsory revisions
The authors report their results using medians (non-parametric) but have used a one way ANOVA test which is a parametric test. Either the data should be reported as means with 95% confidence intervals or use the Kruskal Wallis test for comparison. Similarly, as faecal elastase-1 can be considered as positive or negative, have the authors looked at proportional analysis using CHI square or fisher exact testing?

Comment: The reviewer is correct and we apologize for the mistake. As the data was normally distributed (tested with Kolmogorov-Smirnov test) means with 95% confidence intervals have now been used describing the results. Also the figure 1 has been changed accordingly (line indicating now the mean, not median level of each group). We did not use proportional analysis for further analysis of the subjects since we evaluated just their faecal elastase concentration demonstrating that in a normal population of elders individuals there is a significant amount of patients with low elastase levels.

Minor essential revisions
It is unclear in the methods section which faecal elastase-1 sample was used in each participant. They state that 3 samples were used from each participant. Was the lowest result used or was this the average? This requires clarification. There are a few spelling/grammatical errors that require correction: Introduction: noninvasive should be non-invasive. Discussion: "Our results are well comparable with other studies." The word "well" is unnecessary.

Comment: The average of the three stool samples was used. This has been now clearly indicated in the text. Also the other corrections have been made as suggested.

Discussion: "In contrast, its sensitivity in mild pancreatic insufficiency in different studies has been reported to be 16.7% [19], 22% [16], 40% [18], 47% [20], 63% [17] or 65% [13]." This sentence would read better if the range was given followed by the references.

Comment: The sentence has been changed accordingly.

Discussion: "irritable and inflammatory bowel disease [26-28]." This sentence is unclear. Does this mean irritable bowel syndrome and inflammatory bowel disease? If so, there should be a reference relating to irritable bowel syndrome.


Discussion: "is a considerable portion of subjects who might benefit of pancreatic enzyme supplementation therapy." should read "benefit from pancreatic..."

Comment: The sentence has been changed accordingly.
Discussion: "one fifth of the individuals had abnormal fecal elastase-1 levels indicating pancreatic exocrine insufficiency". The word stool is unnecessary.

Comment: The sentence has been changed accordingly.