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REVIEW

Wine, beer or spirit drinking in relation to fatal and non-fatal cardiovascular events: a meta-analysis

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Abstract In previous studies evaluating whether different alcoholic beverages would protect against cardiovascular disease, a J-shaped relationship for increasing wine consumption and vascular risk was found; however a similar association for beer or spirits could not be established. An updated meta-analysis on the relationship between wine, beer or spirit consumption and vascular events was performed. Articles were retrieved through March 2011 by PubMed and EMBASE search and a weighed least-squares regression analysis pooled data derived from studies that gave quantitative estimation of the vascular risk associated with the alcoholic beverages. From 16 studies, evidence confirms a J-shaped relationship between wine intake and vascular risk. A significant maximal protection—average 31% (95% confidence interval (CI): 19–42%) was observed at 21 g/day of alcohol. Similarly, from 13 studies a J-shaped relationship was apparent for beer (maximal protection: 42% (95% CI: 19–58%) at 43 g/day of alcohol). From 12 studies reporting separate data on wine or beer consumption, two closely overlapping dose–response curves were obtained (maximal protection of 33% at 25 g/day of alcohol). This meta-analysis confirms the J-shaped association between wine consumption and vascular risk and provides, for the first time, evidence for a similar relationship between beer and vascular risk. In the meta-analysis of 10 studies on spirit consumption and vascular risk, no J-shaped relationship could be found.

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Introduction

The relationship between alcohol consumption and cardiovascular events or all-cause mortality in apparently healthy people or cardiovascular patients has been depicted as a J-shaped curve attributed to a dose-related combination of beneficial and harmful effects [1–7]. Numerous mechanisms have been proposed that mediate the protective effect of alcohol (ethanol) in cardiovascular disease (e.g., increased levels of high-density lipoprotein cholesterol, decreased levels of low-density cholesterol, reduction in platelet aggregation, beneficial effects on inflammation) [8, 9]. On the other hand, anti-atherogenic and anti-thrombotic effects and regulation of endothelial function were mainly ascribed to polyphenolic and phenolic constituents of (red) wine [10] and beer [11, 12], respectively.

The influence of separate wine or beer consumption on health outcomes has been examined in various conditions: while experimental studies suggest an alcohol-independent protective role of wine-derived polyphenols on cardiovascular risk [10], epidemiological evidence of a greater effect of wine versus beer or spirits is lacking. In 2002, some of us performed a meta-analysis focused on this issue [2] and observed a J-shaped relationship for increasing wine consumption and vascular risk; however a similar association for beer could not be established. In the following years, additional studies have been published (especially on beer consumption) and a new statistical method tailored for meta-analytic investigation of non-linear dose–response effects became available [13].

Therefore, the aim of this study was to update (increased number of studies), to improve (more refined methodology of analysis), and to extend (including spirits as a third type of alcoholic beverage) our previous meta-analysis on the relationship between alcoholic beverages consumption and vascular risk and to include (when possible) the clinical endpoints of cardiovascular and total mortality.

Materials and methods

Search strategy and data extraction

Our meta-analysis was performed in accordance with the "meta-analysis of Observational Studies in epidemiology" reporting guidelines [14]. Articles were retrieved until March 2011, by search in PUBMED and EMBASE using at least one of the following terms *alcohol*, *wine, beer, liquor, spirits* in combination with, *cardiovascular disease mortality, morbidity, survival, and death,* supplemented by references of the retrieved articles and reviews. Studies were excluded if they were not in English, or only considered one category of risk (i.e., drinkers versus not-drinkers), or mortality for specific causes (except vascular mortality) or when the reference category was not the one with the lowest intake or when relative risks or numbers of cases and person-years were not available. In case of multiple reports, data from the longer follow-up were considered.

A check of abstracts identified by electronic searches using the aforementioned keywords and consequently a full text revision of selected articles considering the inclusion and exclusion criteria was performed. Ninety-seven publications were identified (Fig. 1); two of us independently reviewed articles and agreed to select 18 studies [15–32]. Events for vascular mortality included cardiovascular disease (CVD), coronary heart disease (CHD) and ischemic heart disease (IHD), whereas non-fatal vascular events comprised acute myocardial infarction (AMI), stroke and CHD. Four studies reported results separately for all-cause and vascular mortality [19, 22, 31, 32], two for fatal and non-fatal vascular disease [15, 16], 10 for non-fatal vascular disease (AMI, stroke, CHD, CVD) [17, 18, 20, 23–25, 27, 29, 30], one for all-cause [26] and two for CHD mortality as unique endpoint [21, 28] (Tables 1 and 2). In relation to beverage type, 11 studies investigated the effects of wine, beer and spirits, 2 studies investigated the effects of wine and beer, four studies wine and one study beer only (Table 2).

In seven studies, former drinkers had been excluded from reference group, whereas in other 7 studies, either the inclusion or the exclusion of former drinkers from

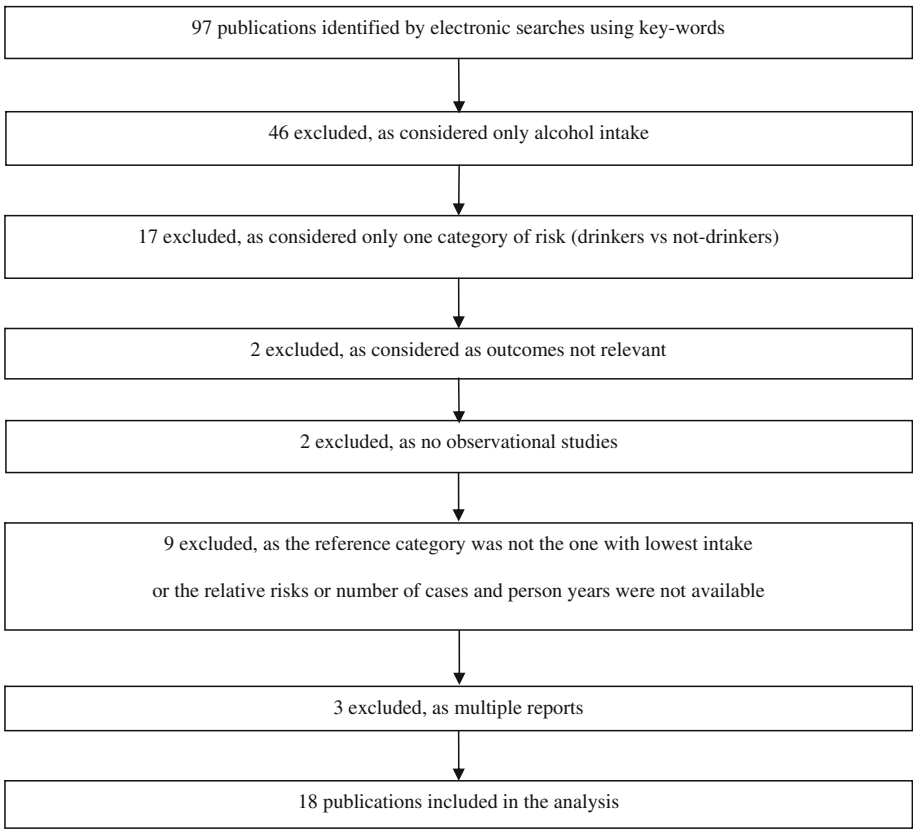

Fig. 1 Flow chart of the selected studies

Table 1 Summary of the characteristics of 18 studies included in the present meta-analyses

First author, year (Ref. #)	Type of study	Country	Follow-up, years	Age	Sex	Endpoint	Type of alcoholic beverage	No. of cases	Total sample size/No. of controls	Former drinkers in reference group	Adjustment
Yano et al. 1977 [15]	Prospective	USA	6	46–68 years	Male	Fatal non-fatal CHD	Wine, beer, spirits	294	7,705	Yes	Age
Stampfer et al. 1988 [16]	Prospective	USA	4	34–59 years	Female	Fatal non-fatal CHD	Wine, beer	320	87,526	Not stated	Age
Bianchi et al. 1993 [17]	Case–control	Italy		18–74 years	Female	AMI	Wine	298	685	Not stated	Age, education, residence, smoking, BMI, coffee intake, history of angina, diabetes, hypertension, hyperlipidaemia, history of heart disease
Tavani et al. 1996 [18]	Case–control	Italy		24–74 years	Male	AMI	Wine, beer, spirits	787	959	Not stated	Age, education, smoking, coffee intake, BMI, serum cholesterol, history of obesity, diabetes, hypertension, hyperlipidaemia, family history of AMI
Renaud et al. 1999 [19]	Prospective	France	15	40–60 years	Male	CHD mortality	Wine	260	36,250	No	Age, smoking, education, BMI
						Total mortality		2,080			
Bobak et al. 2000 [20]	Case–control	Czech		25–64 years	Male	AMI	Beer	202	735	No	Age, district, smoking, education, WHR, personal history of diabetes, high cholesterol concentration
Gronbaek et al. 2000 [21]	Prospective	Denmark	25	20–98 years	Both	CHD mortality	Wine, beer, spirits	1,075	24,523	Not stated	Types of alcohol, age, sex, smoking, educational level, physical activity, BMI
Theobald et al. 2000 [22]	Prospective	Sweden	22	18–65 years	Both	CVD mortality	Wine	117	1,828	No	Sex, age, expected level of need, total alcohol consumption
						Total mortality		283			
Malarcher et al. 2001 [23]	Case–control	USA		15–44 years	Female	Stroke	Wine, beer, spirits	224	392	No	Age, race, education, smoking, BMI, total cholesterol, HDL cholesterol, history of hypertension, coronary heart disease, diabetes and average past alcohol intake in the past year
Tavani et al. 2001 [24]	Case–control	Italy		25–79 years	Both	AMI	Wine, beer	507	478	Not stated	Age, sex, education, BMI, cholesterol, smoking, coffee, physical activity, hyperlipidaemia, diabetes, hypertension and family history of AMI in first degree relatives
Mukamal et al. 2003 [25]	Prospective	USA	12	40–75 years	Male	AMI	Wine, beer, spirits	1,418	38,077	No	Age, smoking, BMI; diabetes, hypertension, hypercholesterolemia, a parental history of AMI; use or non-use of aspirin; physical activity; intake of energy; and energy-adjusted intake of folate, vitamin E, saturated fat, trans fat, and dietary fiber and for all other types of beverage

Table 1 continued

First author, year (Ref. #)	Type of study	Country	Follow-up, years	Age	Sex	Endpoint	Type of alcoholic beverage	No. of cases	Total sample size/No. of controls	Former drinkers in reference group	Adjustment
Nielsen et al. 2004 [26]	Prospective	Denmark	24	>20 years	Both separately	Total mortality	Wine, beer, spirits	7,208	14,223	Yes	Consumption of other beverage types, smoking, BMI, physical activity, cohabitation, income and education
Mukamal et al. 2006 [27]	Prospective	USA	9.2	≥65 years	Both	CHD	Wine, beer, spirits	675	4,410	No	Age, sex, race, education, marital status, smoking, exercise intensity, depression score, frequent aspirin use, BMI, diabetes and intake of other two beverage types
Harriss et al. 2007 [28]	Prospective	Australia	11.4	40–69 years	Both separately	CVD mortality	Wine, beer, spirits	400	38,200	No	Male: age, country of birth, smoking, total daily energy and fruit intake. Female: age, country of birth, smoking, total daily energy and saturated fat intake. All beverages were analysed simultaneously
Schroder et al. 2007 [29]	Case–control	Spain		25–74 years	Male	AMI	Wine, beer, spirits	244	1,270	Yes	Age and other alcoholic beverages
Lu et al. 2008 [30]	Prospective	Sweden	11	30–50 years	Female	AMI	Wine, beer, spirits	170	45,449	Yes	Age, BMI, education, smoking, parity and age at first birth, used OCs
Suadicani et al. 2008 [31]	Prospective	Danemark	16	40–59 years	Male	IHD mortality	Wine	197	3,022	Not stated	Age
						Total mortality		1,204			
Streppel et al. 2009 [32]	Prospective	The Netherlands	40	40–60 years	Male	CVD mortality	Wine, beer, spirits	628	1,373	Not stated	Former drinking, energy intake without alcohol, number of cigarettes smoked, cigarette smoking duration, cigar or pipe smoking, intake of vegetables, fruit, fish, saturated and trans fatty acids, body mass index, prevalence of AMI, stroke, diabetes mellitus and cancer, baseline socioeconomic status and total alcohol intake
						Total mortality		1,130			

AMI acute myocardial infarction, *BMI* body mass index, *CHD* coronary heart disease, *CVD* cardiovascular disease, *IHD* ischemic heart disease, *OC* oral contraceptive, *WHR* waist to hip ratio

reference group was mentioned (Table 1); in 3 studies the reference group included occasional but not former drinkers [19, 20, 22].

The amount of alcohol (grams) in a "drink" was taken as quantified by each article. Adjusted relative risks (RR) for each categories of alcohol consumption were extracted (four studies reported RR adjusted for age only [15, 16, 29, 31] (Table 2)).

Data analysis

Data collected were: (a) the value x of alcohol intake (g/day) assigned as the midpoint of the reported ranges; x was defined as 1.2 times the lower boundary for the open-ended upper categories [33]; (b) frequency counts, adjusted RR, and 95% CI for each x level; (c) covariates describing the characteristics of the study. Inverse-variance-weighed methods, taking into account the correlation between estimates within each study, were used [33]. The models to be fitted were selected among fractional polynomial curves of the second order [33]. Fractional polynomials are a family of models considering power transformations of a continuous exposure variable, restricted to a predefined set of integer and non integer exponents [34]. The regression models were $\log(RR|x) = \beta_1 x^p + \beta_2 x^q$ and the exponents p and q were selected among the set: $(-2, -1, -0.5, 0, 0.5, 1, 2)$. When $p = 0$, x^p is replaced by $\log(x)$, and when $p = q$ the model becomes $\log(RR|x) = \beta_1 x^p + \beta_2 x^q \log(x)$ [13]. The best fit was defined as that with the highest likelihood. To consider differences among studies as a further source of random variability, an additional component of the variance was added in weighing each observation (random-effects model). In sensitivity analysis, comparison of two hierarchical models was tested by the likelihood ratio test including or not in the models the interaction terms between the covariates (design of study, country setting, duration of follow-up) and alcohol intake (amount) [35]. To make some allowance for multiple comparisons, 95% CIs were used in subgroup analyses, and pairwise contrasts were adjusted following the Sidak method, as outlined by Ludbrook [36]. All analyses were carried out using a SAS *macro* [13] (SAS, 9.1.3 for Windows, Cary, NC: SAS Institute Inc. 1989). The hypothesis that publication bias might affect the validity of the estimates was tested by a funnel-plot-based approach. A simple test of asymmetry of the funnel plot was used according to the method proposed by Egger et al. [37]. The symmetry of funnel plots was measured applying the following linear model: $RRj/se(RRj) = \alpha + \gamma * 1/se(RRj)$, where $RRj/se(RRj)$ is the standard normal deviate (RR divided by its standard error); $1/se(RRj)$ the precision of the estimate; and α and γ are the unknown parameters of the model. The correction for publication bias was performed pooling studies after the exclusion of the ones that determined the asymmetry of the funnel plot. We assessed the quality of each study using both the Newcastle-Ottawa Scale [38] and a quality scale that also considered the assessment of alcohol drinking [39]. Estimations of the metrics "maximal protection" and "reversion point" from the pooled dose–response curves were used to help data interpretation. Imprecision in the evaluation of these metrics from fitting of data is unavoidable; thus, point estimates of these parameters should not be emphasized.

Results

From ninety-seven identified publications 79 studies were excluded with the criteria shown in Fig. 1. More than half were excluded since they did not distinguish wine, beer or spirits intake (n. 46) or only compared abstention with a unique category of alcohol intake (n. 17).

The main characteristics of the 18 studies included in this analysis are reported in Tables 1 and 2.

Wine consumption and fatal or non-fatal vascular events

From 16 studies [15–19, 21–25, 27–32] (11 prospective studies involving 288,363 individuals with 5,554 combined fatal or non-fatal cardiovascular events and 5 case–control studies involving 2,060 cases and 3,784 controls), 17 dose–response independent relationships were obtained for wine consumption and vascular risk, since one study reported results separately for men and women [28]. Symmetric funnel plots ($\alpha = 0$) were obtained for 12.5–25 and 25–60 g/day categories of alcohol intake (Fig. 2a); for the 1–12.5 category a slightly deviation from symmetry was observed ($\alpha \neq 0$, $P = 0.009$). The best-fitting model was obtained when $p = q = 0.5$, corresponding to the model: $\text{Log}(RR) = \beta_1\sqrt{x} + \beta_2\sqrt{x} * \log(x)$, for both the fixed and random models. The deviances of fixed and random effects models fell from 131.89 to 30.39 ($P < 0.001$ for difference), suggesting heterogeneity among studies. In subsequent analyses, using a random effects model with $p = q = 0.5$, we explored the possible role of study characteristics in explaining the inter-study heterogeneity. Fitted parameters for the random model were $\beta_1 = -0.20$ (SE = 0.059; $P < 0.001$) and $\beta_2 = 0.04$ (SE = 0.015; $P = 0.004$) (Table 3). The relationship observed has to be interpreted as a J-shaped curve; the association with a lower vascular risk was apparent up to 72 g/day and the lowest risk was seen at 21 g/day, (RR = 0.69; 95% CI: 0.58–0.82) (Fig. 3). After the exclusion of studies determining the asymmetry in the funnel plot [16, 28, 29] and then studies only adjusted for age [15, 16, 29, 31], the J-shape curve was confirmed (Table 3).

Table 2 Relative risks (RR) and 95% confidence interval (CI) for several clinical outcomes at different levels of alcoholic beverages intake as reported by authors (18 studies)

First author, year (Ref. #)	Endpoint	Wine			Beer			Spirits		
		Intake	RR	95% CI	Intake	RR	95% CI	Intake	RR	95% CI
Yano et al. 1977 [15]	Fatal non-fatal CHD	0	1		0	1		0	1	
		1 mL/day	0.67	0.4–1.1	1–299 mL/day	0.74	0.57–0.97	1–2 mL/day	0.93	0.69–1.25
		≥2 mL/day	0.71	0.44–1.16	≥300 mL/day	0.57	0.42–0.77	≥3 mL/day	0.71	0.51–0.99
Stampferet al. 1988 [16]	Fatal non-fatal CHD	0	1		0	1				
		1–53 mL/day	0.9	0.7–1.2	1–106 mL/day	0.3	0.2–0.8			
		≥53 mL/day	0.4	0.2–0.8	>106 mL/day	1	0.6–1.6			
Bianchi et al. 1993 [17]	AMI	0	1							
		≤1 drink/day	0.8	0.5–1.2						
		1–2 drinks/day	1	0.6–1.5						
		2–3 drinks/day	1.7	0.8–3.5						
		>3 drinks/day	2.4	1–5.7						
Tavani et al. 1996 [18]	AMI	0	1		0	1		0	1	
		≤ 2 drinks/day	1	0.7–1.4	1 drink/day	1	0.7–1.3	1 drink/day	1.0	0.8–1.3
		2–4 drinks/day	0.9	0.7–1.3	>1 drink/day	0.9	0.6–1.4	>1 drink/day	1.0	0.6–1.8
		4–6 drinks/day	0.9	0.6–1.4						
		6–7 drinks/day	0.7	0.3–1.5						
		>7 drinks/day	0.6	0.4–1						
Renaud et al. 1999 [19]	CHD mortality,	0	1							
		1–21 g/day	0.99	0.67–1.48						
		22–32 g/day	0.55	0.37–0.81						
		33–54 g/day	0.52	0.36–0.74						
		55–98 g/day	0.69	0.48–0.98						
		99–131 g/day	0.85	0.31–2.34						
		≥131 g/day	1.08	0.61–1.91						
	Total mortality	0	1							
		1–21 g/day	0.80	0.67–0.95						
		22–32 g/day	0.67	0.58–0.77						
		33–54 g/day	0.71	0.63–0.82						
		55–98 g/day	1.01	0.89–1.16						
		99–131 g/day	1.41	1.02–1.96						
		≥131 g/day	1.81	1.5–2.18						
Bobak et al. 2000 [20]	AMI				<0.5 L/week	1				
					0.5–3.9 L/week	0.65	0.42–1			
					4–8.9 L/week	0.34	0.19–0.61			
					≥9 L/week	0.54	0.25–1.14			

Table 2 continued

First author, year (Ref. #)	Endpoint	Wine			Beer			Spirits		
		Intake	RR	95% CI	Intake	RR	95% CI	Intake	RR	95% CI
Gronbaek et al. 2000 [21]	CHD mortality	0	1		0	1		0	1	
		1–7 drinks/week	0.74	0.63–0.86	1–7 drinks/week	0.78	0.67–0.91	1–7 drinks/week	0.97	0.83–1.12
		8–21 drinks/week	0.64	0.48–0.84	8–21 drinks/week	0.63	0.52–0.77	8–21 drinks/week	0.78	0.59–1.03
		>21 drinks/week	0.75	0.39–1.45	>21 drinks/week	0.78	0.58–1.05	>21 drinks/week	1.12	0.55–2.28
Theobald et al. 2000 [22]	CVD mortality	0	1							
		1–49 g/week	0.57	0.27–1.2						
		50–139 g/week	0.41	0.16–1.06						
		≥140 g/week	1.49	0.19–11.74						
	Total mortality	0	1							
		1–49 g/week	0.54	0.32–0.88						
		50–139 g/week	0.59	0.35–0.98						
		≥140 g/week	1.51	0.46–4.97						
Malarcher et al. 2001 [23]	Stroke	0	1		0	1		0	1	
		<12 g/week	0.56	0.3–1.04	<12 g/week	0.75	0.39–1.44	<12 g/week	1.04	0.55–1.98
		12 g/week–12 g/day	0.57	0.25–1.29	12 g/week–12 g/day	1.67	0.86–3.24	12 g/week–12 g/day	2.53	1.15–5.57
		≥12 g/day	1.85	0.31–10.94	≥12 g/day	0.73	0.29–1.84	≥12 g/day	2.18	0.68–7.04
Tavani et al. 2001 [24]	AMI	0	1		0	1				
		≤1 drink/day	0.7	0.4–1	≤1 drink/day	0.6	0.4–0.9			
		1–3 drinks/day	0.5	0.3–0.8	>1 drink/day	0.4	0.3–0.7			
		>3 drinks/day	0.5	0.3–0.8						
Mukamal et al. 2003 [25]	AMI	0	1		0	1		0	1	
		0.1–9.9 g/day	1.06	0.85–1.19	0.1–9.9 g/day	0.93	0.83–1.04	0.1–9.9 g/day	1.03	0.91–1.16
		10–14.9 g/day	1.48	1.05–2.09	10–14.9 g/day	0.78	0.61–1.01	10–14.9 g/day	0.79	0.66–0.95
		≥15 g/day	0.64	0.32–1.29	15–49.9 g/day	0.57	0.37–0.89	15–49.9 g/day	0.67	0.53–0.84
					>50 g/day	0.34	0.12–0.92	>50 g/day	0.54	0.31–0.92
Nielsen et al. 2004 [26]	Total mortality									
	Female	Never/rarely	1		Never/rarely	1		Never/rarely	1	
		Montly	0.87	0.79–0.96	Montly	0.98	0.88–1.08	Montly	0.92	0.83–1.02
		Weekly	0.79	0.69–0.91	Weekly	1.01	0.9–1.14	Weekly	1.03	0.89–1.18
		1–2 drinks/day	0.75	0.61–0.92	1–2 drinks	1.07	0.91–1.25	1–2 drinks	1.14	0.96–1.36
		>2 drinks/day	0.78	0.52–1.15	>2 drinks	1.31	0.92–1.88	>2 drinks	1.13	0.74–1.74
	Male	Never/rarely	1		Never/rarely	1		Never/rarely	1	
		Montly	0.9	0.83–0.98	Montly	0.86	0.77–0.97	Montly	0.91	0.83–0.99
		Weekly	0.8	0.71–0.9	Weekly	0.95	0.85–1.06	Weekly	1.02	0.91–1.13
		1–2 drinks/day	0.93	0.77–1.12	1–2 drinks/day	0.91	0.81–1.02	1–2 drinks	0.93	0.81–1.07
		>2 drinks/day	0.9	0.64–1.25	>2 drinks/day	1.14	1.02–1.27	>2 drinks	1.12	0.92–1.37

Table 2 continued

First author, year (Ref. #)	Endpoint	Wine			Beer			Spirits		
		Intake	RR	95% CI	Intake	RR	95% CI	Intake	RR	95% CI
Mukamal et al. 2006 [27]	CHD	0	1		0	1		0	1	
		<1 drink/week	0.71	0.54–0.93	<1 drink/week	1.07	0.80–1.43	<1 drink/week	1.10	0.82–1.48
		1–6 drinks/week	0.95	0.69–1.30	1–6 drinks/week	0.89	0.60–1.31	1–6 drinks/week	1	0.71–1.40
		≥7 drinks/week	0.70	0.44–1.11	≥7 drinks/week	0.71	0.43–1.19	≥7 drinks/week	0.89	0.61–1.30
Harriss et al. 2007 [28]	CVD mortality									
	Female	None	1							
		0–10 g/day	0.59	0.36–0.95						
		>10 g/day	0.43	0.23–0.78						
	Male	None	1		None	1		None	1	
		0–20 g/day	0.88	0.65–1.21	0–20 g/day	1.24	0.9–1.71	0–10 g/day	1	0.74–1.35
		20–40 g/day	0.72	0.45–1.16	20–40 g/day	1.25	0.78–2.02	10–20 g/day	0.89	0.36–2.18
		>40 g/day	0.94	0.55–1.60	>40 g/day	0.74	0.37–1.48	>20 g/day	2.57	1.19–5.56
Schroder et al. 2007 [29]	AMI	0	1		0	1		0	1	
		<20 g/day	0.21	0.12–0.35	<20 g/day	0.17	0.09–0.31	<20 g/day	0.23	0.12–0.44
		≥20 g/day	0.3	0.16–0.56	≥20 g/day	0.22	0.09–0.52	≥20 g/day	0.81	0.3–2.2
Lu et al. 2008 [30]	AMI	0	1		0	1		0	1	
		≤ 100 mL/week	0.8	0.5–1.1	≤ 200 mL/week	0.7	0.5–1	≤ 16 mL/week	0.8	0.5–1.1
		> 100 mL/week	0.7	0.5–1	> 200 mL/week	0.7	0.5,1	> 16 mL/week	0.7	0.4–1
Suadicani et al. 2008 [31]	IHD mortality	0	1							
		1–8 drinks/week	0.6	0.4–0.96						
		>8 drinks/week	0.7	0.5–1.2						
	Total mortality	0	1							
		1–8 drinks/week	0.9	0.7–1.06						
		>8 drinks/week	0.9	0.7–1.09						
Streppel et al. 2009 [32]	CVD mortality	0	1		0	1		0	1	
		<20 g/day	0.68	0.53–0.86	<20 g/day	0.91	0.72–1.14	<20 g/day	0.93	0.7–1.24
		≥20 g/day	2.2	0.3–16.4	≥20 g/day	1.26	0.55–2.88	≥20 g/day	0.88	0.47–1.64
	Total mortality	0	1		0	1		0	1	
		<20 g/day	0.73	0.62–0.87	<20 g/day	0.98	0.83–1.17	<20 g/day	0.97	0.8–1.18
		≥20 g/day	1.21	0.17–8.82	≥20 g/day	1.37	0.74–2.53	≥20 g/day	1.09	0.69–1.73

AMI acute myocardial infarction, *CHD* coronary heart disease, *CI* confidence interval, *CVD* cardiovascular disease, *IHD* ischemic heart disease, *RR* relative risk

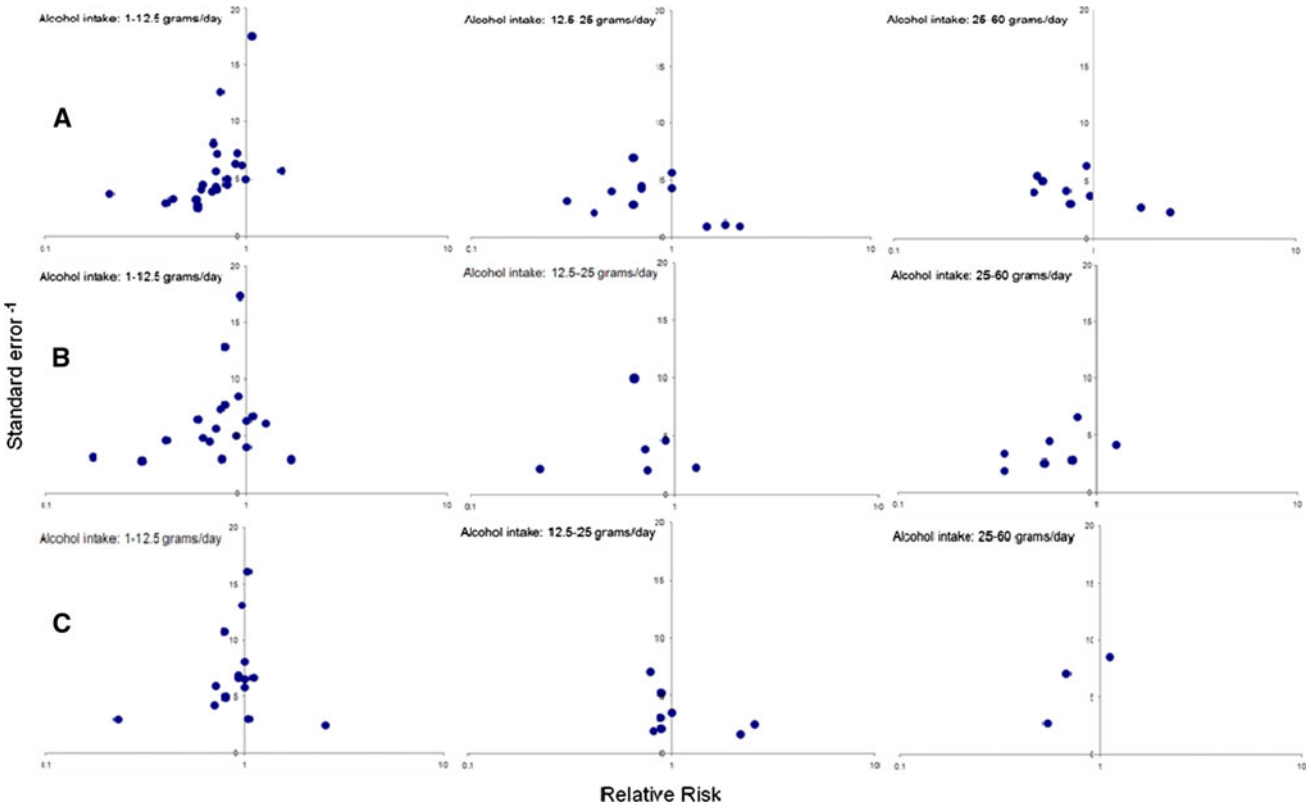

Fig. 2 Funnel plot for different intake categories (1–12.5 g/day, 12.5–25 g/day, 25–60 g/day) for meta-analyses on wine (**a**), beer (**b**) and spirit (**c**) consumption and vascular risk

In quality analyses, using both scales (The Newcastle-Ottawa Scale [38] and the score used by Tramacere et al. [39]), no heterogeneity of results was found according to the stratification of studies in low and high quality (*data not shown*).

When subgroup analyses were performed separately considering cohort or case–control studies, the maximal protection of about 30% in the range of 20–25 g/day of alcohol was confirmed in both pooled data (Table 3, $P = 0.7$). Pooled analyses of 6 studies [19, 22, 23, 25, 27, 28] that formally excluded former drinkers from the reference category, confirmed the maximal protection (28%; 95% CI: 9–44%) at moderate wine consumption against vascular risk (Table 3). In sensitivity analyses separately investigating the relationship between wine consumption and vascular events in 5 Mediterranean [17–19, 24, 29], 5 Northern European [21, 22, 30–32] and 6 Western (USA and Australia) [15, 16, 23, 25, 27, 28] countries, the J-shape curves were confirmed and appeared to be very similar among them (Sidak-adjusted P values for pairwise comparisons among countries were not statistically significant (Table 3)). Among cohort studies, the curves for short and long duration of follow-up were different ($P < 0.001$); in particular, β_1 was greater in shorter follow-up studies analysis, whereas β_2 was equal (Table 3). As a consequence, the pooled curves for the duration of follow-up were different for the range at which alcohol remained protective but comparable regarding the maximum protection at ligher doses.

Wine consumption and cardiovascular mortality

Six cohort studies [19, 21, 22, 28, 31, 32], involving 105,196 individuals (2,677 cardiovascular deaths), provided seven dose–response independent relationships for alcohol intake and cardiovascular mortality. The best-fitting model was obtained when $p = q = 0.5$ for both the fixed and random models. Deviances of fixed and random effects models fell from 18.0 to 6.2 ($P < 0.001$ for difference), indicating heterogeneity among studies. An overall J-shaped curve was obtained from the seven adjusted dose–response curves; the maximal protection was 34% at 24 g/day in the random-effects model (Table 3 and Fig. 4).

Wine consumption and mortality for any cause

Five cohort studies [19, 22, 26, 31, 32] (56,696 individuals and 11,905 deaths for any-cause) gathered information on wine consumption and total mortality and provided six

Table 3 Characteristics and results of the best fitting models: meta-analysis of wine consumption

Endpoint	No of curves	No of cases	Total sample size/no of controls	Maximal protection			Reversion point	Parameters of the best fitted model $\text{Log(RR)} = \beta_1\sqrt{x} + \beta_2\sqrt{x}*\log(x)$						
				%	95% CI	g/day	g/day	β_1	SE	*P*	β_2	SE	*P*	P for heterogeneity
Fatal and non-fatal CVD	17			31	19–42	21	72	–0.20	0.06	<0.001	0.04	0.01	0.004	<0.001
Study design[a]														
Cohort studies	12	5,554	288,363	30	16–42	24	56	–0.19	0.06	<0.001	0.04	0.01	0.006	<0.001
Case control studies	5	2,060	3,784	31	2–52	21		–0.20	0.14	0.08	0.04	0.03	0.1	<0.001
Publication bias														
Excluding studies which provided the asymmetry in the funnel plot	14			25	11–36	28	72	–0.14	0.06	0.009	0.03	0.01	0.04	<0.001
Adjustment														
Excluding studies adjusted only for age	13			25	11–37	27	72	–0.14	0.06	0.008	0.03	0.01	0.03	<0.001
Reference group														
Without former drinkers	7			28	9–44	24	54	–0.18	0.08	0.01	0.03	0.02	0.04	<0.001
Country[b]														
Mediterranean countries	5			32	11–49	25	70	–0.20	0.10	0.017	0.04	0.02	0.04	<0.001
Nordic countries	5			35	9–53	10	20	–0.30	0.16	0.034	0.07	0.05	0.09	0.12
USA and Australia	7			24	4–44	7	15	–0.23	0.12	0.03	0.06	0.04	0.08	<0.001
Duration of follow-up[c]														
Short (≤12 years)	7			25	6–38	8	18	–0.20	0.1	0.02	0.05	0.03	0.07	<0.001
Long (>12 years)	5			35	14–51	24	66	–0.23	0.09	0.007	0.05	0.02	0.021	<0.001
CVD, CHD, IHD mortality	7	2,677	105,196	34	18–47	24	66	–0.23	0.08	0.001	0.05	0.02	0.007	<0.001
Total mortality	6	11,905	56,696	25	14–34	10	41	–0.20	0.04	<0.001	0.05	0.01	<0.001	<0.001

CHD coronary heart disease, *CI* confidence interval, *CVD* cardiovascular disease, *IHD* ischaemic heart disease, *RR* relative risk

[a] *P* for difference = 0.7

[b] Sidak-adjusted *P* value for pairwise comparisons among countries Mediterranean countries versus Nordic countries $P = 0.97$; Mediterranean countries versus USA and Australia $P = 0.88$; Nordic countries versus USA and $P = 0$ 0.98

[c] *P* for difference < 0.001

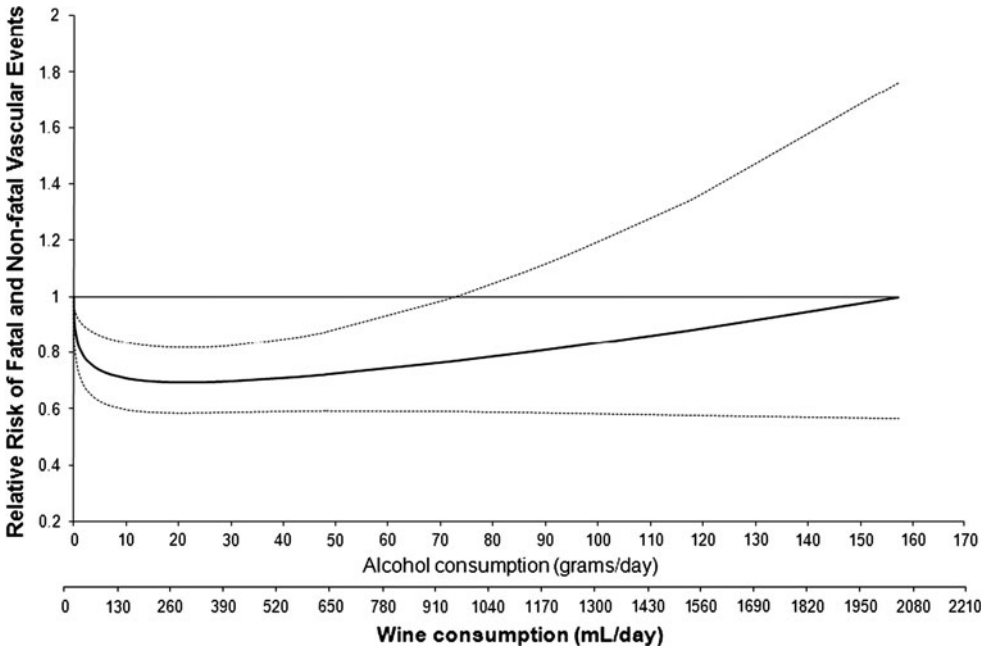

Fig. 3 Pooled curves of relative risk (95% CI: *dotted lines*) of fatal and non-fatal vascular events and wine intake, extracted from 17 independent relationships using random models

dose–response independent relationship, since one study reported results separately for men and women [26]. Random effect model was performed, using the model: $\text{Log(RR)} = \beta_1\sqrt{x} + \beta_2\sqrt{x}*\log(x)$ ($P < 0.001$ for difference random vs. fixed models). In these studies, a J-shape curve was confirmed, with 25% maximal risk reduction at approximately 10 g/day and significant protection up to 41 g/day (Table 3 and Fig. 5).

Beer consumption and fatal or non-fatal vascular events

Thirteen studies [15, 16, 18, 20, 21, 23–25, 27–30, 32] (8 prospective studies involving 224,219 individuals (4,823 events) and five case–control studies involving 1,964 cases and 3,834 controls) provided 13 dose–response independent relationships for beer consumption and fatal or non fatal vascular events. Symmetric funnel plots ($\alpha = 0$) were obtained for all the categories of beer intake, showing the absence of publication bias (Fig. 2b). The best-fitting model was obtained when $p = q = 1$, corresponding to the model: $\text{Log(RR)} = \beta_1 x + \beta_2 x*\log(x)$, for both the fixed and random models. The deviances of fixed and random effects models fell from 104.6 to 32.8 ($P < 0.001$ for difference), suggesting heterogeneity among studies. Using a random effects model with $p = q = 1$, the possible role of study characteristics was explored to explain the inter-study heterogeneity. Fitted parameters for the random model were $\beta_1 = -0.06$ (SE = 0.02; $P = 0.009$) and $\beta_2 = 0.01$ (SE = 0.007; $P = 0.04$) (Table 4). The relationship observed was interpreted as a J-shaped curve; the association with a lower vascular risk was apparent up to 55 g/day and the lowest risk was seen at 43 g/day (RR = 0.58; 95% CI: 0.42–0.81; Table 4 and Fig. 6).

In quality analyses, using both scales mentioned above, no heterogeneity of results was found according to the stratification of studies in low and high quality (*data not shown*). A J-shape relationship between beer consumption and vascular risk was also confirmed by pooling data from case–control studies, with a maximal protection of about 60% at 36 g/day of alcohol (Table 4). However, performing a sensitivity analysis excluding the three studies only adjusted for age [15, 16, 29] or a sub-group analysis of 5 studies [20, 23, 25, 27, 28] that formally excluded former drinkers from the reference category, or by country categorization (Mediterranean [18, 24, 29], Northern European [20, 21, 30, 32] and Western [15, 16, 23, 25, 27, 28] countries), the characteristic J-shape relationship for beer consumption and vascular risk was no more apparent (Table 4).

As a small number of studies only investigated the relationship between beer consumption and cardiovascular [21, 28, 32] and/or total mortality [26, 32], it was not possible to perform any meta-analysis related to these clinical end-points.

Comparison of wine and beer consumption in relation to vascular risk

From 12 studies [15, 16, 18, 21, 23–25, 27–30, 32] (8 prospective studies involving 224,219 individuals (4,823 events) and four case–control studies involving 1,762 cases and 3,099 controls) that reported separate data both on

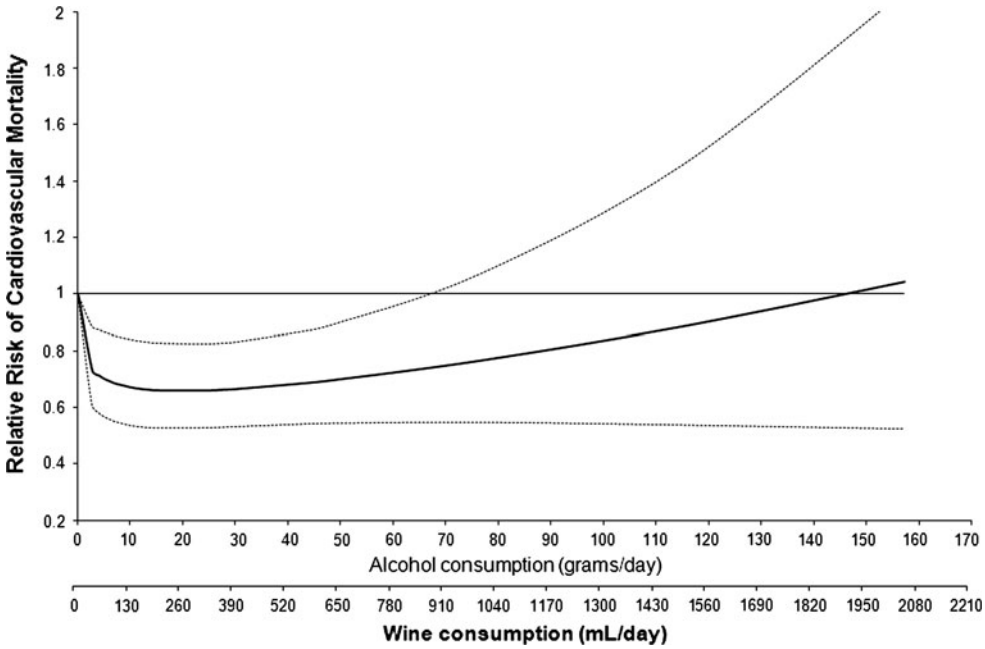

Fig. 4 Pooled curves of relative risk (95% CI: *dotted lines*) of fatal and cardiovascular mortality and wine intake, extracted from seven independent relationships using random models

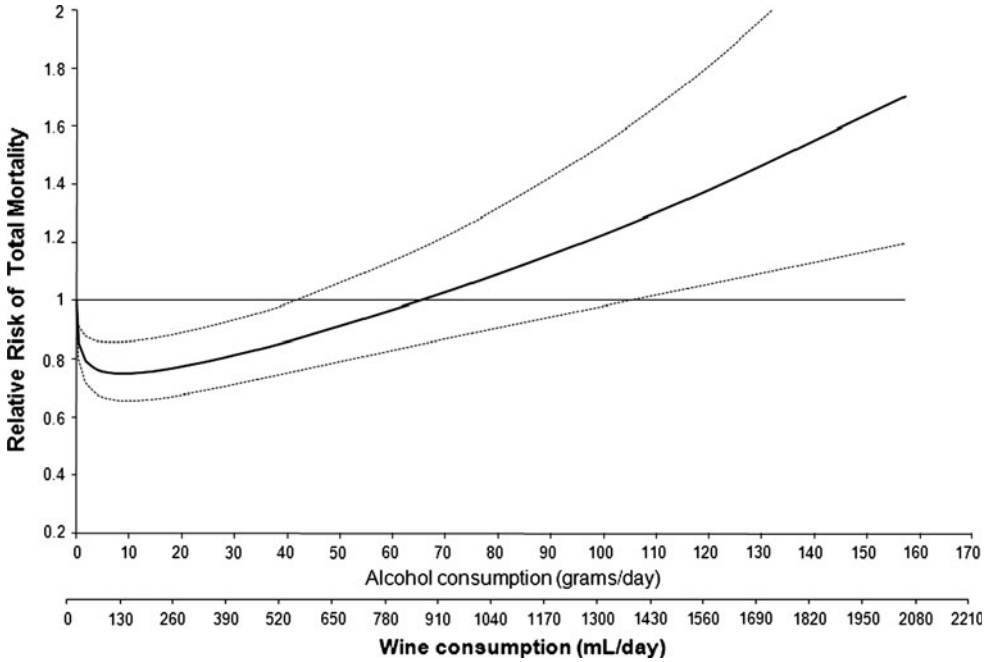

Fig. 5 Pooled curves of relative risk (95% CI: *dotted lines*) of fatal and all-cause mortality and wine intake, extracted from six independent relationships using random models

wine and beer consumption in relationship with vascular risk, two similar dose–response curves were obtained ($P = 0.4$, Table 5 and Fig. 7). The two curves were closely overlapping, especially at light-moderate alcohol consumption and the maximal protection by either beverage was 33% at 25 g/day (Table 5 and Fig. 7). This similarity between wine and beer's protection persisted even when the studies that did not simultaneously adjust for different types of alcoholic beverages or total amount of alcohol, were excluded (Table 5, $P = 0.2$).

Spirit consumption and fatal and non-fatal vascular events

In a meta-analysis of 10 studies [15, 18, 21, 23, 25, 27–30, 32] on spirit consumption and vascular risk (seven prospective studies involving 136,693 individuals (4,523 events) and three case–control studies involving 1,255 cases and 2,621 controls), no J-shaped relationship could be found (Fig. 8). Symmetric funnel plots ($\alpha = 0$) were obtained for all the categories of spirit intake, showing the absence of

Table 4 Characteristics and results of the best fitting models: meta-analysis of beer consumption

Endpoint	No of curves	No of cases	Total sample size/ No of controls	Maximal protection			Reversion point	Parameters of the best fitted model $\text{Log(RR)} = \beta_1 x + \beta_2 x^* \log(x)$						
				%	95% CI	g/day	g/day	β_1	SE	*P*	β_2	SE	*P*	P for heterogeneity
Fatal and non-fatal CVD	13			42	19–58	43	55	−0.06	0.02	0.009	0.01	0.007	0.04	<0.001
Study design														
Cohort studies	8	4,823	224,219					−0.03	0.03	0.2	0.006	0.008	0.2	<0.001
Case control studies	5	1,964	3,834	60	34–64	36	50	−0.11	0.04	0.004	0.02	0.01	0.02	<0.001
Adjustment														
Excluding studies adjusted only for age	10							−0.03	0.02	0.09	0.005	0.006	0.2	<0.001
Reference group														
Without former drinkers	5							−0.008	0.03	0.4	−0.001	0.008	0.4	<0.001
Country[a]														
Mediterranean countries	3							−0.14	0.15	0.2	0.03	0.05	0.3	<0.001
Nordic countries	4							−0.05	0.04	0.1	0.009	0.01	0.2	<0.001
USA and Australia	6							−0.02	0.03	0.3	0.002	0.01	0.4	<0.001

CI confidence interval, *CVD* cardiovascular disease, *RR* relative risk

[a] Sidak-adjusted *P* value for pairwise comparisons among countries Mediterranean countries versus Nordic countries $P = 0.14$; Mediterranean countries versus USA and Australia $P = 0.4$; Nordic countries versus USA and $P = 0.16$

publication bias (Fig. 2c). Neither the first nor the second order terms of the model $\text{Log(RR)} = \beta_1\sqrt{x} + \beta_2\sqrt{x}^*\log(x)$ were statistically significant, the fitted parameters for the random model being $\beta_1 = -0.01$ (SE = 0.10; $P = 0.4$) and $\beta_2 = -0.005$ (SE = 0.03; $P = 0.4$).

As a small number of studies only investigated the relationship between spirits consumption and cardiovascular [21, 28, 32] and/or total mortality [26, 32], it was not possible to perform any meta-analysis related to these clinical end-points.

Discussion

A previous meta-analysis had shown a clear inverse dose–effect curve against vascular events for wine but not for beer intake [2]. Evidence from the current updated and extended meta-analysis confirms the significant reduction of overall vascular risk associated with wine consumption and shows, apparently for the first time, a similar J-shaped relationship between beer intake and cardiovascular risk. Moreover, the comparison of studies which included a parallel, separate evaluation of wine and beer consumption, indicates a similar protecting effect of either beverage against cardiovascular risk (Fig. 7).

Thus, in relation to health, drinking in moderation is more important than the content of the bottle, at least when wine and beer are taken into consideration.

On the contrary, no statistically significant association with vascular events was apparent for the intake of spirits up to 60 g/day, which is the maximum dose investigated in the 10 studies included in this meta-analysis. In several studies spirit consumption mostly occurred as binge drinking (defined as the consumption of three or more drinks within 1–2 h) and was restricted to only few days per week. This may explain the absence of association between moderate spirit consumption and cardiovascular disease observed, in contrast, for the other two alcoholic beverages both in the present meta-analysis and in a previous study [40]. It is known that drinking out of mealtimes and binge drinking are associated with increased CHD risk [41–44], both behaviours being preferentially linked to the type of alcoholic beverage consumed [45–47].

Moderate alcohol drinking reportedly induces healthy changes in lipid profile, vascular, haemostatic and endothelial cell function, platelet aggregation and inflammation [8, 9]. On the other hand, beer and wine contains different substances that might provide additional cardiovascular benefit to that obtained by alcohol. If liquor -the drink with the purest concentration of alcohol - does not clearly decrease vascular events (the negative association between spirit intake and vascular events was non-significant in the present meta-analysis), it should not lead us to the

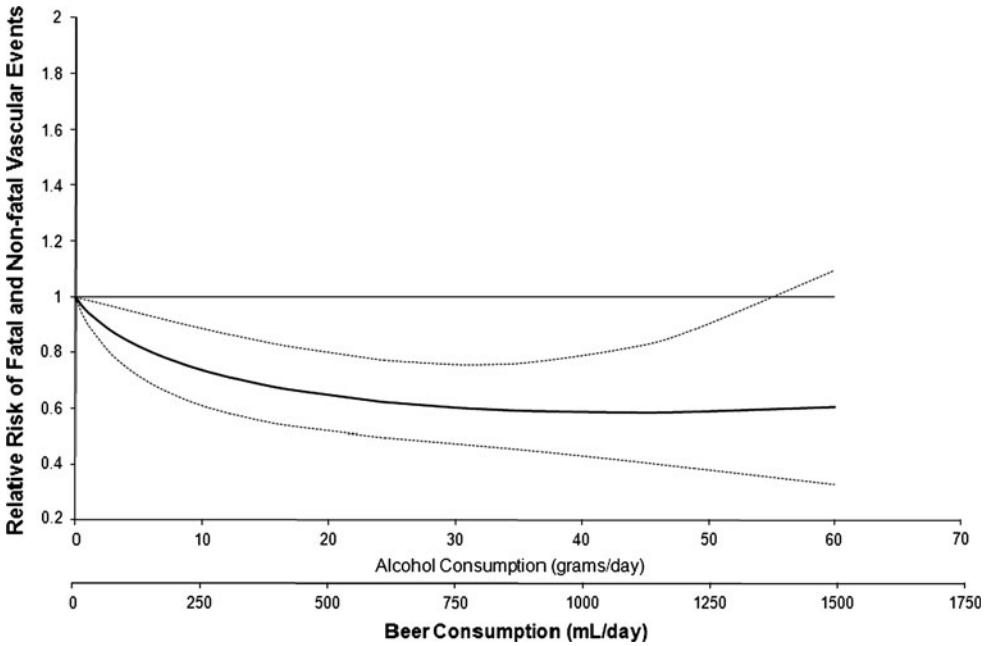

Fig. 6 Pooled curves of relative risk (95% CI: *dotted lines*) of fatal and non-fatal vascular events and beer intake, extracted from 13 independent relationships using random models

Table 5 Results of best fitting models of meta-analysis of studies reported data both on wine and beer consumption in relationship with vascular risk

	No of curves	Maximal protection			Reversion point	Parameters of the best fitted model $\text{Log(RR)} = \beta_1\sqrt{x} + \beta_2\sqrt{x}*\log(x)$						
		%	95% CI	g/day	g/day	β_1	SE	*P*	β_2	SE	*P*	P for heterogeneity
Wine consumption	12	32	18–44	25	70	−0.19	0.07	0.003	0.04	0.02	0.03	<0.001
Beer consumption	12	33	13–48	25	43	−0.17	0.10	0.04	0.03	0.03	0.2	<0.001
Adjusted studies for different types of alcohol beverages or total amount of alcohol intake												
Wine consumption	7					−0.22	0.15	0.06	0.05	0.05	0.2	<0.001
Beer consumption	7					−0.16	0.16	0.16	0.02	0.05	0.3	<0.001

CI confidence interval, *RR* relative risk

conclusion that polyphenolic constituents found in wine or beer are (mainly) responsible for the beneficial effect on vascular events [9–12, 48, 49]. In fact the proportion of subjects consuming liquors is much lower than that consuming wine or beer and patterns of liquor consumption are very different. We cannot therefore exclude that the negative association of wine and beer drinking with cardiovascular events could be (mainly) due to ethanol itself.

Effects of different alcoholic beverages on different clinical outcomes

We tried to dissect the potential benefit of wine or beer consumption on different clinical end-points. Both wine and beer consumption were comparable as far as the reduction of the risk of combined fatal and non fatal cardiovascular events was concerned. Wine drinking was also effective in reducing both cardiovascular and total mortality. The maximum intake of wine at which protection was still apparent decreased from 72 to 66 to 41 g/day when either combined fatal and non fatal vascular events, or cardiovascular mortality or total mortality were considered as endpoint, respectively. At variance, the minimal doses of wine at which its maximal protection could be obtained were 21, 24 and 10 g/day, respectively. Thus, while low-moderate doses are similarly protective against any clinical endpoint considered, the hardest the endpoint, the lowest the amount of wine that starts to be associated with harm. The maximum protection obtained at light-moderate wine intake gradually vanishes at higher doses that differ according to different clinical endpoints, possibly because of increase in harmful collateral effects.

Unfortunately, the very limited data available about either beer or spirit consumption in relation to cardiovascular or total mortality, did not allow us to perform a fully meta-analytic investigation on the latter two beverages.

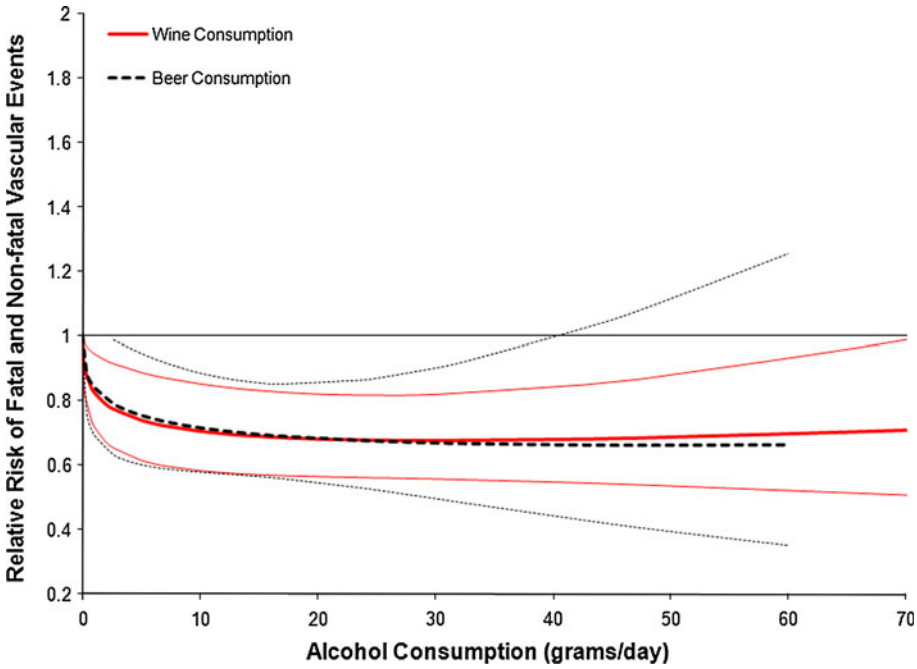

Fig. 7 Curves for wine intake (*solid lines*) and beer intake (*dotted lines*) were extracted from the same studies

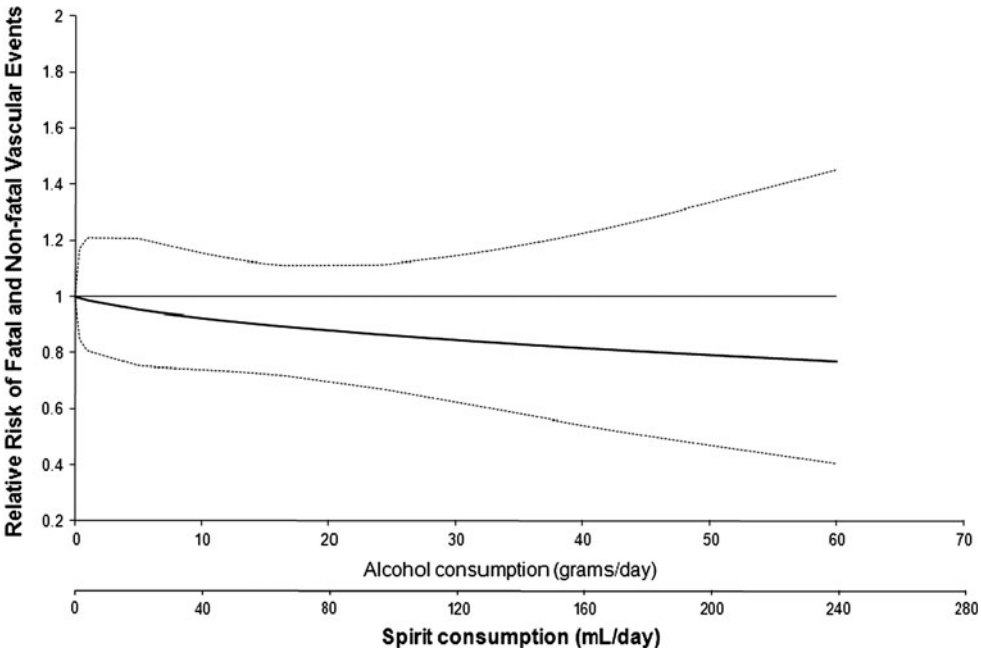

Fig. 8 Pooled curves of relative risk (95% CI: *dotted lines*) of fatal and non-fatal vascular events and spirit intake, extracted from 10 independent relationships using random models

Limitations

All the studies included in our meta-analyses were observational, and could be themselves associated with a number of limitations: the alcohol patterns assessed only once at inclusion into the study, the absence of detailed history of alcohol consumption behavior and the possible changes in alcohol habits could have had an effect on the relation of alcohol consumption with cardiovascular events. Randomized controlled trials would offer a more solid answer than observational studies to many questions in medicine; the latter are mainly restricted, however, to the efficacy of drugs and are difficult and ethically questionable to perform to evaluate alcohol effects [4, 9]. On the other hand, the results of well-designed observational studies (with either a cohort or a case–control design) do not systematically overestimate the magnitude of the effects as compared with those in randomized, controlled trials on the same topic [50]. In particular it is believed that self-reported wine or beer consumption is inaccurate. Under-reporting on wine or beer drinkers would however result in a tendency for relative risks to be biased toward the null

hypothesis, while our meta-analysis showed significant associations. The potential confounding effect of combined drinking of different types of alcoholic beverages in the same population was excluded by pooling data from studies that had taken this issue into consideration (Table 5).

Wine drinkers, at least in some Countries, tend to have a healthier lifestyle profile than beer drinkers. This uncontrolled confounding can be reasonably excluded, as the great majority of studies were adjusted for these variables (Table 1). Furthermore, a sensitivity analysis investigated the relationship between wine or beer consumption and vascular events in Mediterranean and not-Mediterranean Countries, but did find comparable results among them (Tables 3 and 4).

A weakness of all pooling studies on alcohol consumption is the heterogeneity among the reference groups, which sometimes have included lifelong teetotallers, former drinkers and/or occasional drinkers [51]. In few articles of this meta-analysis, the Authors did not clearly state if former or occasional drinkers were excluded from the reference group; however, analysis of five studies on wine consumption that formally excluded former drinkers confirmed the significant relation between drinking in moderation and vascular risk.

The results of any meta-analysis, especially in non-experimental epidemiology, may be invalid due to publication bias [52]. The funnel plot analysis revealed symmetry for all categories of beer, spirit and wine intake, except for the lowest category of wine intake, suggesting the presence of a slight publication bias, if any. However, after the exclusion of the studies which determined the asymmetry in the funnel plot, the J-shape relationship between wine consumption and vascular risk was confirmed.

Alcohol may have different health effects in men and women [3]. Unfortunately, the paucity of data separately reported for either sexes, made it impossible to include men or women in two distinct meta-analyses [2, 4]. Standing from previous data on total alcohol intake [3, 4] optimal consumption of alcohol should be reduced in women- 1 unit a day instead of 2 units in men. However, if this difference holds separately for wine or beer remains to be investigated.

Significant protection could be extrapolated from the curves obtained up to doses of alcoholic beverages of 72 g/day that must be no doubt considered as a heavy intake. Besides the fact that the doses of alcohol associated with maximum protection should be chosen rather than that at which harm may start, the majority of the studies included in our meta-analyses did not in fact investigate such a large range of alcohol intake; the inferences from pooled curves at larger amounts of alcohol were a mathematical trick rather than a finding derived from experimental data. On the contrary, the conclusions obtained on the protection at light-moderate alcohol intake are quite solid as they are based on a very large amount of experimental data.

In conclusion, this meta-analysis provides further evidence for a J-shaped significant inverse association between wine consumption and vascular risk and shows a similar relationship for beer consumption. Dose–response curves from comparable studies appeared substantially similar for either alcoholic beverage. No protection was apparent instead, in association with the consumption of any spirit amount.

The hazards of excess or binge alcohol drinking should be always highlighted and heavy or binge drinkers pushed to cut their consumption to a regular, low-moderate level.

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Conflict of interest This was an investigator-initiated study. The partial sponsor of the study had no role in the selection of articles or conduct of the analyses or drafting of the manuscript. We disclaim any other relationships with industry that might pose a conflict of interest in connection with the submitted article.

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