

1. This meta-analysis however, provides a rather small data sample which is somewhat biased to some Asian countries and its population. Small number of participants increases the bias even more. In fact, the matching case-control does not even match for age, which is a strong risk factor for CVD.

**Response:** Dear Reviewer, you right. We try to collect all available documents by searching in several databases including ISI web of knowledge, PubMed, Scopus, Embase, and Google Scholar without limitation to publication date and language. But we collected only 11 eligible studies, there were limit documents but We had no choice and only these studies were available; we suggested this issue in the limitation section in discussion of the manuscript that our results can be unreliable with this limitation and the findings of this report need to approved by further investigation with more sample size.

2. Several other risk factors of CSX need to be taken into account, mainly socio-economic status, smoking, alcohol consumption, environmental pollution etc. that all lead to endothelial dysfunction.

**Response:** Dear Reviewer, thanks for your suggestions. These risk factors were not specified in the eligible studies except smoking which suggested in the result. There is limitation in access to raw data of the individuals studies. Therefore, due to lack of any data about socio-economic status, alcohol consumption, environmental pollution; we pooled the association between smoking and CSX risk. Please accept this limitation, there is no data about these risk factors except history of smoking that suggested in the results.

3. Authors also state that there is a connection between hypertension and H. Pylori, but in Western countries, H. Pylori infection is in decline and hypertension is growing in prevalence.

**Response:** Dear reviewer, you right. But most of included studies in this analysis is performed in Asian countries (that prevalence of H. pylori infection is high in Asian populations). In addition, according to previous published studies, there is significant association between H pylori infection and hypertension please see this references (“Effect of Helicobacter pylori Treatment on Long-term Mortality in Patients with Hypertension”; “Effect of Helicobacter pylori infection on blood pressure: a community based cross sectional study”; “Association of Pathogen Burden and Hypertension: The Persian Gulf Healthy Heart Study”; “Helicobacter pylori infection and pepsinogen levels have clinical significance in hypertension patients”; and “Eradication of Helicobacter pylori Infection Improves Blood Pressure Values in Patients Affected by

Hypertension"). Therefore, It may that H. pylori infection can damage endothelial that there is numerous meta-analyses about the effect of H. pylori infection and cardiovascular diseases particularly in Asian countries.

4. Authors should also discuss epidemiology of CSX. It is by far not the same disease as the Coronary artery disease, therefore common knowledge on the risk of CAD cannot be directly applied on the CSX. When we want to draw a conclusion that CSX is associated with H.Pylori, we should correct the findings for all already confirmed risk factors of CSX. If not, authors cannot be convinced that some selection bias or absent correction for known risk factors is actually disorting the results. Therefore, authors should discuss known risk factors of CSX, its epidemiology, risk factors and perhaps identify those that could be related to the risk of H.Pylori infection.

**Response:** Dear reviewer, your comment was helpful for us. Indeed CSX is an angina with normal coronary arteries. We apologize, because we are microbiologist, and distinguish between these two term (CVD and CSX) was confusing for us. We explain one paragraph in the text about history, clinical manifestations as well as epidemiology of CSX. It has been suggested that "The prevalence of syndrome X is significantly higher in women compared to men " (for example: [https://doi.org/10.1016/S0008-6363\(01\)00460-6](https://doi.org/10.1016/S0008-6363(01)00460-6)). In addition about risk factors of CSX we review that hypertension, hypercholesterolaemia and smoking can be considered as risk factors of CSX ([https://doi.org/10.1016/S0008-6363\(01\)00460-6](https://doi.org/10.1016/S0008-6363(01)00460-6), <https://doi.org/10.1161/01.CIR.0000116601.58103.62>, <https://doi.org/10.1161/01.CIR.102.19.2359>, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5020293/>, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4561795/>, <https://www.ahajournals.org/doi/full/10.1161/01.CIR.102.19.2359>, [https://www.researchgate.net/publication/327270789\\_Association\\_between\\_Cardiac\\_Syndrome\\_X\\_and\\_Non-dominant\\_Right\\_Coronary\\_Artery](https://www.researchgate.net/publication/327270789_Association_between_Cardiac_Syndrome_X_and_Non-dominant_Right_Coronary_Artery), ) "Endothelial dysfunction in CSX appears to be multifactorial and linked to risk factors such as smoking, obesity, hypercholesterolemia, and inflammation" in <https://www.ahajournals.org/doi/full/10.1161/01.CIR.0000116601.58103.62>

Dear Reviewer, It has been suggested that H. pylori infection can produce several cytokines, such as Tumour Necrosis Factor  $\alpha$  (TNF- $\alpha$ ) which increases serum triglyceride level in animals (<https://pubmed.ncbi.nlm.nih.gov/2754338/>); furthermore, it has been indicated that lipid profile changes is related to the secretion of inflammatory cytokines by cells chronically infected with gram-negative bacteria such as H. pylori (<https://pubmed.ncbi.nlm.nih.gov/8131779/>). Therefore, it may be possible that H. pylori infection caused to CSX partially by dyslipidemia.

5. I miss the exact definition of CSX in the studies, did all patients have coronary angiography? If yes, smoking status should be included in such cases.

**Response:** Dear Reviewer, according to standard definition of CSX, CSX cases characterized using effort angina pectoris, positive exercise test, normal or near normal coronary angiogram that be specified in the manuscript. Coronary angiography of CSX cases is usually normal and we reviewed the eligible studies (n= 11) to answering your comments, but there is no information for results of coronary angiography of CSX cases. However, we measured the frequency of smoking in CSX group as well as OR for smoking and CSX in the result section.

6. Introduction, "H.Pylorus" is used multiple times, then H.Pylori. "Pylori" is the correct latin adjective.

**Response:** Dear Reviewer, we are apologizing for this mistakes, all problems were revised.

7. Authors should be careful in phrasing "support the contribution of infection with this bacterium in susceptibility to CSX". Evidence of association is not evidence for causation.

**Response:** Many thanks for this suggestion, it revised.

Dear reviewers, many thanks for your best suggestion on the present manuscript. we greatly appreciate your time and your kind comments again; your comments reinforced this manuscript and we did our best to respond to your comments carefully. We try to read your all suggestion and substantially revised the manuscript.