

Alcohol Dosing and Total Mortality in Men and Women

An Updated Meta-analysis of 34 Prospective Studies

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Background: Moderate consumption of alcohol is inversely related with coronary disease, but its association with mortality is controversial. We performed a meta-analysis of prospective studies on alcohol dosing and total mortality.

Methods: We searched PubMed for articles available until December 2005, supplemented by references from the selected articles. Thirty-four studies on men and women, for a total of 1 015 835 subjects and 94 533 deaths, were selected. Data were pooled with a weighed regression analysis of fractional polynomials.

Results: A J-shaped relationship between alcohol and total mortality was confirmed in adjusted studies, in both men and women. Consumption of alcohol, up to 4 drinks per day in men and 2 drinks per day in women, was inversely associated with total mortality, maximum protection being

18% in women (99% confidence interval, 13%-22%) and 17% in men (99% confidence interval, 15%-19%). Higher doses of alcohol were associated with increased mortality. The inverse association in women disappeared at doses lower than in men. When adjusted and unadjusted data were compared, the maximum protection was only reduced from 19% to 16%. The degree of association in men was lower in the United States than in Europe.

Conclusions: Low levels of alcohol intake (1-2 drinks per day for women and 2-4 drinks per day for men) are inversely associated with total mortality in both men and women. Our findings, while confirming the hazards of excess drinking, indicate potential windows of alcohol intake that may confer a net beneficial effect of moderate drinking, at least in terms of survival.

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AN INVERSE ASSOCIATION BETWEEN moderate alcohol consumption and coronary heart disease has been shown in observational studies.¹⁻³ Mechanisms supporting this association include increased high-density lipoprotein cholesterol level and fibrinolysis, decreased platelet aggregation and coagulation factors,⁴ and beneficial effects on endothelial function and inflammation.⁵ Nonetheless, abuse of alcohol is unquestionably harmful.⁶⁻⁸ As a consequence, strong interest exists about the possibility that at any dose, the benefit of alcohol can overcome its harmful effects.^{7,8}

The relationship between alcohol and mortality has been depicted as a J-shaped curve, attributed to a combination of beneficial and harmful effects.⁹⁻¹¹ Indeed, if low alcohol intake is inversely related to coronary heart disease, the other side of the coin shows an increased risk of certain cancers, cirrhosis, and death from accidents associated with increased alcohol consumption.⁶

Moreover, whether alcohol has a different role in men and women is still debated. In previous studies, a similar inverse association of low doses of alcohol with cardiovascular disease in men and women was noted,^{7,12} but a meta-analysis of total mortality revealed a J-shaped relation only for men older than 34 years or women older than 54 years.⁹ Herein, we perform an updated meta-analysis of prospective studies to investigate the relationship between alcohol dosing and all-cause mortality, separately in men and women.

METHODS

SEARCH STRATEGY AND DATA EXTRACTION

A PubMed search (www.pubmed.gov) identified studies published until December 2005, without a start date; studies were restricted to humans, and their titles and/or abstracts contained at least 1 of the following terms: *alcohol*, *beer*, *wine*, or *spirits* plus the term *mortal-*

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Table 1. Summary of the Characteristics of 34 Cohort Studies on the Effect of Alcohol Consumption on All-Cause Mortality Included in the Meta-analysis

Source	Country	Follow-up, y	Age Range, y	Total Subjects, No.	Cases, No.	Level of Adjustment*	Subject Sex and Notes
Lin et al, ¹³ 2005	Japan	10	40-79	80 583	7334	1, 3, 5, 6, 7, 8, 9	M and F
Doll et al, ¹⁴ 2005	England	23	48-78	10 741	6425	1, 5	M
Nakaya et al, ¹⁵ 2004	Japan	11	40-64	39 076	1656	1, 3, 4, 5, 8, 9, 10, 17	M and F
Britton and Marmot, ¹⁶ 2004	England	11	35-55	10 214	282	NR	M and F
Tolstrup et al, ¹⁷ 2004	Denmark	8	55-65	43 982	2443	3, 5, 6, 7, 10, 17	M and F
Waskiewicz et al, ¹⁸ 2004	Poland	9.7	35-64	5452	745	1, 3, 5, 11, 12	M and F
Arndt et al, ¹⁹ 2004	Germany	10	25-64	17 165	693	1, 2, 5	M
Malyutina et al, ²⁰ 2002	Russia	9.5	25-64	5645	815	1, 3, 5, 6, 11, 12	M
Rehm et al, ²¹ 2001	United States	11.3	≥18	4258	411	1, 3, 4, 5	M and F
Theobald et al, ²² 2001	Sweden	26	18-65	28 001	4024	NR	M and F
Liao et al, ²³ 2000	United States	6	≥40	29 610	3333	1, 2, 5, 8, 9, 13	M and F
Gaziano et al, ²⁴ 2000	United States	5.5	40-84	89 299	3216	1, 5, 6, 7, 9, 14	M
Wannamethee and Shaper, ²⁵ 1999	England	16.8	40-59	7272	1308	1, 4, 5, 6, 7, 9, 13, 15, 16	M
Hoffmeister et al, ²⁶ 1999	Germany	6.9	25-69	15 400	159	1, 3, 5	M and F
Tsugane et al, ²⁷ 1999	Japan	6	40-59	17 131	491	1, 3, 5, 7, 8, 15, 17	M
Hart et al, ²⁸ 1999	Scotland	21	35-64	5766	1643	1, 3, 5, 6, 11, 12, 13, 15, 16	M
Renaud et al, ²⁹ 1999	France	15	40-60	36 250	3617	1, 3, 5, 6	M; separate data for different types of beverage
Deev et al, ³⁰ 1998	United States and Russia	13	40-69	5565	1258	1, 5, 6	M and F; separate data for United States and Russia
Brenner et al, ³¹ 1997	Germany	7	25-64	6689	140	NR	M
Yuan et al, ³² 1997	China	7.3	45-64	17 861	1198	1, 3, 5, 17	M
Keil et al, ³³ 1997	Germany	7.9	45-64	2084	141	1, 5, 6, 8	M and F
Simons et al, ³⁴ 1996	Australia	6.4	≥60	2787	544	1, 5, 6, 8, 9, 12, 19, 21	M and F
Fuchs et al, ³⁵ 1995	United States	12	34-59	85 709	2658	1, 5, 7, 8, 9, 12, 17, 18, 19, 20	F
Rehm and Sempos, ³⁶ 1995	United States	15	25-74	8662	2128	1, 3, 5, 6, 11, 12, 17	M and F; separate data for ages 25-59 y and ≥60 y
Goldberg et al, ³⁷ 1994	Japan	15	51-75	3793	819	1, 5, 10, 11, 12, 17	M; separate data for ages 51-64 y and ≥65
Gronbaek et al, ³⁸ 1994	Denmark	11	30-79	13 285	2229	NR	M and F
Cullen et al, ³⁹ 1993	Australia	23	≥40	2066	965	1, 3, 5, 8, 9, 10, 11, 12, 13, 15	M and F
Klatsky et al, ⁴⁰ 1992	United States	7	All	124 740	4184	1, 3, 4, 5, 6, 22	M and F
Farchi et al, ⁴¹ 1992	Italy	15	45-64	1536	463	1, 3, 5, 6	M
Andreasson et al, ⁴² 1991	Sweden	15	≥18	49 464	917	NR	M
Boffetta and Garfinkel, ⁴³ 1990	United States	12	40-59	239 462	37 079	1, 5	M
Kono et al, ⁴⁴ 1986	Japan	19	All	3033	804	1, 5	M
Marmot et al, ⁴⁵ 1981	UK	10	40-64	1422	113	1	M
Dyer et al, ⁴⁶ 1981	United States	17	40-55	1832	298	1	M

Abbreviation: NR, not reported.

*Adjustment codes: 1, age; 2, race; 3, education/profession/social class; 4, marital status; 5, smoking status; 6, body mass index; 7, physical activity; 8, hypertension; 9, diabetes mellitus; 10, baseline diseases; 11, blood pressure; 12, cholesterol level; 13, myocardial infarction or coronary heart disease; 14, risk factors for coronary heart disease; 15, forced expiratory volume in 1 second; 16, siblings; 17, dietary factors; 18, aspirin use; 19, family history of myocardial infarction or coronary heart disease; 20, menopausal status; 21, self-rated health; 22, coffee and tea.

ity or death. Assessment of the references was also conducted. Seventy-three publications were identified. Studies were excluded if they considered only 1 category of risk (n=4) or did not report mortality separately for the sexes (n=5); if they considered mortality for specific causes (n=3) or if they comprised multiple reports (n=9) (the longer follow-up was considered); or if the refer-

ence category was not the one with the lowest alcohol intake (n=4) or if relative risks or numbers of cases and person-years were not available (n=14). A total of 34 reports were identified.¹³⁻⁴⁶ Fourteen studies* reported results sepa-

*References 13, 15-18, 21-23, 26, 33, 34, 38-40.

rately for the sexes; 1 study³⁷ reported data for 2 age groups, and 1 study²⁹ for wine and beer. These studies contributed 2 dose-response curves each. Two studies contributed 4 curves: 1 study³⁰ reported results separately for 2 ethnic groups and sexes, and another³⁶ for age groups and sexes. In the end, 56 independent curves were available for meta-analysis, 37 in men and 19 in women.

Whenever possible, adjusted relative risks were extracted; otherwise, crude relative risks and 95% confidence intervals (CIs) were calculated from the number of events.^{16,22,31,38,42}

The amount of a *drink* was taken as quantified by each author whenever possible; otherwise (7 studies) it was considered equivalent to 10 g of ethanol; considering a drink equivalent to either 12 or 14 g of ethanol did not change our results (data not shown).

DATA ANALYSIS

Data collected were as follows: (1) the value x of alcohol intake (measured in grams per day) assigned as the midpoint of the reported ranges; x was defined as 1.2 times the lower boundary for the open-ended upper categories⁴⁷; (2) frequency counts, adjusted relative risks, and 95% CIs for each x level; and (3) covariates describing the characteristics of the study. Inverse variance-weighted methods, taking into account the correlation between estimates within each study, were used.⁴⁷ The models to be fitted were selected among fractional polynomial curves of the second order.⁴⁸ Fractional polynomials are a family of models considering power transformations of a continuous exposure variable, restricted to a predefined set of integer and noninteger exponents.⁴⁹ The regression models were $\log(\text{relative risk [RR]}) = \beta_1 x^p + \beta_2 x^q$ and the exponents p and q were selected among the following set: $\{-2.0, -1.0, -0.5, 0.0, 0.5, 1.0, 2.0\}$. When $p=0$, x^p is replaced by $\log(x)$, and when $p=q$, the model becomes $\log(\text{RR}|x) = \beta_1 x^p + \beta_2 x^q \log(x)$.¹¹ These choices account for a rich set of possible functions, including J-shaped relations and conventional polynomials. The best fit was defined as that with the highest likelihood. This method assumes that the only source of variability is within study (fixed-effects model). 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).⁵⁰ The effects of covariates were evaluated, including appropriate interaction terms between covariate and exposure.⁴⁷ To make some allowance for multiple comparisons, 99% CIs were used in subgroup analyses, and pairwise contrasts were adjusted following the Sidak method, as outlined by Ludbrook.⁵¹ All analyses were carried out using an SAS

Table 2. General Characteristics and Results of Best Fitting Models

Subgroup	Curves, No.	Subjects, No.	Deaths, No.	Maximum Protection, % (99% CI) g/d	Reversion Point, g/d*
All	56	1 015 835	94 533	19 (17-20)†	6
Level of adjustment					
Not adjusted	8	107 653	7 592	36 (21-40)	10
Adjusted at least for age	48	908 182	86 941	17 (15-18)	6
Adjusted for social status too	28	414 680	29 560	18 (15-21)	9
Adjusted for social status and dietary factors too	10	126 712	7 916	18 (12-24)	6
Sex‡					
Women	16	285 490	13 448	18 (13-22)	5
Men	32	622 692	73 493	17 (15-19)	6
Country‡					
Women					
United States	7	182 307	7 576	19 (13-24)	5
Europe	5	34 036	1 464	20 (3-34)	4
Australia, Japan, China	4	69 147	4 408	12 (0-23)	5
Men					
United States	9	404 428	46 278	16 (14-19)	4
Europe	14	121 081	17 812	24 (20-28)	9
Australia, Japan, China	9	97 183	9 403	18 (13-23)	6
Type of reference group‡					
With light and/or former drinkers	21	247 194	23 937	23 (20-26)	8
Without light and/or former drinkers	27	660 988	63 004	16 (14-18)	5
Sample size‡					
Small ($n \leq 6000$)	26	53 901	11 147	17 (15-22)	5
Large ($n > 6000$)	22	854 281	75 794	15 (10-20)	5
Duration of follow-up‡					
Short (≤ 10 y)	22	453 161	25 409	21 (18-25)	6
Long (> 10 y)	26	455 021	61 532	15 (13-27)	6
Year of publication‡					
1981-1998	25	500 552	52 652	15 (13-18)	5
1999-2005	23	407 630	34 289	21 (18-24)	8

Abbreviation: CI, confidence interval.

*The reversion point is defined as the dose of alcohol at which the protection against total mortality is no longer statistically significant at the 99% confidence level.

†95% CI rather than 99% CI.

‡In the 48 adjusted studies.

macro,¹¹ version 8.12 for Windows (SAS Institute Inc, Cary, NC).

RESULTS

ALL STUDIES

Thirty-four studies provided 56 independent dose-response curves for alcohol intake and mortality, for a total of 1 015 835 subjects and 94 533 deaths from any cause. Thirty-seven curves (705 596 subjects and 78 592 deaths) concerned men, and 19 (310 239 subjects and 15 941 deaths), women. Characteristics of the studies are listed in **Table 1**. Briefly, 28 curves were from European, 17 from American, and 11 from other populations. Al-

most half of the studies had a median follow-up longer than 10 years. A category of no alcohol intake that also excluded former drinkers was considered as the reference category for most curves ($n=30$); the others curves used as reference those subjects who declared either no alcohol use ($n=12$) or occasional use ($n=14$); former drinkers were not excluded from either group.

The best fitting model was obtained at $p=q=0.5$, corresponding to the model $\log(\text{RR}) = \beta_1 \sqrt{x} + \beta_2 \sqrt{x} \times \log(x)$. The fitted parameters (SE) were $\beta_1 = -0.1592$ (0.0056) ($P < .001$) and $\beta_2 = 0.0421$ (0.0014) ($P < .001$) (**Table 2** and **Table 3**). The relationship observed has to be interpreted as a J-shaped curve (**Figure 1**)

Table 3. Statistical Characteristics and Results of Best Fitting Models

Subgroup	Parameters of the Best Fitted Model				P Value for Difference
	β_1 (SE)	P Value	β_2 (SE)	P Value	
All	-0.1592 (0.0056)	<.001	0.0421 (0.0014)	<.001	
Level of adjustment					
Not adjusted	-0.2927 (0.0165)	<.001	0.0661 (0.0040)	<.001	
Adjusted at least for age	-0.1437 (0.0059)	<.001	0.0388 (0.0015)	<.001	<.001*
Adjusted for social status too	-0.1425 (0.0094)	<.001	0.0356 (0.0022)	<.001	<.001†
Adjusted for social status and dietary factors too	-0.1594 (0.0215)	<.001	0.0428 (0.0055)	<.001	.03‡
Sex§					<.001
Women	-0.1719 (0.0184)	<.001	0.0533 (0.0056)	<.001	
Men	-0.1445 (0.0063)	<.001	0.0388 (0.0015)	<.001	
Country§					
Women					>.54
United States	-0.1829 (0.0215)	<.001	0.0562 (0.0064)	<.001	
Europe	-0.2047 (0.0657)	<.001	0.0678 (0.0207)	<.001	
Australia, Japan, China	-0.1044 (0.0458)	.01	0.0295 (0.0149)	.02	
Men					.003¶
United States	-0.1489 (0.0088)	<.001	0.0431 (0.0023)	<.001	
Europe	-0.1923 (0.0121)	<.001	0.0460 (0.0028)	<.001	
Australia, Japan, China	-0.1513 (0.0180)	<.001	0.0406 (0.0043)	<.001	
Type of reference group§					<.001
With light and/or former drinkers	-0.1825 (0.0110)	<.001	0.0444 (0.0025)	<.001	
Without light and/or former drinkers	-0.1429 (0.0073)	<.001	0.0405 (0.0019)	<.001	
Sample size§					.61
Small (n≤6000)	-0.1230 (0.0160)	<.001	0.0337 (0.0039)	<.001	
Large (n>6000)	-0.1459 (0.0664)	<.001	0.0393 (0.0016)	<.001	
Duration of follow-up§					<.001
Short (≤10 y)	-0.1852 (0.0110)	<.001	0.0486 (0.0027)	<.001	
Long (>10 y)	-0.1268 (0.0070)	<.001	0.0347 (0.0017)	<.001	
Year of publication§					<.001
1981-1998	-0.1388 (0.0079)	<.001	0.0399 (0.0020)	<.001	
1999-2005	-0.1733 (0.0094)	<.001	0.0432 (0.0022)	<.001	

*For the comparison adjusted (n = 48) vs not adjusted (n = 8).

†For the comparison adjusted for social status (n = 28) vs adjusted except for social status (n = 20).

‡For the comparison adjusted for social status and dietary factors (n = 10) vs adjusted for social status but not for dietary factors (n = 8).

§In the 48 adjusted studies.

||Sidak-adjusted P value for pairwise comparisons among countries for women were United States vs other, P = .59; United States vs Europe, P = .94; Europe vs other, P = .53.

¶Sidak-adjusted P value for pairwise comparisons among countries for men were United States vs other, P < .001; United States vs Europe, P = .002; Europe vs other, P = .003.

since, after an initial decrease in mortality by increasing alcohol intake (a shape depending on the negative value of β_1), the curve reaches a plateau and reverts at higher amounts ($\beta_2 > 0$). The association with a lower mortality was apparent up to 42 g/d (about 4 drinks per day), and the lowest mortality was seen at 6 g/d, or about half a drink daily (RR, 0.81 [95% CI, 0.80-0.83]). The meta-regression analysis was repeated using random-effects models. The model with $p=q=0.5$ was again selected; the curve was very similar (Figure 1), but as expected, CIs were larger. The deviances of fixed and ran-

dom effects models fell from 879.4 to 154.0 ($P < .001$ for the difference), suggesting evidence of heterogeneity among studies. In the following analyses, the role of study characteristics in explaining the interstudy heterogeneity was explored. The model with $p=q=0.5$ was consistently fitted.

ADJUSTED STUDIES

Forty-eight curves (908 182 subjects and 86 941 deaths) were adjusted at least for age; among them, 28 were adjusted for social status too, and 10 for social status and dietary

markers (Table 1). **Figure 2A** shows the pooled curves for different levels of adjustment. The difference was highly significant ($P < .001$), showing that part of the heterogeneity is amenable to adjustment. The association with lower mortality decreased in adjusted studies, maximum protection falling from 36% to 17% (Table 2 and Table 3), but it remained substantial and statistically significant. Adjustment for social status and dietary markers did not affect the results (Table 2 and Table 3 and Figure 2A). In addition, we compared adjusted with nonadjusted data derived from the same studies. Nonadjusted RRs were available for 34 curves. Using nonadjusted data, the pooled curve predicted a maximum protection of 19% (99% CI, 17%-21%) in comparison with 16% (99% CI, 14%-18%) obtained from adjusted data (Figure 2B). Further analyses were conducted on the 48 adjusted curves.

ADJUSTED STUDIES IN MEN AND WOMEN

Among adjusted studies, 32 curves were on men and 16 on women. Overall, the curves for men and women were different ($P < .001$); in particular, β_2 was greater in women, whereas β_1 was not (Table 2 and Table 3). As a consequence, the protection was apparent up to 3 drinks per day in men but only up to 2 drinks per day in women (Table 2 and Table 3 and **Figure 3A**); on the contrary, the maximum risk reduction was similar in men (17%; 99% CI, 15%-19%) and women (18%; 99% CI, 13%-22%). Thirteen studies provided separate curves for men and women recruited from the same population; the pooled curves for men and women were different for the range at which alcohol remained protective but comparable regarding the maximum protection (data not shown).

ADJUSTED STUDIES IN DIFFERENT COUNTRIES

In women, pooled curves obtained using data from the United States or Europe or other countries (Australia, Japan, and/or China)

were comparable (Figure 3B and Table 2 and Table 3) ($P > .54$ for differences between countries). In contrast, strong differences were observed in men (Figure 3C and Table 2 and Table 3) ($P < .003$ for each pairwise comparison, showing that part of heterogeneity in men is attributable to the set of the study). In particular, maximum risk reduction was in the range 20% to 28% in European but 14% to 19% in US studies, and the protection extended up to 6 drinks per day in European but

only up to 3 drinks per day in US studies.

Further subgrouping of US data according to ethnicity provided no evidence of heterogeneity (data not shown).

OTHER SUBGROUP ANALYSES

In studies that used as reference the category of no alcohol intake and excluded former drinkers, the protection was significantly lower ($P < .001$) (Figure 4A and Table 2 and Table 3).

The pooled curves were similar in larger and smaller studies (Figure 4B and Table 2 and Table 3) ($P = .61$).

In studies published before 1998 or with follow-up longer than 10 years, the protection was slightly but significantly lower (Figure 4C and D and Table 2 and Table 3) ($P < .001$).

COMMENT

In this updated meta-analysis of 34 prospective studies, findings were pooled from more than 1 million subjects and almost 100 000 deaths from any cause. We observed a J-shaped relationship between total mortality and alcohol intake, showing that a low level of alcohol consumption is significantly associated with reduced total mortality, while high-level consumption is associated with increased mortality. Our meta-analysis, including 10 articles published after 2000 that could not be considered in former meta-analyses,⁹⁻¹¹ also took advantage of a novel approach recently developed by a team of researchers, including one of us (V.B.).¹¹ Special attention was paid to differences between sexes and to the role of confounding.

The dose-response curves are similar for both sexes when alcohol intake is light, but they differ with heavier intake; in fact, the inverse association in women apparently disappears at doses lower than

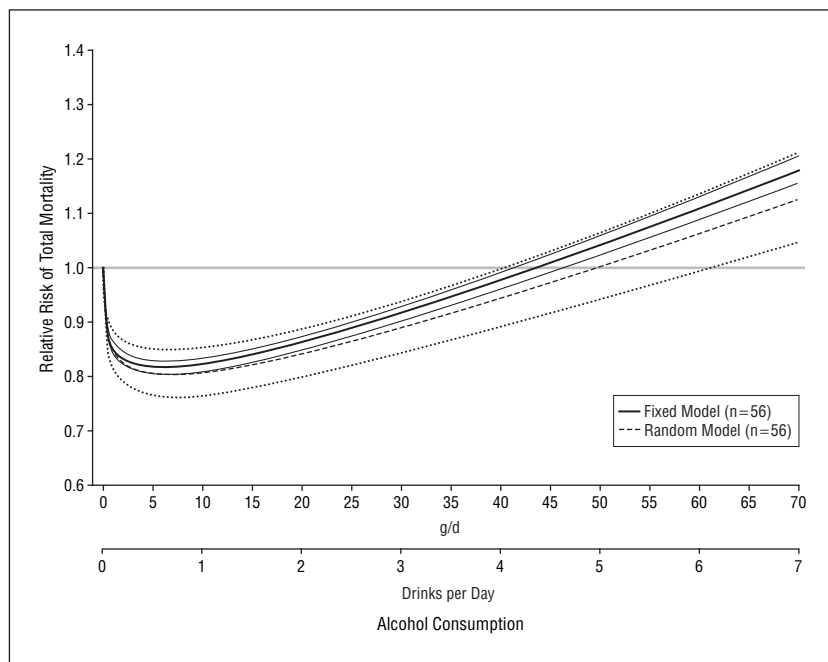


Figure 1. Relative risk of total mortality (95% confidence interval) and alcohol intake extracted from 56 curves using fixed- and random-effects models.

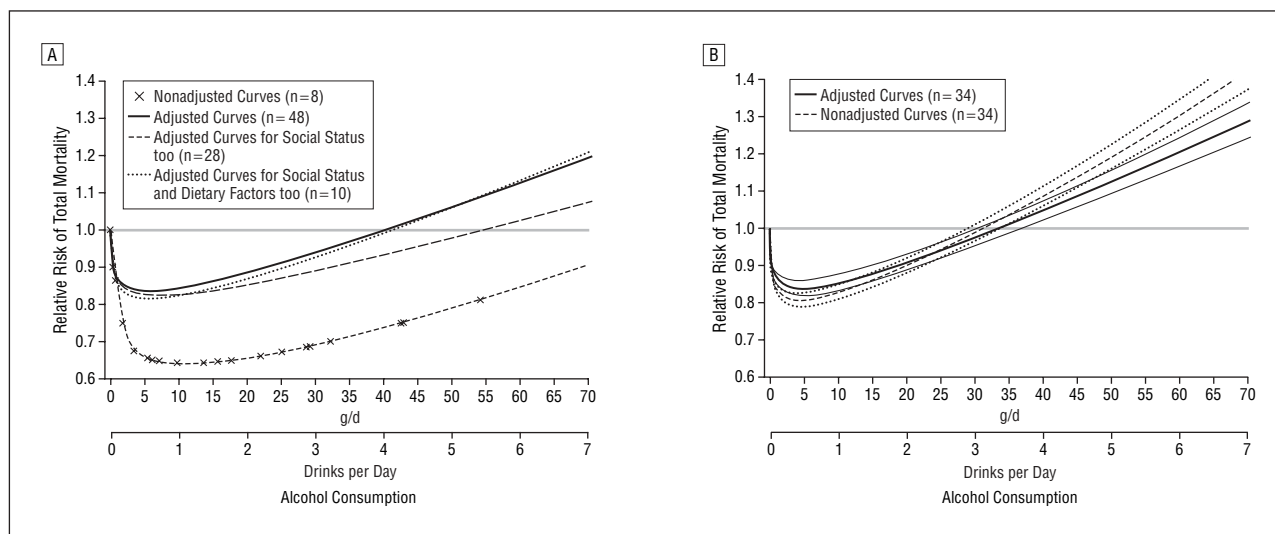


Figure 2. Relative risk of total mortality and alcohol intake curves. A, Plotted according to level of adjustment; confidence intervals overlapped and so, for greater clarity, are not represented. B, Plots include confidence intervals and show adjusted and unadjusted data from 34 curves for which adjusted and unadjusted data were available.

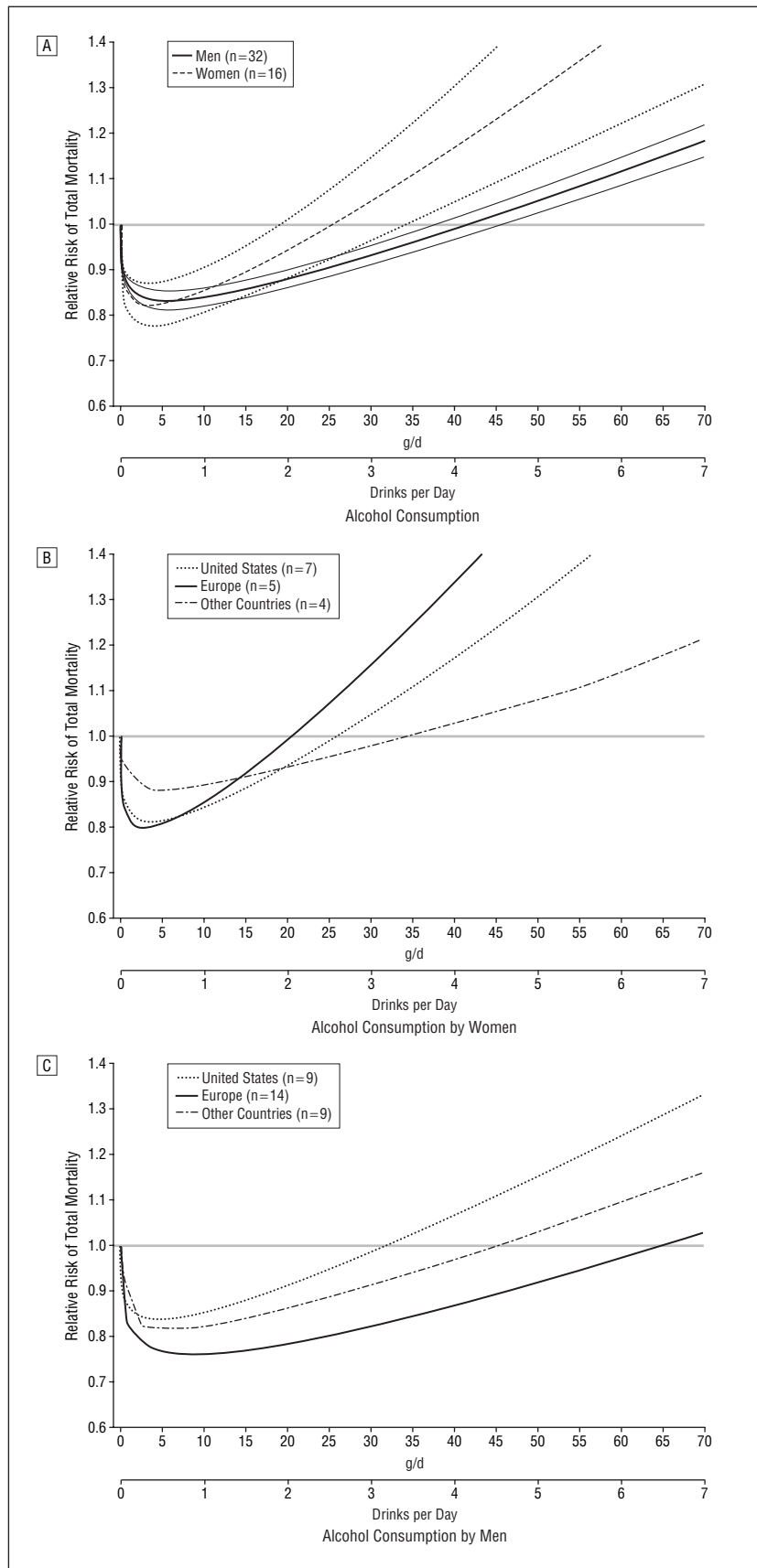


Figure 3. Relative risk of total mortality (99% confidence interval) and alcohol intake in men and women (A) and in women (B) and men (C) in the United States, Europe, and other countries (Australia, Japan, and/or China), extracted from adjusted curves. In B and C, confidence intervals overlapped and so for clarity were not depicted.

in men, in agreement with previous findings.¹⁰ Women are more exposed than men to death for any cause at moderate to high levels of alcohol consumption, probably owing to increasing risk of cancer.⁶ Experimental evidence shows that when men and women consume the same amount of alcohol, women experience higher blood alcohol concentrations. Women metabolize ethanol differently and have a lower gastric alcohol dehydrogenase activity, resulting in higher blood ethanol levels and higher risk of liver disease.⁵² Finally, because premenopausal women have a low incidence of cardiovascular disease, the benefits of alcohol on total mortality may appear to be reduced.

The degree of association was lower in adjusted studies, as might be expected in view of several confounding factors characterizing observational studies on drinking habits^{3,8}; however, the benefit of light to moderate drinking remained in a range of undoubted public health value (15%-18%). Although residual confounding cannot be excluded,⁸ it would be very unlikely to modify the scenario in a substantial manner. We found indeed that when adjusted and unadjusted data derived from the same studies were compared, the maximum protection conferred by light to moderate drinking only decreased from 19% to 16%; we can thus presume that, even in the pessimistic hypothesis that residual confounding would have the same strength in lowering the protection as that of known confounding, the "real" (maximum) protection against total mortality associated with low levels of alcohol consumption would still be higher than 10%. A similar reasoning would also apply to the harm associated with heavier drinking.

The relationship with mortality appears to be lower in US-based than in European studies, but only in men. Such a difference has no obvious explanation. Would women living in either continent follow more comparable drinking habits than men? Would it be linked to the lower amounts of alcohol consumed more regularly by women all over the world? Both the amount and the pattern of drinking is im-

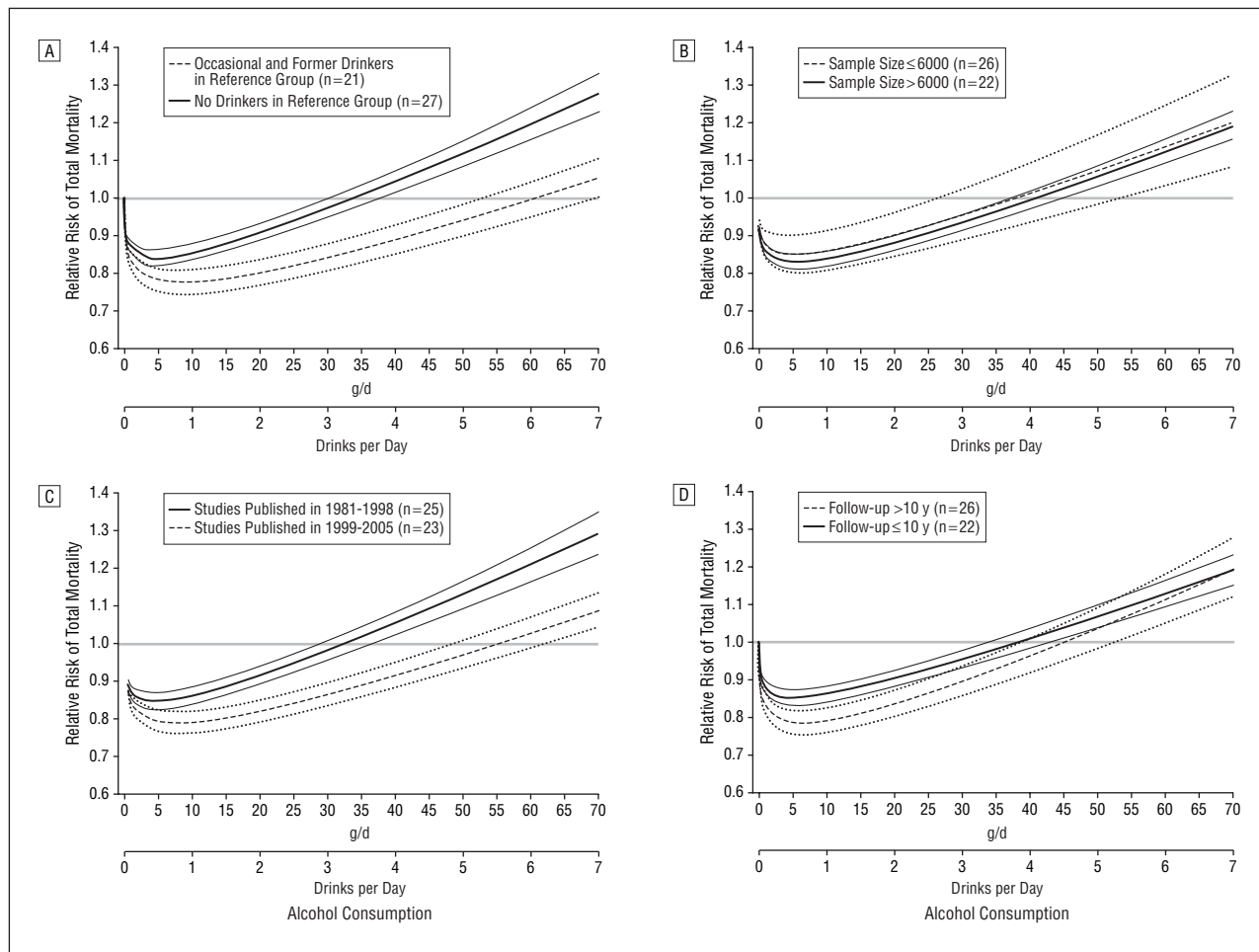


Figure 4. Relative risk of total mortality (99% confidence interval) and alcohol intake stratified according to type of reference category (A), sample size at baseline (B), year of publication (C), and follow-up duration (D).

portant for the effect of alcohol⁵³; in particular, drinking wine at meals (a typical habit in European Mediterranean areas) enhances the ability of wine to prevent the development of atheromatous lesions.⁵⁴ In contrast, binge or irregular drinking, most likely exerted by men, is an unhealthy habit.⁵⁵ Moreover, influence of genetics on the effect of ethanol has also been described.⁵⁶ Possible differences in pattern of drinking and/or in the distribution of genetic factors might explain different results observed in studies conducted in American or European men.

The results of any meta-analysis may be plagued by publication bias; nevertheless, we considered only follow-up studies on total mortality, and it is hard to hypothesize that high-quality studies would not have been published because they reported negative results. We believe therefore that publication bias—if

any—might have only weakly altered our findings.

Underreporting of alcohol consumption would result in a tendency for RRs to be biased toward the null hypothesis, and this may have distorted the shape of the J-curve and the apparent threshold for harm.

The selection of nondrinkers as a reference group has been questioned because this group may include ex-drinkers who stopped drinking because of health problems.^{3,57} A subgroup analysis restricted to studies that excluded either ex-drinkers or very light drinkers from the reference group generated a pooled curve that indeed predicted a lower (though statistically significant) protection, confirming the importance of properly selecting the reference group in studies on alcohol and health.^{3,10,57}

Duration of the follow-up and year of publication have been iden-

tified as other sources of heterogeneity. However, stratification analyses for these characteristics resulted in pooled curves that consistently predicted a substantial reduction in total mortality, within comparable alcohol dose ranges.

Randomized controlled trials offer a more solid answer than observational studies to many questions in medicine, mainly restricted, however, to the efficacy of drugs; controlled intervention trials on diet in general and on alcohol in particular are difficult and ethically questionable to perform.^{7,57} One has therefore to rely on observational studies such as those analyzed here or prospective studies where participants spontaneously decrease alcohol consumption or stop drinking altogether. Interestingly, the first study of the latter type⁵⁸ supports the inverse relation of moderate alcohol intake with coronary heart disease.

In conclusion, this meta-analysis confirms the hazards of excess drinking but also indicates the existence of potential windows of alcohol intake that may confer a net beneficial effect of drinking, at least in terms of survival, both in men and in women. Heavy drinkers should be urged to cut their consumption, but people who already regularly consume low to moderate amounts of alcohol should be encouraged to continue.

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