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LETTER

Modest alcohol consumption decreases the risk of non-alcoholic fatty liver disease: a meta-analysis of 43 175 individuals

Epidemiological studies suggested that the prevalence and the disease severity of non-alcoholic fatty liver disease (NAFLD) are lower for people who drink modest amounts of alcohol than those who are abstainers. Nevertheless, the evidence is still inconclusive because some recently published studies[1] showed that modest alcohol consumption (MAC) increases hepatic fat without increasing the risk of advanced fibrosis.

Remarkably, we found in our population that MAC has a beneficial effect in preventing not only NAFLD but the main features of the metabolic syndrome, including body mass index (BMI), blood pressure, homeostatic model assessment-insulin resistance and C-reactive protein levels. Accordingly, NAFLD and non-alcoholic steatohepatitis (NASH) prevalence, liver enzymes and inflammatory markers were lower in subjects who took modest amounts of alcohol than those who are abstainers (table 1).

Hence, we propose to take advantage of meta-analysis to estimate from published data the effect of MAC on the odds of having NAFLD to give a quantitative assessment of this relationship. The drinkers were classified into two groups: non-drinkers, persons who drinks 0 g/day of alcohol, and light or modest drinkers, persons who drinks less than 40 g/day of alcohol; all the studies accomplished the inclusion criteria.

Thus, we addressed two different relevant clinical questions.

IS MAC ASSOCIATED WITH LOWER PREVALENCE OF NAFLD?

Data regarding MAC and NAFLD were extracted from eight heterogeneous (I^2=80.7, p<0.0001) studies[1–8] that were meta-analysed along with our own data; the analysis included 43 175 adult individuals (30 791 non-drinkers and 12 384 modest drinkers). The analysis showed that MAC was associated with a significant protection from the odds of having NAFLD in both fixed (OR 0.688, 95% CI 0.646% to 0.733%, $p<10^{-8}$) and random models (OR 0.684, 95% CI 0.580% to 0.806%, $p<10^{-5}$) (figure 1). This beneficial effect seems to be independent of covariates such as BMI (meta-regression analysis showed that this association was independent of BMI (slope=0.01, p<0.44), but is much influenced by sex. Of note, among women (n=12 459), the protective effect of MAC on NAFLD was surprisingly higher (about 53%) compared with men (about 30%).

IS MAC ASSOCIATED WITH LOWER PREVALENCE OF NASH AMONG THOSE WITH NAFLD?

MAC was found to have a significant protective effect on the development of NASH in both fixed and random models (OR 0.501, 95% CI 0.340% to 0.740%, p<0.0005) without any evidence of heterogeneity (p=NS, I^2=0); the data are from 822 patients (550 non-drinkers and 272 modest drinkers) diagnosed by liver biopsy in our population and two additional studies.[2–9]

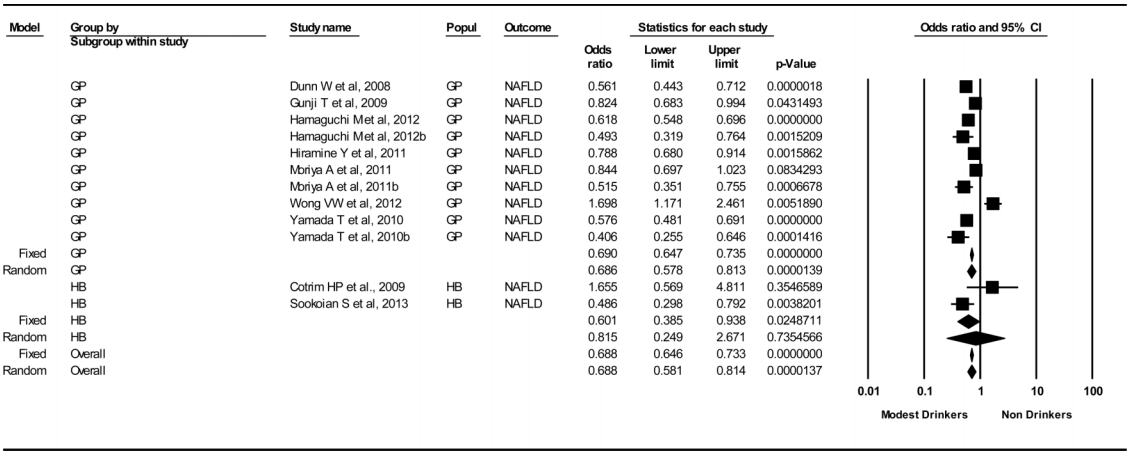
In conclusion, quantitative evidence showed that MAC is associated with a significant protective effect of about 31% on the risk of having NAFLD. Even more remarkable, MAC was associated with an average protective effect of about 50% on the risk of developing an advanced disease stage.

Future research agenda still remains open, looking for answers from cohort prospective studies elucidating the exact role of MAC on the natural history of NAFLD. A note of caution should be added because a previous study showed that NASH patients who report any regular alcohol consumption are 3.6 times more likely to develop liver cancer than abstainers.[10]

Table 1 Clinical and biochemical characteristics of the Argentinean population according to drinking status: non-drinkers versus modest drinkers

Variables	Non-drinkers	Modest drinkers	p Value
Number of subjects	331	83	–
Female/male, n	172/159	40/43	NS
Age, years	52.3±12	48.2±12.3	0.006
Smoking habit, cigarettes/day	2.4±6.9	4.0±9.2	0.04
Physical activity, h/week	1.91±5.3	1.4±2.3	NS
BMI, kg/m^2	30.4±6.3	27.5±5.3	0.0001
Waist circumference, cm	99.2±17.0	94.3±14.8	0.01
Waist/hip ratio	0.91±0.09	0.91±0.08	NS
Body fat content (%)*	37.2±8	32.3±6.4	0.0002
SABP, mm Hg	123.0±16.2	116.8±12.9	0.001
DABP, mm Hg	75.8±10.9	73.3±0.8	0.06
Fasting plasma glucose, mmol/L	5.74±4.49	4.93±1.23	0.0005
Fasting plasma insulin, pmol/L	82.1±65.5	69.3±49.9	0.02
HOMA-IR index	3.1±4.4	2.3±2.0	0.003
Total cholesterol, mmol/L	5.46±1.40	5.38±1.07	NS
HDL cholesterol, mmol/L	1.29±0.48	1.32±0.33	NS
LDL cholesterol, mmol/L	3.26±1.29	3.30±1.03	NS
Triglycerides, mmol/L	1.91±1.22	1.48±0.76	0.009
Uric acid, mmol/L	268±318	243±95	0.0001
Leukocyte count, cells/μL	7371.5±2078	6885±2062	NS
C-reactive protein; mg/L	7.8±6.17	5.5±3.0	0.009
ALT, U/L	59.5±99.0	44.7±46.5	0.004
AST, U/L	41.3±44.9	31.8±23.4	0.001
GGT, U/L	3.9±0.9	3.7±1.0	0.05
AP, U/L	227.4±125.0	194.0±223	0.0003
Histological features†			
Degree of steatosis, %	55.2±23.5	50.0±27.8	NS
Necroinflammatory activity	1.03±0.9	0.6±0.9	0.01
Fibrosis stage	0.9±1.25	0.4±1.6	0.03

Results are expressed as mean±SD. p Value stands for statistical significance using Mann–Whitney U test, except for female/male proportion that p value stands for statistical significance using χ^2 test. NS, non-significant. All measurements are in standard units.
All the investigations performed in this study were conducted in accordance with the guidelines of the 1975 Declaration of Helsinki. Written consent from individuals was obtained in accordance with the procedures approved by the Ethical Committee of the authors' institution.
*Measurement of body fat content was performed by using a bioelectrical impedance method at 50 kHz and 500 μA.
†Total of patients with liver biopsy: 197 (NASH=117, simple steatosis=80).
ALT and AST, serum alanine and aspartate aminotransferase; AP, alkaline phosphatase; BMI, body mass index; GGT, gamma-glutamyl transpeptidase; HDL, high-density lipoprotein; HOMA, homeostatic model assessment; IR, insulin resistance; LDL, low-density lipoprotein; SABP and DABP, systolic and diastolic arterial blood pressure.



Model	Group by Subgroup within study	Study name	Popul	Outcome	Odds ratio	Lower limit	Upper limit	p-Value
	GP	Dunn W et al, 2008	GP	NAFLD	0.561	0.443	0.712	0.0000018
	GP	Gunji T et al, 2009	GP	NAFLD	0.824	0.683	0.994	0.0431493
	GP	Hamaguchi M et al, 2012	GP	NAFLD	0.618	0.548	0.696	0.0000000
	GP	Hamaguchi M et al, 2012b	GP	NAFLD	0.493	0.319	0.764	0.0015209
	GP	Hiramine Y et al, 2011	GP	NAFLD	0.788	0.680	0.914	0.0015862
	GP	Moriya A et al, 2011	GP	NAFLD	0.844	0.697	1.023	0.0834293
	GP	Moriya A et al, 2011b	GP	NAFLD	0.515	0.351	0.755	0.0006678
	GP	Wong VW et al, 2012	GP	NAFLD	1.698	1.171	2.461	0.0051890
	GP	Yamada T et al, 2010	GP	NAFLD	0.576	0.481	0.691	0.0000000
	GP	Yamada T et al, 2010b	GP	NAFLD	0.406	0.255	0.646	0.0001416
Fixed	GP				0.690	0.647	0.735	0.0000000
Random	GP				0.686	0.578	0.813	0.0000139
	HB	Cotrim HP et al., 2009	HB	NAFLD	1.655	0.569	4.811	0.3546589
	HB	Sookoian S et al, 2013	HB	NAFLD	0.486	0.298	0.792	0.0038201
Fixed	HB				0.601	0.385	0.938	0.0248711
Random	HB				0.815	0.249	2.671	0.7354566
Fixed	Overall				0.688	0.646	0.733	0.0000000
Random	Overall				0.688	0.581	0.814	0.0000137

Figure 1 Summary estimates for OR (effect); the corresponding 95% CI (lower and upper) and significance (p value) were calculated by fixed and random effects meta-analysis for non-alcoholic fatty liver disease (as dichotomous variable) between non-drinkers and modest drinkers. The first author of the study and the year of publication are shown after the study name; b stands for female data; Popul indicates design features. GP, general population; HB, hospital-based. In the graph, numbers indicate OR, filled squares stand for the effect of individual studies and filled diamonds express combined fixed and random effects. The symbol size is proportional to the number of individuals involved in each study.

In addition, further exploration in future epidemiological studies should answer the question of whether different kinds of beverages are equally beneficial or able to protect against NAFLD.

Meanwhile, the deleterious effects of excess drinking must always be highlighted to NAFLD patients, but they might be allowed to drink low amounts of alcohol, including a narrow window between maximum protection and harm, which is not the same in men and women.

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Contributors SSdesigned the study, collected data, analysed data, collected patients' data, performed liver biopsy and wrote the manuscript. GC collected patients' data and performed LB. CJP designed the study, collected data, analysed data and wrote the manuscript.

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