SUPPLEMENTAL MATERIAL

Alcohol and immediate risk of cardiovascular events:

A systematic review and dose-response meta-analysis

Data Synthesis and Analysis

Meta-Analysis of Any Alcohol Intake

For each outcome and hazard period, we included one estimate per study. For studies that did not report an overall estimate, we first pooled the RRs across sex and/or levels of alcohol consumption by using a random-effects model. We used DerSimonian and Laird[1] random-effects models to pool the RRs across studies for each outcome and each hazard period, and we generated a forest plot for each analysis, with the studies sworted by publication year. Because the DerSimonian and Laird methods can underestimate statistical heterogeneity when heterogeneity is high or few studies are pooled, we conducted sensitivity analyses using the Profile Likelihood estimation method.[2] Results were almost identical between the two methods, so DerSimonian and Laird results are presented in the text and figures. We conducted sensitivity analyses to evaluate potential information bias by excluding one study at a time to assess the influence of individual studies on the pooled estimate. Using the Egger[3] test and visual inspection of funnel plots,[3] we explored the possibility of publication bias due to missing or different estimates from small studies with less precise estimates compared to larger studies with greater precision. In a sensitivity analysis, we included estimates from case-control studies that did not account for confounders, and we conducted an analysis restricted to studies with only IS rather than a combined endpoint of both IS and HS.

Dose-Response Meta-Analysis

To examine the impact of the amount of alcohol consumed prior to event onset, we generated a forest plot for each analysis, with studies sorted by amount of alcohol. We conducted a dose-response meta-analysis for each outcome and the risk in the day and week following intake. For each study, we assigned the median or mean grams of alcohol intake for each exposure level to the corresponding RR. When the median or mean intake per category was not reported, we assigned the midpoint of the upper and lower boundaries in each category. When the median intake for the lowest category was not provided, we assumed a value of zero. If the upper boundary was not reported, we assigned a value of 1.2 times the lower boundary for that category, as in previous work.[4] When a study used different amounts of intake for men and women to calculate a single RR, we calculated a weighted average of the median dose according to the sample sex distribution. When a study reported alcohol consumption in number of drinks, we converted it to grams assuming that one drink contains 12 grams of alcohol if standard drink size was not defined.

To examine potential nonlinear relationships between alcohol intake and cardiovascular risk, we performed 2-stage random-effects dose–response meta-analyses.[5] ENREF 8 First, we constructed study-specific restricted cubic spline models with 3 knots at fixed percentiles (10%; 50%; 90%) of the exposure distribution[6] using generalized least square regression that accounts for the correlation between estimates within each study.[7] Second, we combined study-specific estimates and the variance/covariance matrix using a random-effects model.[1] We conducted a test for the overall significance of the curve by testing the joint impact of the spline transformations. We examined whether a nonlinear relationship exists by testing the null hypothesis that the regression coefficients of the spline transformations are all equal to zero. We did not have sufficient statistical power to formally assess whether the associations were

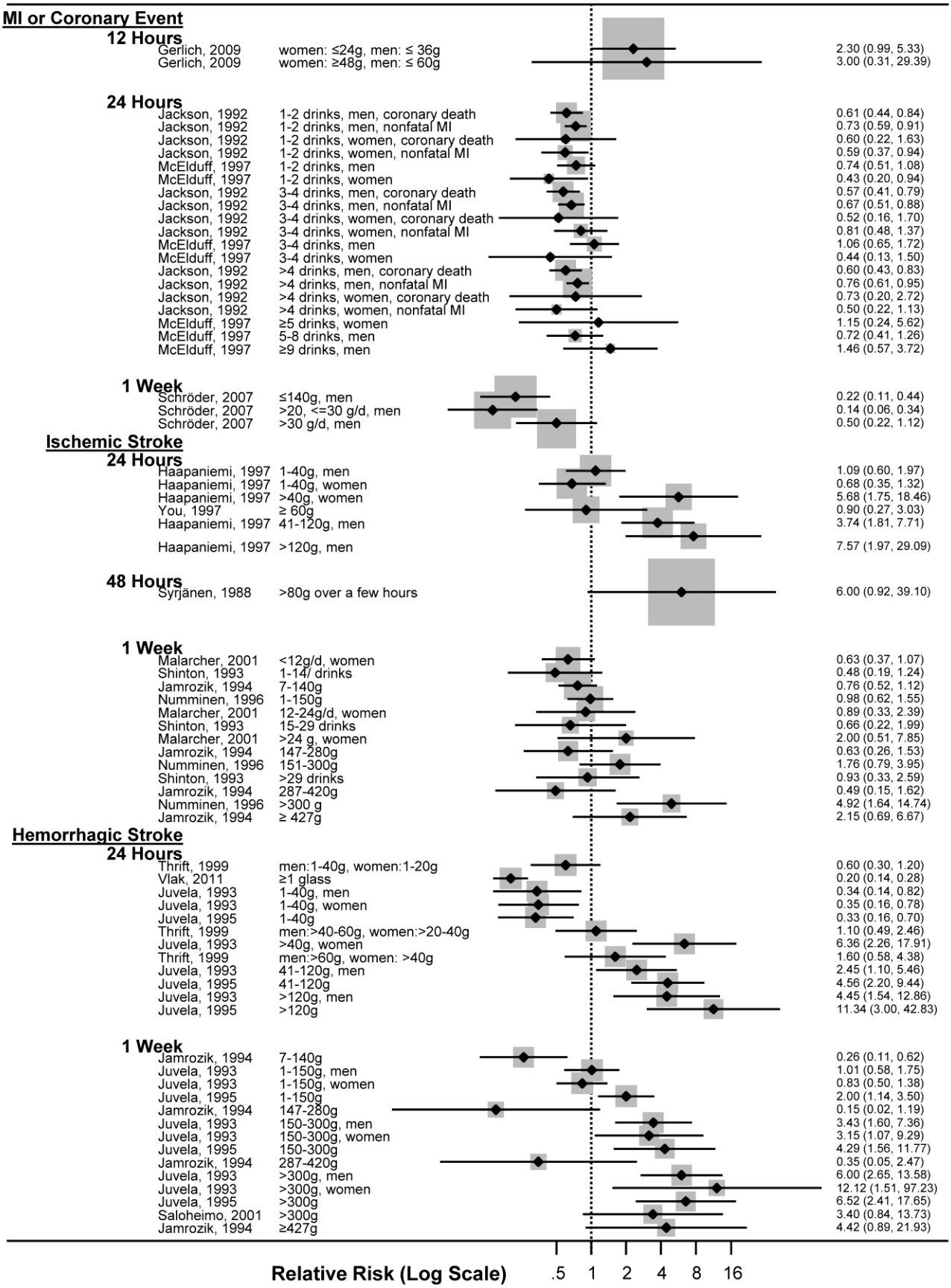
different for men and women, so we qualitatively assessed whether there were apparent differences when sex-specific estimates were available.

For the analyses of any intake and the dose-response analyses, we evaluated heterogeneity across studies with the Cochrane Q χ^2 test[8] and we calculated the I^2 statistic to quantify the proportion of between-study heterogeneity attributable to variability in the association rather than sampling variation; values of 25%, 50% and 75% were considered to represent low, medium and high heterogeneity respectively.[9]

Supplementary Figure 1 Legend

Forest plot of relative risks (RRs) and 95% confidence intervals (CIs) for the association between alcohol consumption and cardiovascular events in the following day and week by amount of alcohol intake. Squares indicate study-specific RR estimates, with the size of the square reflecting the proportion of the DerSimonian and Laird weights; horizontal lines indicate the 95% CI. The dotted line indicates the value for no association. The RRs and 95% confidence intervals for each amount are presented in the column on the right. These values were used to conduct the dose-response meta-analyses and resulting splines in the Figure 4 that accounts for the covariance among the estimates from a single study.

Supplementary Figure 1


MI or Coronary Event
12 Hours
Gerlich, 2009 women: ≤24g, men: ≤ 36g 2.30 (0.99, 5.33)
Gerlich, 2009 women: ≥48g, men: ≤ 60g 3.00 (0.31, 29.39)
24 Hours
Jackson, 1992 1-2 drinks, men, coronary death 0.61 (0.44, 0.84)
Jackson, 1992 1-2 drinks, men, nonfatal MI 0.73 (0.59, 0.91)
Jackson, 1992 1-2 drinks, women, coronary death 0.60 (0.22, 1.63)
Jackson, 1992 1-2 drinks, women, nonfatal MI 0.59 (0.37, 0.94)
McElduff, 1997 1-2 drinks, men 0.74 (0.51, 1.08)
McElduff, 1997 1-2 drinks, women 0.43 (0.20, 0.94)
Jackson, 1992 3-4 drinks, men, coronary death 0.57 (0.41, 0.79)
Jackson, 1992 3-4 drinks, men, nonfatal MI 0.67 (0.51, 0.88)
Jackson, 1992 3-4 drinks, women, coronary death 0.52 (0.16, 1.70)
Jackson, 1992 3-4 drinks, women, nonfatal MI 0.81 (0.48, 1.37)
McElduff, 1997 3-4 drinks, men 1.06 (0.65, 1.72)
McElduff, 1997 3-4 drinks, women 0.44 (0.13, 1.50)
Jackson, 1992 >4 drinks, men, coronary death 0.60 (0.43, 0.83)
Jackson, 1992 >4 drinks, men, nonfatal MI 0.76 (0.61, 0.95)
Jackson, 1992 >4 drinks, women, coronary death 0.73 (0.20, 2.72)
Jackson, 1992 >4 drinks, women, nonfatal MI 0.50 (0.22, 1.13)
McElduff, 1997 ≥5 drinks, women 1.15 (0.24, 5.62)
McElduff, 1997 5-8 drinks, men 0.72 (0.41, 1.26)
McElduff, 1997 ≥9 drinks, men 1.46 (0.57, 3.72)
1 Week
Schröder, 2007 ≤140g, men 0.22 (0.11, 0.44)
Schröder, 2007 >20, <=30 g/d, men 0.14 (0.06, 0.34)
Schröder, 2007 >30 g/d, men 0.50 (0.22, 1.12)
Ischemic Stroke
24 Hours
Haapaniemi, 1997 1-40g, men 1.09 (0.60, 1.97)
Haapaniemi, 1997 1-40g, women 0.68 (0.35, 1.32)
Haapaniemi, 1997 >40g, women 5.68 (1.75, 18.46)
You, 1997 ≥ 60g 0.90 (0.27, 3.03)
Haapaniemi, 1997 41-120g, men 3.74 (1.81, 7.71)
Haapaniemi, 1997 >120g, men 7.57 (1.97, 29.09)
48 Hours
Syrjänen, 1988 >80g over a few hours 6.00 (0.92, 39.10)
1 Week
Malarcher, 2001 <12g/d, women 0.63 (0.37, 1.07)
Shinton, 1993 1-14/ drinks 0.48 (0.19, 1.24)
Jamrozik, 1994 7-140g 0.76 (0.52, 1.12)
Numminen, 1996 1-150g 0.98 (0.62, 1.55)
Malarcher, 2001 12-24g/d, women 0.89 (0.33, 2.39)
Shinton, 1993 15-29 drinks 0.66 (0.22, 1.99)
Malarcher, 2001 >24 g, women 2.00 (0.51, 7.85)
Jamrozik, 1994 147-280g 0.63 (0.26, 1.53)
Numminen, 1996 151-300g 1.76 (0.79, 3.95)
Shinton, 1993 >29 drinks 0.93 (0.33, 2.59)
Jamrozik, 1994 287-420g 0.49 (0.15, 1.62)
Numminen, 1996 >300 g 4.92 (1.64, 14.74)
Jamrozik, 1994 ≥ 427g 2.15 (0.69, 6.67)
Hemorrhagic Stroke
24 Hours
Thrift, 1999 men:1-40g, women:1-20g 0.60 (0.30, 1.20)
Vlak, 2011 ≥1 glass 0.20 (0.14, 0.28)
Juvela, 1993 1-40g, men 0.34 (0.14, 0.82)
Juvela, 1993 1-40g, women 0.35 (0.16, 0.78)
Juvela, 1995 1-40g 0.33 (0.16, 0.70)
Thrift, 1999 men:>40-60g, women:>20-40g 1.10 (0.49, 2.46)
Juvela, 1993 >40g, women 6.36 (2.26, 17.91)
Thrift, 1999 men:>60g, women: >40g 1.60 (0.58, 4.38)
Juvela, 1993 41-120g, men 2.45 (1.10, 5.46)
Juvela, 1995 41-120g 4.56 (2.20, 9.44)
Juvela, 1993 >120g, men 4.45 (1.54, 12.86)
Juvela, 1995 >120g 11.34 (3.00, 42.83)
1 Week
Jamrozik, 1994 7-140g 0.26 (0.11, 0.62)
Juvela, 1993 1-150g, men 1.01 (0.58, 1.75)
Juvela, 1993 1-150g, women 0.83 (0.50, 1.38)
Juvela, 1995 1-150g 2.00 (1.14, 3.50)
Jamrozik, 1994 147-280g 0.15 (0.02, 1.19)
Juvela, 1993 150-300g, men 3.43 (1.60, 7.36)
Juvela, 1993 150-300g, women 3.15 (1.07, 9.29)
Juvela, 1995 150-300g 4.29 (1.56, 11.77)
Jamrozik, 1994 287-420g 0.35 (0.05, 2.47)
Juvela, 1993 >300g, men 6.00 (2.65, 13.58)
Juvela, 1993 >300g, women 12.12 (1.51, 97.23)
Juvela, 1995 >300g 6.52 (2.41, 17.65)
Saloheimo, 2001 >300g 3.40 (0.84, 13.73)
Jamrozik, 1994 ≥427g 4.42 (0.89, 21.93)
Relative Risk (Log Scale)
.5
1
2
4
8
16

Supplementary Table 1. Characteristics of Studies of Alcohol Consumption and Cardiovascular Events Included in the Meta-Analysis, 1987-2015

Author, Year	Country	Sample Size	Age	Sex	Design	Outcome	Hazard Periods (Hours)	Adjustments
Jackson, 1992	New Zealand	526 cases, 1183 controls	35 - 64 years	70% men, 30% women	Case-control	Nonfatal MI and Coronary Death	24	Matched for age and sex Adjusted for age, smoking, usual alcohol consumption
McElduff, 1997	Australia	600 cases, 801 controls	35 - 69 years	68% men, 32% women	Case-control	Nonfatal and Fatal Major Coronary Event	24	Adjusted for age, smoking, high blood pressure, high cholesterol concentration, previous MI, stroke, angina, usual alcohol consumption
Marshall, 2000	New Zealand	547 cases, 1582 controls	35 - 74 years	85% men, 15% women	Case-crossover	Nonfatal MI and Coronary Death	24	Self-matched
Schröder, 2007	Spain	244 cases, 1270 controls	25 - 74 years Mean: 51.6	100% men	Case-control	Nonfatal MI and Coronary Death	168	Matched for region Adjusted for age, smoking, education, leisure-time activity, total, LDL and HDL-cholesterol, DM, hypercholesterolemia drug, HTN
Gerlich, 2009	Switzerland	250 cases	30 - 88 years Mean: 59.7	79% men, 21% women	Case-crossover	Incident Nonfatal MI	12	Self-matched
Gerlich, 2010	Switzerland	397 cases	29 - 88 years Mean: 59.7	79% men, 21% women	Case-crossover	Incident Nonfatal MI	12	Self-matched
Leon, 2010	Russia	28 cases, 28 controls	25 - 54 years	100% men	Case-control	Death from MI, IHD, Hemorrhagic Stroke	168	Matched by age Adjusted for education and smoking
Leong, 2014	52 Countries	11,652 cases	Mean: 57.5	75% men, 25% women	Case-crossover	Incident Nonfatal MI	24	Self-matched
Mostofsky, 2015	United States	3,869 cases	Mean: 61.4	68% men, 32% women	Case-crossover	Nonfatal MI	1,24	Self-matched
Taylor, 1985	United States	17 cases, 17 controls	Mean: 39.5	59% men, 41% women	Case-control	Ischemic Stroke and Hemorrhagic Stroke	24	Matched by age, sex, race, day of week admitted to the hospital Crude estimate

Author, Year	Country	Sample Size	Age	Sex	Design	Outcome	Hazard Periods (Hours)	Adjustments
Gorelick, 1987	United States	205 cases, 410 controls	43-89 years Mean: 65.0	66% men, 34% women	Case-control	Incident Nonfatal Ischemic Stroke	24,72	Matched by age, sex, race, method of hospital payment Adjusted for cigarette smoking, HTN
Syrjänen, 1988	Finland	54 cases, 54 controls	17-49 years Mean: 37.8	61% men, 39% women	Case-control	Nonfatal Ischemic Stroke	48	Matched for age and sex
Shinton, 1993	England	125 cases, 198 controls	35 - 74 years Median: 64.1	Not reported	Case-control	Nonfatal Ischemic Stroke, Intracerebral Hemorrhage, Subarachnoid Hemorrhage	168	Matched for age and sex
Jamrozik, 1994	Australia	59 cases, 279 controls	Not reported	Not reported	Case-control	Nonfatal Ischemic Stroke, Primary Intracerebral Hemorrhage	168	Matched for age and sex Adjusted for tobacco, HTN, DM, stroke or TIA, MI, adding salt to food, consume fish>2X/ month
Numminen, 1996	Finland	426 cases, 157 controls	Mean: 46.3	68% men, 32% women	Case-control	Incident Nonfatal Ischemic Stroke	168	Adjusted for age, sex, CHD, MI, DM, hyperlipidemia, atrial fibrillation, heavy drinking, HTN, current smoking, platelet count
You, 1997	Australia	201 cases, 201 controls	15 - 60 years Mean: 45.4	60% men, 40% women	Case-control	Incident Nonfatal Ischemic Stroke	24	Matched by neighborhood, age, sex Adjusted for cigarette smoking, HTN, high cholesterol, CHD, DM, oral contraceptive, physical exercise
Haapaniemi, 1997	Finland	506 cases, 345 controls	16 - 60 years Mean: 47.9	71% men, 29% women	Case-control	Incident Nonfatal Ischemic Stroke	24,168	Adjusted for sex, age, smoking status, current smoking, cardiac disease, HTN, DM, hyperlipemia, history of TIA, migraine, heavy drinking
Bråthen, 2000	Norway	91 cases, 254 controls	Mean: 48.2	50% men, 50% women	Case-control	Nonfatal Ischemic Stroke	72	Not reported

Author, Year	Country	Sample Size	Age	Sex	Design	Outcome	Hazard Periods (Hours)	Adjustments
Malarcher, 2001	United States	224 cases, 392 controls	15 - 44 years	100% women	Case-control	Incident Nonfatal Ischemic Stroke	24,168	Matched by age and region of residence Adjusted for age, race, education, smoking, BMI, total and HDL cholesterol, history of HTN, CHD, DM, average alcohol intake in past year
Mostofsky, 2010	United States	390 cases	Mean: 68.4	54% men, 46% women	Case-crossover	Nonfatal Ischemic Stroke	1,24	Self-matched
Vlak, 2011	Netherlands	250 cases	Mean: 54.7	25% men, 75% women	Case-crossover	Nonfatal Intracranial Aneurysm	24	Self-matched
Juvela, 1993	Finland	278 cases, 314 controls	15 - 60 years Mean: 43.8	52% men, 48% women	Case-control	Nonfatal Subarachnoid Hemorrhage	24,168	Matched by age, sex, day of onset of symptoms, and acuteness of the disease onset Adjusted for HTN, age, smoking status
Juvela, 1995	Finland	156 cases, 332 controls	16 - 60 years Mean: 47.3	59% men, 41% women	Case-control	Incident Nonfatal Intracerebral Hemorrhage	24,168	Matched by hospital, sex, age, day of onset of symptoms, and acuteness of onset Adjusted for HTN, alcohol within day or week, sex, age,BMI, and smoking status
Thrift, 1999	Australia	331 cases, 331 controls	18 - 80 years Mean: 63.4	60% men, 40% women	Case-control	Incident Nonfatal Intracerebral Hemorrhage	24	Matched by neighborhood, sex, and age Adjusted for cholesterol, previous CVD, DM, exercise, BMI, smoking, education, day of week of stroke (cases) or interview (controls)
Saloheimo, 2001	Finland	98 cases, 206 controls	36 - 90 years Mean: 65.7	58% men, 41% women	Case-control	Nonfatal Intracerebral Hemorrhage	168	Matched for age and sex Adjusted for age, sex, treated and untreated HTN, IS, epistaxis, epilepsy, recent physical exertion

DM=diabetes mellitus
HTN=hypertension
BMI=body mass index
TIA=transient ischemic attack
CHD=coronary heart disease
CVD=cardiovascular disease

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