Alcohol Intake and Risk of Coronary Heart Disease in Younger, Middle-Aged, and Older Adults

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Background—Light to moderate alcohol consumption is associated with a reduced risk of coronary heart disease. This protective effect of alcohol, however, may be confined to middle-aged or older individuals. Coronary heart disease incidence is low in men <40 years of age and in women <50 years of age; for this reason, study cohorts rarely have the power to investigate the effects of alcohol on coronary heart disease risk in younger adults. This study examined whether the beneficial effect of alcohol on coronary heart disease depends on age.

Methods and Results—In this pooled analysis of 8 prospective studies from North America and Europe including 192 067 women and 74 919 men free of cardiovascular diseases, diabetes, and cancers at baseline, average daily alcohol intake was assessed at baseline with a food frequency or diet history questionnaire. An inverse association between alcohol and risk of coronary heart disease was observed in all age groups; hazard ratios among moderately drinking men (5.0 to 29.9 g/d) 39 to 50, 50 to 59, and ≥60 years of age were 0.58 (95% confidence interval [CI], 0.36 to 0.93), 0.72 (95% CI, 0.60 to 0.86), and 0.85 (95% CI, 0.75 to 0.97) compared with abstainers. However, the analyses indicated a smaller incidence rate difference between abstainers and moderate consumers in younger adults (incidence rate difference, 45 per 100 000; 90% CI, 8 to 84) than in middle-aged (incidence rate difference, 64 per 100 000; 90% CI, 24 to 102) and older (incidence rate difference, 89 per 100 000; 90% CI, 44 to 140) adults. Similar results were observed in women.

Conclusion—Alcohol is also associated with a decreased risk of coronary heart disease in younger adults; however, the absolute risk was small compared with middle-aged and older adults. **(*Circulation*. 2010;121:1589-1597.)**

Key Words: age groups ■ alcohol consumption ■ coronary disease ■ epidemiology

The association between alcohol intake and coronary heart disease (CHD) has been thoroughly investigated over the past decades with regard to both the amount and type consumed.[1–4] In recent years, the importance of drinking pattern has also been considered.[5–7] In general, alcohol intake is consistently linked with a lower risk of CHD. Age-specific incidence rates of CHD vary considerably, being very low in men <40 years of age and in women <50 years of age.[8] For this reason, the statistical power to investigate the effects of alcohol on CHD in younger adults is limited. Most results are obtained from cohorts consisting of middle-aged and older adults, and only a few studies have addressed the effects of alcohol on CHD in younger adults.[9,10] In principle, the cause of CHD among younger adults may differ from that among older individuals; for instance, relatively more cases of CHD among younger adults may be attributable to genetic causes.[11,12] Hence, alcohol may not necessarily protect against CHD in this age group. We pooled data from 8 studies to increase sample size and to enable the investi-

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gation of associations between alcohol intake and CHD in subsets of populations defined by age group.

Clinical Perspective on p 1597

Methods

Study Population

The analyses were based on data from the Pooling Project of Diet and Coronary Disease. The inclusion criteria were the following: a prospective study with at least 150 incident coronary cases, assessment of usual dietary intake, and a validation study of the diet assessment method. The following 12 studies met these criteria and agreed to share data: Adventists Health Study (AHS),[13] Atherosclerosis Risk in Communities Study (ARIC),[14] α-Tocopherol, β-Carotene Cancer Prevention Study (ATBC),[15] Finnish Mobile Clinic Health Examination (FMC),[16] Glostrup Population Study (GPS),[17] Health Professionals Follow-Up Study (HPFS),[18] Israeli Ischemic Heart Disease Study (IIHD),[19] Iowa Women's Health Study (IWHS),[20] Nurses' Health Study (NHS),[21] Västerbotten Intervention Program (VIP),[22] and Women's Health Study (WHS).[23] The AHS included only nondrinkers, and the FMC and IIHD studies were excluded from the present analysis because of missing information on alcohol intake. In addition, IWHS was excluded from main analyses because of self-reported information on CHD. The 8 remaining studies are presented in Table 1. The NHS was divided into 2 segments, thereby taking advantage of repeated assessments on dietary intake and the long follow-up period. The 2 segments are referred to as NHSa (1980 to 1986) and NHSb (1986 to 1996). The second segment comprised only women who remained free of CHD after the first follow-up period, and cases were included in whichever segment they occurred.

Measurements

Average daily alcohol intake was assessed at baseline with a food frequency or diet history questionnaire inquiring about typical intake of alcoholic beverages. For each beverage, grams of daily alcohol intake were calculated from information on the amount and frequency of consumption and the alcohol content of the beverage. Study-specific conversion factors for the alcohol content were used. A standard drink contains ≈10 to 15 g pure alcohol. Total alcohol intake was given by the sum of the beverage-specific intakes.

The outcome of interest was incident CHD events (both fatal and nonfatal). All 8 included studies used validated methods to define nonfatal and fatal CHD cases.[24]

Statistical Methods

Participants were excluded if they reported energy intakes beyond 3 SD from the study-specific, log-transformed mean energy intake of the baseline population (1% of the study population). Persons <35 years of age or with a history of cardiovascular disease, diabetes, or cancers (other than nonmelanoma skin cancer) were also excluded. Participants were followed up from baseline to date of CHD event, date of death, or end of follow-up, whichever occurred first. Follow-up periods <10 years (ARIC and GPS) were truncated to reduce heterogeneity. Individual studies were combined through the use of an aggregated pooled analysis technique allowing for calculation of a single exposure-effect estimate while adjusting for study origin.[25]

The hazard ratios of CHD were ascertained by the Cox proportional-hazards regression model with age as underlying time

Table 1. Baseline Characteristics of Included Studies

Study and Sex	Baseline Cohort*	Year of Questionnaire	Mean Age (90% Limit), y	Follow-Up, Person-y	CHD Cases, n		Alcohol Intake	
					CHD Deaths	Total CHD Events	Median† (5th–95th Percentile), g/d	Abstainers, %
ARIC								
Male	5217	1987–1989	54.6 (45–64)	45 652	51	267	12.1 (1.9–56.6)	45.8
Female	6462	1987–1989	53.9 (45–64)	58 019	18	122	6.8 (1.5–30.2)	69.8
ATBC								
Male	21 141	1984–1988	57.3 (50–69)	121 813	534	1339	13.7 (0.8–62.3)	10.2
GPS								
Male	1658	1974–1995	51.9 (35–80)	14 365	79	102	20.8 (2.7–72.6)	6.2
Female	1666	1974–1995	51.5 (35–80)	14 605	34	34	8.9 (1.3–35.1)	18.0
HPFS								
Male	41 754	1986–1988	53.4 (39–77)	383 206	421	1273	9.7 (1.0–46.1)	23.0
NHSa								
Female	81 415	1980–1982	47.1 (35–66)	513 915	97	397	5.6 (0.8–35.0)	31.4
NHSb								
Female	61 706	1986–1988	52.6 (39–66)	607 049	208	696	4.9 (0.9–35.9)	34.2
VIP								
Male	9521	1992–1996	49.1 (39–70)	39 230	38	134	4.4 (0.2–15.8)	4.7
Female	10 555	1992–1996	49.3 (39–70)	43 872	4	23	1.7 (0.1–7.3)	11.4
WHS								
Female	37 272	1992–1995	53.9 (38–89)	190 755	10	152	3.7 (0.9–28.4)	40.0
Total								
Male	79 291	1974–1996	54.0 (35–80)	604 266	1123	3115	9.6 (0.9–50.4)	18.5
Female	199 076	1974–1996	50.4 (35–89)	1 428 216	371	1424	4.7 (0.8–35.0)	33.9

*Sample size after exclusion of participants with baseline cardiovascular diseases, cancers, diabetes mellitus, and missing information on alcohol intake.
†Median values were calculated for drinkers only.

Table 2. Baseline Characteristics of Women in the Pooled Cohort According to Daily Alcohol Intake

			Alcohol Intake, g/d				
	Total	Nondrinkers	0.1–4.9	5.0–14.9	15.0–29.9	30.0–59.9	≥60.0
n*	192 067	65 121	67 187	39 177	12 258	7418	906
CHD events, n	1365	596	390	241	65	58	15
Age, mean (SD), y	50.4 (7.6)	51.0 (7.7)	49.8 (7.7)	50.1 (7.5)	50.5 (7.4)	51.1 (7.3)	51.3 (7.2)
Education, low, n (%)†	8276 (4)	2186 (3)	4719 (7)	936 (2)	322 (3)	96 (1)	17 (2)
Smokers, n (%)	44 513 (23)	11 971 (18)	14 547 (22)	10 454 (27)	3628 (30)	3426 (46)	487 (54)
BMI, mean (SD), kg/m^2	25.0 (10.1)	26.0 (5.3)	25.1 (4.5)	24.0 (3.8)	23.7 (3.6)	23.9 (3.8)	24.4 (4.2)
Physical inactivity, n (%)	66 248 (25)	24 382 (37)	21 858 (33)	12 760 (33)	3859 (31)	2971 (40)	418 (46)
Diet, median (5th–95th percentile)							
Polyunsaturated fat,‡ g/d	5.4 (3.3–8.4)	5.5 (3.4–8.6)	5.4 (3.4–8.4)	5.4 (3.4–8.4)	5.3 (3.2–8.3)	4.8 (2.8–7.9)	4.0 (2.2–6.9)
Monounsaturated fat,‡ g/d	13.1 (8.1–20.5)	13.1 (7.9–20.7)	13.0 (8.3–20.5)	13.2 (8.4–20.5)	12.9 (8.2–19.7)	12.3 (7.7–19.0)	10.6 (6.4–16.8)
Saturated fat,‡ g/d	12.8 (7.7–20.0)	12.7 (7.5–20.1)	13.0 (8.0–20.2)	12.9 (7.9–20.1)	12.6 (7.6–19.7)	11.9 (7.2–18.6)	10.3 (5.7–16.8)
Fiber,‡ g/d	15.4 (8.4–25.7)	15.7 (8.5–26.7)	15.9 (8.9–26.1)	15.0 (8.3–24.4)	14.2 (7.8–23.1)	12.2 (6.7–20.4)	10.3 (5.0–18.9)
Cholesterol,‡ mg/d	254 (139–458)	252 (134–464)	249 (137–451)	264 (148–460)	263 (151–464)	252 (143–443)	222 (121–394)
Total energy, kcal/d	1603 (900–2627)	1579 (871–2637)	1581 (893–2589)	1614 (915–2608)	1678 (977–2689)	1758 (1070–2749)	2008 (1283–3050)
Hypertension, n (%)	35 637 (19)	13 566 (21)	11 695 (17)	6271 (16)	2137 (17)	1695 (23)	273 (30)
Dyslipidemia, n	20 850 (11)	8389 (13)	6599 (10)	3787 (10)	1217 (10)	731 (10)	127 (14)

Differences in distribution of covariates across levels of alcohol consumption were tested by ANOVA (age, BMI), Kruskal-Wallis (dietary factors), and χ^2 tests (education, smoking, physical activity, hypertension, and dyslipidemia). All tests showed statistically significant differences ($P<0.0001$).

*After exclusion of participants with missing information on any of the relevant covariates.

†Defined as less than high school.

‡Energy adjusted.

scale, allowing for delayed entry (left censoring).[26] Absolute risks (incidence rates) describing the scale of CHD according to sex, age, and level of alcohol intake were estimated by means of Poisson regression.[27] Absolute risk differences were calculated, and 90% confidence limits were derived by bootstrap estimation (5000 replications) with the 5th and 95th percentiles of the distribution as the lower and upper limits.

We performed primary analyses considering the risk of CHD in categories of alcohol consumption (0, 0.1 to 4.9, 5.0 to 14.9, 15.0 to 29.9, 30.0 to 59.9, and ≥60.0 g/d in women; 0, 0.1 to 4.9, 5.0 to 14.9, 15.0 to 29.9, 30.0 to 59.9, 60.0 to 89.9, and ≥90.0 g/d in men) both for each individual study and for the pooled cohort. The study population was analyzed separately in the following 3 age groups: 39 to 49.9, 50 to 59.9, and ≥60 years. Age was updated during follow-up, and participants were assigned to the appropriate age category; thus, each person could contribute person-time at risk to >1 age category.

Additional analyses exploring the risk of CHD per alcohol increment (1 g/d) were performed. Alcohol was modeled continuously using second-degree fractional polynomials, thus allowing for a single turning point (the nadir) in the risk function. Following the results of Corrao and others,[1] a model describing the dose-response relationship of alcohol on CHD including both a linear and root-squared term of alcohol was applied.

The *P* value for the test for trend was obtained by assigning the median value within categories of alcohol intake and using this variable as a continuous variable. SAS statistical package version 9.1 was used for all analyses.[28]

We harmonized the variables of the different studies, and the following set of potential confounders was identified on the basis of the method of causal diagrams as suggested by Greenland and others[29]: educational level (less than high school, high school, more than high school), smoking (never smokers, ex-smokers, and current smokers of 1 to 4, 5 to 14, 15 to 24, or ≥25 cigarettes per day), body mass index (BMI; <18.5, 18.5 to 24.9, 25.0 to 29.9, and ≥30 kg/m^2), total energy intake (kcal/d), and energy-adjusted quintiles of cholesterol, dietary fiber, saturated fat, monounsaturated fat, and polyunsaturated fat intake. Physical activity measures varied across the cohorts, measured either according to an energy expenditure score of weekly time spent on various activities during the past year (ARIC, HPFS, NHS, VIP, and WHS) or according to the intensity of the average weekly physical activity during the past 12 months (ATBC, GPS). These measures were harmonized to a 5-level variable from 1 (least active) to 5 (most active).[30–32] In addition, models were stratified by study origin and baseline year to account for differences in follow-up procedures or questionnaire design and period effects. Information on postmenopausal hormone therapy use was unavailable in VIP; therefore, the main analyses for women did not include adjustment for this factor. Sensitivity analyses included measures of self-reported history of physician-diagnosed elevated cholesterol (dyslipidemia) and hypertension (yes/no).

Results

Baseline Characteristics

Baseline characteristics of participants from the 8 included studies are shown in Table 1. In total, the pooled study population comprised 199 076 women and 79 291 men who experienced 1424 and 3115 coronary events during 1 428 216 and 604 266 person-years of follow-up, respectively. Baseline age of participants varied from 35 to 89 years in women and from 35 to 80 years in men with a mean age of 50.4 and 54.0 years, respectively. The proportion of nondrinkers varied substantially between studies from 11.4% to 53.0% in women and from 4.7% to 45.8% in men. Median alcohol intakes varied from 4.4 to 20.8 g/d in men and from 1.7 to 8.9 g/d in women.

Tables 2 and 3 show characteristics of participants included in the pooled cohort according to alcohol consumption. Heavier alcohol intake was associated with higher proportions of smokers, physical inactivity, and hypertension and lower median intakes of fat and fiber; a moderate alcohol intake was associated with the highest median cholesterol intake compared with abstainers and heavy drinkers. In men,

Table 3. Baseline Characteristics of Men in the Pooled Cohort According to Daily Alcohol Intake

			Alcohol Intake, g/d					
	Total	Nondrinkers	0.1–4.9	5.0–14.9	15.0–29.9	30.0–59.9	60.0–89.9	≥90.0
n*	74 720	13 904	19 030	20 556	11 375	7789	1546	520 (1)
CHD events, n	2961	623	737	751	449	311	59	31
Age, mean (SD), y	54.0 (8.4)	54.4 (8.6)	53.3 (8.7)	53.6 (8.5)	54.6 (7.6)	55.2 (7.6)	55.2 (7.6)	55.8 (6.2)
Education, low, n (%)†	20 773 (28)	2513 (18)	6125 (32)	5580 (27)	3590 (32)	2283 (29)	450 (29)	232 (45)
Smokers, n (%)	28 144 (38)	3338 (24)	6086 (32)	7409 (36)	5688 (50)	4254 (55)	952 (62)	417 (80)
BMI, mean (SD), kg/m^2	25.8 (8.2)	26.0 (3.8)	25.8 (3.4)	25.7 (3.4)	25.8 (3.4)	25.9 (3.5)	26.1 (3.9)	26.5 (4.1)
Physical inactivity, n (%)	18 850 (25)	3740 (27)	4411 (23)	4489 (22)	2956 (26)	2421 (31)	572 (37)	261 (80)
Diet, median (5th–95th percentile)								
Polyunsaturated fat,‡ g/d	5.4 (3.3–8.9)	5.5 (3.3–9.0)	5.3 (3.4–8.8)	5.4 (3.4–8.9)	5.4 (3.2–9.0)	5.2 (3.0–8.8)	4.6 (2.6–8.2)	4.1 (2.2–7.8)
Monounsaturated fat,‡ g/d	12.8 (8.5–16.8)	12.9 (8.0–17.3)	12.8 (8.6–16.8)	12.9 (8.8–16.8)	12.9 (9.0–16.6)	12.4 (8.3–16.3)	11.3 (7.4–15.4)	10.5 (6.8–15.5)
Saturated fat,‡ g/d	13.2 (7.5–23.8)	12.3 (6.9–22.8)	13.6 (7.7–24.0)	13.3 (7.7–24.0)	13.9 (7.8–24.5)	13.2 (7.4–23.5)	12.7 (6.5–21.6)	13.3 (6.5–21.0)
Fiber,‡ g/d	19.8 (11.5–32.3)	20.7 (11.6–35.7)	21.0 (12.7–33.5)	20.1 (12.3–31.8)	19.1 (11.5–30.1)	17.0 (10.1–27.4)	14.6 (8.3–24.5)	12.9 (6.6–21.2)
Cholesterol,‡ mg/d	322 (174–573)	315 (161–568)	303 (166–536)	322 (177–566)	349 (193–602)	343 (190–610)	323 (176–606)	324 (167–544)
Total energy, kcal/d	2135 (1149–3671)	1929 (1044–3438)	2047 (1120–3537)	2111 (1173–3598)	2311 (1274–3823)	2387 (1344–3911)	2652 (1518–4138)	3054 (1570–4662)
Hypertension, n (%)	14 388 (19)	2759 (20)	3292 (17)	3634 (18)	2246 (20)	1902 (24)	421 (27)	134 (26)
Dyslipidemia,§ n	5076 (9)	1145 (10)	1114 (8)	1312 (9)	720 (11)	609 (13)	147 (17)	29 (16)

Differences in distribution of covariates across levels of alcohol consumption were tested by ANOVA (age, BMI), Kruskal-Wallis (dietary factors), and χ^2 tests (education, smoking, physical activity, hypertension, and dyslipidemia). All tests showed statistically significant differences ($P<0.0001$).

*After exclusion of participants with missing information on any of the relevant covariates.

†Defined as less than high school.

‡Energy-adjusted.

§This information was not available for ATBC.

a higher frequency low educational level was observed among participants in the highest alcohol group. Similar distributions of covariates according to alcohol intake were observed across cohorts.

Alcohol Consumption and Risk of CHD

Tables 4 and 5 show the relative risks (hazard ratios) of CHD by categories of alcohol intake for each of the studies and pooled estimates for women and men. In women, an inverse relation between alcohol intake and CHD was found in each individual study except for VIP. The confidence bounds around risk estimates for this particular study were very broad because the reference category included only 2 cases. In men, an inverse relation was observed in all studies. In the pooled analysis, we observed a significantly lower risk of CHD among women with an

Table 4. Study-Specific and Pooled Hazard Ratios of CHD for Categories of Daily Alcohol Intake for Women

			Hazard Ratio (95% CI) by Daily Alcohol Intake, g/d					
	n	Hazard Ratio, Nondrinkers (CHD=606)	0.1–4.9 (CHD=397)	5.0–14.9 (CHD=242)	15.0–29.9 (CHD=65)	30.0–59.9 (CHD=60)	≥60.0 (CHD=15)	*P* for Trend
Study specific								
ARIC	6406	1.00 (Reference)	0.84 (0.44–1.59)	0.58 (0.29–1.17)	0.78 (0.30–2.00)	NA§	NA§	0.0738
GPS	1509	1.00 (Reference)	0.75 (0.27–2.06)	0.89 (0.31–2.55)	1.15 (0.31–4.23)	0.52 (0.05–5.21)	NA§	0.8418
NHSa	79 479	1.00 (Reference)	0.73 (0.57–0.94)	0.72 (0.55–0.95)	0.59 (0.38–0.94)	0.49 (0.29–0.82)	1.64 (0.77–3.49)	0.1548
NHSb	60 083	1.00 (Reference)	0.78 (0.65–0.94)	0.67 (0.54–0.84)	0.47 (0.32–0.69)	0.57 (0.39–0.82)	0.60 (0.26–1.38)	0.0003
VIP	9758	1.00 (Reference)	2.26 (0.28–18.47)	2.17 (0.12–38.67)	NA§	NA§	NA§	0.8654
WHS	34 832	1.00 (Reference)	1.02 (0.69–1.50)	0.81 (0.49–1.35)	0.37 (0.11–1.19)	0.58 (0.18–1.90)	1.32 (0.18–9.95)	0.1768
Pooled								
Age adjusted*	192 067	1.00 (Reference)	0.78 (0.69–0.89)	0.73 (0.62–0.84)	0.57 (0.44–0.74)	0.80 (0.61–1.05)	1.71 (1.02–2.86)	0.1112
Smoking adjusted†	192 067	1.00 (Reference)	0.75 (0.65–0.85)	0.62 (0.53–0.72)	0.47 (0.36–0.61)	0.52 (0.39–0.68)	1.02 (0.61–1.70)	<0.0001
Multivariable‡	192 067	1.00 (Reference)	0.78 (0.69–0.90)	0.68 (0.59–0.80)	0.52 (0.40–0.67)	0.53 (0.39–0.70)	0.93 (0.55–1.58)	<0.0001

*Also adjusted for year of baseline questionnaire.

†Also adjusted for age and year of baseline questionnaire.

‡Multivariable hazard ratios were adjusted for age, year of baseline questionnaire, smoking, BMI, education, physical activity, energy intake, polyunsaturated fat, monounsaturated fat, saturated fat, fiber, cholesterol intake, and study origin.

§Not applicable because of a limited number of cases.

Table 5. Study–Specific and Pooled Hazard Ratios of CHD for Categories of Daily Alcohol Intake for Men

	n	Hazard Ratio, Nondrinkers (CHD=623)	Alcohol Intake, g/d						*P* for Trend
			0.1–4.9 (CHD=737)	5.0–14.9 (CHD=751)	15.0–29.9 (CHD=449)	30.0–59.9 (CHD=311)	60.0–89.9 (CHD=59)	≥90.0 (CHD=31)	
Study specific									
ARIC	5166	1.00 (Reference)	1.16 (0.78–1.71)	1.29 (0.93–1.79)	0.87 (0.57–1.32)	0.73 (0.44–1.22)	0.74 (0.27–2.04)	1.40 (0.56–3.54)	0.4499
ATBC	21 119	1.00 (Reference)	0.86 (0.71–1.03)	0.86 (0.72–1.03)	0.70 (0.58–0.85)	0.61 (0.49–0.77)	0.48 (0.32–0.74)	0.80 (0.51–1.27)	0.0001
GPS	1294	1.00 (Reference)	0.84 (0.30–2.32)	0.54 (0.21–1.38)	0.60 (0.24–1.50)	0.44 (0.16–1.18)	0.37 (0.09–1.52)	NA§	0.0304
HPFS	38 654	1.00 (Reference)	1.00 (0.85–1.17)	0.75 (0.63–0.88)	0.69 (0.56–0.86)	0.66 (0.52–0.83)	0.65 (0.41–1.01)	0.17 (0.02–1.23)	<0.0001
VIP	8486	1.00 (Reference)	0.50 (0.28–0.93)	0.24 (0.11–0.48)	0.25 (0.07–0.91)	0.73 (0.09–5.85)	NA§	NA§	0.009
Pooled									
Age-adjusted*	74 719	1.00 (Reference)	0.95 (0.85–1.06)	0.84 (0.75–0.93)	0.75 (0.66–0.85)	0.74 (0.64–0.85)	0.70 (0.53–0.91)	0.96 (0.67–1.39)	<0.0001
Smoking-adjusted†	74 719	1.00 (Reference)	0.94 (0.84–1.05)	0.81 (0.72–0.90)	0.71 (0.63–0.81)	0.66 (0.58–0.76)	0.60 (0.46–0.79)	0.81 (0.57–1.18)	<0.0001
Multivariable‡	74 719	1.00 (Reference)	0.96 (0.86–1.08)	0.83 (0.74–0.92)	0.72 (0.64–0.82)	0.66 (0.57–0.76)	0.58 (0.44–0.77)	0.77 (0.53–1.13)	<0.0001

*Also adjusted for year of baseline questionnaire.

†Also adjusted for age and year of baseline questionnaire.

‡Multivariable hazard ratios were adjusted for age, year of baseline questionnaire, smoking, BMI, education, physical activity, energy intake, polyunsaturated fat, monounsaturated fat, saturated fat, fiber, cholesterol intake, and study origin.

§Not applicable because of a limited number of cases.

alcohol intake of up to 60 g/d and among men with an alcohol intake of up to 90 g/d.

We also performed analyses describing the risk of CHD according to alcohol consumption modeled as a continuous variable (Figure 1). In both men and women, a reduction in CHD risk was observed at low to moderate levels of alcohol. The relative risk of CHD was 0.58 (95% confidence interval [CI], 0.49 to 0.68) in women and 0.69 (95% CI, 0.62 to 0.76) in men with a daily intake of 30 g/d, corresponding to ≈2 to 3 drinks. Higher levels of alcohol consumption were not associated with any discernible additional protection in women and with only modest protection in men.

Alcohol Consumption and Risk of CHD in Age Strata

We estimated the risks of CHD according to alcohol intake separately for 3 age groups (≤50, 50 to 59, and ≥60 years; Figure 2). In all age groups and for both men and women, a decreased risk of CHD according to alcohol intake was observed but with broader confidence bounds for the youngest age group. The test for interaction between alcohol and age was not statistically significant in either women ($P=0.34$) or men ($P=0.25$). We also modeled the risk continuously for the different age groups and observed similar shapes of the curves (data not shown).

Incidence rates of CHD in women and men according to alcohol intake and age are displayed in Figure 3. As expected, the incidence of CHD was much lower in the younger compared with older participants. The incidence rates of CHD among female abstainers in the 3 age groups were 11 (95% CI, 1 to 109), 41 (95% CI, 1 to 400), and 103 (95% CI, 9 to 1018) per 100 000, respectively. In male abstainers, the incidence rates were 114 (95% CI, 77 to 171), 262 (95% CI, 201 to 343), and 454 (95% CI, 354 to 553) per 100 000 for the 3 age groups, respectively. In all age groups and in both men and women, the incidence rate was lower among participants with a low to moderate alcohol intake compared with abstainers. In women, the incidence rate differences between drinking 0 g/d and 5.0 to 29.9 g/d were 3 (90% CI, −1 to 25), 16 (90% CI, 0 to 111), and 35 (90% CI, 0 to 250). For men, the corresponding incidence rate differences were 45 (90% CI, 8 to 84), 64 (90% CI, 24 to 102), and 89 (90% CI, 44 to 140) per 100 000.

Sensitivity Analyses

Heterogeneity between study-specific effects was assessed by the inclusion of an interaction term between alcohol and study origin under the null hypothesis of no between-study differences in the relative risk of CHD by alcohol intake,[1,25] with no sign of heterogeneity detected ($P=0.95$ in women, $P=0.12$ in men). In addition, comparing pooled risk estimates

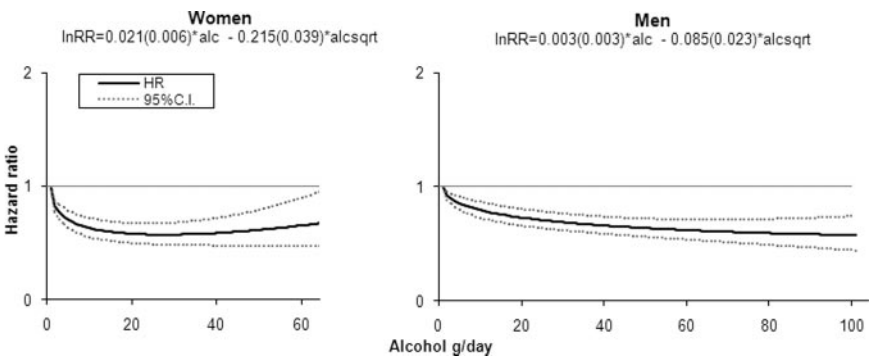

Figure 1. Relative risk functions (95% CI) describing the dose-response relation between alcohol intake and risk of CHD. Analyses were adjusted for year of baseline questionnaire, education, smoking, BMI, physical activity, total energy intake, polyunsaturated fat, monounsaturated fat, saturated fat, fiber, and cholesterol intake. The fitted model (SE) is reported. The 99th percentile of cases was 64 g/d in women and 90 g/d in men. The highest alcohol intake in observed cases was 90 g/d in women and 215 g/d in men.

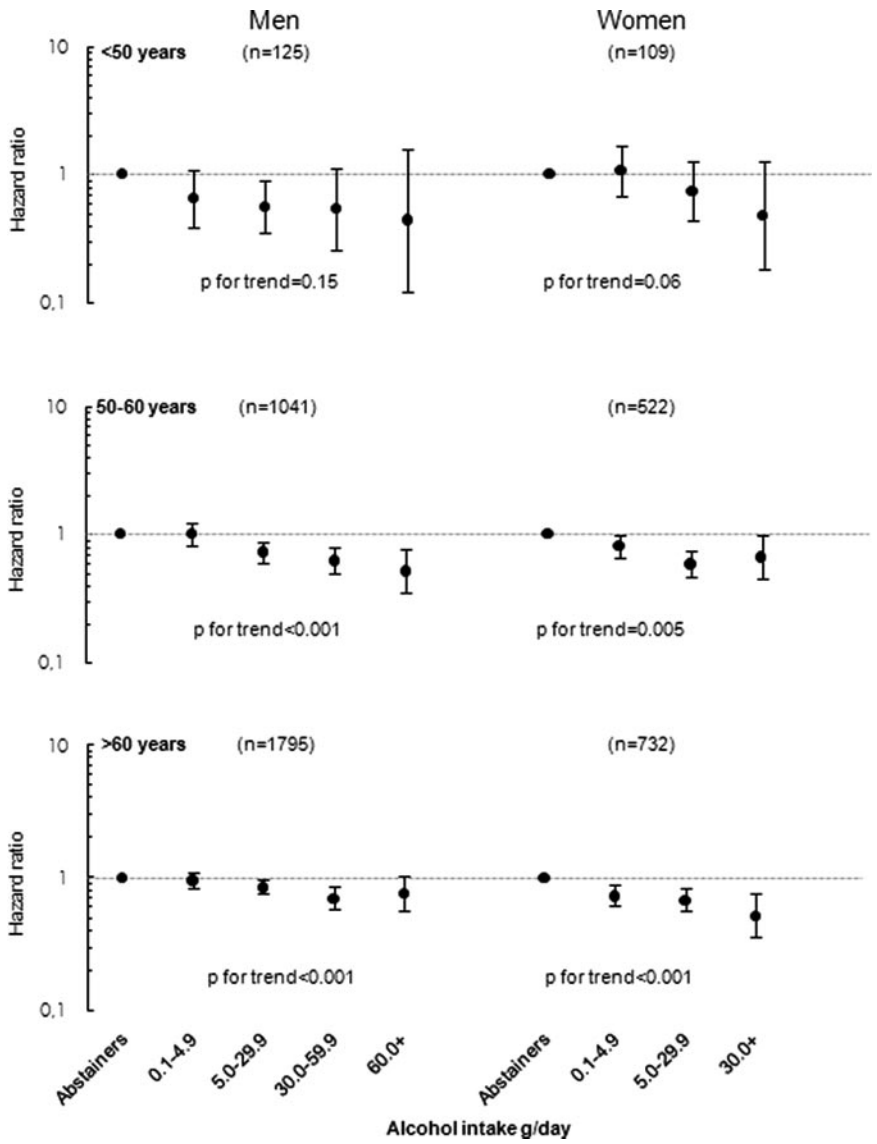

Figure 2. Sex- and age-specific pooled hazard ratios of CHD for categories of daily alcohol intake. Multivariable hazard ratios were adjusted for year of baseline questionnaire, education, smoking, BMI, physical activity, total energy intake, polyunsaturated fat, monounsaturated fat, saturated fat, fiber, and cholesterol intake. n indicates number cases for each sex and age group.

after systematically excluding each study at a time confirmed that no single study strongly influenced the pooled estimates.[33] Hence, the pooled hazard ratios are considered appropriate summaries of the study-specific data. Performing a test for interaction between age (time scale) and alcohol consumption did not yield violations of the proportional-hazards assumption for either women ($P=0.10$) or men ($P=0.22$).

Separate analyses were performed for fatal and nonfatal events to examine whether the effect of alcohol on CHD differed according to the severity of the outcome. The results of this analysis did not reveal obvious differences between the 2 measures of outcome, although a tendency toward an elevated risk of fatal CHD was observed for the highest alcohol category in both women and men (data not shown).

To examine the possibility that latent baseline symptoms of CHD might reduce the alcohol intake, thereby biasing the results, we performed analyses in which the first 2 or 4 years after baseline were excluded. This did not attenuate the estimates (data not shown).

Additional analyses for women were performed to examine whether adjustment for postmenopausal hormone replacement therapy had an impact on results. This involved excluding participants with unavailable information on this particular covariate (n=9799, 5% of the study population). In the remaining cohorts, postmenopausal hormone replacement therapy did not appreciably affect the association between alcohol and risk of CHD. In addition, the inclusion of history of hypertension and dyslipidemia as covariates in the model did not affect the risk estimates of CHD according to alcohol consumption. Furthermore, an analysis was performed including the IWHS (n=29 801). This inclusion also did not change the hazard ratios appreciably (data not shown).

A test for interaction between alcohol and smoking was performed to examine whether the estimates of the effect of alcohol on CHD risk differed according to smoking status. Smoking did not modify the association between alcohol and CHD in either men ($P=0.79$) or women ($P=0.14$). Additional analyses including nonsmokers only were performed separately for women (n=100 144) and

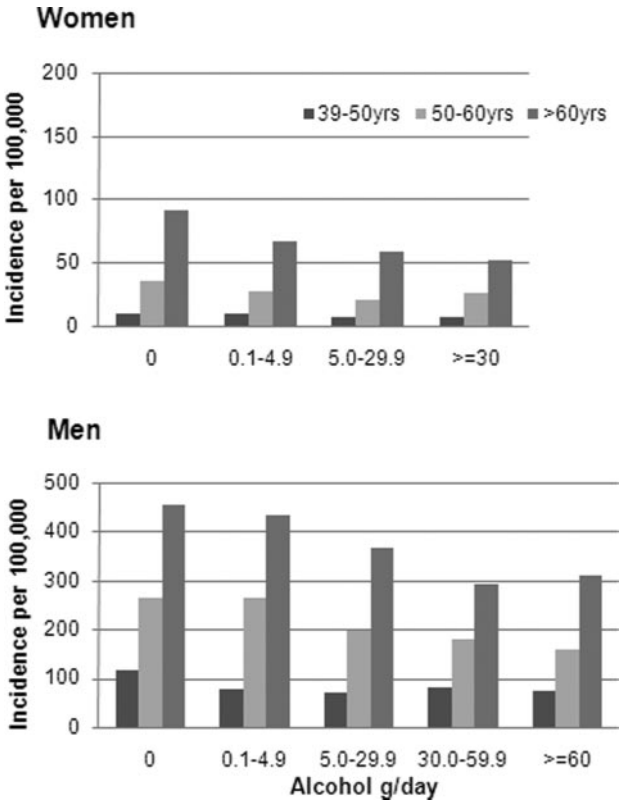

Figure 3. Incidence rates of CHD according to age and alcohol intake. Analyses were adjusted for year of baseline questionnaire, education, smoking, BMI, physical activity, total energy intake, polyunsaturated fat, monounsaturated fat, saturated fat, fiber, and cholesterol intake.

men (n=46 576) for alcohol levels of 0, 0.1 to 14.9, 15.0 to 29.9, and ≥30.0 g/d and showed similar associations (data not shown).

Discussion

In this pooled cohort of 8 prospective studies, we observed a lower risk of CHD among men and women with a light to moderate alcohol intake compared with nondrinkers. This finding was consistent across different age groups without significant variations in dose response.

The current data on the effect of alcohol on CHD in younger adults are sparse. In a study based on the Honolulu Heart Program, the authors compared CHD risk according to conventional risk factors in middle-aged and older men (age, 45 to 93 years). Compared with nondrinkers, they observed a lower risk of CHD among drinkers in middle-aged but not among older participants (≥75 years) and concluded accordingly that the relation between alcohol and CHD weakened with age. The study, however, was limited by the simple categorization of alcohol intake into drinkers or nondrinkers and included men only.[10]

Several plausible explanations for the lowered risk of CHD among moderate drinkers exist. Among those explanations, the evidence is probably strongest for a mechanism involving alcohol increasing high-density lipoprotein cholesterol and reducing plasma fibrinogen levels, thereby reducing platelet aggregability.[7,34] The hypothesized J-shaped relation between alcohol intake and diabetes mellitus could also explain some of the benefit from alcohol intake.[35,36] In addition, alcohol has an effect on plasminogen activator inhibitor-1 that would tend to reduce thrombosis.[37]

Previous studies have suggested that the causes of CHD in younger adults differ from the mechanisms involved with CHD in older persons. Results from the Honolulu Heart Program indicated that the effect of hypertension, BMI, and cholesterol on CHD differed according to age. For instance, the relative risk of CHD in hypertensive men declined from 3.7 in those 45 to 54 years of age to 1.7 in those ≥75 years of age. Similarly, associations between BMI and total cholesterol weakened with advancing age.[10] The Coronary Artery Risk in Young Adults (CARDIA) study of men and women 33 to 45 years of age found that alcohol intake was associated with expected dose response between alcohol and high-density lipoprotein cholesterol levels and an inverse relation between alcohol and fibrinogen levels.[9] They also observed an increased risk of coronary calcification with greater alcohol consumption. Because coronary calcification is a marker of atherosclerosis, this result in young adults is not consistent with the results of the present study.[9]

Another aspect of alcohol consumption related to age is drinking patterns. Younger adults may tend to binge drink more often than older persons, which may increase their risk of CHD[5,7,9]; however, findings from the CARDIA study did not indicate a protective effect of alcohol intake on coronary calcification in younger adults even after the exclusion of binge drinkers.[9]

Our findings suggest a J-shaped curve in women, but in men, the risk did not increase significantly at high amounts of alcohol. Biomarkers that mediate the association between alcohol and decreased risk of CHD such as high-density lipoprotein and fibrinogen are found to explain a larger proportion of the association among men than among women, which may indicate that alcohol has specific effects on such mediators according to sex.[7] Other biological explanations for sex-specific associations include differences in alcohol pharmacokinetics (ie, processing and elimination of alcohol in the body), which depend largely on body composition.[38,39] However, because the risk curves of this study were modeled separately for the 2 sexes, comparisons between them are not straightforward.

The present study is one of only a few existing studies focusing on the effects of alcohol on CHD according to age. Our work was based on a large body of data with thorough measurements of alcohol intake and relevant covariates. A strength was the availability of diet data in the Pooling Project of Diet and Coronary Disease that enabled adjustment for potential dietary confounders. The size of the study population allowed us to perform subset analyses exploring the association between alcohol and CHD in strata of younger men and women, aspects that even large individual cohorts do not have the power to address. The findings of the present study were strengthened by the prospective design, which provided information on the sequence of events allowing for conclusions on causality, assuming proper confounding control. Potential confounders of the association between alcohol and CHD were carefully selected on the basis of directed

acyclic graphs, ensuring a minimally sufficient set of covariates. Furthermore, the inclusion criteria of the Pooling Project of Diet and Coronary Disease enabled adjustment for relevant dietary factors, which most previous studies did not control for. The pooled analyses included both cohorts and intervention studies from North America and Europe, and similar effects were observed across the studies. Finally, an advantage of the Pooling Project is the inclusion of previously unpublished results, thereby reducing the risk of publication bias.

However, several limitations of the study should also be considered. We focused on the importance of the amount of alcohol consumed; however, other aspects of patterns of alcohol intake may be equally important and were not addressed. Our study included only information on current alcohol consumption and confounders at baseline. For this reason, the reference category of abstainers may contain former drinkers who quit because of existing illness, which could cause a moderate alcohol intake to appear more protective than it is. Although several studies that included only lifelong or long-term abstainers in this category have confirmed a protective effect of alcohol even among healthy individuals,[6,40] the "sick-quitter" hypothesis is relevant in the present context because older age groups may include more abstainers who stopped drinking because of illness (eg, hypertension).

As mentioned, patterns of alcohol consumption (eg, choice of alcohol type and frequency of consumption) may differ considerably with age, which we did not account for. Our findings of protective effects of alcohol on CHD in all examined age groups may indicate that neither the type of alcohol nor the frequency of consumption modifies the influence of alcohol on CHD considerably. However, future research based on observational studies should emphasize other measures of alcohol intake such as frequency of alcohol consumed. Furthermore, cohort studies with information on lifetime alcohol intake or repeated measurements of alcohol intake and potential confounders could contribute valuable insight because changes in alcohol intake over a given period may be of great importance. Additional experimental studies are also needed to expand the knowledge of biological mechanisms.

Furthermore, this study focused only on CHD events. Overall effects of alcohol on all-cause morbidity and mortality must be considered if we are to optimize alcohol guidelines for different age groups of the population. The lower risk of all-cause mortality is expected to be caused mainly by the effects of alcohol on CHD. In this study, a lower risk of CHD was observed in all examined age groups in moderate alcohol consumers compared with abstainers; however, the absolute risk of CHD was rather low in the youngest age group. Thus, considering the increasing contribution of CHD to all-cause mortality with age, it is reasonable to assume that the protective effect of alcohol on all-cause mortality is mostly pronounced in older age groups. This issue has been addressed in a few previous studies indicating that the protective effect of alcohol consumption on mortality in general is confined to middle-aged and older individuals.[4,41,42] Unfortunately, information on all-cause mortality was not collected in the database of the Pooling Project of Diet and Coronary Disease.

Conclusions

This study supports current knowledge that alcohol in moderate amounts protects against CHD in both men and women. Our findings further suggest that this effect is also present in younger age groups. However, younger adults are at low risk for CHD, and the beneficial effects obtained by a moderate alcohol intake may be negligible compared with the increased risk of, for instance, traffic accidents and cancer. Recommendations on alcohol intake among younger adults should consider all-cause mortality and morbidity.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The association between alcohol consumption and decreased risk of coronary heart disease is well established, but possible age differences are plausible because of potential pathogenic differences in coronary heart disease events occurring in younger compared with middle-aged or older individuals. We studied these relations in a large population of men and women 35 to 89 years of age at baseline. We observed a lower risk of coronary heart disease among men and women with a light to moderate alcohol intake compared with nondrinkers, and this finding was consistent and of similar size in all age groups. However, the absolute risk of CHD was small in the youngest age group, and risk differences between abstainers and light to moderate alcohol consumers were of negligible size. Therefore, our results provide strong evidence for a lower risk of coronary heart disease among moderate consumers relative to nondrinkers in younger, middle-aged, and older adults; however, considering absolute risks across age groups, younger adults are not likely to benefit from an overall recommendation of moderate alcohol intake.

Alcohol Intake and Risk of Coronary Heart Disease in Younger, Middle-Aged, and Older Adults

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