Hypertension

REVIEW

Alcohol Intake and Risk of Hypertension: A Systematic Review and Dose-Response Meta-Analysis of Nonexperimental Cohort Studies

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BACKGROUND: Alcohol consumption has been associated with higher blood pressure and an increased risk of hypertension. However, the possible exposure thresholds and effect-modifiers are uncertain.

METHODS: We assessed the dose-response relationship between usual alcohol intake and hypertension incidence in nonexperimental cohort studies. After performing a systematic literature search through February 20, 2024, we retrieved 23 eligible studies. We computed risk ratios and 95% CI of hypertension incidence using a nonlinear meta-analytic model based on restricted cubic splines, to assess the dose-response association with alcohol consumption.

RESULTS: We observed a positive and almost linear association between alcohol intake and hypertension risk with risk ratios of 0.89 (0.84–0.94), 1.11 (1.07–1.15), 1.22 (1.14–1.30), and 1.33 (1.18–1.49) for 0, 24, 36 and 48 g/d, respectively, using 12 g alcohol/d as the reference value. In sex-specific analyses, the association was almost linear in men over the entire range of exposure but only observed above 12 g/d in women, although with a steeper association at high levels of consumption compared with men. The increased risk of hypertension above 12 to 24 g alcohol/d was similar in Western and Asian populations and considerably greater in White than in Black populations, mainly due to the positive association in women at moderate-to-high intake.

CONCLUSIONS: Overall, our results lend support to a causal association between alcohol consumption and risk of hypertension, especially above an alcohol intake of 12 g/d, and are consistent with recommendations to avoid or limit alcohol intake. Sex and ethnicity appear to be major effect-modifiers of such association.

Key Words: alcohol intake ■ cardiovascular disease ■ hypertension ■ prevention ■ public health

Alcohol is a water-soluble, psychoactive, and addictive substance whose consumption may result in severe adverse health effects and about 3 million deaths each year globally, particularly at moderate-to-high consumption levels.[1,2] To minimize these harmful effects, many governments and international agencies have implemented policies aimed at reducing alcohol intake.[3,4]

Alcohol consumption has been associated with a variety of cardiovascular disease outcomes, including cardiomyopathies, coronary artery disease, stroke, and increased blood pressure (BP),[5] the latter end point of BP having been recently reviewed through a dose-response meta-analysis.[6] However, uncertainties exist regarding its association with the risk of hard outcomes including hypertension, particularly at low levels of alcohol intake and whether sex and race modify the association.[7–9] We took advantage of a new statistical technique that allows pooling and flexible modeling of the dose-response relationship between exposures and end points to assess the overall association between chronic alcohol intake and risk of hypertension in nonexperimental longitudinal studies.

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.124.22703.

For Sources of Funding and Disclosures, see page 1714.

REVIEW

Nonstandard Abbreviations and Acronyms	
ADH	alcohol dehydrogenase
ALDH	aldehyde dehydrogenase
APOL1	apoliprotein L1
BP	blood pressure
DBP	diastolic blood pressure
RR	risk ratio
SBP	systolic blood pressure

METHODS

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines,[10] and its protocol was registered in PROSPERO (no. CRD42022314389).

Literature Search and Study Selection

We conducted a systematic literature search in PubMed and Embase, using the keywords: “”alcohol”, “hypertension,” “blood pressure,” “stroke,” “humans,” “cohort,” “case-cohort” and “English” or “Italian,” for nonexperimental cohort studies published before February 20, 2024. Full literature search strategies are reported in Table S1. Using the Population, Exposure, Comparator, Outcome and Study Design approach,[11] we included studies that reported the association between alcohol exposure and the incidence of hypertension. Details of study identification and selection are reported in the Supplemental Methods.

Data Extraction

Three authors (M.C., I.I., and S.D.F.) extracted the information using a standardized data collection form. We recorded the following data: (1) study details (first author name, study design, publication year), (2) study participant characteristics (country, study cohort, sex, age, sample size, ethnicity, smoking assessment), (3) exposure characteristics (definition, data collection methods and categories of intake), (4) outcome characteristics: definition, outcome assessment methods, number of cases, hypertension risk ratios (RRs) with 95% CIs or SEs, duration of follow-up; (5) covariates employed in multivariable analyses. The risk estimates were recorded both for the overall study population and for different subgroups, as available. We systematically contacted the authors of eligible studies when information was missing but needed for inclusion of the study in our meta-analysis.

For the definition of hypertension incidence, we used the method employed in each study, for example, the use of BP thresholds or antihypertensive drug treatment for hypertension, and additionally evaluated the risk of bias assessment.

We extracted all details regarding alcohol consumption reported in each original publication and we used the methods for the assessment of alcohol dose in our analyses. For each intake category, we recorded the range of the dose or its mean or median value, depending on the available data. For studies reporting alcohol intake as frequency in drinks/wk or drinks/mo, we transformed the data into drinks/day by either dividing by 7 or dividing monthly intake reports by 30.4. We then converted the exposure to grams/day according to the size of a standard drink specifically considered in each study. When no information about the size of a standard drink was available, we considered that a World Health Organization country-specific standard drink contains 15 to 17.7 mL of alcohol corresponding to 12 to 14 g of alcohol.[2,12] For 1 study carried out in China,[13] the UK standard drink specification of 8 g of alcohol was used for the conversion.

Risk of Bias Assessment

Details of the risk of bias assessment are reported in the Supplemental Methods. The internal validity of eligible studies was assessed using the Risk of Bias in Nonrandomized Studies of Exposure tool[14] considering the following risk of bias domains: (1) confounding, (2) selection of participants into the study, (3) exposure assessment (4) departure from intended exposure, (5) missing data, (6) outcome ascertainment, and (7) selective reporting (Table S2). The overall results were tiered as follows: if at least 1 domain was found to identify a high risk of bias, the overall risk was considered high; if more than 1 domain was found to identify a moderate risk of bias, the overall risk was considered to be moderate; and if all domains were at low risk of bias, the overall risk was considered to be low.

Data Analysis

To perform the dose-response meta-analysis, we used the 1-stage dose meta-analysis methodology, which allows modeling of RR across the range of alcohol exposure including studies with missing covariates (eg, number of incident cases and total study population) and provides a good approximation of the overall risk estimates using aggregated instead of the original data.[15] The analysis was based on a restricted maximum likelihood random effects model and used restricted cubic splines with 3 knots at fixed percentiles (10th, 50th, and 90th) of alcohol intake distribution.[15] We selected the optimal number of knots according to Akaike’s information criterion, and we used the knot placement recommended by Harrell.[16] For each alcohol category, we abstracted the mean intake (or median in case of unavailability of means) from the study, together with the RR and its 95% lower and upper bounds, and the number of cases and person-years. When means or medians were not available, we assigned the midpoint in each of the exposure categories in the model. For open categories where the lower of the upper 95% bound was missing, we entered a value that was 20% higher or lower than the closest cut point.[17–19] In addition to the overall analysis, we carried out subgroup analyses by stratifying for sex, geographic region, and ethnicity, whenever possible. We conducted sensitivity analyses that excluded studies that were categorized as being at high risk of bias, those using different cutoffs for definition of hypertension or not reporting such criteria, and studies in which smoking was not included in the multivariate model. We also assessed the influence of duration of follow-up by performing a stratified analysis using 20 years as the reference. We eventually provided a graphical overlay of study-specific trends using predicted study-specific curves showing the influence of variation across studies.[15,20,21] All analyses were carried out by using Stata-MP software (v18.0, Stata Corp, College Station, TX, 2023), specifically the “meta,” “mkspline,” and “drmeta” routines.

RESULTS

Details of the literature search are presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (Figure 1). We identified 7695 records of potential interest, from which 486 were removed as duplicates and 6974 were excluded after title and abstract screening, leaving 235 studies for full-text assessment. After evaluating the full text, we excluded 212 additional articles for the reasons reported in Figure 1. This included studies that had employed a cross-sectional or case-control design (n=29); letters, conference abstracts, and reviews (n=23); use of an ineligible study population (such as diseased participants; n=9); duplicate use of study populations (n=16); lack of exposure assessment information or inapplicable exposure assessment (n=23), incorrect (n=103) or unreported outcomes (n=9). One article was included following citation chasing.[22]

Details of the 23 articles included in our meta-analysis are presented in the Table.[9,13,22–43] Eight studies were conducted in the United States,[24–26,31,38–40,42] 1 in the United Kingdom,[27] 4 in Japan,[32,33,35,36] 5 in China,[13,23,28,37,41] 3 in South Korea,[9,30,43] and 2 in continental Europe (Spain and Eastern Finland).[22,34] The studies were published between 1990 and 2023, with a sample size that exceeded 600 000 participants and 45 000 incident cases of hypertension during a median/mean follow-up period ranging from 2 to 22 years. Most of the studies included men and women, but 3 did not specify participant sex.[25,34,41] Two studies were carried out in the same cohort[13,23] but with different lengths of follow-up. The study with longer follow-up that only reported results for the overall population was included in the main analysis,[13] while the other study with a shorter period of follow-up that reported results separately for men and women was considered for our sex-specific analyses.[23] Participant ages ranged from 18 to 90 years. Most of the studies defined hypertension as an average systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg, or treatment with antihypertensive medication. One study used higher cut points for diagnosis of hypertension (systolic BP ≥160 mm Hg or diastolic BP ≥95 mm Hg),[25] another used a cut-point of ≥159/90 mm Hg until 1999, ≥140/90 mm Hg from 2000 to 2007, ≥130/85 mm Hg from 2008 to 2010, and subsequently ≥140/90 mm Hg or initiation of antihypertensive treatment,[36] and 1 study used self-reported diagnosis of hypertension.[31] All of the studies recorded incidence of hypertension as the primary outcome and diagnosis of hypertension was generally based on a review of medical records. In all studies, alcohol exposure was assessed using an adjusted dose value. Alcohol intake was assessed by dietary intake using simple or standardized questionnaires,[24,27,28,30–33,35,37–41] interview-based questionnaire,[9,26,36] or interviews by trained and certified

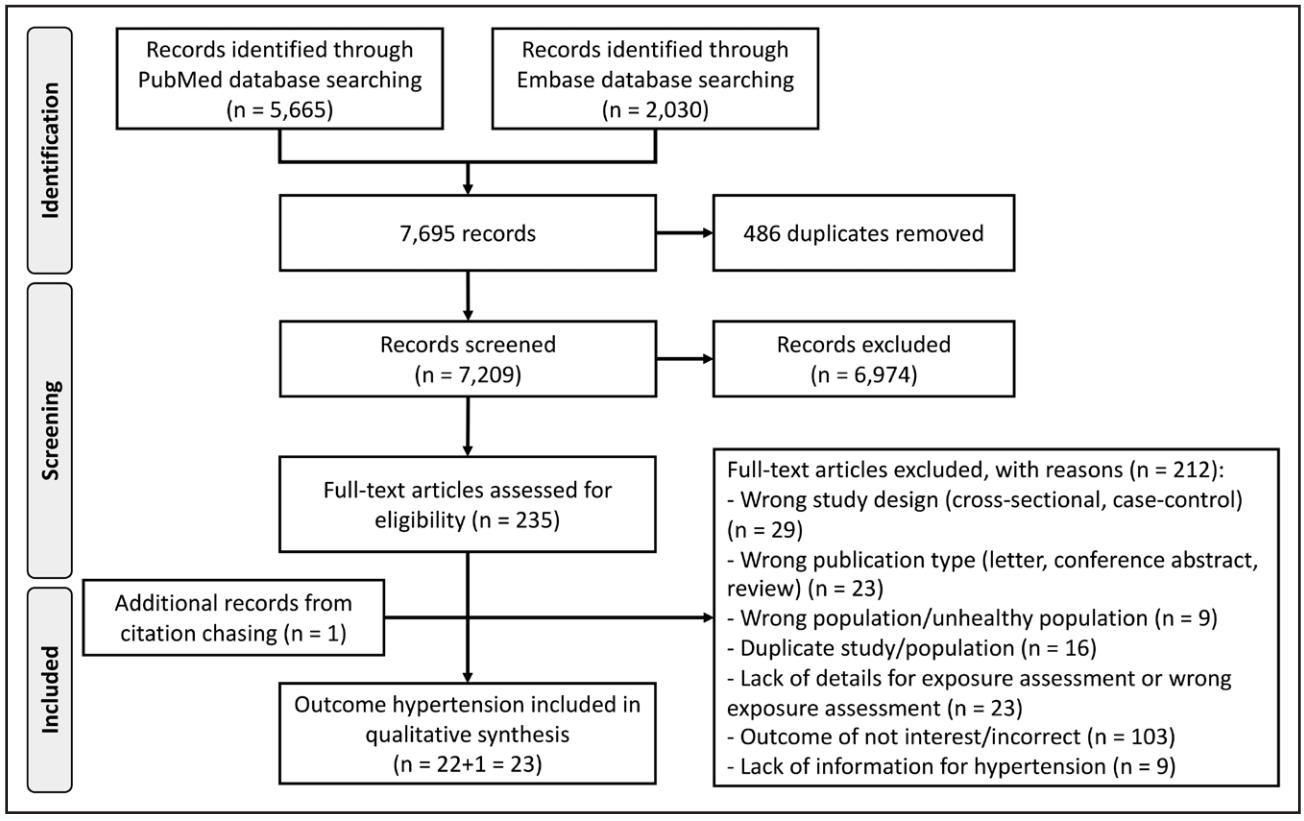

Figure 1. Flow chart of systematic literature search on alcohol exposure and hypertension up to February 20, 2024.

Table. Characteristics of the Studies Included

Reference	Cohort, region	Study period	Follow-up, y	Total population	Age range, y	Hypertension criteria	Exposure assessment method	Alcohol intake*	Adjustment factors
Bai et al[23]	CHNS,† China	1989–2000	2000–2011	1164 men and 1587 women)	18–60	SBP≥140 mm Hg and DBP≥90 mm Hg, or use of antihypertensive medications, or having received a previous diagnosis by a physician	Interviews and physical examinations trained and certified by health professionals. Alcohol intake reported in g/d at baseline with updates during follow-up	0 0.1–10.0 10.1–25.0 >25.0	Age, income, employment status, education, province, urban, or rural and for all of the factors that appear in the table (body mass index, smoke, physical activity hours per day, quintile for Dietary Approaches to Stop Hypertension score)
Banda et al[24]	The Aerobics Center Longitudinal Study, United States	1974–2003	1974–2004	14568 men	20–82 (mean age, 44.0±9.3)	Resting BP≥140/90 mm Hg	Standardized questionnaire. Alcohol intake reported in drinks/wk at baseline. A conversion factor was used considering a standard drink containing 14 g of alcohol	0 1–14 >14	Age (single year), examination year, survey response pattern, resting systolic and diastolic blood pressure, diabetes, family history of hypertension, smoking status, physical activity, body mass index, total cholesterol, fasting glucose, metabolic equivalents
Curtis et al[25]	Black residents of Pitt County, North Carolina, United States	1988	5 y	652 women, 318 men	25–50	SBP≥160 mm Hg or DBP≥95 mm Hg, or antihypertensive treatment	Dietary intake and FFQ. Alcohol intake reported in drinks/wk at baseline (1988) and at follow-up (1993), considering 12 oz of beer, 4 oz of wine, 1.5 oz of liquor. A conversion factor was used considering a standard drink containing 14 g of alcohol	0 <1 ≥1 to <7 ≥7	Age, body mass index, blood pressure, sex, and age by sex interaction
Fuchs et al[26]	The ARIC study participants, United States	1987–1989	6 y	8334	45–64	SBP≥140 mm Hg or DBP≥90 mm Hg, or antihypertensive treatment	Interviewer administered dietary questionnaire. Alcohol intake reported in g/wk at baseline, considering 13.2 g for 12 oz of beer, 10.8 g for 4 oz of wine, and 15.1 g for 1.5 oz of liquor	0 1–299 ≥210	Age, body mass index, education, physical activity and diabetes
Halanych et al[27]	The CARDIA Study, cohort of Black and European-American men and women, United Kingdom	1985–1986	20 y	4711	18–30	BP≥140/90 mm Hg, or taking antihypertensive medication	Questionnaire. Alcohol intake reported in drinks/wk at baseline, considering 1 drink of beer, wine, and liquor containing typically 17.0, 16.7, and 19.2 mL of ethanol. A conversion factor was used considering a standard drink containing 13.47 g of alcohol	Men 0 <7 7–14 >14 Women 0 <4 4–7 >7	Age, family history of hypertension, body mass index, smoking status, race, sex, education, income, difficulty paying for basics, and difficulty paying for medical care
Im et al[28]	China Kadoorie Biobank (CKB study design), China	2004–2008	12.1 (interquartile range 11.1–13.1) years	512 724 (men 210 205 and women 302,519)‡	30–79	BP≥140/90 mm Hg (*ICD-10*)	Questionnaire. Alcohol intake reported in g/wk at baseline, considering beverage volume and assuming alcohol content of 4% for beer, 12% for grape wine, 15% for rice wine, 38% for weak spirit, and 53% for strong spirit	0 <140 140–279 280–419 ≥420	Age, education, and smoking

(*Continued*)

Table. Continued

Reference	Cohort, region	Study period	Follow-up, y	Total population	Age range, y	Hypertension criteria	Exposure assessment method	Alcohol intake*	Adjustment factors
Jung et al[29]	The Multi-Rural Communities Cohort (MRCohort) in rural areas in South Korea	2005	2007–2013	4989	≥40	BP≥140/90 mm Hg	Dietary intake and FFQ. Alcohol intake reported in mL/d at baseline and at each follow-up, considering beverage volume of 200 mL for beer and wine, 300 mL for takju, 50 mL for soju and refined rice wine, 20 mL for whiskey, and a standard drink containing 10–15 mL of alcohol, converting 1 mL to 0.79 g	0 >0 to <15 ≥15 to <30 ≥30	Age, higher education, farmer, married, smoking status, regular exercise, waist circumference and sodium intake
Lee et al[30]	The Asan retrospective cohort, South Korea	1990–1991	6.2 y	2411 (1467 men and 944 women)	20–75	SBP≥140 mm Hg and DBP≥90 mm Hg, or use of antihypertensive medications, or having received a previous diagnosis by a physician	Questionnaire. Alcohol intake reported in g/d at baseline, considering beverage type (beer, wine, whiskey, and traditional Korean soju, makgulri and jungjong)	<1 1–9 10–29 ≥30	Age, body mass index, total cholesterol level, smoking pack-year index, family history of hypertension, and frequency of exercise
Lui et al[31]	US National Longitudinal Survey of Youth 1979 Cohort (NLSY79), United States	1979	1979–2012	8289	21–55	Self-reported diagnosis of hypertension (cutoff not reported)	Health modules. Alcohol intake reported in drinks/wk at baseline and during follow-up. A conversion factor was used considering a standard drink containing 14 g of alcohol	Men: 0 <14 14 to <28 dk/m 14 to <28 ≥28 Women: 0 <7 7 to <14 dk/m 7 to <14 ≥14	Sex, race
Naga et al[32]	Japanese male workers at manufactory company, Japan	2002–2010	8 y	7511	≤25 to ≥55	BP≥140/90 mm Hg, or taking antihypertensive medication	Questionnaire and annual workers-health screening. Alcohol intake reported in g/wk at baseline, considering the conversion of Japanese traditional go unit corresponding to 500 mL of beer, 180 mL of wine, 110 mL of distilled spirits, and 60 mL of whiskey and a conversion factors of 1 go=22 g of alcohol	0 1–76 77–153 154–307 ≥308	Age, smoking, body mass index, job schedule type, habitual exercise, blood test measurements (creatinine, uric acid, aspartate aminotransferase, total serum cholesterol, HbA1c)
Nakanishi et al[33]	Japanese male office workers, Japan	1990, May	1990–1999	1130	30–59	SBP≥140 mm Hg or DBP≥90 mm Hg	Questionnaire. Alcohol intake reported in g/d at baseline, using Japanese conversion tables	0 0.1–22.9 23.0–45.9 46.0–68.9 ≥69.0	Age, body mass index, cigarette smoking, total cholesterol level, triglyceride level, and fasting plasma glucose level

(*Continued*)

Table. Continued

Reference	Cohort, region	Study period	Follow-up, y	Total population	Age range, y	Hypertension criteria	Exposure assessment method	Alcohol intake*	Adjustment factors
Niskanen et al[22] citation chasing	The Kuopio Ischemic Heart Disease Risk Factor Study, Europe (Eastern Finland)	1987–1989	11 y	379 men	42, 48, 54, or 60	SBP≥140 mm Hg and DBP≥90 mm Hg, or use of antihypertensive medications	Instructed dietary recording for a 4-d period and by a self-administered questionnaire for the previous 12 mo. Alcohol intake reported in g/wk at baseline (into categories) and during follow-up (only continuous), considering a standard drink containing 12 g of alcohol	0 1–83 ≥84	Age, smoking, adult socioeconomic status, leisure-time physical activity, presence of cardiovascular disease, intake of energy-adjusted dietary factors (dietary intake of saturated fat, sodium, potassium, and fruits and vegetables), and baseline systolic blood pressure, waist girth, concentrations of insulin, glucose, and high-density lipoprotein-cholesterol
Núñez-Córdoba et al[34]	The SUN Study, Europe (Spain)	1999, December	4.2 y (2.5–6.1)	9963	20–90	Medical diagnosis of HP, BP≥140/90 mm Hg, or antihypertensive medication	Dietary intake and FFQ. Alcohol intake reported in drinks/d at baseline, considering a standard drink containing 13.7 g of pure alcohol	0 0.1–0.5 >0.5	Age, sex, total energy intake, body mass index, physical activity, family history of hypertension, hypercholesterolemia, sodium intake, potassium intake, low-fat dairy products consumption, fruit consumption, vegetable consumption, olive oil consumption, cereal fiber intake, vegetable protein intake, caffeine consumption, fish consumption, and smoking
Ohmori et al[35]	Inhabitants of subrural community of Hisayama, adjacent to Fukuoka City, Southern Japan	1978	10 y (average period 9.2 y)	433 men and 668 women	≥40	BP≥140/90 mm Hg, starting antihypertensive drugs or both	Self-administered questionnaire. Alcohol intake reported in g/d at baseline, considering number of frequency of beer (bottle, can of mL), wine (glass), sake/shochu (using Japanese traditional go unit, approximately corresponding to 23 g of alcohol), whiskey (glass), and other beverages	0 <23 23–45 46–68 ≥69	Age, body mass index
Okubo et al[36]	The IPHS, Japan	1993–2004	1993–2010	37310 men and 78426 women	40–79	BP≥140/90 mm Hg or initiation of treatment for hypertension (≥159/90 mm Hg until 1999; ≥140/90 mm Hg from 2000 to 2007; ≥130/85 mm Hg from 2008 to 2010)	Interviews Alcohol intake reported in g/d at baseline, considering the conversion of the Japanese traditional go unit corresponding to 23 g of alcohol	0 1.0–19.9 20.0–39.9 40.0–59.9 ≥60.0	Age, body mass index, systolic blood pressure, serum total cholesterol, serum total cholesterol level, serum high-density lipoprotein-cholesterol level, serum triglyceride level, antidyslipidemic medication use, blood glucose level, prediabetes, and diabetes, antidiabetes medication use, and smoking status

(*Continued*)

Table. Continued

Reference	Cohort, region	Study period	Follow-up, y	Total population	Age range, y	Hypertension criteria	Exposure assessment method	Alcohol intake*	Adjustment factors
Peng et al[37]	Kailuan Study, Male coal mine workers from Kailuan Coal Group, Northern China	2006, July	4 y	32389	28–80	Onsite measured BP≥140/90 mm Hg, self-report of diagnosed hypertension, self-report of newly initiated antihypertensive treatment	Standardized questionnaire. Alcohol intake reported in g/d at baseline, considering beverage volume and assuming alcohol content of 3% for beer, 10% for wine, and 45% for liquor, and a standard drink containing 14 g of alcohol	0 1–24 15–49 50–99 100–149 ≥150	Age, exercise, smoking status, the type of work (mental or physical work) and salt intake, body mass index, history of high cholesterol, and history of diabetes
Qiu et al[13]	CHNS,† China	1993–2015	22 y	5298	>18, (mean age, 62.6)	Current use of antihypertensive treatment or a diagnosis by a physician. Criteria reported in previous studies on the same cohort: SBP≥140 mm Hg and DBP≥90 mm Hg, or use of antihypertensive medications, or having received a previous diagnosis by a physician	Interviews and physical examinations trained and certified by health professionals. Alcohol intake reported unit/wk at baseline and at follow-up visits (at least 3 records for inclusion), considering 600 mL at 4% for beer, 50 mL at 10% for wine, and 50 mL at 38% for liquor using 2010 China monitoring report on chronic disease risk factors and concerted using alcohol unit of 8 g/d.	0 2.2 17.2 51.8	Age, sex, marital status, education, residence area, smoking status, mean body mass index, mean waist circumference
Saremi et al[38]	Residents of a Native American community, United States	1978–1992	10 y (up to 2001)	2411	≥20	BP≥140/90 mm Hg, or taking antihypertensive medication	Simple questionnaire. Alcohol intake reported in drinks/day at baseline. A conversion factor was used considering a standard drink containing 14 g of alcohol	0 1–2 ≥3	Age, body mass index
Sesso et al[39]	The PHS, US male physicians, United States	1982	17–21.8 y	13455	40–84	Self-reported BP≥140/90 mm Hg, or taking antihypertensive medication	Questionnaire. Alcohol intake reported in drinks/wk at baseline, considering 1 glass, bottle or can for beer, 4 oz for wine, and 1 drink shot for liquor. A conversion factor was used considering a standard drink containing 14 g of alcohol	0 1–3 dk/m 1 2–4 5–6 1 dk/d	Age, exercise, parental history of myocardial infarction <60 y, aspirin, beta-carotene, smoking status, body mass index, history of high cholesterol and history of diabetes
Sesso et al[39]	The WHS, US women health professionals, United States	1992	9.8–10.9 y	28848	45	Self-reported BP≥140/90 mm Hg, or taking antihypertensive medication	Questionnaire. Alcohol intake reported in drinks/wk at baseline, considering 1 glass, bottle or can for beer, 4 oz for wine, and 1 drink shot for liquor. A conversion factor was used considering a standard drink containing 14 g of alcohol	0 1–3 dk/m 1 2–4 5–6 1 dk/d	Age, exercise, parental history of myocardial infarction <60 y, aspirin, alpha-carotene, vitamin E treatment, postmenopausal status, smoking, hormone replacement therapy, body mass index, history of high cholesterol, and history of diabetes
Thadhani et al[40]	The Nurses' Health Study II, United States	1989	8 y	70891	25–42	Self-reported, BP≥140/90 mm Hg	Questionnaire. Alcohol intake reported in g/d at baseline, considering 12.8 for 12 oz of beer, 11 g for 4 oz of wine, and 14 g for 1.5 oz of liquor, and a standard drink containing 12 g of alcohol	0 ≤0.25 0.26–0.50 0.51–1.00 1.01–1.50 1.51–2.00 >2.00	Age, body mass index, race, smoking, history of elevated cholesterol level, family history of hypertension, physical activity and oral contraceptive use

(*Continued*)

Table. Continued

Reference	Cohort, region	Study period	Follow-up, y	Total population	Age range, y	Hypertension criteria	Exposure assessment method	Alcohol intake*	Adjustment factors
Wang et al[41]	The GPHCS, China	2010–2012	2016–2020	5625	≥18	SBP≥140 mm Hg and DBP≥90 mm Hg, or self-reported doctor diagnosis of hypertension or use of antihypertensive medications	Questionnaire. Alcohol intake reported in g/d at baseline, considering beverage type (beer, wine, liquor <42% and ≥42%) and volume	0 0–12 12–24 >24	Age, sex, area, ethnicity, marriage, occupation, smoking status, exercise, and history of diabetes, SBP, total cholesterol, triglycerides, high-density lipoprotein-cholesterol-C, low-density lipoprotein-cholesterol, baseline body mass index
Witteman et al[42]	The Nurses' Health Study, United States	1976	4 y	58218	39–59	Self-reported SBP≥140 mm Hg or DBP≥90 mm Hg	Dietary intake and FFQ. Alcohol intake reported in g/d at baseline, considering 13.2 g for 12 oz of beer, 10.8 g for 4 oz of wine, and 15.1 g for 1.5 oz of liquor	0 0.1–9 10–19 20–34 ≥35	Age, Quetelet index (body mass index)
Yoo et al[9]	The rural-based CAVAS study of the KoGES, South Korea	2004–2008	2 y	6259	40–69	BP≥140/90 mm Hg	Interview-based questionnaire. Alcohol intake reported in g/d at baseline, considering beverage type (beer, soju, wine and liquor) and glass size	Men: 0 <5 ≥5, <30 ≥30 Women: 0 <5 ≥5, <15 ≥15	Area of residence, age, sex, body mass index, smoking status, physical activity, high-density lipoprotein-cholesterol level, family history of hypertension, and sodium level
Yoo et al[9]	The Ansang Ansung study of the KoGES, South Korea	2001–2002	12 y	2461	40–69	BP≥140/90 mm Hg	Interview-based questionnaire. Alcohol intake reported in g/d at baseline and at follow-up, considering beverage type (beer, soju, wine and liquor) and glass size	Men: 0 <5 ≥5, <30 ≥30 Women: 0 <5 ≥5, <15 ≥15	Area of residence, age, sex, body mass index, smoking status, physical activity, high-density lipoprotein-cholesterol level, family history of hypertension, and sodium level

ARIC indicates Atherosclerosis Risk in Communities; BP indicates blood pressure, CARDIA, Coronary Artery Risk Development in Young Adults; CHNS, China Health and Nutrition Survey; DBP, diastolic blood pressure; FFQ, food frequency questionnaire; GPHCS, Guizhou Population Health Cohort Study; IPHS, Ibaraki Prefectural Health Study; KoGES, Korean Genome and Epidemiology study; PHS, Physicians' Health Study; SBP, systolic blood pressure; and WHS, Women's Health Study.

*Values in g/d when not differently reported in drinks/day (dk/d), drinks/mo (dk/m), or drinks/wk (dk/w).

†For the China Health and Nutrition Survey, we used the Qiu 2022[13] for the overall analysis and Bai 2017[23] for the analyses stratified by sex.

‡Analysis of risk of hypertension were reported for men only.

health professionals.[13,22,23] Four of the self-report studies used a food frequency questionnaire.[25,29,34,42] Details of the methods used for exposure assessment and calculation of alcohol dose are presented in the Table. Specifically, 14 studies reported alcohol consumption using gram per day (or gram per week),[9,22,23,26,30–33,35–37,40–42] and 2 other studies used unit per day[13] and milliliters per day[29] with direct conversion into gram per day. Conversely, 8 studies used frequency of drinks,[24,25,27,28,31,34,38,39] with the consequent need to evaluate the amount of alcohol in the standard drink alternatively considered in each study to convert data for the analysis. All but 2 studies accounted for body mass index or waist circumference as potential confounders in the analysis.[28,31] Most but not all[13,25,26,28,31,38,42] studies included smoking as a possible confounding factor. All but 1 study adjusted for age.[31] Additional confounders considered when available were family history of hypertension[24,27,30,40] and cholesterol levels,[22,24,30,33,34,36,39–41] potassium (3 studies) and sodium intake (4 studies),[22,29,34,37] and diabetes (6 studies).[24,26,36,37,39,41]

Almost all of the studies assessed alcohol consumption at baseline only, with only a few evaluating drinking habits at follow-up visits[9,13,22,23,25,29,31] and using the follow-up assessments for their estimation of hypertension risk. One study[25] assessed how change in drinking habits affected hypertension risk through categorization into discontinued, continued, or newly initiated alcohol consumption. Another study[22] reported risk of hypertension for alcohol consumption at follow-up using linear continuous increases only, hampering the use of their data in our analysis. One study[23] only reported

the risk of hypertension for baseline intake of alcohol despite assessing consumption at multiple time points. Conversely, 1 study[29] reported alcohol consumption at baseline and follow-up and reported risk estimates for both assessments and their average. Finally, 2 studies assessed alcohol consumption for the overall period of investigation (baseline and follow-up), with 1 study evaluating multiple time points and estimating lifetime drinking patterns,[31] and another study[9] evaluating both baseline and follow-up and reporting a 10-year drinking habit.

Details of the risk of bias assessment and the overall risk of bias for the studies included in the final analysis are reported in Table S3. Only 3 of the studies were at high risk of bias.[22,30,31] Five of the studies were judged to be at low risk of bias,[9,29,33,36,39] while the remaining studies were at moderate risk of bias due to either confounding,[25,35,38,42] exposure misclassification,[13,23,24,32,35,37,38,41] missing data,[26,30,34,40,42] and inadequate outcome ascertainment.[13,23]

Study-specific and summary RRs for hypertension incidence by comparing the highest with the lowest category of alcohol intake are reported in the forest plot in Figure S1. Overall, the RR of hypertension was 1.39 (95% CI, 1.25–1.56). The association was stronger in men than in women with RRs of 1.52 (95% CI, 1.35–1.71) and 1.18 (95% CI, 0.96–1.46), respectively (Figures S2 and S3).

In Figure 2, we present the results of the dose-response meta-analysis in the overall population and men and women. In the overall analysis (22 studies), there was a linear positive association between alcohol consumption and incidence of hypertension above an alcohol intake of 12 g/d, with RRs using 12 g/d as reference of 0.89 (95% CI, 0.84–0.94), 1.11 (95% CI, 1.07–1.15), 1.22 (95% CI, 1.14–1.30), 1.33 (95% CI, 1.18–1.49) at 0, 24, 36, and 48 g/d of alcohol consumption, respectively. In sex-stratified analyses, men (18 studies) demonstrated a linear positive association between alcohol intake and risk of hypertension, steeper in the range 0 to 36 g/d, but the risk flattened at higher level of intake, with RRs using 12 g/d as reference of 0.86 (95% CI, 0.82–0.90), 1.12 (95% CI, 1.09–1.16), 1.21 (95% CI, 1.15–1.27), and 1.27 (95% CI, 1.20–1.35) at 0, 24, 36, and 48 g/d of alcohol consumption, respectively (Figure 2). In women (12 studies), for whom risk estimates were statistically unstable compared with men, there was no indication of an increased risk of hypertension up to 12 g/d of alcohol consumption, while the risk started to increase at higher intakes of alcohol with a steeper slope at increasing levels of consumption and RRs, using 12 g/d as the reference, of 0.99 (95% CI, 0.81–1.21), 1.14 (95% CI, 1.04–1.24), 1.38 (95% CI, 1.07–1.78), and 1.69 (95% CI, 1.09–2.62) at 0, 24, 36 and 48 g/d of alcohol consumption, respectively. Sensitivity analysis excluding studies at high risk of bias did not substantially change the findings (Figure S4). Exclusion of studies using cutoffs for definition of hypertension higher than BP ≥140/90 mm Hg or not reporting them yielded similar results (Figure S5). Conversely, exclusion of studies that did not adjust for smoking yielded similar results although the association was generally less steep with lower RRs compared with the analysis considering all studies (Figure S6). The stratified analyses by duration of follow-up (<20 and ≥20 years) yielded substantially similar patterns for the association, although it was less steep for studies with a longer duration of follow-up (Figure S7).

In the subgroup analysis of the 11 studies conducted in Asian populations (Figure 3), we identified an almost linear positive association between alcohol intake and the risk of hypertension in the range of 0 to 36 g/d of alcohol intake, with a less steep increase in risk at the highest level of exposure. Using 12 g/d as the reference group, RRs were 0.85 (95% CI, 0.80–0.89), 1.14 (95% CI, 1.10–1.19), 1.25 (95% CI, 1.17–1.34), and 1.34 (95% CI, 1.23–1.45) at 0, 24, 36, and 48 g/d of alcohol consumption, respectively. In contrast, pooling of the 11 studies conducted in Western populations identified usual alcohol intake as having little association with risk of hypertension for intakes up to 12 gr per day, while at higher intakes a positive association emerged, with an upward inflection in the shape of the curve. In these Western populations, using 12 g/d as the reference group RRs were 0.95 (95% CI, 0.85–1.05), 1.11 (95% CI, 1.05–1.17), 1.26 (95% CI, 1.09–1.45), and 1.43 (95% CI, 1.12–1.84) at 0, 24, 36, and 48 g/d of alcohol consumption, respectively. Sex-stratified analyses in the Asian and Western populations (Figure 3) showed rather different shapes. In men, the association between alcohol intake and risk of hypertension was roughly similar between Asian and Western populations (11 and 7 studies, respectively) though with a steeper increase and higher RRs in the formers. In women, no association emerged in Asian population (though based on 3 studies only, and limited to a narrow range of intake), while in Western women (7 studies) a positive association started to emerge approaching 24 g/d of alcohol (corresponding to 2 drinks) and showed a steep increase above that amount.

One study only[31] reported data for Hispanics and half of the studies carried out in Western population did not specify ethnicity. Stratified analysis by ethnicity was therefore only feasible in a small number of studies for Black (4 studies) and White (4 studies) populations.

The association between alcohol consumption in Black population showed no overall increase in the risk of hypertension, while in sex-specific analysis a weak positive association was apparent in men (3 studies), while in women a higher risk emerged only in those consuming little or no alcohol (3 studies; Figure 4).

In White population, the was no association between alcohol intake and risk of hypertension at low levels of consumption (<12 g/d), while risk considerably and

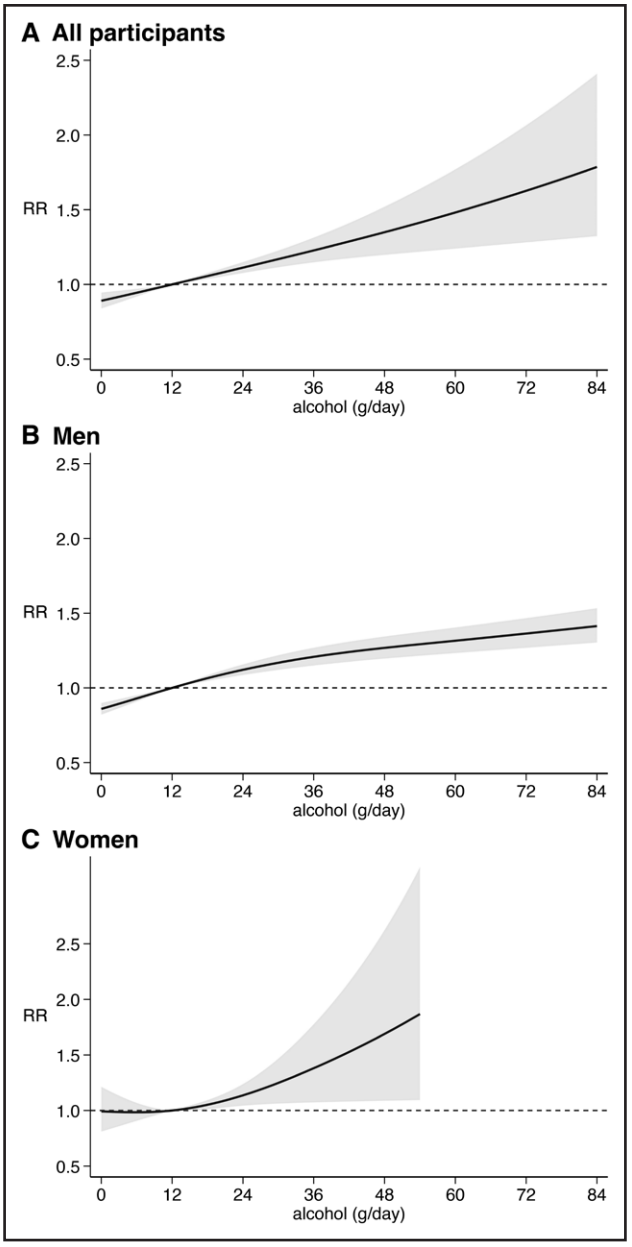

Figure 2. Dose-response meta-analysis of the risk ratio (RR) of hypertension according to alcohol consumption (g/day). Analysis presented in (**A**) all study participants (22 studies[9,13,22,24–42]), in (**B**) men (18 studies[9,22–24,26–33,35–39,41]), and in (**C**) women (12 studies[9,23,26,27,29,31,36,38–42]). Overall spline curve (black solid line) with 95% confidence limits (gray area).

steeply increased above 24 g/d. In sex-specific analysis, such association was only partially confirmed in men (4 studies), with an apparent increased risk above 24 g/d. Conversely, in women, a considerably and steeply increasing risk emerged above intakes of 12 g/d (4 studies), and also abstainers showed an increased risk, similar to that noted in Black women.

Sensitivity analysis investigating study-specific curves showed high variation across studies, especially in the overall and men-restricted analyses (Figure S8). Assessment of publication bias through funnel plots analysis showed little evidence of small-study bias, as suggested by a substantially symmetrical distribution in overall and sex-specific analyses (Figure S9).

DISCUSSION

In this systematic review and meta-analysis, we found that increasing alcohol consumption was positively and almost entirely linearly associated with the risk of new-onset hypertension in the overall analysis, but in women the excess risk was apparent only above an alcohol intake of about 12 g/d. In addition, the shape of the increasing RR in men and women was different, with a trend toward an attenuation of the increase in risk in men at higher levels of alcohol consumption, while in women the opposite was true, with a dose-response curve that showed a trend towards a steeper pattern at higher levels of alcohol consumption. This suggests that sex acts as an effect-modifier for the association between alcohol intake and risk of hypertension, and that low levels of alcohol consumption may not increase the risk of hypertension in women, while at higher levels of alcohol intake the risk of hypertension appears to be higher than in men. Therefore, based on our analysis, a moderate to high usual intake of alcohol seems to be a risk factor for hypertension in both men and women, with a stepper slope in women. In contrast, at low levels of alcohol intake, an increased risk of hypertension may only apply in men.

The association between alcohol consumption and hypertension is especially important because of the high prevalence of alcohol consumption above a light intake in many countries and the well-demonstrated association between hypertension and adverse effects, including risk of cardiovascular disease, cognitive decline, and kidney damage.[44–47] Our findings have implications for public health and recommendations related to the safety of alcohol consumption, both for men (in whom, any consumption may be detrimental, but particularly a high consumption) and women (in whom 1–1.5 drinks a day may not to be related to an excess risk of hypertension). In a previous meta-analysis, a similar alcohol intake threshold for risk of hypertension was identified in women while no inflection point and therefore no safe range of intake was identified in men.[8]

Our findings are in contrast with previous reports suggesting that light to moderate alcohol consumption does not adversely affect the risk of hypertension, and may even decrease it depending on sex and ethnicity,[26,48] since the RR pattern we computed did not suggest any beneficial effect of low levels of alcohol consumption compared with no consumption and especially with a high consumption for risk of hypertension. In a previous meta-analysis, based on a smaller number of studies, there was a slight indication of an inverse association

 Hypertension. 2024;81:1701–1715. DOI: 10.1161/HYPERTENSIONAHA.124.22703

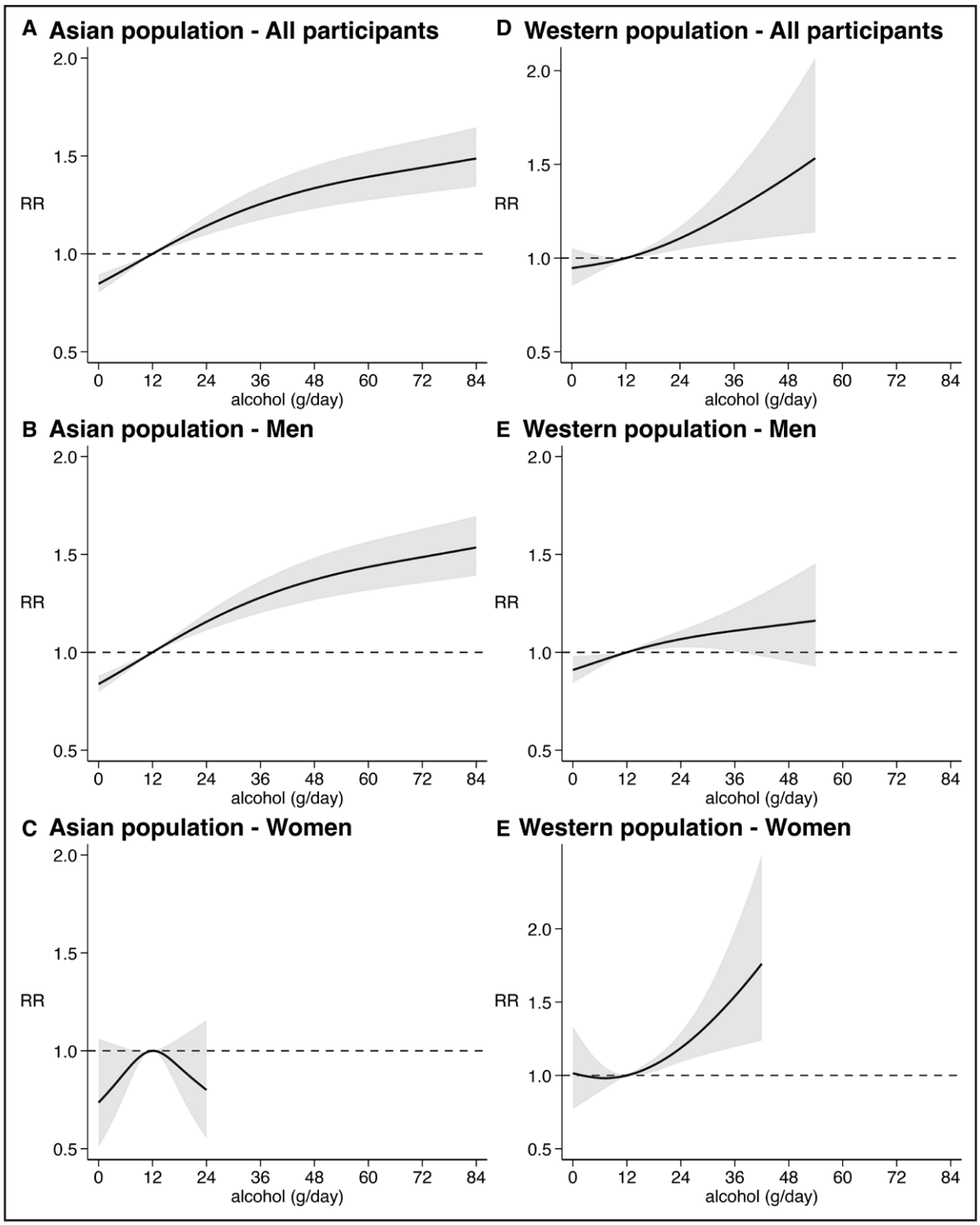

Figure 3. Dose-response meta-analysis of the risk ratio (RR) of hypertension according to alcohol consumption (g/day) divided by region and sex.

Analysis presented by Asian and Western region and sex (Asian [**A**] n=11 studies overall,[9,13,28–30,32,33,35–37,41] [**B**] n=11 studies in men,[9,23,28–30,32,33,35–37,41] and [**C**] n=3 in women,[9,29,36] and Western, (**D**) n=11 studies overall,[22,24–27,31,34,38–40,42] (**E**) n=7 studies in men,[22,24,26,27,31,38,39] and (**F**) n=7 in women[26,27,31,38–40,42]). Overall spline curve (black solid line) with 95% confidence limits (gray area).

with the risk of hypertension in women consuming small amounts of alcohol, that is, 1 to 2 drinks/day (RR, 0.95 [95% CI, 0.89–1.02]).[8]

In our meta-analysis, the increased risk of hypertension with an intake of 12 g/d in men, and 24 g/d in women was modest in clinical terms (+10% to 12%)

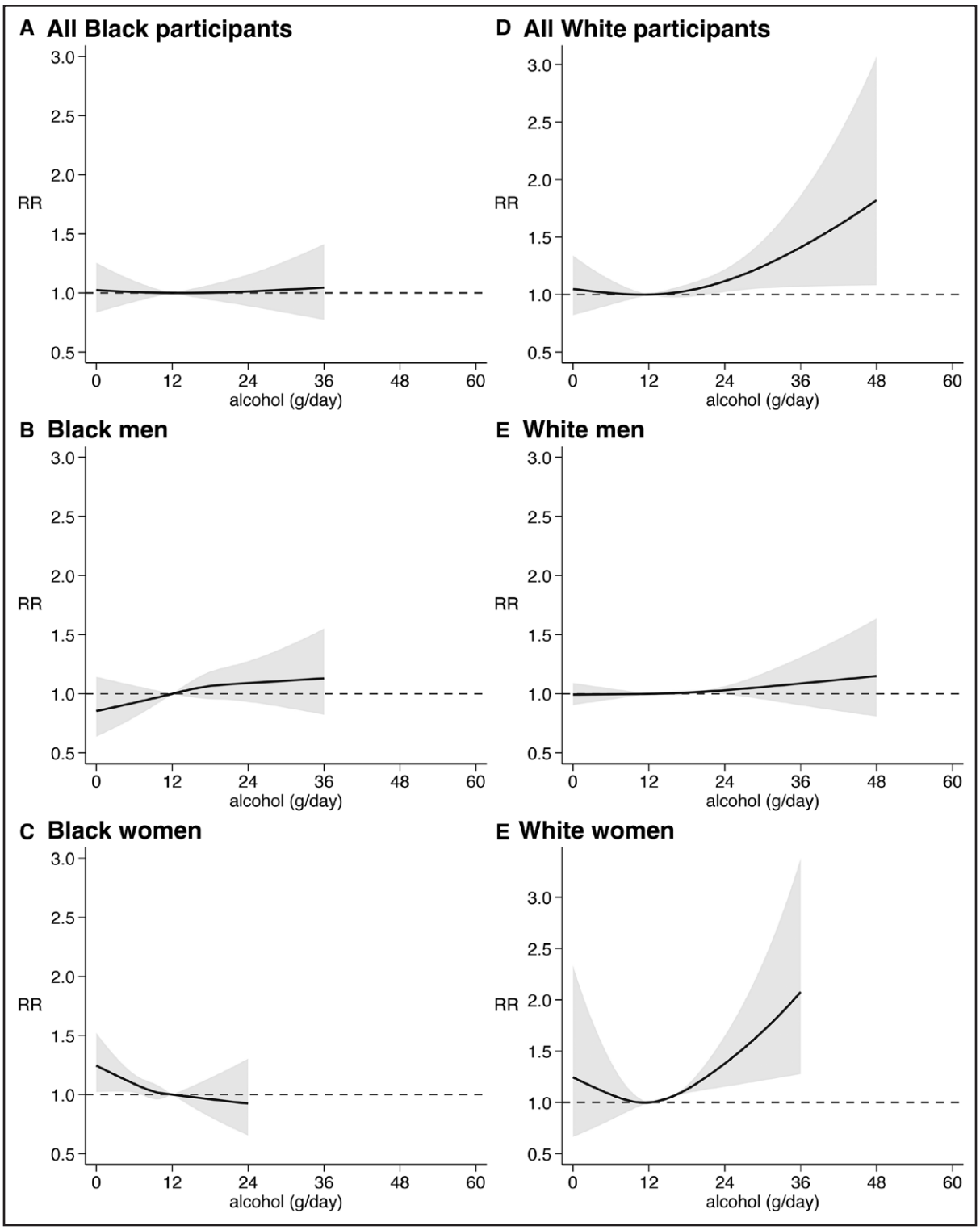

Figure 4. Dose-response meta-analysis of the risk ratio (RR) of hypertension according to alcohol consumption (g/day) divided by ethnicity and sex.

Analysis presented stratified by Black and White populations and by sex (Black population, [**A**] n=4 studies overall,[25–27,31] [**B**] n=3 in men,[26,27,31] and [**C**] n=3 in women[26,27,31]; White population, [**D**] n=5 studies overall,[24,26,27,31,42] [**E**] n=4 studies in men,[24,26,27,31] and [**F**] n=4 studies in women[26,27,31,42]). Overall spline curve (black solid line) with 95% confidence limits (gray area).

and less than that noted for other exposures such as excessive sodium consumption.[49] However, the modest hypertension risk associations noted at low levels of alcohol consumption may be relevant for population health, supporting public health recommendations to avoid or limit alcohol consumption as much as

possible to prevent the increase of BP and onset of hypertension.

With reference to subgroup analyses by continent and ethnicity, we found an indication for a threshold of risk of hypertension in Westerners, but not in Asians, and evidence of effect-modification by sex in both populations. In fact, there was an indication for a lower susceptibility to an adverse effect of alcohol consumption on hypertension risk in Western compared with Asian men, but this was not true for women. In the latter, clear evidence of increased risk emerged only in Western women and above the approximate threshold of 12 g/d, although the limited number of studies hampers the interpretation of these results. The differences across ethnic groups could be explained by genetic factors and particularly by a lower expression of ADH (alcohol dehydrogenase) and aldehyde dehydrogenase (ALDH) in Asians compared with Westerners.[50,51]

The findings of the study suggest a possibly lower susceptibility to the effect of alcohol consumption in Black population, despite the unfortunately limited number of studies that reported specific analyses in Black and White populations, particularly for sex-specific analyses, and the related uncertainties. Both in Black and White populations there was little evidence for a detrimental effects of increased alcohol consumption up to 12 to 24 g/d in the overall population and both sexes, though in White population a higher consumption started to be associated with an increased hypertension risk, mainly due to a steep increase in women. A tendency for a weaker association between alcohol consumption and BP in Black population has long been noted,[52] and a lower susceptibility has been found in Black population for other health conditions and it has been ascribed to genetic influences, especially to APOL1 (apoliprotein L1) genotype.[53] Unfortunately, no genetic data were available in the dataset we studied. In addition, residual confounding might still explain the differences we identified for the alcohol-hypertension risks in Black and White populations.[54] Finally, it is worth noting that in the analysis stratified for both sex and ethnicity, Black and White women not consuming any alcohol exhibited a slightly increased risk of hypertension as compared with low consumers, though this finding was based on a small number of studies, thus it needs to be confirmed by additional investigations.

Risk of bias in the included studies appeared to have little impact on the dose-response estimates, as demonstrated by our analysis restricted to studies with low to moderate risk of bias. In addition, the overall analysis did not appear to be driven by the results of a specific study, and such consistency supports the validity of the overall meta-analysis and the shape of association we obtained when pooling the individual studies.

There is biological plausibility for the detrimental effect of alcohol on the risk of hypertension. One potential mechanism for an alcohol effect on BP and risk of hypertension is stimulation of the renin-angiotensin-aldosterone system[55] with a resultant increase in angiotensin II and plasma cortisol levels.[56] Additional possibilities are sympathetic nervous system stimulation due to increases in noradrenaline levels,[57–61] decrease of baroreceptor sensitivity,[62–64] and an increase of intracellular calcium leading to blood vessel constriction,[1,65] Hormonal factors might also explain the different associations between alcohol intake and the risk of hypertension in men and women particularly at low levels of intake, given the relevance of ovarian hormones and of testosterone in BP regulation.[66–69]

The use of baseline assessment of alcohol consumption is a limitation of our review since we could not rule out the risk of exposure misclassification and change over time of drinking habits due to the limited number of studies that provided alcohol consumption reports during follow-up and the inability to consider study duration within our model. However, 1 study[25] that investigated the risk of hypertension in participants who changed their alcohol consumption, reported that those who discontinued alcohol consumption experienced no substantial change in their BP levels and no increase in hypertension risk. Conversely, those who continued or initiated alcohol consumption during follow-up showed an increased risk of hypertension.

In our analysis, we used aggregated rather than individual participant data for our analyses. Obtaining individual data would likely have been difficult if not impossible for the studies selected. In addition, there is evidence that using the 1-stage approach for the calculation of risk ratio estimates generally allows a good approximation of the estimates that are obtained by the pooling of individual data.[15] Another limitation inherent in our study database was the relatively small number of studies that reported findings by ethnicity, precluding the implementation of stratified dose-response analysis in Hispanics and highly limiting the precision of our risk estimates in Black and White populations, particularly in sex-stratified analyses. Finally, our findings may not apply to ranges of alcohol consumption outside those reported in the included studies, generally in the range of 0 to 84 g/d for men and even lower for women, such as in individuals characterized by extremely high amounts of average alcohol consumption, or binge consumption patterns.

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Sources of Funding

This project was supported by grant Fondo di Ateneo per la Ricerca (FAR) 2023 from the University of Modena and Reggio Emilia. T. Filippini was supported by grants Progetti di Rilevante Interesse Nazionale (PRIN) 2022 (no. 2022MHM-RPR) and Progetti di Rilevante Interesse Nazionale (PRIN) 2022 PNRR (no. P20229KSXB) from the Italian Ministry of University and Research funded by European Union – Next Generation EU. P.K. Whelton was supported by National Institutes of Health Centers of Biomedical Excellence grant (P20GM109036).

Disclosures

None.

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