PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Soft Drink Intake and Progression of Radiographic Knee Osteoarthritis: Data from the Osteoarthritis Initiative
AUTHORS	Lu, Bing; Ahmad, Oneeb; Zhang, Fang-Fang; Driban, Jeffrey; Duryea, Jeffrey; Lapane, Kate; McAlindon, Timothy; Eaton, Charles

VERSION 1 - REVIEW

REVIEWER	George Peat Professor of Clinical Epidemiology Arthritis Research UK Primary Care Centre Keele University, UK No conflicts of interest to declare.
REVIEW RETURNED	30-Apr-2013

GENERAL COMMENTS	This study estimates the direction and magnitude of association between soft drink consumption measured at baseline and progression over 4 years in medial tibiofemoral knee osteoarthritis in adults with a mean age of 62 yrs and evidence of medial tibiofemoral osteoarthritis at baseline. The authors find a dose-response relationship in men, particularly non-obese men, but not in women. It is an important study with a novel hypothesis that builds on the role of nutrition in OA incidence and progression. OAI provides arguably the best source of data for this enquiry, particularly on OA progression, and in my opinion the authors' handling and reporting of this data is exemplary. It is clearly written, rigorous in design and execution, and generally well-judged in interpretation. 1. Exposure measurement (p6). As per outcome measurement, the authors could provide the specific variable code used to define exposure. It was unclear what the basis for combining categories was. 2. Statistical analysis (p7). The term 'exploratory analyses' is rather misleading. What the authors appear to have undertaken is a very sensible evaluation of the distribution (but not joint distribution) of exposure, outcome, and covariates. One potential source of residual confounding is poor fit of the parameters to the covariate data. Did the authors attempt to fit non-linear terms where appropriate to covariates, e.g. BMI and PASE at baseline? 3. Attrition. The follow-up rates are high in OAI but I missed the actual numbers lost to follow-up by exposure status. 4. Residual confounding. The authors state that 'we controlled for potential confounding by most known risk factors…' (p11) but the issue of residual confounding due to incomplete adjustment for the causal mechanism represented by these risk factors deserves some

	recognition in the Discussion. Two possibilities: (i) as the association was strongest in non-obese men and the exposure was most common in younger men, could heavy physical activity – either sports/gym or occupational (working up a thirst?!) - be a potential confounder given that the PASE was developed for elderly populations and may not adequately capture the spectrum of physical activity among younger population (reference 24 is weak), (ii) the cumulative effect of weight gain and maintenance of overweight/obesity prior to baseline may have a lagged effect that is only partially adjusted by using baseline BMI or weight change in the prospective period (e.g. Wills ARD 2012 on lifetime BMI and risk of incident knee OA). This argument may of course also apply to the exposure of interest. Minor P8. Suggest 'All categories of soft drink intake were represented in participants at baseline.'

REVIEWER	Weiya Zhang Assosicate Professor and Reader University of Nottingham UK COI: none
REVIEW RETURNED	30-Apr-2013

THE STUDY	It is not clear to me what are "soft drinks" that the auhors attempted to define. This has not been clearly defined in the methods. Stweented soft drinks could be anything. It would be helpful if the authors could provide a list of the soft drinks they classifid. The authors used standard radiographic method to measure the joint space wdith. There is nothing new. The abstract overstated the method and it made me think that they used more advanced imaging such as MRI. I recommend that the authors spell out radiographic measures that would be much clearer to me.
RESULTS & CONCLUSIONS	Two potential confounding factors (beer and alcohol consumption, and gout) have yet to be adjusted. The measure of the soft drinks in the past 12 months at baseline may not open to misclassification bias. This has been discussed as a caveat of this study.
REPORTING & ETHICS	I haven't come across this. The authors need to clarify the ethical issues even for a database study.
GENERAL COMMENTS	Good design, sound methods, novel finding (if it is true) and well written paper! [1] The definition of soft drinks needs further clarification. Would be very helpful if you could provide a list of soft drinks you attempted to define in the methods; [2] I cannot see any information about alcohol consumption, especially beer, neither for comorbidities eg, gout. It is well known that beer and fructose are the risk factors for gout, and gout is associated with OA. Whether they confounded the association identified by this study remains unknown.

	[3] Please spell out the radiograph measures for progression and only TF joint and medial compartment were examined for this study in the abstract (and key messages if possible). Please discuss this may be one of the caveats for the study.

VERSION 1 – AUTHOR RESPONSE

Reviewer:George Peat
Professor of Clinical Epidemiology
Arthritis Research UK Primary Care Centre
Keele University, UK

No conflicts of interest to declare.

This study estimates the direction and magnitude of association between soft drink consumption measured at baseline and progression over 4 years in medial tibiofemoral knee osteoarthritis in adults with a mean age of 62 yrs and evidence of medial tibiofemoral osteoarthritis at baseline. The authors find a dose-response relationship in men, particularly non-obese men, but not in women.

It is an important study with a novel hypothesis that builds on the role of nutrition in OA incidence and progression. OAI provides arguably the best source of data for this enquiry, particularly on OA progression, and in my opinion the authors' handling and reporting of this data is exemplary.

It is clearly written, rigorous in design and execution, and generally well-judged in interpretation.

1. Exposure measurement (p6). As per outcome measurement, the authors could provide the specific variable code used to define exposure. It was unclear what the basis for combining categories was.

Thank you for your suggestion. The ways to combine soft drink categories were not consistent in literature. Many published studies in obesity and other chronic diseases research used the similar cut-off points, such as, <1, 2-4, 5-6, >6/week. (such as: JAMA. 2010;304(20):2270-2278, and N Engl J Med 2012;367:1387-96.). Our sample are primarily old people with less soft drink intake than general population. We used very close cut-off point, 0, <1, 2-4,>5 /week.

2. Statistical analysis (p7). The term 'exploratory analyses' is rather misleading. What the authors appear to have undertaken is a very sensible evaluation of the distribution (but not joint distribution) of exposure, outcome, and covariates. One potential source of residual confounding is poor fit of the parameters to the covariate data. Did the authors attempt to fit non-linear terms where appropriate to covariates, e.g. BMI and PASE at baseline?
For any continuous variables, we tested linearity assumption of linear model first. We didn't find non-linear relationship between BMI, PASE and JSW change. For BMI, we used WHO categories. For PASE, we used continuous scale.

3. Attrition. The follow-up rates are high in OAI but I missed the actual numbers lost to follow-up by exposure status.

Thanks. We added the rate of loss to follow up in the "Subjects" section. The overall loss to follow up rate was 16.8% over 4 years.
4. Residual confounding. The authors state that 'we controlled for potential confounding by most known risk factors…' (p11) but the issue of residual confounding due to incomplete adjustment for the causal mechanism represented by these risk factors deserves some recognition in the Discussion. Two possibilities: (i) as the association was strongest in non-obese men and the exposure was most

common in younger men, could heavy physical activity – either sports/gym or occupational (working up a thirst?!) - be a potential confounder given that the PASE was developed for elderly populations and may not adequately capture the spectrum of physical activity among younger population (reference 24 is weak), (ii) the cumulative effect of weight gain and maintenance of overweight/obesity prior to baseline may have a lagged effect that is only partially adjusted by using baseline BMI or weight change in the prospective period (e.g. Wills ARD 2012 on lifetime BMI and risk of incident knee OA). This argument may of course also apply to the exposure of interest.

Thank you for your great suggestions. In OAI, the participants were primarily older people, the mean age at baseline is 61 years old with range of 45 to 79. Only 14% of them were less than age 50. So we used PASE as the physical activity measure. We could not consider the younger people in the analysis.

We totally agree that BMI may have lagged or cumulative effect, however we only have BMI measure after baseline. We could not evaluate the long-term BMI effect as a possible confounding factor. However, BMI is highly correlated across years in adult life in general.

Minor
P8. Suggest ‘All categories of soft drink intake were represented in participants at baseline.’

Thank you.

Reviewer: Weiya Zhang
Assosicate Professor and Reader
University of Nottingham
UK

COI: none

It is not clear to me what are "soft drinks" that the auhors attempted to define. This has not been clearly defined in the methods. Stweented soft drinks could be anything. It would be helpful if the authors could provide a list of the soft drinks they classifid.

The authors used standard radiographic method to measure the joint space wdith. There is nothing new. The abstract overstated the method and it made me think that they used more advanced imaging such as MRI. I recommend that the authors spell out radiographic measures that would be much clearer to me.

Two potential confounding factors (beer and alcohol consumption, and gout) have yet to be adjusted.

The measure of the soft drinks in the past 12 months at baseline may not open to misclassification bias. This has been discussed as a caveat of this study.

The authors need to clarify the ethical issues even for a database study.

Good design, sound methods, novel finding (if it is true) and well written paper!

[1] The definition of soft drinks needs further clarification. Would be very helpful if you could provide a list of soft drinks you attempted to define in the methods;

That is a great question. OAI just used simplified FFQ. The original question is that “regular soft drinks/bottled drinks like Snapple (not diet drinks), drink how often, past 12 months.” We don’t have

detailed information about the types of soft drinks. But it does not include diet drink. We believe it could represent the sugar-sweetened beverage in general.
[2] I cannot see any information about alcohol consumption, especially beer, neither for comorbidities eg, gout. It is well known that beer and fructose are the risk factors for gout, and gout is associated with OA. Whether they confounded the association identified by this study remains unknown.

Thank you for your suggestion. We added covariate self-reported gout (overall 3.63%), beer and total alcohol intake. However, they were not significant in the model (Gout: p=0.285; Beer intake: p=0.664; Overall alcohol intake in grams/day: p=0.559). Also additional adjustment didn't change the results.

[3] Please spell out the radiograph measures for progression and only TF joint and medial compartment were examined for this study in the abstract (and key messages if possible). Please discuss this may be one of the caveats for the study.

We added quantitative medial tibiofemoral JSW in abstract. Thanks a lot.

We agree that standard radiographic method is nothing new. Dr Duryea, the co-author of this manuscript, is an international leader to develop a software based method to measure JSW in mm. The validation study shows a high correlation with MRI measure. JSW method is reliable with much lower cost compared to MRI measure.

VERSION 2 – REVIEW

REVIEWER	George Peat Professor of Clinical Epidemiology Keele University UK No conflicts of interest
REVIEW RETURNED	13-May-2013

THE STUDY	I apologise for not making myself clear in the original review. The authors are able to specify variables using their variable label names in OAI (e.g. kXR_SQ_BU). I am asking that they do the same for their exposure measurement in this study since this will permit readers to repeat the analyses if necessary, but more likely just be able to know precisely what question and response options formed the basis of exposure measurement (the choice of categorisation for analysis was not really a concern for me).
RESULTS & CONCLUSIONS	The authors have left unmodified their statement of limitations in the Discussion: "We cannot prove that the observed associations are causal because residual confounding could theoretically affect the observed associations. However, we controlled for potential confounding by most known risk factors that are plausibly associated with soft drink consumption and changes in these variables over time." The point I raised in my original review, and which the authors' response appears to accept, is that because the effect of BMI may be lagged, and that the cumulative exposure to overweight/obesity will not be perfectly correlated with baseline BMI, adjustment for baseline BMI cannot be so confidently assumed to have removed the confounding influence of BMI. It is a simple matter for the authors to insert a sentence to this effect and thereby help readers recognise this potential source of residual confounding in this (and every other similar) study. Regarding adjustment for physical activity, I am aware of the age

	distribution of OAI and the authors' response did not provide a convincing rebuttal of the point that the PASE may have afforded a less than optimal adjustment for physical activity in the younger participants. I am aware of no validation studies in adults aged <65 years (e.g. Terwee et al., 2011), i.e. over half the sample in the current study. Again, it seems rather simple for this potential source of residual confounding to be acknowledged by the authors without seriously threatening the conclusions of the study as they stand.

REVIEWER	Weiya Zhang Associate Professor and Reader The University of Nottingham UK
REVIEW RETURNED	21-May-2013

REPORTING & ETHICS	not sure about ethics for this database study. I guess this has been obtaioend by OAI which may be described in the methods.
GENERAL COMMENTS	All my comments have been addressed and the paper is ready for publication.

VERSION 2 – AUTHOR RESPONSE

Reviewer: George Peat
Professor of Clinical Epidemiology
Keele University
UK

No conflicts of interest

I apologise for not making myself clear in the original review. The authors are able to specify variables using their variable label names in OAI (e.g. kXR_SQ_BU). I am asking that they do the same for their exposure measurement in this study since this will permit readers to repeat the analyses if necessary, but more likely just be able to know precisely what question and response options formed the basis of exposure measurement (the choice of categorisation for analysis was not really a concern for me).
Thanks. We have added the variable name for exposure variable in section “Assessment of soft drink consumption”.

The authors have left unmodified their statement of limitations in the Discussion: "We cannot prove that the observed associations are causal because residual confounding could theoretically affect the observed associations. However, we controlled for potential confounding by most known risk factors that are plausibly associated with soft drink consumption and changes in these variables over time."
The point I raised in my original review, and which the authors' response appears to accept, is that because the effect of BMI may be lagged, and that the cumulative exposure to overweight/obesity will not be perfectly correlated with baseline BMI, adjustment for baseline BMI cannot be so confidently assumed to have removed the confounding influence of BMI. It is a simple matter for the authors to insert a sentence to this effect and thereby help readers recognise this potential source of residual confounding in this (and every other similar) study.
Thank you for your thoughtful suggestion. We updated the discussion about the limitation.

Regarding adjustment for physical activity, I am aware of the age distribution of OAI and the authors' response did not provide a convincing rebuttal of the point that the PASE may have afforded a less than optimal adjustment for physical activity in the younger participants. I am aware of no validation

studies in adults aged <65 years (e.g. Terwee et al., 2011), i.e. over half the sample in the current study. Again, it seems rather simple for this potential source of residual confounding to be acknowledged by the authors without seriously threatening the conclusions of the study as they stand.

We have included some comments for PASE.

Reviewer: Weiya Zhang
Associate Professor and Reader
The University of Nottingham
UK

I'm not sure about ethics for this database study. I guess this has been obtaioend by OAI which may be described in the methods.
Yes, we have included a statement in section “Ethics approval”.

All my comments have been addressed and the paper is ready for publication.