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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 31854
Title: Markers of systemic inflammation and colorectal adenoma risk: meta-analysis of observational studies
Reviewer's code: 00227433
Reviewer's country: United Kingdom
Science editor: Ya-Juan Ma
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This systematic review and meta-analysis represents an interesting collation of evidence to date on three inflammatory markers (CRP, IL-6 and TVF-alpha) in relation to colorectal adenoma risk. Overall no significant associations are detected between these markers and adenoma risk, although some stratified/subgroup analysis of CRP and adenoma risk did result in significant positive associations. Overall, the review brings additional knowledge to this subject and would be a welcome summary that would likely be informative to other researchers working in this field. Care has been taken to ensure duplicate study populations are not represented, which is excellent. The review is also largely well conducted and written. However, some analyses and interpretation of results require further consideration as outlined below. Major comments 1. There are a multitude of subgroup and stratified analyses presented (at least 12, across 3 different inflammatory markers, meaning the likelihood of at least 2 false positive results). The review does not appear to have had a protocol published prior to this draft, therefore it is difficult to justify that all of these analyses were considered a priori. Many appear to be arbitrary and at least two should be removed entirely from

the review – namely subgroup analysis by sample size (why 200 as a cut-off?) and NOS quality score (8 as a cut-off, despite all studies being considered high quality?). All others require further justification in the methods for why these are being performed. 2. The results text reporting the subgroup/stratified results needs to be more reflective of the many non-significant findings, rather than just highlighting the significant ones – for example through the addition of concise sentences summarising 'no significant associations were observed for IL-6 and adenoma risk in other stratified analyses including by....etc'. This would help to give a more balanced tone for results. 3. There is no justification for why analysis by advanced adenoma status is considered more important than the others, aside from that this resulted in a statistically significant finding. Although clinically more important, due to the points made above, this subgroup analysis should be moved to the table of subgroup/stratified analyses, rather than presented in the main Forest plot figure for CRP results. 4. The definition of 'advanced' adenoma does not seem consistent with international criteria – usually an adenoma >10mm, not >5mm, is considered to be advanced. Moreover, the inclusion of HGD and tubulovillous/villous features in advanced adenoma definitions is only applicable to US studies. I am unsure if Japanese guidelines include these as features of advanced adenomas, but certainly the UK study would not have applied these criteria. Furthermore, the authors acknowledge that multiplicity and size was only addressed by two studies, and both of these are key features of 'advanced' adenomas. Therefore, there is a risk of misclassification bias in other adenoma studies that have not denoted 'advanced' adenomas. Overall, I have concerns about the definition of non-advanced adenomas and advanced adenomas used throughout, and the lack of generalisability of this definition between regions. These results should also be toned down considerably within the review (including removal from the Forest plot, as above), and discussion of these limitations emphasised instead. The abstract and conclusions/core tips should certainly not focus on these findings. 5. Discussion of differences in results for CRP (and IL-6 to a lesser extent) where confounders such as smoking have been adjusted are well outlined in terms of being potential mediators of the association and the potential issue of uncontrolled confounding. Could the authors also please comment on the timing of measurements and the potential bias of reverse causation? Minor comments 6. Please add dates searched to the abstract and metho.