Systematic Review/Meta-analysis

ANNALS OF MEDICINE & SURGERY

OPEN

Examining the French paradox: a systematic review of red wine consumption and cardiovascular risk

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Background: The French paradox, characterized by a lower prevalence of coronary heart disease (CHD) despite a diet rich in saturated fats, challenges conventional beliefs linking saturated fat intake to CHD risk. Despite high saturated fat consumption, the French exhibit lower CHD rates, sparking interest in the potential cardiovascular benefits of red wine (RW), a staple of the Mediterranean diet rich in polyphenols like resveratrol.

Objectives: The objective of this systematic review is to examine the potential advantages of RW and its components in enhancing cardiovascular health among patients with CHD.

Methods: Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a thorough search of PubMed, Cochrane, ScienceDirect, and Google Scholar was conducted to identify relevant studies published from inception to July 2024. Eligible studies investigating the association between RW consumption and cardiovascular risk factors/outcomes within the French paradox context were included. Data extraction and eligibility criteria ensured methodological rigor.

Results: Of the 812 studies initially screened, 36 met the inclusion criteria in accordance with the PRISMA guidelines. Among these, 28 reported positive effects of RW on cardiovascular parameters, including improvements in lipid profiles, reductions in inflammatory markers, enhanced endothelial function, and modulation of gut microbiota. Two studies identified adverse effects, while six found no significant associations. Collectively, these findings suggest that moderate RW consumption – attributable primarily to its polyphenolic compounds such as resveratrol – may confer cardioprotective benefits, particularly in patients with CHD.

Conclusion: This review supports the French paradox by highlighting that moderate RW consumption may improve cardiovascular health through lipid modulation, endothelial function, and anti-inflammatory effects – mainly due to its polyphenols rather than alcohol. However, individual responses and lifestyle factors may influence outcomes, warranting further research.

Keywords: atherosclerosis, cardiovascular, french paradox, review, RW, saturated fats

Introduction

The French paradox refers to apparent inconsistency in epidemiological findings, which indicate that despite consuming a diet rich in saturated fats, the French population has a lower prevalence of coronary heart disease (CHD) compared to countries where people consume fewer saturated fats. This seems to contradict the widely held belief that saturated fat intake increases the risk of CHD. If the association between saturated fat and CHD is valid, then it would be expected that the French would have a higher incidence of CHD than countries with lower saturated fat consumption[1]. In a research conducted by Serge Renaud *et al*, involving 34 000 men in middle age from Eastern France and a 12-year follow-up period, it was noted that consuming an average of 48 g of alcohol per day, mainly in the form of wine, led to a 30% lower mortality rate from cardiovascular diseases (CVD) and a 20% reduction in mortality from all causes[2].

HIGHLIGHTS

- Moderate RW intake may benefit cardiovascular health in patients with CHD.
- RW polyphenols, especially resveratrol, improve lipids and endothelial function.
- Individual lifestyle and genetic factors may modify RW's health impact.
- Anti-inflammatory properties of RW may reduce atherosclerosis risk.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2025) 87:8757–8769

Received 11 June 2025; Accepted 2 October 2025

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/annals-of-medicine-and-surgery.

Published online 15 October 2025

http://dx.doi.org/10.1097/MS9.0000000000004096

Research suggests that a Mediterranean diet leads to a lower incidence of CVD. Red wine (RW) being a traditional component of the Mediterranean diet has many beneficial effects that are closely related to the phenolic content and profile of RW[3]. RW is enriched with polyphenols, namely resveratrol and piceatannol[4]. The polyphenols present in RW are phytochemicals and/or synthetic chemical compounds having beneficial effects on human health[5]. Of particular interest is resveratrol, which is a non-flavonoid polyphenolic compound also known as 3,4,5-trihydroxystilbene, and has gained recognition as an active compound found in RW that can prevent CHD[6]. Polyphenols present in RW are responsible for the prevention of platelet aggregation, modification of lipid profile, and promotion of vasodilation, thus making RW cardioprotective[3].

A key uncertainty in the French paradox is whether the cardioprotective effects of RW are attributable primarily to its ethanol content, its polyphenolic constituents, or a synergistic interaction between the two. For instance, ethanol has been shown to elevate high-density lipoprotein cholesterol (HDL-C)[7], while polyphenols such as resveratrol reduce oxidative stress and improve endothelial function. Dealcoholized RW has shown cardiovascular effects separate from alcohol, pointing toward polyphenols as the main mediators, while trials involving other alcoholic drinks emphasize the possible role of alcohol[8]. This uncertainty is the main knowledge gap that the current review aims to answer.

Although several studies have explored the potential benefits of RW consumption, the evidence remains inconsistent and limited. However, variations in study populations and methodologies highlight the need for further investigation. This systematic review aims to assess the cardiovascular effects of RW and its components, focusing on their role in improving heart health. This review acknowledges TITAN guidelines 2025[9].

Materials and methods

Search strategy

This systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A thorough investigation of relevant literature from renowned databases, such as PubMed, Cochrane, Science Direct and Google Scholar, was conducted from their inception up to January 2025. The search strategy involved the use of carefully selected keywords and phrases aligned with the objectives of the study. Terms such as "French Paradox, RW, wine, cardiovascular, CHD, CHD, atherosclerosis" and related expressions were employed. We utilized MeSH terms and Boolean operators such as "AND" and "OR" strategically to formulate a comprehensive search algorithm, ensuring the inclusion of relevant studies while increasing the scope of the search. The complete search strategy has been given in the Supplemental Digital Content, available at: http://links.lww.com/MS9/B9.

Additionally, manual searches of the reference list of included studies and relevant reviews were conducted to ensure a thorough exploration of the literature

Eligibility criteria

In determining eligibility criteria for this systematic review, precision and relevance were prioritized to ensure the selection of studies pertinent to the investigation of RW consumption and cardiovascular risk in the context of the French paradox. Peer-reviewed research articles, observational studies, and clinical trials were considered for inclusion. Included studies were required to investigate the association between RW consumption and cardiovascular risk factors or outcomes, such as incidence of CVD, mortality rates, or biomarkers of cardiovascular health. Studies published in the English language and those involving human subjects were eligible for inclusion. Studies not directly addressing the relationship between RW consumption and cardiovascular risk within the context of the French paradox were excluded. Additionally, non-English language publications, unpublished works, and grey literature such as conference abstracts were excluded from consideration. Case reports and case series were also excluded as well as studies involving nonhuman populations.

Data extraction

The data extraction process was conducted systematically to capture relevant information from included studies. Two independent reviewers screened titles and abstracts of retrieved records to identify potentially eligible studies. Full-text articles of relevant records were then assessed for eligibility based on predefined criteria. A standardized data extraction template was employed to extract key information from eligible studies, including study characteristics, participant demographics, RW consumption patterns, cardiovascular outcomes, and relevant findings. Any discrepancies between reviewers were resolved through discussion or consultation with a third reviewer.

Results

Study selection and characteristics

The study selection process adhered to PRISMA guidelines, ensuring transparency and reproducibility. A comprehensive search across databases yielded a total of 812 studies, from which 168 duplicates were removed, resulting in 644 unique studies. Following the screening of titles and abstracts, a further refinement led to the exclusion of 549 studies that did not meet predefined criteria. Subsequent evaluation of the full text of 95 articles resulted in the exclusion of 59 studies that did not align with the eligibility criteria. Ultimately, 36 studies were deemed suitable for inclusion in the systematic review. Details of the study selection process are presented in a PRISMA flowchart (Figure 1), the key characteristics of the included studies are summarized in Table 1, and the key findings of the included studies are summarized in Table 1.

The reviewed studies span from 1999 to 2025 and included randomized controlled trials, cohorts, and cross-sectional studies across multiple countries. Most studies investigated the effect of RW, compared with other alcoholic and nonalcoholic beverages, Sample size ranged from 11 to over 6389 participants. While the primary intervention was RW, some studies included other factors such as polyphenol intake or dietary interventions aiming to assess their impact on health-related outcomes. A summary of the baseline characteristics of studies included in this systematic review is given in Table 1.

Table 1

Baseline characteristics and summary of the findings of included studies

Author	Year	Country	Study design	Sample size	Intervention	Control	Markers evaluated	Key findings	Conclusion	Effect on cardiovascular health
Imhof *et al* [10]	2008	Germany	RCT	49	RW	Water	Monocyte migration (MCP-1, FMLP)	Both ethanol and dealcoholized RW significantly reduced MCP-1- and FMLP-induced monocyte migration, with ethanol showing a slightly stronger effect.	Ethanol and RW polyphenols reduce monocyte migration, with ethanol being marginally more effective.	Positive
Marfella *et al* [11]	2006	Italy	RCT	131	RW	Abstinence	Nitrotyrosine, CRP, TNF-α, IL-6, IL-18	Compared to the intervention group, the control group had higher MPI, lower transmitral and pulmonary venous flow, elevated inflammatory markers, lower insulin or HOMA, and did not show the HDL increase – though both groups reduced glucose, total cholesterol, and LDL	The intervention group showed better cardiovascular and metabolic outcomes, including reduced inflammation and improved HDL levels.	Positive
Wotherspoon *et al* [12]	2019	USA	Randomized cross-over trial	77	RW and Vodka	Nonalcoholic beverages	CRP, IL-6, IL-18, ICAM-1, VCAM-1, leptin, APO A1, APO B, adiponectin, MMP-9, TIMP-1, CASP-1, cystatin C	Vodka significantly increased adiponectin and APO A1 (while RW did not), but both interventions raised leptin to a similar degree.	Vodka improved adiponectin and APO A1, while both beverages similarly increased leptin.	No effect
Hansen *et al* [13]	2005	Denmark	RCT	69	RW and RGE	Water	Blood lipids, fibrinogen, FVIIc, CRP, blood pressure, body weight, BMI	RW increased HDL-C by 6% and lowered fibrinogen by 5% with minimal weight change, while other treatments reduced HDL-C, raised fibrinogen, and caused slightly greater weight loss, without affecting blood pressure.	RW improved HDL-C and fibrinogen levels without significant weight changes.	Positive
Golan *et al* [14]	2018	Israel	RCT	87	RW and RGE	Water	Blood lipids (HDL-C, cholesterol), fibrinogen, FVIIc, CRP, blood pressure, body weight, BMI	RW raised HDL-C by 6% and lowered fibrinogen by 5% with minimal weight impact, while the control group reduced HDL-C and increased fibrinogen, and neither affected blood pressure.	RW positively influenced HDL-C and fibrinogen without impacting blood pressure.	Positive
Whelan *et al* [15]	2004	New Zealand	RCT	14	RW and WW	Abstinence	Endothelial function (flow-mediated dilatation), lipid profiles, blood alcohol levels, plasma polyphenols	Both red and white wines improved endothelial function at 360 min, raised triglycerides and had no effect on polyphenols	Both wine types enhanced endothelial function but increased triglycerides.	Positive
de Moraes *et al* [16]	2022	Brazil	RCT	40	RW or Cachaça	Abstinence	CRP, lipid profile, platelet aggregation, glycemic profile	Moderate daily consumption of RW led to a significant decrease in platelet aggregation and a notable weight gain, while moderate cachaça intake caused a significant increase in platelet aggregation without affecting weight.	RW decreased platelet aggregation and caused slight weight gain.	Positive

(*Continues*)

Table 1

(Continued).

Author	Year	Country	Study design	Sample size	Intervention	Control	Markers evaluated	Key findings	Conclusion	Effect on cardiovascular health
Haas *et al* [17]	2019	Brazil	RCT	84	RW	Abstinence	TMAO, HDL, resveratrol, phenylalanine (decreased), benzoate (decreased), tyrosine (decreased), tryptophan (decreased), bile acids (primary: cholate, taurocholate; secondary: deoxycholate, lithocholate sulfate), androgenic steroids (elevated), beta-oxidation (decreased)	RW slightly lowered TMAO (not significant), significantly increased HDL, resveratrol, and androgenic steroids, reduced various plasma amino acids and bile acids, and decreased beta-oxidation.	RW improved HDL and androgenic steroids while reducing amino acids and bile acids.	Positive
Haas *et al* [18]	2022	Brazil	RCT	84	RW	Abstinence	Gut microbiota, plasma TMAO, plasma metabolomics (amino acids, carbohydrates, lipids, vitamins)	RW consumption increased Parasutterella, altered 39 plasma metabolites (including riboflavin and ascorbate precursors), and left TMAO unchanged	RW modulated gut microbiota and plasma metabolites without affecting TMAO.	No effect
Salazar *et al* [19]	2022	Spain	Cross-sectional study	2318	Assessment of polyphenol intake		Atherosclerotic plaques (carotid, femoral), CACS, total cholesterol, LDL, HDL, triglycerides, fasting glucose, blood pressure, BMI, waist circumference	Higher intakes of flavonoids, stilbenes, and tyrosols were linked to significantly lower risks of femoral plaques, carotid plaques, and coronary calcium, independent of lipids and blood pressure.	Flavonoids and related compounds reduced atherosclerotic plaque risks.	Positive
Barden *et al* [20]	2013	Australia	RCT	25	RW or DRW	Placebo	Blood pressure, heart rate, plasma 20-HETE, EETs, endothelin-1, F2-isoprostanes	RW lowered blood pressure, raised heart rate, kept 20-HETE higher over 24 h, and had no significant effects on EETs, F2-isoprostanes, or endothelin-1, with blood ethanol disappearing in 24 h.	RW reduced blood pressure and increased heart rate, with sustained 20-HETE levels.	Positive
Van Bussel *et al* [21]	2017	The Netherlands	Cohort study	801	RW and Ethanol	Abstinence	Endothelial dysfunction: von Willebrand factor, sICAM-1, VCAM-1, endothelial selectin, thrombomodulin, FMD; Inflammation: CRP, serum amyloid A, IL-6, IL-8, TNF-α, sICAM-1	Moderate or high alcohol and RW intake were linked to lower endothelial dysfunction scores and nonsignificantly higher FMD, with only RW also reducing low-grade inflammation scores.	RW improved endothelial function and reduced inflammation.	Positive
Ogunmoroti *et al* [22]	2021	USA	Cohort study	6389	Consumption of RW, beer, or liquor	Abstinence	CVH score (smoking, physical activity, BMI, diet, total cholesterol, blood pressure, blood glucose)	Moderate wine consumption (1–2 drinks/day) increased odds of optimal CVH, whereas higher beer or liquor intake (>2 drinks/day) lowered those odds	Moderate wine consumption was associated with better cardiovascular health.	Positive

(*Continues*)

Table 1

(Continued).

Author	Year	Country	Study design	Sample size	Intervention	Control	Markers evaluated	Key findings	Conclusion	Effect on cardiovascular health
Di Renzo *et al* [23]	2018	Italy	RCT	55	Ethanol (RW, WW, Vodka) plus MeDM or HFM	MeDM or HFM without alcohol	oxLDL-C, gene expression (*CAT, SOD2, GPX1*)	RW lowered oxLDL-C versus HFM and uniquely upregulated *CAT, SOD2*, and *GPX1*, while WW and VDK downregulated *CAT* and variably influenced *SOD2*.	RW reduced oxLDL-C and upregulated antioxidant genes.	Positive
Fantin *et al* [24]	2015	UK	Randomized cross-over trial	18	RW	Abstinence	Heart rate, blood pressure, QKd interval	Moderate RW consumption (two glasses) led to a significant increase in heart rate during the drinking period and a moderate rise in diastolic blood pressure. It caused a reduction in arterial compliance the following morning indicated by QKd interval decrease.	RW intake increased heart rate during drinking and reduced arterial compliance the next morning, indicating increased vascular stiffness and a delayed vasoconstrictive effect.	Negative
Apostolidou *et al* [25]	2015	Greece	Randomized cross-over trial	30	RW	Placebo	TAC, lipid profile, vitamin E, cardiovascular risk indexes (LDL/HDL, vitamin E/TC)	RW consumption significantly boosted TAC and Vitamin E levels (especially in AHC), with a marginal decrease in LDL/HDL ratio and a significant rise in Vitamin E/TC ratio.	RW enhanced antioxidant capacity and vitamin E levels.	Positive
Laura Di Renzo *et al* [26]	2015	Italy	Randomized cross-over trial	73	NPVRW ± McDM	Abstinence	ox-LDL, gene expression (oxidative stress, inflammasome, drug metabolism pathways)	ox-LDL levels rose by 17.56% from B to McDM, then dropped by 20.94% with NPVRW added to McDM, with no significant changes observed when comparing B to NPVRW or McDM + NPVRW.	RW mitigated the rise in ox-LDL caused by high-fat meals.	Positive
Blanch *et al* [27]	2012	Spain	Randomized cross-over trial	40	RW and Gin	Abstinence	Blood pressure, plasma NO	DRW significantly lowered systolic and diastolic BP and increased plasma NO compared to gin, while RW showed similar trends without reaching statistical significance.	Dealcoholized RW reduced BP and increased NO more effectively than gin.	Positive
Estruch *et al* [10]	2004	Spain	Randomized cross-over trial	30	RW or Gin	Abstinence	Cellular adhesion molecules, chemokines	RW intake significantly raised ECG levels and reduced monocyte adhesion markers, soluble endothelial adhesion molecules, hs-CRP, and fibrinogen, while gin showed less pronounced or opposite effects.	RW reduced inflammation and adhesion markers more than gin.	Positive

(*Continues*)

Table 1

(Continued).

Author	Year	Country	Study design	Sample size	Intervention	Control	Markers evaluated	Key findings	Conclusion	Effect on cardiovascular health
Blanch *et al* [28]	2012	Spain	Randomized cross-over trial	73	DRW and Gin	Abstinence	Inflammatory markers, cell adhesion molecules (leukocytes)	Alcohol increased IL-10 and reduced macrophage-derived chemokines, while RW's phenolics lowered adhesion molecules and IL-6 and inhibited immune cell activation, with both ethanol and phenolics downregulating CD40, CD40L, IL-16, MCP-1, and VCAM-1.	RW's phenolics and ethanol jointly reduced inflammation and adhesion molecules.	Positive
Agewall *et al* [29]	2000	New Zealand	Randomized cross-over trial	12	RW	DRW	Brachial artery diameter, blood flow, heart rate, plasma ethanol	RW with alcohol increased resting vascular parameters and plasma ethanol, whereas de-alcoholized RW significantly improved flow-mediated dilation without affecting resting measures.	Dealcoholized RW improved endothelial function without altering resting measures.	Positive
Vázquez-Fresno *et al* [30]	2012	Spain	Randomized cross-over trial	61	DRW or RW	Abstinence	Urine metabolic profile	Alcohol-related markers, gut microbiota markers, and branched-chain amino acid metabolites increased after all interventions, with the largest rises observed in the RWA and RW groups.	RW altered urine metabolites linked to alcohol and gut microbiota.	No effect
Jensen *et al* [31]	2006	Norway	Randomized cross-over trial	93	RW	Abstinence	Plasma viscosity, fibrinogen	Wine consumption lowered plasma viscosity by 0.026 mPa·s and fibrinogen by 0.17 g/L, with these effects lasting even after abstention.	Wine reduced plasma viscosity and fibrinogen persistently.	Positive
Retterstol *et al* [32]	2005	Norway	Randomized cross-over trial	87	RW	Abstinence	CRP, fibrinogen, cholesterol, HDL, TAGs, ALAT, GGT, albumin, transferrin, SBP, DBP	CRP levels remained unchanged while fibrinogen levels dropped by 3% during the wine period.	Wine reduced fibrinogen without affecting CRP.	Positive
Cuevas *et al* [33]	2000	Chile	RCT	11	RW and HFD	HFD	Endothelial function (FMD), glucose, lipids (total cholesterol, LDL, TAGs, SFA, MUFA, PUFA, VLCn-3), vitamins (C, E, lycopene, folic acid, B12), homocysteine	EF significantly improved with wine in the HFD group (from 2.9% to 6.6%; $P = 0.001$), while the control group saw a nonsignificant increase.	Wine improved endothelial function in high-fat diet consumers.	Positive
Kiviniemi *et al* [34]	2007	Finland	Randomized cross-over trial	22	RW	DRW	CFR	Moderate RW significantly improved CFR, whereas de-alcoholized RW had no significant effect.	Alcohol-containing RW enhanced coronary flow reserve.	Positive

(*Continues*)

Table 1

(Continued).

Author	Year	Country	Study design	Sample size	Intervention	Control	Markers evaluated	Key findings	Conclusion	Effect on cardiovascular health
Rifler *et al* [35]	2011	France	RCT	29	RW	Water	Total cholesterol, LDL, erythrocyte membrane fluidity, antioxidant status	After 14 days, the intervention group showed lower total cholesterol and LDL, alongside increased erythrocyte membrane fluidity and enhanced antioxidant status	RW improved lipid profiles, membrane fluidity, and antioxidant status.	Positive
McDonagh *et al* [36]	2018	UK	Randomized cross-over trial	12	PR-RW	Water	Blood pressure, NO biomarkers (plasma NO_2^-)	Compared to control, systolic BP was reduced by 4 mmHg in NIT-RW, 3 mmHg in NIT-A, and 2 mmHg in NIT-CON, with plasma NO_2^- peaking at 292 nM for NIT-RW and 318 nM for NIT-A. Both NIT-RW and NIT-A interventions lowered systolic BP compared to control, and the associated peaks in plasma NO_2^- suggest that increased nitric oxide bioavailability may be driving these cardiovascular benefits	Nitrate-rich RW reduced systolic BP, likely due to increased NO bioavailability.	Positive
Papamichael *et al* [37]	2007	Greece	Randomized cross-over trial	30	RW/WW and Olive Oil	Water	Augmentation index, heart rate, peripheral/aortic blood pressures	All intervention combinations significantly reduced arterial stiffness – as reflected by lower AIx – and postprandial central pressures also diminished, indicating improved vascular function.	Interventions reduced arterial stiffness and improved vascular function.	Positive
Williams *et al* [38]	2004	New Zealand	Randomized cross-over trial	26	RW and WW	Isoenergetic nonalcoholic beverage (raspberry cordial)	Blood pressure, heart rate, TG, TC, HDL, glucose, IL-6, ICAM-1, VCAM-1	Red and white wine significantly raised plasma IL-6 (56% and 63%, respectively) versus 11% with a nonalcoholic beverage, with blood alcohol peaking at 1 h and normalizing by 6 h	Both wines increased IL-6, suggesting acute inflammatory effects.	Negative
Djousse *et al* [39]	1999	USA	Randomized cross-over trial	26	RW	Isocaloric control beverage (Coca-Cola Classic)	Flow-mediated dilation, triglycerides, cholesterol, HDL, factor VII, fibrinogen	Flow-mediated dilation was similar between RW and control ($P = 0.77$), while both meals significantly raised triglyceride levels.	RW did not improve endothelial function but increased triglycerides.	No effect
Tousoulis *et al* [40]	2008	Greece	RCT	83	RW, WW and Whisky	Water	Endothelial function (reactive hyperemia), inflammation (IL-6, TNF-α , and CRP), thrombosis (vWF, PAI-1, and tPA)	RW and beer both enhanced reactive hyperemia and reduced vWF levels, while inflammatory markers remained unchanged.	RW and beer improved microvascular function and reduced vWF.	Positive

(*Continues*)

Table 1

(Continued).

Author	Year	Country	Study design	Sample size	Intervention	Control	Markers evaluated	Key findings	Conclusion	Effect on cardiovascular health
Haas *et al* [41]	2022	USA	Randomized cross-over trial	42	RW	Abstinence	Plasma TMAO, gut microbiota composition	Plasma TMAO levels were unchanged, but significant gut microbiota remodeling and improved redox homeostasis were observed in plasma metabolomics.	RW modulated gut microbiota and redox homeostasis without affecting TMAO.	No effect
Jespersen *et al* [42]	2018	USA	Cross sectional study	5825	RW	Abstinence	UACR, eGFR	Light wine consumers showed lower CVD prevalence (5.8% vs 10.7%) and a 29% reduced adjusted odds (OR 0.71, $P = 0.02$) compared to non-wine drinkers.	Light wine consumption was associated with lower CVD risk.	Positive
Blackhurst *et al* [43]	2006	South Africa	RCT	15	HFD with RW/WW	HFD only	Lipid biochemistry, lipid peroxidation, *in vitro* oxidation, plasma catechin, ORAC	TG and PL in the CM fraction remained unchanged with wine consumption. Adding wine to the meal did not significantly alter outcomes. Neither lag times nor AUC from the CM were significantly affected by wine ($P = 0.54$ and $P = 0.49$). Plasma catechin levels significantly increased after consuming wine with the meal ($P = 0.001$)	Wine did not affect triglyceride or phospholipid levels in CM fraction.	No effect
van der Gaag *et al* [44]	2004	Netherlands	Randomized cross-over trial	11	RW, Beer and Gin	Carbonated Water	Alcohol concentrations, paraoxonase activity/ mass, HDL-C, apo A-I, paraoxonase genotypes	Higher RW consumption leads to higher BAC at 1 and 3 h post intake. Paraoxonase mass was slightly elevated with alcohol versus water, though not statistically significant. Moderate daily RW consumption raised HDL-C and apo A-I levels similarly across beer, wine, and spirits, correlating with increased paraoxonase activity.	Three weeks of moderate RW consumption increased serum paraoxonase activity and significantly raised HDL-C and apo A-I levels.	Positive

AIx, augmentation index; ALAT, Alanine Aminotransferase; APO a1, apolipoprotein A1; APO B, apolipoprotein B; BAC, blood alcohol concentration; CACS, Coronary Artery Calcium Score; CASP-1, caspase-1; CD40, Cluster of Differentiation 40; CD40L: CD40 Ligand; CFR, Coronary Flow Velocity Reserve; CRP, C-reactive protein; CVH: Cardiovascular Health; DBP, diastolic blood pressure; DRW, dealcoholized RW; EET, Epoxyeicosatrienoic Acid; eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilation; FMLP, N-formylmethionyl-leucyl-phenylalanine; FVIIc, Factor VII coagulant activity; GGT, Gamma-Glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; HETE, Hydroxyeicosatetraenoic Acid; HFD, high fat diet; HFM, high fat meal; HOMA, Homeostatic Model Assessment; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; McDM, modified Mediterranean diet meal; MCP-1, monocyte chemoattractant protein-1; MeDM, Mediterranean diet meal; MMP-9, matrix metallopeptidase 9; MUFA, monounsaturated fatty acids; NIT, Non-Invasive Test; NO, nitric oxide; NPVRW, non-purified RW; ORAC, oxygen radical absorbance capacity; oxLDL-C, oxidized low-density lipoprotein cholesterol; PAI-1, plasminogen activator inhibitor-1; PUFA, polyunsaturated fatty acids; QKd, QRS complex onset to Korotkoff sound at diastolic pressure interval; RCT, randomized controlled trial; RGE, red grape extract; RW, red wine; RWA, Red Wine Abstainers; SBP, systolic blood pressure; SFA, saturated fatty acids; sICAM, Soluble Intercellular Adhesion Molecule; TAC, total antioxidant capacity; TC, total cholesterol; TG, triglycerides; TIMP-1, tissue inhibitor of metalloproteinases-1; TMAO, trimethylamine N-oxide; TNF-α, tumor necrosis factor-alpha; tPA, tissue plasminogen activator; UACR, urinary albumin-creatinine ratio; VCAM-1, vascular cell adhesion molecule-1; VDK, Vitamin K–dependent proteins; VLCn-3, very long-chain omega-3 fatty acids; vWF, von willebrand factor; WW, white wine.

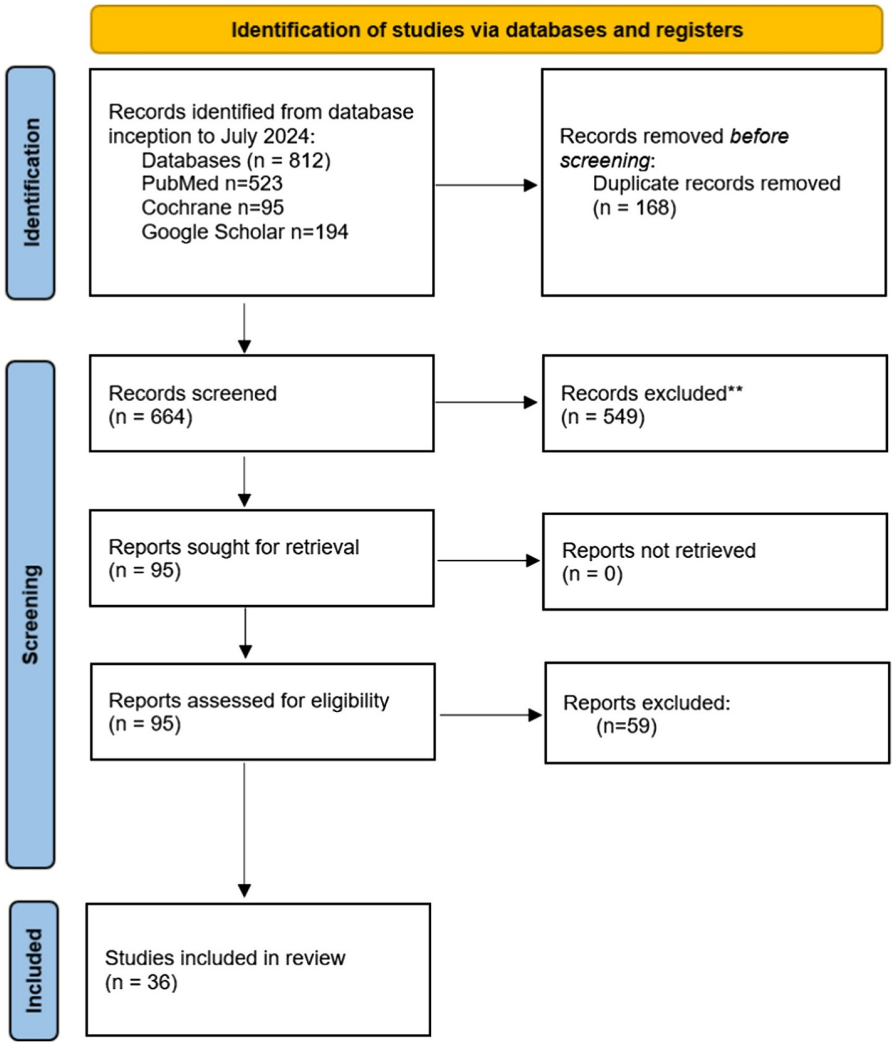

Figure 1. PRISMA flowchart for literature retrieval.

Summary of study outcomes

This systematic review included 36 studies that assessed the effect of RW consumption on cardiovascular health by reporting various cardiovascular biomarkers such as HDL-C, low-density lipoprotein cholesterol (LDL-C), trimethylamine *N*-oxide, etc., and other cardiovascular parameters such as endothelial functioning, arterial compliance, etc. Among these studies, 28 reported positive effects on cardiovascular health such as improved HDL cholesterol, reduced fibrinogen, platelet aggregation, and blood pressure, improved endothelial function as well as increased antioxidant capacity and anti-inflammatory markers. 6 studies found no significant effect, often noting unchanged inflammatory markers, endothelial function, or lipid levels. 2 studies noted negative effects, such as increased arterial stiffness and inflammatory markers (e.g., IL-6). These results also highlight the complexity of RW effects on CHD which may depend on dosage, frequency, and individual patient factors. The details of the findings in the included studies are given in Table 1.

Of the 12 studies evaluating lipid metabolism, 10 reported increases in HDL-C and/or reductions in LDL-C or fibrinogen, 1 found no significant effect, and 1 noted adverse increases in triglycerides. Among eight studies assessing blood pressure, six demonstrated reductions in systolic and/or diastolic pressure, one found no effect, and one reported increased arterial stiffness. In six studies measuring endothelial function, five showed significant improvements in flow-mediated dilation or related indices, while one found no change. Regarding inflammatory markers [C-reactive protein (CRP), Interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α)], seven studies reported reductions, five reported no significant changes, and two reported increases. For platelet function and coagulation, five studies demonstrated decreased platelet aggregation or fibrinogen, whereas one study showed no effect. Finally, studies assessing gut microbiota and metabolomic outcomes ($n = 4$) generally reported shifts in microbial composition or metabolite profiles, although these changes were not consistently linked to clinical outcomes.

While most included studies focused on surrogate biomarkers, a few reported direct CHD-related outcomes. For example, Jespersen *et al*[42] found that light wine consumers had 29% reduced odds of cardiovascular risk. Similarly, Marfella *et al*[11] observed that moderate RW consumption after myocardial infarction was associated with improved cardiac prognosis and reduced inflammatory markers. Conversely, Fantin *et al*[24] reported that RW intake increased arterial stiffness the following morning which suggests potential harm in such cases These findings indicate that while RW may modestly reduce CHD risk when consumed in moderation, effects are inconsistent and influenced by factors such as dose and other coexisting factors

Quality assessment of included studies

The quality of the included randomized controlled trials (RCTs), cohorts, and cross-sectional studies was assessed using the Joanna Briggs Institute critical appraisal checklist. Out of 33 included RCTs, 22 studies were of high quality and 11 studies were of medium quality. The two included cohorts were both of high quality. Similarly, the two included cross-sectional studies were of high quality, the complete quality appraisal detail is given in the Supplemental Digital Content, available at: http://links.lww.com/MS9/B9.

Discussion

This systematic review indicates that moderate RW consumption is generally associated with positive cardiovascular outcomes. Of the 36 included studies, 28 reported improvements in lipid metabolism, inflammatory status, and vascular endothelial health, which can collectively reduce CHD risk. However, discrepancies were found among the outcomes of the included studies as 6 studies showed no significant effect of RW on cardiometabolic markers, and 2 (of the 36 included studies) even suggesting that it had a negative impact hence underscoring the need for further investigation into long-term clinical impacts.

The popular belief that consumption of a diet rich in saturated fats is linked to a higher prevalence of CVD seems to be contradicted by various research findings on the French population, which indicate the opposite to be true, the French paradox. Despite the consumption of a diet rich in saturated fats, the French have a surprisingly lower rate of CHD as compared to those who consume a diet low in saturated fats. This paradox relates to the consumption of the Mediterranean diet. The Mediterranean diet is known to include RW, whose polyphenolic components are proposed to exert positive effects on cardiovascular health.

Various studies corroborate the positive effects of RW, or its components, on cardiovascular health. For example, according to some RCTs, RW consumption leads to better lipid profiles, specifically higher HDL-C as well as lower fibrinogen, a protein that plays a role in blood clotting[13,14]. Lower fibrinogen levels indicate a lower risk of blood clots, and higher HDL-C relates to a lower risk of atherosclerotic changes and, consequently, lower risk of heart disease. The way they do so needs to be researched; however, it is speculated to be a consequence of the way the chemicals in RW interact with lipid metabolism. RW has been found beneficial in terms of its impact on endothelial function[15,21]. A healthy endothelium is necessary for the maintenance of blood flow, regulation of blood pressure, and prevention of atherosclerosis. Endothelial dysfunction is one of the earliest events in the sequelae of CVD, including heart attack, stroke, and other related disorders. One mechanism by which RW is speculated to improve endothelial function is through upregulation of nitric oxide production, which in turn is instrumental in vasodilation, thus regulating blood flow.

Many of the beneficial effects of RW can be attributed to its antioxidant properties. Antioxidants such as polyphenols reduce oxidative stress and inflammation, thus contributing to the betterment of cardiovascular outcomes. They neutralize free radicals, which are unstable substances that contribute to cell damage and, in turn, chronic diseases. The study by Salazar *et al* further emphasizes the anti-atherosclerotic effects of RW by highlighting a significant association between a higher intake of flavonoids, stilbenes, and tyrosols – polyphenolic constituents of RW – and a lower risk of atherosclerosis[19]. The proposed mechanism by which polyphenols exert their anti-atherosclerotic effects includes inhibition of oxidation of LDL-C, reduction of platelet aggregation, and improvement in insulin sensitivity. In addition, Di Renzo *et al* found that RW consumption decreases oxLDL-C levels and upregulates the expression of antioxidant genes, thus enhancing the body's ability to fight oxidative stress at the cellular level[23].

However, the effects of RW are not uniform across all studies. For instance, some studies report an increased triglyceride level after RW consumption[15,39]. Increased triglycerides are associated with a greater risk of heart attack and stroke. This takes into account the consideration of potential adverse effects of excessive alcohol consumption. Other research suggests that the benefits of RW are dependent on several other factors, including dietary habits, physical activity levels, and genetic predisposition. For instance, Ogunmoroti *et al* brought into account the fact that where moderate consumption of RW was associated with better cardiovascular outcomes, excessive consumption of other alcoholic beverages, including liquor and beer, deteriorated the cardiovascular outcomes, thus underscoring the importance of considering other lifestyle habits when studying health effects of RW[22]. This suggests that the beneficial effects of RW are offset by the negative impacts of other alcoholic beverages containing higher quantities of alcohol as compared to polyphenols.

It is essential to interpret these findings in the context of modifiable risk factors. RW's effects on lipid metabolism and endothelial function are particularly relevant in patients with metabolic diseases, because such conditions cumulative progressively smaller improvements in cardiometabolic biomarkers can lead to significant reduction in cardiovascular risk. However, in patients with liver disease or alcohol dependence, the potential harms clearly outweigh any benefits. Therefore, the incorporation of RW into clinical recommendations should be individualized and considered only in conjunction with established evidence-based interventions.

The role of alcohol in the previously observed effects is a hot topic for debate among researchers. According to some studies, both alcohol and nonalcohol components are responsible for observed effects[27,45], indicating a synergistic response where the alcohol component in moderate amounts raises HDL-C while polyphenols exert antioxidant effects, thus synergistically improving cardiovascular health. On the other hand, other studies suggest that dealcoholized RW can provide some benefits, in terms of improving endothelial function independent of the

alcohol component[28,29]. This further implies that alcohol is not the primary contributor to the observed beneficial effects. As suggested by Wotherspoon *et al*, different alcoholic beverages exert their effects on different biomarkers and metabolic processes[12]. For instance, vodka, which contains minimal polyphenol content, increased adiponectin, a hormone that enhances insulin sensitivity and provides protection against inflammation, and apolipoprotein A-1, a constituent of HDL-C. On the other hand, RW does not have the same effect on these markers. Nevertheless, both vodka and RW increased the leptin levels, a hormone involved in the regulation of appetite and energy balance.

Many studies have examined several other biomarkers beyond the lipid profiles. These physiological parameters and biomarkers include CRP, IL-6, and TNF-α. These biomarkers are key indicators of inflammation in the body. These studies reported mixed results, where some indicated a reduction in the aforementioned markers, suggesting a strong anti-inflammatory response[10,11], while others did not report any significant changes. These discrepancies can be attributed to differences in study design, population characteristics, the amount and type of RW consumed, and the specific methods used to measure inflammatory markers.

The impact of RW on gut microbiota and metabolomics is emerging as an area of growing interest. Microbiota refers to the complex community of microorganisms inhabiting the digestive tract that plays a crucial role in human health, influencing metabolism, immune function, and inflammation. Haas *et al* found that RW exerts its effects through gut microbiota remodeling, thus altering the types and proportions of bacteria present in the gut, and altered metabolites, suggesting changes in the body's metabolic processes[18]. However, the mechanisms whereby RW interacts with gut microbiota and metabolic processes are not exactly known, and further research is required.

The findings of this review suggest that RW should not be considered a primary intervention for cardiometabolic risk management, but rather as a potential adjunct. For patients who already consume alcohol, clinicians may advise that, if wine is selected, it should be limited to moderate quantities within the context of a Mediterranean dietary pattern. However, RW should not be initiated in abstainers for the purpose of cardiovascular prevention, given the associated risks of alcohol dependence and hepatotoxicity. Notably, any potential benefits of RW may be most pertinent in individuals with multiple modifiable risk factors, such as dyslipidemia, endothelial dysfunction, or metabolic syndrome.

This review includes only English language, peer-reviewed literature, excluding conference abstracts and unpublished data, thus risking language and publication bias. Moreover, the lack of stratified analysis to determine whether the effects differed by the amount of wine consumed, duration of consumption, and frequency further adds to the limitations of this review. The confounding by diet, exercise, socioeconomic status, and genetic predisposition has not been addressed. Most of the included studies primarily assessed surrogate biomarkers (e.g., HDL-C, CRP, endothelial function) rather than clinical outcomes such as myocardial infarction, stroke, or mortality. This reliance on surrogate endpoints limits the ability to calculate absolute or relative risk reductions and should be considered when interpreting the clinical significance of our findings. A meta-analysis could be attempted in the future, but would be limited by the heterogeneity of interventions, comparators, dosages, and outcome measures across studies.

Conclusion

This systematic review explores the French Paradox and supports the idea that moderate RW consumption may offer beneficial effects on the cardiovascular system such as improved lipid profiles, enhanced endothelial function, and reduced oxidative stress and inflammation. While many studies show beneficial effects, others report mixed or null outcomes—highlighting that RW's impact is not universal and may vary depending on factors such as dosage, duration, genetic predisposition, and baseline health status. Overall, RW's cardioprotective potential appears to result more from its polyphenol content than the alcohol itself, but further research is needed to clarify its role and optimal use. Clinicians should therefore frame RW not as a treatment, but as a lifestyle factor that may contribute modestly to improved lipid and endothelial profiles when consumed in moderation within a healthy diet

Disclosure statement

Generative AI tools, including ChatGPT (OpenAI, GPT-4, November 2024) and DeepSeek (December 2024), were employed via cloud-based APIs to support language refinement and summarization during the drafting and revision process. To minimize potential algorithmic bias, all AI-generated outputs were carefully reviewed for clinical accuracy and relevance, with particular consideration given to underrepresented perspectives. The authors adhered to established ethical standards and report no conflicts of interest with AI vendors. Only prompts such as "rephrase in academic research language" and "rephrase the text" were utilized; complete prompt logs are available upon request to ensure transparency and reproducibility. All inputs were fully de-identified, and the outputs were verified and refined by the authors to maintain accuracy, compliance, and research integrity.

Ethical approval

Ethics approval was not required for this systematic review as per exemption granted by King Edward Medical University.

Consent

Informed consent was not required for this systematic review, as no direct human participants were involved in the study

Sources of funding

None.

Author contributions

D.B.: conceptualization, methodology, investigation, writing – original draft, formal analysis, visualization, project administration, and supervision; S.F.H.B.: data curation, investigation, writing – original draft, validation, visualization, and supervision; M.K.B.A.:

investigation, methodology, writing – review and editing, and validation; A.A.Q.: investigation, data curation, and writing – review and editing; M.R.: formal analysis, visualization, and writing – review and editing; M.S.: validation and writing – review and editing; M.T.: data curation, investigation, and resource provision; Y.R.: investigation, resources, and writing – review and editing; K. M.: investigation and resource provision; M.A.Q.: writing – review and editing; Z.R.: writing – review and editing; R.Y.: contributed to resources and writing; M.N.A.: project administration, writing – review and editing, and validation.

Conflicts of interest disclosure

All Authors declare no conflicts of interest.

Guarantor

Muhammad Numan Awais

Research registration unique identifying number (UIN)

Registered on OSF: https://doi.org/10.17605/OSF.IO/H8A2T

Provenance and peer review

The paper was not invited.

Data availability statement

All data extracted for this systematic review are fully presented within this publication. For any further information or clarification, please contact the corresponding author.

Acknowledgements

None.

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