

ANSWERING REVIEWERS



January 11th, 2016

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 23707-Revised manuscript).

Title: Socio-economic status and lifestyle factors are associated with achalasia risk: a population-based case-control study.

Authors: Helen G Coleman, Ronan T Gray, Kar W Lau, Conall McCaughey, Peter V Coyle, Liam J Murray and Brian T Johnston

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 23707

The manuscript has been improved according to the suggestions of reviewers:

Reviewer 1 (00044326)

Achalasia is a neurodegenerative motility disorder that results in loss of normal lower oesophageal sphincter function and aperistalsis. This is the first study to assess the relationship between socio-economic status and achalasia. 1.lower socio-economic status is associated with increased gastro-intestinal infection risk in this region..how you can prove the association of achalasia and viral infection 2.how you can prove the association between achalasia and prenatal infection 3.family history (what is the incidence in the same family) which has the same enviroment.

Response: Since this is an observational study, we cannot prove the associations between achalasia and viral infection or prenatal infection or family history, within our current study design. We describe these only as biologically plausible mechanisms for the associations observed with socio-economic and demographic factors in our study, and have generated hypotheses that fit with other available evidence from cross-sectional studies of viral infection prevalence in achalasia patients, including this study population (Lau et al, 2010, reference #8). The cross-sectional study design precludes the ability to prove an association, since we cannot prove which came first – the infection or the achalasia. Only a prospective study design can truly evaluate this, but given the rarity of achalasia and difficulty in measuring viral infection status, it would be difficult to assess these factors. Only five of the cases in our study reported a family history of the condition, therefore our study is too small to comment on family history as a risk factor (either due to genetics or shared environmental exposures) for achalasia. We do state that 'Further case-control and cohort studies verifying our results are required' in our penultimate discussion paragraph.

Reviewer 2 (03478000)

The authors of the manuscript investigated lifestyle and household factors as potential etiology of achalasia. Results showed that low socio-economic background and pet ownership increasing incidence of achalasia, on other side alcohol consumption and smoking do not influence on achalasia. This article is interesting, but it has some weak points that require further attention.

1) Some points in Introduction section are not necessary and should be removed:

- mentioned modality of treatment, pneumatic dilation and myotomy; for remember new treatment includes per

oral endoscopic myotomy (POEM).

- complication of achalasia such as aspiration pneumonia and esophageal cancer.

All of this don't refer with aims of study.

Response: These sentences have been removed in line with the reviewers' suggestions.

2) Manometry as an ultimate diagnostic tool of achalasia should be mentioned in Introduction section; without this explanation first sentence in Subject recruitment section stays unclear.

Response: An additional sentence describing manometry as a diagnostic tool for achalasia has now been integrated into the first section of the introduction.

3) Similarities in age and sex distribution for controls reflect the frequency-matched case-control study design. This sentence should be in Subject recruitment section.

Response: This sentence has been removed from the results text, and merged with the previously existing sentence in the Methods, Subject recruitment section: 'Controls were frequency-matched within groups defined by age (<50, 50-69, ≥70 years) and sex to their corresponding cases, therefore similarities in age and sex distribution reflect this study design.'

4) The Discussion section is too long and can be shortened.

Response: The overall discussion has now been reduced from 4.5 to 4 pages in length.

Reviewer 3 (00055273)

Coleman et al. present a questionnaire based populational inquiry about risk factors for achalasia. The topic is interesting and some data is original. The authors discussed well their findings. In my opinion, the manuscript could be shortened a bit by decreasing the excessive number of references and deleting table 4. The authors made their point that alcohol and tobacco is not linked to achalasia without the aid of this table.

Response: We have now removed Table 4, and have changed the corresponding results text to state 'data not shown'. The number of references has been reduced slightly from 42 to 36, as a consequence of changes in response to other reviewer comments. This seems in line with other published case-control studies.

Thank you again for considering our manuscript for publication in the *World Journal of Gastroenterology*.

Sincerely yours,



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