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Dear Dr Fletcher,

RE: Manuscript ID BMJ.2016.034988 entitled "Association of clinically recorded alcohol consumption with the initial presentation of twelve cardiovascular diseases: a population-based cohort study using linked health records"

Thank you for your recent correspondence. We are delighted to have been offered the opportunity to submit a revised version of this manuscript for further consideration by the BMJ.

We appreciate the referees' constructive feedback. As requested, we have responded to their reports in a point-by-point manner, including substantial new analyses. We believe that the quality of the manuscript has improved as a result of the editors' and referees' comments.

We look forward to your response.

Yours sincerely,

Dr Steven Bell (on behalf of all co-authors)

Editorial comments:

1. We enjoyed reading your manuscript and it covers a topic that will be of interest to many of our readers and to the general public. The size of the research database means you can usefully comment on clinical sub groups that many cohorts are too small to study.

Our response: We are glad that you enjoyed reading our manuscript and believe that it will be of wide interest to the readers of the BMJ as well as the general public.

We agree and feel that it is worth re-emphasising that our study delivers several world-firsts that significantly enhance the field of alcohol and cardiovascular epidemiology as well as having direct implications for contemporary clinical practice. These include, but are not limited to, being the first study to use clinically recorded alcohol consumption data, the only study to examine the initial presentation of 12 different cardiovascular diseases in the same sample (some of which have *never* been investigated before), in addition to being the largest contemporary study of alcohol consumption and cardiovascular disease (and all-cause mortality) world-wide.

To put the latter into context, our findings for all-cause mortality (arguably the most studied endpoint in alcohol epidemiology) are based on a sample almost twice as large in size and with more than double the number of deaths than the most recent meta-analysis of studies that exclude former and occasional drinkers from the non-drinking group [1]. Stemming from this, naturally, our study is magnitudes larger than the most recent meta-analyses of alcohol and aggregated CVD events as well as specific CVD phenotypes.

The fact that our study is based on a contemporary sample is also a major strength. Alcohol consumption measured at the baseline of most studies to date does not necessarily reflect the drinking practices in modern society (nor necessarily does using the most recent intake in existing studies, if the most recent measure of drinking was 20 or so years ago). Furthermore, the prescribing habits as well as distribution of risk factors and incidence of specific cardiovascular diseases has also changed over time. This has implications for conclusions drawn from these studies as well as the meta-analysis of such findings. Our data are directly relevant to the drinking habits encountered by health workers in present day practice further underscoring the clinical utility of our findings.

Our data having been extracted from electronic clinical records is another major asset. The information we have used is directly actionable because it is recorded by health care professionals – this makes it intrinsically relevant in clinical practice. This is to be contrasted with the scores of studies in which data on alcohol consumption is measured in research conditions entirely divorced from care. The data we have used is exactly that which a clinician would use in routine clinical practice when making a decision on what advice and/or treatment to provide to a patient.

To our knowledge we are the only study to have concentrated on the initial presentation of a range of cardiovascular diseases within a competing risk framework (i.e. patients can only experience one initial presentation), including some manifestations for the first time ever. Having shown that heterogeneous associations exist for level of alcohol consumption and the initial presentation of different cardiovascular disease has direct implications for what can be measured and incorporated within disease-specific risk prediction algorithms and form the basis for intervention.

2. Our main reason for not offering to publish your study is we cannot tell how reliable the information on the "exposure" variable is. We are aware that UK doctors have a

financial incentive to record information on alcohol consumption for patients with some chronic conditions and this could bias the information available to you for your analysis. What proportion of adult records contain an entry for alcohol consumption? If this proportion were high (say 60 to 70%) then we would have more confidence in the new information provided by your study and would be willing to reconsider a revised version of your manuscript. If it were only the minority of patients however then we would not be able to offer publication.

Our response: These are concerns that we also had before commencing the project, so we entirely understand your reservations. However, we were initially reassured after examining the association between our clinically recorded alcohol variable and various cardiovascular traits which revealed findings concordant with those from investigator led observational cohort studies (see Figure 1 below for biological validation of the clinically recorded alcohol consumption categories using HDL-C, systolic blood pressure and GGT, and eFigure 3 for a more comprehensive overview). Our concerns were further quelled after relating our exposure to aggregate CVD endpoints and all-cause mortality – with the findings again comparable to those from major bespoke studies and meta-analyses. Also conscious of the possibility that financial incentives for UK doctors to record information on alcohol consumption introduced in 2004 may have introduced bias in our measure, we carried out a sensitivity analysis restricting our sample to participants who entered the study following this (eFigure 13 in the resubmission). We observed the same pattern of results suggesting that this change did not distort our findings.

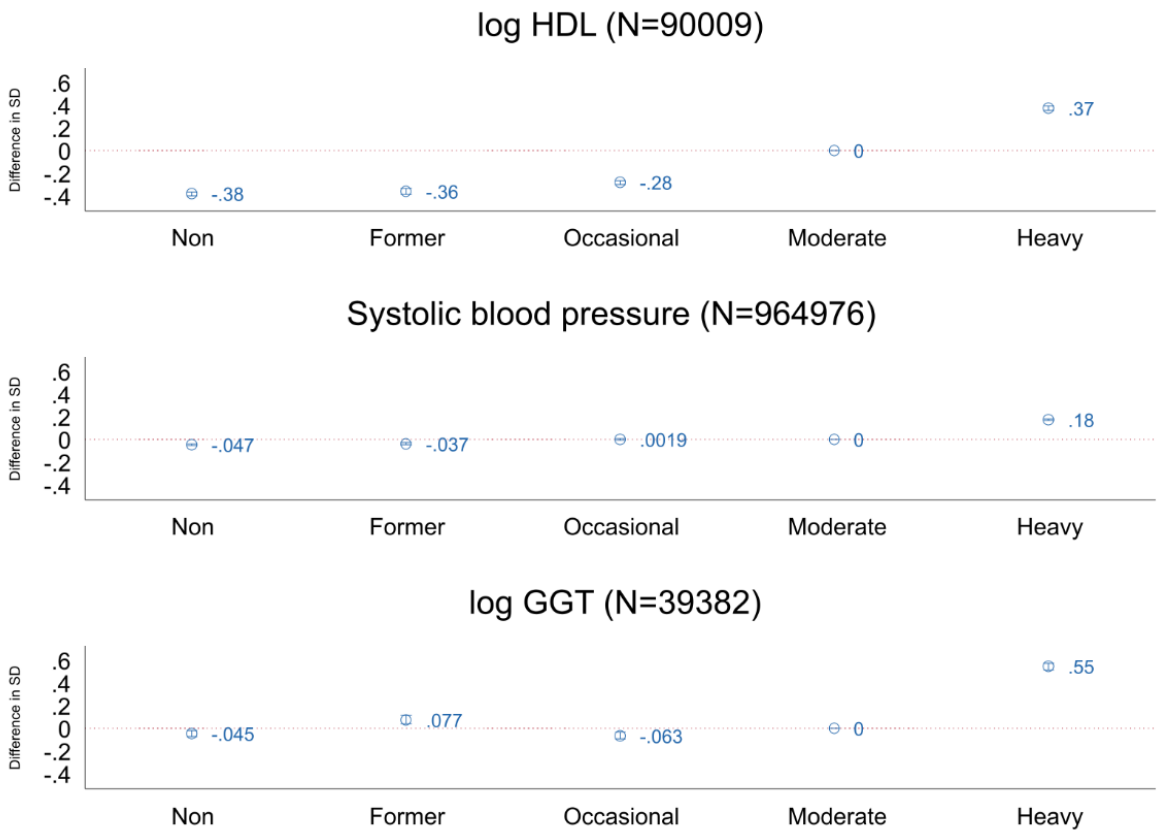

Figure 1 – Standard deviation differences in the association of clinically recorded alcohol categories with HDL cholesterol, systolic blood pressure and gamma-glutamyl transferase (adjusted for age and sex)

57% of our sample have an observed alcohol measure which is very close to the 60% threshold proposed (coincidently, in the sensitivity analysis limited to participants entering the study from 2004 onwards, 69% of our sample had data present on alcohol consumption and our conclusions were unaltered). In modern studies (recruited this millennium) there are *no* large population based cohorts with anywhere close to the 57% coverage that we have. For example, the UK Biobank, a considerably smaller population of just 500k participants, represents only 5.5% of those invited [2] and this figure diminishes even further when limiting the sample to those who have sufficient information on alcohol consumption present to disaggregate this behaviour into the five drinking categories used in our study (<4%). Similarly, our coverage of 57% compares very favourably to the response rates of the much smaller, but highly influential, Health Survey for England [3] (ranging from 37 to 59% between 1994 and 2009, with an average effective response rate of 49% during this period) for which population level statistics on alcohol consumption in England are derived from.

Table 1 - Response rates in the Health Survey for England (HSE) 1994-2009

HSE YEAR	Household response rate	Adults in household response rate	Effective response rate[a]
1994	77	71	55
1995	78	73	57
1996	79	75	59
1997	76	71	54
1998	74	69	51
1999	76	70	53
2000	75	68	51
2001	74	67	50
2002	74	67	50
2003	73	66	48
2004	72	66	48
2005	74	64	47
2006	68	61	41
2007	64	58	37
2008	64	58	37
2009	68	61	41
AVERAGE	**73**	**67**	**49**

[a] Adults in household response rate as a percentage of household response rate. N.B. These figures are *before* excluding those who did not provide sufficient information to derive the five category alcohol consumption variable used in our study.

We also feel that it is worth re-emphasising that that the alcohol consumption data used in our study have direct clinical relevance as this information is recorded in routine practice and is therefore the type of data that a clinician will base their subsequent advice/treatment on in the "real-world". Some of the limitations highlighted in the reviewer reports are presented in the frame of a researcher (e.g. beverage specific effects), which we agree with, but we believe that our thorough examination of clinically recorded alcohol codes, including areas where information is lacking, is actually another strength of our study. The direct clinical implication of this is that we have highlighted areas where measurement of alcohol consumption can be improved (e.g. drinking pattern) in clinical practice.

An additional strength of our exposure variable is that it was obtained over time. This enabled us to look back through an individual's entire clinical record to better disaggregate

non- and former drinkers (something that existing, bespoke investigator led studies would not be able to do at baseline). This distinction, as well as that of occasional and non-drinkers, is necessary and contributes towards on-going debates around the protective effects of moderate drinking, as others have argued that failure to do so (which is the case in a large proportion of existing studies of alcohol consumption and aggregated CVD/specific CVD phenotypes, see eTable 1) biases the non-drinking group through inclusion of those who may have quit/reduced their alcohol consumption due to ill health in such a way that it artificially shows moderate drinking to be protective [1]. So our study, in addition to being larger than existing meta-analyses, also better accounts for one of the primary sources of bias present in studies of alcohol and CVD to date.

3. The reviewers' comments are at the end of this letter. If you do decide to resubmit your manuscript please respond to each of their comments in your revision.

Our response: As requested, we have responded to all of the thoughtful comments in the referee reports submitted by Professors Ellison and Rimm in a point-by-point manner below. We have also updated our manuscript to incorporate relevant studies that have been published on the topic since the original submission.

Reviewer #1 (Professor R. Curtis Ellison, Boston University School of Medicine):

1. Overall, this paper reports a well-done analysis, based on a very large population-based group of subjects. Given the limitations of exposure data, and the need to assign subjects with many descriptions of their drinking into a limited number of exposure groups, a large degree of misclassification of drinking habits would be expected.

Our response: We thank Professor Ellison for his positive comments on our study. We agree that there are limitations to the means of quantifying our exposure and will elaborate on several of these issues when raised in his report below.

2. It is especially important that the type of alcoholic beverage consumed, and the pattern of drinking (e.g., regular versus binge) are not known; such information could play a role in how to interpret the results of the study.

Our response: We agree that not being able to incorporate this information in our analyses is a limitation – one we acknowledged in our initial submission (page 16, lines 3-11). However, as we also noted in the discussion section of our original manuscript, findings relating to beverage specific effects are largely mixed and this limitation does not detract from our ability to examine the role of average level of alcohol consumption in the initial presentation of a broad range of cardiovascular disease phenotypes within the same sample. We make it clear in our discussion section that a logical next step forward following our work is to try to quantify the extent to which factors such as absolute amount of alcohol consumed, beverage preference, drinking pattern and other contextual factors may be differentially associated with (or modify the association of) specific CVDs.

3. A strength of the study, related to its large size, is that multiple end-points can be evaluated. The authors should report results not only for the initial presentation of CVD but also for the most serious "hard" outcomes. When doing this, they might also consider removing what are apparently "soft" endpoints (such as stable angina and TIA). However, the most important end-point, total mortality, is only presented in one figure and essentially not discussed at all in the text.

Our response: Figure 1 of the manuscript presents results for major aggregated endpoints of CHD and CVD, furthermore, we present analyses limited to secondary care/mortality records in the online appendix; the latter of which does not include stable angina or TIA as competing endpoints. With regard to all-cause mortality, undoubtedly this is the most serious outcome, however, it is peripheral to the primary aim of this study which was to determine whether heterogeneous associations exist between alcohol consumption and the initial presentation of a range of pathologically distinct cardiovascular diseases. With that said, we acknowledge that we should discuss this important finding in more detail in the main text and have done so in the revised submission (elaborated on further below in response to comment #19), as follows:

"Our findings for aggregated endpoints are in line with previous observational studies, showing that the non-drinking group from whom former and occasional drinkers have been removed have an increased risk of CHD, CVD and all-cause mortality, while heavy drinkers have an elevated risk of experiencing all but CHD, compared to moderate drinkers. This lends further support to the validity of using routinely collected clinical data on alcohol consumption in research and risk prediction algorithms" (page 14)

4. There are no data presented from this study to warrant the global recommendations for the public discussed in the conclusions of the authors, that no non-drinker should be encouraged to begin drinking to prevent disease. Further, the failure to

emphasize that both non-drinkers and heavy drinkers are at risk for greater total mortality than moderate drinkers should be mentioned.

Our response: Upon reflection, we agree that this part of our conclusion perhaps goes beyond the data we present in the manuscript. Accordingly, we have altered this section of the discussion to more tentatively make the same point – as the concerns we have raised with respect to elevated risk of certain cancers, liver disease, etc in adopting moderate drinking remain valid (this point is acknowledged in new UK Chief Medical Officers' Alcohol Guidelines Review [4]). The relevant text in the revised manuscript is as follows:

"Similarly, while we found that moderate drinkers were less likely to initially present with several CVDs than non-drinkers, it could be argued that it would be unwise to encourage individuals to take up drinking as a means of lowering their CVD risk (although it must be noted that the findings from this study do not directly support this as we did not consider transitions from non-drinking to drinking). This is because there are arguably safer and more effective ways of reducing cardiovascular risk, such as increasing physical activity and smoking cessation, which do not incur increased risks of alcohol-related harm such as alcohol dependence, liver disease and cancer. It is also worth bearing in mind that our focus was on risk of initial presentation with one CVD rather than another, not absolute CVD risk. Ultimately an individual's decision to drink should not be considered in isolation of other health behaviours or risk factors and instead be motivated by their own personal circumstances" (page 19).

As noted in response to comment #3 we now also acknowledge that non-drinkers also have a lower risk of all-cause mortality.

5. Page 6, Line 16 - As stated, the "growing skepticism" has been fueled primarily from commentaries, not from new scientific data. Many of the early "errors" from observational data (e.g., separating never drinkers from ex-drinkers) have been corrected or adjusted for in recent research without changing the overall relation between alcohol and cardiovascular disease.

Our response: We acknowledge that commentary pieces do make up a considerable proportion of the body of work that proposes that the cardioprotective effects of alcohol intake may have been over-estimated or are in fact entirely artefactual. We also agree that many studies that have attempted to correct for known biases, such as removing former drinkers from never drinkers, continue to show the same pattern of association (as we do in this study). Nevertheless, irrespective of the primary source driving the cynicism, the point that there is growing scepticism towards the finding that moderate drinking universally confers beneficial effects cannot be refuted. This is also reflected in, for example, the recent UK Chief Medical Officers' Alcohol Guidelines Review [4] and the Australian national alcohol guidelines [5].

6. Page 6, Line 46 - Thus far, the Mendelian Randomization studies have been very poor, using an inadequate genetic measure for the instrumental variable. In particular, the paper by Holmes et al referred to has been shown by many statisticians and other scientists to be misguided and misinterpreted.

Our response: While we agree that there are limitations to the Mendelian randomization studies conducted on the topic of alcohol consumption and cardiovascular diseases/traits to date, we do not think it is fair to label them all as very poor. It is outside the scope of the present investigation and this response letter to justify/defend the study published in the BMJ by Holmes *et al*. We briefly present the primary finding and note that a sister paper by the same group showed that non-linear associations exist between genetically predicted alcohol consumption and a variety of CV biomarkers when relaxing one of the standard assumptions

underlying instrumental variable analyses. This equates to less than 2% of the word count of the revised manuscript. But given the concerns raised here by Professor Ellison, we have also added a note to the effect that there are also critical commentaries on the study by Holmes and colleagues, as follows:

"As noted previously, there is growing belief that the cardiovascular benefits of moderate drinking may have been overestimated, including a recent large scale Mendelian randomisation study which found no protective effects of moderate alcohol intake for aggregate CVD (although there have been some critical commentaries of this study, e.g [references])" (page 18).

We have refocussed our discussion of the existing literature and it is now more transparent/agnostic in style, favouring neither one viewpoint or methodology.

7. Page 9, Line 38 - The amount of information available on subjects for previous drinking is not discussed, so it is difficult to determine how good the categorization was for "never drinkers" or "ex-drinkers."

Our response: Thank you for this thoughtful comment. We used a patient's entire clinical record as recorded on CPRD. We make this clearer in our revised submission as well as providing the number of never drinkers re-coded as former drinkers on the basis of clinical drinking history as well as having a past entry for alcohol abuse. This is available in the revised online supplementary material:

"We reclassified non-drinkers as former drinkers if they had any record of drinking recorded in their entire clinical record entered on CPRD prior to study entry (in cases whereby non-drinkers had no record of drinking before entering the study we assumed that they were not former drinkers). This resulted in 19,853 (out of 184,747; 10.7%) non-drinkers being recoded as former drinkers, a further 6,826 (3.7%) participants were reclassified through having a positive history of alcohol abuse. A flow diagram outlining our coding algorithm is presented in eFigure 2 and the exact Read codes used to define drinking categories are presented in eTable 2" (revised supplementary material, page 12)

8. Page 10, Line 5 - There is no mention of total mortality here (or elsewhere in the text); it should be mentioned as it is the most reliable outcome measure available.

Our response: In having stated that cause-specific mortality was available via the Office for National Statistics we thought that it was implicit that total mortality data was also recorded (with it being the aggregate of cause-specific mortality). We also stated that total mortality was one of our secondary outcomes on page 10, line 14 of the initial submission.

9. Page 10, Line 44 - The initial presentation is fine, but it would also have been useful to do sensitivity analyses for the "most serious presentation" (e.g., "hard" CVD end-points, mortality)

Our response: As noted above, in response to comment #3, the findings from these analyses are available in Figure 1 of the main manuscript as well as in the online supplementary material (eFigures 11 and 12).

10. Page 11, Line 39 - eFigure3 is difficult to interpret, and could be eliminated.

Our response: We are sorry that Professor Ellison found eFigure 3 difficult to interpret. We added this bar chart in the supplementary material to describe the distribution of initial CVD presentations (and non-CVD mortality) by drinking categories as this information is routinely

presented in papers. As such, we would prefer for it to be included in the online material, but would be happy to omit it should the handling editor deem it appropriate.

11. Page 15, Line 32 - Many cohort studies also report recent intake, as well as previous estimates of alcohol consumption.

Our response: While it is true that some studies take into account the most recent as well as previous drinking, this practice is far from the norm, and certainly no study on the role of alcohol consumption in the development of CVD that has used a contemporary sample of this size exists. The point we were trying to convey in this section is that alcohol consumption measured at the baseline of most studies to date does not necessarily reflect the drinking practices in modern society (nor necessarily does using the most recent intake in existing studies, if the most recent measure of drinking was 20 or so years ago). Furthermore, the prescribing habits as well as distribution of risk factors and incidence of specific cardiovascular diseases has also changed over time.

12. Page 15, Line 50 - It is interesting that subjects reporting “drunkenness,” “Hangover,” “Inebriety NOS,” “Intoxication,” etc. were included in the “Moderate” category. Were sensitivity analyses done with reclassification of such subjects into the “Heavy Drinker” category?

Our response: We agree that this is a potential source of bias and have refined our drinking categories further in the revised submission. This includes recoding the clinical entries that are perhaps more reflective of heavy drinking as such. We re-ran all analyses (main and supplementary) using this updated drinking variable and our findings were mostly unchanged – with notable exceptions that the lower risk of aggregated CHD in the heavy drinking group was eliminated (previously HR 0.90, 95% CI 0.84-0.95; increasing to 0.97, 0.90-1.06) and the protective effect of higher levels of alcohol intake for myocardial infarction also attenuated (HR 0.78 → 0.88 although this remained statistically significant; p=0.04).

13. Page 16, Line 36 - Using the patient’s “entire clinical history” to define them as former drinker is fine, but no description is given as to how much clinical history was available for review.

Our response: As noted in response to comment #7, we agree that our initial description of this information was less than ideal. As such, we have specified that this consisted of the entire clinical record as entered on CPRD prior to study entry.

14. Page 16, Line 56 - The Holmes et al paper is a poor study to base decisions upon.

Our response: No decisions in this study were based on the work by Holmes *et al.* (our study protocol [ClinicalTrials.gov identifier: NCT01864031] was registered online 2 years before their study was published). Line 56 on page 16 of the initial submission was merely included to quantify the statement that there is a growing belief that the cardioprotective effects of moderate drinking may have been overestimated. The largest empirical investigation specifically claiming to show this in recent years is the Mendelian randomization study by Holmes and colleagues. Irrespective of the alleged weaknesses of that study, it cannot reasonably be contested that it is the most often cited by those cynical of the protective effects of moderate drinking.

15. Page 17, Line 16 - This reviewer doubts that heavy drinkers will be able to change their intake based on this revelation.

Our response: We understand that not all heavy drinkers would necessarily change their drinking in response to such findings, however, this does not detract from the point being

made that the results from this study could be incorporated in individual risk prediction algorithms, etc to be used in clinical practice.

16. Page 17, Line 35 - This suggests that excluding “soft” end-points (e.g., TIA, stable angina), or using the most serious outcome rather than the initial presentation might be an interesting endeavor.

Our response: We agree that this would be an interesting endeavour, however, it falls outside the scope of the current study (focusing on only the “most serious” presentation would change the entire focus of the study and represent a severe deviation from the pre-registered analytic protocol/research question). Furthermore, doing so would detract from the overall aims of the study to elucidate the association of alcohol consumption with a range of cardiovascular disorders, some of which are under researched, either because they are not often collected in existing observational studies or because they are too rare to study in comparatively smaller samples. It is also not clear how one would rank 14 cardiovascular disorders in order of their seriousness (e.g. is dying from a MI more “serious” than dying from an AAA?). Additionally, as noted above in response to comments #3 and 9, findings excluding “soft” endpoints are available in the supplementary material and are essentially unchanged from those when also using primary care records.

17. Page 17, Lines 44-52 - This is supposition by the authors but not dealt with in their analyses. And it is annoying to see the old adage that you can get the same effect of moderate drinking from other behaviors. Has any of the investigators shown how easy or difficult it is to get people to start exercising or lose weight? No one is suggesting either this or that, but in incorporating a number of behaviors into an overall healthy lifestyle.

Our response: We realise that it is often easier said than done to increase levels of physical activity, stop smoking, lose weight, etc. However, irrespective of this, the point being made that these means of lowering cardiovascular risk do not come with the potential side effects associated with adopting moderate drinking such as increasing the risk of developing alternative disorders, including certain cancers, liver disease and alcohol use disorders remains valid (a point endorsed in the UK alcohol guidelines [4] and the American Heart Association [6]). In our revised manuscript we have altered the text to more clearly indicate that the data presented in this study cannot necessarily be used to support this notion and that a person’s decision to drink should be motivated by their individual circumstances. This text is quoted above in response to comment #4 but included again here:

“Similarly, while we found that moderate drinkers were less likely to initially present with several CVDs than non-drinkers, it could be argued that it would be unwise to encourage individuals to take up drinking as a means of lowering their CVD risk (although it must be noted that the findings from this study do not directly support this as we did not consider transitions from non-drinking to drinking). This is because there are arguably safer and more effective ways of reducing cardiovascular risk, such as increasing physical activity and smoking cessation, which do not incur increased risks of alcohol-related harm such as alcohol dependence, liver disease and cancer. It is also worth bearing in mind that our focus was on risk of initial presentation with one CVD rather than another, not absolute CVD risk. Ultimately an individual’s decision to drink should not be considered in isolation of other health behaviours or risk factors and instead be motivated by their own personal circumstances” (page 19).

18. Page 17, Line 55 - It is noted that the authors do not mention that total mortality is lower for moderate drinkers than for non-drinkers. Further, by ignoring the soft CVD end-points, by far the largest numbers of subjects who might benefit from moderate

drinking are those with MI, CHF, and PAD (each group made up of more than 10,000 subjects).

Our response: We have revised our discussion section to additionally reflect on the finding that moderate drinkers also have a lower risk of all-cause mortality (and aggregated CHD and CVD events) than non-drinkers – noting that this is present even after removing occasional and former drinkers from this group. The relevant text is included in response to comment #3 and again here as follows:

"Our findings for aggregated endpoints are in line with previous observational studies, showing that the non-drinking group from whom former and occasional drinkers have been removed have an increased risk of CHD, CVD and all-cause mortality, while heavy drinkers have an elevated risk of experiencing all but CHD, compared to moderate drinkers. This which lends further support to the validity of using routinely collected clinical data on alcohol consumption in research and risk prediction algorithms" (page 14)

19. Page 18, Line 15 - Again, focusing on hard CVD outcomes and especially on total mortality not included in these conclusions.

Our response: The hard aggregate CVD endpoints as well as total mortality are secondary outcomes (as stated in our methodology section). We wrote our conclusion section to focus on the primary aims of the study (specific cardiovascular phenotypes), however, as noted above in response to comment #18, we have revised this slightly in the resubmission to also acknowledge the aggregate/all-cause mortality findings to provide a more holistic discussion of the findings of our study.

20. Figure 1 - This is an impressive figure (especially when reporting all-cause mortality for 136,894 subjects). Should these striking results not temper the conclusions of the authors?

Our response: We thank Professor Ellison for his positive comments about Figure 1. As documented above, we now make reference to the findings for all-cause mortality (which are based on a sample almost twice as large in size and with more than double the number of deaths than the most recent meta-analysis of studies on alcohol consumption and mortality that exclude former and occasional drinkers from the non-drinking group [1]) in the discussion section. The same caveat noted in response to comment #3, that death from all-causes was not one of the primary endpoints of this study, applies here and it is for that reason that the findings concerning total mortality do not prominently feature in our overall conclusions.

Reviewer #2 (Professor Eric Rimm, Harvard T.H. Chan School of Public Health):

1. The authors have used a very efficient design to link data from national electronic health records to investigate the relationship of alcohol to number of CVD-related outcomes, some of which have been under studied. The analyses conducted seem appropriate and the results are clearly displayed although other potentially more enlightening sub analyses could be conducted and included in the online supplement. Several other comments are noted below in the sections where they occur.

Our response: We thank Professor Rimm for his positive evaluation of our study.

2. Moderate and heavy drinking not defined in the abstract. Because this is an internationally read journal definitions will differ by reader and therefore should be defined in the abstract.

Our response: We are sorry for this omission. We now define moderate/heavy drinking in the abstract, as follows:

"[…] compared to moderate drinking (consumption within contemporaneous UK weekly/daily guidelines of 21/3 and 14/2 units for men and women, respectively). Heavy drinking (exceeding guidelines) conferred an elevated risk […]"

3. There is substantial detail here on MR analyses and biomarkers. It would be best to shorten the introduction and move this discussion to the end of the paper to allow this important content to be discussed in the context of the current analyses.

Our response: We agree that the balance of the introduction and discussion sections in the initial submission was perhaps a little off. Accordingly, we have revised our manuscript; less emphasis is now placed on describing the findings from Mendelian randomisation studies and biomarkers in the introduction (short of setting the scene as to why we might anticipate that alcohol may be differentially associated with a variety of CVDs). This detail is now provided predominantly in the revised discussion section when contextualising the findings from our own study.

4. Alcohol categorization is not clearly defined in the paper or e-supplement but may be my lack of knowledge of the English health system. Each participant is routinely asked by their GP or practice nurse about drinking. Is there standard text that is used or does each medical professional ask in a way that they see fit depending on the region of the country, own personal bias (does the person asking the questions drink), or sex. Men may answer differently to a male than a female and it is well known that physicians who abstain query differently than moderate or heavy drinkers. Also, it has been documented that that participants respond more honestly to a paper response where they know that the medical professional will not pass judgment on their response. The figures used to validate are very helpful but still may obscure misclassification of heavy or binge drinkers into the moderate levels of consumption due to under reporting at the high level.

Our response: We thank Professor Rimm for these thoughtful suggestions. We have developed our description of how alcohol was categorised in the main manuscript as well as supplementary material in the revised submission (including the addition of a new eFigure 2 that we hope better conveys the algorithm we implemented). We agree that there are a number of important caveats to the way we have defined/categorised alcohol consumption in the current study and have expanded our discussion of the limitations of defining our exposure by including these additional points, as follows:

"Furthermore, no standard questions about drinking were used by all health professionals during the study period meaning that their own personal biases may have resulted in further misclassification,[7] *for example, whether they drink or not. Additionally, individuals may respond more honestly when recording their alcohol consumption on a paper questionnaire than directly to a medical professional (differential reporting by gender, fear of being judged, etc) but there was no way to quantify what proportion of data were collected by either method. […] Frequency of consumption is an important omission as it is known that the vast majority of individuals do not spread their drinking equally across the week and even isolated episodes of heavy drinking are enough to eliminate the protective effects observed for CHD in otherwise moderate drinkers"* (page 17)

It is widely acknowledged that collecting information on alcohol intake is problematic – even in bespoke studies; a certain degree of misclassification bias is inevitable. However, measurement error should not substantially affect estimates of the association between alcohol intake and health outcomes [8] – a point acknowledged in the limitations section of a relatively recent publication on the topic of alcohol and cancer risk in the BMJ [9].

While we acknowledge that differences exist in the way that health care professionals record alcohol consumption, we feel that it is important to stress that the data on alcohol consumption used in this study are clinically relevant (arguably more so than data collected in research settings divorced from care) as this information is recorded in routine practice so it is exactly the sort of information that a clinician will base their subsequent advice and/or treatment on in day to day clinical practice. Furthermore, combining data collected using different methods has been standard practice in every meta-analysis of alcohol consumption and aggregated CVD (plus other) events to date, so we do not consider our approach any more inherently biased than that.

5. Controlling for potential mediators of the alcohol CVD relationship such as BMI or diabetes can cause bias in results in unexpected direction. Although unlikely here, it would be much easier for the reader to understand the results if, instead of controlling for BMI or diabetes, the results were stratified within categories of BMI and diabetes.

Our response: Our decision not to adjust for putative mediators in the primary analyses was for precisely this reason. At the outset of the project we only specified examining whether the association differed in sub-groups of men and women, for which there was an *a prori* hypothesis that the association may differ. We were keen to avoid subgroup analyses for which there is no reason to anticipate the association differing between categories as these can often result in spurious associations being observed [10]. However, for the sake of completeness we have now carried out further analyses in categories of smoking status (in response to comment #8) and BMI. These analyses were restricted to observed data as it is not possible to estimate statistical models using imputed data whereby the number of subjects differs between datasets (i.e. an individual may be predicted to be a smoker in the first dataset, but not the second). These findings are included in the revised supplementary material and referred to briefly in the updated manuscript.

We also carried out the analysis by diabetes status but found that the number of events within drinking categories for certain endpoints was prohibitive of any real conclusions being drawn. For this reason, we include the forest plot of the 12 CVD outcomes in those with diabetes here but have not incorporated it in the revised manuscript:

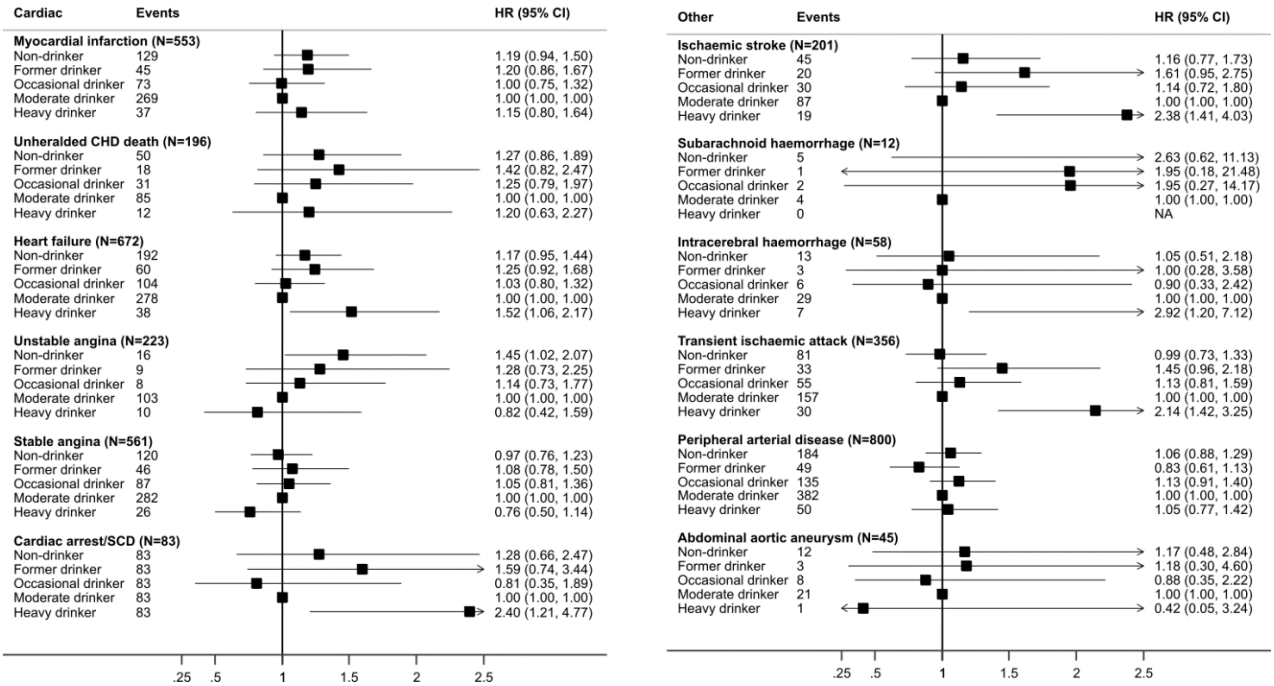

Figure 2 - Multivariable adjusted hazard ratios of 12 cardiovascular diseases in a cohort of 32,115 diabetic adults

We hope that you agree, given the sample size limitations, these analyses do not add much additional value to our already comprehensive study.

6. The authors state “Another strength of our use of a contemporary cohort is that our exposure variable reflects current patterns of alcohol consumption encountered in present day clinical practice”. In fact that overstates the strengths. They did not have information on patterns of consumption but rather only average consumption. In the supplement it states that only ~1000 people provided data on binge drinking and the authors did not have any data on frequency of drinking, but rather assumed that reported consumption was average per day spread out across a week. This is hardly better than the many past studies that had information on frequency, amount, binge, and beverage type. In most studies less than 20% of the population drinks daily so clearly there is misclassification due to frequency of drinking per week.

Our response: Our choice of wording in the sentence quoted here, is upon reflection, inappropriate. We did not mean for “pattern” to be interpreted as the drinking pattern of individuals but instead the current drinking habits encountered in modern clinical practice. We have revised this sentence to clarify this:

“Another strength of our use of a contemporary cohort is that our exposure variable reflects the drinking habits encountered by health workers in present day clinical practice” (page 16)

We have also expanded our initial discussion of the limitations of not being able to more distinctly separate important elements, such as drinking frequency and pattern, in the current study as follows:

“Frequency of consumption is an important omission as it is known that the vast majority of individuals do not spread their drinking equally across the week and even isolated episodes of heavy drinking are enough to eliminate the protective effects observed for CHD in otherwise moderate drinkers” (page 17)

7. I thought it amusing that the authors chose to make the judgement that even in light of their results that it be unwise to encourage individuals to take up drinking to lower

CVD risk (p.17 lines 46-50) because of other lifestyle factors like non- smoking and physical activity known to lower CVD. The authors did not sufficiently account for smoking in their analyses (dose and duration) and had no data on physical activity as a potentially important covariate. Finally, the authors said nothing and had no way to account for differences in diet, mental health, or many other behavioral factors known to predict CVD and also be associated with alcohol. Controlling for social deprivation does not adequately account for this. Is there any way to link any of the participants in this study with parallel cohort studies ongoing in England that would have data on diet, physical activity, etc to confirm or estimate the effect of these potential biases?

Our response: Professor Ellison also expressed concerns about our decision to state that it would be unwise to encourage individuals to take up drinking as a means of lowering CVD. We have tempered this conclusion somewhat in the revised manuscript but stand by the statement that alternate means of reducing cardiovascular risk, such as increased physical activity of smoking cessation, do not come with some of the potential side effects associated with adopting moderate drinking (a viewpoint also endorsed in the UK and Australian national alcohol guidelines and supported by the American Heart Association [4–6]).

With respect to appropriate adjustment for smoking status, we agree that the measure we included in our analyses has limitations. Unfortunately, information on amount of cigarettes smoked (as well as other smoking related traits such as age at initiation, pattern/duration of smoking and second-hand smoke exposure) are lacking in the pre-existing electronic databases we used. Regrettably it is also not possible to link participants from this study with parallel cohort studies in the UK (as the record linkage is made via a Trusted Party) in order to ascertain the extent to which the exclusion of other important confounders such as diet and physical activity may bias our findings. However, by assessing the relatively negligible changes in the magnitude of the effect estimates observed for alcohol and aggregated CHD [11], ischaemic stroke [12] and myocardial infarction [13] pre- and post-adjustment for dietary components and physical activity in large studies to date, we are somewhat confident that even if we were able to adjust for these factors, our overall conclusions would not materially change. However, in response to this concern, we have expanded the discussion of our study's limitations to more strongly emphasise the possibility for residual confounding by smoking dose and lack of adjustment for physical activity and diet. Furthermore, we now include adjustment for whether participants were offered dietary advice (an admittedly poor proxy for true dietary status) in the most comprehensively adjusted model. As anticipated this did not alter our overall conclusions.

8. Table 1 - Do the authors have information on dose of smoking? This can be a very strong confounder because of the strength of association with alcohol and with CVD outcomes. Controlling for dose and pack years is necessary. Consistent with this, presenting results among non-smokers only would reduce concerns of residual confounding.

Our response: As mentioned in our response to comment #7, regrettably we do not have information on dose of smoking. Our edits with respect to residual confounding highlighted above also serve to address this comment. The relevant text in the revised manuscript is as follows:

"Finally, as with all observational studies we were unable to exclude residual confounding, for example, we did not have information on amount of cigarettes smoked (as well as other smoking related traits such as age at initiation, pattern/duration of smoking and second-hand smoke exposure), dietary habits or level of physical activity as these are lacking in the pre-existing electronic databases we used. However, by assessing the relatively negligible changes in the magnitude of the effect estimates observed for alcohol and aggregated CHD, ischaemic stroke and myocardial infarction pre- and post-adjustment for dietary components

and physical activity in large studies to date, we are somewhat confident that even if we were able to adjust for these factors, our overall conclusions would not materially change" (page 18).

Similarly, in our response to comment #5, we noted that we carried out analyses stratified by smoking status which are now made available in the online appendix. It is worth noting that as these analyses were restricted to observed data out of necessity, we encountered a noticeable drop in statistical power, and while there were some differences between the point estimates in subgroups for certain endpoints (mostly rarer events), the confidence intervals often overlapped and included the point estimates presented in the main paper. In light of this, we argue that our interpretation did not substantially change when examining the findings within any of the subgroup analyses suggested, showing further the robustness of our novel findings.

9. Strange that the authors show a supplemental figure with a very strong dose response between alcohol and HDL-C yet in this table the results are completely null. Why the inconsistency?

Our response: The result presented in supplementary figure 3 is adjusted for age and sex in addition to HDL-C having been log transformed (to improve the assumptions underlying linear regression), whereas those presented in table 1 were not. This is the reason for the inconsistency. We now present median (25^{th} and 75^{th} percentiles) values of HDL-C in table 1 which are concordant with the regression analyses in the supplemental material.

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