CLINICAL RESEARCH STUDY

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Alcohol Consumption and Cardiovascular Health

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ABSTRACT

BACKGROUND: Studies evaluating alcohol consumption and cardiovascular diseases have shown inconsistent results.

METHODS: We performed a systematic review of peer-reviewed publications from an extensive query of Ovid MEDLINE, Ovid Embase, Ovid Cochrane Database of Systematic Reviews, Scopus, and Web of Science from database inception to March 2022 for all studies that reported the association between alcohol consumption in terms of quantity (daily or weekly amounts) and type of beverage (wine, beer or spirit) and cardiovascular disease events.

RESULTS: The study population included a total of 1,579,435 individuals based on 56 cohorts from several countries. We found that moderate wine consumption defined as 1-4 drinks per week was associated with a reduction in risk for cardiovascular mortality when compared with beer or spirits. However, higher risk for cardiovascular disease mortality was typically seen with heavier daily or weekly alcohol consumption across all types of beverages.

CONCLUSIONS: It is possible that the observational studies may overestimate the benefits of alcohol for cardiovascular disease outcomes. Although moderate wine consumption is probably associated with low cardiovascular disease events, there are many confounding factors, in particular, lifestyle, genetic, and socioeconomic associations with wine drinking, which likely explain much of the association with wine and reduced cardiovascular disease events. Further prospective study of alcohol and all-cause mortality, including cancer, is needed.

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KEYWORDS: Alcohol consumption; Beer consumption; Cardiovascular disease; Liquor consumption; Wine consumption

INTRODUCTION

The US Department of Agriculture 2015 to 2025 Dietary Guidelines for Americans[1] define moderate drinking as having up to 1 drink per day for women and up to 2 drinks per day for men. Alcohol consumption above the recommended limits was associated with higher all-cause and

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cause-specific mortality risk (39%-126%).[2] Alcohol may contain polyphenols, amino acids, and minerals,[3] although the content varies considerably among types of alcohol (beer vs red wine vs white wine vs spirit). A complete understanding of these complex mechanisms in human health is limited. Several studies have shown that alcohol consumption has a J-shaped or biphasic relationship with cardiovascular disease.[4,5] In a recent report, analyses suggest that any quantity of alcohol has a deleterious effect on cancer risk.[4] Our study is unique in that it relies on data culled from more than 1 million individuals. We include both alcoholic beverage quantity (daily or weekly amounts) and type of beverage (wine, beer, or spirits) in relation to cardiovascular disease events. Additionally, very few meta-analyses have included spirits when the association of alcohol is examined in relation to these cardiovascular disease outcomes.

CLINICAL SIGNIFICANCE

- It is possible that the observational studies may overestimate the benefits of alcohol for cardiovascular disease outcomes.
- Moderate wine consumption may be associated with low cardiovascular disease events.
- There are many confounding factors, in particular, lifestyle, genetic, and socioeconomic associations with wine drinking, which likely explain much of the association with wine and reduced cardiovascular disease events.
- Further prospective study of alcohol and all-cause mortality, including cancer, is needed.

METHODS

We performed a systematic review of peer-reviewed publications from an extensive query of Ovid MEDLINE, Ovid Embase, Ovid Cochrane Database of Systematic Reviews, Scopus, and Web of Science from database inception to March 2022. Search strategy included MESH headings and keywords related to alcohol and cardiovascular disease (Supplementary Material, available online). We identified studies based on appropriate types of study (observational study, prospective cohort study, randomized controlled trial, or case control design) and the exposure (alcohol consumption). We were unable to perform meta-analysis of the results due to tremendous heterogeneity among the included studies related to intervention, comparison, outcomes, and timing. Instead, we qualitatively synthesized the results and summarized key features and characteristics (eg, study populations, design, interventions, outcomes, and conclusions) of the included studies.

RESULTS

After exclusions in our initial electronic search, we identified and reviewed a total of 56 studies related to alcohol consumption and cardiovascular outcomes. Most common adjustments were age, body mass index, hypertension, and diabetes. As for alcoholic beverages and the relationship with developing coronary artery disease, 19 total studies were included for a total of 1,009,067 individuals; 51.1% were men (Table 1). Studies were published since 1986 and included a diverse group of participants from countries all over the world. Most of the studies were prospective, but several were case-control studies or cross-sectional. Results were variable across these cohorts, but there was a notable pattern of significantly lower hazard ratios (HRs) for coronary artery disease in low to moderate alcohol consumers (defined by weekly and daily consumption thresholds) across all categories of alcoholic beverages.

Table 2 summarizes alcohol consumption and the association with myocardial infarction (238,273 individuals). Most of these studies demonstrated a significantly lower HR for myocardial infarction in individuals with moderate to higher levels of alcohol consumption for all 3 types of beverages.

Table 3 summarizes the association between alcohol consumption and cardiovascular disease mortality (570,368 individuals with mean follow-up 11.7 years). For studies that evaluated low-moderate amounts of weekly or daily alcohol (wine, beer, or spirits) consumption, there were significantly lower risk ratios/HRs for cardiovascular disease mortality. Regardless of the specific alcoholic beverage included in the studies, the risk for cardiovascular disease mortality remained lower. Only a handful of studies noted a significantly higher risk for mortality that was associated with either heavier weekly alcohol consumption (either wine, beer, or spirits) or a history of alcohol consumption in the past. Direct comparisons of alcoholic beverages and the effects on cardiovascular disease mortality within the same cohort showed that moderate wine consumption has a 25% reduction in risk for cardiovascular mortality when compared with beer or spirits (HR 0.75; 95% confidence interval, 0.59-0.96) (Table 3). Higher risk for cardiovascular disease mortality was typically seen with heavier daily or weekly alcohol consumption, across all types of beverages.

DISCUSSION

Beer Consumption and Cardiovascular Outcomes

Beer contains a wide variety of nonalcoholic components (eg, compounds derived from benzoic and cinnamic acids, catechins, procyanidins, humulones, and prenilchalcones)[6,7] that differ from those in red wine, which has amino acids, minerals, and polyphenols (phenolic acid, prenylated chalcones, flavonoids, catechins). It also has been observed that xanthohumol inhibited the oxidation of low-density lipoprotein (LDL) in vitro induced by Cu^{2+},[8] as well as lipid peroxidation of liver microsomes in rats.[9]

Table 1 Included Studies for Alcohol Consumption and CAD

First Author	Year	Country	Number of Participants	Men	Type of Study	Age, Years	Follow-Up	Type of Drink	Comparison	OutcomeHR (95% CI)
Bos[68]	2010	Netherlands	10,530	0	Prospective	—	9.4 y	White wine	5-29.9 vs 0-4.9 g/wk	0.96 (0.76-1.21)
								White wine	30-69.9 vs 0-4.9 g/wk	1.1 (0.74-1.66)
								White wine	>70 vs 0-4.9 g/wk	0.96 (0.59-1.57)
								Red wine	5-29.9 vs 0-4.9 g/wk	0.74 (0.56-0.97)
								Red wine	30-69.9 vs 0-4.9 g/wk	0.77 (0.52-1.14)
								Red wine	>70 vs 0-4.9 g/wk	0.71 (0.43-1.16)
								Beer	5-29.9 vs 0-4.9 g/wk	1 (0.68-1.49)
								Beer	30-69.9 vs 0-4.9 g/wk	0.84 (0.49-1.43)
								Liquor	5-29.9 vs 0-4.9 g/wk	1.04 (0.76-1.41)
								Liquor	30-69.9 vs 0-4.9 g/wk	0.93 (0.61-1.41)
								Liquor	>70 vs 0-4.9 g/wk	1.17 (0.82-1.69)
								Fortified wine	5-29.9 vs 0-4.9 g/wk	1.03 (0.8-1.33)
								Fortified wine	30-69.9 vs 0-4.9 g/wk	1.01 (0.67-1.52)
								Fortified wine	>70 vs 0-4.9 g/wk	0.85 (0.6-1.19)
								White wine, red wine, beer, liquor, fortified wine	0-4.9 g/wk vs lifetime abstainer	0.98 (0.76-1.27)
								White wine, red wine, beer, liquor, fortified wine	5-29.9 g/wk vs lifetime abstainer	0.75 (0.57-0.98)
								White wine, red wine, beer, liquor, fortified wine	30-69.9 g/wk vs lifetime abstainer	0.92 (0.68-1.24)
								White wine, red wine, beer, liquor, fortified wine	70—139.9 g/wk vs lifetime abstainer	0.72 (0.52-1.01)
								White wine, red wine, beer, liquor, fortified wine	≥ 140 g/wk vs lifetime abstainer	0.65 (0.46-0.9)
Brenner[69]	2001	Germany	791	267 cases	Case control	57.7 cases 55.8 control		Wine, beer, mixed	Drinkers vs nondrinkers	0.55 (0.37-0.83)
								Beer only	Beer only vs nondrinkers	0.5 (0.3-0.84)
								Wine only	Wine only vs nondrinkers	0.95 (0.57-1.59)
								Mixed	Mixed vs nondrinkers	0.42 (0.27-0.66)
								Wine, beer, mixed	≤ 125 g/wk vs nondrinkers	0.56 (0.36-0.86)
								Wine, beer, mixed	> 125 g/wk vs nondrinkers	0.55 (0.35-0.86)
Foerster[70]	2009	Switzerland	5769	2574	Cross-sectional	52.5 ± 10.6	—	Wine, beer, spirits		Did not include as mean ± SE ()
Gigleux[71]	2006	Canada	1966	1966	Prospective	IHD-free men - 56 ± 7 IHD cases - 59 ± 7	13 y	Wine, beer, spirits	≥15.2 vs <1.3 g/d	0.51 (0.33-0.8)
								Wine, beer, spirits	5.5-15.1 vs <1.3 g/d	0.81 (0.55-1.21)
								Wine, beer, spirits	1.3-5.4 vs <1.3 g/d	0.87 (0.6-1.27)
Klatsky[72]	1986	US	85,001	37,605	Prospective cohort	—	5 y	Wine, beer, liquor	Ex-drinkers vs abstainers	0.99 (0.72-1.36)
								Wine, beer, liquor	<1 drink/mo vs abstainers	0.93 (0.74-1.18)
								Wine, beer, liquor	<1 drink/d, >l drink/mo vs abstainers	0.65 (0.51-0.82)
								Wine, beer, liquor	1-2 drinks/d vs abstainers	0.55 (0.42-0.72)
								Wine, beer, liquor	3-5 drinks/d vs abstainers	0.54 (0.38-0.76)
								Wine, beer, liquor	6-8 drinks/d vs abstainers	0.52 (0.26-1.05)
								Wine, beer, liquor	>9 drinks/d vs abstainers	0.47 (0.15-1.49)
								Beer	Beer vs liquor	1.01 (0.69-1.46)
								Wine	Wine vs liquor	0.89 (0.64-1.24)

Table 1 (*Continued*)

First Author	Year	Country	Number of Participants	Men	Type of Study	Age, Years	Follow-Up	Type of Drink	Comparison	OutcomeHR (95% CI)
Klatsky[73]	1997	US	128,934	56,730	Prospective cohort	40.6	6 y	Red wine, beer, liquor, white wine	All drinkers (>1 drink/mo vs abstainers)	0.79 (0.71-0.88)
									<1 drink/d vs abstainers	0.93 (0.8-1.09)
									1-2 drinks/d vs abstainers	0.77 (0.65-0.91)
									≥3 drinks/d vs abstainers	0.71 (0.59-0.86)
									All drinkers (>1 drink/mo vs abstainers)	0.76 (0.65-0.89)
									<1 drink/d vs abstainers	0.83 (0.7-0.98)
									1-2 drinks/d vs abstainers	0.64 (0.52-0.79)
									≥3 drinks/d vs abstainers	0.6 (0.42-0.85)
Marques-Vidal[74]	2004	France, Northern Ireland	9750	9750	Prospective cohort	Divided by alcohol and country	5 y	Wine, beer, spirits, cider	0-128 mL pure ethanol/wk vs none	0.74 (0.45-1.21)
								Wine, beer, spirits, cider	128-265 mL pure ethanol/wk vs none	0.65 (0.39,1.08)
								Wine, beer, spirits, cider	265-441 mL pure ethanol/wk vs none	0.48 (0.28-0.81)
								Wine, beer, spirits, cider	≥441 mL pure ethanol/wk vs none	0.37 (0.22-0.64)
								Wine, beer, spirits, cider	0-128 mL pure ethanol/wk vs none	0.67 (0.36-1.27)
								Wine, beer, spirits, cider	128-265 mL pure ethanol/wk vs none	0.81 (0.46-1.46)
								Wine, beer, spirits, cider	265-441 mL pure ethanol/wk vs none	0.88 (0.5-1.54)
								Wine, beer, spirits, cider	≥441 mL pure ethanol/wk vs none	0.7 (0.38-1.29)
								Wine	Wine vs none	0.89 (0.82-0.98)
								Beer	Beer vs none	0.94 (0.74-1.01)
								Spirits	Spirits vs none	1.04 (0.83-1.43)
								Wine, beer, spirits, cider	Total alcohol vs none	0.96 (0.84-0.97)
								Wine	Wine vs none	0.33 (0.11-0.96)
								Beer	Beer vs none	0.99 (0.89-1.07)
								Spirits	Spirits vs none	1.03 (0.93-1.22)
								Wine, beer, spirits, cider	Total alcohol vs none	0.99 (0.92-1.06)
								Wine, beer, spirits	Alcohol vs no alcohol	1.001 (1-1.003)
								Wine, beer, spirits	Drinker group 1 (<15 g/d) vs nondrinkers	0.61 (0.4-0.94)
								Wine, beer, spirits	Drinker group 2 (≥15 g/d) vs nondrinkers	0.68 (0.41-1.12)
								Wine, beer, spirits	Drinker group 1 (<15 g/d) vs lifetime abstainer	0.61 (0.39-0.95)
								Wine, beer, spirits	Drinker group 2 (≥15 g/d) vs lifetime abstainer	0.67 (0.39-1.14)
								Wine, beer, spirits	Drinker group 1 (<15 g/d) vs occasional drinker	0.71 (0.42-1.19)
								Wine, beer, spirits	Drinker group 2 (≥15 g/d) vs occasional drinker	0.75 (0.46-1.23)
								Wine, beer, spirits	Former drinker vs lifetime abstainer	0.97 (0.56-1.71)
Rimm[76]	1991	US	44,059	44,059	Prospective cohort	0 g/d 0.1-5 g/d 5.1-30 g/d >30 g/d	72,290 person-years	Wine, beer, spirits	0.1-5 g/d vs 0 g/d	0.99 (74-1.33)
									5.1-30 g/d vs 0 g/d	0.74 (0.56-0.97)
									>30 g/d vs 0 g/d	0.53 (0.35-0.79)

Table 1 (*Continued*)

First Author	Year	Country	Number of Participants	Men	Type of Study	Age, Years	Follow-Up	Type of Drink	Comparison	OutcomeHR (95% CI)
Roy[99]	2010	India	8930	8930	Cross-sectional I would delete	Alcohol users - 42.8 ± 11.0 Nonusers- 42.8 ± 11.1	—	Wine, beer, spirits	Alcohol users vs nonusers	1.4 (1-1.9)
								Wine, beer, spirits	Occasional users (less than once a week) vs nonusers	1.2 (0.8-1.6)
								Wine, beer, spirits	Regular users (once or more in a week) vs nonusers	1.6 (1-2.2)
								Wine, beer, spirits	Past users (quit at least 6 months ago) vs nonusers	2.1 (1.1-3)
								Local spirits	Local spirits vs none	1.8 (1-2.6)
								Branded spirits	Branded spirits vs none	1.5 (0.9-2.2)
								Wine, beer, spirits	<14 g/d vs no alcohol	1.3 (1.2-1.5)
								Wine, beer, spirits	14-28 g/d vs no alcohol	1.6 (1-2.3)
								Wine, beer, spirits	>28 g/d vs no alcohol	2 (1.2-2.6)
Schutte[111]	2020	UK	446,439	206,088	Prospective cohort	56.4 ± 8.1	7.05 y	Beer/cider	Beer/cider vs other alcohol drinkers	1.12 (0.99-1.26)
								Champagne/white wine	Champagne/white wine vs other alcohol drinkers	0.84 (0.72-0.98)
								Red wine	Red wine vs other alcohol drinkers	0.88 (0.77-0.99)
								Spirits	Spirits vs other alcohol drinkers	1.17 (1.02-1.35)
Snow[100]	2009	Canada	1154	580	Prospective cohort	—	10 y	Wine, beer, spirits	0.65-5.77 g vs <0.65 g/d	1.66 (0.2-13.92)
									5.78-18.1 g vs <0.65 g/d	0.57 (0.06-5.52)
									>18.1 vs <0.65 g/d	0.44 (0.04-4.59)
									>18.1 (heavy) episodic vs <0.65 g/d	4.13 (1.46-11.62)
									0.65-5.77 g vs <0.65 g/d	0.98 (0.4-2.37)
									5.78-18.1 g vs <0.65 g/d	0.75 (0.29-1.95)
									>18.1 vs <0.65 g/d	0.28 (0.08-0.93)
									>18.1 (heavy) episodic vs <0.65 g/d	1.76 (0.81-3.82)
									0.65-2.92 g vs <0.65 g/d	1.13 (0.07-18.39)
									2.93-9.15 g vs <0.65 g/d	2.95 (0.29-29.69)
									>9.15 g vs <0.65 g/d	1.96 (0.17-22.19)
									>9.15 g (heavy) episodic vs <0.65 g/d	1.09 (0.99-1.19)
									0.65-2.92 g vs <0.65 g/d	1.35 (0.51-3.57)
									2.93—9.15 g vs <0.65 g/d	2.12 (0.82-5.48)
									>9.15 g vs <0.65 g/d	0.44 (0.09-2.02)
									>9.15 g (heavy) episodic vs <0.65 g/d	0 (0-∞)
Song[101]	2018	US	156,728	142,622	Prospective cohort	65.3 ± 12.1	2.9 y	Wine, beer, spirits	Former drinkers vs never drinkers	1.02 (0.92-1.13)
									≤6 g/d vs never drinkers	0.83 (0.74-0.93)
									>6-12g/d vs never drinkers	0.77 (0.67-0.87)
									>12—24g/d vs never drinkers	0.71 (0.62-0.81)
									>24-36g/d vs never drinkers	0.62 (0.51-0.76)
									>36-48 g/d vs never drinkers	0.58 (0.46-0.74)
									AUD/heavy drinkers (>48 g/d) vs never drinkers	0.95 (0.85-1.06)
Stampfer[77]	1988	US	87,526	0	Prospective cohort	34-59	334,382 person-years	Wine, beer, spirits	<1.5 g/d vs 0 g/d	0.7 (0.5-1.1)
									1.5-4.9 g/d vs 0 g/d	0.5 (0.4-0.8)
									5-14.9 g/d vs 0 g/d	0.5 (0.4-0.8)
									15-24.9 g/d vs 0 g/d	0.6 (0.3-1.1)
									>25 g/d vs 0 g/d	0.6 (0.3-1)

Table 1 (*Continued*)

First Author	Year	Country	Number of Participants	Men	Type of Study	Age, Years	Follow-Up	Type of Drink	Comparison	OutcomeHR (95% CI)
Wannamethee[78]	1999	UK	7272	7272	Prospective cohort	40-59	16.8 y	Wine, beer, spirits	None vs occasional (<1 unit per week)	1.03 (0.78-1.37)
								Wine, beer, spirits	Light (1-15 units per week) vs occasional	0.76 (0.64-0.91)
								Wine, beer, spirits	Moderate (16-42 units per week), vs occasional	0.78 (0.65-0.94)
								Wine, beer, spirits	Heavy (more than 6 units per day) vs occasional	0.75 (0.59-0.95)
								Beer	Regular drinker vs occasional drinker	0.78 (0.63-0.97)
								Spirits	Regular drinker vs occasional drinker	0.57 (0.39-0.85)
								Beer and spirits	Regular drinker vs occasional drinker	0.75 (0.5-1.1)
								Wine	Regular drinker vs occasional drinker	0.92 (0.51-1.67)
								Wine/sherry, beer, spirits	Regular drinker vs occasional drinker	1.23 (0.54-2.79)
								Spirits, beer	Spirits vs beer in occasional and regular drinkers	1.07 (0.9-1.26)
								Wine, beer	Wine vs beer in occasional and regular drinkers	0.82 (0.64-1.04)
Wellmann[79]	2004	Germany	2710	1345	Prospective cohort	35-64	10 y in men 10.1 in women	Wine, beer, spirits	0.1-19.9 g/d vs 0 g/d	0.34 (0.17-0.69)
									20.0-39.9 g/d vs 0 g/d	0.43 (0.22-0.81)
									40.0-79.9 g/d vs 0 g/d	0.7 (0.4-1.22)
									>80.0 g/d vs 0 g/d	0.33 (0.12-0.89)
									Quitter vs nondrinker	0.78 (0.32-1.87)
									Starter vs nondrinker	0.32 (0.09-1.18)
									Constant drinker 0.1-19.9 g/d vs nondrinker	0.29 (0.12-0.7)
									Constant drinker 20.0-39.9 g/d vs nondrinker	0.39 (0.17-0.87)
									Constant drinker 40.0—79.9 g/d vs nondrinker	0.6 (0.29-1.24)
									Constant drinker >80.0g/d vs nondrinker	0.29 (0.1-0.86)
Woodward[80]	1995	Scotland			Cross-sectional	40-59	—	Wine, beer, spirits	1-7 Units/wk vs 0	0.99 (0.7-1.41)
									8-15 Units/wk vs 0	0.99 (0.69-1.42)
									16-29 Units/wk vs 0	0.97 (0.66-1.43)
									>30 Units/wk vs 0	1.04 (0.67-1.61)
									1-2 Units/wk vs 0	0.57 (0.36-0.91)
									3-5 Units/wk vs 0	0.62 (0.41-0.96)
									6-9 Units/wk vs 0	0.74 (0.47-1.15)
									>10 Units/wk vs 0	0.61 (0.37-1.01)
Keil[81]	1997	Germany	2087	1074	Prospective cohort	45-64	7.9 y	Beer	Drinkers vs nondrinkers	0.55 (0.29-1.02)
									0.1-19.9 g/d vs nondrinkers	0.54 (0.24-1.2)
									20-39.9 g/d vs nondrinkers	0.48 (0.21-1.09)
									40-79.9 g/d vs nondrinkers	0.63 (0.3-1.29)
									>80 g/d vs nondrinkers	0.48 (0.18-1.28)
Biddinger[82]	2022	UK	371,463	172,400	Cohort	57.0 ± 7.9	~ 6 y	Wine, beer, spirits	Light drinkers vs none	1.7 (1.2- 2.3)
									Moderate drinkers vs none	1.7 (1.1-2.7)
									Heavy drinkers vs none	2.1 (1.1- 3.9)
									Abuse drinkers vs none	5.7 (2.4-13.5)

AUD = alcohol use disorder; CAD = coronary artery disease; IHD = ischemic heart disease; CI - Confidence interval.

Table 2 Included Studies for Alcohol Consumption and Myocardial Infarction

First Author	Year	Country	Number of Participants	Men	Type of Study	Age, Years	Follow-Up	Type of Drink	Comparison	OutcomesHR (95% CI)
Gigleux[71]	2006	Canada	1966	1966	Prospective	—	13 y	Wine, beer, spirits	≥15.2 vs <1.3 g/d	0.51 (0.33-0.8)
									5.5-15.1 vs <1.3 g/d	0.81 (0.55-1.21)
									1.3-5.4 vs <1.3 g/d	0.87 (0.6-1.27)
Klatsky[72]	1986	US	85,001	37,605	Prospective cohort	—	5 y	Wine, beer, spirits	Ex-drinkers vs abstainers	1.19 (NR-NR)
									<1 drink/mo vs abstainers	0.97 (NR-NR)
									< 1 drink/d, > l drink/mo vs abstainers	0.72 (NR-NR)
									1-2 drinks/d vs abstainers	0.54 (NR-NR)
									3-5 drinks/d vs abstainers	0.38 (NR-NR)
									6-8 drinks/d vs abstainers	0.7 (NR-NR)
									>9 drinks/d vs abstainers	0.31 (NR-NR)
Marques-Vidal[74]	2004	France, Northern Ireland	9750	9750	Prospective cohort	—	5 y	Wine, beer, spirits, cider	0-128 mL pure ethanol/wk vs none	0.54 (0.29-1.02)
									128-265 mL pure ethanol/wk vs none	0.45 (0.23-0.87)
									265-441 mL pure ethanol/wk vs none	0.37 (0.19-0.73)
									≥ 441 mL pure ethanol/wk vs none	0.26 (0.13-0.54)
									0-128 mL pure ethanol/wk vs none	0.62 (0.27-1.45)
									128-265 mL pure ethanol/wk vs none	0.69 (0.31-1.52)
									265-441 mL pure ethanol/wk vs none	0.56 (0.25-1.28)
									≥441 mL pure ethanol/wk vs none	0.43 (0.17-1.09)
								Wine	Wine vs none	0.88 (0.78-1)
								Beer	Beer vs none	0.89 (0.58-0.99)
								Spirits	Spirits vs none	1.09 (0.95-1.58)
								Wine, beer, spirits, cider	Total alcohol vs none	0.95 (0.8-0.98)
								Wine	Wine vs none	0.18 (0.03-1.29)
								Beer	Beer vs none	0.97 (0.81-1.08)
								Spirits	Spirits vs none	1.01 (0.84-1.26)
								Wine, beer, spirits, cider	Total alcohol vs none	0.98 (0.85-1.06)
Park[75]	2017	Korea	8330	3936	Prospective cohort	40-49 y, n = 3876 (46.5%)	10 y	Wine, beer, spirits	Drinker group 1 (<15 g/d) vs nondrinkers	0.44 (0.21-0.92)
						50-59 y, n = 2220 (26.7%)			Drinker group 2 (≥15 g/d) vs nondrinkers	0.42 (0.19-0.93)
						60-69 y, n = 2234 (26.8%)			Drinker group 1 (<15 g/d) vs lifetime abstainer	0.41 (0.19-0.9)
									Drinker group 2 (≥15 g/d) vs lifetime abstainer	0.39 (0.16-0.91)
									Drinker group 1 (<15 g/d) vs occasional drinker	0.65 (0.29-1.45)
									Drinker group 2 (≥15 g/d) vs occasional drinker	0.51 (0.23-1.12)
									Former drinker vs lifetime abstainer	0.84 (0.35-1.98)
Rimm[57]	1991	US	44,059	44,059	Prospective cohort	0 g/d	72,290 person-years	Wine, beer, spirits	0.1-5 g/d vs 0 g/d	0.99 (0.65-1.51)
						0.1-5 g/d			5.1-30 g/d vs 0 g/d	0.71 (0.47-1.06)
						5.1-30 g/d			>30 g/d vs 0 g/d	0.65 (0.37-1.31)
						>30 g/d				
Stampfer[77]	1988	US	87,526	0	Prospective cohort	34-59	334,382 person-years	Wine, beer, spirits	<1.5 g/d vs 0 g/d	0.7 (0.5-1.1)
									1.5-4.9 g/d vs 0 g/d	0.5 (0.4-0.8)
									5-14.9 g/d vs 0 g/d	0.5 (0.4-0.8)
									15-24.9 g/d vs 0 g/d	0.6 (0.3-1.1)
									>25 g/d vs 0 g/d	0.6 (0.3-1)
Kauhanen[93]	1997	Finland	1641	1641	Prospective cohort	6 or more 50.4 (6.0)	7.7 y	Beer	6 or more vs <3 bottles	0.96 (0.39-2.35)
						3-5 51.2 (5.6)		Beer	3-5 bottles vs <3 bottles	1.28 (0.85-1.93)
						<3 52.4 (5.0)				
Biddinger[62]	2022	UK	371,463	172,400	Cohort	57.0 ± 7.9	~ 6 y	Wine, beer, spirits	Light drinkers vs none	1.3 (0.89- 2.11)
									Moderate drinkers vs none	2.6 (1.39- 4.94)
									Heavy drinkers vs none	1.8 (0.78- 4.30)
									Abuse drinkers vs none	7.3 (2.28-23.84)

Table 3 Included Studies for Alcohol Consumption and Cardiovascular Mortality

First Author	Year	Country	Number of Participants	Men	Type of Study	Age, Years	Follow-Up	Type of Drink	Comparison	Outcome HR (95% CI)
Behrens[83]	2011	Sweden	49,259	0	Prospective	—	713,295 person-years	Wine, beer, spirits	0.1-1.4 g/d vs 0 g/d	0.76 (0.48-1.2)
									1.5-4.9 g/d vs 0 g/d	0.57 (0.36-0.91)
									5.0-9.9 g/d vs 0 g/d	0.85 (0.52-1.38)
									10.0+ g/d vs 0 g/d	0.55 (0.27-1.12)
									0.1-19.9g/d vs 0 g/d	0.69 (0.46-1.01)
Berberian[84]	1994	Netherlands	1620	760	Prospective survey based	—	10 y	Wine, beer, spirits	Occasional (<1 time a week) vs no drinks and ex-drinkers	0.23 (0.07-0.73)
									Frequent (one time a week or more) vs no drinks and ex-drinkers	0.61 (0.26-1.38)
									Daily alcohol vs no drinks and ex-drinkers	0.37 (0.13-1)
Bertoia[85]	2012	US	93,676	0	Prospective	—	3 y	Wine, beer, spirits	Never drinker vs 0.1-5 g	1.85 (0.86-3.98)
									Former drinker vs 0.1-5 g	0.92 (0.47-1.81)
									5.1-10 g vs 0.1-5 g	0.64 (0.38-1.1)
									10.1-30 g vs 0.1-5 g	0.86 (0.55-1.32)
									>30 g vs 0.1-5 g	0.83 (0.42-1.64)
Dai[86]	2015	US	843	843	Prospective	48 ± 3.1	41 y	Wine, beer, spirits	Per 10-g increment in alcohol intake	0.97 (0.94-1.01)
Deev[87]	1998	Russia, US	8164	3808	Prospective	—	13 y	Wine, beer, spirits	Had at least 1 drink last year but none last week vs nondrinker	0.76 (0.47-1.22)
									0 < g last week ≤ 12 vs nondrinker	0.54 (0.35-0.84)
									12 < g last week ≤ 24 vs nondrinker	0.39 (0.23-0.67)
									> 24 g last week vs nondrinker	0.48 (0.3-0.77)
									Had at least 1 drink last year but none last week vs nondrinker	0.76 (0.48-1.18)
									0 < g last week ≤ 12 vs nondrinker	0.79 (0.51-1.21)
									12 < g last week ≤ 24 vs nondrinker	0.68 (0.42-1.11)
									> 24 g last week vs nondrinker	0.98 (0.62-1.56)
									Had at least 1 drink last year but none last week vs nondrinker	0.51 (0.31-0.82)
									0 < g last week ≤ 6 vs nondrinker	0.45 (0.27-0.75)
									> 6 g last week vs nondrinker	0.38 (0.23-0.62)
									Had at least 1 drink last year but none last week vs nondrinker	0.78 (0.53-1.14)
									0 < g last week ≤ 6 vs nondrinker	0.63 (0.37-1.06)
									> 6 g last week vs nondrinker	1.2 (0.54-2.65)
Diem[88]	2003	Switzerland	287	162	Prospective	46.2 ± 5.9	12.6 ± 0.6 y	Wine, beer, spirits	1-15 g/d vs 0 g/d	0.87 (0.25-2.52)
									16—30 g/d vs 0 g/d	0 (0-0.92)
									>30 g/d vs 0 g/d	0.37 (0.01-2.42)
Grabas[89]	2016	Netherlands	1919	1599		67.0 [IQR 12.5]	2.2 y [IQR 2.0]	Wine, beer, spirits	0 units/wk vs 1—14 units/wk	1.42 (0.84-2.38)
									15-21 units/wk vs 1—14 units/wk	1.63 (0.8-3.29)
									>21 units/wk vs 1—14 units/wk	1.7 (0.94-3.06)

Table 3 (*Continued*)

First Author	Year	Country	Number of Participants	Men	Type of Study	Age, Years	Follow-Up	Type of Drink	Comparison	Outcome HR (95% CI)
Harriss[90]	2007	Australia	38,200	15,156	Prospective cohort	40-69; grouped by sex and drinking	11.4 y	Wine, beer, spirits	Former drinkers vs lifetime abstainers	2.58 (1.51-4.41)
									Occasional drinkers (<10 g/wk) vs lifetime abstainers	1.65 (0.92-2.96)
									1.43-20 g/d vs lifetime abstainers	1.39 (0.92-2.09)
									>20-40 g/d vs lifetime abstainers	1.01 (0.63-1.63)
									>40 g/d vs lifetime abstainers	1.27 (0.79-2.04)
									Former drinkers vs lifetime abstainers	1.25 (0.57-2.74)
									Occasional drinkers (<10 g/wk) vs lifetime abstainers	1.07 (0.6-1.89)
									1.43-20 g/d vs lifetime abstainers	0.82 (0.5-1.34)
									>20-40 g/d vs lifetime abstainers	1.03 (0.62-1.72)
									>40 g/d vs lifetime abstainers	0.43 (0.19-0.95)
Hernandez-Hernandez[91]	2015	Spain	14651	—	Prospective cohort	No total cohort mean age; grouped by drinking	9.7 y	Wine, beer, spirits	Abstainers vs MADP score high (7-9)	1.91 (0.52-6.98)
									MADP score Low (0-2) vs high (7-9)	3.35 (0.77-14.5)
									MADP score Low (0-2) vs high (7-9)	2.64 (1.11-6.23)
									Alcohol intake low vs moderate	1.53 (0.64-3.81)
									Alcohol intake high vs moderate	3.24 (0.93-11.65)
									Regular vs distributed	1.07 (0.39-2.88)
									Concentrated vs distributed	0.50 (0.15-1.68)
									Yes vs no	1.62 (0.65-4.12)
									No vs yes	1.08 (0.46-2.62)
									With meals, no vs yes	1.40 (0.62-3.27)
									No vs yes	0.89 (0.43-1.91)
									Excess vs no excess	1.68 (0.73-4.08)
Hoffmeister[92]	1999	Germany	15,400	7677	Prospective cohort	25-69	6.9 y	Wine, beer, spirits	1-20 vs 0 g/d	0.42 (0.2-9)
									21-40 vs 0 g/d	0.72 (0.34-1.53)
									40-80 vs 0 g/d	0.73 (0.31-1.74)
									>80 vs 0 g/d	0.35 (0.05-2.67)
									1-20 vs 0 g/d	0.68 (0.25-1.86)
									21-40 vs 0 g/d	1.62 (0.51-5.16)
									40-80 vs 0 g/d	1.38 (0.3-6.28)
Kauhanen[93]	1997	Finland	1641	1641	Prospective cohort	6 or more 50.4 (6.0) 3-5 51.2 (5.6) <3 (reference group) 52.4 (5.0)	7.7 y	Beer	6 or more vs <3 bottles	7.05 (1.93-25.67)
									3-5 bottles vs <3 bottles	2.4 (0.95-6.06)
Laatikainen[94]	2003	Finland	5092	5092	Prospective cohort	Drinkers with heavy pattern - 42.1 (10.5) No heavy drinking occasions - 45.5 (11.2)	7.3 y	Wine, beer, spirits	Heavy drinkers vs other drinkers	1.77 (1.01-3.08)

Table 3 (*Continued*)

First Author	Year	Country	Number of Participants	Men	Type of Study	Age, Years	Follow-Up	Type of Drink	Comparison	Outcome HR (95% CI)
Malyutina[96]	2002	Russia	6502	6502	Prospective cohort	25-64	9.5 y	Wine, beer, spirits	Nondrinkers vs none	1.55 (1.16-2.09)
									<40 g vs none	0.71 (0.42-1.22)
									40-79 g vs none	0.78 (0.53-1.15)
									80-119 g vs none	0.85 (0.57-1.27)
									120-159 g vs none	1.25 (0.81-1.95)
									≥160 g vs none	0.91 (0.65-1.29)
Mukamal[95]	2010	US	10670	—	Prospective cohort	—	5 y	Wine, beer, spirits	Lifelong infrequent drinker vs never drinker	0.96 (0.89-1.03)
									Former drinker vs never drinker	1.02 (0.94-1.11)
									Light (≤3 drinks/wk) vs never drinker	0.71 (0.61-0.83)
									Moderate (>3—7 drinks/wk for women and >3—14 drinks/wk for men) vs never drinker	0.65 (0.53-0.79)
									Heavy (>7 drinks/wk for women and >14 drinks/wk for men) vs never drinker	0.96 (0.83-1.11)
Mukamal[97]	2001	US	1913	1318	Prospective cohort	Abstainers - 65 (12) <7 - 60 (12) >7 - 57 (12)	3.8 y	Wine, beer, spirits	<7 drinks/wk vs abstainers	0.75 (0.55-1.02)
									≥7 drinks/wk vs abstainers	0.67 (0.41-1.17)
Pai[98]	2012	US	1818	1818	Prospective cohort	40-75	20 y	Wine, beer, spirits	0.1-9.9 g/d vs 0 g/d	0.74 (0.54-1.02)
									10.0-29.9 g/d vs 0 g/d	0.58 (0.39-0.84)
									≥30.0 g/d vs 0 g/d	0.98 (0.6-1.6)
Renaud[114]	2004	Europe	36,583		Prospective cohort	Abstainers 47.98 ± 5.692 Wine drinkers 48.39 ± 5.69 Other drinkers 47.28 ± 5.55	13-21 y	Wine	Moderate wine drinkers (<60 g alcohol/d and no beer) vs abstainers	0.755 (0.591-0.965)
									Wine drinkers of ≥60 g/d vs abstainers	0.971 (0.748-1.261)
									Moderate other drinkers (<60 g alcohol/d) vs abstainers	0.853 (0.631-1.153)
									Other drinkers of ≥60 g/d vs abstainers	0.951 (0.729-1.241)
Renaud[113]	1998	Europe	34,014	34014	Prospective cohort	48.87	418,068 person-years	Wine, beer, spirits	1-21 g/d vs 0-Occasionaly	0.83 (0.55-1.25)
									22-32 g/d vs 0-Occasionaly	0.65 (0.45-0.95)
									33-54 g/d vs 0-Occasionaly	0.72 (0.52-1)
									55-76 g/d vs 0-Occasionaly	0.73 (0.48-1.1)
									77-128 g/d vs 0-Occasionaly	0.67 (0.48-0.94)
									>128 g/d vs 0-Occasionaly	0.75 (0.48-1.18)
Rimm[112]	1991	US	44,059	44059	Prospective cohort	0 g/d 0.1-5 g/d 5.1-30 g/d >30 g/d	72,290 person-years	Wine, beer, spirits	0.1-5 g/d vs 0 g/d	1.1 (0.52-2.36)
									5.1-30 g/d vs 0 g/d	0.71 (0.34-1.49)
									>30 g/d vs 0 g/d	0.66 (0.24-1.82)
Stampfer[77]	1988	US	87,526	0	prospective cohort	34-59	334,382 person-years	Wine, beer, spirits	<1.5 g/d vs 0 g/d	0.7 (0.2-1.7)
									1.5-4.9 g/d vs 0 g/d	0.2 (0.1-0.6)
									5-14.9 g/d vs 0 g/d	0.3 (0.1-0.9)
									15-24.9 g/d vs 0 g/d	0.2 (0.03-1.2)
									>25 g/d vs 0 g/d	0.6 (0.2-1.9)

Table 3 (*Continued*)

First Author	Year	Country	Number of Participants	Men	Type of Study	Age, Years	Follow-Up	Type of Drink	Comparison	Outcome HR (95% CI)
Streppel[110]	2009	Netherlands	1373	1373	Prospective cohort	49 ± 6	40 y	Wine, beer, spirits	>0 to 20 g/d vs 0	0.7 (0.55-0.89)
									>20 g/d vs 0	0.83 (0.56-1.22)
									>0 to 20 g/d vs 0	0.92 (0.58-1.46)
									>0 to 20 g/d vs 0	0.81 (0.48-1.35)
									>20 g/d vs 0	0.78 (0.09-6.73)
									>0 to 20 g/d vs 0	1.44 (0.72-2.86)
									>20 g/d vs 0	0.93 (0.2-4.32)
Suhonen[109]	1987	Finland	4532	4532	Prospective cohort	40-64	2 y for SCD (5 y total)	Wine, beer, spirits	Alcohol consumers vs abstainers	2.5 (1.1-5.9)
Theobald[108]	2000	Sweden	1828	—	Prospective cohort	18-65	22y	Wine	Wine vs no wine drinker	0.49 (0.28-0.9)
									Beer vs no beer drinker	1.15 (0.67-1.99)
									Spirits vs no spirits drinker	0.88 (0.48-1.59)
									Ex-drinkers vs 1-49 gram/wk	3.05 (1.37-6.77)
									Lifelong abstainers vs 1-49 g/wk	1.09 (0.48-2.48)
									50-139 g/wk vs 1-49 g/wk	1.39 (0.8-2.42)
									140+ g/wk vs 1-49 g/wk	1.77 (0.77-4.08)
Trevisan[107]	2001	Italy	15,649	8980	Prospective cohort	30-59	7 y	Wine	Wine with meals vs Nondrinkers	0.5 (0.33-0.74)
									Wine outside meals vs Nondrinkers	0.81 (0.45-1.43)
									Wine + liquor vs Nondrinkers	0.62 (0.38-1.03)
Tverdal[106]	2017	Norway	115,592	53,819	Prospective cohort	40-44	16 y	Wine, beer, spirits	Men - 0, not teetotal vs teetotal	0.53 (0.37-0.77)
									Men - >0-<0.5 units/d vs teetotal	0.43 (0.29-0.63)
									Men - 0.5-<1.0 units/d vs teetotal	0.4 (0.28-0.59)
									Men - 1.0-<1.5 units/d vs teetotal	0.48 (0.32-0.71)
									Men - 1.5-<2.0 units/d vs teetotal	0.46 (0.3-0.71)
									Men - 2.0-<3.0 units/d vs teetotal	0.38 (0.23-0.62)
									Men - 3.0-<4.0 units/d vs Teetotal	0.51 (0.27-0.95)
									Men - 4.0+ units/d vs teetotal	0.48 (0.23-1)
									Women - 0, not teetotal vs teetotal	0.63 (0.38-1.06)
									Women - >0-<0.5 units/d vs teetotal	0.54 (0.31-0.94)
									Women - 0.5-<1.0 units/d vs teetotal	0.61 (0.34-1.09)
									Women - 1.0-<1.5 units/d vs teetotal	0.61 (0.29-1.32)
									Women - 1.5-<2.0 units/d vs teetotal	0.4 (0.14-1.18)
									Women - 2.0-<3.0 units/d vs teetotal	0.23 (0.03-1.72)
									Women - 3.0-<4.0 units/d vs teetotal	0.85 (0.11-6.39)

Table 3 (*Continued*)

First Author	Year	Country	Number of Participants	Men	Type of Study	Age, Years	Follow-Up	Type of Drink	Comparison	Outcome HR (95% CI)
Waśkiewicz[105]	2004	Poland	5352	2686	Prospective cohort	Male abstainers 52.8 1 tertile 51.6 2 tertile 48.6 3 tertile 47.2 Female abstainers 53 1 tertile 50.9 2 tertile 48.7 3 tertile 46	56,261.9 person-years	Wine, beer, spirits	1 tertile (mean alcohol intake - 1.1 g/d) vs abstainers 2 tertile (mean alcohol intake - 3.9 g/d) vs abstainers 3 tertile (mean alcohol intake - 28.2 g/d) vs abstainers 1 tertile (mean alcohol intake - 0.2 g/d) vs abstainers 2 tertile (mean alcohol intake - 0.4 g/d) vs abstainers 3 tertile (mean alcohol intake - 2.8 g/d) vs abstainers	0.584 (0.369-0.924) 0.588 (0.366-0.944) 0.6 (0.364-0.989) 0.581 (0.339-0.996) 0.432 (0.228-0.817) 0.329 (0.135-0.804)
Yuan[104]	1997	China	18,244	18,244	Prospective cohort	45-64	6.7 y	Wine, beer, spirits	1-28 drinks/wk vs nondrinkers >28 drinks/wk vs nondrinkers	0.64 (0.41-0.998) 0.88 (NR-NR)
Hart[103]	1999	Sweden	5766	5766	Prospective cohort	35-64	5141 person- years	Wine, beer, spirits	1-7 units/wk vs none 8-14 units/wk vs none 15-21 units/wk vs none 22-34 units/wk vs none ≥35 units/wk vs none	1.13 (0.9-1.42) 0.79 (0.61-1.01) 1.06 (0.81-1.38) 1.01 (0.77-1.34) 1 (0.75-1.35)
Suadicani[102]	2008	Denmark	3022	3022	Prospective cohort	63 y (range, 53-74)	16 y	Wine	1-8 drinks/wk vs 0 drinks of wine/wk >8 drinks/wk vs 0 drinks of wine/wk 1-8 drinks/wk vs alcohol abstainers >8 drinks/wk vs alcohol abstainers	0.7 (0.5-0.98) 0.9 (0.6-1.2) 0.6 (0.4-0.96) 0.7 (0.5-1.2)
Wannamethee[78]	1999	UK	7272	7272	Prospective cohort	40-59	16.8 y	Spirits, beer	Spirits vs beer in occasional and regular drinkers Wine vs beer in occasional and regular drinkers	1.02 (0.83-1.25) 0.71 (0.52-0.98)

IQR = interquartile range; MADP = Mediterranean alcohol-drinking pattern; SCD = Sudden Coronary Death; CI - Confidence interval .

Moderate beer consumption (1 drink/d for women and 1-2 drinks/d for men) perhaps reduces cardiovascular risks due to a mechanism of prevention of LDL oxidation and induction of cholesterol efflux from macrophages, a process considered a first step in the reverse cholesterol transport pathway.[10,11] Beer can also influence high-density lipoprotein (HDL)-induced cholesterol efflux, increase ABCA1-mediated cholesterol efflux,[12] enhance the antioxidant capacity of HDL, elevate plasma HDL cholesterol (HDL-c) levels,[13,14] and acutely improve arterial properties.[15] Non-alcoholic-related beer components protect against hyperlipidemia-induced coronary endothelial dysfunction by counteracting vascular oxidative damage and preserving the Akt/endothelial nitric oxide synthase pathway.[16] The anti-inflammatory mechanisms of the bioactive compounds of beer are mainly due to the inhibition of inducible nitric oxide synthase and the inhibition of the activity of cyclooxygenase 1.[6,17]

One study reported that low-moderate beer consumption is associated with HDL efflux capacity.[18] In a randomized control trial, moderate beer consumption for 4 weeks raised HDL-c levels by a mean of 2.2 mg/dL in individuals with an LDL-c <130 mg/dL;[19] circulating HDL quality was improved already in the 4-week period by rendering HDL particles functionally active to prevent LDL oxidation and facilitate cell-cholesterol efflux. However, regular beer intake increased the plasma gamma-glutamyl transferase levels in 15% of subjects because beer is primarily metabolized in the liver using enzyme alcohol dehydrogenase,[20] and therefore, patients with liver disease or at risk for liver injury (eg, those with nonalcoholic fatty liver disease or chronic hepatitis) should avoid beer consumption. One meta-analysis demonstrated that alcohol is a major risk factor for liver cirrhosis, with risk increasing exponentially.[21] Moreover, women may be at higher risk compared with men, even with little alcohol consumption. Additionally, alcohol consumption has a causal association with cancers of the oral cavity, pharynx, larynx, esophagus, lungs, liver, colon, rectum, and, in women, the breast. However, some studies did not find the association between alcohol consumption and cancers.

Wine Consumption and Cardiovascular Outcomes

Wine can be classified into white wine and red wine for evaluation in studies and because of different mechanisms for cardioprotective benefits. In the 1980s, the French paradox was observed due to low cardiovascular disease mortality (primarily from coronary artery disease) despite high intake of dietary cholesterol and saturated fat.[22,23] There was also the indirect observation that the French population consumed red wine with their diet, which was mostly high in saturated fat, and this correlation between wine and cardiovascular disease protection was attributed to the consumption of red wine.[24] Red wine primarily contains polyphenols, which are a combination of both flavonoids (eg, anthocyanins and flavan-3-ols) and nonflavonoids (eg, resveratrol, cinnamates, and gallic acid). In fact, flavonoids such as Flavan-3-ols are the most abundant and contain up to 50% of the total phenolic constituents.[25] Wine promotes cardiovascular health via multiple mechanisms. These include polyphenols lowering plasma concentrations of pro-oxidant and inflammatory molecules and leukocyte adhesion molecules, improving homeostasis model assessment of insulin resistance values and blood pressure, reducing phospholipids oxidation, modulating cell signaling pathways, reducing platelet aggregation,[26-28] decreasing highly sensitive C-reactive protein, as well as concentrations of monocyte and endothelial adhesion molecules.[29,30] St Leger et al[31] reported a negative correlation between alcohol consumption and ischemic heart disease deaths, and attributed this observation predominantly to wine. Several explanations for the French paradox have been postulated,[24] with epidemiologists presenting strong correlations in favor of wine (both white and red), with other scientific literature criticizing these observations. Compared with beer or spirits, consumption of wine has been independently associated with improvements in heart rate variability, a marker of autonomic balance.[32] In the CASCADE trial, in individuals with slow ethanol metabolizers (alcohol dehydrogenase alleles carriers *ADH1B*1*), wine consumption is associated with better glycemic control (eg, fasting plasma glucose, homeostatic model assessment of insulin resistance, and hemoglobin A1c) compared with individuals with fast ethanol metabolizers (homozygous *ADH1B*2*).[33] Indeed, studies on wine consumption and cardiovascular disease are primarily based on observational studies. There is the risk of bias from confounding factors (eg, socioeconomic status, neighborhood, culture, physical activity, exercise) or unmeasured confounding (eg, genetics, gut microbiome).

Red Wine Consumption and Cardiovascular Outcomes

Compared with white wine, red wine has an approximately 10-fold higher polyphenolic content due to red wine's grape fermentation.[34] Unfortunately, few studies directly compare the different effects on cardiovascular health of red wine vs white wine.

Red wine promotes cardiovascular health via mechanisms of polyphenols, improved endothelial function, and increased circulating endothelial progenitor cells and nitric oxide levels.[35] Red wine has higher levels of bioflavonoids (with antioxidant, antiplatelet, and antiendothelin-1 effects),[36] polyphenolic mixtures such as flavonoids (eg, catechin/epicatechin/quercetin, procyanidins, and anthocyanins), polymeric tannins, and resveratrol (eg, 3,5,4′-trihydroxystilbene).[37] In general, red wine contains abundant polyphenols and is, perhaps, considered a crucial polyphenol source in the diet.[38] Red wine may be associated with increased HDL-c,[39,40] improved insulin resistance[28,41] and oxidative stress,[42,43] and downregulated serum

concentrations of CD40 antigen, CD40 ligand, interleukin-16, monocyte chemotactic protein-1, and vascular cell adhesion molecule-1.[26] It also can reduce the propensity of LDL to undergo lipid peroxidation.[44] In addition, a recent study found that people who drank red wine had increased gut microbiota diversity (a sign of gut health) compared with non-red-wine drinkers, as well as an association with lower levels of obesity and "bad" cholesterol.[45]

Although alcohol increases triglyceride levels, very low-density lipoprotein production, and triglyceride enrichment of HDL, little is known about alcohol's effect on lipoprotein (a). In the CASCADE trial, 224 abstainers with type 2 diabetes were randomized to consume red wine, white wine, or mineral water for 2 years.[33] This long-term randomized controlled trial among well-controlled diabetics found that initiating moderate red wine is associated with increased HDL-c levels by 2.0 mg/dL and decreased the total cholesterol-to-HDL-c ratio by 27%. Moreover, red wine is associated with a reduction in components of the metabolic syndrome by 34%, compared with the changes in the water group. In fact, some studies performed in women observed that daily doses of 15-20 g of alcohol such as red wine were sufficient to elicit anti-inflammatory effects similar to those observed in men who consumed higher doses of wine.[46]

White Wine Consumption and Cardiovascular Outcomes

Compared with red wine, studies in white wine are inconclusive, and its mechanism for cardiovascular benefits is unclear. Clinical trials have suggested that white wine, particularly aged white wine, could promote cardiovascular health via various mechanisms. These include repair and maintenance of endothelial integrity, antioxidative and antiatherogenic effects, an increase in HDL-c, increase in paraoxonase-1 and glutathione peroxidase, reduced glutathione levels, a decrease in superoxide dismutase activity, and a decrease in oxidation protein products and thiobarbituric acid reactive substance concentrations.[47] However, one non-placebo-controlled trial suggests that regular daily white wine consumption could potentially lead to a proatherogenic increase in homocysteine concentrations.[48] There were, however, limitations in this study, such as the number of participants in each drinking pattern group (wine and beer drinkers). The difference in protective effect between red wines and white wines is perhaps due to the polyphenolic ratio. However, one study suggested that tyrosols (relatively unknown active compounds identified in white wines), along with known compounds such as caffeic acid, and shikimic acids, could potentially explain the biological mechanisms and association between white wine and cardiovascular disease.[49] Some studies suggested that wine acutely improves endothelial function in patients with coronary artery disease, and a moderate daily intake of white wine with dinner can have antioxidative and cardioprotective effects.[50,51] However, there are also studies that have reported no differences in the effects of red and white wines on endothelial function.[50] Further research is needed to compare directly between red wine and white wine consumption on cardiovascular disease effects. Methodology to stratify confounders (eg, subgroup analysis) or identify unknown confounders using machine learning is needed in alcohol research.

Liquor/Other Alcohol Consumption and Cardiovascular Outcomes

There is no study directly on liquor or distilled spirits and the associations with cardiovascular disease outcomes. Liquor or spirits such as gin and vodka do not have a significant number of polyphenols or other nonalcoholic compounds with purported cardiovascular benefits. Therefore, data are relatively limited. One longitudinal study indicated that the use of spirits at least once a week may be associated with a slightly reduced risk of acute myocardial infarction among coronary artery disease-free men aged 30-59 years, but has no impact on total mortality compared with men using less spirits.[52] Several studies on spirit consumption and vascular risk found no J-shaped correlation.[53-56] No statistically significant association with vascular events was apparent for the intake of spirits up to 60 g/d, which is the maximum dose investigated in the 10 studies included in this meta-analysis. Indeed, several studies noted that spirit consumption mostly occurred as binge drinking (defined as the consumption of 3 or more drinks within 1-2 hours) and was restricted to only a few days per week. This may explain the absence of association between moderate spirit consumption and cardiovascular disease benefit in the present review and in a previous study.[57] There are limited studies on the subtypes of liquor (whiskey, gin, rum, tequila) and cardiovascular disease. Researchers assessed whether consumption of 100 mL of whisky or red wine by healthy male subjects increased plasma total phenol content and antioxidant capacity. They found that consumption of phenolic-containing alcoholic beverages transiently raised total phenol concentration and enhanced the antioxidant capacity of plasma.[58] This is compatible with suggestions that moderate alcohol usage and increased antioxidant intake decrease the risk of coronary heart disease.

Overall, although head-to-head comparisons between classes of alcoholic beverages are very limited, there may be underlying cardiovascular benefits from moderate alcohol consumption. However, further studies with confounder correction are needed to dissect this potential association before serious recommendations can be made. However, due to the many health risks linked to alcohol consumption (ie, dementia, alcohol use disorder, liver cirrhosis),[21] no long-term randomized trials of alcohol consumption have been performed.[59]

Limitations

There are significant limitations of the present study. Most meta-analyses fit linear models ignoring the J shape, or did

not use nondrinkers as the reference. First, the included studies are confounded by diet. For example, wine consumption is more often a component of the Mediterranean diet, while beer/liquor intake is more commonly accompanied by diets rich in oily and fried foods.[60,61] Second, there is no genetic factor.[62] A recent mendelian randomization study showed evidence of a causal relationship between higher alcohol consumption and an increased risk of stroke and peripheral artery disease.[63] The causal role of alcohol consumption for other cardiovascular diseases requires further research. Third, there is no drink pattern adjusted. Although some studies adjusted, the direction and magnitude of the effects of adjustment need to be further explored. Studies show that binge drinking is associated with increased coronary artery disease risk,[64] while alcohol is most cardioprotective when consumed prior to or during a meal.[65] For example, studies showed that wine drinkers who participated in this study reported a healthier diet than did drinkers of beer or spirits.[66,67] Fourth, a lack of behavioral pattern adjustment is a limitation. For example, the Finnish study found that in their study population, men who drank spirits also regularly smoked.[52] Fifth, most importantly, there were no adjustments for socioeconomic status. For example, a recent study suggested that coincident, favorable lifestyle factors attenuated the observational benefits of modest alcohol intake.[62] Moreover, it is likely that any particular benefit of wine over beer and spirits is prone to confounding by diet and socioeconomic status.[66] Sixth, a limitation of many cohort studies is that they only have baseline estimates of alcohol intake, which may change over time. Finally, it is possible that the observational studies overestimate the benefits of alcohol for cardiovascular disease outcomes. Case-control and cross-sectional studies typically are more prone to bias and reverse causation. In fact, there is increasing concern about a greater risk of breast cancer and other cancers with even moderate alcohol intake. Further meta-analysis in alcohol and all-cause mortality is needed.

CONCLUSIONS

In individuals without liver disease, low to moderate amounts of weekly or daily alcohol consumption may be beneficial to cardiovascular health. Specifically, strong evidence has suggested that low-moderate amounts of weekly or daily red wine consumption may be particularly associated with low cardiovascular events. However, the relationship between alcohol consumption and cardiovascular disease appears to be biphasic and have a J-shape association. Heavy alcohol consumption could be harmful. Further prospective studies with correction of potential confounders (eg, lifestyle factors, socioeconomic status) are urgently needed. Further clinical trials, if able to be undertaken safely, are warranted to adequately determine the effect of alcohol consumption on cardiovascular disease.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2022.04.021.

SUPPLEMENTARY MATERIAL

eMethods: Search Strategies

No restrictions were placed on language or publication date. Search strategy included MESH headings and keywords including "alcohol," "alcohol consumption," "cardiovascular disease," "cardiovascular events," "diabetes," "hypertension," "high blood pressure," "hyperlipidemia," "dyslipidemia," "arrhythmia," "coronary artery disease," "ischemic heart disease," "acute myocardial infarct," "acute coronary syndrome," "stroke," "heart failure," "cardiac failure," "cardiac insufficiency," and "cardiomyopathy." We identified studies based on appropriate types of study (observational study, prospective cohort study, randomized controlled trial, or case control design) and the exposure (alcohol consumption). We excluded animal studies, editorials, and reviews. Two investigators independently reviewed abstracts for potentially eligible studies. Full text reports were then assessed for eligibility and disagreements were resolved by consensus discussion. We were unable to perform meta-analysis of the results due to tremendous heterogeneity among the included studies related to intervention, comparison, outcomes, and timing. Instead, we qualitatively synthesized the results and summarized key features and characteristics (eg, study populations, design, interventions, outcomes, and conclusions) of the included studies.

Cochrane searches

Search	PubMed Terms	Results
S1: alcohol (all types)		
S2: cardiovascular diseases	TOPIC: ("Cardiovascular Diseases" OR arrhythmia* OR "Atrial Fibrillation" OR "Atrial Flutter" OR "Bradycardia" OR "Tachycardia" OR "Ventricular Fibrillation" OR "heart failure" OR "cardiac failure" OR "myocardial failure" OR "cardiac insufficiency" OR cardiomyopath* OR myocarditis OR stroke* OR "cardiac arrest" OR "Cardiopulmonary Arrest" OR asystole* OR "sudden cardiac death" OR "cardiovascular disease" OR "Cardiovascular Diseases" OR "Heart Diseases" OR "Heart Disease" OR "coronary heart disease" OR "coronary heart diseases" OR "coronary disease" OR "coronary diseases" OR "coronary artery disease" OR "ischemic heart disease" OR "ischaemic heart disease" OR "Myocardial Ischemia" OR "Myocardial Ischemias" OR "Myocardial Ischaemia" OR "Myocardial Ischaemias" OR "acute coronary syndrome" OR "myocardial infarction" OR "myocardial infarct" OR "heart attack" OR "heart attacks" OR "cardiovascular events" OR "cardiovascular event")	1,519,764
S3: beer	TS=(beer*)	27,406
S4: red wine	TS=("red wine" OR "red wines" OR (red NEAR/3 wine))	13,947
S5: white wine	TS=("white wine" OR "white wines" OR (white NEAR/3 wine)	4533
S6: all wine		
S7: **all alcohols + CVD**	S1 AND S2	
S8: **beer** + CVD	S2 AND S3	**801**
S9: **red wine** + CVD	S2 AND S4	**1913**
S10: **white wine** + CVD	S2 AND S5	**198**
S11: **all wine** + CVD — red, white, not specified	S2 AND S6	
S12**: "other" alcohol** + CVD — those not returned in S8, S9, S10 or S11	S7 NOT S3 NOT S4 NOT S5 NOT S6	
S13: resveratrol	S2 AND resveratrol	

CVD = cardiovascular disease

Embase searches

Search	PubMed Terms	Results(link to PubMed)
S1: alcohol (all types)		
S2: cardiovascular diseases	'cardiovascular disease'/exp OR arrhythmia*:ab,ti,kw OR 'atrial fibrillation':ab,ti,kw OR 'atrial flutter':ab,ti,kw OR 'bradycardia':ab,ti,kw OR 'tachycardia':ab,ti,kw OR 'ventricular fibrillation':ab,ti,kw OR 'heart failure':ab,ti,kw OR 'cardiac failure':ab,ti,kw OR 'myocardial failure':ab,ti,kw OR 'cardiac insufficiency':ab,ti,kw OR cardiomyopath*:ab,ti,kw OR myocarditis:ab,ti,kw OR stroke*:ab,ti,kw OR 'cardiac arrest':ab,ti,kw OR 'heart arrest':ab,ti,kw OR 'cardiopulmonary arrest':ab,ti,kw OR asystole*:ab,ti,kw OR 'sudden cardiac death':ab,ti,kw OR 'cardiovascular disease':ab,ti,kw OR 'cardiovascular diseases':ab,ti,kw OR 'heart diseases':ab,ti,kw OR 'heart disease':ab,ti,kw OR 'coronary disease':ab,ti,kw OR 'coronary diseases':ab,ti,kw OR 'coronary artery disease':ab,ti,kw OR 'myocardial ischemia':ab,ti,kw OR 'myocardial ischemias':ab,ti,kw OR 'myocardial ischaemia':ab,ti,kw OR 'myocardial ischaemias':ab,ti,kw OR 'acute coronary syndrome':ab,ti,kw OR 'myocardial infarction':ab,ti,kw OR 'myocardial infarct':ab,ti,kw OR 'heart attack':ab,ti,kw OR 'heart attacks':ab,ti,kw OR 'heart infarction':ab,ti,kw OR 'heart infarct':ab,ti,kw OR 'cardiovascular events':ab,ti,kw OR 'cardiovascular event':ab,ti,kw	4,834,122
S3: beer	'beer'/exp OR beer:ti,ab,kw OR beers:ti,ab,kw	16,020
S4: red wine	'red wine'/exp OR 'red wine':ti,ab,kw OR 'red wines':ti,ab,kw OR ((red NEXT/3 wine):ti,ab,kw) OR ((red NEXT/3 wines):ti,ab,kw)	6862
S5: white wine	'white wine'/exp OR 'white wine':ti,ab,kw OR 'white wines':ti,ab,kw OR ((white NEXT/3 wine):ti,ab,kw) OR ((white NEXT/3 wines):ti,ab,kw)	1904
S8: **beer** + CVD	S2 AND S3	**1515**
S9: **red wine** + CVD	S2 AND S4	**1665**
S10: **white wine** + CVD	S2 AND S5	**184**

CVD = cardiovascular disease.

PubMed Searches

Search	PubMed Terms	Results(link to PubMed)
S1: alcohol (all types)	alcohol drinking OR wine OR wines OR beer[tw] OR beers[tw] OR ethanol OR alcoholic beverages	286,810
S2: cardiovascular diseases	("Cardiovascular Diseases"[mh] OR arrhythmia*[tw] OR "Atrial Fibrillation"[tw] OR "Atrial Flutter"[tw] OR "Bradycardia"[tw] OR "Tachycardia"[tw] OR "Ventricular Fibrillation"[tw] OR "heart failure"[tw] OR "cardiac failure"[tw] OR "myocardial failure"[tw] OR "cardiac insufficiency"[tw] OR cardiomyopath*[tw] OR myocarditis[tw] OR stroke*[tw] OR "cardiac arrest"[tw] OR "Cardiopulmonary Arrest"[tw] OR asystole*[tw] OR "sudden cardiac death"[tw] OR "cardiovascular disease"[tw] OR "Cardiovascular Diseases"[tw] OR "Heart Diseases"[tw] OR "Heart Disease"[tw] OR "coronary heart disease"[tw] OR "coronary heart diseases"[tw] OR "coronary disease"[tw] OR "coronary diseases"[tw] OR "coronary artery disease"[tw] OR "ischemic heart disease"[tw] OR "ischaemic heart disease"[tw] OR "Myocardial Ischemia"[tw] OR "Myocardial Ischemias"[tw] OR "Myocardial Ischaemia"[tw] OR "Myocardial Ischaemias"[tw] OR "acute coronary syndrome"[tw] OR "myocardial infarction"[tw] OR "myocardial infarct"[tw] OR "heart attack"[tw] OR "heart attacks"[tw] OR "cardiovascular events"[tw] OR "cardiovascular event"[tw])	2,756,209
S3: beer	beer[tw] OR beers[tw]	10,963
S4: red wine	“red wine”[tw] OR “red wines”[tw] OR (red AND "white wine") OR (red AND "white wines")	4992
S5: white wine	“white wine”[tw] OR “white wines”[tw] OR (white AND "red wine") OR (white AND "red wines")	1553
S6: all wine	wine[tw] OR wines[tw]	21,600
	S1 AND S2	17,481

(*Continued*)

Search	PubMed Terms	Results(link to PubMed)
S7: **all alcohols + CVD**		
S8: **beer** + CVD	S2 AND S3	**704**
S9: **red wine** + CVD	S2 AND S4	**897**
S10: **white wine** + CVD	S2 AND S5	**109**
S11: **all wine** + CVD — red, white, not specified	S2 AND S6	2300
S12**: "other" alcohol** + CVD — those not returned in S8, S9, S10 or S11	S7 NOT S3 NOT S4 NOT S5 NOT S6	14,780
S13: resveratrol	S2 AND resveratrol	1692

CVD = cardiovascular disease

Web of Science searches

Search	PubMed Terms	Results
S1: alcohol (all types)		
S2: cardiovascular diseases	TOPIC: ("Cardiovascular Diseases" OR arrhythmia* OR "Atrial Fibrillation" OR "Atrial Flutter" OR "Bradycardia" OR "Tachycardia" OR "Ventricular Fibrillation" OR "heart failure" OR "cardiac failure" OR "myocardial failure" OR "cardiac insufficiency" OR cardiomyopath* OR myocarditis OR stroke* OR "cardiac arrest" OR "Cardiopulmonary Arrest" OR asystole* OR "sudden cardiac death" OR "cardiovascular disease" OR "Cardiovascular Diseases" OR "Heart Diseases" OR "Heart Disease" OR "coronary heart disease" OR "coronary heart diseases" OR "coronary disease" OR "coronary diseases" OR "coronary artery disease" OR "ischemic heart disease" OR "ischaemic heart disease" OR "Myocardial Ischemia" OR "Myocardial Ischemias" OR "Myocardial Ischaemia" OR "Myocardial Ischaemias" OR "acute coronary syndrome" OR "myocardial infarction" OR "myocardial infarct" OR "heart attack" OR "heart attacks" OR "cardiovascular events" OR "cardiovascular event")	1,519,764
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S5: white wine	TS=("white wine" OR "white wines" OR (white NEAR/3 wine)	4533
S6: all wine		
S7: **all alcohols + CVD**	S1 AND S2	
S8: **beer** + CVD	S2 AND S3	**801**
S9: **red wine** + CVD	S2 AND S4	**1913**
S10: **white wine** + CVD	S2 AND S5	**198**
S11: **all wine** + CVD — red, white, not specified	S2 AND S6	
S12**: "other" alcohol** + CVD — those not returned in S8, S9, S10 or S11	S7 NOT S3 NOT S4 NOT S5 NOT S6	
S13: resveratrol	S2 AND resveratrol	

CVD = cardiovascular disease