Peer review of, '**Mortality and morbidity risks from alcohol consumption in Australia: Analyses using an Australian adaptation of the Sheffield Alcohol Policy Model (v2.7) to inform the development of new alcohol guidelines'**

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EXECUTIVE SUMMARY

Context

The aim of this report was to provide independent review of a modelled evaluation of the mortality and morbidity risks associated with alcohol consumption in Australia, which was conducted by investigators at the University of Sheffield (the 'SAPM-AU report'). This modelled report comprised part of the evidence used to inform the development of Guideline 1 of the *Draft Australian Guidelines to Reduce Health Risks from Drinking Alcohol* by the National Health and Medical Research Council's (NHMRC) Alcohol Working Committee. The draft guideline states that: **To reduce the risk of harm from alcohol-related disease or injury, healthy men and women should drink no more than 10 standard drinks a week and no more than 4 standard drinks on any one day.**

This review considered the overall study methods and outcomes described in the final report on the modelling by the researchers at the University of Sheffield (Angus et al., 2019). This review involved assessing the submitted report; original model software/code was not sited or reviewed. The method of assessment involved reviewing the description of each component of the modelling and interpretation for methodological strengths and limitations, and noting the potential impacts of the limitations on the results. Key aspects considered included the data inputs that were used, the model structure, and the analyses, sensitivity analyses and measures of uncertainty around the estimates produced by the model. Through the review process we identified various aspects of the methods and assumptions on which we required further clarification. These questions were addressed by the authors of the SAPM-AU report, and, where appropriate, their responses have been incorporated into our review.

Summary of the findings of this review

The modelling of mortality and morbidity risks attributable to alcohol consumption in Australia appears to be a comprehensive evaluation of the health impacts of alcohol consumption. Efforts have been made to take into account the impact of different levels and patterns of alcohol consumption on the risk of mortality or morbidity for many different health conditions. This approach allows for more nuanced modelling of the combined risks associated with alcohol consumption than would be possible with a more simplified approach. The use of large-scale meta-analyses and international reviews to inform the dose-specific risks for each of these health conditions is also a strength.

There are, however, some aspects of the modelling approach (as with all models) to be considered when interpreting the results. We consider that these are as follows:

- A calibration approach was used to produce the risk curves for some health conditions. A more detailed exposition on the external/predictive validation of the calibrated model would be an informative complement to future evaluations.
- In general, while it is not always possible or appropriate to provide measures of uncertainty for the results produced by the model, there are some uncertainties that can be specified or further explored with sensitivity analyses, allowing for a better understanding of the robustness of the outcomes to key underlying assumptions. In particular, more exploration (sensitivity analysis) of the choice to use a linear form for the calibrated risk curves and the possible impact of using other functional forms for these relationships would be useful for future evaluations. However, a justifiable approach was taken for the base case scenario, and we note that the priorities for sensitivity analysis were discussed and agreed with the GDG [Guideline Development Group] and NHMRC.
- Only the harms of current drinking were modelled, not of former drinking behaviours.

Regarding the interpretation of the results by the NHMRC Alcohol Working Committee, the presented sensitivity analysis (considering the possibility that there are no or little protective effects for certain health conditions) suggested consumption as low as 2.5 drinks per week. The draft recommendation of no more than 10 drinks per week is consistent with the modelled results when it was assumed that there are some protective effects for certain health conditions at low levels of consumption.

Conclusion

In reviewing the report of the modelled analysis we have identified some limitations and matters to consider in interpretation, as is the case for all modelled evaluations. These matters could be explored in the development of future iterations of the SAPM-AU. Overall, the modelling underpinning the draft NHMRC alcohol guidelines appears to be a comprehensive and robust evaluation of the health impacts of alcohol consumption in Australia.

Detailed evaluation of modelled analysis methods and findings

1. Summary of methods

The modelled evaluation was conducted using the Australian adaptation of the Sheffield Alcohol Policy Model (SAPM-AU) v2.7. The model used Australian alcohol consumption data, Australian alcohol-related mortality and morbidity data, and international and Australian estimates of the magnitude of the risk association between alcohol consumption and 42 health conditions that are causally related to alcohol consumption. Using these inputs, literature-derived and calibrated risk curves for alcohol consumption and mortality or morbidity by sex and drinking pattern (number of days of alcohol consumption per week) were generated, and these were summed to estimate total risk. The level of consumption that resulted in a 1 in 100 lifetime risk of alcohol-attributable mortality was then estimated by sex and drinking pattern. Sensitivity analyses examined the impact of varying the risk threshold (0 risk, 1 in 1000, 1 in 500 and 1 in 50), removing protective effects from the model, inserting a threshold below which drinkers have the same risk as abstainers, and using a single all-cause mortality risk curve rather than the summation of the risk curves of the 42 health conditions.

For those consuming alcohol on 3 days per week (the estimated average frequency for the Australian population), a 1 in 100 lifetime risk of alcohol-attributable mortality was estimated to be associated with 12.5 standard drinks per week for men and with 10.5 standard drinks per week for women. In the sensitivity analysis that removed protective effects from the model, the same risk of alcohol-attributable mortality was associated with 2.5 standard drinks per week for both men and women, while the sensitivity analysis that used a single all-cause mortality risk curve yielded an estimate of 29.0 standard drinks per week for both men and women. The sensitivity analyses that examined alternative risk thresholds and inserting a threshold below which drinkers have the same risk as abstainers demonstrated a relatively small impact on the results.

2. Comments on data sources

This section assesses the sources of data used in the SAPM-AU, including Australian alcohol consumption data, Australian alcohol-related mortality and morbidity data, and estimates of the risk association between alcohol consumption and 42 health conditions. In general, efforts have been made to incorporate detailed Australian-specific data in the SAPM-AU.

2.1 Australian alcohol consumption data

Information on current Australian drinking patterns was used to inform the SAPM-AU, considering both overall level of alcohol consumption and days per week of drinking. We consider that the selection of 3 days per week rather than 2 to use as the average number of drinking days per week is appropriate, as the graduated frequency method used in the National Drug Strategy Household Survey to obtain an estimate of approximately 3 days per week is likely to be the most accurate

method of the three survey results considered. It should be noted that only the harms of current drinking were modelled, not of former drinking.

2.2 Australian alcohol-related mortality and morbidity data

The use of Australian alcohol-related mortality and morbidity data (sourced from the Australian Institute of Health and Welfare and the National Hospital Morbidity Database) appears reasonable, but it should be noted that one limitation is that the NHMD only captures serious health conditions.

This point was raised with the authors, and it was confirmed that this was a limitation. The authors also clarified that the choice of hospitalisation as a proxy for morbidity comes from the SAPM's origins as a health economic evaluation tool (where hospitalisation data allows for healthcare costs to be estimated).

2.3 Estimates of the risk association between alcohol consumption and 42 health conditions

Risk estimates for 42 health conditions sourced from systematic reviews and meta-analyses (and calibrated estimates for certain health conditions) are included. International meta-analysis estimates of risk were prioritised over Australian-specific evidence, as it was stated that the international evidence would provide more accurate estimates (page 48). In our view this was a reasonable decision. It should be noted that in the draft alcohol guidelines it is stated that for evidence to be used in revising the guidelines, it had to be "*Publicly available and published in the English language in peer reviewed journals*" (page 10), so there is some possibility that important studies in the grey literature or not written in English were not captured.

2.4 Population age structure data

There is a minor point of discrepancy regarding the Australian estimated resident population (ERP) data used in the model. On page 16, the report states that "*Data on the current age-sex breakdown of the Australian population come from figures published by the Australian Bureau of Statistics relating to the estimated population at 30th June 2017. SAPM-AU requires population figure[s] for each single year of age in the model (ages 18-89), however the published figures grouped ages 85-89 together. We estimated single year populations for these ages by partitioning the five-year figures for each gender assuming the same within-group age distribution to the 80-84 year-old age group.*" As the referenced publication by the Australian Bureau of Statistics includes a table which provides the Australian ERP by single year of age (from ages 0 to 100+ years), it is unclear why those data were not used. (see: https://www.abs.gov.au/AUSSTATS/ABS@Archive.nsf/log?openagent&3101059.xls&3101.0&Time%20Series%20Spreadsheet&44190BA59EC8025DCA25836800100219&0&Jun%202018&20.12.2018&Latest).

However, when this question was raised with the authors it was shown that there was only a very small difference between the estimated and actual data for ages 85-89 years, and so the impact on the results would be minimal.

3. Comments on model structure, calibration, validation and sensitivity/supplementary analyses

This section summarises our assessment of various aspects of the SAPM-AU structure and calibration, validation and the sensitivity and supplementary analysis. We identified two main areas for comment - the external/predictive validation of the model including the procedure used to produce the risk curves for some health conditions, and the possibility of providing more detailed measures of uncertainty for the results and around the relative risk functional form used in the calibration.

3.1 Model validation

The SAPM-AU uses mortality and morbidity relative/absolute risk curves for 42 separate health conditions to quantify the lifetime mortality and morbidity risks associated with different levels of alcohol consumption. A number of these risk curves were obtained directly from the literature, while the remainder were calibrated (here called 'derived risk curves'). In this calibration procedure, the model assumes that the risk curve is a linear function of mean alcohol consumption or daily peak consumption, and uses Australian data on mortality and morbidity related to each condition (together with alcohol-attributable fractions from the literature if the condition is partially attributable to alcohol consumption) to fit the unknown parameters (coming from the linear functional assumption).

Although calibration was reported, the follow-up step of external/predictive validation of model outcomes against independent data sources was not reported. The validation process *per se*, would not change the results of the current evaluation but would add an extra layer of information that can be used to assess the robustness of the predictions in future. There are many forms of validation that can be considered; the choice of approaches depends on what is feasible for a particular model given particular data sources. (For an example summarising the validation of a model used extensively in policy evaluations in another health context see Lew JB et al. MDM 2020[1]). The importance of validation and the possible approaches to validation are detailed in a Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7:

> *"Trust and confidence are critical to the success of health care models. There are two main methods for achieving this: transparency (people can see how the model is built) and validation (how well the model reproduces reality)."*[2]

In direct correspondence with the authors we suggested some possible approaches to validation; in response the authors cited technical objections (to the particular ideas we raised), data limitations, and resource limitations. Whilst we acknowledge that undertaking extensive validation would indeed

[1] Lew JB, Greuter MJE, Caruana M, He E, Worthington J, St John DJ, Macrae FA, Feletto E, Coupé VMH, Canfell K. Validation of Microsimulation Models against Alternative Model Predictions and Long-Term Colorectal Cancer Incidence and Mortality Outcomes of Randomized Controlled Trials.Med Decis Making. 2020 Aug;40(6):815-829.
[2] Model Transparency and Validation: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. Value in Health 2012.

require more resources and would be subject to uncertainty, the outcomes would not be used in the final predictions of any particular analysis but would help underpin interpretation of the predictions made. It is therefore recommended that external/predictive validation be discussed in more detail for reports of future evaluations using the SAPM-AU.

3.2 Statistical uncertainty

On page 47 the report states that *"Second, we do not provide measures of statistical uncertainty (e.g. confidence intervals) around our results. This is because SAPM-AU draws on sources of evidence that often do not report statistical uncertainty. More importantly, the limitations in SAPM-AU and the wider epidemiological evidence-base, which we discuss above, contribute substantial methodological uncertainty. This means any confidence interval would potentially mislead readers regarding the precision of our results, as it would pertain only to one part of the uncertainty that is known to exist around any given result. Instead, we examine uncertainty via a set of scenario analyses investigating the sensitivity of the results to particular alternative assumptions, evidence or modelling methodologies, as described in Section 2.4."*

While it is correct that measures of statistical uncertainty such as confidence intervals might not be appropriate for the results in the report as the authors described, there are other uncertainties in the model that can be specified, explored and a range presented around the point estimates to give the reader an idea of the variability in the outcomes.

Specifically, uncertainty arising from the alcohol-attributable fractions (AAFs) used in the calibration for risk curves for partially attributable acute conditions could be further quantified. (Note that we could not find a reference to the source literature for these AAFs in the report but in response to our question regarding the source literature for the AAFs used in the risk curve calibration the authors provided a spreadsheet detailing the AAFs and their sources).

It would also be useful to address the uncertainty around the relative risk functional form used in the calibration. On page 23 the report states that "*There is no clear consensus in the literature about the most appropriate functional form for dose-response curves such as this, with existing evidence supporting log-linear, linear and linear-log specifications. In the absence of either robust evidence or a clear rationale we therefore assume a linear form as the most parsimonious option.*" Although this is a justifiable approach for the base case scenario, exploring different functional forms would help the reader assess the importance of this assumption to the final modelled outcomes.

These issues were raised with the authors, and detailed responses were received. The authors stated that "*the reviewers should note that each scenario explored within a sensitivity analysis requires us to run the Sheffield Alcohol Policy Model (SAPM) 75 times to obtain a full set of results. This limited the number of sensitivity analyses that could be undertaken and increased the importance of the prioritisation process. We undertook three sensitivity analyses, some containing multiple scenarios. These were selected in consultation with the GDG [Guideline Development Group] and NHMRC,*

drawing on our experience and knowledge from undertaking similar analyses during development of the 2016 UK drinking guidelines".

We agree that the decision to perform a smaller number of prioritised sensitivity analyses was reasonable given limited time resources.

The authors also clarified that sensitivity analysis SA2 used an alternative functional form of the risk curves (a "threshold" effect). Therefore, two functional forms were modelled in total.

3.3 Modelling short-term alcohol consumption

In regard to short-term alcohol consumption, the authors state that "*SAPM-AU also requires a measure of drinking patterns in order to estimate risks associated with acute harms (i.e. those harms associated with intoxication). This was taken from existing derived variables in the NDSHS dataset describing respondents' drinking levels on their heaviest drinking day in the last year*" (page 16).

While it is a limitation of the model that a more detailed measure of short-term alcohol consumption was not used, from correspondence with the authors it is apparent that data of the required level of detail is not available in Australia. The authors explained that "*using more detailed measures of alcohol consumption patterns would require two things: detailed individual level data on alcohol consumption patterns in the Australian population and a mechanism for associating specific drinking patterns with specific levels of risk*". The authors mentioned that this could be achieved using a 'drinking diary' approach as has been done before in the UK for individuals in the SAPM, however this was not possible for SAPM-AU given limited time resources. The authors stated that it would not be appropriate to use UK 'drinking diary' data for SAPM-AU given the differences in drinking cultures and contexts between the two countries. In this context we agree that the choice to use the available Australian data comprising heaviest drinking day in the last year was appropriate.

3.4 Use of hospitalisation data as a proxy for morbidity

The authors state: "*We derived the morbidity data used in the model from admissions counts reported in the National Hospital Morbidity Database from the period 01/01/2012 to 31/12/2016. The database provided total counts of admissions for each age-gender group for each of the 42 health conditions included in the SAPM-AU. These are combined within the model with data on the average number of hospital admissions per year for somebody presenting with each of the 42 health conditions in order to estimate the underlying prevalence of each health condition within each modelled subgroup*" (pages 16-17).

Even though morbidity data were ultimately not considered in the formulation of Guideline 1, we feel that it could be acknowledged that hospitalisations are an imperfect measure of morbidity. Some health conditions and injuries are more likely to result in hospitalisation than others, and not all hospitalisations are associated with equivalent morbidity. In correspondence with the authors on this point they clarified that the choice of hospitalisation as a proxy for morbidity comes from the SAPM's origins as a health economic evaluation tool (where hospitalisation data allows for healthcare costs to

be estimated), and was also due to the limitations of all other alternative approaches, including the use of YLDs. The authors stated that one of the major complications in using YLDs is the requirement for prevalence data for each health condition across population subgroups. Therefore, we feel that the author's choice to use of hospitalisation data in this context is reasonable.

3.5 Modelling heavy episodic drinking for chronic health conditions

The model included an adjustment for chronic ischaemic heart disease due to evidence that a heavy episodic drinking pattern is associated with additional risk. There is also evidence that heavy episodic drinking is related to additional increased risk of ischaemic stroke, non-ischaemic cardiovascular disease, infectious disease, and liver cirrhosis (Rehm et al., 2017). It was unclear to us why a heavy episodic drinking pattern was not also considered for these chronic health conditions, but in correspondence with the authors they clarified that this reflected the availability of methodological evidence informing how to undertake the adjustment. There was only enough evidence to inform the heavy episodic drinking adjustment for ischaemic heart disease, and not for any of the other chronic health conditions which also have increased risk associated with heavy drinking. We considered, after taking into account this clarification, that this was a reasonable approach.

3.6 Sensitivity analysis removing protective effects from the model

In the description of the sensitivity analysis in which the protective effects of alcohol consumption were removed from the model, the authors state: "*Risk functions for the following conditions in the base case model all include reduced mortality or morbidity risks relative to abstainers at some levels of alcohol consumption for men or women: acute myocardial infarction, chronic ischaemic heart disease, hypertension, stroke and diabetes*" (page 26). It is stated on page 17 and shown in the risk curves in Figure 5 on pages 20 and 21 that there are protective associations for non-Hodgkin's lymphoma and acute pancreatitis, so it was unclear why these conditions were not also listed above. This was clarified by the authors, who confirmed that the protective effects for non-Hodgkin's lymphoma and acute pancreatitis were also removed in this sensitivity analysis.

3.7 Sensitivity analysis using a single all-cause mortality risk curve

The sensitivity analysis in which a single all-cause mortality risk curve was used, incorporated risk estimates from a systematic review and meta-analysis by Stockwell et al. (Stockwell et al., 2016). The model used the main risk function from this meta-analysis, where 74 out of 87 included studies had a reference group containing ex-drinkers and occasional drinkers. The authors stated that "*Stockwell et al. found that controlling for or excluding studies with such biases in a meta-analysis of alcohol's relationship with all-cause mortality attenuated the cardioprotective effect to non-significance, although this may be due to only a small number of studies remaining in the analysis after the exclusions (e.g. only 13 out of an initial 87 selected studies had no abstainer biases)*" (page 45). As such, one of the other risk curves reported in the meta-analysis by Stockwell et al. (e.g. adjusting for type of reference group and other study design characteristics when analysing the 87 studies, restricting analysis to the 13 studies without ex-drinkers and occasional drinkers in the reference

group, or restricting analysis to 6 high quality studies – all of which did not find a significant protective effect for moderate drinkers) could also have been used in the SAPM-AU single all-cause mortality risk curve sensitivity analysis.

When this was raised with the authors they clarified that this would amount to a "*sensitivity analysis on a sensitivity analysis*", and so other sensitivity analyses were prioritised given limited time resources. After taking into account this clarification we agree this was a reasonable approach.

3.8 The fitting of fractional polynomial curves

One of the last steps in the modelling procedure was to fit fractional polynomial curves to the estimates obtained from the model and use polynomial equations to identify the consumption levels for different risk thresholds (as outlined on page 25 of the final report). We suggest that presenting the model estimates and the fitted curves graphically, together with the polynomial equations, would be useful to the reader. However, in correspondence with the authors they explained that "*for each modelled scenario (i.e. the base case and each sensitivity analysis) there are 28 different curves (relative and absolute risks for 7 different consumption patterns for men and women)*", and that presenting each of these curves would be beyond the scope of the review. An example curve was provided by the authors. Given limited time resources we agree it is reasonable that these graphs were not included.

3.9 Lag time between exposure and health outcomes

The report did not provide a description of the assumptions about potential lag time between exposure and disease outcome. Questions regarding the modelling of lag time and the potential impact on the interpretation of the main findings were raised with the authors. They stated that lag times are "*not a relevant consideration in this project. This is because we were not modelling the impact of an intervention, where effects develop over time. Instead, we were modelling levels of current alcohol-related harm and the expected levels of harm under alternative consumption scenarios*". The authors also clarified the limitation that "*our approach does make the assumption that current harm is related only to current consumption levels, when in reality we would expect current harm to be related to consumption in the past for those health conditions with time lags between exposure and harm. As such, where consumption levels have fallen in recent years, we will underestimate the proportion of current harm which is attributable to alcohol for those conditions, and vice versa where consumption levels have risen*". The authors also clarified that they had previously tested taking into account the age and sex structure of the population changing over time in the modelling for the UK alcohol guidelines, and found only a "*negligibly small*" effect, and therefore this was not performed for SAPM-AU. We believe that this is a helpful clarification that should be taken into account when interpreting the model results.

3.10 Health conditions included in the model

Forty-two health conditions were included in the model, grouped into four categories: chronic and partially attributable to alcohol consumption, acute and partially attributable to alcohol consumption,

chronic and wholly attributable to alcohol consumption, acute and wholly attributable to alcohol consumption. The large number of health conditions considered is a strength, but the choice of some health conditions included in the model required further clarification:

1. The protective association between alcohol consumption and non-Hodgkin's lymphoma was included as a health condition in the model. The International Agency for Research on Cancer (IARC) does not presently consider the inverse association between alcohol and non-Hodgkin's lymphoma to be causal (IARC 2010; IARC 2012). There have been reports of inverse associations between alcohol consumption and Hodgkin's lymphoma, thyroid cancer and kidney cancer (Bagnardi et al., 2015), which are all also not presently considered to be causal by IARC (IARC 2010; IARC 2012), and none of these were included in the model.
2. Prostate cancer was an included health condition in the model, but IARC does not presently consider the association between alcohol consumption and prostate cancer to be causal (IARC 2010; IARC 2012).
3. There were some additional health conditions that could have been included in the model that appeared in a recent review of alcohol consumption and burden of disease (Rehm et al., 2017). These were sexually transmitted infections including HIV, Alzheimer's disease and other dementias, and oesophageal varices. If these were included the association between alcohol consumption and mortality and morbidity may have increased more steeply. Although, the authors do state: "*The analyses also do not examine risks for conditions where causality is complex or still to be established that may have a large effect of the overall risk curve such as dementia and depression*" (page 49).

In response to these questions the authors clarified that "*The list of conditions for SAPM-AU was discussed extensively with both the Guideline Development Group (GDG) and the commissioners of our work at NHMRC*", and that considerations included health conditions included in previous versions of the SAPM (sourced from previous evidence reviews and consultation with experts in alcohol epidemiology), health conditions identified in the evidence review stage of the NHMRC guideline development process where the GDG judged that evidence for causality was sufficient, and the exclusion of conditions where causality is complex or still to be established *and* the effect on the risk curve would be large. It is therefore reasonable that the conditions identified in our third point were excluded (except perhaps for oesophageal varices where the effect on the risk curve would probably be small).

The authors also clarified that the decision on which risk curves should be used in the modelling involved discussions with the GDG and the NHMRC, that they considered the risk curves used in previous versions of the SAPM, and that they "*updated risk curves to use more recent high-quality meta-analyses identified during the GDG's evidence review*".

3.11 Assumption of independence between health conditions included in the model

The model did not appear to consider the interdependence of various health conditions, whereby one health condition is a risk factor or a precursor to another health condition. For example:

- Alcoholic liver disease and fatty liver disease are precursors to chronic hepatitis, fibrosis and cirrhosis of the liver, which in turn is also a precursor to liver cancer
- Alcoholic gastritis is a risk factor for stomach cancer
- Chronic pancreatitis is a risk factor for pancreatic cancer
- Hypertension is a risk factor for other cardiovascular disease conditions and type 2 diabetes

This point was raised with the authors and they clarified that "*these considerations are only relevant for morbidity outcomes, as mortality can only happen once, from a single cause*". However, we suggest future work could consider the possibility that in primary studies there may be difficulties with assigning cause of death in people with multiple alcohol-related conditions; this requires careful consideration of the source information and methods for derivation of AAFs in primary studies.

The authors further clarified that they did not include comorbidities in the modelling due to "*a lack of robust epidemiological evidence on how risks from multiple conditions interact at the individual level*" and that "*fully capturing individual disease trajectories would require an individual-level simulation model. Developing such a model would be a substantial undertaking and was outside the scope of the commissioned work*".

We note the response and agree that the decision not to model interactive effects or co-morbidities was reasonable given the framework of this analysis. We feel these points are useful clarifications to be noted in the interpretation of results.

4. Interpretation of the results and applicability to Guideline 1

This section considers issues relevant to the interpretation of the results provided in the final report of the SAPM-AU, and how these results are applied in the development of the NHMRC's guideline for reducing the risk of alcohol-related harm for adults.

In the draft *Australian guidelines to reduce health risks from drinking alcohol* it is stated that "*The Expert Committee advised that there was not sufficiently strong new or further evidence (despite the above sex differences) to consider separate guideline advice for men and women*" (page 22). However, it should be noted that in the primary modelled analysis it was estimated that a 1 in 100 lifetime risk of alcohol-attributable mortality was associated with 12.5 and 10.5 standard drinks per week for men and women, respectively.

Several health conditions for which there is a protective association between alcohol consumption and risk were included in the main model. A sensitivity analysis was also performed which excluded

these protective associations. For those consuming alcohol on 3 days per week (the estimated average for Australians), the primary analysis estimated that a 1 in 100 lifetime risk of alcohol-attributable mortality was associated with 12.5 and 10.5 standard drinks per week for men and women, respectively, while the estimates in the sensitivity analysis that removed protective effects from the model were substantially lower at 2.5 standard drinks per week for both men and women. Further, the authors outlined the evidence that casts doubt on the protective effects of alcohol consumption in section 4.3.1.2 of the report, and concluded that "*Overall, the research discussed above suggests there is good reason to be concerned about the existence, scale and associated consumption level of any cardioprotective effect. It is beyond the scope of this report to provide a judgement on whether the available evidence is conclusive regarding these concerns. We simply note that there is robust evidence that, at a minimum, the cardioprotective effect observed in standard epidemiological studies is over-estimated. SA1, which examines the effect of removing all protective effects from SAPM, indicates the impact such overestimation may have on our results. The need to align judgements on the existence of cardioprotective effects with the weight placed on the base case analysis versus SA1 should be borne in mind when communicating to the public the final guidelines and the role of the present report in developing that guideline"* (pages 46-47). There is also a limitation of the SAPM-AU itself that the authors state is likely to lead to an overestimate of protection: "*drinkers who consume less than 420g per week and more than 60g on any one day still receive protective effects. In this regard, SAPM-AU is likely to overestimate the extent of cardioprotective effects*" (page 48). It is therefore clear that any assumptions about protective effects of alcohol consumption are a crucial consideration in any modelling of alcohol-related mortality, however, evidence on the protective effects of alcohol consumption is still inconsistent.

4.1 Alcohol-attributable mortality versus morbidity

A 1 in 100 lifetime risk of alcohol-attributable mortality is not the only outcome to consider. Non-fatal cancer, CVD and liver disease all entail a significant burden of disease to the individual. Perhaps a note could be added that if one seeks to limit their lifetime risk of death *or* incidence of serious disease or injury (e.g., cancer, CVD, liver disease, or injury resulting in hospitalisation) to 1 in 100, a level of drinking lower than the guideline based on mortality alone would be required.

When the authors were asked to comment on the broader implications of their results for risk on serious disease or injury, they stated that "*more generally, it is standard practice internationally for drinking guidelines to be set with reference to mortality risks and an alternative approach would need to be justified in the context of the published literature on this topic. It is of course reasonable to adopt an alternative approach but we feel that is a matter for the GDG to consider and beyond the scope of our commission*".

4.2 Lifetime risk of alcohol-attributable mortality versus years of life lost

The authors state that *"SAPM-AU only provides risk estimates for mortality and morbidity separately rather than in a single metric, such as quality-adjusted life-years (QALYs). The potential years of life*

lost for different consumption levels and patterns is also not provided and this introduces uncertainty regarding the extent to which premature mortalities occur at younger or older ages" (page 48).

Figures 9 and 10 appear to show that, for all levels of drinking in the population combined, the protective effects of alcohol consumption only outweigh the harmful effects at older ages. This reflects the finding that the protective effects relate mainly to CVD mortality, which occurs predominantly in older age. If the protective effects mainly occur in older age, this may only translate into relatively few years of life gained, compared to the years of life lost for deaths from all other causes that occur on average at younger ages. Therefore, if years of life lost were considered, it is likely that the protective effects of alcohol consumption would be less important than indicated in the current model using lifetime risk of alcohol-attributable mortality.

When the authors were asked to comment on the likely differences in their findings and implications if they had used YLL (or QALYs or YLDs) as an outcome, they stated that "*While we agree that the question of when deaths from alcohol occur may be a relevant consideration, there is no established precedent or proposed method in the scientific literature for the setting of guidelines with reference to YLLs or other similar measures. Given the limitations of the evidence base to inform current methods of setting guidelines (see (Holmes et al., 2019)), it does not seem appropriate within the terms of our commission to speculate on appropriate guidelines informed by alternative measures. We have, however, previously undertaken some modelling work in this area assessing the potential YLL attributable to alcohol in the UK (Holmes et al., 2016)."* [3]

Conclusion

In reviewing the report of the modelled analysis we have identified some limitations and matters to consider in interpretation, as is the case for all modelled evaluations. These matters could be explored in the development of future iterations of the SAPM-AU. Overall, the modelling underpinning the draft NHMRC alcohol guidelines appears to be a comprehensive and robust evaluation of the health impacts of alcohol consumption in Australia.

[3] *Holmes, J., Angus, C., Meier, P.S., Brennan, A., 2016. Potential Years of Life Lost (PYLLs) due to alcohol consumption in the UK. Sheffield. AND Holmes, J., Angus, C., Meier, P.S., Buykx, P., Brennan, A., 2019. How should we set consumption thresholds for low risk drinking guidelines? Achieving objectivity and transparency using evidence, expert judgement and pragmatism. Addiction 114, 590–600. https://doi.org/10.1111/add.14381*".

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