ALCOHOL BEVERAGES AUSTRALIA

Submission to the National Health and Medical Research Council

Draft Australian Guidelines to Reduce Health Risks from Drinking Alcohol

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Executive Summary

ABA considers the National Health and Medical Research Council's (NHMRC) guidelines on the consumption of alcohol to be an important and integral tool to help the public make informed choices when it comes to their alcohol consumption. The final Guidelines will also provide the evidence base for governments, medical professionals, policy makers, industry, academics and interest groups to work to reduce harmful alcohol consumption.

ABA agrees with, and supports, the intended outcomes of the draft Guidelines. That is, to help Australian men and women make informed choices when it comes to their alcohol consumption.

However, in their current form, the draft Guidelines fail due to the risks and benefits of alcohol consumption lacking balance, with the findings not supported by evidence. In addition, the draft Guidelines have been presented in a 'one size fits all' approach, which does not facilitate informed choice and is grossly misleading.

The overall approach to Guideline One raises issues. The approach has been based on the arbitrary estimate of three drinking days and recommends the same drinking threshold for men and women. Neither of these are approaches are scientifically based. Further, they are inconsistent with the evidence presented in the Sheffield Alcohol Policy Model for Australia (SAPM-AU) and the Government's own National Health Survey and National Drug Strategy Household Survey.

Tables 1 and 2 do not support a blanket guideline of no more than 10 standard drinks per week and no more than 4 standard drinks in any one day, in healthy adults regardless of gender. We regard it as critical that there are more accurate and effective guidelines for drinkers, which have differing consumption guidelines for men and women. This must be based on the evidence relied upon in the formulation of this report; as it stands the section does not paint an accurate picture of the risks associated with alcohol consumption and, therefore, may be construed as deliberately misleading.

Genuine and transparent processes with scientific rigour should be core to the work carried out by the NHMRC. For this reason, it is worrying that the SAPM-AU modelling, upon which the guidelines rely, has not been made available for consideration. SAPM-AU is central to the development and outcome of the Guidelines. It is unacceptable – both scientifically and for transparency – that the SAPM-AU, the methodology and the assumptions underpinning it are denied public scrutiny. Any recommendations cloaked in such secrecy undermine the rigour, integrity and credibility of the final Guidelines. There is no legitimate reason for the model not to be presented to the public and to be subject to scientific scrutiny.

In developing the Guidelines, the most important stakeholder has been overlooked: Australian consumers. Australian consumers have been notably left out from any meaningful involvement in the Guidelines' development. Without consumer involvement, the Guidelines run the real risk of being unacceptable to the public and, in turn, their implementation unfeasible. Considering that Government research found that the public considered the 2009 Guidelines 'unrealistic', these harsher more restrictive, less balanced and poorly targeted Draft Guidelines do not provide more hope of being found to be acceptable by the public, arguably stand far less chance of public acceptance.

ABA believes strongly that these Guidelines should play an important role for the Australian public. The choices they seek to inform are made every day by Australian men and women, and it is critical that these choices are based on scientifically rigorous and transparent processes.

The NHMRC has developed an enviable reputation as one of the world's leading scientific and research organisations. It has enshrined principles and codes that require adherence to research rigour, transparency and reproducibility.

The disimpassioned observer would be concerned over the appointment of certain members to the Alcohol Working Committee; the selective tendering and oversight of Sheffield Alcohol Research Group to conduct the modelling; and how evidence has been treated and classified.

Despite raising these concerns throughout this process and affording the NHMRC the opportunity to manage these clear issues, no action has been taken.

It is now beholden on the NHMRC to correct these errors to ensure the final recommendations carry the same rigour as the NHMRC's long history of providing advice to Australians on a wide range of health matters including nutrition, infant feeding, infection control, blood lead levels, drinking water quality and the health effects of fluoridating drinking water.

Section One: Aim and Intended Outcomes of the Draft Guidelines

Key points and recommendation

- ABA supports the proposed outcome of the Draft Guidelines - to 'help people make informed decisions about how much alcohol they choose to drink.'
- In its current form, the Draft Guidelines do not provide the information required for the consumer to make an informed choice as:
    - the information on the risks and benefits of alcohol consumption is unbalanced and lacking in evidence; and
    - it has been developed with a 'one size fits all' approach which does not reflect reality for Australian men and women.

ABA recommends

- The Draft Guidelines be reviewed to ensure that there is a balanced and evidence-based approach to both the risks and benefits of alcohol consumption and health.
- Consequentially, Guideline One be reviewed to better reflect the spectrum of drinking occasions and the situations in which men and women make decisions around drinking.

Aim and Intended Outcomes of the Draft Guidelines

The very first paragraph of the document expresses the intended outcome of the guidelines - to *'help people make informed decisions about how much alcohol they choose to drink.'*[1]

In the media statement provided by the NHMRC regarding the release of the Draft Guidelines Prof Kelso also emphasised the importance of informed choice as being the aim of the Guidelines:

> *We're not telling Australians how much to drink. We're providing advice about the health risks from drinking alcohol so that we can all make informed decisions in our daily lives.*[2]

ABA supports this position, and believes that, in adopting this approach, the Draft Guidelines will best serve consumers - by acknowledging that those who choose to consume alcohol be given the best information available to allow them to make properly informed decisions on how much and how often they wish to do so.

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[1] *Draft Australian Guidelines to Reduce Health Risks from Drinking Alcohol*, 2019

[2] Kelso, A. 2019, *Reducing the health risks from drinking alcohol*, NHMRC <https://www.nhmrc.gov.au/about-us/news-centre/reducing-health-risks-drinking-alcohol>

ABA submits that a directive approach to the Guidelines, without choice, should be avoided to ensure that the aim of the Guidelines can be met.

Concept of Informed Choice

The concept of 'informed decision' encompasses[3]:

- presentation of alternatives to allow individuals to select options that are best suited to their individual circumstances; and
- information provided on the benefits and disadvantages of the alternatives based on the best available evidence.

Have the Draft Guidelines achieved the aim?

ABA submits that while the intention of the Draft Guidelines and commentary from the NHMRC has stressed the importance of informed choice, the Guidelines themselves fail to reflect this aim for the following reasons:

1. The information in the Draft Guidelines does not take a balanced view of the evidence on the risks and benefits of alcohol consumption, which impedes consumers' ability to make informed choices.

In particular, the aim of informed consent is not supported by the Draft Drinking Guidelines in that an unbalanced view has been taken in relation to the risks and benefits of alcohol consumption. Most concerning is the *lack of evidence* used when discussing the issue of risks and benefits of alcohol consumption. ABA's concerns regarding this approach, especially in relation to Guideline One, are outlined under section 3.

For the avoidance of doubt, ABA does not encourage those who choose not to drink to take up alcohol consumption in order to benefit from protective health outcomes. However, consumers are entitled to the full evidence base when it comes to alcohol consumption and their health, including a full and proper discussion of established benefits.

2. Draft Guideline One has been developed with a 'one size fits all' approach, which does not reflect reality for most Australian men and women.

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[3] See for example:

- Braddock III CH, Edwards KA, Hasenberg NM, Laidley TL, Levinson W. (1999). Informed Decision Making in Outpatient Practice: Time to Get Back to Basics. *JAMA* 1999; 282(24):2313–2320.
- Price, E. L., Bereknyei, S., Kuby, A., Levinson, W., & Braddock, C. H., 3rd (2012). New elements for informed decision making: a qualitative study of older adults' views. *Patient education and counseling*, *86*(3), 335–341.
- Woolf, Steven & Chan, Evelyn & Harris, Russell & Sheridan, Stacey & Braddock, Clarence & Kaplan, Robert & Krist, Alex & O'Connor, Annette & Tunis, Sean. (2005). Promoting informed choice: Transforming health care to dispense knowledge for decision making. *Annals of internal medicine*. 143. 293-300.
- Krist, Alex H., Tong, Sebastian T., Aycock, Rebecca A., Longo, Daniel R. (2017). Engaging patients in decision-making and behavior change to promote prevention. *Information Services & Use*, vol. 37, no. 2, pp. 105-122.

ABA submits that even if consumers could accept the risk assessment as laid out in the Guidelines, Guideline One does not present this information in a manner that facilitates an informed decision. Instead Guideline One dictates to consumers a single premise of how alcohol should be consumed, which actually relates to risk thresholds for a small and defined demographic, with no reference to the differing ways in which Australian men and women engage over a beer, cider, wine, spirit or cocktail.

This view is supported by Data Analysis Australia's Report:

> *[T]he guidelines represent a simplified summary of one set of behaviours that might be considered to have an acceptable risk, while not presenting different behaviours that might have similar or lower levels of risk. Hence, the guidelines do not encourage informed decision making despite the statement that "understanding the risks helps Australians make informed choices about their health."*

Re-centring the Guidelines to facilitate informed choice

ABA submits that the Draft Guidelines require review to ensure that every section has been written with the aim of allowing for informed choice to be achieved by consumers. In particular, ABA recommends:

- the Draft Guidelines be reviewed to ensure that there is a balanced and evidence-based approach to both the risks and benefits of alcohol consumption and health; and
- consequentially, Guideline One be reviewed to better reflect the spectrum of safe drinking thresholds and the situations in which men and women make decisions around drinking.

Section Two: Approach to Guideline One

Key points and recommendation

- Guideline One has recommended the same level of consumption for men and women despite the overwhelming evidence showing the risk profile of men and women is different, for example that is the case with the modelling produced by SAPM-AU being different for men and women.
- Guideline One has been based on a drinking pattern of three times a week despite:
  - admitting that the three days a week estimation is 'highly uncertain'; and
  - the data from NHS and NDSHS on which they have relied showing that alcohol consumption varies greatly between consumers and that three days a week is not the most common or average consumption pattern.
- The statement in Guideline One that '*The less you choose to drink, the lower your risk of alcohol-related harm*' does not match the evidence in SAPM-AU that establishes a protective effect from certain alcohol consumption patterns.

ABA recommends:

- To ensure that Guideline One is developed using a scientifically valid approach that will allow the Australian public, medical professionals, policy makers and other stakeholders to have faith in their credibility, the approach to the Guidelines must be reconsidered.

Men and women should have different advice

Guideline One has recommended the same level of consumption for men and women. This recommendation has been made despite it being inconsistent with a substantial body of evidence.

SAPM-AU has modelled the risks for men and women separately. The outcome is different risks for men and women consuming alcohol. For ease of reference this can be observed in the following tables:

Men

Table 1: Absolute lifetime risk of alcohol-attributable mortality for men by mean weekly consumption and days per week across which consumption is evenly spread

Mean consumption (std. drinks/week)	Drinking days per week						
	7	6	5	4	3	2	1
7	-4.9%	-4.9%	-4.7%	-4.2%	-3.2%	-0.9%	4.3%
14	-2.3%	-1.7%	-0.9%	0.3%	2.1%	5.0%	10.3%
21	1.4%	2.4%	3.6%	5.0%	6.9%	9.6%	14.8%
28	5.5%	6.7%	7.9%	9.4%	11.2%	13.5%	18.7%
35	9.7%	10.9%	12.1%	13.4%	15.1%	17.1%	22.3%
42	14.1%	15.0%	16.0%	17.2%	18.7%	20.8%	25.9%
49	18.5%	18.9%	19.7%	20.7%	22.1%	24.6%	29.5%

Women

Table 2: Absolute lifetime risk of alcohol-attributable mortality for women by mean weekly consumption and days per week across which consumption is evenly spread

Mean consumption (std. drinks/week)	Drinking days per week						
	7	6	5	4	3	2	1
7	-3.9%	-3.9%	-3.7%	-3.2%	-2.3%	0.0%	4.0%
14	0.1%	0.6%	1.4%	2.5%	4.1%	6.9%	10.8%
21	5.1%	5.8%	6.8%	8.2%	9.8%	12.2%	16.0%
28	10.3%	11.0%	12.1%	13.4%	15.0%	16.7%	20.4%
35	15.3%	16.1%	17.0%	18.2%	19.6%	21.0%	24.5%
42	20.2%	20.9%	21.7%	22.7%	23.8%	25.2%	28.4%
49	24.8%	25.5%	26.1%	26.9%	27.8%	29.6%	32.5%

The results from the modelling clearly state that:

> *men are at a lower risk than women from alcohol consumption at all levels of consumption.*[4]

While the Draft Guidelines have attempted to provide a reason for providing the same guidelines for men and women, the reasons are not based on science or the evidence as the modelling clearly shows differing risk levels for men and women.

ABA submits that any guidelines on alcohol consumption must be reflective of the science and evidence of differing risk levels for men and women.

Basing the Guidelines on three drinking days a week is flawed

The Draft Guidelines use an estimate of three drinking days per week as the basis for Guideline One as being the average number of drinking occasions for Australians who consume alcohol. In doing so the Draft Drinking Guidelines admit that:

> *It should be noted that these estimates remain highly uncertain.*[5]

'Highly uncertain' should not be the level of evidence that is acceptable in the development of the Draft Guidelines. In order to achieve the aim of the Guidelines which is to 'help people make informed decisions' it is unacceptable to allow Guideline One to be based on such uncertain evidence. This high degree of uncertainty nullifies any evidence presented and therefore is no longer credible for the Australian public.

The uncertainty of the estimate of three drinking days per week is apparent when looking at the data on which it was based. This data came from the National Drug Strategy Household Survey (NDSHS) 2016 and the National Health Survey (NHS) 2014-15.

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[4] The University of Sheffield, *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 Final report*, 2019, p8

[5] *Draft Australian Guidelines to Reduce Health Risks from Drinking Alcohol: Appendix 1*, 2019, p60

The NDSHS collected detailed information on the drinking frequency of Australians 18 years and over who consumed alcohol in the last 12 months as outlined in the table below:[6]

Drinking frequency	Males	Females	Persons
Every day	9.7	5.7	7.7
5 to 6 days a week	11.4	7.5	9.4
3 to 4 days a week	16.8	13.3	15.1
1 to 2 days a week	23.8	21.5	22.7
2 to 3 days a month	16.4	16.6	16.5
About 1 day a month	7.9	11.9	9.8
Less often	12.8	21.4	17.0
No longer drink	1.3	2.2	1.7

Note: Base is people that have had an alcoholic drink in the previous 12 months.
Source: NDSHS 2016

The NHS collected detailed information on the drinking frequency of Australians 15 years and over who consumed alcohol in the last 12 months as outlined in the table based on ABS data below:

	PROPORTION OF PERSONS (%)		
Frequency of alcohol consumption	Males	Females	Persons
Every day	9.9	5.0	7.5
5 to 6 days a week	10.7	6.5	8.7
3 to 4 days a week	16.5	12.2	14.5
1 to 2 days a week	27.8	24.5	26.2
2 to 3 days a month	12.8	13.3	13.0
1 day a month	8.6	11.1	9.8
Less than once a month	13.7	26.6	19.9

Based on ABS data

National Health Survey 2014-15

The NHS also collected information from Australians who drank alcohol in the last week on whether the amount they consumed was more, less or the same amount as most weeks. This is shown in the table based on ABS data below:

	PROPORTION OF PERSONS (%)		
Whether amount of alcohol consumed is about the same, more or less than most weeks	Males	Females	Persons
More	30.1	34.5	32.1
About the same	60.1	56.7	58.6
Less	9.8	8.8	9.4

Based on ABS data

National Health Survey 2014-15

[6] Source: AIHW, National Drug Strategy Household Survey 2016

The data from the NDSHS and NHS both show that:

- the frequency of alcohol consumption varies greatly amongst consumers
- more consumers drink 5-7 days a week than 3-4 days a week
- more consumers drink less often than once a month than 3-4 days a week

This data shows that there is no evidence base or justifiable reason to select three days a week as a basis for the Guidelines.

It would be a simple common observation to recognise that a person's patterns of consumption change, but it can be easily demonstrated. The NHS shows that, on any given week, a large percentage of consumers (41.5%) can be said to have varied their alcohol consumption from the 'usual' amount.

The changing consumption patterns over the course of a year is also reflected in the Australian Bureau of Statistics' (ABS) Retail Trade data. Retail data shows significant fluctuations in retail liquor sales across the year indicating that Australian consumers do not have a single pattern of consumption.

Source: ABS, 8501.0 Retail Trade, Australia

To ensure a guideline that is inclusive of the varied drinking patterns of Australians, the final guideline advice should be revised in their form to be reflective of these patterns.

While we can only hypothesise as to how and why the Alcohol Working Committee came up with a recommendation of 10 a week and that this was subsequently approved by the NHMRC CEO and Council, the decision to do so has achieved a new global low in the amounts recommended against those of other countries.

Statement 'The less you choose to drink, the lower your risk of alcohol-related harm' is not reflective of the evidence

Guideline One makes the following statement:

> *The less you choose to drink, the lower your risk of alcohol-related harm.*

ABA submits that this statement does not correspond to the results of the modelling from SAPM-AU.

ABA has significant concerns regarding SAPMAU as outlined in Section Three: Modelling and Evidence Base. Despite this, the model is still clear in its establishment of a protective effect when consuming alcohol in particular patterns compared to abstaining from alcohol.

Considering that the statement 'the less you choose to drink, the lower your risk of alcohol-related harm' ignores the evidence that establishes a protective effect, as reflected in SAPM-AU it must be removed from Guideline One.

Section Three: Modelling and Evidence Base

Key points and recommendation

- SAPM-AU assign thresholds to alcohol-attributable conditions as part of their modelling process. In the past, SARG caution against the use of assigning risks to certain conditions for low alcohol consumption. Despite this, SAPM-AU uses the risk threshold it had cautioned against without explanation.
- Data Analysis Australia (DAA) has undertaken a review of the Draft Guidelines with reference to the SAPM-AU at the request of ABA. Its five key findings have pointed out serious shortcomings with SAPM-AU.
- The lack of transparency and access to SAPM-AU means that is it not possible to fully critique the model or have trust in its scientific rigour.
- The section 'Balancing the evidence on the range of effects of consuming alcohol' requires a balanced approach to both the benefits and risks of consuming alcohol. The lack of balance places in jeopardy the credibility of the Guidelines and means that consumers are not fully informed of the risks and benefits of the choices they make.

ABA recommends:

- In order to use SAPM-AU as the modelling basis for the Guidelines, NHMRC should either:
    - arrange for the SAPM-AU to be available to allow for the requisite level of transparency and access to ensure it is fit for purpose, or
    - failing to secure access to the Model, the NHMRC should reconsider the use of the Sheffield Alcohol Policy Model to inform the Guidelines.

Repetition of past mistakes

We have previously corresponded with the NHMRC over the Select Tender and appointment of Sheffield. It is not our intention to re-prosecute those concerns in this submission, but they still stand.

The Sheffield Alcohol Research Group was commissioned by Public Health England in 2014 to use their Sheffield Alcohol Policy Model (SAPM) to model 'safe' levels of alcohol consumption for new drinking guidelines in the UK.

As part of that commission, the Guideline Development Group requested that SARG assign a different consumption threshold (i.e. zero) to wholly alcohol-attributable conditions in the base case of their report. Correspondence which came to light through Freedom of Information requests in the UK revealed a highly sceptical response from SARG: 'Our view remains that it does not seem right to assign people drinking at very low levels a risk of

acquiring alcoholic liver disease and similar conditions. Unless there are strong opposing views, we think it better to keep the threshold in the base case.'[7]

This makes perfect sense as it is medically impossible for a person who drinks in moderation to acquire alcoholic liver disease or similar.

Despite these reservations, SARG did agree to adopt a different threshold for the base case of their model. They did however include this commentary in their final report:

> *These results suggest the base case should not be accepted uncritically as the implied guideline thresholds are sensitive to alternative assumptions and baseline data and there are not strong arguments for preferring the base case specifications over those used in the sensitivity analyses.*[8]

We know the implications of this change as the FOI process uncovered what the model produced prior to its abandonment of proper scientific modelling principles:

UK Standard Drinks Pre-distortion	***UK Standard Drinks After-distortion***	***Percentage Change***
Men – 21.2	*Men – 12.5*	*41%*
Women – 17.6	*Women – 14.1*	*20%*

Despite their own initial criticism, and criticism by others following the release of the UK guidelines, SARG has now again used this highly flawed model in their report for the NHMRC:

> *There is uncertainty regarding the level of consumption above which mortality and morbidity risks for wholly alcohol-attributable conditions begin to rise. In the base case model, we assume this consumption threshold is zero for both chronic and acute conditions (i.e. that risk increases with any level of alcohol consumption) in line with the work undertaken as part of the 2016 UK drinking guidelines review.*[9]

SARG has not explained or reconciled their repeated use of this flawed model despite with their criticisms. It also raises significant questions over the AWC and NHMRC management of

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[7] Snowdon, C. 2019, 'Sheffield's hired guns return to the scene of the crime', *Velvet Glove Iron Fist*, weblog, <https://velvetgloveironfist.blogspot.com/2019/12/sheffields-hired-guns-return-to-scene.html>

[8] The University of Sheffield, *Mortality and morbidity risks from alcohol consumption in the UK: Analyses using the Sheffield Alcohol Policy Model (v2.7) to inform the UK Chief Medical Officers' review of the UK lower risk drinking guidelines Final report*, 2016, p9 and 53

[9] The University of Sheffield, *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 Final report*, 2019, p26

the SARG contract when such pre-existing flaws to the model are relatively common knowledge and easily discoverable.

There are no grounds for using the outputs of this model to inform the Guidelines. In fact, doing so represents a flouting of the evidence base.

Sheffield Alcohol Policy Model Australia

ABA has commissioned DAA to review the Draft Guidelines with reference to the SAPM-AU model. The lead statistician on the review was Dr John Henstridge. Dr Henstridge is:

- past President of the Statistical Society of Australia,
- past President of the Geostatistical Association of Australasia,
- past Adjunct Professor of Statistics at the University of Western Australia,
- past board member of Science and Technology Australia,
- Fellow and Chartered Statistician of the Royal Statistical Society,
- member of the International Association for Statistical Computing,
- member of the Australian Mathematical Society, and
- Accredited Statistician of the Statistical Society of Australia

The report makes five findings as follows:

Finding 1. The methodology behind the Guidelines relies heavily upon modelling conducted (apparently under contract) by the Sheffield Alcohol Research Group using an adaptation of the Sheffield Alcohol Policy Model (SAPM). This model has not been made available for independent review and hence does not represent open and transparent science.

Finding 2. The SAPM was primarily developed to assess the possible effects of certain alcohol control measures, particularly those relating to prices. These aspects of the model are not necessarily relevant to the context of the guidelines and it is not clear whether they impact upon the utility of the model for the current context.

Finding 3. There appears to be a substantial disconnect between the outputs of the Sheffield model and the draft guideline. In particular, the draft guidelines (a) lose the difference between males and females, and (b) for people who avoid binge drinking, they understate the average number of drinks that might be considered low risk.

Finding 4. The model scenario SA1 that assumes that low levels of alcohol consumption has no protective effect does not exist has a major effect on the model that substantially increases the aetiological fraction mortality attributable to alcohol. This effect is not explicitly presented, and no evidence is presented that the aetiological fraction thus calculated is reasonable.

Finding 5. The Guidelines are inconsistent in their attitude towards the protective effects of low levels of alcohol consumption. The guideline is fundamentally based upon the assumption that there is a protective effect – if there was not then the methodology would lead to a recommended level that is a small fraction of the guideline. However, at the same time it is stated that "all alcohol consumption comes with some degree of risk".

From these findings it can be concluded that in its current form, the SAPM-AU modelling cannot be relied on to inform the Drinking Guidelines. The lack of transparency with SAPM-AU is also cause for concern. As DAA point out in their report:

> *[t]his review must be regarded as an interim review. Without proper access to the most important modelling work in the Report, it is impossible to have confidence in the accuracy or relevance of the central parts of the Report. We strongly recommend that either the model be made freely available or it not be used until a satisfactory independent review is conducted.*

Treatment of the evidence of relating to the benefits and risks of alcohol consumption

ABA holds serious concerns regarding the approach taken by the Draft Guidelines on page 22 under the heading *Balancing the Evidence on the Range of Effects of Consuming Alcohol*. This section is particularly important as it is vital that the information on both protective and detrimental effects of alcohol consumption be simply and honestly explained to consumer. This will facilitate the aim of informed choice to be achieved by the Guidelines.

The section is less than a page long and only 569 words, yet it contains 11 statements that have either been made without reference or have been made via selective references, with what would appear to be the aim of casting doubt over the long standing evidence of the protective effects of moderate alcohol consumption in relation to cardiovascular disease. The statements are as follows:

- "Lower levels of alcohol consumption have been thought to provide some protection against cardiovascular diseases, particularly coronary heart disease. However, there is growing uncertainty about the evidence underpinning such 'protective effects (The University of Sheffield 2019)."
- "This doubt has largely arisen because of the improved approaches to research study designs. This includes the ability to use new kinds of evidence, such as Mendelian randomisation studies."
- "These newer studies greatly reduce some of the challenges of earlier evidence. These challenges included the lack of clarity about changes in drinking patterns being due to illness, not because the person chose not to drink alcohol and was otherwise healthy."

- “They also include the challenge of having accurate information about the exposure to alcohol, due to the fact that a lot of earlier evidence is based on self-reporting of alcohol consumption, and this can often be inaccurate.”

- “The evidence also suggests that alcohol may either not protect against coronary heart disease, or that the extent of previous protection was over-estimated.”

- “With regard to cardiovascular disease, the evidence of an association between increasing risk of stroke with increasing alcohol consumption has become clearer in recent years.”

- “In addition, most studies which show cardiovascular benefits of low-level alcohol consumption, also show that such protection, if it exists, peaks at very low doses, for example, at less than half to one standard drink per day (Di Castelnuovo et al. 2006)”

- “Further there are safer ways to reduce risk of coronary heart disease, such as by maintaining a healthy weight, reducing blood pressure and not smoking.”

- “If coronary heart disease protective effects do exist, the modelling for these guidelines shows it is likely that they only offset harm from alcohol in people aged over 70 years and over.”

- “If there are protective effects for coronary heart disease in selected groups, the increase risk of alcohol consumption from other health conditions such as cancer still remains.”

- “If such protective effects are over estimated, this could lead to the recommended alcohol consumption limits in the guidelines being too high.”

Detailed analysis of these statements and their short-comings are considered at Appendix A.

By way of summary, the main cardioprotective mechanistic effects of alcoholic beverages were determined by experimental and clinical studies between 1980 and 2005 after observations of a j-shaped relationship between alcohol consumption and cardiovascular disease. Many of these studies are scientifically superior to more recent studies, but due to the NHMRC only accepting evidence from 1 January 2007, they have not even been considered. Even superior studies after this date have received unequal attention as outlined later in our submissions on the GRADE system.

Cardiovascular disease (CVD) involves a complex interplay between multiple altered cellular and molecular functions in heart muscle (i.e., cardiomyocytes), blood vessels (i.e., endothelial cells), vascular smooth muscle cells, blood cells (i.e., platelets and monocytes) and plasma

components (i.e., lipoproteins, and blood clotting and blood flow factors) as well as gene function (Booyse et al. 2007[10]).

Accordingly, there are multiple biological mechanisms involved in reducing the risk of CVD and include haemostatic effects on blood pressure and blood flow, anti-inflammatory effects and enhanced endothelial function, that is the ability of the artery wall to expand and contract, thus providing a protective effect during the early phases of atherosclerosis (Ross 1999[11], Esposito et al. 2004[12], Lopez-Garcia et al. 2004[13], Collins et al. 2009[14]).

The CVD (and overall) health effects of alcohol consumption are both acute and chronic (accumulative) and are strongly determined by the quantity and pattern of alcohol consumption.

The accepted interpretation of the J-shaped curve relating alcohol intake to cardiovascular events or mortality is that the lowest point on the curve (light-to-moderate drinking) represents optimum exposure to alcohol, and the increased risk in abstainers or heavy drinkers reflects the consequence of sub-optimal exposure. The nadir of J-shaped curves for alcohol is proposed as a healthy range for the general population. This nadir, however, varies between study analyses and meta-analyses. The nadir quoted on page 22 of the Draft Australian guidelines to reduce health risks from drinking alcohol (2019), refers to Di Castelnuovo et al. 2006)[15] which was at 6 g alcohol/day or approximately one-half of a 10 g standard drink/day (19% risk reduction) but lower mortality compared with no alcohol consumption was observed with up to 4 drinks/day in men and 2 drinks/day in women. More recent meta-analyses specific to CVD also observed a J-shaped curve but with a nadir variously ranging from >2.5 to 30 g alcohol/day (Yoon et al. 2020[16], Huang et al. 2014[17], Mostofsky et

[10] Booyse FM, Pan W, Grenett HE, Parks DA, Darley-Usmar VM, Bradley KM, Tabengwa EM. Mechanism by which alcohol and wine polyphenols affect coronary heart disease risk. Ann Epidemiol. 2007 May;17(5 Suppl):S24-31

[11] Ross. R. (1999) Atherosclerosis--an inflammatory disease. N..Engl. J. Med. 340: 115-126.

[12] Esposito, K., Marfella, R., Ciotola, M., Di Palo, C., Giugliano, F., Giugliano, G., D'Armiento, M., D'Andrea, F., Giugliano, D. (2004) Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. J.A.M.A. 292: 1440-1446.

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al. 2016[18], Ronksley et al. 2011[19], Constanzo et al. 2010[20]) in those reporting alcohol per day rather than week (Xi et al. 2017)[21]. It is apparent that the study chosen by the NHMRC for its nadir is significantly lower than more recent and scientifically robust studies.

The clinical and experimental literature is consistent in that the pattern of alcohol consumption required to maintain cardio protection is regular consumption, which can be determined as daily (McElduff and Dobson 1997[22]). This regularity is related to short-term effects on the prevention and dissolving of blood clots, which are readily reversible. For example, the acute local effects of moderate alcohol consumption on various haemostatic variables such as platelet aggregation and fibrinolysis are, however, temporary and return to normal within 24 hours (Renaud et al. 1992[23], Renaud 1994[24], Hendriks et al. 1994[25], Booyse et al. 1999[26]). The regularity is also related to longer-term effects on plasma antioxidant capacity, on LDL oxidation and on systolic blood pressure (Klatsky et al. 1977[27], Klatsky et al. 1990[28], Gillman et al. 1995[29], Klatsky 1995[30]).

Despite this evidence, the Draft Guidelines have gone to great lengths to cast doubt on the significant and in-depth research that has found a protective effect when it comes to alcohol and cardiovascular disease. If there were any doubts as to the effect of alcohol on

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[28]Klatsky, A.L., Armstrong, M.A. and Kipp, H. (1990) Correlates of alcoholic beverage preference: traits of persons who choose wine, liquor or beer. British Journal of Addiction, 85, 1279–1289.
[29] Gillman, M.W., Cook, N.R., Evans, D., Rosner, B. and Henneckens, C.H. (1995) Relationship of alcohol intake with blood pressure in young adults. Hypertension, 25, 1106–1110.
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cardiovascular disease, a systematic review of the evidence base on alcohol consumption and cardiovascular disease could and should have been undertaken.

There have been four systematic reviews commissioned as part of the Draft Drinking Guidelines development process. However, no clear reasoning has been provided as to the requisite threshold required to trigger the need for a systematic review. There has also been no clear information provided on the rationale for who has been appointed to undertake the systematic reviews.

From the documentation it can vaguely be assumed that the trigger for undertaking a review is that there is insufficient or inconclusive evidence to be able to draw a conclusion regarding the health outcome.

The Draft Guidelines have chosen not to undertake the same process for cardiovascular disease and to instead simply cast doubt over the protective evidence. A systematic review could have been used to dispel any concerns regarding the protective evidence. It is unclear why the approach of seeking out the evidence was not taken when it came to cardiovascular disease.

This section would also benefit from consideration of alcohol's other protective effects when consumed in moderation, such as on ischaemic stroke, non-Hodgkin's lymphoma, dementia, type II diabetes; and when taken as a whole on all-cause mortality.

ABA submits that the section *Balancing the Evidence on the Range of Effects of Consuming Alcohol* be reviewed critically in the aim of producing a balanced and evidence-based approach to the effects of consuming alcohol. It is tantamount to the concept of informed choice that consumers be fully informed of the effects of alcohol consumption and that the evidence of protective effects of alcohol should be approached with scientific rigour rather than what appears to be a cherry-picking exercise.

If the NHMRC wants to adopt a systematic review of the evidence, it may be beneficial to begin with information relating the biomedical mechanism of alcohol-related health benefits. A summary of this information is provided at Appendix B.

Outcomes of the application of the GRADE system

Any systematic review is limited by the choice of the underlying literature, where the number, depth and quality of the literature varies, as well as the methodology employed. Therefore, not all meta-analyses are equal and, comparatively, will not necessarily provide the same or even a similar result.

A significant issue is the choice of meta-analysis included in the *Evaluation of submitted evidence on the health effects (harms and benefits) of alcohol consumption*. For example, while there may be one, two, three or more meta-analyses found published between their allotted time frame (January 2007-January 2017), only the most up to date one with the most

recent studies included has always been chosen. Invariably, and in particular re cardiovascular relationships with alcohol consumption, they are deemed to be 'poor quality' according to the GRADE system they are using.

On page 17 it states that 'currency of the systematic review' is part of criterion for inclusion, but surely quality is also an important criterion. This is particularly relevant for the evaluation of cardiovascular relationships with alcohol consumption, where the single meta-analysis chosen (Stockwell et al. 2016) provided markedly different conclusions to previously published meta-analyses analysing additional studies in their allotted time frame such as Ronksley et al. (2011)[31] and Jayasekara et al. (2014)[32], or those subsequently published between January 2017 and December 2018, for example, such as Colpani et al. (2018)[33]. Furthermore, the methodology of the chosen Stockwell et al. (2016) meta-analysis had been recently criticised by Ding and Mukamal (2017)[34] as follows:

> *"The authors…in their earlier study on alcohol and mortality (Stockwell et al., 2016), apply a mixed-effects model to analyse dose-response data points across all studies. Unfortunately, dose-response data yield relative-risk values that are correlated with each other, because they share a common reference group. As a result, basic mixed-model regressions are flawed when applied to meta-analysis, and, instead, the gold-standard Greenland and Longnecker (1992) method for dose-response metaanalysis is required. This method is well validated, available within major statistical software packages, and reasonably considered the gold standard (Orsini et al., 2012). Failure to use such a method would lead to invalid standard errors, confidence intervals that are wider than the true effect, and improper meta-analytic weighting (as seen in subgroup analyses). Thus, because the estimates were not pooled properly, it is uncertain if their findings still hold."*

In addition, there is no rationale as to why the more recently published meta-analyses (after January 2017) that were provided to the NHMRC on request during the two-year review process, were not included, especially when they may have been of higher quality and potentially answered outstanding research questions as evidenced on page 49, for example.

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[31] Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ. 2011 Feb 22;342:d671. doi: 10.1136/bmj.d671.

[32] Jayasekara H, English DR, Room R, MacInnis RJ. Alcohol consumption over time and risk of death: a systematic review and meta-analysis. Am J Epidemiol. 2014 May 1;179(9):1049-59. doi: 10.1093/aje/kwu028.

[33] Colpani, V., Baena, C.P., Jaspers, L., van Dijk, G.M., Farajzadegan, Z., Dhana, K., Tielemans, M.J., Voortman, T., Freak-Poli, R., Veloso, G.G.V., Chowdhury, R., Kavousi, M., Muka, T., Franco, O.H. (2018) Lifestyle factors, cardiovascular disease and all-cause mortality in middle-aged and elderly women: a systematic review and metaanalysis. European Journal of Epidemiology 2018; pre-publication. https://doi.org/10.1007/s10654-018-0374-z

[34] Ding, E.L., Mukamal, K.J. Robustness of the J-Shaped Association of Alcohol With Coronary Heart Disease Risk. Journal of Studies on Alcohol and Drugs 2017 78:3, 389-391

Furthermore, little data is provided on the reduced risk of dementia/cognitive decline associated with moderate alcohol consumption; the evidence evaluation only discusses the harmful effects of heavier alcohol consumption on page 9.

It states on page 107 that “potential bias…consequently, this reduces the confidence of these results as there may be residual confounding present”, which is further discussed on page 108. Instead of worrying about heterogeneity of results from different studies, the evaluation should instead, or at least as well, focus on the homogeneity of many studies.

Section Four: Acceptability, feasibility and consumer involvement

Key points and recommendation

- According to Government research, the 2009 Guidelines were not considered to be acceptable by consumers as they were unrealistic and too extreme.
- When the current Guidelines are found to be unacceptable to consumers due to being unrealistic, it is unlikely that the implementation of the Draft Guidelines will be feasible as consumers will be resistant to accept.
- There was a lack of consumer involvement in the development of the Guidelines, ultimately leading to the requirements of the *Guidelines or Guidelines* for consumer involvement not being met.

ABA recommends that:

- Genuine consumer involvement (regarding the wide range demographics of consumers) be undertaken to increase the acceptability and feasibility of the Guidelines.

Acceptability and feasibility

Regarding the acceptability of Guideline One, the Draft Guidelines conclude that:

> *It is expected that Australians will vary in their views regarding whether they consider this recommendation acceptable.*[35]

ABA submits that a very limited view has been taken to consider the acceptability of the Draft Guidelines. It is unacceptable to brush aside the views of consumers in terms of acceptability by simply saying the level of acceptability will vary.

In fact, the lack of rigour associated with the understanding of the acceptability of the Draft Guidelines is a symptom of the lack of consumer involvement in the development of the Guidelines as discussed below. If the Draft Guidelines had been developed with consumer involvement, there would be a clearer understanding of what is, in fact, acceptable to the consumer.

The lack of engagement in the Draft Guidelines on the issue of acceptability leads to some very pertinent questions the final Guidelines must consider:

- How will acceptability vary?
- To what extent will acceptability vary?
- Who is it that will/won't accept the Guideline?
- Why will/won't the Guideline be considered acceptable?

[35] *Draft Australian Guidelines to Reduce Health Risks from Drinking Alcohol*, 2019, p25

- What will be the impact of Guidelines that are not acceptable to the public at large?

Government study shows the 2009 Guidelines are not considered acceptable by consumers and as the Draft Guidelines are more restrictive, they are less likely to be accepted by consumers.

In 2011 the Australian Government, through the then Department of Health and Ageing (now Department of Health), set out to understand the views of consumers to the 2009 Guidelines of no more than two standards drinks a day. In doing so they commissioned Horizon Research to undertake a study.

The findings of the study can be succinctly summarised as follows:

> [T]he [2009] recommendations were quickly dismissed as ***unrealistic***, something that was far too extreme and removed from current behaviour.[36]

Other findings from the study include:

- The perception of the Guidelines was that they "come from 'miserable old people' trying to stop others having a good time."[37]
- There was "surprise and considerable disbelief"[38] about the 2009 guidelines.
- The Guidelines "did not engage participants or motivate them to consider their drinking behaviour."[39]

Considering that Draft Guideline One is more restrictive than the 2009 Guidelines, it is highly unlikely that consumers will be less likely to accept Draft Guideline One.

The Draft Guidelines have not sufficiently considered the issue of feasibility.

The Draft Guidelines have approached the issue of feasibility in the following manner:[40]

> *The recommendations are considered feasible to implement given they are similar to the 2009 recommendations, which the majority of the population drink in accordance with.*
>
> *…*
>
> *The success of the guidelines in improving health outcomes is entirely dependent on their successful dissemination, public communications and ongoing community awareness raising about the guidelines (including to health professionals), which the Australian Government is responsible for.*

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[36] *National Alcohol Harm Reduction Strategy: Resource Evaluation*. Horizon Research, March 2011, p22
[37] Idem, p21
[38] Idem, p22
[39] Ibid.
[40] *Draft Australian Guidelines to Reduce Health Risks from Drinking Alcohol*, 2019, p26

It is concerning that the Draft Guidelines assert that the success of the guidelines is 'entirely dependent' on their communication. We believe that the evidence from the department's 2011 survey shows that the success of the guidelines and their feasibility are much more dependent on their acceptability than any form of public communication.

Consumer involvement in the Guideline Development Process

NHMRC's *Guidelines for Guidelines* highlights the important role that consumers play throughout the guideline development process. The *Guidelines for Guidelines* go so far as to say:

> *Guidelines can only meet the needs of the population if they are developed with meaningful and authentic engagement with consumers.*

The *Guidelines for Guidelines* provide clear direction on the requisite involvement of consumers in the guideline development process. For ease of reference, ABA summarised the principles for good governance in consumer involvement in the table below. We have also provided an analysis of the NHMRC's adherence to these principles during the development of the Draft Guidelines.

Table One: Analysis of Implementation of NHMRC's Principles for Consumer Involvement in Draft Drinking Guidelines

Principles from *Guidelines for Guidelines*	Implemented?	Analysis
Guidelines seeking NHMRC approval must involve consumers as members of the guideline development group and throughout the guideline development process. Ideally you will have more than one consumer in your guideline development group and seek out consumers from diverse or marginalised backgrounds to make sure their voices are heard.		The two consumer advocates on the guideline development committee have, respectively, a history of parental advocacy and work on FASD, and a history of work with the indigenous community. Parents and members of the indigenous population make up an important but not complete representation of consumers of alcohol. One of the consumer advocates is a former Board member of the Foundation for Alcohol Research and Education (FARE) – Australia's leading anti-alcohol advocacy group. There is no mention of what work the AWC or the NHMRC Secretariat undertook in seeking out diverse or marginalised voices.
You should make sure that decisions about how and when consumers are engaged with are clearly documented in the final guideline.		No mention of consumer engagement. Consumer advocates listed as guideline development group members are only inferred examples of consumer engagement.
Decisions about the recruitment of consumers should be well-documented and refer to clearly specified requirements based on the goals of each stage of development.		There is no example of this in the information made available to the public.

Consumer input into guideline development should be reported in the guideline itself to ensure that your guidelines are transparent and can be evaluated by others at a later stage.	🔴	No mention of consumer input. No transparency, no chance for evaluation.
You must ensure that you have captured an authentic consumer perspective and that the multiple voices and lived experiences of people and communities affected by the guideline are heard. Failure to listen will severely compromise the effectiveness of your guideline and will neither adequately address consumer needs nor produce the desired health outcomes.	🔴	No evidence that any authentic consumer perspectives or lived experiences were sought or considered in the drafting of the guidelines. No evidence, reference or acknowledgement of the Horizon Research of consumer perspective to the 2009 Guidelines.
NHMRC requirements: Guidelines approved by NHMRC must meet all requirements as outlined in the Procedures and requirements for meeting the NHMRC standard. The following requirements are relevant to consumer involvement: A.4 Consumers participate in the guideline development, and the processes employed to recruit, involve and support consumer participants are described.	🔴	No evidence of consumer participation. No processes to recruit, involve or support consumer participants are described.
A.4.1 (desirable) The guideline development process includes participation by representatives of Aboriginal and Torres Strait Islander peoples and culturally and linguistically diverse communities (as appropriate to the clinical need and context), and the processes employed to recruit, involve and support these participants are described.	🔴	No processes to recruit, involve or support Nicole Hewlett or other representatives of Aboriginal and Torres Strait Islander peoples and culturally and linguistically diverse communities are described.

Legend: 🟢 = successfully implemented 🟡 = partially implemented 🔴 = not implemented

While we acknowledge there was a public call for evidence, the call was limited to "high quality studies based on scientific research"[41] and not lived experiences of the Australian population. Furthermore, "evidence from [the public call for evidence] was not formally evaluated, and as such did not inform the guideline recommendations"[42].

As outlined above, consumer involvement is key to ensure that the Guidelines will be acceptable to consumers and in turn their implementation feasible. As such it is imperative to reconsider consumer involvement in the guideline development process to date.

[41] *Draft Australian Guidelines to Reduce Health Risks from Drinking Alcohol: Appendix 2*, 2019, p64
[42] *Draft Australian Guidelines to Reduce Health Risks from Drinking Alcohol*, 2019, p6

Section Five: Supplementary Issues

Timeframe for Submissions

ABA submits that the timeframe for submissions has been inadequate. When considering the timeframe for the submissions process it is important to note that:

- The Draft Guidelines were made available just before the Christmas and New Year period, meaning that there have been substantial delays in obtaining the required information from key contacts in the NHMRC, AIHW and Sheffield University.
- The supporting material and evidence for the Draft Guidelines amounts to over 1 000 pages of material including more than 3 000 citations. It is a significant challenge to process and provide feedback on the volume of material presented within the submission timeframe.
- The Guideline development process has taken over three years and has been resource intensive which is reflective of the complex nature of the evidence base and processes. It follows that the submission process will be equally complex and deserving of providing the public with adequate time to consider, analyse and provide feedback on the evidence.

We understand that there are timelines that the NHMRC have set for the review of the Guidelines to take place. However, we note that these timelines have been pushed back previously and we submit that of all the reasons to extend timelines, the need to facilitate review of the evidence and provide comprehensive feedback should be paramount.

In addition, we understand that the timeframe for public consultation in the *National Health and Medical Research Council Act* (1992) (the Act) is 30 days and that a greater period of time has been allowed for this submission process. However, this is a **minimum** standard set by the Act. By no means does the Act place an upper limit on the consultation period.

While ABA was afforded an extension of a week, the extension was insufficient and essentially did not allow us to make a fully considered submission. ABA submits that the NHMRC should accept additional feedback on the Guidelines, not just from ABA but from all members of the public.

Independent Expert Review

ABA notes that the Draft Guidelines indicate that there will be independent expert reviewers appointed to review the Draft Guidelines. The Draft Guidelines state:

> *The NHMRC project team and Alcohol Working Committee advised on acceptance criteria for nominations for individuals who could undertake expert review of the draft guidelines following public consultation.*

Good governance would dictate that the Alcohol Working Committee (AWC), who were essentially responsible for the guideline review process, would not be involved in any way in

the independent review process. As such it is concerning that the AWC has been involved in setting the criteria for the selection of those who will be responsible for the review of their work. This is not reflective of independence.

The scope of the review also has significant shortcomings. In particular, there has been no indication that the SAPM-AU and its application will be considered as part of the independent review. It is impossible to consider this a full and independent process when the core of the Guidelines, the SAPM-AU, is exempt from review.

ABA recommends the criteria of the independent reviewers be reconsidered without the involvement of the AWC. The SAPM-AU should not be exempted from the review process, instead the model should be made available and reviewed by suitably qualified and independent reviewers.

Name of the Draft Drinking Guidelines

The Draft Drinking Guidelines have taken their title from the 2009 Guidelines as follows:

> *Australian Guidelines to Reduce Health Risks from Drinking Alcohol*

It is important to note that the 2001 Guidelines were titled:

> *Australian Alcohol Guidelines: Health Risks and Benefits*

The title of the Guidelines is important in setting the scene for the tone and information being communicated. This is particularly important considering that the aim of the Drinking Guidelines is to 'help people make informed decisions'.

To allow for informed choices, both the risks and benefits of alcohol consumption must be communicated. To allow for informed choice, it is important the title of the Guidelines is reflective of both the risks and benefits of alcohol consumption.

As such, ABA submits that the Guidelines should be titled *Australian Alcohol Guidelines: Health Risks and Benefits*, to better reflect the aim of helping consumers to make informed choices.

Concept of 'Living Guidelines'

The Draft Guidelines have outlined a shift in the process for reviewing the Guidelines as follows:

> *NHMRC is increasingly developing 'living' guidelines, using methods that enable elements or modules of a guideline to be updated as the evidence changes to ensure guidelines are current, relevant and responsive to emerging evidence. For this guideline, NHMRC has presented the recommendations and other information in the*

> *MAGICapp platform to allow for a 'living' guideline, one where NHMRC can update any part of the guideline should the relevant body of evidence change.*[43]

ABA submits that the concept of 'living guidelines' presents significant challenges to ensuring a rigorous evidence base is maintained for the Drinking Guidelines into the future.

The Draft Drinking Guidelines suggest that the living guidelines will allow for updates to be made 'as the evidence changes.' This raises some fundamental questions:

- What is the threshold for 'evidence changes'?
- Who determines that the 'evidence change' has occurred?
- How often is new evidence considered?
- Do other parties have a right to contest or critique the evidence?
- Are living guidelines ever reviewed in their entirety?
- How are issues such as consumer input reconciled in 'living' guidelines?
- How is the form of the guidelines considered (i.e. Guidelines presented in a weekly v daily value)?

These are fundamental issues that have not been considered and also highlight the potential issues that can arise from the concept of 'living guidelines'. As such, ABA does not support the move to 'living guidelines' without the provision of substantially more information and consultation on how this concept will be delivered.

[43] *Draft Australian Guidelines to Reduce Health Risks from Drinking Alcohol*, 2019, p5

Appendix A: Critique of 'Balancing the evidence on the range of effects of consuming alcohol'

1. **Lower levels of alcohol consumption have been thought to provide some protection against cardiovascular diseases, particularly coronary heart disease. However, there is growing uncertainty about the evidence underpinning such 'protective effects (The University of Sheffield 2019).**

   The evidence also suggests that alcohol may either not protect against coronary heart disease, or that the extent of previous protection was over-estimated.

There is consistent evidence from observational studies and meta-analyses of these studies undertaken over the last three decades regarding the beneficial health effects of regular moderate alcohol consumption on fatal and nonfatal cardiovascular disease (CVD) and total mortality, both in healthy adults and in CVD patients, and when never drinkers are used as the comparison participant population. The dose-effect relationship is characterized by a J-shaped curve and supported by plausible biological mechanisms. Epidemiological research is generally given a lower place in the hierarchy of causal inference than truly experimental research.

Cardiovascular disease (CVD) is an overarching medical term for heart and circulatory related diseases such as high blood pressure, coronary heart disease (also referred to as ischaemic heart disease and coronary artery disease), heart attacks, heart failure, arrhythmias and atrial fibrillation, and strokes. Coronary heart disease and strokes, however, are the most common forms of CVD. While the relationship between alcohol consumption and overall CVD is considered as J-shaped with moderate alcohol consumption conferring lowest risk compared with abstinence and heavier consumption, the relationship between alcohol consumption and the individual forms of CVD can differ. For example, the most clear-cut J-shaped relationships are between alcohol consumption and coronary heart disease, heart attacks and ischaemic stroke. Studies also suggest that while light and moderate alcohol consumption is associated with a reduced risk of CVD and coronary heart disease, heavy alcohol consumption does not necessarily increase this risk. This association is observed irrespective of current or averaged lifetime alcohol consumption.

A 2010 review of 44 cohort and case-control studies undertaken from 1980 to 2010 on alcohol consumption and coronary heart disease calculated a 25% (0.12 to 36%) and 46% (35 to 55%) reduced risk of developing coronary heart disease for men and women, respectively (Padilla et al. 2010[44]). This was observed at an average intake of 63 g alcohol/day for men but only 14 g/day for women. Previously, Corrao et al. (2004[45]) only observed a similar maximal reduced

[44] Padilla H, Michael Gaziano J, Djoussé L. (2010) Alcohol consumption and risk of heart failure: a meta-analysis. Phys Sportsmed. 2010; 38(3): 84-89.

[45] Corrao G, Bagnardi V, Zambon A, La Vecchia C. (2004) A meta-analysis of alcohol consumption and the risk of 15 diseases. Prev Med. 38(5): 613-19.

coronary heart disease risk at 20 g alcohol/day for men and women, although cardio-protection was observed up to 72 g/day. The corresponding maximal reduced risk of coronary heart disease mortality was calculated as 22% (0.3 to 37%) at 31 g alcohol/day for men and 18% (0.4 to 26%) at 11 g/day for women. The studies all had life-time abstainers as the reference category to avoid the confounding proposed by Fillmore et al. (2006) and to provide strength of the evidence of a cardioprotective and causal association. Indeed, the authors concluded that "based on our meta-analysis, some form of cardioprotective association for ischaemic heart disease [coronary heart disease] morbidity and mortality is hard to deny, given epidemiological evidence." The gender difference in the calculated risk probably reflects the different physiology of men and women. For example, women typically have lower body weight, smaller liver capacity to metabolize alcohol, and a higher proportion of body fat, which together contribute to women achieving higher blood alcohol concentrations than men for the same amount of alcohol consumed (Wilsnack et al. 2013[46]). It also reflects that women are more sensitive or susceptible to organ and tissue damage from alcohol than men.

The most comprehensive and relatively recent review of 84 prospective studies undertaken from 1980 to 2009 also used lifetime abstainers as the reference category (Ronksley et al. 2011). Alcohol consumption of 2.5 to 14.9 g/day was consistently associated with a 14-25% reduced risk of CVD mortality, and specifically the incidence of, and mortality from coronary heart disease. This reduced risk was observed for both men and women for coronary heart disease, but the reduction was less for women for stroke, consistent with observations of other meta-analyses. The inclusion of former drinkers did not appear to bias the association of alcohol consumption with CVD. As concluded by Ronksley et al. (2011), the overall association between alcohol consumption and CVD and coronary heart disease was actually apparent over 10 years ago, and more recent studies and meta-analyses undertaken have not significantly altered the estimated associations. This was also reiterated by Rehm et al. (2017)[47] who state that "While these beneficial effects have been put into question for different reasons (e.g. [174,258,259]), and whil they may be overestimated using standard epidemiological methodology because of biased comparison groups [260], biological pathways corroborate some protective effect".

Analysis of 44 cohort and case-control studies undertaken from 1980 to 2010 on alcohol consumption and coronary heart disease calculated a 25% and 46% reduced risk of developing

[46] Wilsnack SC, Wilsnack RW, Kantor LW. (20130 Focus on: women and the costs of alcohol use. Alcohol Res. 35(2): 219-28.

[47] Rehm J, Gmel GE Sr, Gmel G. et al. (2017) The relationship between different dimensions of alcohol use and the burden of disease-an update. Addiction.;112(6):968-1001.

coronary heart disease for men and women, respectively (Roerecke and Rehm 2012, 2014)[48]. For average alcohol consumption in relation to lifetime abstainers, the relationship is clearly J-shaped, supported by short-term experimental evidence and similar associations irrespective of potential confounders, except among smokers. Women experience slightly stronger beneficial associations although an earlier upturn to a detrimental effect at lower levels of average alcohol consumption compared to men.

A growing number of studies appear to be obscure their own data that shows a cardioprotective effect from moderate alcohol consumption (Ricci et al. 2018, Wood et al. 2018)[49]. These studies omit any comparison between drinkers and non-drinkers in the abstract or the text, hiding their data in supplementary tables not normally reviewed by readers. Their hidden data shows that the moderate consumption of alcohol (≤200 g/week or 20 10 g standard drinks) reduces the risk of death from CVD events by >30% and total mortality by >15% compared to lifetime abstainers/never drinkers, and where non-drinkers have a much higher mortality risk in all but the highest categories of alcohol consumption.

2. This doubt has largely arisen because of the improved approaches to research study designs. This includes the ability to use new kinds of evidence, such as Mendelian randomisation studies.

Although Mendelian randomization studies can be employed as an additional or supplementary analytical methodology [224,259], their underlying assumptions are problematic if two dimensions are to be analysed simultaneously with one instrumental variable, as in the analyses on the impact of alcohol consumption on ischaemic heart diseases. (Holmes et al. 2014[50], Frick and Rehm 2016[51]). Further, even Mendelian randomization studies yield results with differing conclusions (Han et al., 2013[52]; Holmes et al., 2014[50]).

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[48] Roerecke M, Rehm J. (2012) The cardioprotective association of average alcohol consumption and ischaemic heart disease: a systematic review and meta-analysis. Addiction. 107(7): 1246-60. Roerecke M, Rehm J. (2014) Alcohol consumption, drinking patterns, and ischemic heart disease: a narrative review of meta-analyses and a systematic review and meta-analysis of the impact of heavy drinking occasions on risk for moderate drinkers. BMC Med., 12:182.

[49] Ricci C, Wood A, Muller D. et al. (2018). Alcohol intake in relation to non-fatal and fatal coronary heart disease and stroke: EPIC-CVD case-cohort study. BMJ. 361:k934. doi: 10.1136/bmj.k934; Wood AM, Kaptoge, S, Butterworth AS, et al. (2018). Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. Lancet. 391(10129):1513-1523. doi: 10.1016/S0140-6736(18)30134-X.

[50] Holmes M V, Dale C E, Zuccolo L. et al. (2014) Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. BMJ 349: g4164. doi: 10.1136/bmj.g4164.

[51] Frick U, Rehm J. (2016) Can we establish causality with statistical analyses? The example of epidemiology. In: Wiedermann W., von Eye A., editors. Statistics and Causality: Methods for Applied Empirical Research. Hoboken, NJ: Wiley; pp. 407–432.

[52] Han H, Wang H, Yin Z, Jiang H, Fang M, Han, J. (2013). Association of genetic polymorphisms in ADH and ALDH2 with risk of coronary artery disease and myocardial infarction: a meta-analysis. Gene, 526, 134–141. doi:10.1016/j.gene.2013.05.002

Mendelian randomisation studies do not consistently suggest that low levels of alcohol consumption are not cardioprotective and are not necessarily an improved approach to research study designs and should not be used to replace conventional observational studies but rather to complement them.

Mendelian randomisation studies use genetic variants as variables to investigate the causal relationship between potentially modifiable risk factors and health outcomes[53]. While they are less likely to be affected by unmeasured confounding or reverse causation than conventional observational or self-reported studies, they depend on underlying assumptions, the plausibility of which must be evaluated and the relevance of the results interpreted in consideration of other sources of evidence including conventional observational studies. This evaluation and consideration do not necessarily happen, however, as exemplified in a Mendelian randomisation meta-analysis undertaken by Holmes et al. (2014), and incorrect conclusions can subsequently be drawn. The conclusions of such Mendelian randomisation studies are only sound if their underlying assumptions are sound and integrated and combined with conventional observational studies, and hence can often be controversial[54].

Studies applying the alcohol dehydrogenase (ADH) gene polymorphisms for obtaining an estimate of alcohol's effects on cardiovascular disease (CVD) were actually first published in 2001[55]. ADH gene polymorphisms alter the rate of alcohol metabolism.

Holmes et al. (2014)[56], for example, used ADH gene polymorphisms and a mendelian randomisation design[57] to evaluate whether moderate alcohol consumption increased or decreased the risk of CVD, that is, the direction of alcohol's effects but they did not evaluate the magnitude of alcohol's effects. It was assumed that inheriting the A-allele of the ADH1B locus was equivalent to being randomly assigned to drink less alcohol. Holmes et al. (2014) found that A-allele carriers drank less and had lower cardiovascular risk. They concluded that alcohol drinking increases cardiovascular risk and prior observational evidence should be revisited. They drew this conclusion without ever presenting conventional observational analyses using reported drinking to predict coronary heart disease.

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[53] Davies NM, Homes MV, Davey Smith G. (2018). Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians BMJ 2018; 362 doi: https://doi.org/10.1136/bmj.k601 (Published 12 July 2018) Cite this as: BMJ 2018;362:k601 https://www.bmj.com/content/362/bmj.k601.full

[54] Hernán MA, Robins JM. (2008) Instruments for causal inference: an epidemiologist's dream? Epidemiology 2006;17:360-72; Stampfer MJ. ITT for observational data: worst of both worlds? Epidemiol. 19:783.

[55] Hines LM, Meir SM, Stampfer J, et al. (2001) Genetic Variation in Alcohol Dehydrogenase and the Beneficial Effect of Moderate Alcohol Consumption on Myocardial Infarction. N Engl J Med. 344:549-555; DOI: 10.1056/NEJM200102223440802.

[56] Holmes MV, Dale CE, Zuccolo L, et al. (2014) for the Association between alcohol and cardiovascular disease: mendelian randomisation analysis based on individual participant data. BMJ. 349:g4164

[57] Davey Smith G. (2010) Mendelian randomization for strengthening causal inference in observational studies: application to gene by environment interaction. Perspect Psychol Sci. 5:527-545.

Holmes et al. (2014) inferences rest on two assumptions, similar to those of a randomised controlled trial assigning individuals to treatment to reduce drinking, except here the ADH1B allele is the treatment. First, they assumed the 'trial' was randomised, that is, they assumed that adults 'assigned' the A-allele and controls 'not assigned' the allele would have had identical cardiovascular risk without these assignments. Second, they assumed that assignment to the allele had no effect on CVD besides effects mediated by drinking. Although the assumptions made in mendelian randomisation parallel the assumptions made about real treatments in randomised trials, those same assumptions are usually less plausible in mendelian randomisation studies and merit more evaluation.

Glymour et al. (2014)[58] asks the questions as to how do these compare to assumptions in conventional observational studies of drinking and CVD? After all, new methods with somewhat implausible assumptions may be preferable to traditional methods resting on even less plausible assumptions. Although rarely stated explicitly, conventional observational studies—studies using drinking to predict CVD—can explore cause and effect only by assuming that drinking is effectively randomly allocated. Essentially this is assuming that the study has appropriately accounted for every factor that influences both drinking and CVD (confounders), an almost impossible task in observational research despite sophisticated statistical techniques such as propensity scores used to account for multiple covariates.

Both conventional and mendelian randomisation approaches thus rely heavily on unprovable assumptions, so controversy is unsurprising. Because the two sets of assumptions are very different, results are most convincing when both approaches give the same answer. Holmes et al. (2014) results suggest the answers diverge for this research question, and which consequently forces a choice to be made as to which is most plausible.

Glymour (2014) [58] also suggests that challenging assumptions is an important part of interpreting all observational work, and justifying assumptions is an important part of reporting it. For example, mendelian randomisation studies assume that effects of ADH1B polymorphisms on CVD risk operate only via drinking. Holmes et al. (2014) try to show this by exploring whether ADH1B predicts coronary heart disease among people with similar levels of alcohol consumption. Although estimates are imprecise, results suggest that ADH1B predicts CVD risk even within groups of people with similar alcohol use. The allele, however, should not predict cardiovascular risk among adults who all drink roughly the same amount and conclusions should, therefore, be considered cautiously. Because alcohol use is imperfectly measured it is still possible that, for example, moderate drinkers with the A-allele drink slightly less than moderate drinkers without it. There is a further problem with this particular allele as a proxy for alcohol consumption. ADH1B polymorphisms influence alcohol

[58] Glymour MM. (2014) Alcohol and cardiovascular disease. BMJ. 349:g4334. doi: 10.1136/bmj.g4334.

metabolism and, therefore, influence exposure to both alcohol and its metabolites[59]. If these metabolites influence risk of CVD, one of the core assumptions underlying mendelian randomisation is violated.

One of the most surprising conclusions by Holmes et al. (2014) is that reduced drinking is beneficial even for light to moderate drinkers. The analyses presented in their paper cannot establish this claim, however, because they rely on how much alcohol use individuals actually report. To evaluate whether effects of reducing drinking for moderate drinkers are similar to effects for heavy drinkers, one approach would define moderate and heavy drinking as separate variables and conduct a multiple-variable instrumental variables analysis[60].

More recently, Tolstrup et al. (2016)[61] used both observational and Mendelian randomisation analyses to evaluate whether alcohol consumption is associated with the risk of atrial fibrillation (AF), and to determine whether people with high cardiovascular risk are more sensitive towards alcohol than people with low risk. Unfortunately, Tolstrup et al. (2016) did not have data to identify binge drinkers, which tend to show greater adverse cardiovascular events than regular moderate drinkers whose weekly consumption may be the same. The main results of the study were that men consuming more than 14 drinks/week, especially those consuming more than 28 drinks/week, had an increase in risk of AF, but no significant increase in risk was seen for any level of alcohol consumption among women. When genotypes affecting alcohol metabolism (AHD1B, ADH1C) were studied in a Mendelian randomisation analysis, Tolstrup et al. (2014) stated that they "found no evidence to support causality of the observational findings." The results of this study, however, reflect the findings of most previous prospective studies and meta-analyses of little effect of light drinking on AF, but an increase in risk for heavier drinkers. The study also showed that the effects of alcohol consumption on the risk of AF were not different between participants who had CVD or were at high-risk of CVD than for other participants. While Mendelian randomisation using genetic factors affecting alcohol metabolism has been touted as an unbiased approach for judging causal health effects of alcohol, there are questions about the adequacy of such instruments for judging effects. In the present study, their use did not suggest that the relationship shown by the self-report of alcohol by participants necessarily indicated a causal association of alcohol with AF. Overall, the data suggested that heavy drinking may increase the risk of AF, but there is little evidence of a meaningful increase in risk from light drinking, where such levels of alcohol consumption have been shown from many previous studies to significantly lower the risk of CVD and total mortality.

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[59] Kang G, Bae KY, Kim SW, et al. (2014) Effect of the allelic variant of alcohol dehydrogenase ADH1B* 2 on ethanol metabolism. Alcohol Clin Exp Res. 38: 1502-1529.

[60] Wooldridge JM. (2013) Introductory econometrics: a modern approach. 5th ed. Cengage South-Western.

[61] Tolstrup JS, Wium-Andersen MK, Ørsted DD, Nordestgaard BG. (2016). Alcohol consumption and risk of atrial fibrillation: Observational and genetic estimates of association. Eur J Prevent Cardiol. pre-publication. DOI: 10.1177/2047487316641804

3. These newer studies greatly reduce some of the challenges of earlier evidence. These challenges *included the lack of clarity about changes in drinking patterns being due to illness, not because the person chose not to drink alcohol and was otherwise healthy*.

While using last-year abstention as the comparison group may bias results by introducing 'sick-quitters', use of lifetime can also be unreliable (Rehm et al. 2008)[62]; studies undertaken since 2005/2006 on which the 2009 and draft 2019 alcohol drinking guidelines are based, however, have not used last-year abstention.

The 'challenges' raised in newer studies were actually recognized by others in the field as early as 1995 and suitable corrections have generally been undertaken since then. Furthermore, the numerous meta-analyses that have been undertaken over the past 15 years that have adjusted for proposed bias from changes in drinking patterns being due to illness (referred to as the 'sick-quitter' hypothesis), have consistently shown that there is a cardioprotective effect for regular light to moderate alcohol consumption.

Indeed, one of the earliest confounders recognized by epidemiologists was that some of the 'non-drinkers' in their studies were former heavy drinkers and had stopped drinking due to adverse health effects. Scientists then began to collect precise data on previous drinking, to better control for drinking pattern (previous intake, regular versus binge drinking), smoking, physical activity, obesity, and other risk factors for disease and mortality. In almost every well-conceived and controlled study done, it was found that when ex-drinkers were not included in the referent group (and the group consisted only of lifetime abstainers) and other known confounders were also adjusted for, there was still a strong 'J-shaped curve' for cardiovascular disease (CVD) and mortality for moderate drinkers. This pattern has been found consistently in studies from North and South America, Europe, and Asia, in cultures where alcohol consumption varies from the occasional subject to the large majority of people.

In 'historical' meta-analyses published in 2002 and 2006 by Di Castelnuovo et al.[63], the inclusion or not of former drinkers in the control groups, adjustment for any possible variables including socio-economic status and year of publication was addressed. In each analysis, they observed the classical J-shaped curve both on fatal and non-fatal CV events and total mortality. Occasionally, the adjustment even resulted in an improved benefit by wine or beer moderate consumption. For example, in Di Castelnuovo et al. (2006), the authors concluded that a subgroup analysis restricted to studies that excluded either ex-drinkers or very light drinkers from the reference group generated a pooled curve that indeed predicted a lower (though statistically significant) protection, confirming the importance of properly selecting the reference group in studies on alcohol and health. The degree of association was lower in adjusted studies, as might be expected in view of several confounding factors characterizing

[62] Rehm J, Irving H, Ye Y, Kerr W C, Bond J, Greenfield T K. (2008) Are lifetime abstainers the best control group in alcohol epidemiology? On the stability and validity of reported lifetime abstention. Am J Epidemiol. 168: 866–871.

[63] Di Castelnuovo A, Rotondo S, Iacoviello L, Donati MB, de Gaetano G. (2002) Meta-analysis of wine and beer consumption in relation to vascular risk. Circulation. 105:2836-2844; Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, de Gaetano G. (2006) Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. Arch Intern Med. 166:2437-2445.

observational studies on drinking habits. The benefit of light to moderate drinking, however, remained in a range of undoubted public health value (15%-18%). Although residual confounding cannot be excluded, it would be very unlikely to modify the scenario in a substantial manner. They found that when adjusted and unadjusted data derived from the same studies were compared, the maximum protection conferred by light to moderate drinking only decreased from 19% to 16%. It can this be presumed that, even in the pessimistic hypothesis that residual confounding would have the same strength in lowering the protection as that of known confounding, the 'real' (maximum) protection against total mortality associated with low levels of alcohol consumption would still be higher than 10%. A similar reasoning would also apply to the harm associated with heavier drinking.

A paper by Jackson et al. (2005)[64] and subsequent papers by Fillmore et al. (2006 and 2007) suggested, however, that "this view is contested", and argued that "any coronary protection from light to moderate drinking will be very small and unlikely to outweigh the harms".

The meta-analysis by Fillmore et al. (2006)[65] of 54 previously published epidemiological studies on all-cause mortality and 35 on coronary heart disease mortality has suggested, however, that confounding has led to bias in the majority of studies showing less CVD among light-to-moderate drinkers, and consequently that the cardio-protection afforded by alcoholic beverages may have been over-estimated. They also suggested that calculations of mortality from heavier drinking may also be over-estimated. Indeed, while they conceded that "…alcohol [among other substances, lifestyles and behaviors] conveys benefit to the heart" they also concluded "…that the actual outcomes in human populations for cardiac benefit have been exaggerated…". In addition, in further communications from Fillmore et al. (2007)[66], they suggested that if there is a protective effect of light-to-moderate alcohol consumption against the incidence of CHD or any other diseases, we currently do not know enough to recommend regular alcohol consumption for health reasons, and, from 2006, this should be taken into account in both policy and clinical practice.

Evidence, that is, sound scientific data over more than three decades suggest, however, that moderate alcohol consumers are at considerably lower risk of CVD, and newer studies also indicate that they are at lower risk of other diseases of ageing (Klatsky and Udaltsova 2007[67], Panel Discussion I 2007[68], Fuller 2011[69]). Analysis of 84 longitudinal cohort studies of CVD comparing alcohol consumers with abstainers, for example, showed that the pooled adjusted

[64] Jackson, R, Broad, J, Connor, S, Wells, S. (2005) Alcohol and ischaemic heart disease: probably no free lunch. Lancet. 366 (9501):1911-1912.

[65] Fillmore, KM, Kerr, WC, Stockwell, T, Chikritzhs, T, Bostrom, A. (2006). Moderate alcohol use and reduced mortality risk: Systematic error in prospective studies. Addict. Res. Theory. 14(2): 101-112.

[66] Fillmore, KM, Stockwell, T, Chikritzhs, T, Bostrom, A, Kerr, W. (2007) Moderate alcohol use and reduced mortality risk: systematic error in prospective studies and new hypotheses. Ann. Epidemiol. 17(5, Supplement 1): S16-S23.

[67] Klatsky AL, Udaltsova N. (2007). Alcohol drinking and total mortality risk. Ann. Epidemiol. 17(5, Supplement 1): S63-S67.

[68] Panel Discussion I (2007) Does alcohol consumption prevent cardiovascular disease? Proceedings of an international conference. Ann. Epidemiol. 17: S37–S39.

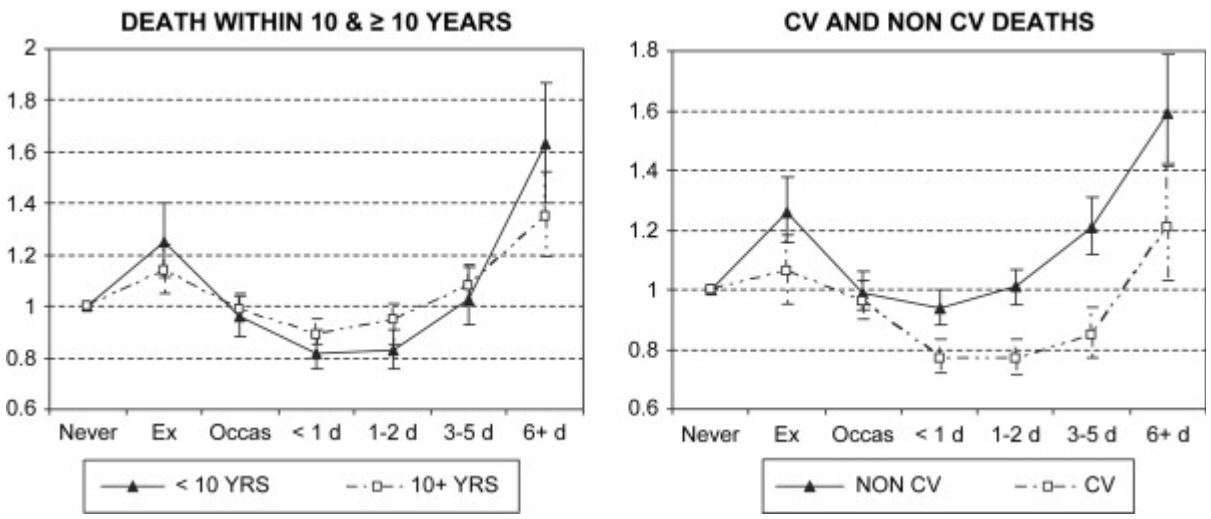
[69] Fuller TD. (2011) Moderate alcohol consumption and the risk of mortality. Demography. DOI 10.1007/s13524-011-0035-2

relative risks for alcohol consumers relative to abstainers in random effects models for the outcomes of interest were: "0.75 (95% confidence interval 0.70 to 0.80) for CVD mortality (21 studies), 0.71 (0.66 to 0.77) for incident coronary heart disease (29 studies), 0.75 (0.68 to 0.81) for coronary heart disease mortality (31 studies), 0.98 (0.91 to 1.06) for incident stroke (17 studies), and 1.06 (0.91 to 1.23) for stroke mortality (10 studies)" (Ronksley et al. 2011)[70]. If the relative risk was 1.0, the risk would be the same for alcohol consumers and abstainers. This analysis also showed that alcohol consumption at 2.5–14.9 g/day was consistently associated with a 14–25% reduction in the risk of all outcomes assessed compared with abstaining from alcohol. Consistent with a J-shaped relationship, risk increased with increased consumption, but differed for different CVD outcomes. The cardioprotective association with alcohol was consistently observed in diverse patient populations and in both men and women and was apparent when controlling for known confounders such as cigarette smoking, diet and exercise.

Klatsky and Udaltsova (2007) reworked previously published data (Klatsky et al. 1992[71], Klatsky 2003[72]) to address the purported confounding and potential over-estimation of a health benefit from moderate alcohol consumption claimed by Fillmore et al. (2006, 2007), and showed a shallower but still significant J-shaped relationship between alcohol consumption and all-cause mortality risk. The data was of 21,535 deaths through to 2002, where the follow-up included 2,618,523 person-years of observation with a mean follow-up of 20.6 years (Figure 1). Their re-analysis reconfirmed the relationship previously published with an increased risk for individuals consuming more than three (14 g) drinks per day and a reduced risk at three or less drinks (14 g) per day, almost always due to a reduced risk of death from CVD. Former consumers were observed to be at increased risk of death from non-CVD and occasional consumers were observed to have a risk similar to lifelong abstainers.

[70] Ronksley, PE, Brien, SE, Turner, BJ, Mukamal, KJ, Ghali, WA. (2011) Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. Br. Med. J. 34(3): 363-370.
[71] Klatsky AL, Armstrong MA, Friedman GD. (1992) Alcohol and mortality. Ann. Intern. Med. 117(8): 646.
[72] Klatsky AL. (2003) Drink to your health? Scientific American. 288(2): 75.

Figure 1. J-shaped curve from re-analysis of data by Klatsky and Udaltsova (2007).



Fully adjusted model for interval between baseline data and death (*left hand side figure*) where all relations appear to become attenuated with passage of time. This probably is due to a general reduction of alcohol intake in the population, resulting in less harm from heavy drinking and less benefit from light-moderate drinking. Fully adjusted model for cardiovascular (*CV*) and non-cardiovascular (non-CV) deaths (*right hand side figure)*.

Subsequently, Fuller (2011) aimed to determine the extent to which the 'confounding and bias' in early epidemiologic studies led to potentially erroneous conclusions about the inverse association between moderate alcohol consumption and CVD. The analysis was based on prospective data for more than 124,000 persons interviewed in the U.S. National Health Interview Surveys of 1997 through 2000 and was designed to avoid the 'errors' of some earlier studies including those identified by Fillmore et al. (2006). The results support the significant majority of prospective studies and indicate that moderate alcohol consumers have a lower risk of CVD and all-cause mortality. Fuller (2011) contended that these results lend credence to the argument that the inverse association between moderate alcohol consumption and mortality is causal.

There are also other studies where neither type of 'error' studied by Fillmore et al. (2006) was present. For example, a study by Mukamal et al. (2006)[73] on a large group of older adults which separated lifetime abstainers from former drinkers, and occasional drinkers from regular light drinkers, demonstrated reductions in the risk of a variety of cardiovascular outcomes from moderate consumption, as did Di Castelnuovo et al. (2006). In another study

[73] Mukamal KJ, Conigrave KM, Mittleman MA, Camargo CA Jr, Stampfer MJ, Willett WC, Rimm EB. (2003) Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. N Engl J Med. 348(2):109-118.

on older people by Tolvanen et al. (2005)[74] where ex-drinkers were separated from lifetime abstainers, total mortality was highest in the ex-drinkers and lifetime abstainers, and 30-40% lower in current consumers. In addition, another study by Klatsky et al. (2005)[75] which identified lifetime abstainers and separated occasional drinkers from regular light drinkers showed that consumption of one to two drinks/day was associated with 40% less risk of heart failure associated with coronary artery disease. Further, another study by Holahan et al. (2010)[76], which assessed total mortality in 1,824 middle-aged and older people followed for 20 years, even controlling for a wide range of traditional and non-traditional confounding factors associated with abstention, including those identified by Fillmore et al. (2006), ex-drinkers and lifetime abstainers and heavy drinkers (>42 g alcohol/day) continued to show increased mortality risks of 51 and 45%, respectively, compared to moderate drinkers (14 to <42 g alcohol/day).

Eight commentaries were subsequently published in the February 2007 edition of the journal Addiction Research and Theory following a panel discussion at the Symposium on moderate alcohol consumption: health risks and benefit on 17-18 May 2006 (Ellison 2007, Ellison and Martinic 2007, Panel Discussion I 2007). One of the salient points to come out of the commentaries, as well as from May 2007 edition of The Annals of Epidemiology, is that there is evidence for plausible biological mechanisms for protection against coronary heart disease by moderate alcohol consumption which adds credence to a causal hypothesis. These mechanisms include effects via the high density lipoprotein cholesterol, improved haemostatic factors, improved endothelial function, and a lower risk of diabetes mellitus. These were well summarised by Brien et al. (2011) who stated: “Favourable changes in several cardiovascular biomarkers (higher levels of high density lipoprotein cholesterol and adiponectin, and lower concentration of fibrinogen) provide indirect pathophysiological support for a protective effect of moderate alcohol use on coronary heart disease.”

Further evidence is found in an earlier meta-analysis of 42 experimental studies, which examined the effects of alcohol consumption on cardiovascular biomarkers, attributed the cardioprotective effect of light-to-moderate alcohol consumption: 60% to effects on high density lipoprotein, 20-30% to fibrinogen, 5-10% to insulin and 0-5% to other haemostatic factors (Rimm et al. 1999). The meta-analysis also estimated that 30 g of alcohol per day would increase the plasma concentration of high-density lipoprotein (HDL) by approximately 4 mg/dL which would be associated with a 17% reduction in risk of coronary heart disease. It would also decrease the plasma concentration of fibrinogen by approximately 0.075 g/L, which would be associated with a 12.5% reduction in risk of coronary heart disease (Hines and Rimm 2001). This translated into an overall 24.7% reduction in the risk of coronary heart disease from the consumption of 30 g of alcohol per day. Klatsky and Udaltsova (2007) further

[74] Tolvanen E, Seppä K, Lintonen T, Paavilainen P, Jylhä M. (2005) Old people, alcohol use and mortality. A ten-year prospective study. Aging Clin. Exp. Res, 17(5): 426-433.

[75] Klatsky AL, Chartier D, Udaltsova N, Gronningen S, Brar S, Friedman GD, Lundstrom R.J. (2005) Alcohol drinking and risk of hospitalization for heart failure with and without associated coronary artery disease. Am J Cardiol. 96(3): 346-3451.

[76] Holahan CJ, Schutte KK, Brennan PL, Holahan CK, Moos BS, Moos RH. (2010) Late-Life Alcohol Consumption and 20-Year Mortality. Alcohol Clin Exp Res. 34(11): 1961-1971.

translated this into a 10% reduction in risk of all-cause mortality. Interestingly, in their reply to the eight commentaries on this point, Fillmore et al. (2007) does not dispute the evidence for plausible biological mechanisms and merely suggests that "the lot falls to epidemiology to establish whether human populations will benefit greatly from the use of alcohol and if they should be advised to use the substance for medicinal purposes".

More recently, Würtz et al. (2016)[77] further found that alcohol consumption is associated with a complex metabolic signature. From an assessment of 86 metabolic measures, and complementing the results Rimm et al. (1999), key associations with moderate alcohol consumption were increases in HDL and its subclasses, decreases in the size of low density lipoprotein (LDL), an increase in monounsaturated fatty acids and a decrease in omega-6 fatty acids, and lower concentrations of glutamine and citrate, which are cardioprotective effects. The majority of metabolic biomarkers, however, showed different associations according to the estimated amount of alcohol consumed. Lipid biomarkers, for example, generally displayed U-shaped associations with alcohol consumption while other biomarkers displayed linear associations. Long-term changes in alcohol consumption were associated with a pattern of metabolic changes similar to the metabolic signature of alcohol observed cross-sectionally, where the tracking of this complex metabolic signature of alcohol consumption suggest that the metabolic changes arise, at least partly, due to alcohol consumption.

Another meta-analysis from a related research group was subsequently published in 2016[78], a decade after Fillmore et al. (2006), with the same aim to determine whether misclassifying former and occasional drinkers as abstainers and other potentially confounding study characteristics underlie observed positive health outcomes for low volume drinkers in prospective studies of all-cause mortality. Stockwell et al. (2016) resurrected the arguments of, and quoted the previous and discredited paper by Fillmore et al. (2006), expressing concern about the inclusion of sick quitters in the non-drinking population in an effort to demonstrate that epidemiologists have still not properly adjusted for confounders in determining the presence of the J-shaped curve for CVD and mortality.

Stockwell et al. (2016) have similarly biased their meta-analysis by selecting a small number of studies for their meta-analysis, discarding 2,575 identified studies and analysing only 87, and then they found some reason to exclude almost all of these studies to reach a conclusion that "…there was no significant protection for low-volume drinkers (RR = 1.04, 95% CI [0.95, 1.15])" based on what is apparently only six remaining studies. The studies that they analysed related reported consumption to disease, but they carefully avoided hundreds of validated studies that showed reduced disease among moderate drinkers. In contrast to Fillmore et al. (2006), however, Stockwell et al. (2016) also discounted the many animal and human studies undertaken over the past five decades that have provided extensive evidence for biological

[77] Würtz P, Cook S, Wang Q, et al. (2016) Metabolic profiling of alcohol consumption in 9778 young adults. Int J Epidemiol. pre-publication: doi: 0.1093/ije/dyw175

[78] Stockwell T, Zhao J, Panwar S, Roemer A, Naimi T, Chikritzhs T. (2016) Do "Moderate" Drinkers Have Reduced Mortality Risk? A Systematic Review and Meta-Analysis of Alcohol Consumption and All-Cause Mortality. J Stud Alcohol Drugs. 77:185–198.

mechanisms [79] of alcohol's cardioprotective effects. Essentially, moderate alcohol consumption decreases all of the risk factors for CVD, including low HDL-cholesterol, elevated LDL-cholesterol, endothelial dysfunction, coagulopathies, inflammation, abnormal glucose metabolism, such that the consistent finding of lower CVD risk among moderate alcohol consumers in all well-done cohort studies is strongly supported by experimental evidence of the mechanisms.

The stated purpose of this new analysis was to determine whether misclassifying former and occasional drinkers as abstainers and other potentially confounding study characteristics underlie observed positive health outcomes for low volume drinkers in prospective studies of mortality. Unfortunately, the authors included in their analyses a number of old epidemiologic studies and did not acknowledge that when the "errors" that they have commented on in the past (such as including heavy ex-drinkers in the no-alcohol referent group) have been dealt with in the majority of studies over the past decade. The authors still excluded the vast majority of these well-done studies in their new meta-analysis. Results of essentially all studies that adjust for their concerns continue to show a significant and meaningful reduction in the risk of CVD and total mortality from the moderate intake of wine and alcohol.

Interestingly, Stockwell et al. (2016) did not comment on, or refer to, the conclusions of Roerecke and Rehm (2014) [80] from their relatively recent meta-analysis on the role of confounders in explaining the observed association of alcohol with health outcomes. Roerecke and Rehm (2014) stated that the "Results from our quantitative meta-analysis showed that drinkers with average intake of < 30 g/day and no episodic heavy drinking had the lowest IHD (ischaemic heart disease) risk (relative risk = 0.64, 95% confidence interval 0.53 to 0.71). Drinkers with episodic heavy drinking occasions had a risk similar to lifetime abstainers (relative risk = 1.12, 95% confidence interval 0.91 to 1.37)." Further, these two authors who have traditionally been concerned that confounding and errors weaken the purported relation between alcohol and a lower risk of CVD, concluded: "For drinkers having one to two drinks per drinking day without episodic heavy drinking, there is substantial and consistent evidence from epidemiological and short-term experimental studies for a beneficial association with IHD risk when compared to lifetime abstainers. The alcohol-IHD relationship fulfils all criteria for a causal association proposed by Hill."

Thus, these newer studies that purportedly greatly reduce some of the challenges of earlier evidence, instead markedly distort the accumulated scientific evidence on alcohol and CVD, where the biased selection of studies that are included undermines the value of the papers, but more importantly promulgates misinformation in the name of appropriate scientific method. Failure to acknowledge the robust body of knowledge that supports the opposite conclusion, and disqualification of extensive animal and cell culture studies that offer

[79] Brien SE, Ronksley PE,Turner BJ, Mukamal KJ, Ghali WA. (2011) Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. BMJ.342:d636; doi:10.1136/bmj.d636.

[80] Roerecke M, Rehm J. (2014) Alcohol consumption, drinking patterns, and ischemic heart disease: a narrative review of meta-analyses and a systematic review and meta-analysis of the impact of heavy drinking occasions on risk for moderate drinkers. BMC Med. 12:182.

plausible biologic explanation of observed benefits, is unconscionable. Indeed, the overwhelming body of observational scientific data, as well as an immense number of experimental studies, support the contention that, for most middle-aged and older men and women who choose to do so, the regular consumption of small amounts of an alcoholic beverage can be considered as one component of a 'healthy lifestyle.' Such a habit has been shown to be associated with a lower risk of CVD and of total mortality.

4. **They also include the challenge of having accurate information about the exposure to alcohol, due to the fact that a lot of earlier evidence is based on self-reporting of alcohol consumption, and this can often be inaccurate.**

Self-report measures have demonstrated reasonable levels of reliability and validity; at the same time, they offer the means to assess alcohol use in a manner that is relatively inexpensive, non-invasive and acceptable to respondents[83]. There are a wide variety of different self-report instruments are available for use in clinical settings and in research. Each measure has its own strengths and limitations that may influence response accuracy depending on the data-gathering situation. Self-report methods justifiably will continue to be the major source of information about human drinking behaviour. Accordingly, the majority of studies, both earlier and more recently are based on, and continue to be based on, the self-reporting of alcohol consumption.

This includes two large population-based cohort studies recently published by Kunzmann et al (2018[81]) from the US Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and Xi et al. (2017[82]) from 13 waves of the National Health Interview Surveys (1997 to 2009). These studies using self-reported measures to assess alcohol consumption, both support a J-shaped association between alcohol and all-cause and CVD mortality in older adults, which remains after adjustment for cancer risk.

It is well recognised that response behaviour is influenced by the interaction of social context factors, respondent characteristics, and task attributes. Self-report methods offer a reliable and valid approach to measuring alcohol consumption. The accuracy of such methods, however, can be improved by research directed at understanding the processes involved in response behaviour (Del Boca and Darkes 2003)[83].

It is also true that in observational studies epidemiologists have to rely on their human participants to tell them what they actually drink, and there is always the chance that there will be mistakes in their reporting, especially under-reporting of alcohol. Consequently, self-reported alcohol consumption data are prone to bias and are challenging to harmonise across studies conducted over different time periods that used varying instruments and methods to record such data. In The Svalbard Study, for example, which was a unique setting for

[81] Kunzmann AT, Coleman HG, Huang WY, Berndt SI. (2018) The association of lifetime alcohol use with mortality and cancer risk in older adults: A cohort study. PLoS Med. 15(6):e1002585. doi: 10.1371/journal.pmed.1002585.
[82] Xi B, Veeranki SP, Zhao M, Ma C, Yan Y, Mi J. (2017) Relationship of Alcohol Consumption to All-Cause, Cardiovascular, and Cancer-Related Mortality in U.S. Adults. J Am Coll Cardiol. 70(8):913-922.
[83] Del Boca FK, Darkes J. (2003) The validity of self-reports of alcohol consumption: state of the science and challenges for research. Addiction. 98 Suppl 2:1-12.

validation of self-reported alcohol consumption, the self-reported volume accounted for approximately 40% of the sales volume (Høyer et al. 1995[84]), where coverage of sales estimates by surveys varied between 39% for Germany and 56% for France.

Underestimation of alcohol consumption in observational studies, however, is less than in typical population surveys (Boniface et al. 2014, Stockwell et al. 2018[85]), where increasingly epidemiologists have become better able to identify and adjust for such potential bias and are increasingly able to recognize under-reporting of alcohol (Klatsky et al. 2006, Klatsky and Udlaltsova 2007, Klatsky et al. 2014). The Kaiser Permanente Study, for example, found the underreporting of alcohol consumption actually partially explained the increased prevalence of hypertension among individuals reporting one to two drinks per day (Klatsky et al. 2006[86]). It also partially explained the apparent increased risk of cancer among light-moderate drinkers (Klatsky et al., 2014[87]). In addition, it also partially explained the apparent magnitude of benefit of lighter drinking (Klatsky and Udaltsova 2007[88]). Furthermore, in an observational study from Italy of men aged 45-64 years who were followed for total mortality from 1965 to 1995, men reporting drinking approximately five drinks/day had a longer life expectancy than occasional drinkers and heavy drinkers. Underreporting was not an issue in this population with almost no non-drinkers and total acceptance of drinking wine with meals (Farchi et al. 2000[89]).

However, in addition to average volume of alcohol consumption in determining the risk relationships between alcohol consumption and alcohol-related diseases and injuries, Rehm et al. (2003)[90] found that pattern of drinking was an additional influencing factor for alcohol-related diseases such as coronary heart disease. Consequently, the influence of self-reported patterns of drinking rather than self-reported volume in alcohol exposure may be underestimated because pattern measures have not been consistently included in epidemiologic studies (Martin et al. 2014[91]).

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[84] Høyer G, Nilssen O, Brenn T, Schirmer H. (1995) The Svalbard study 1988-89: a unique setting for validation of self-reported alcohol consumption. Addiction 90:539-544.

[85] Boniface S, Kneale J, Shelton N. (2014) Drinking pattern is more strongly associated with under-reporting of alcohol consumption than socio-demographic factors: evidence from a mixed-methods study. BMC Public Health. 14:1297. doi: 10.1186/1471-2458-14-1297; Stockwell T, Zhao J, Sherk A, Rehm J, Shield K, Naimi T. (2018) Underestimation of alcohol consumption in cohort studies and implications for alcohol's contribution to the global burden of disease. Addiction. 113(12):2245-2249. doi: 10.1111/add.14392.

[86] Klatsky AL, Gunderson EP, Kipp H, Udaltsova N, Friedman GD. (2006) Higher prevalence of systemic hypertension among moderate alcohol drinkers: an exploration of the role of underreporting. J Stud Alcohol. 67:421-428.

[87] Klatsky AL, Udaltsova N, Li Y, Baer D, Nicole Tran H, Friedman GD. (2014) Moderate alcohol intake and cancer: the role of underreporting. Cancer Causes Control. 25:693-699. doi: 10.1007/s10552-014-0372-8.

[88] Klatsky AL, Udaltsova N. (2007) Alcohol Drinking and Total Mortality Risk. Ann Epidemiol. 17:S63–S67.

[89] Farchi G, Fidanza F, Giampaoli S, Mariotti S, Menotti A. (2000) Alcohol and survival in the Italian rural cohorts of the Seven Countries Study. Int J Epidemiol. 29:667-671.

[90] Rehm J, Room R, Graham K, Monteiro M, Gmel G, Sempos CT. (2003) The relationship of average volume of alcohol consumption and patterns of drinking to burden of disease: an overview. Addiction. 98(9):1209-1228.

[91] Valencia Martín JL, González MJ, Galán I. (2014) [Methodological issues in the measurement of alcohol consumption: the importance of drinking patterns]. Rev Esp Salud Publica. 88(4):433-46. doi: 10.4321/S1135-57272014000400002.

Currently, data from essentially all observational studies, including those that control for all known confounders, are consistent with the animal and human experimental data, and support that light to moderate alcohol consumption decreases the risk of atherosclerosis, for example, which is a primary risk factor for developing CVD.

5. With regard to cardiovascular disease, the evidence of an association between increasing risk of stroke with increasing alcohol consumption has become clearer in recent years.

Evidence of an association between alcohol and stroke has been well documented over the past 50 years. There are two primary types of stroke, ischaemic and haemorrhagic, which are caused by different biological mechanisms, and hence affected differently by alcohol consumption, and more importantly, different amounts of alcohol consumption.

The most comprehensive and relatively recent review of 84 prospective studies undertaken from 1980 to 2009 and using lifetime abstainers as the reference category (Ronksley et al. 2011)[92] found that alcohol consumption of 2.5 to 14.9 g/day (≤1.5 10 standard drinks) was consistently associated with a 14-25% reduced risk of cardiovascular disease (CVD) mortality, and specifically, the incidence of, and mortality from stroke per se. This reduced risk was observed for both men and women. Inclusion of former drinkers also did not appear to bias the association of alcohol consumption with CVD. A smaller relatively recent systematic review and meta-analysis of 27 prospective studies on alcohol consumption and different stroke types similarly found that light and moderate alcohol consumption was inversely associated with ischaemic stroke and not associated with any haemorrhagic stroke subtypes. Heavy consumption of greater than 40 g/day, however, was associated with an increased risk of all stroke types and subtypes with a stronger association for haemorrhagic strokes (Larsson et al. 2016)[93].

Indeed, although a relatively recent multicentre case-cohort study (Ricci et al 2018[94]) and a combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies (Wood et al. 2018[95]) found an increased risk for stroke, both ischaemic and haemorrhagic, this is not consistently observed in case-controlled and cohort studies, and meta-analyses of these studies. Indeed, Ricci et al. (2018) actually found a J-shaped association between baseline alcohol consumption and risk of both ischaemic and haemorrhagic stroke where risk increased at ≥30 g/day (see Table 3 of Ricci et al. 2018). These relationships were observed with both current alcohol consumption and lifetime alcohol

[92] Ronksley, PE, Brien, SE, Turner, BJ, Mukamal, KJ, Ghali, WA (2011) Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. Br Med J. 34(3): 363-370.

[93] Larsson SC, Wallin A, Wolk A, Markus HS. (2016) Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis. BMC Med. 14(1):178.

[94] Ricci C, Wood A, Muller D, et al. (2018) Alcohol intake in relation to non-fatal and fatal coronary heart disease and stroke: EPIC-CVD case-cohort study. BMJ. 361:k934. doi: 10.1136/bmj.k934.

[95] Wood AM, Kaptoge S, Butterworth AS, Emerging Risk Factors Collaboration/EPIC-CVD/UK Biobank Alcohol Study Group et al. (2018) Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. Lancet.391(10129):1513-1523. doi: 10.1016/S0140-6736(18)30134-X. Erratum in: Lancet. 391(10136):2212.

consumption as the comparison, where never-drinkers and former drinkers had similar risk for non-fatal coronary heart disease and stroke but had approximately 20% higher risk compared with light and moderate alcohol consumers. In their Supplementary Appendix (see Table 8), however, >0 and ≤50g/week was not associated with risk of any type of stroke. Unfortunately, the exclusion of never-drinkers as a reference group in the main analyses of Wood et al. (2018), essentially eliminated the ability to evaluate for any potentially beneficial or adverse effects of light-to-moderate drinking as compared with non-drinking. The absence of an abstainer category in the presentation of the results also gives the grossly misleading impression that 100 g of alcohol/week is an acceptable threshold of risk, from which mortality risk increases with rising intake. In fact, however, this amount must be consumed to obtain any benefit effects, which is then eroded with higher levels of consumption until the mortality rate for abstainers is reached. The overall finding is actually little different from many other studies of this type.

Usually a J-shaped relationship between alcohol consumption and risk of stroke is observed although the nadir of the curve is shallower than that for risk of CHD (Iso et al. 1995, Leppala et al. 1999, Djousse et al. 2002, Nielsen et al. 2005, Bazzano et al. 2007, Bos et al. 2010, Zhang et al. 2014, Larrson et al. 2016)[96]. For example, light alcohol consumption is associated with a reduced risk of ischaemic and total stroke, whereas heavy alcohol consumption is associated with an increased risk of total stroke. Moderate alcohol consumption, however, had little or no effect on the risks of total stroke, haemorrhagic stroke and ischaemic stroke.

Alcohol has a different relationship with the risk of each type of stroke. Ischaemic stroke results from the blockage of an intracerebral artery, either through a local blood clot or a distal embolism, which can be which may be a blood clot, a fat globule or a gas bubble in the bloodstream. Its risk factors are atrial fibrillation and hypertension (Manolio et al. 1996[97]). Consequently, the apparent inverse association of moderate alcohol consumption and risk of ischaemic stroke occurs at a lower amount of alcohol and with a lower magnitude of risk reduction than does the corresponding association with risk of coronary heart disease (Klatsky et al. 2001, Reynolds et al. 2003, Mukamal et al. 2005a, Mukamal et al. 2006, Ronksley et al.

[96] Bos S, Grobbee DE, Boer JM, Verschuren WM, Beulens JW. (2010) Alcohol consumption and risk of cardiovascular disease among hypertensive women. Eur J Cardiovasc Prev Rehabil.17:119-126; Iso H, Kitamura A, Shimamoto T. et al. (1995) Alcohol intake and the risk of cardiovascular disease in middle-aged Japanese men. Stroke. 26:767-773; Leppälä JM, Paunio M, Virtamo J. et al. (1999) Alcohol consumption and stroke incidence in male smokers. Circulation. 100:1209-1214; Djoussé L, Ellison RC, Beiser A, Scaramucci A, D'Agostino RB, Wolf PA. (2002) Alcohol consumption and risk of ischemic stroke: the Framingham Study. Stroke. 33:907-912; Nielsen NR, Truelsen T, Barefoot JC. et al. (2005) Is the effect of alcohol on risk of stroke confined to highly stressed persons? Neuroepidemiol. 25:105-113; Bazzano LA, Gu D, Reynolds K. et al. (2007) Alcohol consumption and risk for stroke among Chinese men. Ann Neurol. 62:569-578; Zhang C, Qin YY, Chen Q. et al. (2014) Alcohol intake and risk of stroke: a dose-response meta-analysis of prospective studies. Int J Cardiol. 174:669-677; Larsson SC, Wallin A, Wolk A, Markus HS. (2016) Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis. BMC Med.14:178. Christensen AI, Nordestgaard BG, Tolstrup JS. (2018) Alcohol Intake and Risk of Ischemic and Haemorrhagic Stroke: Results from a Mendelian Randomisation Study. J Stroke. 20:218-227.

[97] Manolio TA, Kronmal RA, Burke GL, O'Leary DH, Price TR. (1996) Short-term predictors of incident stroke in older adults The Cardiovascular Health Study Stroke. 27(9): 1479-86.

2011[98]). Only a regular pattern of light to moderate consumption is associated with a reduced risk of ischaemic stroke (Mukamal et al 2005b, Ruidavets et al. 2010[99]). For example, in the Prospective Epidemiological Study of Myocardial Infarction (PRIME), binge drinking approximately doubled the risk of an ischaemic stroke compared with regular consumption (Ruidavets et al. 2010).

There is consensus among studies that heavy alcohol consumption is always associated with a higher risk of both ischaemic and haemorrhagic strokes. The relationship between moderate alcohol consumption and haemorrhagic is less certain. Some studies have observed a J-shaped relationship while others observed a dose-dependent linear relationship between the amount of alcohol consumed and the risk of haemorrhagic stroke (Klatsky et al. 2002, Ariesen et al. 2003, Corrao et al. 2004, Feigin et al. 2005, Patra et al. 2010[100]). If J-shaped, the optimal amount of alcohol is even lower than that for ischaemic stroke. For example, while Corrao et al. (2004) calculated a significantly increased risk for ischaemic stroke at 100 g alcohol/day, for haemorrhagic stroke this was calculated at 50 g/day. This difference in risk between stroke types may be associated with an alcohol-induced increase in blood pressure in heavier consumers (Klatsky et al. 2002, Iso et al. 2004[101]).

These observations reflect the alcohol induced reduction in blood clotting which decreases the risk of a blood clotting-related event such as a myocardial infarction and an ischaemic stroke, but increases the risk of bleeding or a haemorrhage in the brain (Renaud and de Lorgeril 1992[102]). Another two, albeit smaller, relatively recent meta-analyses also support either no association between light to moderate alcohol consumption and risk of different types of haemorrhagic strokes although heavy alcohol consumption of >30 g/day increased

[98] Klatsky AL, Armstrong MA, Friedman GD, Sidney S. (2001) Alcohol drinking and risk of hospitalization for ischemic stroke. Am J Cardiol. 88(6): 703-6; Reynolds K, Lewis B, Nolen JD, Kinney GL, Sathya B, He J. (2003) Alcohol consumption and risk of stroke: a meta-analysis. JAMA. 289(5): 579-88; Mukamal KJ, Chung H, Jenny NS, Kuller LH, Longstreth WT Jr, Mittleman MA, Burke GL, Cushman M, Beauchamp NJ Jr, Siscovick DS. (2005) Alcohol use and risk of ischemic stroke among older adults: the cardiovascular health study. Stroke. 36(9): 1830-4; Mukamal KJ, Ascherio A, Mittleman MA, Conigrave KM, Camargo CA Jr, Kawachi I, Stampfer MJ, Willett WC, Rimm EB. (2005) Alcohol and risk for ischemic stroke in men: the role of drinking patterns and usual beverage. Ann Intern Med. 142(1):11-19.

[99] Ruidavets J-B, Ducimetièere, P, Evans A, Montaye M, Haas B, Bingham A, Yarnell J, Amouye, P, Arveiler, D, Kee F, Bongard V, Ferrières J. (2010) Patterns of alcohol consumption and ischaemic heart disease in culturally divergent countries: the Prospective Epidemiological Study of Myocardial Infarction (PRIME). Br Med J. 341:c6077 doi:101136/bmjc6077.

[100] Klatsky AL, Armstrong MA, Friedman GD, Sidney S. (2002) Alcohol drinking and risk of hemorrhagic stroke Neuroepidemiol. 21(3): 115-122; Ariesen MJ, Claus SP, Rinkel GJ, Algra A. (2003) Risk factors for intracerebral hemorrhage in the general population: a systematic review. Stroke. 34(8): 2060-2065; Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, Anderson CS. (2005) Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. Stroke. 36(12): 2773-2580; Patra J, Taylor B, Irving H, Roerecke M, Baliunas D, Mohapatra S, Rehm J. (2010) Alcohol consumption and the risk of morbidity and mortality for different stroke types--a systematic review and meta-analysis. BMC Public Health. 10:258.

[101] Iso H, Baba S, Mannami T, Sasaki S, Okada K, Konishi M, Tsugane S, JPHC Study Group. (2004) Alcohol consumption and risk of stroke among middle-aged men: the JPHC Study Cohort I. Stroke. 35(5): 1124-1129.

[102] Renaud S, de lorgeril M. (1992) Wine, alcohol, platelets, and the French paradox for coronary heart disease. Lancet. 339(8808): 1523-6.

risk compared with abstainers (Zhang et al. 2014, Yao et al 2016 [103]).

6. In addition, most studies which show cardiovascular benefits of low-level alcohol consumption, also show that such protection, if it exists, peaks at very low doses, for example, at less than half to one standard drink per day (Di Castelnuovo et al. 2006)

The well-recognized J-shaped association has been reported for over four decades (Klatsky et al. 1974[104], Marmot et al. 1981[105]). Since then, a wide range of cohort studies and meta-analyses have confirmed the robust conclusions of a J-shaped association, in which low-volume alcohol consumption is associated with lower risk of cardiovascular diseases such as coronary heart disease (Ronksley et al. 2011[106]). Indeed, the strength of the association has been little changed by studies published since the early 1990s. Furthermore, long-term, randomized trials of alcohol have confirmed the protective effects of alcohol on cardiovascular risk factors (Gepner et al. 2015, Marfella et al. 2006, Shai et al. 2007[107]). These low volumes have ranged from >2.5 up to 30 mg alcohol/day depending on the study.

The optimal pattern of moderate alcohol consumption to reduce risk is approximately daily, and the optimal amount is approximately 10 to 20 g alcohol/day, which is supported by experimental animal and human biological data (Mukamal et al. 2003, Veenstra et al. 1990, Rehm et al. 20003, Mukamal et al, 2005, Lakshman et al. 2010, Chiva-Blanch et al. 2013[108]).

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[103] Zhang C, Qin YY, Chen Q, Jiang H, Chen XZ, Xu CL, Mao PJ, He J, Zhou YH. (2014) Alcohol intake and risk of stroke: a dose-response meta-analysis of prospective studies. Int J Cardiol. 174(3):669-77; Yao X, Zhang K, Bian J, Chen G. (2016) Alcohol consumption and risk of subarachnoid hemorrhage: A meta-analysis of 14 observational studies. Biomed Rep. 5(4):428-436.

[104] Klatsky A L, Friedman G D, Siegelaub AB. (1974). Alcohol consumption before myocardial infarction. Results from the Kaiser-Permanente epidemiologic study of myocardial infarction. Ann Intern Med. 81, 294–301.

[105] Marmot MG, Rose G, Shipley MJ, Thomas BJ. (1981). Alcohol and mortality: a U-shaped curve. Lancet. 317(8220): 580–583.

[106] Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. (2011). Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ. 342, d671. doi:10.1136/bmj.d671

[107] Gepner Y, Golan R, Harman-Boehm I. et al. (2015). Effects of initiating moderate alcohol intake on cardiometabolic risk in adults with type 2 diabetes: A 2-year randomized, controlled trial. Annals of Internal Medicine, 163, 569–579; Marfella R, Cacciapuoti F, Siniscalchi, M. et al. (2006). Effect of moderate red wine intake on cardiac prognosis after recent acute myocardial infarction of subjects with Type 2 diabetes mellitus. Diabetic Medicine: A Journal of the British Diabetic Association. 23: 974–981; Shai I, Wainstein J, Harman-Boehm I, Raz I, Fraser D, Rudich A, Stampfer MJ. (2007). Glycemic effects of moderate alcohol intake among patients with type 2 diabetes: a multicenter, randomized, clinical intervention trial. Diabetes Care. 30, 3011–3016.

[108] Mukamal KJ, Conigrave KM, Mittleman MA et al (2003) Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. N Engl J Med 348:109–118; Veenstra J, Ockhuizen T, van de Pol H, Wedel M, Schaafsma G (1990) Effects of a moderate dose on blood lipids and lipoproteins postprandially and in the fasting state. Alcohol Alcohol 25(4):371–377; Rehm J, Sempos CT, Trevisan M (2003) Alcohol and cardiovascular disease—more than one paradox to consider average volume of alcohol consumption, patterns of drinking and risk of coronary heart disease—a review. J Cardiovasc Risk. 10:15–20; Mukamal KJ, Maclure M, Muller JE, Mittleman MA (2005) Binge drinking and mortality after acute myocardial infarction. Circulation. 112:3839–384; Lakshman R, Garige M, Gong M, Leckey L, Varatharajalu R, Zakhari S. (2010) Is alcohol beneficial or harmful for cardioprotection? Genes Nutr. 5(2):111-20.; Chiva-Blanch G, Arranz S, Lamuela-Raventos RM, Estruch R. (2013) Effects of wine, alcohol and polyphenols on cardiovascular disease risk factors: evidences from human studies. Alcohol Alcohol. 48(3):270-277.

Daily consumption, for example, has been shown to reduce the risk of coronary heart disease by 37% compared to alcohol consumption just once a week (Mukamal et al. 2005[109]).

An earlier meta-analysis of 42 experimental studies, which examined the effects of alcohol consumption on cardiovascular biomarkers, attributed the cardioprotective effect of light-to-moderate alcohol consumption: 60% to effects on high density lipoprotein (HDL) cholesterol, 20-30% to fibrinogen, 5-10% to insulin and 0-5% to other haemostatic factors (Rimm et al. 1999[110]). The meta-analysis also estimated that 30 g of alcohol per day would increase the plasma concentration of HDL by approximately 4 mg/dL which would be associated with a 17% reduction in risk of coronary heart disease where low plasma/serum concentrations of HDL cholesterol are a strong, in-dependent risk factor for CVD. It would also decrease the plasma concentration of fibrinogen by approximately 0.075 g/L, which would be associated with a 12.5% reduction in risk of coronary heart disease (Hines and Rimm 2001[111]). This translated into an overall 24.7% reduction in the risk of coronary heart disease from the consumption of 30 g alcohol/day. Klatsky and Udaltsova (2007) further translated this into a 10% reduction in risk of all-cause mortality. More recently, consumption of 30 g alcohol/day for four weeks as beer or gin by high CVD risk male participants was associated with clinically significant changes in blood lipids and their constituents, for example, serum HDL-cholesterol concentration increased by approximately 5%, ApoA- by approximately 6%, ApoA-II by approximately 7% and adiponectin by approximately 7%, while coagulation factors such as serum fibrinogen concentration decreased by approximately 8%, and the plasma inflammatory biomarker interleukin (IL)-5 by approximately 14%; phenolic compounds also exhibited effects (Chiva-Blanch et al. 2014)[112]. This was in comparison to the non-alcoholic beer and gin consumption intervention. Similar cardioprotective effects were also observed for wine consumption equivalent to 30 g alcohol/day (Chiva-Blanch et al. 2013[113]).

Meta-analyses of cohort studies that measured current alcohol consumption show a J-shaped relationship between mortality and alcohol consumption with sex-specific thresholds. For example, a significant mortality risk reduction up to 20 g/day for men and up to 10 g/day for women by English et al. (1995)[114] and up to 40 g/day for men and up to 20 g/day for women

[109] Mukamal KJ, Jensen MK, Grønbæk M et al. (2005) Drinking frequency, mediating biomarkers, and risk of myocardial infarction in women and men. Circulation. 112:1406–1413

[110] Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. (1999). Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. Br Med J. 319(7224): 1523-1528.

[111] Hines LM, Rimm EB. (2001). Moderate alcohol consumption and coronary heart disease: a review. Postgrad. Med. J. 77(914): 747-752.

[112] Chiva-Blanch G, Magraner E, Condines X. et al. (2015) Effects of alcohol and polyphenols from beer on atherosclerotic biomarkers in high cardiovascular risk men: a randomized feeding trial. Nutr Metab Cardiovasc Dis. 25(1):36-45. 8

[113]Chiva-Blanch G, Urpi-Sarda M, Ros E. et al. (2013) Effects of red wine polyphenols and alcohol on glucose metabolism and the lipid profile: a randomized clinical trial. Clin Nutr. 32(2):200-206.

[114] English DR, Holman CDJ, Milne E et al. (1995) The Quantification of Drug Caused Morbidity and Mortality in Australia. 1995 edn. Canberra, Australia: Commonwealth Department of Human Services and Health.

by Di Castelnuovo et al. (2006)[115], not simply the stated "less than half to one standard drink per day".

This is also supported by meta-analysis by Klatsky and Udaltsova (2007)[116] suggests that the cardiprotection extends to approximately 40 g alcohol/day, as did studies by Doll et al. (2005)[117], Mukamal (2006[118], 2010[119]), Bergmann et al. (2013)[120] and Jayaskara et al. (2015)[121] the latter using lifetime alcohol consumption in an Australian population. The cardioprotection afforded by alcoholic beverages decreases and the risk of any adverse effects increases, however, when consumption increases from light-to-moderate to heavy (Rimm et al. 1999, Jackson et al. 2003, Malinski et al. 2004, Beulens et al. 2010, Constanzo et al. 2010[122]). Furthermore, the supplementary data to Wood et al. (2018)[123] clearly show that the risk of all cardiovascular events is lower for light/moderate consumers, and in particular, there was a J-shaped relationship between the risk of alcohol consumption and all cardiovascular events; the greatest reduction in the risk was at 100-200 g/week of alcohol, i.e. 1-2 10 standard drinks/day or 10-20 g alcohol/day. Also, never-drinkers even had a greater risk of all cardiovascular events than consumers who drank >600 g/week of alcohol, i.e. more than 60 standard drinks/week.

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[115] Di Castelnuovo A, Costanzo S, Bagnardi V et al. (2006) Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. Arch Intern Med. 166(22):2437–2445.

[116] Klatsky AL, Udaltsova N. (2007) Alcohol drinking and total mortality risk. Ann Epidemiol. 17(5, Supplement 1): S63-S67.

[117] Doll R, Peto R, Boreham J, Sutherland I. (2005) Mortality in relation to alcohol consumption: a prospective study among male British doctors. Int J Epidemiol. 34(1): 199-204.

[118] Mukamal KJ, Chiuve SE, Rimm EB. (2006) Alcohol consumption and risk for coronary heart disease in men with healthy lifestyles Arch Intern Med. 166(19): 2145-2150.

[119] Mukamal KJ, Chen CM, Rao SR, Breslow RA. (2010) Alcohol consumption and cardiovascular mortality among US adults, 1987 to 2002. J Am Coll Cardiol. 55(13): 1328-1335.

[120] Bergmann MM, Rehm J, Klipstein-Grobusch K et al. (2013) The association of pattern of lifetime alcohol use and cause of death in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Int J Epidemiol. 42:1772–1790

[121] Jayasekara H, MacInnis RJ, Hodge AM, Hopper JL, Giles GG, Room R, English DR. (2015) Alcohol consumption for different periods in life, intake pattern over time and all-cause mortality. J Public Health (Oxf). 37(4):625-633.

[122]Rimm, EB, Williams, P, Fosher, K, Criqui, M, Stampfer, MJ. (1999) Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. Br Med J. 319(7224): 1523-1528; Jackson VA, Sesso HD, Buring JE, Gaziano JM. (2003) Alcohol consumption and mortality in men with preexisting cerebrovascular disease. Arch Intern Med. 163(10): 1189-1193; Malinski MK, Sesso HD, Lopez-Jimenez F, Buring JE, Gaziano JM. (2004) Alcohol consumption and cardiovascular disease mortality in hypertensive men. Arch Intern Med. 164 :623–628; Beulens JW, Algra A, Soedamah-Muthu SS, Visseren FL, Grobbee DE, van der Graaf Y; SMART Study Group. (2010) Alcohol consumption and risk of recurrent cardiovascular events and mortality in patients with clinically manifest vascular disease and diabetes mellitus: the Second Manifestations of ARTerial (SMART) disease study. Atherosclerosis. 212: 281-286; Costanzo S, Di Castelnuovo A, Donati MB, Iacoviello L, de Gaetano G. (2010) Cardiovascular and overall mortality risk in relation to alcohol consumption in patients with cardiovascular disease. Circulation. 121(17): 1951-1859.

[123] Wood AM, Kaptoge S, Butterworth AS, et al. (2018) for the Emerging Risk Factors Collaboration/EPIC-CVD/UK Biobank Alcohol Study Group (120 authors). Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. Lancet. 391:1513-1523.

7. If coronary heart disease protective effects do exist, the modelling for these guidelines shows it is likely that they only offset harm from alcohol in people aged over 70 years and over.

The cardioprotective effects of regular moderate alcohol consumption are usually observed when risk factors for coronary heart disease become evident such as approximately age 40 years in men and 45-50 years in women during perimenopause and post-menopause (Klatsky and Udaltsova 2007[124], Snow et al. 2009[125]). Furthermore, Gronbaek et al. (1998)[126] reported identical J-shaped relationships between all-cause mortality and alcohol consumption for middle-aged and older participants. Thun et al. (1997)[127] noted decreased risk of all-cause mortality with usual consumption for both middle-aged (30–59 years) and older (60–79 years) men and women. Furthermore, studies do not suggest a decreased cardioprotective effect of usual alcohol consumption as a function of age but rather a preservation of its beneficial effects, at least in men and at the generally moderate amounts of alcohol consumption (Snow et al. 2009).

The relationship between alcohol consumption and the risk of all-cause mortality does appear to be age dependent (Rehm and Sempos 1995[128]). A cardioprotective effect is first observed, however, when risk factors for CVD begin to influence medium and long-term health, that is, at approximately age 40 years for men and approximately age 50 years for women (Tolstrup and Gronbeck 2007, Hvidtfeldt et al. 2010 [129]). Accordingly, in women, onset of cardioprotection depends on the age of onset of menopause and use of hormone replacement therapy (Stampfer et al. 1988, Klatsky et al. 1992, Holman et al. 1996, Thun et al. 1997, Di Castelnuovo et al. 2006, Klatsky and Udaltosova 2007, Snow et al. 2009[130]).

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[124] Klatsky AL, Udaltsova N. (2007) Alcohol drinking and total mortality risk, Ann Epidemiol. 17(5) Suppl: S63-67.

[125] Snow WM, Murray R, Ekuma O, Tyas SL, Barnes GE. (2009) Alcohol use and cardiovascular health outcomes: a comparison across age and gender in the Winnipeg Health and Drinking Survey Cohort. Age Ageing. 38(2): 206-212.

[126] Grønbaek M, Deis A, Becker U, Hein HO, Schnohr P, Jensen G, Borch-Johnsen K, Sørensen TI. (1998) Alcohol and mortality: is there a U-shaped relation in elderly people? Age Ageing. 27(6):739-744.

[127] Thun MJ, Peto R, Lopez AD, Monaco JH, Henley SJ, Heath CW Jr, Doll R. (1997) Alcohol consumption and mortality among middle-aged and elderly U.S. adults. N Engl J Med. 337(24):1705-1714.

[128] Rehm J, Sempos CT. (1995) Alcohol consumption and all-cause mortality. Addiction. 90(4): 471-480.

[129] Tolstrup J, Grönbeck M. (2007) Alcohol and atherosclerosis: recent insights. Curr Atheroscler Rep. 9: 116-24; Hvidtfeldt UA, Tolstrup JS, Jakobsen MU. et al. (2010) Alcohol and intake and risk of coronary heart disease in younger, middle-aged and older adults. Circulation. 121: 1589-1597; Holman CDJ, English DR, Milne E, Winter MG. (1996) Meta-analysis of alcohol and all-cause mortality: a validation of NHMRC recommendations. Med J Aust. 164: 141-145; Thun MJ, Peto R, Lopez A, Monaco JH, Henley SJ, Heath CW, Doll. R. (1997) Alcohol consumption and mortality among middle-aged and elderly US adults. N Engl J Med. 337: 1705-1714; Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, de Gaetano G. (2006) Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. Arch Intern Med. 166: 2437-2445; Klatsky AL, Udaltsova N. (2007) Alcohol drinking and total mortality risk. Ann Epidemiol. 17(5, Supplement 1): S63-S67; Snow WM, Murray R, Ekuma O, Tyas SL, Barnes GE. (2009) Alcohol use and cardiovascular health outcomes: a comparison across age and gender in the Winnipeg Health and Drinking Survey Cohort. Age Ageing. 38(2): 206-212.

[130] Stampfer, MJ, Colditz, GA, Willett, WC, Speizer, FE and Hennekens, CH. (1988) A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. N Engl J Med. 319:267–273; Klatsky AL, Armstrong MA, Friedman GD. (1992) Alcohol and mortality. Ann Intern Med. 117(8): 646-654.

Furthermore, initiation of moderate alcohol consumption at ages 45-64 years is also associated with an up to 40% reduction in CVD risk compared to both abstinence and light consumption after approximately four years which was maintained even when other CVD risk factors were considered (Sesso et al. 2000, Friesema et al. 2007, King et al. 2008[131]).

Cardioprotection generally continues past 65 and 75 years of age (Simons et al. 2000, Perissinotto et al. 2010, McCaul et al. 2010, Simons et al. 2014[132]). Simons et al. (2014), for example, in a population of 2805 non-institutionalised participants aged 60 years and older, observed that at 20 years of follow-up, there is significant protection from CVD for moderate alcohol consumers compared to both abstainers and heavy consumers. In addition, men and women consuming any alcohol survived 12 months longer than their abstinent peers. This relationship did not appear to be impacted or mediated by the CVD risk factors of diabetes, hypertension, obesity or the ratio of LDL to HDL cholesterol.

There is also data, however, that suggests that the consumption of alcohol at a younger age does reduce the risk of CVD at a later age [98,99,100,101] by modulating certain biomarkers for CVD (Power et al. 1998, Green et al. 2009, Wakabayashi and Araki 2010, Okwuosa et al. 2013 [133]). Although complex and requiring clarification, the US Coronary Artery Risk Development in Young Adults (CARDIA) and other subsequent studies showed that early adolescent and young adult levels of modifiable risk factors for CVD, albeit low, were equally or more informative about odds of coronary artery disease in middle age than subsequent levels (Loria et al. 2007, Hartiala et al. 2012, Hartiala et al. 2016, Wilkins et al. 2016[134]). This

[131] Sesso HD, Stampfer MJ, Rosner B, Hennekens CH, Manson JE, Gaziano JM. (2000) Seven-year changes in alcohol consumption and subsequent risk of cardiovascular disease in men. Arch Intern Med. 160(17): 2605-2612; Friesema IH, Zwietering PJ, Veenstra MY, Knottnerus JA, Garretsen HF, Lemmens PH. (2007) Alcohol intake and cardiovascular disease and mortality: the role of pre-existing disease. J Epidemiol Community Health. 61(5) :441-6; King DE, Mainous AG 3rd, Geesey ME. (2008) Adopting moderate alcohol consumption in middle age: subsequent cardiovascular events. Am J Med. 121(3): 201-206.

[132] Simons L, McCallum AJ, Friedlander Y, Ortiz M, Simons J. (2000) Moderate alcohol intake is associated with survival in the elderly: the Dubbo Study. Med J Aust. 173(3): 1211–1224; Perissinotto E, Buja A, Maggi S, Enzi G, Manzato E, Scafato E, Mastrangelo G, Frigo AC, Coin A, Crepaldi G, Sergi G, ILSA Working Group. (2010) Alcohol consumption and cardiovascular risk factors in older lifelong wine drinkers: the Italian Longitudinal Study on Aging. Nutr Metab Cardiovasc Dis. 20(9): 647-55; McCaul KA, Almeida OP, Hankey GJ, Jamrozik K, Byles JE, Flicker L. (2010) Alcohol use and mortality in older men and women. Addiction. 105(8): 1391-1400; Simons L. (2014) Alcohol intake and survival in Australian seniors: the Dubbo Study. Nutr Aging. 2(2-3): 85-90.

[133] Power C, Rodgers B, Hope S. (1998) U-shaped relation for alcohol consumption and health in early adulthood and implications for mortality Lancet. 352: 877; Green D, Foiles N, Chan C, Schreiner PJ, Liu K. (2009) Elevated fibrinogen levels and subsequent subclinical atherosclerosis: the CARDIA Study. Atherosclerosis. 202(2): 623-631; Wakabayashi I, Araki Y. (2010) Influences of gender and age on relationships between alcohol drinking and atherosclerotic risk factors Alcohol Clin Exp Res. 34(Suppl 1): S54-60; Okwuosa TM, Klein O, Chan C, Schreiner P, Liu K, Green D. (2013) Long-term change in alcohol-consumption status and variations in fibrinogen levels: the coronary artery risk development in young adults (CARDIA) study. BMJ. 3(7). pii: e002944. doi: 10.1136/bmjopen-2013-002944.

[134] Loria CM, Liu K, Lewis CE, Hulley SB, Sidney S, Schreiner PJ, Williams OD, Bild DE, Detrano R. (2007) Early adult risk factor levels and subsequent coronary artery calcification: the CARDIA Study. J Am Coll Cardiol. 49(20):2013-2020; Hartiala O, Magnussen CG, Kajander S et al. (2012). Adolescence risk factors are predictive of coronary artery calcification at middle age: the cardiovascular risk in young Finns study. J Am Coll Cardiol. 60(15):1364-1370; Hartiala O, Kajander S, Knuuti J. et al. (2016). Life-course risk factor levels and coronary artery calcification. The Cardiovascular Risk in Young Finns Study. Int J Cardiol. 225:23-29; Wilkins JT, Li RC, Sniderman A, Chan C,

indicates that that adolescent and young adult risk factor levels and activities that attenuate them, play an important role in the pathogenesis of coronary heart disease and is associated with coronary heart disease at middle and older age. Conversely, the impact of heavy episodic alcohol consumption, that is, binge drinking, during adolescence and young adulthood on the cardiovascular system should not be underestimated (Russell et al. 2019 [135]).

8. If there are protective effects for coronary heart disease in selected groups, the increase risk of alcohol consumption from other health conditions such as cancer still remains.

The relationship between alcohol consumption and risk of death from all causes is complex where the reduced risk in death from cardiovascular disease is attenuated by the increased risk in death from cancers. A J-shaped relationship, however, is still observed between average lifetime alcohol consumption and death from all causes in the majority of studies. Given that cardiovascular disease and cancers have multiple risk factors which accumulate with age, including present and past alcohol consumption, measurement of average lifetime alcohol consumption avoids the bias that occurs when separating former drinkers from current drinkers, which Fillmore et al. (2006) and Stockwell et al. (2016) have alleged invalidates the J-shaped relationship between alcohol consumption and risk of death from cardiovascular disease. Kunzmann et al. (2018)[136] using average lifetime alcohol consumption as the reference group observed J-shaped associations between average lifetime alcohol consumption and overall mortality, cardiovascular-related mortality, and combined risk of death or cancer. In comparison to lifetime light alcohol drinkers (1±3 drinks per week), lifetime never or infrequent drinkers (<1 drink/week), as well as heavy (2±<3 drinks/day) and very heavy drinkers (3+ drinks/day) were also observed to have increased overall mortality and combined risk of cancer or death.

An aim of studies of the consumption of alcoholic beverages and mortality is to establish the net effects of alcohol at the population level and to derive conclusions at the aggregate level. The balance between net health benefits and risks from alcohol consumption is directly related to the distribution of causes of death in a population and to subgroups within a population. These subgroups include young adults, middle aged adults and the elderly. It has been observed for approximately three decades that the light to moderate consumption of alcoholic beverages also reduces the risk of death from all-causes within a population (Klatsky et al. 1992, Holman et al. 1996, Gaziano et al. 2000, Gmel et al. 2003, Britton and Marmot 2004, Wellman et al. 2004, Di Castelnuovo et al. 2006, Klatsky and Udaltsova 2007, Jayasekara et al. 2014, Xi et al. 2017, Kunzmann et al. 2018[137]). This J-shaped relationship between alcoholic

Lloyd-Jones DM. (2016) Discordance Between Apolipoprotein B and LDL-Cholesterol in Young Adults Predicts Coronary Artery Calcification: The CARDIA Study. J Am Coll Cardiol. 67(2):193-201.

[135] Russell M, Fan AZ, Freudenheim JL, Dorn J, Trevisan M. (2019) Lifetime Drinking Trajectories and Nonfatal Acute Myocardial Infarction. Alcohol Clin Exp Res. 43(11):2384-2394.

[136] Kunzmann AT, Coleman HG, Huang W-Y, Berndt SI. (2018) The association of lifetime alcohol use with mortality and cancer risk in older adults: A cohort study. PLoS Med. 15:e1002585.

[137] Klatsky AL, Armstrong MA, Friedman GD. (1992) Alcohol and mortality Ann Intern Med. 117(8): 646-654; Holman CDJ, English DR, Milne E, Winter MG. (1996) Meta-analysis of alcohol and all-cause mortality: a

beverages and all-cause mortality results from the net sum of reduced risks of death from CVD, diabetes, cognitive function disorders such as dementia, as well as from certain cancers, and increased risks of death from short-term harms and long-term harms. Short-term harms include accidents such as drowning and suicides and are generally associated with binge drinking patterns. Long-term harms include certain cancers, liver cirrhosis, pancreatitis and alcohol-related CVD, and are associated with continuous heavier consumption over many years, where risk increases linearly with consumption above moderation.

The 1996 Australian meta-analysis by Holman et al. (1996) of 16 longitudinal cohort studies undertaken between 1980 and 1993, was the first to suggest that the J-shaped relationship between alcohol and CVD could be extended to total or all-cause mortality. A 16 and 12% reduction in risk of death from all-causes was calculated for men and women, respectively, at 10-19 and 1-9 g alcohol/day.

Indeed, since the publication of the 2009 *Australian guidelines to reduce health risks from drinking alcohol*, peer-reviewed evidence has continued to be consistent that there is a J-shaped relationship between current alcohol consumption and death from all causes for both men and women, including Australians. This has been extended to average lifetime alcohol consumption. Measurement of average lifetime alcohol consumption avoids the bias that occurs when separating former drinkers from current drinkers, which Fillmore et al. (2007) and Stockwell et al. (2017) alleged invalidates the J-shaped relationship between alcohol consumption and risk of death from CVD. The J-shaped relationship primarily reflects the reduced risk of CVD and particularly coronary heart disease, also referred to as coronary artery disease and ischaemic heart disease; coronary heart disease is the leading cause of death in Australia as well as worldwide for both men and women. In 2015, it caused 12.4% of Australian deaths and 15.5% worldwide[138].

The relationship between alcohol and cancer, however, is complex. Alcohol does not initiate, promote or progress all types of cancers, and the International Agency for Research on Cancer

validation of NHMRC recommendations. Med J Aust. 164: 141-145; Gaziano JM, Gaziano TA, Glynn RJ, Sesso HD, Ajani UA, Stampfer MJ, Manson JE, Hennekens CH, Buring JE. (2000) Light-to-moderate alcohol consumption and mortality in the Physicians' Health Study enrollment cohort. J Am Coll Cardiol. 35(1): 96-105; Gmel G, Gutjahr E, Rehm J. (2003) How stable is the risk curve between alcohol and all-cause mortality and what factors influence the shape? A precision-weighted hierarchical meta-analysis. Eur J Epidemiol. 18(7):631-642; Britton A, Marmot M. (2004) Different measures of alcohol consumption and risk of coronary heart disease and all-cause mortality: 11-year follow-up of the Whitehall II Cohort Study. Addiction. 99(1): 109-16; Wellmann J, Heidrich J, Berger K, Döring A, Heuschmann PU, Keil U. (2004) Changes in alcohol intake and risk of coronary heart disease and all-cause mortality in the MONICA/KORA-Augsburg cohort 1987-97. Eur J Cardiovasc Prev Rehabil. 11(1): 48-55; Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, de Gaetano G. (2006) Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. Arch Intern Med. 166: 2437-4; Klatsky AL, Udaltsova N. (2007) Alcohol drinking and total mortality risk. Ann Epidemiol. 17(5, Supplement 1): S63-S67; Jayasekara H, English DR, Room R, MacInnis RJ. (2014) Alcohol consumption over time and risk of death: a systematic review and meta-analysis. Am J Epidemiol. 179(9): 1049-1059; Xi B, Veeranki SP, Zhao M, Ma C, Yan Y, Mi J. (2017) Relationship of Alcohol Consumption to All-Cause, Cardiovascular, and Cancer-Related Mortality in U.S. Adults. J Am Coll Cardiol. 70:913–92; Kunzmann AT, Coleman HG, Huang W-Y, Berndt SI. (2018) The association of lifetime alcohol use with mortality and cancer risk in older adults: A cohort study. PLoS Med. 15:e1002585. https://doi.org/10.1371/journal.pmed.1002585.

[138] http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2015~Main%20Features~Ischaemic%20Heart%20Disease~10001

(IARC) lists alcohol among carcinogens causing only oral cavity, pharynx, larynx, squamous cell oesophagus (collectively known as the upper aero-digestive tract), liver and colorectum cancers as well as female pre and post-menopausal breast cancer (IARC Working Group 2010). These cancers are referred to as alcohol-attributable cancers, and there is sufficient or convincing evidence of the attributions (World Cancer Research Fund International 2018), as shown in Table 1.

Table 1. Alcohol attributable cancers and level of evidence (World Cancer Research Fund International CUP 2018)

Cancer type	Level of evidence of increased risk	Alcohol threshold
Mouth, larynx, pharynx	Convincing	No threshold
Oesophagus (squamous cell carcinoma)	Convincing	No threshold
Stomach	Probable	Based on intakes >45 g ethanol/day
Liver	Convincing	Based on intakes >45 g ethanol/day
Colorectum	Convincing	Based on intakes >30 g ethanol/day
Breast pre-menopause	Probable	No threshold
Breast post-menopause	Convincing	No threshold
Skin (melanoma)	Limited	
Pancreas	Limited	
Prostate	Limited	
Lung	Limited	

Cancer causation is multifactorial. Alcohol consumption is a voluntary and hence modifiable risk factor for cancer. Other modifiable risk factors include tobacco smoking, inadequate diet, insufficient physical activity, being overweight and obese, as well as exposure to solar UV radiation, infectious agents and hormones in oral contraceptives and hormone replacement therapy. The cumulative effect of these risk factors contributes to the occurrence of cancer. Accordingly, all alcohol-attributable cancers have multiple risk factors. Alcohol consumption itself is not the primary risk factor for any of these cancers but is secondary to tobacco smoking, inadequate diet, insufficient physical activity, being overweight or obese and exposed to infectious agents depending on the cancer. In 2010, 10% of alcohol-attributable cancers occurring in Australian adults could be attributed to alcohol consumption (Pandeya et al. 2015[139]).

In 2010, as a cause of all cancers, alcohol consumption (2.8%) was listed after tobacco smoking (13.4%) which was the leading cause of all cancers, solar UV radiation (6.2%), inadequate diet (6.1%), being overweight or obese (3.4%) and infectious agents (2.9%)

[139] Pandeya, N, Wilson, LF, Webb, PM, Neale, RE, Bain, CJ, Whiteman, DC (2015). Cancers in Australia in 2010 attributable to the consumption of alcohol. Australian and New Zealand journal of public health 39(5): 408-413.

(Whiteman et al. 2015[140]). Consequently, any changes in the incidence of alcohol-attributable cancers will reflect the cumulative change in the prevalence of all risk factors for that cancer and not just alcohol consumption. In addition, the prevalence of certain of these other risk factors is increasing in the Australian population, such as being overweight or obese, while others are decreasing such as tobacco smoking.

When cancer is included in all-cause mortality calculations, the J-shaped relationship is maintained but is adversely modified to reflect its relatively linear risk relationship with alcohol consumption. For example, there is a consistent association between alcohol consumption and alcohol-attributable cancers, but the data are generally inconsistent regarding an association between alcohol consumption and risk of other cancers. These associations, however, are modified by both amount and pattern of alcohol consumption as well as by other factors, and also differ between cancers. Indeed, there are a number of types of cancer, especially those of the upper aero-digestive tract that are clearly increased among heavy drinkers, especially among participants who are also heavy smokers, while cancer of the liver can be a result of alcoholic liver cirrhosis, related to long-term heavy drinking.

The Global Burden of Disease Study 2016[141], from a series of meta-analyses, found that the relative risk of the incidence of and death from seven alcohol attributable cancers monotonically increased with alcohol consumption and from any alcohol consumption. There were, however, clear differences in each dose-response curve such as in the steepness of the gradient of each cancer's graph as well as trajectory. The risk of breast cancer in women is also usually found to be slightly higher in even very light and light drinkers than it is among non-drinkers. This has been a common finding, although some studies suggest that the pattern of drinking, the estimated level of underreporting of alcohol consumption, use of hormone replacement therapy, level of folate intake and other dietary factors, and genetic predisposition, may all affect and confound this association.

Correspondingly, an increased risk for alcohol-attributable cancers has been shown for heavy drinkers, but generally not for light or moderate alcohol consumers. This is exemplified in a relatively recent meta-analysis of 60 studies which focused on the association between very light (≤0.5 drink/day), light (≤1 drink/day), or moderate drinking (1-2 drinks/day) and the risk of cancer incidence and mortality (Choi et al. 2017[142]). Overall, very-light drinking was found not to be associated with the incidence of most cancers except for female breast cancer and male colorectal cancer and was associated with a decreased incidence of both female and male lung cancer and both female and male thyroid cancer. Moderate alcohol consumption significantly increased the incidence of male colorectal cancer and female breast cancer, whereas it decreased the incidence of both female and male haematologic malignancy. The relationships between breast and colorectal cancer and very-light alcohol consumption were, however, weak (OR=1.09 and 1.04, respectively) and despite statistical significance, not

[140] Whiteman, D.C., Webb, P.M., Green, A.C., et al. (2015). Cancers in Australia in 2010 attributable to modifiable factors: summary and conclusions. Australian and New Zealand journal of public health 39(5):477-484.
[141] GBD 2016 Alcohol Collaborators. (2018) Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 392(10152):1015-1035.
[142] Choi Y-J, Myung S-K, Lee J-H. (2017) Light Alcohol Drinking and Risk of Cancer: A Meta-analysis of Cohort Studies. Cancer Research and Treatment. pre-publication release.

necessarily related to causality. Unfortunately, there was a lack of data on the net effects in terms of the effects of alcohol consumption on total mortality.

Furthermore, studies have also shown a reduced risk of cancer with lighter alcohol consumption compared with both abstinence and heavier consumption, for example, light to moderate alcohol consumption may, however, protect against Hodgkin's and non-Hodgkin's lymphomas and renal call cancers, and is not associated, positively or negatively, with any other cancers (Bagnardi et al. 2015[143]).

Other recent analyses have, however, addressed both the association between alcohol and cancers as well as the association between alcohol consumption and all-cause mortality, including calculations by Kunzmann et al. (2018)[144] from a population-based cohort study of approximately 100,000 older participants who were followed for a median of 8.9 years. There were large numbers of deaths (n=9,599) and incident cancers (n=12,763) diagnosed during follow up, which should lead to more precise estimates of effect. They found that light-to-moderate drinking was associated with lower total mortality, but the risk of incident cancer increased with greater alcohol consumption, especially consumption of beer or spirits. The analyses indicated, however, that the slightly increased risk of cancer associated with moderate alcohol consumption was less than the beneficial effect on mortality. Specifically, in comparison with never drinkers or very light (<1 drink/week) drinkers, the study showed lower mortality for "light-to-moderate" alcohol consumers (up to 2 drinks/day) but greater mortality among participants classified as "heavy" (2 to < 3) or "very heavy" (3+ drinks/day) consumers. In beverage-specific analyses, there was a slight increase in total mortality for reported consumption of spirits starting at the consumption of approximately 1 ½ drinks/day and for beer at or above about 2 drinks/day; no significant increase in cancer risk was associated with wine consumption, regardless of the amount. Kunzmann et al. (2018) concluded that "there is a J-shaped association between alcohol and mortality in older adults, which remains after adjustment for cancer risk." Kunzmann et al. (2018) showed, essentially for the first time in a single study, how the beneficial effects of light and moderate drinking on CVD and total mortality exceed the slight increase in cancer risk for alcohol consumption at this level. In other words, while even light-to-moderate drinking may be associated with a slight increase in the risk of certain cancers, such drinking still favourably affects the overall risk of mortality.

Similarly, Xi et al. (2017)[145] found a clear J-shaped curve for the relation of alcohol to mortality, with lower total, cardiovascular, and even cancer mortality rates for light and moderate drinkers who do not binge drink, with increased total mortality and cancer mortality for those classified as "heavy" drinkers. The usual finding in prospective or longitudinal cohort studies has been that light-to-moderate alcohol consumers tend to be at

[143] Bagnardi V, Rota M, Botteri E. et al. (2015). Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. British J Cancer 112(3): 580-593.

[144] Kunzmann AT, Coleman HG, Huang W-Y, Berndt SI. (2018) The association of lifetime alcohol use with mortality and cancer risk in older adults: A cohort study. PLoS Med. 15:e1002585. https://doi.org/10.1371/journal.pmed.1002585.

[145] Xi B, Veeranki SP, Zhao M, Ma C, Yan Y, Mi J. (2017) Relationship of Alcohol Consumption to All-Cause, Cardiovascular, and Cancer-Related Mortality in U.S. Adults. J Am Coll Cardiol. 70:913–992

lower risk for total mortality and show greater longevity of life, even when other lifestyle/demographic factors known to affect longevity are adjusted for in the analysis. This analysis is important as it presents data on the relationship of alcohol consumption to total mortality as well as to specific mortality from CVD and cancer for a large number of participants (333,247) of whom 34,754 died (including 8,947 CVD deaths and 8,427 cancer deaths), during a follow-up period averaging 8.2 years; only lifetime abstainers (31.3% of participants) were included in the reference group. Furthermore, by adjusting for a number of chronic diseases, and carrying out sensitivity analyses with a two-year lag period for mortality, the investigators improved their ability to avoid having their results affected by "sick quitters." Xi et al. (2017) concluded that their analysis shows that light and moderate drinkers have a lower risk of total mortality, as well as mortality from CVD, coronary heart disease, and cerebrovascular disease. The protective effects of alcohol for such cardiovascular outcomes were not present for participants who reported binge drinking or for those reporting what was defined as "heavy" drinking (>7 drinks/week for women and older men, 14 drinks/week for younger men). Interestingly, the mortality risk for light and moderate drinking was also significantly reduced for deaths attributed to cancer; this may have possibly resulted from participants with cancer who actually died from CVD having their deaths attributed to cancer. Participants reporting heavy drinking and those with binge drinking showed increased risk of all-cause and cancer mortality, with no significant effect on CVD outcomes. The key results of this study are that there is a very clear J-shaped curve for the relation of alcohol to mortality, with lower total, cardiovascular, and even cancer mortality rates for light and moderate drinkers who do not binge drink. There was increased total mortality and cancer mortality for those classified as "heavy" drinkers.

In addition, an Australian analysis of the association of all-cause mortality with alcohol consumption for different periods in life, such as lifetime, current baseline and past, supported existing evidence that low amounts of alcohol consumption for middle aged men (<40 g/day using lifetime alcohol intake) and women (<10 g/day using lifetime alcohol intake) are associated with reduced mortality (Jayasekara et al. 2015[146]). Associations between all-cause mortality and lifetime, current baseline and past alcohol consumption were all J-shaped while higher mortality risk for consistent heavy drinking (> 40 g/day) from a young age was also found. Consistent moderate alcohol consumption from age 20 years to baseline age was associated with a 16% decreased in death from all-causes.

These large longitudinal cohort studies provide additional data supporting a J-shaped curve for the association of alcohol consumption with mortality. Thus, data continue to indicate that the light-to-moderate consumption of alcoholic beverages without binge drinking reduces total mortality as well as death from CVD or cancer. While some studies have led to proclamations that no alcohol consumption is preferable for the prevention of cancer, other studies suggest that it is important to consider not only cancer, but other diseases. For example, coronary heart disease, ischaemic stroke, diabetes, and dementia (all of which are important causes of disability and death) occur less frequently among moderate drinkers than

[146] Jayasekara H, MacInnis RJ, Hodge AM, Hopper JL, Giles GG, Room R, English DR. (2015) Alcohol consumption for different periods in life, intake pattern over time and all-cause mortality. J Public Health (Oxf). 37(4):625-633.

among non-drinkers. Most importantly, however, the risk of total mortality is almost always found to be lower among light to moderate drinkers than among abstainers.

The reduced risk of death from all causes from regular moderate alcohol consumption is also seen in the increase in life years, increase in life years free of CVD, and increase in survival after onset of CVD for both men and women.

While regular moderate alcohol consumption consistently appears additive to other healthy lifestyle factors to reduce the risk of death from all causes, the lowest risk always includes regular moderate alcohol consumption. It should be recognised in any rhetoric, however, that regular moderate alcohol consumption should be considered as an important complement, but not as an alternative, to other healthy lifestyle factors and habits that lower the risk of chronic diseases. In addition, heavy alcohol consumption in earlier in life and then abstinence adversely modified the J-shaped relationship to increase the risk of all-cause mortality in men.

9. Further there are safer ways to reduce risk of coronary heart disease, such as by maintaining a healthy weight, reducing blood pressure and not smoking (The University of Sheffield 2019).

Regular moderate alcohol consumption is recognised as a healthy lifestyle factor additive to that of maintaining a healthy weight, reducing blood pressure and not smoking to reduce the risk of coronary heart disease. It is not replaced by maintaining a healthy weight, reducing blood pressure and not smoking.

It is well documented that moderate alcohol consumption reduces the risk of dying from all or any causes such as coronary heart disease, which is referred to as all-cause mortality, and is considered as one of at least four or more healthy lifestyle factors.

This cardioprotection from moderate alcohol consumption has been consistently observed for both men (Mukamal et al. 2006[147]) and women (Djoussé et al. 2009[148]) in diverse ethnic populations. It is also generally observed when controlling for known confounding factors such as body mass index (BMI), cigarette smoking, diet and exercise (Waśkiewiczet al. 2004, Bryson et al. 2006, Mukamal et al. 2006, Ford et al. 2011, Shuval et al. 2012, Soedamah-Muthuet al. 2013, Keyes et al. 2019, Suliga et al. 2019[149]). Indeed, Rimm and Moats (2007)[150] addressed the issue of residual confounding by healthy lifestyle in drinkers in a large prospective study by restricting analysis to only 'healthy' men (who did not smoke cigarettes, exercised, ate a healthy diet, and were not overweight). Within this group, men who consumed alcohol moderately had a 62% (11-84%) reduced risk for coronary heart disease compared with lifetime abstainers, providing further evidence to support the hypothesis that the inverse association of alcohol to coronary heart disease is causal, and not confounded by healthy lifestyle behaviours.

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[147] Mukamal KJ, Chiuve SE, Rimm EB. (2006) Alcohol consumption and risk for coronary heart disease in men with healthy lifestyles Arch Intern Med. 166(19): 2145-2150.

[148] Djoussé L, Lee IM, Buring JE, Gaziano JM. (2009) Alcohol consumption and risk of cardiovascular disease and death in women: potential mediating mechanisms. Circulation. 120(3): 237-244.

[149] Waśkiewicz A, Sygnowska E, Drygas W. (2004) Relationship between alcohol consumption and cardiovascular mortality--the Warsaw Pol-MONICA Project. Kardiol Pol. 60(6): 552-562; Bryson CL, Mukamal KJ, Mittleman MA, Fried LP, Hirsch CH, Kitzman DW, Siscovick DS. (2006) The association of alcohol consumption and incident heart failure: the Cardiovascular Health Study. J Am Coll Cardiol. 48(2):305-311; Mukamal KJ, Ding EL, Djoussé L. (2006) Alcohol consumption, physical activity, and chronic disease risk factors: a population-based cross-sectional survey. BMC Public Health. 6:118; Ford ES, Zhao G, Tsai K, Li C. (2011) Low-risk lifestyle behaviors and all-cause mortality: Findings from the National Health and Nutrition Examination Survey III Mortality Study. Am J Pub Health. 101: 1922-1929; Shuval K, Barlow CE, Chartier KG, Gabriel KP. (2012) Cardiorespiratory fitness, alcohol, and mortality in men: the Cooper Center longitudinal study. Am J Prev Med. 42(5): 460-467; Soedamah-Muthu SS, De Neve M, Shelton NJ, Tielemans SM, Stamatakis E. (2013) Joint associations of alcohol consumption and physical activity with all-cause and cardiovascular mortality. Am J Cardiol. 112(3): 380-386; Keyes KM, Calvo E, Ornstein KA. Rutherford C. Fox MP, Staudinger UM, Fried LP. (2019) Alcohol Consumption in Later Life and Mortality in the United States: Results from 9 Waves of the Health and Retirement Study. Alcoholism: Clin Exp Res. 43:1734-1746; Suliga E, Kozieł D, Ciesla E, Rebak D, Głuszek-Osuch M, Naszydłowska E, Głuszek S. (2019) The Consumption of Alcoholic Beverages and the Prevalence of Cardiovascular Diseases in Men and Women: A Cross-Sectional Study. Nutrients. 11(6):1318. doi: 10.3390/nu11061318. PMID: 31212846; PMCID: PMC6628509.

[150] Rimm EB, Moats C. (2007) Alcohol and coronary heart disease: Drinking patterns and mediators of effect. Annal Epidemiol. 15(7): S3-S7.

Evidence that alcohol is one of at least four or more healthy lifestyle factors comes from the US Centers for Disease Control and Prevention (CDC) that examined the relationship between four low-risk behaviours and mortality in 16,598 individuals over 18 years (Ford et al. 2011)[151]. The four low-risk lifestyle factors were not smoking, eating a healthy diet, physical activity and moderate alcohol consumption which was defined as >0-≤28 g/day for men and >0-≤14 g/day for women. The number of low-risk behaviours adopted was inversely related to the risk for mortality. Compared with individuals who had no low-risk behaviours, which included abstinence from alcohol as well as excessive alcohol consumption, those who had adopted all four experienced significantly reduced all-cause mortality, mortality from cancers, cardiovascular diseases (CVD), and other causes. Their calculations suggested that men and women were 63% less likely to die, 66% less likely to die from cancer, 65% less likely to die from CVD and 57% less likely to die from other causes. When moderate alcohol use was removed from the calculations, the mortality risk for those who also consumed alcohol was significantly lower than for those having only the three other lifestyle factors.

Previously moderate alcohol consumption, defined as 5-30 g/day, had been included as one of five low-risk behaviours associated with a reduced risk of coronary artery disease, irrespective of concurrent medication for high blood pressure or a high cholesterol concentration (Chiuve et al. 2006)[152].

An earlier Australian study examined 7,989 individuals aged 65-83 years for five years and showed consistent results with the CDC (Spencer et al. 2005)[153]. The eight low-risk behaviours included ≤20 g alcohol/day. Individuals adopting five or more of the selected low-risk behaviours had a lower risk of death from any cause within five years compared with those adopting less than five. More importantly, this study showed that while most individuals already have some healthy habits, almost all could make changes to their diet and lifestyle to improve their health. The study did not suggest abstinence from alcohol, and avoidance of heavier alcohol consumption was also inferred. A similar subsequent Australian study of 24,159 individuals aged over 65 years also showed that the almost daily regularity of such alcohol consumption conferred a lower risk of all-cause mortality over 10 years compared with abstainers or very occasional drinkers (McCaul et al. 2010)[154]. An examination of 2,805 individuals for 20 years in the Australian *Dubbo Study of the Elderly*, showed that in addition to lower all-cause mortality, the risk of CVD, cancers, type 2 diabetes and dementia, was

[151] Ford ES, Zhao G, Tsai K, Li C. (2011). Low-risk lifestyle behaviors and all-cause mortality: findings from the National Health and Nutrition Examination Survey III Mortality Study. Am J Pub Health. 101:1922–1929.
[152] Chiuve SE, McCullough ML, Sacks FM, Rimm EB. (2006). Healthy lifestyle factors in the primary prevention of coronary heart disease among men: benefits among users and nonusers of lipid-lowering and antihypertensive medications. Circulation. 114:160–167.
[153] Spencer CA, Jamrozik K, Norman PE, Lawrence-Brown M. (2005). A simple lifestyle score predicts survival in healthy elderly men. Prev Med. 40:712–717.
[154] McCaul KA, Almeida OP, Hankey GJ, Jamrozik K, Byles JE, Flicker L. (2010). Alcohol use and mortality in older men and women. Addiction. 105(8):1391-1400.

similarly decreased by any alcohol consumption. Any alcohol consumption decreased all-cause mortality by 18% for men and 23% for women (Simons et al. 2011)[155].

Larsson et al. (2017) also focussed on differences in the risk of mortality and in survival associated with four low-risk lifestyle factors in, namely non-smoking; physical activity at least 150 min/week; alcohol consumption of 0–14 drinks/week; and a healthy diet, with the latter defined as a modified Dietary Approaches to Stop Hypertension (DASH) Diet score above the median. At baseline, the 64,093 Swedish participants were aged 45 to 83 years and were free of cancer and CVD. Each of the four low-risk lifestyle factors was associated with an approximate 50% reduced risk of all-cause mortality and increased survival time, that is, longevity. Not smoking had the strongest effect on reducing death from all-causes, while having a healthy diet, exercising and moderate alcohol consumption all make additional contributions. Adoption of all four low-risk lifestyle factors conferred an additional 4.1 years for men and 4.9 years for women compared with individuals with no or one healthy lifestyle factor. Furthermore, the associations of the low-risk lifestyle factors with all-cause mortality and longevity were not modified by incidence of diabetes, high blood pressure or high cholesterol concentration. The implications of these observations are that even individuals who may be challenged by genetic or socioeconomic predispositions to earlier morbidity and mortality, by adopting certain healthy lifestyle habits can help them reach their greatest potential for a healthier and longer lifespan.

More recently, the US Nurses' Health Study and the Health Professionals Follow-up Study (Li et al.[156]) of 78,865 participants importantly demonstrated the joint effects of five now refined low-risk lifestyle factors on disease-specific and total mortality in very large cohorts of participants. Similar to Spencer et al. (2005) and Ford et al. (2011), the healthy lifestyle factors evaluated were never smoking, a body mass index of 18.5 to 24.9 kg/m2, ≥30 min/d of moderate to vigorous physical activity, moderate alcohol consumption and a high diet quality score (upper 40%). The similarity in education and other socio-economic factors of the participants in these studies tends to reduce potential confounding by such factors. There were more than 42,000 deaths in their cohorts during follow-up periods extending up to 34 years. The effects of these factors on subsequent risk of mortality were unexpected; for participants meeting criteria for all five factors versus none, there was an 84% reduction in all-cause mortality, 65% less cancer mortality, and 82% less CVD mortality. The overall effect was associated with 12 to 14 additional years of life after age 50 for participants meeting criteria for all five factors. This study strongly suggests that the leading causes of premature death throughout the developed world are, to a large extent, preventable.

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[155] Simons, L.A., et al., (2000) Moderate alcohol intake is associated with survival in the elderly: the Dubbo Study. Med J Aust. 173(3): 121-124. Simons, L.A., et al., (2006) Lifestyle factors and risk of dementia: Dubbo Study of the elderly. Med J Aust. 184(2): 68-70. Simons, L.A. (2014) Alcohol intake and survival in Australian seniors: the Dubbo study. Nutr Aging. 2(2-3): 85-90. Simons, L.A. et al. (2011) Predictors of long-term mortality in the elderly: the Dubbo Study. Intern Med J. 41(7): 555-560.

[156] Li Y, Pan A, Wang DD, Liu X, Dhana K, Franco OH, Kaptoge S, Di Angelantonio E, Stampfer M, Willett WC. Hu FB. (2018) Impact of Healthy Lifestyle Factors on Life Expectancies in the US Population. Circulation. 137:00–00. (Pre-publication). DOI: 10.1161/CIRCULATIONAHA.117.032047.

There are two recent meta-analysis of such studies, analysing 59 and 22 papers, respectively. The first paper was undertaken to evaluate the association between these modifiable low-risk lifestyle factors with CVD and mortality in both post-menopausal middle-aged and elderly women. Disease prevalence and physiological effects differ between women and men, and accordingly different lifestyle factors may affect the risk of CVD differently in women and men (Colpani et al. 2018[157]), where the risk of CVD following menopause increases to be similar to that of men (Maas and Appelman 2010[158]). The four low-risk lifestyle factors were defined as never smoking, body mass index <25 kg/m2, physical activity and moderate alcohol consumption between 8-14 g alcohol/day. Leisure time physical activity, walking and moderate alcohol consumption were the lifestyle risk factors most associated with a reduced risk of CVD, death from CVD and death from all-causes, where the more healthy or low-risk lifestyle factors a subject had, the greater the influence on CVD and all-cause mortality. These observations are also consistent with those observed in men and in a broader age range of women. The second paper focussed only on CVD incidence and found that adherence to these four low-risk lifestyle factors was associated with a reduced risk of 66% for CVD, 60% for stroke, and 69% for heart failure. More importantly, however, a dose-response effect was found for reduced risk and adherence to one, two, three or four factors simultaneously, suggesting that these factors are additive (Barbarsko et al. 2018[159]); which was also found in the earlier CDC study (Ford et al. 2011).

Furthermore, it has been shown that although older moderate alcohol consumers aged over 55 years may have better risk factor profiles than abstainers, including higher socioeconomic status and fewer functional limitations and psychosocial factors, which explain some of the survival advantage associated with alcohol consumption, moderate alcohol consumers still maintain their survival advantage even after adjustment for these factors (Lee et al. 2009[160], Holahan et al. 2010[161]). Moderate alcohol consumption was even associated with a lower risk of all-cause mortality in former problem drinkers (Holahan et al. 2010).

In addition to lower mortality, it has also been subsequently shown that women surviving to age 70 years and older who were moderate alcohol consumers, generally had less disability and disease, and more signs of 'successful ageing.' (Sun et al. 2011)[162]. For 'regular' moderate alcohol consumers (on 5-7 days/week), there was an approximately 50% greater chance of such successful ageing compared with non-drinkers.

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[157] Colpani V, Baena CP, Jaspers L, van Dijk GM, Farajzadegan Z, Dhana K, Tielemans MJ, Voortman T, Freak-Poli R, Veloso GGV, Chowdhury R, Kavousi M, Muka T. Franco OH. (2018) Lifestyle factors, cardiovascular disease and all-cause mortality in middle-aged and elderly women: a systematic review and metaanalysis. Eur J Epidemiol. pre-publication. https://doi.org/10.1007/s10654-018-0374-z

[158] Maas AH, Appelman YE. (2010) Gender differences in coronary heart disease. Neth Heart J. 18(12):598-602. doi: 10.1007/s12471-010-0841-y. PMID: 21301622; PMCID: PMC3018605.

[159] Barbaresko J, Rienks J, Nöthlings U. (2018) Lifestyle indices and cardiovascular disease. Risk: a meta-analysis. Am J Prevent Med. 55(4):555-564.

[160] Lee SJ, Sudore RL, Williams BA, Lindquist K, Chen HL Covinsky KE. (2009) Functional limitations, socioeconomic status, and all-cause mortality in moderate alcohol drinkers. J Am Geriatr Soc. 57:955–962.

[161] Holahan CJ, Schutte KK, Brennan PL, Holahan CK, Moos BS, Moos RH. (2010). Late-life alcohol consumption and 20-year mortality. Alcohol Clin Exp Res. 34:1961–1971.

[162] Sun Q, Townsend MK, Okereke OI. et al. (2011). Alcohol consumption at midlife and successful ageing in women: a prospective cohort analysis in the Nurses' Health Study. PLoS Med 8:e1001090.

Alcohol consumption in later life has reportedly increased in Australia and internationally. These observations in older adults are thus of clinical importance given that compared with younger people, older individuals have a decreased ability to metabolize alcohol and an altered volume of distribution (due to reduced lean body mass and total body water), which contributes to a relative increase in blood levels for a fixed amount of alcohol consumed compared with younger adults. Indeed, even after adjustment for confounders, current abstainers drinking after age 56 years (and now aged 79-89 years) in the US *Health and Retirement Study* had the highest risk of subsequent mortality, consistent with sick quitters, and moderate alcohol consumption was associated with a lower mortality rate compared with occasional drinking, though smokers and men evidenced less of an inverse association. Moderate consumption for men was reporting 1-3 drinks/day without binge drinking and for women reporting 1-2 drinks/day without binge drinking. Quantitative bias analyses further indicated that omitted confounders would need to be associated with approximate four-fold increases in mortality rates for men and approximate nine-fold increases for women to change the results (Keyes et al. 2019[163]). A strength of this study was that there were multiple, bi-annual assessments of alcohol consumption over 16 years (data on frequency and quantity, and whether there was binge drinking) and other time-variable factors for 7,904 participants, so that changes in consumption could be evaluated.

In addition, the US *Health and Retirement Study* has previously reported that moderate alcohol consumption independently confers reduced frailty risk for both older men and women (Shah et al. 2018[164]), predicts fewer depressive symptoms among older adults (Paulson et al. 2018[165]) where social interaction is essential to the seemingly beneficial effect of moderate alcohol consumption on depressive symptomatology and functional ability (Scott et al. 2018[166]). Quality of life is relatively little considered factor in epidemiological studies of successful ageing and alcohol consumption, yet we know from the US Rancho Bernardo Study of Healthy Ageing and indeed from the Australian *Dubbo Study of the Elderly*, that a higher quality of life is associated with higher cognitive, mental and physical health and generally, longevity (Simons et al. 2006, Simons et al. 2014, Richards et al. 2017[167]).

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[163] Keyes KM, Calvo E, Ornstein KA. Rutherford C. Fox MP, Staudinger UM, Fried LP. (2019) Alcohol Consumption in Later Life and Mortality in the United States: Results from 9 Waves of the Health and Retirement Study. Alcoholism: Clin Exp Res. 43:1734-1746.

[164] Shah M, Paulson D, Nguyen V. (2018) Alcohol Use and Frailty Risk among Older Adults over 12 Years: The Health and Retirement Study. Clin Gerontol. 41:315-325.

[165] Paulson D, Shah M, Herring D, et al. (2018) The relationship between moderate alcohol consumption, depressive symptomatology, and C-reactive protein: the Health and Retirement Study. Int J Geriatr Psychiatry. 33:316-324.

[166] Scott RG, Wiener CH, Paulson D. (2018) The Benefit of Moderate Alcohol Use on Mood and Functional Ability in Later Life: Due to Beers or Frequent Cheers? Gerontologist. doi: 10.1093/geront/gny129.

[167] Simons LA, Simons J, McCallum J, Friedlander Y. (2006) Lifestyle factors and risk of dementia: Dubbo Study of the elderly. Med J Aust. 184 (2): 68-70. || doi: 10.5694/j.1326-5377.2006.tb00120.x; Simons, L.A. (2014) Alcohol intake and survival in Australian seniors: The Dubbo Study. Nutr Aging. 2(2-3):85-90; Richard EL, Kritz-Silverstein D, Laughlin GA, Fung TT, Barrett-Connor E, McEvoy LK. (2017) Alcohol Intake and Cognitively Healthy Longevity in Community-Dwelling Adults: The Rancho Bernardo Study. J Alzheimers Dis. 59(3):803-814.

10. If such protective effects are over estimated, this could lead to the recommended alcohol consumption limits in the guidelines being too high.

Evidence favouring a causal cardioprotective effect of moderate alcohol consumption include proper time sequence, consistency in diverse healthy or unhealthy populations, plausible biological mechanisms, relative specificity for atherothrombotic conditions, controlled trial data for surrogate end points, and weakness of data supporting alternative explanations[168]. The risks of moderate alcohol consumption, however, differ by sex, age, personal history, and family history. Advice by medical practitioners about diet and lifestyle should be balanced and based on sound science.

From biological mechanistic studies, the optimal or most cardioprotective amount of alcohol is up to 20 g alcohol/day for women and up to 30 g alcohol/day for men, which is consistent with that determined in meta-analyses by Rimm et al. (1999)[169] and supported by Brien et al. (2011)[170]. These calculations suggest that alcohol reduces the risk of cardiovascular disease (CVD) by reverse cholesterol transport, haemostasis and insulin sensitivity mechanisms. In a clinical context, the alcohol-induced changes in high density lipoprotein cholesterol (HDL), fibrinogen and adiponectin are pharmacologically relevant and comparable if not greater than that induced by traditional US Food and Drug Administration-approved drug therapy (Brien et al. 2011). These cardioprotective amounts are consistent with the current Australian drinking guidelines to reduce risks from drinking alcohol and with the majority of international recommended drinking guidelines for the general population[171].

In addition, blood alcohol concentration (BAC) is measured in mg of alcohol per 100 mL of blood. An individual's BAC will generally increase by 10 mg of alcohol per 100 mL of blood (for men) or 0.01 g%, and 30 mg of alcohol per 100 mL of blood (for women) or 0.03 g% for each 10 g standard drink of alcohol , although there can be up to four-fold intra-individual as well as inter-individual variation in the rate of absorption. Consequently, the current guideline #1 of a maximum of two 10 g standard drinks per day for both men and women ensures that the

[168] Corrao G, Bagnardi V, Zambon A, La Vecchia C. (2004) A meta-analysis ofalcohol consumption and the risk of 15 diseases. Prev Med. 38:613–9.4; Klatsky AL. (2009) Alcohol and cardiovascular diseases. Expert Rev Cardio-Vasc Ther. 7:499–506.5; Zakhari S. (1999) Molecular mechanisms underlying alcohol-induced cardio-protection: contribution of hemostatic components. Alcohol Clin Exp Res.23:1108–10.6; Booyse FM, Parks DA. (2001) Moderate wine and alcohol consumption: beneficial effects on cardiovascular disease. Thromb Haemost. 86:517–528.

[169] Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. (1999) Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. Br Med J. 319(7224): 1523-1528.

[170] Brien SE, Ronksley PE, Turner BJ, Mukamal KJ, Ghali WA. (2011) Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. Br Med J. 342:d636; doi:101136/bmjd636.

[171] International Alliance for Responsible Drinking (IARD). (2019). Drinking guidelines: General population. Retrieved from https://iard.org/science-resources/detail/Drinking-Guidelines-General-Population

BAC is kept approximately between 0.02 and 0.06 g%, which is generally not associated with injury to body organs and tissues (Dasgupta 2017)[172], or where a person cannot function within their normal range of cognitive and physical abilities (National Health and Medical Research Council 2001)[173].

[172] Dasgupta, A. (2017) Alcohol a double edged sword. In: Alcohol, drugs, genes and clinical laboratory. Contemporary Security Management (Fourth Edition); p 1-21.

[173]National Health and Medical Research Council (2001) Australian alcohol guidelines: health risks and health benefits. Commonwealth of Australia; p 126.

Appendix B: Biological mechanisms of alcohol-related health benefits

The biological mechanisms of alcohol-related benefits from light to moderate alcohol consumption are well documented and have been determined from multiple test tube, animal and human studies undertaken over the past 40 years. They principally relate to protection from cardiovascular (coronary and vascular) diseases and their primary risk factor, atherosclerosis, which result from an interaction of lipids, haemostasis, inflammatory, endothelial factors and hormonal factors. A systematic review and meta-analysis of interventional studies on the effects of alcohol consumption on 21 biological markers associated with risk of coronary heart disease showed (Brien et al. 2011[174]), and supported other observational analyses and meta-analyses (Rimm et al. 1999, Djousse et al. 2009, Vu et al. 2016, Huang et al. 2017[175]), that light to moderate amounts of alcohol improve the lipid profile by increasing high density lipoprotein (HDL) cholesterol and its constituents. HDL is involved in inhibiting oxidation, inflammation, activation of the endothelium, coagulation, and platelet aggregation all of which are associated with atherosclerosis leading to coronary heart disease and peripheral artery disease. Alcohol also has two inter-related anti-blood clotting mechanisms involved in decreasing coagulation and increasing fibrinolysis, reduces the production and concentration of inflammatory biomarkers associated with local inflammation associated with atherosclerosis, and increases hormone levels such as adiponectin and insulin associated with atherosclerosis (Stockley 2015[176]).

[174] Brien SE, Ronksley PE, Turner BJ, Mukamal KJ, Ghali WA. Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studie.s Br Med J. 2011; 342:d636; doi:101136/bmjd636.

[175] Rimm, EB, Williams, P, Fosher, K, Criqui, M, Stampfer, MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. Br Med J. 1999: 319(7224): 1523-8; Djoussé L, Himali JJ, Beiser A, Kelly-Hayes M, Wolf PA. Apolipoprotein e, alcohol consumption, and risk of ischemic stroke: the Framingham Heart Study revisited. J Stroke Cerebrovasc Dis. 2009; 18(5): 384-8; Vu KN, Ballantyne CM, Hoogeveen RC, Nambi V, Volcik KA, Boerwinkle E, Morrison AC. Causal Role of Alcohol Consumption in an Improved Lipid Profile: The Atherosclerosis Risk in Communities (ARIC) Study. PLoS One. 2016 Feb 5;11(2):e0148765Huang Y, Li Y, Zheng S, Yang X, Wang T, Zeng J. Moderate alcohol consumption and atherosclerosis : Meta-analysis of effects on lipids and inflammation. Wien Klin Wochenschr. 2017 Nov;129(21-22):835-843.

[176] Stockley, C.S. The relationship between alcohol, wine and cardiovascular diseases - a review. Nutrition and Aging 3: 55–88; 2015.

Table. Summary of proposed effects of the alcohol component of all alcoholic beverages on biomarkers associated with CVD (Stockley 2015[177]).

	Specific effect	Proposed actions	Evidence*
Improves blood lipid profile (plasma concentration of "good" HDL to "bad" LDL) associated with atherosclerosis	Increases HDL cholesterol	Removes LDL cholesterol from blood vessel wall Prevents LDL oxidation and adhering to blood vessels walls to form atherosclerotic plaques	Very good evidence Potentially accounts for 60% of alcohol's effects
Decreases blood clotting (thrombosis) and improves blood flow	Decreases fibrinogen (blood clotter protein)	Reduces blood clotting by preventing stabilization of a forming blood clot	Very good evidence Potentially accounts for 20-30% of alcohol's effects
	Decreases platelet activation	Reduces blood clotting by preventing initial aggregation and adhesion of platelets to form a blood clot	Good evidence
	Decreases activity of haemostatic factors VII and VIII	Reduces blood clotting	Fair evidence
	Increases tissue type plasminogen activator (t-PA)	Increases fibrinolysis (dissolving of blood clots)	Fair evidence
	Increases urokinase type plasminogen activator (u-PA)	Increases fibrinolysis (dissolving of blood clots)	Fair evidence
	Decreases plasminogen activator inhibitor-1 (PAI-1)	Increases fibrinolysis (dissolving of blood clots)	Fair evidence
Decreases local inflammation associated with atherosclerosis	Decreases C-reactive protein	Decreases atherosclerosis	Good evidence
	Decreases pro-inflammatory cytokines	Decreases atherosclerosis	Fair evidence
	Decreases soluble inflammatory mediators and adhesion molecules	Decreases atherosclerosis	Fair evidence
Increases hormone levels associated with atherosclerosis	Increases concentration of adiponectin	Decreases atherosclerosis by inhibiting the adherence of monocytes and suppressing the accumulation of modified LDL in blood vessel walls. Also decreases endothelial damage and Increases NO.	Accumulating evidence
	Reduces concentration of insulin (and insulin resistance)	Decreases atherosclerosis by decreasing effects on blood vessel walls, e.g. decreases stimulation of smooth muscle cell proliferation and of glucose incorporation into lipids.	Accumulating evidence
	Increases concentration of estrogen	Decreases atherosclerosis by effects on hepatic cholesterol metabolism to decrease plasma LDL concentrations	Fair evidence

[177] Stockley, C.S. The relationship between alcohol, wine and cardiovascular diseases - a review. Nutrition and Aging 3: 55–88; 2015.