Gastroenterology

How safe is Moderate Alcohol Consumption in Overweight and Obese Individuals?

--Manuscript Draft--

Manuscript Number:	GASTRO-D-15-01896R2
Full Title:	How safe is Moderate Alcohol Consumption in Overweight and Obese Individuals?
Article Type:	Invited 2016 14th Issue: Fatty Liver Disease
Keywords:	Alcoholic liver disease; body mass index; moderate alcohol consumption; Nonalcoholic fatty liver disease; nonalcoholic steatohepatitis; mendelian randomization
Corresponding Author:	Silvia C Sookoian, MD, PhD Instituto de Investigaciones Medicas.A. Lanari. CONICET. Ciudad Autonoma de Buenos Aires, Buenos Aires ARGENTINA
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Instituto de Investigaciones Medicas.A. Lanari. CONICET.
Corresponding Author's Secondary Institution:	
First Author:	Silvia C Sookoian, MD, PhD
First Author Secondary Information:	
Order of Authors:	Silvia C Sookoian, MD, PhD
	Carlos Jose Pirola
Order of Authors Secondary Information:	
Abstract:	NA

How safe is Moderate Alcohol Consumption in Overweight and Obese Individuals?

Silvia Sookoian[1] MD, PhD and Carlos J Pirola[2] PhD, FAHA

[1]Department of Clinical and Molecular Hepatology, Institute of Medical Research A Lanari-IDIM, University of Buenos Aires- National Scientific and Technical Research Council (CONICET), Ciudad Autónoma de Buenos Aires, Argentina

[2]Department of Molecular Genetics and Biology of Complex Diseases, Institute of Medical Research A Lanari-IDIM, University of Buenos Aires-National Scientific and Technical Research Council (CONICET), Ciudad Autónoma de Buenos Aires, Argentina

Grant Support:

This study was partially supported by grants PICT 2010-0441 and PICT 2012-0159 (Agencia Nacional de Promoción Científica y Tecnológica).

Abbreviations:

ADH, alcohol dehydrogenase

ALD, alcoholic liver disease

BMI, body mass index

CI, confidence interval

CVD, cardiovascular disease

HCC, hepatocellular carcinoma

MAC, moderate alcohol consumption

MetS, metabolic syndrome

MR, mendelian randomization

NAFLD, nonalcoholic fatty liver disease

NASH, nonalcoholic steatohepatitis

OR, odds ratio

T2D, type 2 diabetes

Correspondence:

Silvia Sookoian, M.D, PhD and Carlos J. Pirola, PhD

Instituto de Investigaciones Médicas, IDIM-CONICET

Combatientes de Malvinas 3150, CABA-1427, Argentina

E-mail: sookoian.silvia@lanari.fmed.uba.ar and pirola.carlos@lanari.fmed.uba.ar

Phone: 54-11-4514 8701 ext. 167/Fax: 54-11-4523 8947

Disclosures

The authors have no conflict of interest to declare.

Author Contributions:

SS and CJP: study concept and design; data acquisition; data analysis and interpretation; drafting of the manuscript; securing funding.

The prevalence of nonalcoholic fatty liver disease (NAFLD) has reached global epidemic proportions [1], paralleling that of the increasing trends in the prevalence of obesity and type 2 diabetes (T2D). In fact, obesity is one of the most frequently associated comorbidities of NAFLD [2], and furthermore, NAFLD and obesity integrate the myriad of risk factors for cardiovascular disease (CVD) clustered in the metabolic syndrome (MetS).

By definition, NAFLD is characterized by abnormal liver fat accumulation in the absence of significant alcohol consumption and other causes of secondary hepatic steatosis. Once diagnosed, the treatment of NAFLD is complex and often requires pharmacological intervention to control associated-risk factors, and or/ lifestyle modifications.

Conflicting results on whether social or moderate alcohol consumption (MAC) is detrimental or beneficial leave physicians uncertain as to whether or not to apply tight restrictions or allow low levels of social alcohol use for potential health benefit.

The first clinical dilemma: The complex balance between epidemiological evidence and clinical decision-making

Over the last decade, there has been a growing body of evidence supporting the notion that MAC (up to ~ 30 g per day) reduces the risk of MetS-related phenotypes, including T2D [3], arterial hypertension [4], CVD [5], systemic inflammation and prothrombotic state [6], and all-cause mortality rates [7].

The Third National Health and Nutrition Examination Survey showed that the odds of obesity are lower among subjects who consume less than five drinks per week compared with non-drinkers [8].

Summarized quantitative evidence from nine cross-sectional studies on NAFLD suggests possible favorable effects of MAC on liver fat accumulation by reducing the risk of having

NAFLD (OR [odds ratio] 0.68, 95% confidence interval [CI]: 0.580–0.80, $p<10^{-5}$) by about ~31% in a pooled sample of 43,175 individuals, including 30,791 non-drinkers and 12,384 modest drinkers [9]. The beneficial effect of MAC on NAFLD seems to be very much influenced by sex, suggesting that sexual dimorphism plays a significant role [9]. Furthermore, MAC showed a protective effect of about ~ 50% on the risk of developing nonalcoholic steatohepatitis-(NASH) (OR 0.50, 95% CI: 0.34–0.74, p<0.0005) – data from 822 patients diagnosed by liver biopsy (550 non-drinkers and 272 modest drinkers) [9]. As well, a longitudinal study from Japan that included 5437 individuals evaluated for over ~10 years showed that the adjusted hazard risk of MAC for the development of NAFLD was 0.69 (95% CI 0.57-0.84) when compared to non-drinkers [10].

Together, all the above-mentioned epidemiological associations are interpreted as following a J-shaped curve (**Figure 1**), of which the valley is defined -in the great majority of the studies- as 20 or 30 g daily for women or man, respectively. The nadir of the curve at 20-30 g per day is equivalent to "two drinks" per day in some other reports, in which a "drink" represents a standard unit of alcohol measurement.

The potential benefits and harm associated with MAC or heavy alcohol consumption, respectively, have a direct impact on liver-related outcomes, MetS and CV- health; however, the point at which the amount of alcohol ceases to be beneficial to become harmful remains unclear. For example, the definition of MAC based on the number of "drinks" as standard units of alcohol measurement could introduce uncertainties in what threshold should clinicians use to distinguish between protection and harm because the definition of "standard drink" differs among countries (~14 g of alcohol in the United States, ~8 g in England or 19.75 g in Japan).

Moreover, many questions regarding the putative protective effect of MAC on patients with underlying liver disease remain unanswered (**Figure 1**). For instance, a retrospective cohort-study showed that subjects consuming either moderate or heavy amounts of alcohol while having severe liver fibrosis have an increased risk of developing hepatocellular carcinoma (HCC) [11]. Then, a question is raised as to where should the line be drawn between the "benefit" and the "harm", specifically for patients with chronic liver disease and liver fibrosis, including NAFLD.

The second clinical dilemma: Protective associations with MAC are questioned because of problems with confounding and causation

The beneficial effects of MAC on overall health-related outcomes have raised much criticism. First, data on "alcohol assessment" and "drinking patterns" could be of limited quality, particularly in population-based studies. Second, the main outcomes may not have been properly adjusted by confounding factors, and third, most of the studies are based on an observational design that is unable to determine causality.

A clear example that supports both the first and second criticism is illustrated by the results of the Health Survey for England, a population-based study that includes up to ~10 waves. This study that links health-related behavior to mortality showed that the protective effects of MAC on overall mortality-rates are attenuated after excluding "former-drinkers" from the abstainer group [12]. A thorough age-stratified analysis that used self reported "never-drinkers" as the reference group suggested that the beneficial dose-response association between MAC and mortality was restricted to women aged 65 years or more [12]. Likewise, a meta-analysis that explored the association between MAC and T2D, including 1,902,605 controls and 125,926 cases, revealed that reductions in the risk of T2D associated with MAC may be specific to

women, and stratification of data including the "never-drinking" category abolished the protective effects [3].

Indeed, it is speculated that the systematic misclassification of "past-drinkers" and "occasional-drinkers" to the "abstainer" or "non-drinkers" categories provides an explanation for the supposedly beneficial effect of MAC on health-related outcomes. Conversely, the self-report of alcohol consumption may be biased from heavy-drinkers that could recognize themselves as moderate-drinkers.

The third and strongest criticism concerns the cross-sectional nature of the majority of published evidence. The ideal study should be able to assess the "cumulative lifetime-effect/s of MAC", which can only be explored in prospective-cohorts studies.

To add concern to disbelief, the results of a prospective study that included 88,084 women and 47,881 men from the Nurses' Health Study and Health Professionals Follow-up Study in the US concluded that compared to non-drinkers, MAC is associated with a minimal though not significant "increased-risk" of total cancer OR (1.02, 95% CI 0.98 -1.06 and 1.05, 95% CI 0.97-1.12 in women and men, respectively); however, this risk is particularly important in women in whom cancers increase even within the range of up to "one drink a day" [13].

Finally, another skeptical quote on the apparent beneficial effects of MAC is given by the fact that the evidence is not supported by randomized studies. Nevertheless, it could be virtually impossible and ethically questionable to operate on the randomization of a variable such as "alcohol consumption". An exception of this can be found in a recent small randomized trial on the effect of red wine on blood pressure [14].

The "omics" era and mendelian randomization (MR)-studies to overcome limitations of epidemiological studies: Is MAC liver-protective or liver-harmful? Does the dose make the poison?

NAFLD and obesity are complex diseases whose pathogenesis is under the influence of the effect of multiple gene variants. Interestingly, NAFLD and alcoholic liver disease (ALD) share not only common pathogenic mechanisms [15] but predisposing genetic risk. The most remarkable example of a "common genetic-modifier" on the risk of liver fat accumulation and disease severity in NAFLD and ALD is given by the missense rs738409 variant located in *PNPLA3* locus [16, 17].

Nevertheless, the effect/s of alcohol consumption have been largely attributed to a genetic variation in enzymes that mediates its metabolism in the liver, particularly in genes that codify members of the alcohol dehydrogenase (ADH) family and cytochrome P450 (CYP) superfamily. Variants in the ADH-family influence the conversion of alcohol to acetaldehyde, and also the individual ethanol-oxidizing capacity; these variants may also indirectly influence the "drinking pattern", as binge-drinking seems to be absent in carriers of the low alcohol-metabolizing variants due to the unpleasant effects of alcohol.

The implementation of MR studies would –theoretically- overcome the challenges of designing randomized control trials because these genetic explorations show an association between a variant and a disease (or disease risk) under the assumption that genetic allocation is not only "random" and "free of confounding factors", but also that genotypes are not modified by the disease. Recent studies have focused on this premise by selecting variants located in *ADH1B* (Alcohol Dehydrogenase 1B) or *ALDH2* (Aldehyde Dehydrogenase 2) not only because of its participation in alcohol metabolism but also their influence on alcohol use, dependence, and

"alcohol-related flushing symptoms". Emerging results based on this strategy added a "pinch of skepticism" on the benefits of MAC, however they are still not entirely clear. **Indeed, recent MR trials have not only failed to demonstrate a benefit of alcohol on cardiometabolic risk factors but that it may be harmful.** For instance, results from a large MR meta-analysis of 56 studies, including 261, 991 individuals of European descent, suggested that subjects with a "genetic predisposition" to consume less alcohol (carriers of the *ADH1B* -rs1229984-A allele) have lower odds of developing CVD regardless of whether they were light, moderate, or heavy drinkers [18]. Surprisingly, the authors concluded that the reduction of alcohol consumption, even for moderate drinkers, may be beneficial to CV health [18].

This conclusion challenged the J-shaped curve theory as the authors observed that individuals below the nadir with a genetic predisposition to consume less alcohol (carries of the A allele consumed 17.2% fewer units of alcohol per week) had lower odds of developing CVD at all categories of alcohol consumption [18]. Recent MR studies from Asia have replicated the finding that MAC is not beneficial for heart function [19] or CV risk factors, such as blood lipid levels [20] but could be detrimental; of note, these studies reported also sexual differences in the effects of MAC on CV health.

What could be the potential reasons why these studies are discrepant from other studies that show the J-shaped benefit? One potential explanation could be that variants in ADH-family explain a small fraction of the variance in reported alcohol intake [21]. In fact, in the study of Holmes et al. the average carriage of rs1229984 A-alleles was 7% [18]. Thus, other factors, including additional locus and even environmental factors might explain the effects of alcohol on CV health.

Some other issues conspire against the notion that MR will provide a definitive answer. For example, MR studies are conducted under the assumption that rs1229984 is a good surrogate or "genetic proxy" of the "amount of alcohol" consumption. However, it is dubious that categorization by genotypes, which is limited to 3 categories, reflects the portion of disease variability associated with the range of absent to low / moderate amount of alcohol ingestion. Carrying a gene variant associated with an "unpleasant" effect of alcohol does not entirely discriminate between "non-drinkers" versus "modest-drinkers", neither indicates the optimum alcohol amount because even if a subject carries the "protective-allele" against alcohol consumption, they still might drink light amounts of alcohol without necessarily experiencing flushing symptoms.

Whether this strategy would overcome the doubts surrounding the potential benefits of MAC on liver fat accumulation or obesity is still unknown.

In summary, although we know that alcohol dose makes the poison, we don't know what the optimum point (dose) is. Thus, the potentially confounding selection bias would remain unsolved. Furthermore, the putative link has to be established between variants in *ADH1B* and *ADH1C* and endogenous alcohol production by the microbiome, which seems to be an important risk factor for NASH development [22].

How safe is MAC in overweight and obese individuals with NAFLD?

The complexity of the problem is even more difficult to uncover in clinical scenarios in which two or more diseases interact with each other; this is the case of obese individuals with NAFLD. Results from recent studies suggest that the protection of MAC against developing NAFLD is abolished in subjects that are overweight or obese, while alcohol -regardless of the amount- is associated with a dose-related effect on liver fat accumulation. For instance, data from a

population-based study from Germany showed that the risk of NAFLD increases with both increasing levels of average daily alcohol consumption and increasing body mass index (BMI) [23]. Interestingly, in non-obese males, the consumption of up to ~20 g per day of alcohol was associated with an OR of NAFLD of 5.04 (95 % CI 1.16-21.8), while the same amount of alcohol in overweight subjects was associated with an OR of 14.8 (95 % CI 3.5-64.2) and in obese subjects with an OR of 35.2 (95 % CI 8.3-149) [23]. Nevertheless, the combined dose-response effect of alcohol intake and BMI on NAFLD observed in males was not replicated in females [23]. By contrast, a study from Japan including 8029 subjects concluded that MAC was a significant negative risk factor for NAFLD, even in obese individuals, regardless of the sex (OR, 0.74 for non-obese and 0.39 for obese patients, respectively) [24].

We performed a meta-regression analysis of pooled estimates (n = 42,059 participants from six combined studies) [9, 24] between the log-transformed ORs of having NAFLD in modest-drinkers vs. non-drinkers, and the difference of BMI between the two groups. Interestingly, we observed a significant correlation (slope ± SE: 0.28±0.06, $p = 1 \times 10^{-6}$) between the pattern of alcohol drinking, BMI and NAFLD, suggesting that the protective effect of MAC on the risk of NAFLD might be explained in part by a reduction in the BMI (**Figure 2**). In fact, in these studies, BMI was lower in moderate drinkers compared to abstainers (random effect, standardized difference ± SE:-0.55±0.17, p<0.002). A note of caution should be added, because the analysis included cross-sectional studies, which -as already mentioned- allow inferring associations yet do not demonstrate causality.

Finally, the putative protection of MAC against NAFLD in obese individuals could be justifiably questioned because of the lack of studies exploring the long-term cumulative effect of MAC on liver fibrosis and cancer development. Alcohol use and obesity showed a synergistic association

with the risk of incident HCC in a large study from Taiwan (n= 89,293); among alcohol drinkers, the cumulative risk of HCC in non-obese subjects was 2.7% vs. 8.7% in obese participants [25].

The future research agenda is open: More questions than answers

The effect of MAC on NAFLD, and its association with obesity or overweightness are not only complex and multifaceted, but also difficult to measure. To strengthen the evidence and translate the results into clinical-decision making, we need answer various questions that would probably delineate a future patient-oriented research agenda. For example, the definition of MAC is arbitrary; so, we need to know exactly how much is safe, and how much is not in patients with NASH and fibrosis; further necessary definitions include the potential effect of drinking patterns and alcohol types, and whether the window between maximum protection and harm is the same in men and women.

On the other hand, the potential "cumulative-effect" of MAC on the modulation of factors involved in the pathogenesis of NAFLD should be carefully addressed; these include the inflammasome, gut microbiota and intestinal permeability, and obesity-related carcinogenesis.

An additional challenge concerns the putative synergic effect of MAC and "endogenous ethanol-synthesis in the gastrointestinal tract", which could ameliorate the "benefits" in specific clinical scenarios, such as obese patients with NASH and fibrosis [26].

In summary, the future research agenda still remains open, looking for answers from cohort prospective studies elucidating the exact role of MAC on the disease progression of obese patients with NAFLD. In addition, further mechanistic studies are required to bring robust biological evidence on the long-term effects of MAC on the natural history of NAFLD and MetS.

Concluding remarks

The management of patients with NAFLD is a challenge. Whether the evidence and previous knowledge on the putative beneficial effects of MAC are robust enough to provide patients with advice is still unknown. In addition, the question “To drink or not to drink” in patients with liver fibrosis, including obese patients with NAFLD, cannot be answered until obtaining the highest level of evidence, which will be hopefully endowed by large, prospective and randomized –if possible- clinical trials.

In the meanwhile, individual clinical judgment should be used to provide patients a medical advice. In the author's opinion that does not necessarily reflect the wide range of practice amongst physicians around the world, obese patients with NASH and advanced fibrosis should be regarded as a “high-risk" population for progressing to end-stage liver disease; hence, alcohol drinking should be avoided.

FIGURE LEGENDS:

FIGURE 1

Graphical summary of the current epidemiological evidence regarding the effects of moderate alcohol consumption (MAC) on liver disease, obesity and cardiovascular health

The graph summarizes the effect of MAC as following a J-shaped curve that relates the amount of alcohol intake to the risk of suffering from liver, cardiovascular or gastrointestinal disease, and cancer as an optimum point at which "moderate-drinking" is associated with the lowest risk and "heavy-drinking" is associated with the higher.

At the bottom, the picture highlights what remains to be clarified and what appears promising to delineate a future patient-oriented research agenda.

FIGURE 2

Meta-regression analysis of pooled estimates between the log-transformed odds ratio of having NAFLD in modest-drinkers vs. non-drinkers, and the difference of BMI between the two groups

Data on NAFLD and BMI according to alcohol consumption was extracted from a total of six studies (five studies that were previously included in a meta-analysis [9] and an updated- reference [24] that displayed extractable data). Each circle represents a study; all studies included adult (age ranging from 20 to 75 years) male and female subjects. Studies that disclosed data on male and female for each category of alcohol drinking (modest-drinkers vs. non-drinkers) were plotted in separate circles, one for each sex; characteristics of the studies are described in greater detail in the **Supplementary Material**.

REFERENCES

1. Satapathy SK, Sanyal AJ. Epidemiology and Natural History of Nonalcoholic Fatty Liver Disease. Semin Liver Dis 2015;35:221-235.

2. Loomba R, Sanyal AJ. The global NAFLD epidemic. Nat Rev Gastroenterol Hepatol 2013;10:686-690.

3. Knott C, Bell S, Britton A. Alcohol Consumption and the Risk of Type 2 Diabetes: A Systematic Review and Dose-Response Meta-analysis of More Than 1.9 Million Individuals From 38 Observational Studies. Diabetes Care 2015;38:1804-1812.

4. Briasoulis A, Agarwal V, Messerli FH. Alcohol consumption and the risk of hypertension in men and women: a systematic review and meta-analysis. J Clin Hypertens (Greenwich) 2012;14:792-798.

5. Di CA, Rotondo S, Iacoviello L, et al. Meta-analysis of wine and beer consumption in relation to vascular risk. Circulation 2002;105:2836-2844.

6. Wannamethee SG, Lowe GD, Shaper G, , et al. The effects of different alcoholic drinks on lipids, insulin and haemostatic and inflammatory markers in older men. Thromb Haemost 2003;90:1080-1087.

7. Gronbaek M, Johansen D, Becker U, et al. Changes in alcohol intake and mortality: a longitudinal population-based study. Epidemiology 2004;15:222-228.

8. Arif AA, Rohrer JE. Patterns of alcohol drinking and its association with obesity: data from the Third National Health and Nutrition Examination Survey, 1988-1994. BMC Public Health 2005;5:126.

9. Sookoian S, Castano GO, Pirola CJ. Modest alcohol consumption decreases the risk of non-alcoholic fatty liver disease: a meta-analysis of 43 175 individuals. Gut 2014;63:530-532.

10. Hashimoto Y, Hamaguchi M, Kojima T, et al. The modest alcohol consumption reduces the incidence of fatty liver in men: a population-based large-scale cohort study. J Gastroenterol Hepatol 2015;30:546-552.

11. **Suh B, Yun JM**, Park S, et al. Prediction of future hepatocellular carcinoma incidence in moderate to heavy alcohol drinkers with the FIB-4 liver fibrosis index. Cancer 2015; 121:3818-3825.

12. Knott CS, Coombs N, Stamatakis E, et al. All cause mortality and the case for age specific alcohol consumption guidelines: pooled analyses of up to 10 population based cohorts. BMJ 2015;350:h384.

13. Cao Y, Willett WC, Rimm EB, et al. Light to moderate intake of alcohol, drinking patterns, and risk of cancer: results from two prospective US cohort studies. BMJ 2015;351:h4238.

14. Mori TA, Burke V, Beilin LJ, et al. Randomized Controlled Intervention of the Effects of Alcohol on Blood Pressure in Premenopausal Women. Hypertension 2015; 66:517-523.

15. Sookoian S, Pirola CJ. Systems biology elucidates common pathogenic mechanisms between nonalcoholic and alcoholic-fatty liver disease. PLoS One 2013;8:e58895.

16. Chamorro AJ, Torres JL, Miron-Canelo JA, et al. Systematic review with meta-analysis: the I148M variant of patatin-like phospholipase domain-containing 3 gene (PNPLA3) is significantly associated with alcoholic liver cirrhosis. Aliment Pharmacol Ther 2014;40:571-581.

17. Sookoian S, Pirola CJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. Hepatology 2011;53:1883-1894.

18. **Holmes MV, Dale CE**, Zuccolo L, et al. BMJ 2014;349:g4164.

19. Au Yeung SL, Jiang C, Long M, et al. Evaluation of Moderate Alcohol Use With QT Interval and Heart Rate Using Mendelian Randomization Analysis Among Older Southern Chinese Men in the Guangzhou Biobank Cohort Study. Am J Epidemiol 2015;182:320-327.

20. **Taylor AE, Lu F**, Carslake D, et al. Exploring causal associations of alcohol with cardiovascular and metabolic risk factors in a Chinese population using Mendelian randomization analysis. Sci Rep 2015;5:14005.

21. Au Yeung SL, Jiang CQ, Cheng KK, et al. Evaluation of moderate alcohol use and cognitive function among men using a Mendelian randomization design in the Guangzhou biobank cohort study. Am J Epidemiol 2012;175:1021-1028.

22. Zhu L, Baker SS, Gill C, et al. Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. Hepatology 2013;57:601-609.

23. **Lau K, Baumeister SE**, Lieb W, et al. The combined effects of alcohol consumption and body mass index on hepatic steatosis in a general population sample of European men and women. Aliment Pharmacol Ther 2015;41:467-476.

24. Takahashi H, Ono M, Hyogo H, et al. Biphasic effect of alcohol intake on the development of fatty liver disease. J Gastroenterol 2015; 50:1114-1123.

25. Loomba R, Yang HI, Su J, et al. Synergism between obesity and alcohol in increasing the risk of hepatocellular carcinoma: a prospective cohort study. Am J Epidemiol 2013;177:333-342.

26. Engstler AJ, Aumiller T, Degen C, et al. Insulin resistance alters hepatic ethanol metabolism: studies in mice and children with non-alcoholic fatty liver disease. Gut 2015. [Epub ahead of print].

Figure 1

Click here to download Figure SookoianFigure 1.tif

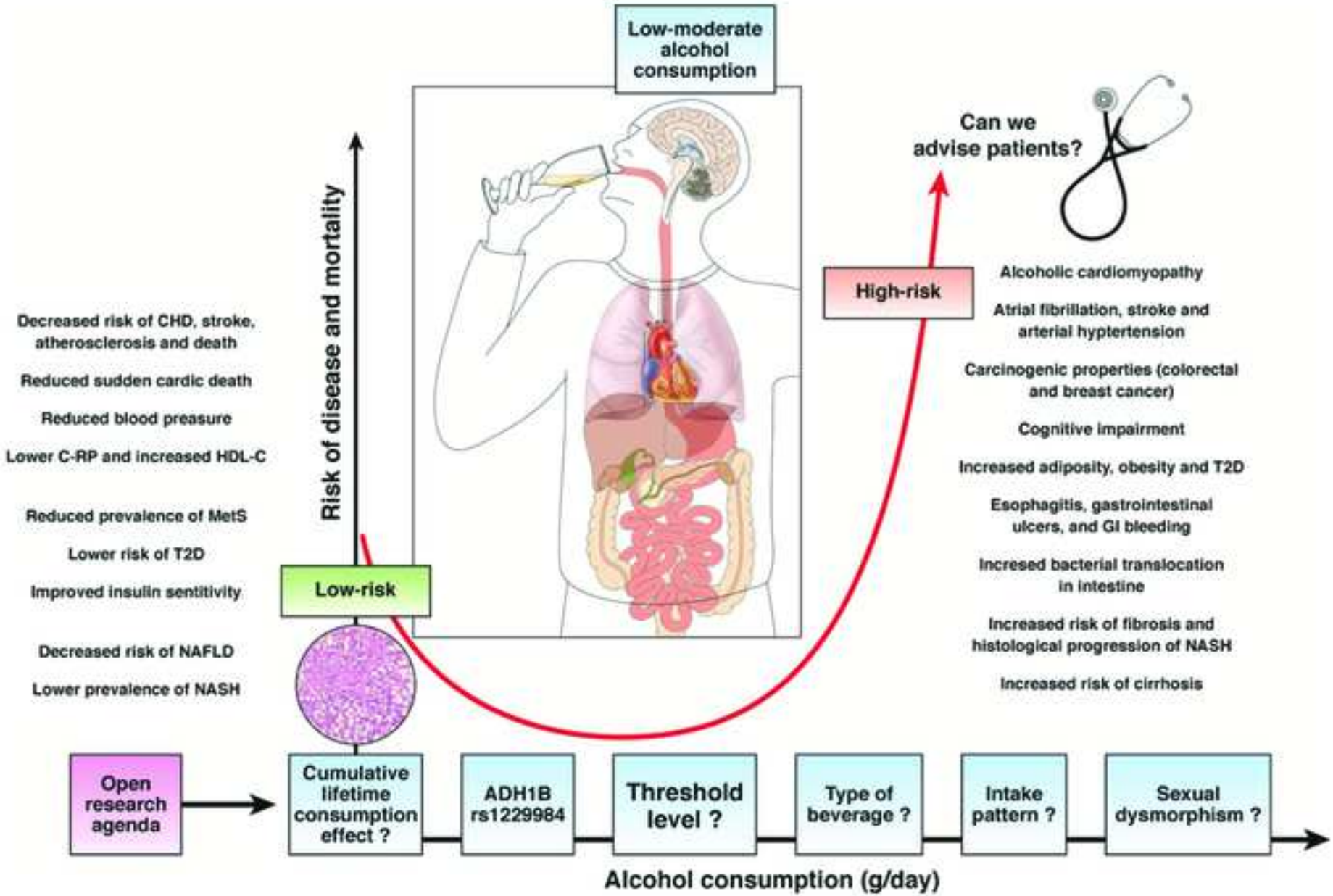
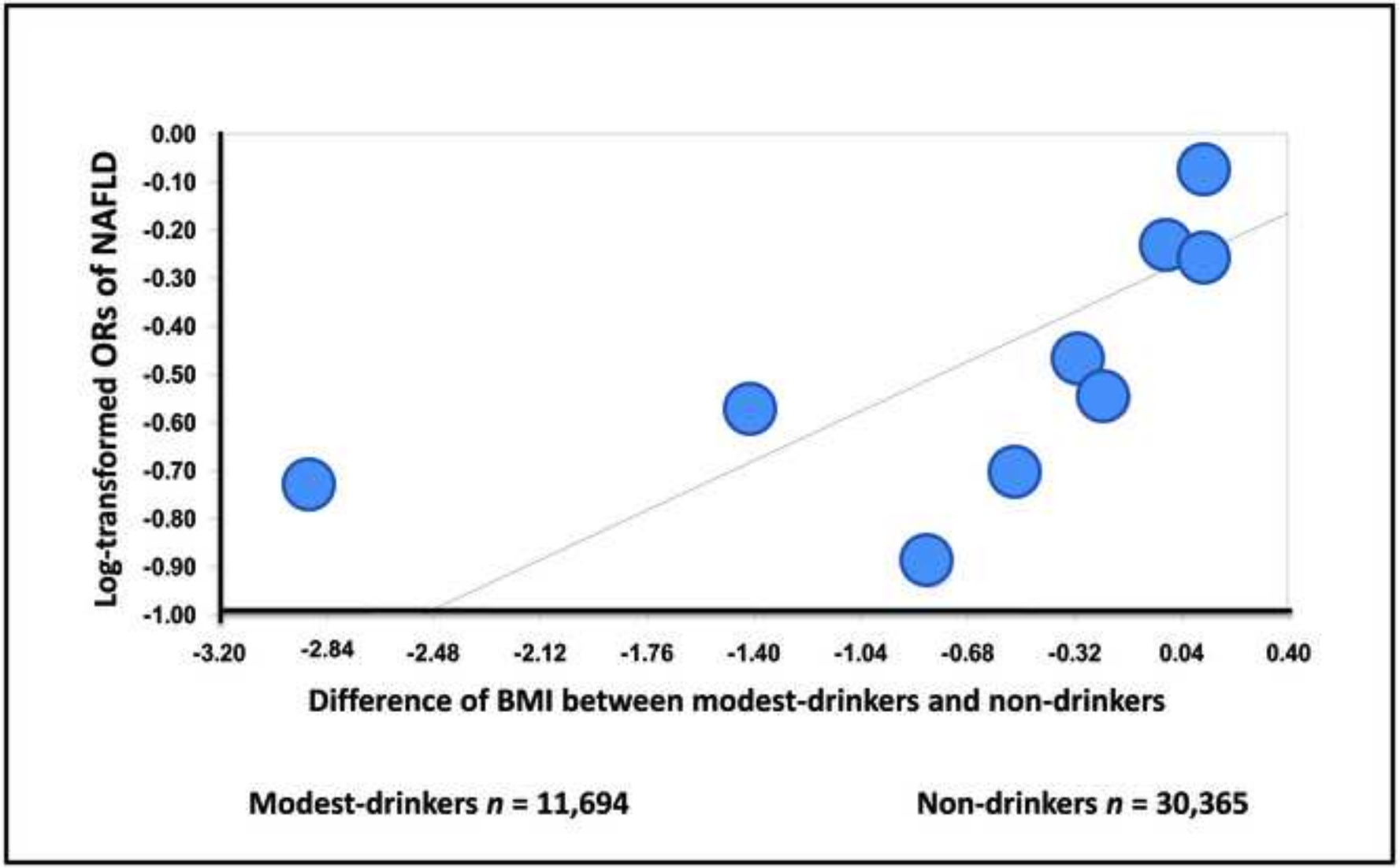


Figure 2

Click here to download Figure Figure 2.tif



SUPPLEMENTARY MATERIAL

How safe is Moderate Alcohol Consumption in Overweight and Obese Individuals?

Silvia Sookoian[1] MD, PhD and Carlos J Pirola[2] PhD, FAHA

[1]Department of Clinical and Molecular Hepatology, Institute of Medical Research A Lanari-IDIM, University of Buenos Aires- National Scientific and Technical Research Council (CONICET), Ciudad Autónoma de Buenos Aires, Argentina
[2]Department of Molecular Genetics and Biology of Complex Diseases, Institute of Medical Research A Lanari-IDIM, University of Buenos Aires-National Scientific and Technical Research Council (CONICET), Ciudad Autónoma de Buenos Aires, Argentina

Characteristics of the studies included in the Meta-regression analysis of pooled estimates between the log-transformed odds ratio of having NAFLD in modest-drinkers vs. non-drinkers, and the difference of BMI between the two groups

First author, year. (Ref #)	Country, city.	Non-drinkers/ modest drinkers (n) Male/Female	Clinical condition	BMI mean±SD Non-drinkers/ modest drinkers	Categories of alcohol consumption	Type of alcoholic beverage	Assessment of NAFLD	Outcome NAFLD (n=Non-drinkers/ modest drinkers)	Outcome of histological evaluation (n=Non-drinkers/ modest drinkers
Dunn W, 2008 [1]	USA, Multi-city Multi-ethnic # NHANES III	7211/ 945 Mixed data on male and female	General population health survey	27.5±6.2 /26.1±5.2	Non drinkers vs. modest drinkers (up to an average of 1 drink per day= 4 once of wine)	Wine	Suspected NAFLD based on liver enzymes and healthy cut point*	1032/81	NA
Hamaguchi M, 2012 [2]	Japan, Gifu.	Men: 6154/ 1734 Women: 6893/406	General population health checkup	Men: 23.5±3.3 / 23.2±2.9 Women: 21.4 ± 3.2 / 20.9 ± 2.7	Non drinkers vs. Light consumption (40-140 g/week).	Not specified	Liver US	Men: 2248/ 457 Women: 717/ 22	NA
Yamada T, 2010 [3]	Japan, Okazaki.	Men: 1181/1502 Women: 2888/368	General population Health checkup	Men: 23.1±3.2 / 22.9±2.8 Women: 22.3±3.3 / 21.4±2.8	Non drinkers vs. Daily moderate drinkers (1 drink=23 g alcohol/day)	One drink was defined as 500 ml of beer (4–5% alcohol or 180 ml of sake).	Liver US	Men: 337/ 281 Women: 358/ 20	NA

Hiramine Y, 2011 [4]	Japan, Kagoshima.	847/4550 Mixed data on male and female	General population Health checkup	23.7 /23.7	Non drinkers vs. light drinkers (who drink 1-5 days/month = 20-39 g /day)	Not specified	Liver US	382/ 1788	NA
Sookoian S, 2013 [5]	Argentina, Buenos Aires.	331/83 Mixed data on male and female	Prevalence of NAFLD in general population	30.4±6.3/ 27.5±5.3	Non drinkers vs. modest drinkers: alcohol intake <= 20 g of alcohol /day	Wine	Liver US and liver biopsy to NAFLD patients	228/ 43 (Liver US)	NASH 109/8 Simple Steatosis 65/15
Takahashi H, 2015 [6]	Japan, Saga, Hiroshima and Kochi.	Men: 2908/ 1845 Women: 1942/ 264	General population Health checkup	Men: 23.6±3 / 23.7±2.9 Women: 21.6 ± 3.0 / 21.7 ± 3.1	Non-drinkers: <20 g daily, moderate drinkers: 20–50 g daily.	Not specified	Liver US	Men: 1163/ 1133 Women 296/ 32	NA

Studies were included in the meta-regression analysis if full details on NAFLD and body mass index were provided according to Non drinkers and modest drinkers categories. ND: Non drinkers, MD: Modest drinkers, H-MRS: Proton-magnetic resonance spectroscopy, US: ultrasound, NA: not available.

White, black or Mexican American.

Sake contains 22 g of alcohol per unit (180 mL). Each amount of other beverages consumed was converted into units of sake (500 mL of beer, 240 mL of wine and 60 mL of liquor were equal to a unit of sake) and added up.

REFERENCES

1. Dunn W, Xu R, Schwimmer JB. Modest wine drinking and decreased prevalence of suspected nonalcoholic fatty liver disease. Hepatology 2008;47:1947-1954.

2. Hamaguchi M, Kojima T, Ohbora A, et al. Protective effect of alcohol consumption for fatty liver but not metabolic syndrome. World J Gastroenterol 2012;18:156-167.

3. Yamada T, Fukatsu M, Suzuki S, et al. Alcohol drinking may not be a major risk factor for fatty liver in Japanese undergoing a health checkup. Dig Dis Sci 2010;55:176-182.

4. Hiramine Y, Imamura Y, Uto H, Koriyama et al. Alcohol drinking patterns and the risk of fatty liver in Japanese men. J Gastroenterol 2011;46:519-528.

5. Sookoian S, Castano GO, Pirola CJ. Modest alcohol consumption decreases the risk of non-alcoholic fatty liver disease: a meta-analysis of 43 175 individuals. Gut 2014;63:530-532.

6. Takahashi H, Ono M, Hyogo H, et al. Biphasic effect of alcohol intake on the development of fatty liver disease. J Gastroenterol 2015.

Headshot Sookoian

Click here to download Supporting Document headshot Sookoian.tif

Headshot Pirola

Click here to download Supporting Document headshot Pirola.tif