

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Associations of cigarette smoking, betel quilt chewing and alcohol drinking with high-sensitivity C-reactive protein in early radiographic knee osteoarthritis: a cross-sectional study
AUTHORS	Zhang, Yi; Zeng, Chao; Wei, Jie; Li, Hui; Yang, Tuo; Yang, Ye; Deng, Zhen-han; Ding, Xiang; Lei, Guanghua

VERSION 1 - REVIEW

REVIEWER	Yueh-Han Hsu 1 Department of Public Health and Department of Health Services Administration, China Medical University, Taiwan; 2Department of Internal Medicine, Division of Nephrology, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Taiwan; 3Department of Nursing, Min-Hwei Junior College of Health Care Management, Taiwan
REVIEW RETURNED	01-Jan-2016

GENERAL COMMENTS	<p>The authors of the manuscript entitled “Associations of cigarette smoking, betel quilt chewing and alcohol drinking with high-sensitivity C-reactive protein in early radiographic knee osteoarthritis” conducted a cross-sectional research to explore the association between levels of hsCRP in early radiographic knee OA with 3 important abused substances, ie., cigarette smoking, alcohol drinking and betel nut chewing. The definition of early radiographic knee OA denoted KL grade 1 or 2 in at least one leg. In total, there were 148 participants with high hsCRP level ($\geq 3.0\text{mg/L}$), of which the proportion of smoking, drinking and betel nut chewing were 41.9% (~62 participants), 44.6% (~66 participants) and 2% (~3 participants). The case number of the participants with low hsCRP ($< 3.0\text{mg/L}$) was 788, of which the proportion of smoking, drinking and betel nut chewing were 29.7% (~234 participants), 42.8% (~337 participants) and 4.7% (~37 participants). The authors concluded that cigarette smoking, but not alcohol drinking nor betel nut chewing, was positively associated with the serum hsCRP level in early radiographic knee OA patients</p> <p>The topic is interesting and important from the perspectives of clinical practice and public health. It is valuable in terms of arousing attention to the important issues – cigarette smoking, alcohol drinking and betel nut chewing.</p> <p>Comments:</p> <p>1. Hs CRP levels in different KL grades of knee OA were different. High-sensitivity C-reactive protein concentration was lower in grade I than in KL-II, -III and -IV knee OA (Hanada et al, Ann Clin Biochem. 2015 Sep 17. pii: 0004563215610142). The inclusion criterium of the present study was ‘KL grade 1 or 2 in at least one leg’; but there was significant difference between the concentration of hsCRP in grade 1</p>
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	<p>and grade 2; the authors may need to make further efforts on this potential misclassification bias.</p> <p>2. Smoking has been shown to be associated with increased concentration of hsCRP in pre-existing literature. This study reported higher levels of hsCRP in the smoking group of early OA but can't provide the causality. The authors may need to tell us what new contribution this research has achieved.</p> <p>3. According to epi data, OA affected mainly female. In addition to gender, other risk factors included age and obesity (Lee et al., Int J Rheum Dis. 2015 Nov 18. doi: 10.1111/1756-185X.12795; Cir Cir. 2015 Dec 11. pii: S0009-7411(15)00221-2). In this present study, most participants were male (76.4% in hi hsCRP group, 68.9% in low hsCRP group), which raised the question of representativeness of the study group for knee OA.</p> <p>4. The authors defined 'elevated hsCRP' by ≥ 3.0mg/L but did not tell how this threshold was decided.</p> <p>5. Lots of other factors were closely associated with elevated hsCRP levels, including rheumatological diseases, infectious disease, even chronic kidney diseases. They should be excluded or adjusted in analysis.</p> <p>6. Lipid levels were included in the analyses, but the author may need to provide evidences to support the association between lipid level and hsCRP. So were the socio-demographic factors.</p> <p>7. Though it is a merit to call attention to alcohol drinking and betel nut chewing, the authors did not provide adequate evidence / literature to support the indication to include these 2 parts into the study. Besides, the case numbers of betel nut chewers were too small for a properly conducted study.</p> <p>8. The prevalence of betel nut chewing in Hunan province was reported to be much higher (~16% [J Oral Pathol Med 2012;41:748-54] to 35.3% [Community Dent Oral Epidemiol 1997;25:177-80]), much higher than the prevalence in this study, which may challenge the validity of the data.</p> <p>9. Based on the research finding and tentative conclusion, Fig 1 provides a speculation rather than a research finding.</p> <p>10. Recommend a professional English editing to make up several grammatical mistakes.</p> <p>11. Inconsistent terminology in areca nut and betel quilt; do they mean same things or not? Need clarification or unification.</p>
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REVIEWER	Fahad Hanna Public Health Program, Department of Health Sciences, Qatar University, Qatar
REVIEW RETURNED	09-Jan-2016

GENERAL COMMENTS	<p>This is a cross-sectional study that looked at the relationship between cigarette smoking, alcohol drinking and betel quilt chewing and hsCRP in subjects with early kneeOA. These sorts of studies can provide basis to further research and strategies for treatment and prevention of OA, however, they can also be complicated due to the nature of hsCRP and its association with a number of physiological and pathological states of the human body. hsCRP has been found in early OA and is universally recognized as a marker for inflammation, or even pre-inflammation, which is what makes it complicated due to the difficulty in addressing this in the studies populations. This is something researchers have to at least acknowledge.</p>
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	<p>Specific comments:</p> <p>Abstract: Background is missing. a line or 2 here to provide the reader with a quick perspective.</p> <p>Method: should indicate here the study design. Results: I personally think that language should be made easier for reader to understand. example, the use of quartiles is not clear that the majority of the population are non-smokers. perhaps numbers of smokers and non-smokers here would be better, then talk about dose response! Conclusion: should add here that being a cross-sectional design results need to be confirmed with a longitudinal study etc. This is mentioned in limitations", however, it is also proper to mention here future direction, i.e. the longitudinal design.</p> <p>Main body: methods- study population: this section should start by describing study population, numbers, age, gender etc. directly followed by inclusion and exclusion criteria. the authors start by discussion the protocol which is clearly not under "population"</p> <p>I am a little worried about hidden confounders here, however, as mentioned above, this can be a little complicated. It would have been great if authors could mention somewhere in their methods that they made all efforts to ensure that inflammation or infection cases were identified, if any. also, adjusting for things like pre-inflammation status is almost impossible. this might not necessarily be a big issue here. I was unsure if authors were claiming that inflammation precedes knee OA or it is a result of OA! perhaps this can be clarified a little better in discussion page 8, line 236 Page 10, Line 291, "potentially confounding factors, especially diabetes and hypertension, were adjusted to improve the reliability of the results" need to add "for" after "adjusted". also, adjusting for confounders is not done to improve reliability but rather to show that association is independent of confounders! I also think that all confounders that the authors adjusted for should be mentioned here.</p> <p>minor comments/suggestions Table 1. should indicate here number of smokers vs non-smokers and so on. this is unclear when looking at this characteristics table Table 2 and 3, either combine both tables into one bigger one or find a way to change the wording of the titles; a little unconventional the way it is now Figure 1. it is unnecessary and almost incorrect</p>
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VERSION 1 – AUTHOR RESPONSE

Replies to the Reviewer: 1

Reviewer Name: Yueh-Han Hsu

Institution and Country: Department of Public Health and Department of Health Services Administration, China Medical University, Taiwan

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Comment 6: The authors of the manuscript entitled “Associations of cigarette smoking, betel nut chewing and alcohol drinking with high-sensitivity C-reactive protein in early radiographic knee osteoarthritis” conducted a cross-sectional research to explore the association between levels of hsCRP in early radiographic knee OA with 3 important abused substances, i.e., cigarette smoking, alcohol drinking and betel nut chewing. The definition of early radiographic knee OA denoted KL grade 1 or 2 in at least one leg.

In total, there were 148 participants with high hsCRP level (≥ 3.0 mg/L), of which the proportion of smoking, drinking and betel nut chewing were 41.9% (~62 participants), 44.6% (~66 participants) and 2% (~3 participants). The case number of the participants with low hsCRP (< 3.0 mg/L) was 788, of which the proportion of smoking, drinking and betel nut chewing were 29.7% (~234 participants), 42.8% (~337 participants) and 4.7% (~37 participants). The authors concluded that cigarette smoking, but not alcohol drinking nor betel nut chewing, was positively associated with the serum hsCRP level in early radiographic knee OA patients

The topic is interesting and important from the perspectives of clinical practice and public health. It is valuable in terms of arousing attention to the important issues – cigarette smoking, alcohol drinking and betel nut chewing.

Response: Thank you so much for your valuable comments.

Comment 7: 1. Hs CRP levels in different KL grades of knee OA were different. High-sensitivity C-reactive protein concentration was lower in grade I than in KL-II, -III and -IV knee OA (Hanada et al, *Ann Clin Biochem.* 2015 Sep 17. pii: 0004563215610142). The inclusion criterium of the present study was ‘KL grade 1 or 2 in at least one leg’; but there was significant difference between the concentration of hsCRP in grade 1 and grade 2; the authors may need to make further efforts on this potential misclassification bias.

Response: We are very sorry for this confusion. If at least one knee joint was graded as K-L 1 or 2, the participant would be diagnosed with early radiographic knee OA (Muneaki Ishijima, Taiji Watari, Kiyohito Naito, et al. Relationships between biomarkers of cartilage, bone, synovial metabolism and knee pain provide insights into the origins of pain in early knee osteoarthritis. *Arthritis Research & Therapy* 2011; 13: R22; J. van Tiel, E. E. Bron, C. J. Tiderius, et al. Reproducibility of 3D delayed gadolinium enhanced MRI of cartilage (dGEMRIC) of the knee at 3.0 T in patients with early stage osteoarthritis. *Eur Radiol* 2013; 23: 496–504; Jasper van Tiel, Max Reijman, Pieter K. Bos, et al. Delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC) Shows No Change in Cartilage Structural Composition after Viscosupplementation in Patients with Early-Stage Knee Osteoarthritis. *PLoS ONE* 2013; 8(11): e79785; Alberto Gobbi • Dnyanesh Lad • Georgios Karnatzikos. The effects of repeated intra-articular PRP injections on clinical outcomes of early osteoarthritis of the knee. *Knee Surg Sports Traumatol Arthrosc* 2014; 20 April Publish Online.). Previous study indicated that high serum hsCRP level may be related to a variety of OA-associated symptoms, such as pain and loss of physical function (Jin X, Beguerie JR, Zhang W, et al. Circulating C reactive protein in osteoarthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015; 74(4): 703-710.). Moreover, some other studies indicated that a higher level of CRP may serve as a predictive factor for OA progression (Spector TD, Hart DJ, Nandra D, et al. Low-level increases in serum C-reactive protein are present in early osteoarthritis of the knee and predict progressive disease. *Arthritis Rheum* 1997; 40(4): 723-727; Smith JW, Martins TB, Gopez E, et al. Significance of C-reactive protein in osteoarthritis and total knee arthroplasty outcomes. *Ther Adv Musculoskelet Dis* 2012; 4(5): 315-325.) and is also associated with a lower gain in muscle strength over time in knee OA patients (Sanchez-Ramirez DC, Van der Leeden M, Van der Esch M, et al. Elevated C-reactive protein is associated with lower increase in knee muscle strength in patients with knee osteoarthritis: a 2-year follow-up study in the Amsterdam Osteoarthritis (AMS-OA) cohort. *Arthritis Res Ther* 2014; 16(3): R123.). We were focusing on the population of early knee OA. It seems effective to relieve OA-associated symptoms and delay OA development by lowering the serum CRP level. The present study showed that cigarette smoking

was positively associated with the serum hsCRP level in early radiographic knee OA patients, independent of some major confounding factors. It seems to be effective to lower the serum CRP level by giving up smoking. We did not explore the association between hsCRP with knee OA.

Comment 8: 2. Smoking has been shown to be associated with increased concentration of hsCRP in pre-existing literature. This study reported higher levels of hsCRP in the smoking group of early OA but can't provide the causality. The authors may need to tell us what new contribution this research has achieved.

Response: We are very sorry for this confusion. Previous study indicated that high serum hsCRP level may be related to a variety of OA-associated symptoms, such as pain and loss of physical function (Jin X, Beguerie JR, Zhang W, et al. Circulating C reactive protein in osteoarthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015; 74(4): 703-710.). Moreover, some other studies indicated that a higher level of CRP may serve as a predictive factor for OA progression (Spector TD, Hart DJ, Nandra D, et al. Low-level increases in serum C-reactive protein are present in early osteoarthritis of the knee and predict progressive disease. *Arthritis Rheum* 1997; 40(4): 723-727; Smith JW, Martins TB, Gopez E, et al. Significance of C-reactive protein in osteoarthritis and total knee arthroplasty outcomes. *Ther Adv Musculoskelet Dis* 2012; 4(5): 315-325.) and is also associated with a lower gain in muscle strength over time in knee OA patients (Sanchez-Ramirez DC, Van der Leeden M, Van der Esch M, et al. Elevated C-reactive protein is associated with lower increase in knee muscle strength in patients with knee osteoarthritis: a 2-year follow-up study in the Amsterdam Osteoarthritis (AMS-OA) cohort. *Arthritis Res Ther* 2014; 16(3): R123.). We were focusing on the population of early knee OA. It seems effective to relieve OA-associated symptoms and delay OA development by lowering the serum CRP level. The present study further showed that cigarette smoking was positively associated with the serum hsCRP level in early radiographic knee OA patients, independent of some major confounding factors. It seems effective to lower the serum CRP level by giving up smoking in early knee OA patients. Maybe this is the new contribution of this research has achieved. This is first study indicated that cigarette smoking was positively associated with the serum hsCRP level in early radiographic knee OA which may provide a new insight into the treatment of early knee OA. (Line 331-335)

Comment 9: 3. According to epi data, OA affected mainly female. In addition to gender, other risk factors included age and obesity (Lee et al., *Int J Rheum Dis*. 2015 Nov 18. doi: 10.1111/1756-185X.12795; *Cir Cir*. 2015 Dec 11. pii: S0009-7411(15)00221-2). In this present study, most participants were male (76.4% in hi hsCRP group, 68.9% in low hsCRP group), which raised the question of representativeness of the study group for knee OA.

Response: We are very sorry for this confusion. In this present study, most participants were actually male (76.4% in hi hsCRP group, 68.9% in low hsCRP group). However, the target population of this study is not the whole OA patients but the early OA patients (KL 1 or 2). Our previous study showed that 58.6% knee OA patients were female which was consistent with studies of other groups (Chao Zeng, Jie Wei, Hui Li, et al. Relationship between Serum Magnesium Concentration and Radiographic Knee Osteoarthritis. *J Rheumatol* 2015; 42: 1231-1236.).

Comment 10: 4. The authors defined 'elevated hsCRP' by ≥ 3.0 mg/L but did not tell how this threshold was decided.

Response: We are very sorry for this confusion. The references has been added into the manuscript. (Line 249, 523-527)

Comment 11: 5. Lots of other factors were closely associated with elevated hs CRP levels, including rheumatological diseases, infectious disease, even chronic kidney diseases. They should be excluded

or adjusted in analysis.

Response: As you suggested, we did a sensitivity analysis by excluding patients with chronic renal failure (diagnosed by serum creatinine $\geq 133 \mu\text{mol/l}$). The results did not change significantly. The data were shown below:

Variable	Adjusted odds ratio	95% confidence intervals	P value
Smoking	<0.01#		
0/day	Reference	Reference	-
1-10/day	1.58	(0.93-2.69)	0.09
11-20/day	1.28	(0.58-2.81)	0.55
>20/day	2.18	(1.25-3.80)	<0.01
Alcohol drinking	1.11	(0.73-1.68)	0.63
Betel quilt chewing	0.36	(0.11-1.22)	0.10

Line (261-262, 293-294)

Comment 12: 6. Lipid levels were included in the analyses, but the author may need to provide evidences to support the association between lipid level and hsCRP. So were the socio-demographic factors.

Response: We are very sorry for this confusion. The references has been added into the manuscript. (Line 257-258, 528-536)

Comment 13: 7. Though it is a merit to call attention to alcohol drinking and betel nut chewing, the authors did not provide adequate evidence / literature to support the indication to include these 2 parts into the study. Besides, the case numbers of betel nut chewers were too small for a properly conducted study.

Response: We are very sorry for this confusion. Since betel quilt chewing and alcohol drinking are the most popular substance abuse habits all over the world, the associations of alcohol drinking with OA and CRP have been observed for decades (Kondo, K., et al., Factors associated with pain and functional limitation in Japanese male patients with knee osteoarthritis. *Rheumatol Int*, 2007. 27(12): p. 1135-42; Muthuri, S.G., et al., Beer and wine consumption and risk of knee or hip osteoarthritis: a case control study. *Arthritis Res Ther*, 2015. 17: p. 23; Albert, M.A., R.J. Glynn and P.M. Ridker, Alcohol consumption and plasma concentration of C-reactive protein. *Circulation*, 2003. 107(3): p.443-7. Zairis, M.N., et al., C Reactive protein, moderate alcohol consumption, and long term prognosis after successful coronary stenting: four year results from the GENERATION study. *Heart*, 2004. 90(4): p. 419-24; Raum, E., et al., Long-term and short-term alcohol consumption and levels of C-reactive protein. *Int J Cardiol*, 2007. 121(2): p.224-6; Averina, M., et al., C-reactive protein and alcohol consumption: Is there a U-shaped association? Results from a population-based study in Russia. The Arkhangelsk study. *Atherosclerosis*, 2006. 188(2): p.309-15.). However, they are still controversial and inconclusive. On the contrary, few studies have explored the associations of betel quilt chewing with OA or CRP (Tsai, A.C. and H.J. Tsai, The association of age, gender, body fatness and lifestyle factors with plasma C-reactive protein concentrations in older Taiwanese. *J Nutr Health Aging*, 2010. 14(6): p. 412-6; Shafique, K., et al., Areca nut chewing and systemic inflammation: evidence of a common pathway for systemic diseases. *J Inflamm (Lond)*, 2012. 9(1): p. 22.). Therefore, we examined the associations of betel quilt chewing and alcohol drinking with the serum hsCRP level in early radiographic knee OA patients. (Line 173-176)
Actually the number of betel quilt chewers in this cohort is too small, which has been added into the limitations. (Line 390-391)

Comment 14: 8. The prevalence of betel nut chewing in Hunan province was reported to be much

higher (~16% [J Oral Pathol Med 2012;41:748-54] to 35.3% [Community Dent Oral Epidemiol 1997;25:177-80]), much higher than the prevalence in this study, which may challenge the validity of the data.

Response: We are sorry for this confusion. The prevalence of betel quilt chewing in this cohort is actually lower than that in other Hunan studies. It could be due to the following reasons. Firstly, the population of this study may represent a more affluent group of people in the general population who can afford health screening program. Secondly, the sample size of this study is relatively small (936 subjects). Thirdly, we only concern the current chewers, so the ex-chewers might be ignored. These above might lead to the relative lower prevalence of betel quilt chewers in this present study. (Line 348-356). However, we have already undertaken a high-quality and large-scale epidemiology survey for OA in Hunan rural area. Further prospective study on the relationship between betel quilt chewing and OA is preparing.

Comment 15: 9. Based on the research finding and tentative conclusion, Fig 1 provides a speculation rather than a research finding.

Response: Based on the comments of Reviewer 2 and the non-significant contribution of this figure, it has been deleted.

Comment 16: 10. Recommend a professional English editing to make up several grammatical mistakes.

Response: We are very sorry for this confusion, the manuscript has been corrected for grammatical mistakes and spelling errors by a professional copyediting service.

Comment 17: 11. Inconsistent terminology in areca nut and betel quilt; do they mean same things or not? Need clarification or unification.

Response: We are very sorry for this confusion. The inconsistent terminology has been unified. (Line 338, 343, 345, 347)

Replies to the Reviewer: 2:

Reviewer Name: Fahad Hanna

Institution and Country: Public Health Program, Department of Health Sciences, Qatar University, Qatar

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Comment 18: This is a cross-sectional study that looked at the relationship between cigarette smoking, alcohol drinking and betel quilt chewing and hsCRP in subjects with early knee OA. These sorts of studies can provide basis to further research and strategies for treatment and prevention of OA, however, they can also be complicated due to the nature of hsCRP and its association with a number of physiological and pathological states of the human body. hsCRP has been found in early OA and is universally recognized as a marker for inflammation, or even pre-inflammation, which is what makes it complicated due to the difficulty in addressing this in the studies populations. This is something researchers have to at least acknowledge.

Response: This limitation has been added into the manuscript. (Line 394-397)

Comment 19: Specific comments: Abstract: Background is missing. a line or 2 here to provide the reader with a quick perspective.

Response: Done accordingly. (Line 38-39)

Comment 20: Method: should indicate here the study design.

Response: Done accordingly. (Line 47)

Comment 21: Results: I personally think that language should be made easier for reader to understand. example, the use of quartiles is not clear that the majority of the population are non-smokers. perhaps numbers of smokers and non-smokers here would be better, then talk about dose response!

Response: We are very sorry for the confusion, we have adjusted the text as you suggested. (Line 59-65)

Comment 22: Conclusion: should add here that being a cross-sectional design results need to be confirmed with a longitudinal study etc. This is mentioned in limitations", however, it is also proper to mention here future direction, i.e. the longitudinal design.

Response: Done accordingly. (Line 70-71)

Comment 23: Main body:

methods- study population: this section should start by describing study population, numbers, age, gender etc. directly followed by inclusion and exclusion criteria. the authors start by discussion the protocol which is clearly not under "population"

Response: Done accordingly. (Line 189-197)

Comment 24: I am a little worried about hidden confounders here, however, as mentioned above, this can be a little complicated. It would have been great if authors could mention somewhere in their methods that they made all efforts to ensure that inflammation or infection cases were identified, if any. also, adjusting for things like pre-inflammation status is almost impossible. this might not necessarily be a big issue here.

Response: Sensitivity analysis by excluding patients with chronic kidney diseases showed a similar results. And the limitation "Thirdly, the results of the present study can be complicated due to the nature of hsCRP (universally recognized as a marker for inflammation or even pre-inflammation) and its associations with a number of physiological and pathological states of the human body" has been added into the manuscript. (Line 394-397, 261-262, 293-294)

Comment 25: I was unsure if authors were claiming that inflammation precedes knee OA or it is a result of OA! perhaps this can be clarified a little better in discussion page 8, line 236

Response: We are very sorry for this confusion. The sentence has been rewritten (Line 306-308) and the manuscript has been corrected for grammatical mistakes and spelling errors by a professional copyediting service.

Comment 26: Page 10, Line 291, "potentially confounding factors, especially diabetes and hypertension, were adjusted to improve the reliability of the results" need to add "for" after "adjusted". also, adjusting for confounders is not done to improve reliability but rather to show that association is

independent of confounders! I also think that all confounders that the authors adjusted for should be mentioned here.

Response: Done accordingly. (Line 376-380)

Comment 27: minor comments/suggestions

Table 1. should indicate here number of smokers vs non-smokers and so on. this is unclear when looking at this characteristics table

Response: We have added the number of smoker and non-smoker into the table as you suggested. (table 1)

Comment 28: Table 2 and 3, either combine both tables into one bigger one or find a way to change the wording of the titles; a little unconventional the way it is now

Response: We have combined these two table into a bigger one as you suggested. (table 2)

Comment 29: Figure 1. it is unnecessary and almost incorrect

Response: The figure 1 has been deleted.

Special thanks to the Editors and Reviewers for their valuable comments and suggestions.

VERSION 2 – REVIEW

REVIEWER	Fahad Hanna Qatar University, Qatar
REVIEW RETURNED	10-Feb-2016

GENERAL COMMENTS	<p>The authors have done a very good job, following initial revision. I think this paper is now worthy of publication in the BMJ-Open journal. There are some minor issues which I have spotted and listed here:</p> <p>Abstract:</p> <p>this is how it currently reads "Objective: High-sensitivity C-reactive protein (hsCRP) is possibly related to osteoarthritis (OA) progression and a variety of OA-related symptoms. This study aims to examine the associations of cigarette smoking, betel quilt chewing and alcohol drinking with the hsCRP in early radiographic knee OA."</p> <p>you need to start with "Background" rather than "objectives" and should read as follow:</p> <p>background: Osteoarthritis (OA) is a so and so disease characterized by so and so. High-sensitivity C-reactive protein (hsCRP) is possibly related to osteoarthritis (OA) progression and a variety of OA-related symptoms. Objectives: This study aims to examine the associations of cigarette smoking, betel quilt chewing and alcohol drinking with the hsCRP in early radiographic knee OA."</p> <p>Also, I think that all of the next section should be called "methods" or</p>
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	something like "materials and methods", as opposed to having few subheadings there before you reach the Results section> my point is that you should have the following subheadings/sections in the Abstract: background followed by objectives followed by Methods followed by Results followed by Conclusion.
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VERSION 2 – AUTHOR RESPONSE

Reviewer Name: Fahad Hanna

Institution and Country: Qatar University, Qatar

Please state any competing interests or state 'None declared': No competing interest

Please leave your comments for the authors below

Comment 6: The authors have done a very good job, following initial revision. I think this paper is now worthy of publication in the BMJ-Open journal. There are some minor issues which I have spotted and listed here:

Abstract:

this is how it currently reads

"Objective: High-sensitivity C-reactive protein (hsCRP) is possibly related to osteoarthritis (OA) progression and a variety of OA-related symptoms. This study aims to examine the associations of cigarette smoking, betel quilt chewing and alcohol drinking with the hsCRP in early radiographic knee OA."

you need to start with "Background" rather than "objectives" and should read as follow:

background: Osteoarthritis (OA) is a so and so disease characterized by so and so. High-sensitivity C-reactive protein (hsCRP) is possibly related to osteoarthritis (OA) progression and a variety of OA-related symptoms.

Objectives: This study aims to examine the associations of cigarette smoking, betel quilt chewing and alcohol drinking with the hsCRP in early radiographic knee OA."

Also, I think that all of the next section should be called "methods" or something like "materials and methods", as opposed to having few subheadings there before you reach the Results section> my point is that you should have the following subheadings/sections in the Abstract: background followed by objectives followed by Methods followed by Results followed by Conclusion.