Author’s response to reviews

Title: Adolescent wine consumption is inversely associated with long-term weight gain: Results from follow-up of 20 or 22 years

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Author’s response to reviews:

Thank you for considering publication of our manuscript in JN. We would also like to thank the reviewers for their clear and useful comments, which we have included in the updated script where we considered it appropriate. Reply to the comments can be seen below (@), with line numbers corresponding to the submitted manuscript.

Editor: Please add the dates for data collection to the abstract as it was not clear to the reviewers how old the data used in this manuscript was.

@ We have added the following in the abstract (Line: 5+): “The study was based on data from 720 Danish adolescents aged between 15 to 19 years at baseline from the Danish Youth and Sports Study (YSS). Self-reported alcohol use, height, weight, smoking, social economic status (SES) and physical activity levels were assessed in baseline surveys conducted in 1983 and 1985, and in the follow up survey which was conducted in 2005.”

Reviewer #1: Title: Consider putting directional nature of relationship

@ We have rephrased the title: “Adolescent wine consumption is inversely associated with long-term weight gain: Results from follow up of 20 or 22 years.”

1 Abstract:
1.1 Background: Awkwardly worded - please clarify

@ We have rephrased the background (Line: 2- 4): “Several studies have suggested a link between alcohol consumption and body weight. However, results from longitudinal studies have been inconsistent, and the association between adolescent alcohol consumption long-term weight gain has generally not been examined.”

1.2 Methods: Please include sample size, ages and years when data was collected. Please identify what analyses were conducted.

@ We have added the information (Line: 5+): “The study was based on data from 720 Danish adolescents aged between 15 to 19 years at baseline from the Danish Youth and Sports Study (YSS). Self-reported alcohol use, height, weight, smoking, social economic status (SES) and physical activity levels were assessed in baseline surveys conducted in 1983 and 1985, and in the follow up survey which was conducted in 2005. Multiple linear regression analyses were used to examine the association between alcohol consumption in adolescence and subsequent weight gain later in midlife.”

1.3 Results: Please reword your results. Results are either statistically significant or not. Borderline significance as a term is not recommended. Further, p-values need to be reported.

@ We agree with the reviewer and have now reported p-values and re-worded the result (Line: 11+): “Adolescent total alcohol consumption was inversely associated with subsequent body mass index (BMI) changes into midlife, but the results were not statistically significant (P =0.079) (β -0.14; 95% CI -0.28, 0.005) after adjustment for potential confounders. Wine consumption was found to be inversely associated to subsequent BMI gain (P = 0.001) (β -0.46; 95%CI -0.82, -0.09) while the results were not significant for beer and spirit. The relationship did not differ by gender, but smoking status was found to modify the relationship, and the inverse association between alcohol and BMI gain was seen only among non-smokers (P = 0.01) (β -0.24; 95%CI -0.41, -0.06) while no association was found among smokers. Neither adolescent nor attained socioeconomic status in adulthood modified the relationship between alcohol intake and subsequent BMI gain.”

2 Intro:

2.1 Missing period/full stop in line 37
2.2 Paragraph two of the introduction needs refining as it is currently lacking clarity. This is possibly due to the two ideas being presented (mechanisms and previous studies) and use of linking words and phrases that are un-necessary (this draws the reader’s attention away from what you are trying to say). A prime example of this is the use of 'In agreement' in line 33. Please clarify.

@We have tried to edit the introduction slightly. This should now make it more clear (Line: 29+): “Alcohol is considered to be a risk factor for obesity due to its high calorie content (3, 4) and because alcohol inhibits fat oxidation, which may result in accumulation of fat in adipose tissues (5). However, alcohol is also known to have a high thermogenic effect that may result in increased energy expenditure despite its high calorie content (6). Accordingly, results from previous studies examining the relationship between alcohol consumption and subsequent weight development are conflicting (7–15). Furthermore, prior studies mainly focused on weight changes related to adult alcohol consumption(7, 8, 15). A few studies have examined the association between adolescent alcohol intake and weight gain until adulthood(9–14), but these studies were most often cross sectional or lasted only into young adulthood and thus, it remains unclear whether adult obesity and weight gain into adulthood may be attributed to alcohol consumption during adolescence. Of the few previous prospective studies conducted among adolescents, some found a direct association between a high alcohol consumption and high self-reported weight gain until young adulthood (10, 11) while others found that adolescents with a high alcohol use had a lower risk of becoming obese in young adulthood than adolescents with low intakes (12). The results were mixed for girls and boys (15). The inconsistent results could be partly attributed to variations in the types of alcohol consumed. Previous studies have found mixed result for wine (16, 17, 18, 19), and beer intake (20, 21, 22), while spirit intake was more consistently found to be directly related to risk of weight gain (16, 20, 23). Most of these latter studies were, however, conducted among adult populations and therefore cannot be generalized to adolescents.”

3. Methods:

3.1 Please clarify the use of alcohol consumption data that is >34 years old.

@ We agree that the data is >34 years old. Even though this is a limitation of the study, we believe that the data have allowed us to have a longer follow up period. The section regarding this currently states (Line: 215-219): “Also, it can be argued that adolescent’s lifestyle habits, including their alcohol intake choices and patterns in 1983/85 were most likely different to today (33). However, a potential biologic association between adolescent alcohol intake, which is
occurring during a time in life that may leave imprinting of importance for long term weight development, would not be expected to be different.”

3.2 Methods state that n=1904 were invited and 41% participated, which =781. However, 779 were included in analysis. Please check.

Further, n=779 were eligible for inclusion and 720 were included in the analysis. The exclusion criteria accounts for n=58 instead of n=59 - please check.

@ We agree, additional information is needed in the study population section (Line: 61+): “For the present study, participants were excluded if they had missing data on Body Mass Index (BMI) at baseline or follow up (n 35), had missing information on baseline socioeconomic status (SES) (n 21), or smoking status (n 1) and alcohol consumption (n 1). Moreover, one participant was excluded due to an extreme and unlikely baseline BMI value of 158. After exclusion of the participants with missing values on different variables, the final study population consisted of 720 participants (Figure 1), of whom 294 were male and 426 were female.

3.3 If maternal SES was used in some cases, please state how many this variable was used for.

@ Maternal SES was used for 26 participants. This has been added to the study population section (Line:107) “If no SES were available for father, the maternal SES was used (n = 26)”

3.4 Was a validated questionnaire used to identify alcohol intake and physical activity?

@ The following has been added to the method section (Line: 74): “The questions were based on previously validated frequency questionnaire which sufficiently captured different types of alcohol consumption (24).

@ A validated method was used to collect physical activity data. A reference has been added to support the section (Line: 175): “Each activity and sport were assigned a metabolic equivalent (MET) score, the ratio of work metabolic rate to a standard resting metabolic rate (26).”


4. Statistical analysis:
4.1 Were data tested for normality?

@ The information has been added to statistical analyses section (Line: 123):” Data was tested for normality prior to performing the regression analysis. Model assumptions (investigating linearity of effects on outcomes, consistency with a normal distribution and variance homogeneity) were assessed for the fully adjusted models through residual plots.”

4.2 How were covariates selected? Please provide methodology.

@ We have added following in the statistical analyses section (Line: 127): “Covariates were chosen a priori through potential association with predictors and outcome.”

5. Results:

5.1 Please conduct analyses on non-participants in this sample as the sample size and inclusion criteria is different in the paper referenced.

@ We have now conducted analyses to compare participants and non- participants in the study (Table S1). Results have been added in the result section (Line: 143+): “Comparison of baseline characteristics between excluded and included participants revealed no significant differences between the two groups (Table S1).”

5.2 The result suggesting that there is an inverse relationship between alcohol and BMI needs to be re-written. As it is currently written, the results suggest that there is a relationship. However, the p-values do not suggest this. The wording is misleading. ‘Borderline significance’ as a term is not recommended.

@ We agree with the reviewer. This has now been edited

@ In the abstract section (Line: 11-13): “Adolescent total alcohol consumption was inversely associated with subsequent body mass index (BMI) changes into midlife, but the results were not statistically significant (P=0.079) (β -0.14; 95% CI -0.28, 0.005) after adjustment for potential confounders.”

@ In the result section(Line: 152): “There was no significant association between alcohol consumption during adolescence and change in BMI into midlife (P = 0.079).”
5.3 p-value for interactions was set at >0.1, please explain why the p=0.1 for interaction of potential con-founders is considered significant.

@The following is added to statistical analysis section (Line: 137+): “Results were considered statistically significant for P <0.05 in the primary analyses. However, for interaction analyses P <0.1 was used as the threshold for conducting stratified analyses, as the power to detect interaction effects was small due to the limited sample size.

6. Discussion:

6.1 Main results presented in lines 168-169 are misleading as there is no statistical significance to support the statement that alcohol (more generally) was associated with lower BMI.

@ We agree with the reviewer and this has now been edited (L: 174-176): “In this longitudinal analysis with 20 or 22 year follow up, we found that participants with higher wine consumption during adolescence subsequently gained less weight than those with a lower wine consumption.”

6.2 Line 174 is also misleading and unnecessary as the data suggests no evidence that SES mediates effect.

@ We have added a reference to support the statement (Line: 181). (27)


6.3 Lines 180-184 need to be supported by evidence.

@ References have been added to support the statements (Line: 193)

6.4 Paragraph starting at line 185 repeats information presented in the introduction – please amend

@ We have edited the section slightly (Line:191+)

6.5 Line 209-201 needs to be supported by evidence. Are the drinking habits different and if so by how much?
@ A reference to support the statement has been added. (Line: 215): “Also, it can be argued that Danish adolescent’s lifestyle habits including their alcohol intake choices and patterns in 1983/85 were most likely different to today (33)”

@ In the reference list:


6.6 Line 215 – what type of bias and how does it impact results?

@ Type of bias has been added in the section (Line: 220+): “Moreover, we used self-reported data and hence the study is potentially subject to reporting bias. Previous studies have noted overestimation of self-reported height and underestimation of weight resulting under-estimated BMI (34) particularly among the overweight and obese (35). The consequence of such a differential reporting bias among the overweight and obese is that significant associations may have been overlooked (as for total alcohol), and that “true” associations were even stronger than those observed (as for wine and weight gain)”

6.7 Please comment on whether the legal drinking age may have impacted these results. Further, the units of alcohol were low and whether this impacted on reliability of regression analysis.

@ It is unlikely that the legal age of drinking may have impacted the result. Until 1998 there were no legal drinking age limit. From 1998 the Danish government introduced an age limit of 15 years for purchasing alcohol, but by this time the baseline data were already collected. Although alcohol intake was low, there is no reason to believe that this impacted reliability of regression analysis as the data is reflective of drinking habit of adolescents more so because there was no legal restriction at the time of baseline data collection.

Reviewer #2: The overall content of the study is interesting which may call for other strongest study design. It also recognized a lot of limitations. However, it requires revisions on the specific issues of grammars including use of spaces, full stop and phrases like “we no found” (line 176).

@ corrections made
I’m not sure that the study is a trial because I can’t see intervention and control group assigned by the investigator.

@ The study is a longitudinal observation study. The YSS survey was retrospectively registered in the clinicaltrials.gov as a part of compliance with current requirements and for transparency purposes.

I do not agree that if smoking alone is not associated with weight gain, it is worth to think about interaction. If there are no comparators, I suggest the title longitudinal rather than cohort.

@ The reviewers’ point is not quite clear to us. As smoking is more common among alcohol drinkers, and smoking is known to affect metabolic rate, in addition to just adjusting for smoking, we also examined interaction and conducted stratified analyses to get an estimate of the association between alcohol and weight gain completely independent of smoking status.

Titles of tables lack some essential characteristics.

@ added

The p-value is not significant at its 0.079 which is greater than set point with mixed CI (line 147).

@ It has now been corrected (Line:152): “There was no significant association between alcohol consumption during adolescence and change in BMI into midlife (p = 0.079).”

The issue of multicollinearity has to be addressed.

@ We have added the following to the statistical section (Line: 129): “Multicollinearity was assessed by variance inflation factor (VIF) before inclusion of the independent variables in the regression model (Table S2).”

The authors are supposed to address the following issues before final decision.

About 60% of your eligible were not participated in the analysis. Do you think voluntary participants are similar to non-participants? (64-65).
Based on the comment, the following has been added in the discussion (Line: 241+): “Finally, response at follow up was 42%, only, with the possibility of selection bias and thus the generalizability of these results is unknown. There were no differences in age between participants and non-participants (P= 0.25), while participants had slightly lower baseline BMI (20.6 vs. 20.3 kg/m2), and higher baseline SES (34 vs. 27%). Nevertheless, there is little reason to expect that the biological associations we observed in the present study between adolescent drinking and midlife weight gain cannot be generalized, as also suggested by the lack of modification or confounding by SES.”

Why participants enrolled in the baseline survey without complete data for BMI, SES, and smoking? (67).

Data was collected via self-administered questionnaires, and therefore participants have not necessarily filled in information on all variables included in the current study.

The baseline data were taken in either 1983 or 1985. Why 1984 was exempted? If it was exempted for any justifiable methodological reason, can you declare it was a follow up of 20-22 years?

Thank you for making this point. The study was designed to only sample data in 1983 and 1985, and hence we have now corrected “follow up of 20-22 years” to “follow up of 20 or 22 years” throughout the manuscript.

Why parental weight and height were taken, what it contributed in this analysis?

Parental weight and height were taken to serve the purpose of the original survey objectives. The data is out of the scope of present study and has no contribution in the present analysis. Thus, this information has now been removed from the method section.

Anthropometric data were self-reported (line 6, 60, 86, 216 etc.), if that is the case how you removed a participant due to misreporting of weight (line 69)?

The participant BMI was reported as 158 which by all means is very unlikely. This could potentially be data entry error and therefore was removed from the analysis. This has now been corrected (Line: 63+): “For the present study, participants were excluded if they had missing data on Body Mass Index (BMI) at baseline or follow up (n 35), had missing information on baseline socioeconomic status (SES) (n 21), or smoking status (n 1) and alcohol consumption (n 1). Moreover, one participant was excluded due to an extreme and unlikely baseline BMI value of 158. After exclusion of the participants with missing values on different variables, the final
study population consisted of 720 participants (Figure 1), of whom 294 were male and 426 were female.

How can you rely on self-reported alcohol consumption? Can you rule out flat slop syndrome among drunker?

@ The section regarding self-reported alcohol consumption currently states (Line:221+)
“Moreover, we used self-reported data and hence the study is potentially subjected to reporting bias. Previous studies have noted overestimation of self-reported height and under estimation of weight resulting under-estimated BMI (34) particularly among the overweight and obese (35). The consequence of such a differential reporting bias among the overweight and obese is that significant associations may have been overlooked (as for total alcohol), and that “true” associations were even stronger than those observed (as for wine and weight gain). Although it has been noted that self-reported frequency of alcohol consumption seems adequately reliable and valid for the research purposes (36, 37) and compares well to peer based observation (37), information collected via diet surveys (38) or other questionnaires (38), both over and under reporting of alcohol in adolescence is still possible. This may have inflated our results and hence we could have seen significant associations that should have been insignificant (like for wine). However, whether this bias in reporting of alcohol was also related to adolescent BMI is unknown, and hence we cannot predict if reporting bias may have influenced our observed associations. Also, the varying size of glasses is unaccounted for in the study, which most likely may have attenuated the results.”

Is there any conventionally used p-value to declare borderline statistical significance? How can you declare statistical significance with mixed CI?

@ We agree and have now corrected this.

In the abstract (Line:11-20) "Adolescent total alcohol consumption was inversely associated with subsequent body mass index (BMI) changes into midlife, but the results were not statistically significant (p =0.079) (β -0.14; 95% CI -0.28, 0.005) after adjustment for potential confounders. Wine consumption was found to be inversely associated to subsequent BMI gain (p = 0.001) (β -0.46; 95%CI -0.82, -0.09) while the results were not significant for beer and spirit. The relationship did not differ by gender, but smoking status was found to modify the relationship, and the inverse association between alcohol and BMI gain was seen only among non-smokers (p= 0.01) (β -0.24; 95%CI -0.41, -0.06) while no association was found among smokers. Neither
adolescent nor attained socioeconomic status in adulthood modified the relationship between alcohol intake and subsequent BMI gain.”

@ In the result section (Line: 152): “There was no significant association between alcohol consumption during adolescence and change in BMI into midlife (p = 0.079).”

At what age does the country’s regulation permit alcohol intake? For how long your study participant used to consume alcohol? From the baseline? Now (at a time of second survey) your study participants are adults; can you extrapolate the association of alcohol consumption and BMI to the period of adolescence?

@ Danish government introduced legal age limit of 15 years for alcohol in 1998 for the first time, thus, there was no legal restriction for drinking during the baseline data collection. And, we do not know since what age the participants started drinking.

@ The longitudinal nature of the study is a strength and unfortunately also a limitation to the study. It is difficult to extrapolate the association of alcohol consumption during adolescence to adulthood as the lifestyle and drinking habits may have changed overtime however, studies have shown that alcohol consumption as early as the age of 15 is predictor of alcohol consumption in late adolescence and thereby adulthood.

@ The section in this regard currently states (Line: 271): “Also, it can be argued that Danish adolescent’s lifestyle habits including their alcohol intake choices and patterns in 1983/85 were most likely different to today (33). However, a potential biologic association between adolescent alcohol intake, which is occurring during a time in life that may leave imprinting of importance for long term weight development, would not be expected to be different.”

In what way smoking modified the effect of alcohol in weight gain?

@ In regards to smoking and its effect as an effect modifier, the section in the discussion currently states (Line: 177): “……smoking status was found to modify the relationship between alcohol consumption and weight development where both total alcohol and wine drinking were associated with less gain in BMI into midlife for those who were non-smokers in adolescence, while no associations were observed for the smokers. The observed difference between smokers and non-smokers could potentially be driven by differences in SES (27). However, the association persisted after adjustment for SES and we no found evidence of an interaction between SES and alcohol intake, suggesting this was not the case in our study. Moreover, there was a considerably lower prevalence of smokers than non-smokers, and hence a lack of power may be responsible for the non-significant results among the smokers.”
In this data can we speak of the effect of alcohol among participants. Is it alcohol or other phytochemicals in wine which contributed for inverse relation with weight gain? If it's alcohol, you would expect similar pattern with beer and spirit.

@ It is difficult to rule out the differential effects in relation with weight gain from alcohol and phytochemicals in wine. It could be that it is the combination of both that may be responsible for the effect, which may explain why the observed effect was apparently different to that of beer and spirit. The section concerning this is now edited (Line: 243+): “On the other hand, others have found similar inverse associations (16,17,20) suggesting that phytochemical compounds like resveratrol found in wine may offer additional protection against fat accumulation by inhibiting lipogenesis and de-regulating lipogenic gene expression(31,32). Moreover, resveratrol is known to increase insulin mediated glucose uptake thus, effectively helping to reduce blood glucose levels (32). It is thus possible that the combination of antioxidants and alcohol in wine may have been responsible for the apparent benefits against weight gain from adolescence into midlife. This could also possibly explain why a similar association was not observed in relation to beer and spirit.”

Finally, how do you manage the perception that will be imposed by the readers with an impression "alcohol for obesity management"?

@ Although our present study favors wine consumption in relation prevention of long-term weight gain, it is difficult to assess the independent influence of alcohol on obesity as obesity in itself is a multifactorial condition. This study is merely an attempt to understand the association between alcohol consumption in adolescence and weight gain later into midlife and the results do not indicate clear association. Also, the results should be interpreted with care due to the limitations mentioned above and in the manuscript.