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META-ANALYSIS OF ALCOHOL INTAKE IN RELATION TO RISK OF LIVER CIRRHOSIS

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Abstract — The heterogeneity in the results of observational studies that investigated the association between alcohol consumption and risk of liver cirrhosis was analysed by means of a meta-analysis that included 15 articles published from 1978 to 1997. Relative risks associated with low levels of alcohol intake (25 g/day) ranged from 1.5 [95% confidence interval (CI): 1.4–1.5] for a linear model fitting the results of the six studies performed in Mediterranean areas, to 3.6 (95% CI 3.1–4.3) for a quadratic model fitting the results of the nine studies performed in other areas. A strong indication of heterogeneity was observed when combining all studies. Quadratic term of alcohol intake, quality of the study and area in which the study was performed explained most of this heterogeneity. Efforts should be made to explain the strong heterogeneity in the trend estimates. Reproducible methods to collect relevant and valid information on alcohol intake should be developed and the role of drinking patterns and viral and nutritional factors in modifying the effect of alcohol on the risk of liver cirrhosis should be investigated.

INTRODUCTION

There is general consensus about the causal role of alcohol for the risk of cirrhosis and other chronic diseases of the liver (Rodés *et al.*, 1993). However, the epidemiological literature on the risk of liver cirrhosis in relation to alcohol intake fails to elucidate a number of issues. For example, there is no consensus on the existence of a threshold level of alcohol consumption below which the risk is not detectable (Sørensen, 1989). Moreover, it is not clear if the effect of alcohol intake on the risk of liver disease could be modified by acquired environmental factors, such as drinking patterns, viral factors, and diet (Aricò *et al.*, 1997).

Meta-analysis is the quantitative analysis of a collection of study results (Berlin *et al.*, 1993). It is used to identify sources of variation in findings and to summarize findings with an overall measure of association (Wolf, 1986).

In order to investigate the findings of the epidemiological literature and to identify the sources of the heterogeneity observed between studies, this paper used a meta-analytical approach evaluating data from case-control and cohort studies regarding the relationship between alcohol consumption and the risk of chronic liver diseases.

METHODS

A MEDLINE search of the literature from 1966 up to and including 1996 was performed, supplemented by attention to all references in the articles recovered through MEDLINE. In addition, manuscripts in press known to the authors were included.

Each publication identified by this process was reviewed and included in the analysis if the following criteria were met: (1) case-control or cohort study published as an original article — ecological and prevalence studies and/or abstracts, letters, and editorials were not considered eligible; (2) findings expressed directly as odds ratio or risk ratio considering three or more levels of alcohol consumption; (3) reported number of cases and non-cases and estimates of the odds ratios or risk ratios for each exposure level. When the results of a study were published more than once, only the most recent article was included in the analysis.

Two of us (VB and AZ), blind to the authors'

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names and affiliations and to the results pertaining to alcohol consumption in relation to the risk of liver cirrhosis, independently read and determined whether a study would be included in the meta-analysis.

The same two readers subsequently scored the quality of the eligible studies according to the criteria reported in Appendix 1. Questions were concerned with the study's design (9 questions), the alcohol consumption data collection methods (4 questions) and the data analysis (3 questions). The points awarded for each question were determined according to the question-specific standard scale. Maximum scores were given when methods least likely to result in bias had been used. The quality score for a study was obtained by adding up the points obtained for individual questions. For a perfect study, the sum of the points was 23.

Significant discrepancies between the two readers in their decisions to include/exclude an article and in quality score assignment were resolved in conference.

Preparation of the data of the original studies for the meta-analysis was done according to a three-step procedure.

Firstly, since different studies used different units of measure to express alcohol consumption (grams, millilitres, ounces or drinks consumed every day, week, month, or year), we used grams per day as a standard measure of ethanol consumption and converted all levels differently expressed to this standard, on the basis of the ethanol content of one drink, 1 oz of ethanol or 1 ml of ethanol being 11.5 g, 28 g, and 0.8 g respectively.

Secondly, since the levels of consumption were given as a range, we assigned to each class the dose corresponding to the midpoint of the range. Because the category of high consumption was often open, it was considered to be of the same amplitude as the preceding category and, consequently, the midpoint of this higher consumption arbitrarily chosen range was set as the maximum level of consumption.

Thirdly, every measure of association concerning each level of alcohol consumption and the corresponding confidence interval (CI) were translated into log relative risk and corresponding variance.

The data thus transformed were used to derive pooled estimates of the effect of alcohol consumption on the risk of liver cirrhosis. Several regression models were fitted to estimate the β coefficient, which expresses the variation of the log relative risk at each 1 g/day variation in alcohol consumption. In general, the models were fitted according to the method proposed by Greenland and Longnecker (1992). Briefly, the method provides an estimate of β, and of its standard error, requiring only the summary estimates (log relative risk and corresponding variance) and the marginal data from the study.

Two estimation methods were used. The first, referred to as the 'post-pool method', consisted for each of the included studies of the estimates of the β coefficient and the corresponding variance, and of the subsequent estimate of the pooled β coefficient, as the mean of the individual β coefficients weighted for the inverse of the corresponding variances. The heterogeneity of the effects between studies was tested according to Breslow and Day (1980). In addition to the classical fixed effects model, a random effects model was also fitted. The basic idea of a random effects model is to incorporate the observed variance between studies into the analysis, so that the observed effect of the exposure is assumed as the product of two components: the true effect and the sampling error. In the present paper, the procedure proposed by DerSimonian and Laird (1986) was used to fit the random effects model.

The second method, referred to as the 'pre-pool method', consisted in pooling the original data before the trend analysis. This is a more flexible method, since it allows the inclusion in the analysis of putative sources of heterogeneity of the estimates (Greenland and Longnecker, 1992). In particular, besides the linear effect of alcohol consumption on the risk of liver cirrhosis, the following covariates were included in the analysis: the quadratic term of alcohol consumption; the quality score assigned to each study; the area where the study was performed (Mediterranean vs other areas), the basic design of the study (case-control vs cohort studies); and the outcome measure considered in the study (incident cases vs deaths). The residual deviance (D-statistics) was used to test the goodness-of-fit of each fitted model. In brief, since the D-statistics provide a measure of unexplained variability, the lower the value, the better is the goodness-of-fit of the model to the data. The D-statistics have an

asymptotic χ^2 distribution under the null hypothesis with degrees of freedom (d.f.) obtained by the difference between the number of fitted points and parameters estimated. The comparison between the two models, when feasible, was tested by the difference between the values of the *D*-statistics for the two models (likelihood ratio test). Again, likelihood ratio test statistics have asymptotic χ^2 distribution with d.f. obtained by the difference between the d.f. values of the *D*-statistics of the two models being compared.

The corresponding calculations were carried out using the SAS Institute Inc (1988) IML package. For all hypothesis tests, *P*-values of less than 0.05 were considered significant.

RESULTS

The two readers evaluated 25 articles and manuscripts in press. Ten studies were excluded from the analysis for the following reasons: (a) only two alcohol categories reported (Corrao *et al.*, 1995*a*); (b) insufficient data to characterize exposure in terms of g of alcohol/day (Farchi *et al.*, 1992; Corrao *et al.*, 1995*a*); (c) number of cases and/or non-cases not reported (Klatsky *et al.*, 1990, 1992; Rotily *et al.*, 1990; Farchi *et al.*, 1992); (d) considered only partial results which were subsequently reported in complete form in a more recent article included in the meta-analysis (Kono *et al.*, 1983; Norton *et al.*, 1987; Corrao *et al.*, 1991*a*, 1992, 1995*a*, *b*).

The main characteristics of the remaining 15 studies included in the meta-analysis are summarized in Table 1. A total of 3742 patients were included in the analysis (2724 from case-control studies and 1013 from follow-up studies). Non-cases were 5327 in case-control studies and 526 366 in follow-up studies.

The median quality score was 14 (range: 10–21). Large, but not significant, differences were observed in quality scores between areas (Mediterranean: median 18.5, range 11–21; other: median 14, range 10–16; normal approximation to the Wilcoxon test: $z = 1.79$; $P = 0.0734$), between designs (case-control studies: median 16, range 11–21; follow-up studies: median 13, range 10–16; $z = 1.88$; $P = 0.0608$) and between outcomes (incident cases: median 15, range 11–21; deaths: median 12.5, range 10–16; $z = 1.43$; $P = 0.1521$).

Table 2 reports the individual and pooled β coefficients (and corresponding standard errors) for alcohol intake (g/day) and liver cirrhosis risk. Wide heterogeneity was observed between studies. β estimates ranged from 0.0072 to 0.0448, corresponding to relative risks for 50 g of alcohol/day ranging from 1.4 (95% CI: 1.2–1.7) to 9.4 (95% CI: 6.0–14.7), respectively. Very different pooled β coefficients were obtained by fitting the two regression models ('post-pool method'). A significant heterogeneity between studies was observed by fitting the fixed effects model (heterogeneity χ^2 statistics: $\chi^2_{14} = 635.40$; $P < 0.0001$), but not for the random effects model ($\chi^2_{14} = 13.51$; $P = 0.4868$).

Table 3 shows the results of fitting several regression models ('pre-pool method') investigating the fixed effects of alcohol intake (quadratic and/or linear term), quality score, area, design, and outcome variable on the risk of liver cirrhosis. Significant effects of both linear and quadratic terms of alcohol intake were always observed. Models that, in addition to the linear term, also considered the quadratic term of alcohol intake, fitted the data better (difference of *D*-statistics between models 1 and 6 $= \chi^2_1 = 163.03$; $P < 0.0001$).

A significant improvement of the goodness-of-fit of the model was obtained by adding the quality score to the models that considered only the linear term (models 1 and 2: $\chi^2_1 = 11.16$; $P = 0.0008$) or both linear and quadratic terms (models 6 and 7: $\chi^2_1 = 22.14$; $P < 0.0001$) of alcohol intake. A positive effect of the quality score was observed in model 2. Conversely, when the quality score was included together with other covariates (area, design or outcome), the direction of the association was inverted, so that the risk of liver cirrhosis tended to be lower in studies with higher quality scores.

Adding area or design or outcome as covariates to the models that considered alcohol intake (quadratic and/or linear) and quality score, always improved the goodness-of-fit (area effect: models 2 and 3: $\chi^2_1 = 68.23$; $P < 0.0001$; and models 7 and 8: $\chi^2_1 = 44.53$; $P < 0.0001$; design effect: models 2 and 4: $\chi^2_1 = 49.60$; $P < 0.0001$; and models 7 and 9: $\chi^2_1 = 31.11$; $P < 0.0001$; outcome effect: models 2 and 5: $\chi^2_1 = 50.0$; $P < 0.0001$; and models 7 and 10: $\chi^2_1 = 30.98$; $P < 0.0001$). Studies performed in extra-Mediterranean areas,

Table 1. Description of the 15 studies included in the meta-analysis

	General characteristics of the study				Control of confounders			
Author (year)	Country	Gender	No. of cases	No. of non-cases	In design: matching variables	In analysis: adjustment of the estimates	Reference period of questions on alcohol intake	Outcome variable
Hospital-based case-control studies:								
Pagliaro *et al.* (1982)	Italy	Both	1146	1146	Age, gender, date of admission	Unadjusted	Usual	Incident cases
Corrao *et al.* (1991*b*)	Italy	Both	121	242	Age, gender, region of origin	HBsAg status	Lifetime	Incident cases
Batey *et al.* (1992)	Australia	Both	79	214	Age	Unadjusted	Lifetime	Incident cases
Corrao *et al.* (1993)	Italy	Both	320	320	Age, gender	HBsAg status	Lifetime	Incident cases
Corrao *et al.* (1997)	Italy	Both	462	651	Unmatched	Age, gender, education HBsAg and anti-HCV status	Lifetime	Incident cases
Population-based case-control studies:								
Pequignot *et al.* (1978)	France	Men	184	778	Unmatched	Unadjusted	Usual	Incident cases
Tuyns and Pequignot (1984)	France	Both	417	1976	Unmatched	Unadjusted	Lifetime	Incident cases
Follow-up studies:								
Blackwelder *et al.* (1980)	United States	Men	16	7888	Unmatched	Unadjusted	Usual	Deaths
Klatsky *et al.* (1981)	United States	Both	50	8060	Age, gender, race, cigarette smoking	Unadjusted	Current	Deaths
Gordon and Kannel (1984)	United States	Both	24	4747	Unmatched	Unadjusted	All consumption during follow-up	Deaths
Kono *et al.* (1986)	Japan	Men	43	5135	Unmatched	Age, smoking habits	Usual	Deaths
Boffetta and Garfinkel (1990)	United States	Men	611	276 802	Unmatched	Age, smoking habits	Usual	Deaths
Klatsky and Armstrong (1992)	United States	Both	93	124 740	Unmatched	Unadjusted	Current	Incident cases
Fuchs *et al.* (1995)	United States	Women	52	85 709	Unmatched	Age, smoking habits, BMI, contraceptive use, pathological anemnesy, dietary and reproductive factors	All consumption during follow-up	Deaths
Becker *et al.* (1996)	Denmark	Both	124	13 285	Unmatched	Unadjusted	Usual	Incident cases

BMI, body mass index.

Table 2. β coefficients and corresponding standard errors for alcohol intake and risk of liver cirrhosis

Author (year)	β coefficient	SE
Pequignot *et al.* (1978)	0.0380	0.0029
Blackwelder *et al.* (1980)	0.0422	0.0168
Klatsky *et al.* (1981)	0.0255	0.0053
Pagliaro *et al.* (1982)	0.0126	0.0007
Gordon and Kanel (1984)	0.0117	0.0028
Tuyns and Pequignot (1984)	0.0403	0.0020
Kono *et al.* (1986)	0.0092	0.0050
Boffetta and Garfinkel (1990)	0.0399	0.0016
Corrao *et al.* (1991*b*)	0.0072	0.0017
Batey *et al.* (1992)	0.0448	0.0046
Klatsky and Armstrong (1992)	0.0358	0.0040
Corrao *et al.* (1993)	0.0082	0.0011
Fuchs *et al.* (1995)	0.0331	0.0108
Becker *et al.* (1996)	0.0236	0.0019
Corrao *et al.* (1997)	0.0279	0.0022
Pooled (fixed effects model)	0.0182	0.0005
Pooled (random effects model)	0.0257	0.0036

Estimates are reported for each study (fixed effects model) and for the pooled data set (fixed and random effect models).

those conducted with a follow-up design and those that considered death as an outcome variable tended to report higher slopes.

Although all the considered covariates explained part of the variance between studies, none of the models fitted the data significantly (tabulated $\chi^2_{0\,05;65} = 84.82$).

Table 4 reports several estimates of relative risks (and of corresponding 95% CI) derived from the β coefficients of different models. Higher relative risks were observed by fitting the random effects model and by considering studies performed in non-Mediterranean countries. Higher relative risks for lower doses of consumption were obtained by fitting the models that considered the quadratic term of alcohol intake. Moreover, the latter presented an attenuation or a tendency inversion of the risk function for higher doses. However, independent of the model, lower alcohol consumption (25 g/day) was always associated with a significant increase in the risk of liver cirrhosis.

DISCUSSION

In this analysis, several points have become clear. Firstly, the well-known dose–response relationship between alcohol consumption and risk of liver cirrhosis has been confirmed. Secondly, lower levels of intake appear to be significantly associated with an increased risk of liver cirrhosis. Thirdly, the quality of the study, as well as other methodological factors, significantly influenced the strength of the association.

The results of a meta-analysis may be invalid due to publication bias sometimes referred to as the 'file drawer problem', which occurs when publication depends on factors other than quality alone, e.g. statistical significance of results (Rosenthal, 1979; Simes, 1986). In this way, smaller studies tend to show stronger dose–response relationships (Laupacis, 1997). We believe that this is not the case in our study for a number of reasons. Firstly, as far as we know, all investigations found a clear, positive and significant association between alcohol consumption and risk of cirrhosis and the presence of such a relation can be considered as an indicator of the general validity of the study. Secondly, we did not observe a clear relationship between the number of cases and the magnitude of the slope among the included studies. Thirdly, the focus of seven of the 15 studies included in the meta-analysis was not alcohol (Blackwelder *et al.*, 1980; Klatsky *et al.*, 1981; Gordon and Kannel, 1984; Kono *et al.*, 1986; Boffetta and Garfinkel, 1990; Klatsky and Armstrong, 1992; Fuchs *et al.*, 1995), implying that, at least for these studies, data on alcohol would have been published even in the absence of significant findings.

Perplexities concern results obtained by combining summary data from observational studies, rather than by combining original individual patient data (Stewart and Parmar, 1993). However, excellent quantitative agreement has recently been reported between the combined effect estimates from summarized and individual data (Steinberg *et al.*, 1997).

We used two approaches to control the wide and significant heterogeneity observed between studies. The first consisted of a random effects model that, by incorporating the observed variance between studies into the analysis, allows the derivation of higher variances of the estimates and, consequently, making the hypothesis of homogeneity more likely (Fleiss and Gross, 1991). It has been suggested that estimates obtained by fitting random effects models should

Table 3. Pooled β coefficients and corresponding standard errors for the estimates of the effects of alcohol intake (quadratic and/or linear term), quality score, area in which the study was performed, design and outcome on the risk of cirrhosis

Covariates		Model									
		1	2	3	4	5	6	7	8	9	10
Alcohol linear term (g/day)	β	0.0182*	0.0171*	0.0172*	0.0182*	0.0172*	0.0305*	0.0355*	0.0344*	0.0347*	0.0347*
	SE	0.0005	0.0006	0.0006	0.0006	0.0006	0.0011	0.0015	0.0015	0.0015	0.0015
	z**	38.646	29.843	30.105	31.727	30.058	28.394	23.53	22.723	22.923	22.887
Alcohol quadratic term (g/day)	β						−0.0001*	−0.0001*	−0.0001*	−0.0001*	−0.0001*
	SE						0.0000	0.0000	0.0000	0.0000	0.0000
	z**						12.816	13.139	12.328	12.486	12.481
Quality score	β		0.3451*	−1.2938*	−1.0360*	−1.0506*		−0.5892*	−1.8644*	−1.6448*	−1.6498*
	SE		0.1033	0.2237	0.2216	0.2228		0.1252	0.2285	0.2270	0.2279
	z**		3.342	5.784	4.675	4.716		4.705	8.16	7.248	7.235
Area (Mediterranean = 0 vs others = 1)	β			0.7139*					0.5812*		
	SE			0.0864					0.0871		
	z**			8.260					6.673		
Design (case control = 0 vs cohort = 1)	β				0.6097*					0.4860*	
	SE				0.0866					0.0871	
	z**				7.043					5.577	
Outcome variable (incident cases = 0 vs deaths = 1)	β					0.6402*					0.5074*
	SE					0.0905					0.0912
	z**					7.071					5.565
D-statistics***		758.19*	747.03*	678.80*	697.43*	697.03*	595.16*	573.02*	528.49*	541.91*	542.04*
Degrees of freedom***		68	67	66	66	66	67	66	65	65	65

*$P < 0.05$. **Normal deviate standardized statistics (β/SE) to test the significance of the independent effect of the specific covariate on the risk of liver cirrhosis. ***Goodness-of-fit D-statistics and corresponding degrees of freedom; significance indicates that the model does not fit the data.

Table 4. Relationship between alcohol consumption and the risk of liver cirrhosis according to different models and area in which the study was performed

	Random effects model		All areas		Fixed effects model Mediterranean areas		Other areas	
Alcohol intake (g/day)	RR**	(95% CI)**	RR***	(95% CI)***	RR†	(95% CI)†	RR†	(95% CI)†
Linear term of alcohol intake:								
0	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
25	1.9*	(1.6–2.3)	1.5*	(1.5–1.6)	1.5*	(1.4–1.5)	2.0*	(1.9–2.2)
50	3.6*	(2.5–5.1)	2.4*	(2.2–2.5)	2.2*	(2.1–2.4)	4.1*	(3.6–4.6)
100	13.1*	(6.5–26.5)	5.6*	(5.0–6.3)	4.9*	(4.3–5.6)	16.9*	(13.3–21.6)
150	47.2*	(16.4–136.1)	13.3*	(11.2–15.7)	10.8*	(8.8–13.3)	69.6*	(48.4–100.1)
200	170.7*	(41.6–700.0)	31.4*	(25.1–39.3)	23.9*	(18.1–31.5)	286.4*	(176.4–465.1)
Linear and quadratic terms of alcohol intake:								
0	—	—	1.0	Reference	1.0	Reference	1.0	Reference
25	—	—	2.2*	(2.1–2.4)	2.4*	(2.1–2.7)	3.6*	(3.1–4.3)
50	—	—	4.5*	(3.8–5.4)	5.0*	(3.8–6.6)	10.0*	(6.8–14.7)
100	—	—	13.1*	(8.5–20.3)	16.1*	(8.4–31.0)	34.2*	(13.0–90.5)
150	—	—	24.8*	(11.6–52.7)	33.1*	(10.8–101.9)	40.5*	(7.0–234.1)
200	—	—	30.2*	(9.6–95.2)	43.7*	(8.1–236 4)	16.5*	(1.1–254.3)

*$P < 0.05$. **Uncorrected relative risks (RR) (and corresponding 95% confidence intervals, CI) derived from the β coefficient of the random effects regression model (see Table 2); the model with the quadratic term of alcohol intake is not applicable. ***Relative risks (and corresponding 95% CI) derived from the β coefficient of the fixed regression model after correcting for quality score and area (see models 3 and 8 of Table 3). † Relative risks (and corresponding 95% CI) derived from the β coefficient of the fixed effects regression model after correcting for quality score and stratification for area.

be interpreted with caution, since they cannot be applied to specific target populations and the distribution of the random component often does not find empirical, epidemiological, and biological justifications (Greenland, 1994). Moreover, although in our analysis we obtained homogeneity between studies by fitting a random effects model, it should be remembered that non-significant results of heterogeneity tests should not be used to accept the hypothesis of homogeneity (Greenland, 1987). Rather, significant results should prompt careful attention to heterogeneity (Pladevall-Vila *et al.*, 1996).

These considerations justify the second approach used here, which consisted of an analysis of the sources of heterogeneity between studies. Thus, the main objective of this meta-analysis was not to find a summary estimate of the slope of the function that best fitted the dose–response relationship between alcohol consumption and risk of liver cirrhosis, but, rather, to identify some sources of variability among studies.

An important part of the heterogeneity was explained by the quadratic term of alcohol consumption. Higher relative risks associated with lower intakes and an attenuation of the association for elevated levels of consumption were obtained by fitting quadratic models. A sudden decrease in the relative risk associated with intakes beyond 200 g/day was observed by pooling studies performed in non-Mediterranean areas. This may be due to several factors. Firstly, a survival differential could lead alcoholics to die of causes other than liver cirrhosis before the onset or the clinical manifestation of the disease. Secondly, a selection bias common to all epidemiological studies on this issue is due to the difficulty in interviewing and recruiting patients with higher intakes since they are often admitted as emergencies (Corrao *et al.*, 1991*a*). Thirdly, the fit of the quadratic model is severely hampered by the fact that very few studies investigated the higher intakes. Among the studies included, only three considered intakes beyond 200 g/day (Gordon and Kannel, 1984; Corrao *et al.*, 1991*b*, 1993). Thus, both epidemiological and statistical considerations lead us to suspect the estimates obtained by fitting models that include the quadratic term of alcohol intake.

Another putative source of heterogeneity is the quality of the studies. We are not the first to propose a list of criteria by which to judge the quality of non-experimental epidemiological studies (Friedenreich, 1993). With respect to other lists, however, we considered some questions regarding the methods used for the collection of alcohol consumption data. Although these criteria, and the weights attributed to each of them, were highly arbitrary, we found a significant correlation between quality scores and risk of liver cirrhosis. In particular, our data indicated that studies characterized by high-quality score, tended to report higher risks associated with alcohol intake. However, the increased risks in well-conducted studies were due to the confounding effect of other methodological factors, since an inversion of the quality-associated risk was observed when the estimates were adjusted for the area in which the study was performed, for the study's design or for the outcome considered. This implies that quality scores were not homogeneous between the strata of these last variables and that the quality of the study is negatively correlated with the reported risks.

We also examined three other factors as positive sources of heterogeneity. The first was the area in which the study was performed, since different patterns of alcohol intake are reported in different parts of the world. In particular, Mediterranean drinking habits are characterized by constant daily amounts of alcohol mainly in the form of wine (Aricò *et al.*, 1994) whereas in northern Europe and North America alcohol is mainly consumed during the weekend in the form of beer and spirits. The second factor examined as a putative source of the variability in the reported risk of liver cirrhosis was the study design, and the third was the outcome variable considered by the study, since aetiology is associated with the survival of cirrhotics (D'Amico *et al.*, 1986).

We observed that studies conducted in extra-Mediterranean countries, those performed with a prospective cohort design, and those that considered death due to liver cirrhosis as an outcome variable tended to report higher risks. However, due to the strong correlation between these variables, we cannot assess the independent effect of each of them. In fact, from the nine studies performed in extra-Mediterranean areas, eight were conducted with a prospective cohort design and six investigated the risk of death. Nevertheless, we observed that by adding the area variable to the model that considered alcohol

intake and quality score as covariates, a better goodness-of-fit was obtained with respect to the addition of design or outcome. This suggests that the pattern of intake could modify the effect of alcohol consumption. However, since an unknown part of the area effect could be due to other factors, caution is needed in the interpretation of this result.

Among such possible factors, the prevalence of positivity for viral markers and diet should play an important role in explaining the heterogeneity observed. Only three studies reported relations between alcohol intake and risk of liver cirrhosis adjusted for the serological markers of hepatitis B chronic infection (Corrao *et al.*, 1991*b*, 1993, 1997). Surprisingly, only one study conducted in Italy considered the effects of either the presence of serological markers of chronic hepatitis B and C infections (HBV and HCV, respectively) and alcohol intake (Corrao *et al.*, 1997). We have previously reported that neither HBV nor HCV status confounded the effect of alcohol intake on the risk of cirrhosis (Corrao *et al.*, 1993, 1997), implying that the drinking pattern is independent of the presence of one or both serological markers. This is not surprising, since the subjects are generally unaware of their positivity. If this is true, the estimates of the alcohol-related relative risks unadjusted for viral status could be unbiased. However, the confounding effect of the viral markers should also be manifest in populations other than Italians. Moreover, the recently demonstrated effect of HCV infection in modifying the risk of liver cirrhosis associated with alcohol intake (Corrao and Aricò, 1998) will lead to under-estimation of the dose–response trends. This could explain in part the heterogeneity related to the area in which the study was performed, because of the high variability in the prevalence of viral infections throughout the world.

Particularly intriguing is the hypothesis of the possible role of diet in the area-related heterogeneity. The role of diet in modifying the effect of alcohol on the risk of liver cirrhosis has been alternately emphasized and neglected in the past (Rubin and Lieber, 1974). At present, the hypothesis that specific nutrients might modify the effect of alcohol on the risk of liver damage is supported by numerous experimental studies (Rodés *et al.*, 1993). Only a few epidemiological studies, however, examined the association between the intake of specific food items or nutrients and the risk of cirrhosis (Qiao *et al.*, 1988; Rotily *et al.*, 1990; Batey *et al.*, 1992; Corrao *et al.*, 1995*a*, *b*, 1998). In this context, an epidemiological population study at aggregate level found that in populations with higher pork consumption the effect of alcohol on the mortality for cirrhosis appeared more accentuated (Nanji and French, 1985).

We conclude that, although there is sufficient evidence on the role of alcohol in causing liver cirrhosis, and although it has been demonstrated that low levels of intake, considered clinically innocuous, are associated with an increased risk, efforts should be made to explain the strong heterogeneity in the trend estimates reported in the literature. Reproducible methods to collect relevant and valid information on alcohol intake should be developed and the role of viral and nutritional factors should be investigated.

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APPENDIX 1

Criteria for evaluating design, data collection and data analysis of the epidemiological studies for the construction of the quality score index

Criteria	Items	Scores	No. of studies
Study design:			
Were the target population and the observation period well defined?	No	0	0
	Yes	1	15
Were the cases included representative of all the cases in the target population?	Non-random sample of cases	0	8
	Random sample of cases or all the cases	1	7
Were the non-cases representative of all the subjects free from the diseases in the target population?	Non-random sample of non-cases	0	8
	Random sample of non-cases or all non-cases	1	7
Were the inclusion/exclusion criteria for cases and non-cases clearly defined?	No	0	0
	Partially	1	1
	Yes	2	14
Were the diagnoses made with histologic criteria?	No or not specified	0	6
	Yes	1	9
Were the response rates for cases and controls >75%?	No or not specified	0	5
	Yes	1	10
Were data collected by trained interviewers?	No or not specified	0	5
	Yes	1	10
Were the interviewers blinded with respect to the condition of case or control?	No or not specified	0	9
	Yes	1	6
Questionnaire administration	Self-administered or not specified	0	5
	Interviews administered	1	10
Alcohol consumption data collection methods:			
Reference time period			
(a) Case-control studies	Current consumption	0	0
	Usual consumption before the diagnosis	1	2
	Lifetime consumption	2	5
(b) Cohort studies	Current consumption	0	2
	Usual consumption at some point in the past	1	4
	All consumption during follow-up	2	2
No. of beverages investigated	Only one or not specified	0	2
	Two	1	0
	Three or more	2	13
Alcohol questions	Only usual dose	0	7
	Dose and frequency or dose and duration	1	3
	Dose, frequency and duration	2	5
Was the validity or reproducibility of alcohol questionnaire tested?	No or not specified	0	11
	Yes	1	4
Data analysis methods:			
How many categories of alcohol consumption were considered?	3	0	3
	4–5	1	3
	⩾6	2	9
Were the reported estimates adjusted for the main risk indicators (viral status)?	No	0	12
	Partially	1	2
	Yes	2	1
Was the statistical analysis appropriate?	No (unmatched analysis in matched study)	0	1
	Partially	1	3
	Yes	2	11

Scores attributed to each item and number of studies attributed to each score are reported.