European Journal of Internal Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Review Article

Alcohol use: less is better. An umbrella systematic review of clinical interventions, policies, and dose–response health risks in adults

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ARTICLE INFO

Keywords:
Alcohol drinking
Heavy episodic drinking
Multimorbidity
Internal medicine
Risk Assessment
Health Policy

ABSTRACT

Background: Alcohol is a major modifiable cause of morbidity, premature mortality and health inequalities, yet evidence informing "low-risk" thresholds and prevention strategies is fragmented.
Methods: Umbrella systematic review conducted according to PRISMA 2020 (protocol on OSF). PubMed/MEDLINE and Scopus were searched (Jan 2015–Mar 2026). An overlap-management approach selected an anchor synthesis per research question (Q1-Q37); supporting records were retained for triangulation. Quality appraisal used design-appropriate tools. Synthesis was narrative.
Results: Of 14,991 records, 49 were included (46 systematic reviews/meta-analyses, 2 WHO documents, 1 cross-sectional study) covering 37 pre-specified questions. Across most outcomes, higher intake and riskier patterns were associated with higher risk, with harms evident at levels often labelled 'moderate'. Any drinking increased injury odds (OR 2.80). Dose-response evidence showed steep gradients for cirrhosis (RR 9.35 in women and 2.82 in men at 40 g/day) and small but measurable increases in selected cancers at light drinking (e.g., breast cancer RR 1.05). In primary care, brief interventions reduced consumption at 12 months by -20 g/week. Pricing measures and some availability restrictions were directionally associated with lower consumption and harms, whereas evidence for other policy levers was more heterogeneous.
Conclusions: Overall evidence favoured lower alcohol intake and avoidance of heavy episodic drinking, although confidence varied by endpoint and was limited for several questions by the quality of the available syntheses. Apparent low-dose benefits were not robust to bias-aware analyses. These findings support a pragmatic counselling and policy message of "less is better" rather than a universal safe threshold.

1. Introduction

Alcohol consumption remains a major, yet modifiable, driver of preventable morbidity, premature mortality and health inequalities worldwide. The most recent World Health Organization (WHO) assessment describes alcohol-attributable harm as a persistent public health

Abbreviations: AACODS, Authority–Accuracy–Coverage–Objectivity–Date–Significance; AMSTAR 2, A Measurement Tool to Assess Systematic Reviews 2; AUD, alcohol use disorder; BI, brief intervention; DALY, disability-adjusted life-year; e-SBI/e-SBIRT, electronic screening and brief intervention/referral to treatment; HED, heavy episodic drinking (binge drinking); MASLD, metabolic dysfunction-associated steatotic liver disease (formerly non-alcoholic fatty liver disease); PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RQ, research question; SBIRT, screening, brief intervention, and referral to treatment; SR/MA, systematic review/meta-analysis.

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https://doi.org/10.1016/j.ejim.2026.106837
Received 2 February 2026; Received in revised form 10 March 2026; Accepted 13 March 2026

and health-system challenge, with substantial disparities between and within countries [1]. Population-level modelling from the Global Burden of Disease (GBD) 2020 study further indicates that risk increases across multiple causes of death and disability with increasing consumption, reinforcing the need for prevention strategies that are relevant at both individual and population levels [2]. Importantly, alcohol-related harm is socially patterned: the dose–response relationship between socioeconomic deprivation and alcohol-attributable mortality suggests that similar levels of consumption can translate into markedly different outcomes across social strata [3]. At the same time, alcohol is a Group 1 carcinogen, and cancer risk increases with exposure - an evidence base that complicates public messaging focused exclusively on heavy drinking [4].

For the clinician, alcohol use frequently acts as a cross-cutting determinant that complicates multimorbidity management. In real-world practice, it can worsen blood pressure control, destabilise glycaemia and amplify treatment-related harms through drug-alcohol interactions in settings of polypharmacy, including with anticoagulants and common antihypertensives. Consistent with this clinical footprint, dose-response evidence supports a largely monotonic increase in hypertension risk with increasing alcohol intake, and large-scale synthesis indicates that atrial fibrillation risk also rises with greater consumption [5,6]. Alcohol exposure has additionally been associated with electrocardiographic abnormalities, supporting a broader electrophysiological impact [7]. Alcohol-related risk also intersects with liver and metabolic vulnerability, including MASLD under current multisociety nomenclature, and sex-stratified evidence suggests that women may develop cirrhosis at lower levels of intake than men [8–10]. These patterns underscore that alcohol history and current use are core clinical information for risk stratification and management in internal medicine.

Despite a long-standing public discourse on “low-risk” drinking, the scientific basis for defining a universally safe threshold remains contested. National “lower-risk” guidance often clusters around approximately 100–140 g of pure ethanol per week (e.g., the UK Chief Medical Officers advise not regularly exceeding 14 units/week ≈112 g), whereas WHO Europe has emphasised that no level of alcohol consumption is safe for health [11,12]. Exposure assessment varies widely across studies and is vulnerable to under-reporting, recall bias, misclassification of former drinkers as abstainers, and changes in intake over time [13]. Such limitations can generate apparently protective associations (for example, “J-shaped” curves for cardiovascular outcomes) that may not reflect causal effects. Large individual-participant data analyses have been used to refine risk curves and challenge simplistic threshold narratives, particularly for cardiovascular endpoints [14]. Causal inference approaches that triangulate evidence from genetic instruments have similarly questioned cardioprotective interpretations of moderate intake [15]. More broadly, a systematic review of Mendelian randomisation studies suggests that genetically predicted alcohol consumption is associated with increased risks across several disease domains, supporting a prevention message centred on reduction rather than presumed benefit [16].

From the perspective of clinical prevention, screening, brief intervention, and referral to treatment (SBIRT) remains a cornerstone approach because it can be delivered opportunistically during routine care. A major Cochrane review supports that brief interventions reduce alcohol consumption among hazardous and harmful drinkers who are not actively seeking treatment, although effect sizes are modest at the individual level [17]. However, implementation in routine practice remains low and heterogeneous across settings, reflecting persistent barriers at the patient, clinician and organisational levels [18]. Recent evidence syntheses also emphasise that both delivery modality and context matter: practitioner-delivered interventions tend to achieve larger short-term reductions than purely digital approaches in non-treatment-seeking populations, and trauma and emergency-care pathways have been studied as additional opportunities for intervention [19–21]. For internal medicine, where contact with patients with multimorbidity is frequent, closing the evidence-to-practice gap for alcohol screening and brief counselling is therefore a pragmatic priority.

Clinical actions alone are unlikely to achieve population-level reductions in harm without complementary public health policies. WHO frameworks highlight integrated strategies, including regulation of availability, restrictions on marketing and promotion, and fiscal measures, alongside health service responses [1]. Yet, the policy evidence base is uneven across levers, outcomes and jurisdictions. An umbrella review of alcohol control interventions indicates variable certainty across policy types and highlights limitations in study design, outcome measurement and transferability [22]. Even for high-visibility interventions such as calorie (energy) labelling on alcohol products, evidence remains limited and context-dependent [23].

Given the breadth of alcohol-related outcomes relevant to internal medicine and the proliferation of overlapping evidence syntheses across clinical, behavioural and policy domains, a structured, decision-oriented synthesis is needed to inform coherent risk communication and clinical decision-making. The present umbrella systematic review was designed to summarise and appraise the best available evidence across 37 pre-specified questions spanning patterns of alcohol use, clinical outcomes, vulnerable groups, prevention and treatment strategies, and policy measures.

2. Materials and methods

2.1. Study design and protocol

An umbrella systematic review was conducted to synthesise decision-relevant evidence across 37 pre-specified research questions on alcohol-related risks, interventions and policies in adults. The primary unit of synthesis was secondary evidence (systematic reviews and meta-analyses). In line with the protocol, inclusion of non-review evidence (authoritative surveillance/policy documents and, when necessary, primary studies) was permitted when a research question was not adequately addressed by eligible reviews.

The review followed a protocol-driven workflow. The OSF record (version 2.0, 22 January 2026: https://doi.org/10.17605/OSF.IO/FRTKH) was archived after completion of the initial searches. The research questions, eligibility criteria and overlap-management/anchor framework used in screening were not modified after screening began. The initial database searches were executed on 09 September 2025; to ensure currency, the database searches were updated on 03 March 2026 using the same strategy, covering records indexed from 09 September 2025 to 03 March 2026. Conduct and reporting followed PRISMA 2020; protocol elements were aligned with PRISMA-P where applicable. The evidence corpus was locked on 03 March 2026 following the search update and before final manuscript revision.

2.2. Research questions and eligibility criteria

The review was structured around 37 pre-specified research questions (Q1-Q37) grouped into seven domains: epidemiology and measurement; acute and social harms; major chronic organ-specific risks; dose-response, thresholds and methodological controversies; sensitive subgroups; clinical interventions; and population-level policies and implementation. Each included record was mapped to one or more questions. For reporting, a record could be assigned one or more primary reporting RQs when the same synthesis served as the designated anchor for more than one protocol question; additional mappings were retained when the record also informed other questions as supporting evidence (Supplementary).

Original protocol questions (Q1–Q37) are maintained in Supplementary Table S1 for traceability. The use of narrower synthesis titles in the Results to reflect the specific available evidence is strictly a reporting convention; it does not indicate *post hoc* changes to the original screening or eligibility framework.

The target population was adults (≥18 years). For surveillance questions based on WHO indicators (Q1–Q3 and partly Q9), source populations could include persons aged ≥15 years, as defined by the reporting framework. Eligible exposures comprised quantified alcohol consumption (grams of ethanol and/or standard drinks) and/or drinking pattern (including heavy episodic drinking (HED; binge drinking)). Eligible interventions included clinical strategies (screening, brief interventions, and referral pathways) and population-level policies (pricing/taxation, availability restrictions, marketing restrictions, labelling/warnings, and drink-driving countermeasures). Eligible outcomes encompassed acute harms (injuries/trauma, road traffic outcomes, violence, acute intoxication/poisoning), major chronic outcomes (liver disease, cardiovascular disease, cancer, neurocognitive outcomes and mental health outcomes), overall and cause-specific mortality, and population health indicators (e.g., DALYs) where available, as well as consumption or implementation outcomes when relevant to the question.

The primary time window was 1 January 2015 onwards. Pre-2015 "sentinel" sources were allowed only when they remained the definitive synthesis or authoritative reference for a specific endpoint (e.g., foundational definitions, instruments, or protocol-specified controversies) and no newer eligible synthesis existed. English and Italian records were eligible; non-English/Italian sources were considered only when essential. Narrative/opinion articles without analysable data, purely mechanistic studies without clinical or social outcomes, and very small samples ($n < 100$) were excluded unless justified as sentinel evidence.

2.3. Information sources and search strategy

Two core bibliographic databases (PubMed/MEDLINE and Scopus) were searched (1 January 2015 to 9 September 2025; searches executed 09 September 2025) and updated on 03 March 2026 (covering records indexed from 09 September 2025 to 03 March 2026; searches executed 03 March 2026), supplemented with targeted retrieval of authoritative guidance/surveillance/policy reports and backward and forward citation tracking of included studies. All PRISMA identification, de-duplication, screening and eligibility counts reported in Fig. 1 and in the Results are cumulative across the initial search and the 03 March 2026 update, after integrated de-duplication of records retrieved in both rounds. The database strategy combined alcohol terms with outcome/policy/intervention terms and dose-response or reduction concepts; animal-only records were excluded. Searches captured records indexed as 'epub ahead of print'/online-first where available. Exact search strings, limits and execution dates were recorded in the OSF repository to ensure reproducibility.

2.4. Record management and study selection

Records were exported to a reference manager for de-duplication and then screened in two stages. First, titles/abstracts were screened to identify potentially relevant records. Second, a protocol-based rescreen of potentially relevant records defined the full-text assessment set and a small borderline/contextual set retained for traceability. Titles/abstracts and full texts were screened independently by two reviewers; disagreements were resolved by a third reviewer.

To minimise redundancy and double counting across overlapping reviews, we applied an anchor-based within-question overlap-management procedure, supported by pre-specified triage criteria, to select a primary synthesis for each research question where possible and retain non-overlapping support records [24]. Replacement candidates were pre-identified when access limitations prevented full-text retrieval of a candidate anchor.

2.5. Evidence prioritisation and overlap management (anchor vs support)

For each research question, an anchor record was defined as the best synthesis (or, when necessary, non-review source) used as the primary evidentiary basis for conclusions. When multiple candidate syntheses were eligible, anchor selection followed a predefined hierarchy: (i) methodological credibility (overall AMSTAR 2 confidence when applicable), (ii) recency and coverage (preferentially by search end date; if unavailable, by publication year), (iii) adherence to the research-question-specific PICO/PECO framework and clarity of definitions,

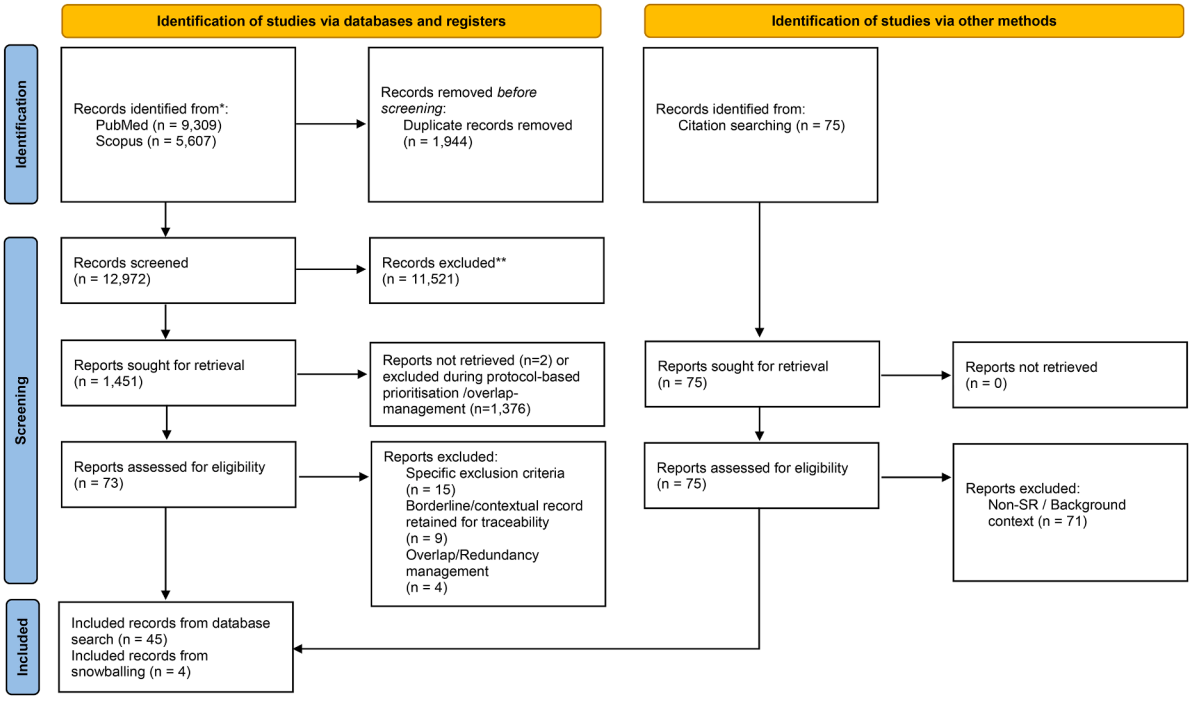

Fig. 1. PRISMA 2020 flow diagram.
Counts shown are cumulative across the initial search and the 03 March 2026 update. Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

and (iv) analytic adequacy and transparency (e.g., dose-response modelling and sensitivity analyses where relevant) [25]. Residual ties were resolved by broader outcome coverage and/or a larger included evidence base, with rationale documented. Additional included records were retained as support evidence when they added non-overlapping outcomes, key subgroups, methodological triangulation, or implementation/policy detail.

2.6. Data extraction

A standardised extraction template was piloted and applied. Data were extracted by one reviewer (TD) and verified by a second reviewer (VD), with disagreements resolved by consensus. Extracted items included: design and setting; population characteristics; exposure/intervention definitions (including units and heavy episodic drinking (HED) when relevant); comparators; outcome definitions; effect measures (e.g., RR/OR/HR/mean difference) with 95 % confidence intervals when available; and narrative notes on major strengths/limitations and applicability. Each record was linked to its research-question mapping and evidentiary role (anchor or support). Detailed extraction fields are provided in the Supplementary materials.

2.7. Quality appraisal

Quality appraisal was performed using tools matched to study design. Systematic reviews/meta-analyses were appraised with AMSTAR 2 and categorised by overall confidence (high, moderate, low, critically low). Grey literature and authoritative reports were appraised using AACODS (Authority, Accuracy, Coverage, Objectivity, Date, Significance). The single primary cross-sectional study was appraised using the Joanna Briggs Institute (JBI) analytical cross-sectional checklist. In the final included corpus ($n = 49$), AMSTAR 2 was applied to 46 records, AACODS to 2 records, and the JBI checklist to 1 record. Reviews rated "Low" or "Critically low" were downgraded mainly for shortcomings in one or more critical AMSTAR 2 domains. Because AMSTAR 2 overall confidence can be lowered by transparency/reporting deficits (e.g., protocol registration; excluded-studies list) as well as by limitations more likely to affect effect estimates (e.g., inadequate risk-of-bias assessment/integration; publication bias), we considered both the overall rating and the nature of the critical-domain limitations when weighting evidence. Where higher-confidence alternatives were available, low/critically low reviews were used mainly as contextual/supporting evidence; when no higher-confidence synthesis existed for a question, the best available review could still serve as an anchor, but certainty was explicitly downgraded and conclusions phrased cautiously.

2.8. Data synthesis

The primary synthesis was a structured narrative synthesis with evidence mapping by research question and domain. To ensure comparability across studies, alcohol consumption metrics were harmonised into grams of pure ethanol per day/week where possible, using 1 standard drink = 10 g ethanol when not explicitly defined by the primary authors; conversions were documented. For each question, findings from the anchor record were reported and support records were used to triangulate direction and magnitude, add outcomes or subgroups not covered by the anchor, and describe implementation and context. No de novo quantitative synthesis across overlapping reviews was undertaken because the evidence was clinically and methodologically heterogeneous; accordingly, synthesis without meta-analysis followed a transparent, structured approach.

2.9. Ethics and transparency

Ethical approval was not required because this study synthesised published and publicly available evidence. Search strategies, screening decisions, full-text overlap-management decisions, research-question mapping, quality appraisal outputs and the final locked corpus register were archived in OSF (https://doi.org/10.17605/OSF.IO/FRTKH) to provide an auditable trail.

3. Results

Dose metrics were harmonised as described in the Methods, using 1 standard drink = 10 g of pure ethanol unless otherwise specified by the original source.

3.1. Study selection

Across the initial database search and the 03 March 2026 update, database searching identified 14,916 records (PubMed $n = 9309$; Scopus $n = 5607$); after integrated de-duplication, 12,972 unique records underwent title/abstract screening. Of these, 11,521 were excluded and 1451 were retained for prioritisation and full-text consideration. Following protocol-based rescreen/prioritisation and within-question overlap management, 1376 reports were not advanced to formal full-text eligibility assessment and 2 could not be retrieved, leaving 73 database reports for formal full-text eligibility assessment. An additional 75 records were identified via citation searching/snowballing. Overall, 49 records met the inclusion criteria (45 from database searches and 4 from snowballing). Of the 73 database candidates assessed at full text, 15 were excluded for prespecified eligibility reasons, 9 were set aside as borderline/contextual rather than included in the primary synthesis, and 4 were removed because a more suitable overlapping synthesis had already been retained. From snowballing, 71 records were excluded from the primary synthesis but informed contextual/background checking. The selection workflow is summarised in Fig. 1.

3.2. Characteristics of included evidence

Forty-nine records were included: 46 systematic reviews/meta-analyses (including one umbrella review and one individual-participant-data meta-analysis), one cross-sectional observational study, and two authoritative policy/technical documents. The evidence base covered seven pre-specified domains spanning epidemiology and measurement, acute and social harms, major chronic organ-specific risks, dose-response/methodological controversies, sensitive subgroups, clinical interventions, and population-level policies. Following eligibility assessment and evidentiary role designation, 30 records served as anchor studies (one per research question where possible), with 19 retained as supporting evidence; study characteristics are summarised in Table 1 and further detailed in the Supplementary materials.

3.3. Methodological quality

Across included systematic reviews/meta-analyses, AMSTAR 2 ratings were predominantly low: 1 review was rated high, 0 moderate, 15 low and 30 critically low. The cross-sectional observational study was rated at low risk of bias. Some AMSTAR 2 downgrading reflected transparency/reporting deficits (e.g., absence of a registered protocol, incomplete reporting of excluded studies, limited disclosure of funding/conflicts of interest, or missing a priori justification of analytical choices), whereas other reviews had limitations more likely to affect effect estimates (e.g., incomplete or non-integrated risk-of-bias assessment, limited exploration of heterogeneity/publication bias, or insufficient sensitivity analyses for exposure definitions and dose-response assumptions). Accordingly, anchor conclusions were weighted by both overall confidence and the nature of the critical-domain limitations; where no higher-confidence synthesis existed, certainty was explicitly downgraded and conclusions were phrased cautiously. A summary

Table 1
Included records (n = 49): characteristics and research-question mapping. Study IDs are used consistently across the manuscript and Supplementary Tables.

Study ID	Year	Design	Population/Setting	Mapped RQ (s)	QA overall	First author	DOI
FT001	2025	Systematic review + meta-analysis	Adults (general)	Q12;Q17	Low	Toubasi	10.1159/000547945
FT002	2025	Systematic review + meta-analysis	ED/trauma/hospital setting	Q27	Critically low	Woliansky	10.1111/1742–6723.14506
FT003	2025	Systematic review (no meta-analysis)	Clinical setting (screening)	Q25	Low	Bisschop	10.1111/dar.13987
FT004	2025	Systematic review (no meta-analysis)	Young adults	Q21	Low	Botella-Juan	10.1016/j.puhe.2025.01.004
FT005	2024	Systematic review + meta-analysis	Adults (general)	Q11	Low	Sim	10.47102/annals-acadmedsg.2023351
FT006	2024	Systematic review + meta-analysis	Adults with cardiometabolic comorbidity/high risk	Q12	Low	Cecchini	10.1161/HYPERTENSIONAHA.124.22703
FT007	2024	Systematic review (no meta-analysis)	Adults (general)	Q17;Q19	Low	Bouajila	10.3389/fepid.2024.1385064
FT008	2024	Systematic review + meta-analysis	Clinical setting (screening)	Q25	Critically low	Wood	10.1001/jama.2024.3101
FT009	2024	Systematic review + meta-analysis	Adults (general)	Q28;Q30	Critically low	Jones	10.1177/29,767,342,241,248,926
FT010	2024	Systematic review + meta-analysis	Adults (general)	Q10;Q24	Low	Llamosas-Falcon	10.1007/s12072–023–10,584-z
FT011	2024	Systematic review + meta-analysis	Adults (general)	Q20	Critically low	Berhe	10.7759/cureus.61323
FT012	2024	Systematic review + meta-analysis	Adults (general)	Q15;Q19	Critically low	Stockwell	10.15288/jsad.23–00,283
FT013	2024	Systematic review + meta-analysis	Adults (general)	Q14	Critically low	Lange	10.1016/j.drugalcdep.2024.111348
FT014	2024	Systematic review + meta-analysis	Adults (general)	Q13	Critically low	Zarezadeh	10.1016/j.arr.2024.102419
FT015	2024	Systematic review (no meta-analysis)	General population (policy evaluation)	Q35	Critically low	Joyce	10.1080/10,550,887.2023.2210020
FT016	2024	Systematic review (no meta-analysis)	General population (policy evaluation)	Q34	Low	Manthey	10.1111/add.16411
FT017	2023	Systematic review + meta-analysis	Clinical setting (screening)	Q29	Low	Tan	10.1111/add.16187
FT018	2023	Systematic review + meta-analysis	Adults with cardiometabolic comorbidity/high risk	Q23	Critically low	Llamosas-Falcon	10.2337/dc23–1015
FT019	2023	Systematic review + meta-analysis	Adults (general)	Q10;Q18	Critically low	Llamosas-Falcon	10.1111/dar.13563
FT020	2023	Systematic review + meta-analysis	Adults (general)	Q11;Q16	Critically low	Jun	10.4178/epih.e2023092
FT021	2023	Systematic review (no meta-analysis)	Acute harms (injury/ED/trauma/community)	Q8	Critically low	Baltariu	10.1016/j.drugalcdep.2023.109830
FT022	2023	Systematic review + meta-analysis	Acute harms (injury/ED/trauma/community)	Q7	Critically low	Kassym	10.3390/healthcare11050758
FT023	2022	Systematic review + meta-analysis	At-risk adult drinkers (community, primary care, workplace)	Q28;Q29	Critically low	Beyer	10.1111/add.15999
FT024	2022	Systematic review + meta-analysis	Adults (general)	Q10	Critically low	Llamosas-Falcon	10.3389/fgstr.2022.1005729
FT025	2022	Systematic review + meta-analysis	Adults (general)	Q11;Q20	Critically low	Kubo	10.1007/s10388–021–00,892-4
FT026	2022	Systematic review + meta-analysis	General population (policy evaluation)	Q36;Q37	Critically low	OHara	10.1111/dar.13519
FT027	2021	Systematic review + meta-analysis	Adults (general)	Q20	Critically low	Lardier	10.3389/fpsyg.2021.675285
FT028	2021	Systematic review + meta-analysis	Adults / general population (socioeconomic gradients in alcohol-attributable mortality)	Q4	Critically low	Probst	10.1186/s12916–021–02,132-z
FT029	2021	Systematic review + meta-analysis	Adults with liver disease risk/diagnosis	Q24	Low	Llamosas-Falcon	10.1016/j.jhep.2021.04.018
FT030	2021	Systematic review (no meta-analysis)	Pregnant people / pregnancy	Q29	Low	Samawi	10.1007/s00737–020–01,100-5
FT031	2020	Systematic review (no meta-analysis)	Adults (general)	Q28	Critically low	Hutton	10.1080/24,694,193.2019.1616008
FT032	2019	Umbrella review (overview of reviews)	General population (policy evaluation)	Q32;Q33;Q34;Q35;Q36;Q37	Low	Siegfried	10.1371/journal.pone.0214865
FT033	2018	Meta-analysis	Adults (general)	Q28	Critically low	Riper	10.1371/journal.pmed.1002714
FT034	2016	Cross-sectional study	Acute harms (injury/ED/trauma/community)	Q9	Low risk of bias	Vardy	10.1136/bmjopen-2015–010,005
FT035	2016	Systematic review + meta-analysis	Adults (general)	Q11;Q16	Critically low	Wang	10.18632/oncotarget.10352

(*continued on next page*)

Table 1 (*continued*)

Study ID	Year	Design	Population/Setting	Mapped RQ (s)	QA overall	First author	DOI
FT036	2016	Systematic review (no meta-analysis)	Adults (general)	Q11	Critically low	Zhao	10.1186/s12885–016–2891-z
FT037	2024	Systematic review (no meta-analysis)	Adults (general)	Q20	Low	Hallihan	10.1016/j.drugalcdep.2024.111406
FT038	2024	Systematic review + meta-analysis	Adults (general)	Q11;Q16	Critically low	Jun	10.3346/jkms.2024.39.e185
FT039	2024	Meta-analysis	Adults (general)	Q11;Q20	Critically low	Terry	10.1186/s13058–024–01,937-z
FT040	2023	Systematic review of meta-analyses (review of reviews)	Adults (general)	Q19	Critically low	Levesque	10.1111/acer.15121
FT041	2023	Individual participant data meta-analysis	Adults (general)	Q13	Critically low	Mewton	10.1111/add.16035
FT042	2022	Authoritative report / policy document	General population (policy evaluation)	Q37	High	World Health Organization	
FT043	2021	Systematic review (no meta-analysis)	Older adults / epidemiological measurement studies (self-report alcohol assessment)	Q5	Critically low	Tevik	10.1371/journal.pone.0261292
FT044	2021	Systematic review (no meta-analysis)	Primary care / implementation (SBI)	Q31	Low	Rosario	10.1186/s13012–020–01,073-0
FT045	2020	Systematic review (no meta-analysis)	General population (policy evaluation)	Q33	Low	Nepal	10.15288/jsad.2020.81.5
FT046	2024	Authoritative report / policy document	General population (surveillance/ trends; WHO report)	Q1;Q2;Q3;Q9	High	World Health Organization	
FT047	2013	Systematic review + meta-analysis	Acute harms (injury/ED/trauma/ community)	Q6	Critically low	Zeisser	10.1111/j.1530–0277.2012.01919.x
FT048	2018	Systematic review + meta-analysis	Primary care	Q26;Q29	High	Kaner	10.1002/14,651,858.CD004148.pub4
FT049	2017	Systematic review + meta-analysis	Pregnant people / pregnancy	Q22	Critically low	Mamluk	10.1136/bmjopen-2016–015,410

quality appraisal of anchor studies is reported in Table 2.

3.4. Summary of findings by domain

A domain-level evidence summary is presented in Table 3, while detailed question-level extractions, the evidence map, and quality-appraisal overviews are provided in the Supplementary materials.

Domain 1 – Epidemiology and measurement

Q1. What are the trends in per-capita alcohol consumption (recorded and unrecorded) since 2010?

WHO surveillance among adults aged ≥15 years indicates that total (recorded + unrecorded) alcohol per-capita consumption decreased from 5.7 L in 2010 to 5.5 L in 2019 (−4.5 %). In 2019, 79 % of consumption was recorded and 21 % unrecorded, supporting a modest global decline rather than a marked downward shift [1].

Q2. What are the trends in heavy episodic drinking (HED) since 2010?

In WHO surveillance, heavy episodic drinking (HED; ≥60 g of pure alcohol on one occasion in the previous 30 days) affected 17 % of adults aged ≥15 years and 38 % of current drinkers in 2019; prevalence remained higher in men than in women (24 % vs 10 %). Age-standardised HED prevalence declined only modestly since 2010, indicating persistent exposure to risky drinking patterns [1].

Q3. What are the trends in alcohol-attributable mortality and burden of disease since 2010?

Between 2010 and 2019, the absolute number of alcohol-attributable deaths declined from about 2.7 million to 2.6 million (−2.5 %), while the alcohol-attributable death rate per 100 000 people fell by 20.2 % and alcohol-attributable DALYs per 100 000 by 18.3 %. Despite this improvement, alcohol still accounted for 4.7 % of all deaths and 4.6 % of all DALYs globally in 2019 [1].

Q4. What is the social gradient in alcohol-related harm, and what does the evidence suggest about alcohol use across socioeconomic groups?

The most robust quantitative evidence concerned alcohol-attributable mortality. In a dose–response meta-analysis of 25 studies, mortality risk increased steeply with socioeconomic disadvantage: compared with the highest education group, the RR at the lowest educational level was 4.50 (95 % CI 3.26–6.40) in women and 6.28 (95 % CI 4.89–8.07) in men; similar gradients were reported for income and occupation. Thus, the included corpus demonstrates a pronounced social gradient in alcohol-attributable mortality, whereas directly pooled estimates for socioeconomic differences in consumption patterns and non-fatal harms were limited [3].

Q5. In older adults, how is self-reported alcohol consumption operationalised in epidemiological studies, and how might this heterogeneity affect comparability of risk estimates?

Across 105 studies in older adults, exposure measurement was highly heterogeneous, with 7 definitions of abstinence, 12 of current drinking, 21 of risky drinking, and standard-drink definitions ranging from 8 to 50 g ethanol. Quantity–frequency questionnaires and AUDIT/AUDIT-C were most common, but this definitional variability reduces between-study comparability and can distort low-dose risk estimates, particularly when abstainers and former drinkers are not clearly separated [13].

Domain 2 – Acute and social harms

Q6. Is acute alcohol use associated with unintentional injuries and trauma?

In a meta-analysis of 14 studies, any alcohol use within 6 h before injury was associated with higher odds of injury than no alcohol use (OR 2.80; 95 % CI 2.21 to 3.54). Because exposure was operationalised as “any” versus “none”, the review supports an acute harmful association but does not define a fine-grained dose–response gradient [26].

Table 2
Quality assessment of anchor studies (summary), using design-appropriate tools (AMSTAR 2 for systematic reviews/meta-analyses; AACODS for authoritative reports).

Study ID	QA tool	QA overall	AMSTAR2 critical flaws (n)	Key limitations
FT001	AMSTAR 2	Low	1	Critical flaws: excluded list
FT002	AMSTAR 2	Critically low	2	Critical flaws: protocol, excluded list
FT003	AMSTAR 2	Low	1	Critical flaws: excluded list; Critical partial: RoB in interpretation
FT004	AMSTAR 2	Low	1	Critical flaws: excluded list
FT006	AMSTAR 2	Low	1	Critical flaws: excluded list
FT007	AMSTAR 2	Low	1	Critical flaws: excluded list; Critical partial: risk of bias
FT009	AMSTAR 2	Critically low	2	Critical flaws: protocol, excluded list
FT010	AMSTAR 2	Low	1	Critical flaws: excluded list
FT012	AMSTAR 2	Critically low	2	Critical flaws: excluded list, publication bias
FT013	AMSTAR 2	Critically low	2	Critical flaws: excluded list, publication bias
FT014	AMSTAR 2	Critically low	2	Critical flaws: protocol, excluded list
FT015	AMSTAR 2	Critically low	2	Critical flaws: protocol, excluded list
FT016	AMSTAR 2	Low	1	Critical flaws: excluded list
FT018	AMSTAR 2	Critically low	2	Critical flaws: excluded list, publication bias
FT019	AMSTAR 2	Critically low	3	Critical flaws: search, excluded list, publication bias
FT020	AMSTAR 2	Critically low	2	Critical flaws: protocol, excluded list
FT021	AMSTAR 2	Critically low	3	Critical flaws: protocol, search, excluded list
FT022	AMSTAR 2	Critically low	3	Critical flaws: protocol, excluded list, publication bias; Critical partial: risk of bias, RoB in interpretation
FT023	AMSTAR 2	Critically low	3	Critical flaws: search, excluded list, publication bias
FT028	AMSTAR 2	Critically low	2	Critical flaws: excluded list, publication bias; Critical partial: risk of bias
FT029	AMSTAR 2	Low	1	Critical flaws: excluded list
FT032	AMSTAR 2	Low	1	Critical flaws: excluded list; Critical partial: search
FT037	AMSTAR 2	Low	1	Critical flaws: excluded list
FT042	AACODS (grey literature)	High		AACODS: WHO publication (high authority, recent, relevant).
FT043	AMSTAR 2	Critically low	2	Critical flaws: protocol, excluded list
FT044	AMSTAR 2	Low	1	Critical flaws: excluded list
FT046	AACODS (grey literature)	High		AACODS: WHO publication (high authority, recent, relevant).
FT047	AMSTAR 2	Critically low	3	Critical flaws: protocol, excluded list, RoB assessment. Critical partial: RoB in interpretation.
FT048	AMSTAR 2	High	0	No critical flaws. Minor non-critical weakness: rationale for study designs not explicitly justified.
FT049	AMSTAR 2	Critically low	2	Critical flaws: excluded list, publication bias (not assessable due to <10 studies per outcome).

Q7. Among drivers with non-fatal road-traffic injuries, how common is alcohol involvement?

Pooling 17 studies ($N = 232,198$ injured drivers), alcohol positivity among non-fatally injured drivers was 16.6 % (95 % CI 12.8–20.3), but heterogeneity was extreme ($I^2 \approx 99.9$ %). Prevalence varied widely by region (from 5.5 % in the Middle East/North Africa/Greater Arabia region to 30.6 % in Asia) and by BAC threshold, so the pooled estimate should be interpreted as a broad average rather than a stable universal value [27].

Q8. What acute effects does alcohol have on social cognition relevant to interpersonal harm?

Across 32 experimental studies, no pooled effect size was available, but narrative synthesis indicated dose-related worsening in specific social-cognitive domains, especially emotion recognition, empathy and theory of mind, after acute alcohol exposure. This evidence is mechanistic and laboratory-based, so it is more informative about pathways to interpersonal harm than about the incidence of violence or harms to others [28].

Q9. What do global burden estimates and hospital-based indicators show about acute alcohol-related intoxication and poisoning requiring urgent care?

WHO estimates indicate that alcohol use disorders, alcohol poisonings and fetal alcohol syndrome caused 156,000 deaths and 19.3 million DALYs globally in 2019. As local clinical-context support rather than a second population estimate, a hospital audit found that 21.0 % of emergency admissions were alcohol-attributable; among those admissions, 26.4 % involved severe/very severe intoxication and 74.6 % chronic alcohol dependence [1,29].

Domain 3 – Major chronic organ-specific risks

Q10. How is alcohol associated with liver disease, and are there sex-specific differences in risk?

Compared with lifetime abstention, alcohol intake was associated with steep, non-linear increases in cirrhosis risk: for cirrhosis morbidity, RR 1.81 (95 % CI 1.68 to 1.94) at 25 g/day and 8.15 (95 % CI 7.46 to 8.91) at 100 g/day; for cirrhosis mortality, RR 2.65 (95 % CI 2.22 to 3.16) at 25 g/day and 16.38 (95 % CI 13.81 to 19.42) at 100 g/day. Supportive sex-stratified evidence suggested higher risk in women at the same intake (e.g., at 40 g/day, RR 9.35 [95 % CI 7.64 to 11.45] in women vs 2.82 [95 % CI 2.53 to 3.14] in men), indicating that both volume and sex modify liver risk [10,30].

Q11. How is alcohol associated with cancer incidence and mortality, including site-specific outcomes?

Across 139 cohort studies, all-cancer incidence increased from RR 1.08 (95 % CI 1.04 to 1.12) at 12.5–24.9 g/day to RR 1.39 (95 % CI 1.29

Table 3
Evidence at a glance: protocol-defined research questions (n = 37) mapped to 7 thematic domains. Detailed question-level extraction and reported synthesis titles underpinning this executive summary are provided in Supplementary Tables S2 and S4–S10.

Domain	RQ(s)	Key message	Direction	Anchor appraisal profile	Anchor study IDs
Domain 1 — Epidemiology, measurement and trends	Q1; Q2; Q3; Q4; Q5	Describes surveillance indicators (per-capita consumption, HED indicators, alcohol-attributable burden) and methodological issues (measurement validity) and inequalities.	Context / mapping	High, Critically low	FT046; FT028; FT043
Domain 2 — Acute and social harms	Q6; Q7; Q8; Q9	Synthesises evidence on acute harms (injuries/trauma, road traffic, social cognition relevant to interpersonal harm, intoxications/poisonings) in relation to alcohol quantity and acute pattern (incl. HED).	Higher intake/pattern → ↑ acute harms	High, Critically low	FT047; FT022; FT021; FT046
Domain 3 — Major chronic diseases (organ-specific)	Q10; Q11; Q12; Q13; Q14	Maps chronic health risks across major organ systems (liver, cancer, cardiovascular, neurocognitive, mental health), highlighting vulnerable groups and clinically relevant endpoints.	Higher intake/pattern → ↑ chronic harms	Low, Critically low	FT010; FT020; FT006; FT001; FT014; FT013
Domain 4 — Dose-response, thresholds, patterns and impact of reduction	Q15; Q16; Q17; Q18; Q19; Q20	Summarises dose–response shapes, threshold debates and the role of heavy episodic drinking; includes evidence on whether reducing consumption/pattern improves outcomes.	Less intake/pattern → ↓ risk (overall); thresholds debated	Low, Critically low	FT012; FT020; FT007; FT019; FT037
Domain 5 — Sensitive subgroups and precautionary messages	Q21; Q22; Q23; Q24	Provides precautionary synthesis for sensitive groups (young adults, pregnancy, cardiometabolic and liver vulnerability) to support risk communication.	Precaution: lower is safer	Low, Critically low	FT004; FT049; FT018; FT029
Domain 6 — Clinical implications: screening, brief interventions and referral	Q25; Q26; Q27; Q28; Q29; Q30; Q31	Summarises test accuracy for screening tools and effectiveness of brief and digital interventions, including referral and implementation strategies in clinical settings.	Interventions → ↓ consumption/pattern	High, Low, Critically low	FT003; FT048; FT002; FT023; FT009; FT044
Domain 7 — High-impact population policies and implementation	Q32; Q33; Q34; Q35; Q36; Q37	Summarises population-level policies (pricing/taxation, availability, marketing restrictions, labelling/warnings, drink-driving) and implementation determinants.	Policies → ↓ consumption/harms (depends on enforcement)	High, Low, Critically low	FT032; FT016; FT015; FT042

QA labels are tool-specific and should not be interpreted as directly comparable across AMSTAR 2, AACODS, and JBI.

to 1.49) at ≥50 g/day, whereas the estimate at 0.01–12.4 g/day (RR 1.02; 95 % CI 0.99 to 1.04) did not clearly indicate excess overall risk. The more consistent low-dose signal was site-specific, with increased risks already evident for breast, oesophageal, colorectal and prostate cancer; the quantitative core of this evidence is incidence rather than cancer mortality [31].

Q12. How is alcohol associated with hypertension and ischaemic stroke, and what broader cardiovascular issues remain controversial?

The strongest quantitative evidence in the included corpus concerned hypertension and ischaemic stroke. Using 12 g/day as the reference, hypertension risk was lower at 0 g/day (RR 0.89; 95 % CI 0.84 to 0.94) and increased at 24 g/day (RR 1.11; 95 % CI 1.07 to 1.15) and 48 g/day (RR 1.33; 95 % CI 1.18 to 1.49); for ischaemic stroke, moderate intake was associated with RR 0.87 (95 % CI 0.83 to 0.92) and heavy intake with RR 1.31 (95 % CI 1.19 to 1.44) versus non-drinking. These findings support endpoint-specific heterogeneity, but the quantitative core of this RQ is hypertension and ischaemic stroke rather than the full CVD spectrum [5,32].

Q13. How is alcohol associated with neurocognitive decline and dementia?

In dose–response meta-analysis, dementia risk was slightly lower at 1–17.5 g/day (RR 0.92; 95 % CI 0.88 to 0.96) but higher above 17.5 g/day (RR 1.23; 95 % CI 1.09 to 1.35) versus abstainers. An IPD meta-analysis in adults aged >60 years similarly found lower dementia incidence in light-to-moderate drinkers (HR 0.78; 95 % CI 0.70 to 0.87), but this apparent J-shaped association should be interpreted cautiously because residual confounding, reverse causation and healthy-drinker selection remain plausible at low intakes [33,34].

Q14. What is the dose–response relationship between alcohol use and death by suicide?

In dose–response meta-analysis, suicide risk increased with average alcohol intake relative to lifetime abstention: at 10 g/day, RR 1.11 (95 % CI 1.05 to 1.18) in men and RR 1.64 (95 % CI 1.07 to 2.51) in women; at 50 g/day, RR 1.71 (95 % CI 1.25 to 2.33) in men and RR 11.75 (95 % CI 1.38 to 100.33) in women. The direct quantitative evidence here concerns death by suicide, with particularly imprecise estimates for women at higher exposure levels [35].

Domain 4 – Dose–response, thresholds and methodological controversies

Q15. For all-cause mortality, is there a safe threshold or an apparent protective effect at low doses?

Across 107 cohort studies, low-volume drinking was not associated with lower all-cause mortality in higher-quality cohorts that excluded former and occasional drinkers from the abstainer group (RR 0.98; 95 % CI 0.87 to 1.11). By contrast, lower-quality studies reported an apparent protective association (RR 0.84; 95 % CI 0.79 to 0.89), indicating that the impression of a “safe” or beneficial low-dose zone is highly sensitive to study design and reference-group definition [36].

Q16. Is cancer risk increased even at low levels of alcohol consumption?

Yes, but the signal is site-specific rather than universal. Compared with 0 g/day, light drinking (0.01–12.4 g/day) was associated with higher risk of breast cancer (RR 1.05; 95 % CI 1.04 to 1.07), oesophageal cancer (RR 1.39; 95 % CI 1.10 to 1.75), colorectal cancer (RR 1.04; 95 % CI 1.02 to 1.07), and prostate cancer in men (RR 1.05; 95 % CI 1.01 to 1.09) [31].

Q17. How robust are apparent cardioprotective effects after confounding and bias are addressed, including through genetic evidence?

Across 70 Mendelian randomisation studies, there was no support for a causal cardioprotective effect of alcohol. Instead, MR evidence

suggested that higher genetically predicted alcohol use is associated with increased cardiometabolic risk, including hypertension (OR 1.28; 95 % CI 1.18 to 1.39) and coronary artery disease (OR 1.38; 95 % CI 1.10 to 1.74) per 1-SD increase in alcohol use, reinforcing the view that apparently protective associations in conventional observational studies are likely confounded [16].

Q18. At the same average alcohol intake, does drinking pattern matter (daily versus *non-daily)?*

Yes, at least for liver outcomes. At the same weekly alcohol volume, daily drinking was associated with higher cirrhosis risk than non-daily drinking (men RR 1.71; 95 % CI 1.23 to 2.23; women RR 1.56; 95 % CI 1.39 to 1.74), indicating that pattern adds risk beyond average volume alone [37].

Q19. Which analytic choices and biases most strongly shift conclusions towards "benefit" rather than "harm"?

The most influential were the composition of the abstainer reference group and susceptibility to reverse causation. When former and occasional drinkers were excluded, low-volume drinking no longer showed a mortality benefit (RR 0.98; 95 % CI 0.87 to 1.11), whereas bias-prone analyses suggested protection (RR 0.84; 95 % CI 0.79 to 0.89); triangulation from Mendelian randomisation further argues against a causal protective effect [16,36].

Q20. Does reducing alcohol consumption improve drinking outcomes and selected downstream health outcomes in practice?

Reduction-oriented interventions consistently improved consumption outcomes, but most trials reported changes in drinking rather than hard clinical or social endpoints. In meta-analysis, the reduction in alcohol intake was small but significant (SMD −0.08; 95 % CI −0.14 to −0.03); complementary observational evidence suggests that stopping drinking may lower selected disease risks, such as ER-positive breast cancer (RR 0.88; 95 % CI 0.79 to 0.98), but the evidence base for mortality, hospitalisation or broad social outcomes remains limited [38–40].

Domain 5 – Sensitive subgroups and precautionary messages

Q21. In young adults, how did the COVID-19 pandemic affect alcohol consumption and drinking patterns, and which subgroups were most affected?

Across 28 observational studies, alcohol use often decreased during periods of restriction, but increases were more likely among young adults with heavier pre-pandemic drinking, psychological distress, loneliness or other baseline vulnerabilities. The overall picture is therefore one of divergent trajectories by baseline risk rather than a uniform pandemic effect [41].

Q22. In pregnancy, which outcomes are associated with low-to-moderate prenatal alcohol exposure, and how certain are the estimates?

Compared with abstinence, light prenatal exposure (≤32 g/week) was associated with a small increase in small-for-gestational-age births (OR 1.08; 95 % CI 1.02 to 1.14), but this estimate was largely driven by one large study. Evidence for preterm birth (OR 1.10; 95 % CI 0.95 to 1.28) and birth weight (MD −13.5 g; 95 % CI −30.3 to 3.3) was imprecise or heterogeneous, supporting a precautionary rather than reassuring interpretation [42].

Q23. In adults with cardiometabolic vulnerability, how are alcohol use and BMI associated with type 2 diabetes risk?

Compared with lifetime abstention, the lowest type 2 diabetes risk in women was observed around 16 g/day (RR 0.69; 95 % CI 0.64 to 0.74), with attenuation of the apparent protection above about 49 g/day (RR 0.82; 95 % CI 0.68 to 0.99); no statistically significant dose–response relationship was observed in men. BMI modified this association, with the apparent protective signal reported mainly in women with BMI ≥25 kg/m^2 and not clearly in men or normal-weight women [43].

Q24. In adults with hepatic vulnerability, how is alcohol use associated with outcomes in chronic hepatitis C, with MASLD and other chronic liver conditions considered narratively?

The clearest pooled evidence concerned chronic hepatitis C. In that population, cirrhosis risk increased by 11.3 % per additional drink/day (β=0.00898 on the log-OR scale), supporting a dose–response association between alcohol use and fibrosis progression. Within the included evidence, directly pooled estimates were HCV-specific, whereas evidence for MASLD was more limited and contextual [44].

Domain 6 – Screening, brief interventions and clinical practice

Q25. Which screening instruments and cut-offs best identify unhealthy alcohol use in clinical practice?

In hospital screening studies, AUDIT at a cut-off ≥4 showed sensitivity 0.93 and specificity 0.78 for alcohol abuse in emergency settings, and ultra-brief tools such as AUDIT-C and RAPS4-QF also performed well. For broader adult screening, an AUDIT score ≥8 increased the likelihood of DSM-5 alcohol use disorder (summary LR 6.5; 95 % CI 3.9–11), but optimal cut-offs varied by setting and target severity [45,46].

Q26. In primary care, does screening and brief intervention reduce drinking and heavy episodic drinking?

In primary care, brief intervention versus minimal/no intervention reduced alcohol consumption at about 12 months by −20 g/week (95 % CI −28 to −12), with only very small reductions in HED frequency (MD −0.08 episodes/week; 95 % CI −0.14 to −0.02). These data support SBI as a pragmatic preventive tool, although hard clinical outcomes were infrequently reported [17].

Q27. In trauma and emergency-care settings, does e-SBI reduce problematic drinking compared with usual care?

The most direct quantitative evidence came from trauma settings. In 4 RCTs (N = 2641), e-SBI versus usual care improved transition away from problematic alcohol consumption at 6 months (μ=1.31; 95 % CrI 0.18 to 1.89) and 12 months (μ=1.02; 95 % CrI 0.25 to 1.45). Evidence for repeat trauma, hospital utilisation or other hard outcomes remained limited, so this RQ is best interpreted as supporting trauma/ED e-SBI rather than all hospital brief interventions [21].

Q28. In at-risk adults, are digital brief interventions effective in reducing hazardous or harmful drinking?

Across 201 RCTs (N = 94,753), digitally delivered interventions reduced consumption at 6 months versus assessment-only control (MD −14 g/week; 95 % CI −22 to −6), but practitioner-delivered interventions achieved larger reductions (MD −28 g/week; 95 % CI −37 to −18). Supportive IPD evidence showed that internet interventions reduced drinking by about 5.02 standard units/week and increased treatment response (OR 2.20; 95 % CI 1.63 to 2.95), indicating that digital approaches are effective but generally less potent than clinician-delivered ones [19,47].

Q29. Which intervention "dose" (duration/intensity) and components make brief interventions most effective?

Higher-intensity practitioner-delivered interventions achieved larger early reductions in drinking than digital approaches at 1 month (MD −23 g/week; 95 % CI −43 to −2) and 6 months (MD −14 g/week; 95 % CI −25 to −3), but this advantage was no longer evident by 12 months. Evidence for additional benefit from extended or booster formats over standard brief intervention was uncertain [17,19].

Q30. In adults with risky substance use identified in healthcare settings, does e-SBIRT improve substance-use outcomes and referral engagement?

Across 10 studies, e-SBIRT reduced past-week drinking frequency at 1 month (SMD −0.23; 95 % CI −0.33 to −0.14), but showed no clear advantage for HED episodes at 6 months, abstinence or most other treatment outcomes. Referral uptake, engagement and continuity-of-care outcomes were reported infrequently and inconsistently, so firm conclusions about active referral pathways cannot yet be drawn [48].

Q31. What barriers and facilitators influence implementation of SBI/e-SBI in routine primary care, and which strategies appear most promising for increasing delivery?

Across 84 studies, implementation research identified 660 barrier data items and 253 facilitator data items across 46 themes. The most frequent barriers were lack of time, limited training/skills, low confidence and suboptimal practice organisation, whereas facilitators included training, organisational support, feedback and workflow tools; this evidence is stronger for identifying determinants of implementation than for proving that any single strategy reliably improves adoption or sustainability across settings [49].

Domain 7 – Population-level policies and implementation

Q32. How effective are pricing and taxation policies, including minimum unit pricing, in reducing alcohol use and harms?

Across 10 systematic reviews on pricing and taxation within an umbrella review of 42 reviews, price/tax increases—including minimum unit pricing—were directionally associated with lower alcohol consumption and alcohol-related harms, but effects were heterogeneous and often not quantified. The overall judgement was therefore "possibly beneficial", with stronger support for the direction of effect than for a single pooled magnitude [22].

Q33. How effective are availability policies, particularly trading hours and outlet density, in reducing alcohol use and harms?

Availability policies showed mixed quantitative evidence overall: in the umbrella review, evidence for trading-hour restrictions was inconclusive, whereas higher outlet density was associated with greater alcohol use and reducing outlet density was judged possibly beneficial. A separate systematic review of interrupted time series studies found that extending on-license trading hours was typically followed by increases in assault, unintentional injury or drink-driving offences, whereas restricting hours was typically followed by decreases in assault and hospitalisations [22,50].

Q34. How effective are alcohol marketing restrictions in reducing alcohol use and harms in the general population?

Across 11 studies of marketing restrictions, six found no effect on alcohol use; among the four studies at low/moderate risk of bias, findings were mixed (one reduction, one null, and two increases in consumption). The available evidence therefore remains limited and heterogeneous rather than clearly supportive of a measurable consumption reduction [51].

Q35. Do alcohol warning labels and health messages change knowledge and attention, and do they also change drinking-related behaviours?

Across 77 studies, warning labels and health messages consistently increased health knowledge and attention compared with standard labels or no warnings. However, effects on purchasing intentions, product choice and actual consumption were generally small and context-dependent, so cognitive/informational effects are better supported than behavioural change [52].

Q36. Which drink-driving countermeasures reduce crashes and mortality?

Across drink-driving countermeasures, evidence was mixed overall. Mass-media campaigns alone did not reduce alcohol-related injuries or fatalities (RR 1.00; 95 % CI 0.94 to 1.06), whereas enforcement intensity appeared more promising: each 1 % increase in DUI arrests was associated with about 11 % fewer alcohol-related fatal crashes up to a saturation point. Taken together, the evidence is more convincing for sustained enforcement than for stand-alone communication campaigns [22,53].

Q37. Which systems, governance, capacity, and industry-related factors shape implementation of alcohol policies?

The WHO Global Alcohol Action Plan identifies major implementation constraints at the system level, notably limited political will and capacity, weak accountability and resourcing, and alcohol-industry interference. It therefore supports multisectoral governance, monitoring, enforcement and explicit safeguards against conflicts of interest; this is best interpreted as authoritative policy-implementation guidance, supplemented—not replaced—by the broader review evidence on policy effectiveness [22,53,54].

4. Discussion

This umbrella systematic review synthesised 49 included records (46 systematic reviews/meta-analyses, two World Health Organization reports, and one cross-sectional study), addressing 37 pre-specified research questions across seven domains. Across most outcomes, the direction of association converged on a pragmatic message: lower alcohol consumption was generally associated with lower risk. Many harms were evident well below conventional 'heavy drinking' thresholds, particularly for injuries and several chronic disease endpoints. When apparent benefits of light-to-moderate drinking were reported, bias-aware evaluation consistently highlighted susceptibility to reverse causation and abstainer misclassification, favouring a cautious 'less is better' interpretation over a threshold-based 'safe dose' narrative [1,16,36,55].

From an internal medicine perspective, the findings are relevant to both acute presentations and chronic multimorbidity. Worldwide, alcohol contributes substantially to avoidable morbidity and mortality, and WHO reporting underscores its role as a major driver of injuries, non-communicable diseases and mental health harms [1]. Importantly, alcohol-related harm is socially patterned: a systematic review and meta-analysis reported a dose–response relationship between socioeconomic deprivation and alcohol-attributable mortality risk [3]. This pattern aligns with the "alcohol harm paradox", whereby more deprived groups experience disproportionate alcohol-attributable harm despite similar or even lower average consumption, plausibly due to clustering of comorbidity and risk factors, more harmful drinking patterns, and reduced access to preventive and treatment services. In routine practice, the internist often observes this disproportionate burden through admissions for alcohol-related liver disease, trauma, infections and

decompensated chronic disease among vulnerable populations [3,56].

Acute harms remained prominent. Meta-analytic evidence showed that alcohol use in the hours before injury was associated with substantially higher injury odds, with risk increasing further at larger acute amounts in studies that reported dose categories [26]. Among non-fatally injured motor vehicle drivers, the pooled prevalence of alcohol positivity was 16.6 %, indicating ongoing relevance for emergency, trauma and prevention services [27]. Experimental evidence suggests that acute intoxication impairs social cognition, including emotion recognition and theory of mind, providing a plausible mechanistic link to conflict and risk-taking [28]. A hospital-based cross-sectional study further illustrated service impact, with alcohol-related conditions accounting for a substantial proportion of emergency admissions and bed-days [29,57].

Liver-related outcomes showed strong and clinically intuitive dose-response patterns. Sex-stratified evidence indicated that women develop cirrhosis at lower levels of average intake than men, with non-linear increases in risk as consumption rises; for example, at 40 g/day the relative risk of cirrhosis morbidity was markedly higher in women (RR 9.35) than in men (RR 2.82) compared with lifetime abstention [10]. Alcohol also accelerated progression of chronic liver disease in the context of hepatitis C, and exposure was associated with worse morbidity and mortality in established cirrhosis [30,44]. Importantly, drinking pattern may matter in addition to volume: at the same weekly alcohol intake, daily drinking was associated with higher cirrhosis risk than non-daily drinking, supporting counselling that addresses both average amount and pattern [37]. In MASLD, one review reported apparently lower prevalence among light drinkers; however, this signal attenuated when former drinkers were removed from the abstainer group and when risk of bias was considered [9,36]. Overall, the liver evidence supports early, proactive reduction advice in patients with metabolic risk factors, viral hepatitis or other liver vulnerability, without assuming a safe level in these groups [9,10,30,37,44].

Alcohol was consistently associated with cancer risk, with evidence of inter-individual susceptibility and some signals at low levels. A systematic review and meta-analysis reported increased cancer risk associated with alcohol flushing syndrome, highlighting vulnerability related to acetaldehyde metabolism [58]. In Asia, reductions in consumption were associated with lower oesophageal cancer morbidity and mortality, supporting primary prevention through reduced intake [59]. Meta-analyses also reported positive associations between alcohol and thyroid and prostate cancer, and the combined exposure to alcohol and smoking showed a dose-dependent increase in overall cancer risk [60–62]. For breast cancer, cessation and risk appeared to vary by hormone receptor status [40]. Importantly, a systematic review of Mendelian randomization studies did not support broad protective effects of low-dose alcohol and instead supported causal associations with multiple cancers and cardiovascular outcomes, reinforcing caution in interpreting “protective” findings from conventional observational designs [16].

Cardiometabolic findings were more heterogeneous, reflecting confounding, heterogeneity in reference groups and outcome-specific risk functions. For ischaemic stroke, a meta-analysis suggested lower risk for light-to-moderate drinking compared with abstinence, whereas higher intake was associated with increased risk [32]. In contrast, hypertension showed a more consistently monotonic dose-response, with increased risk above relatively low levels of consumption [5]. Evidence on type 2 diabetes suggested important effect modification by body mass index and study design, arguing against a simple cardiometabolic 'benefit' narrative [43]. Bias-aware syntheses emphasised that the choice of abstainer reference group, residual confounding and reverse causation can materially alter conclusions about low-dose drinking, and Mendelian randomisation evidence does not support a causal cardioprotective effect [16,36]. Complementing these epidemiologic syntheses, echocardiographic studies in heavy-drinking patients have documented markers of early alcoholic cardiomyopathy [63]. In this context, global comparative risk assessment work has estimated that the level of alcohol consumption that minimises overall health loss across outcomes is approximately zero drinks per week, reinforcing that any putative benefit for a narrow set of outcomes should be weighed against broader harms [64]. Large individual-participant data analyses in current drinkers also suggest that risk thresholds for mortality are lower than many national low-risk guidelines, supporting conservative thresholds in clinical counselling [14].

Neuropsychiatric outcomes warrant similarly cautious interpretation. An individual-participant-data meta-analysis in older adults suggested lower dementia risk among light-to-moderate drinkers compared with abstainers, with higher risk in heavy drinkers [34]. However, a broader systematic review of alcohol exposure and cognitive outcomes reported that higher intake increases dementia risk and that associations at low levels are sensitive to confounding and exposure categorisation [33]. These apparently J-shaped patterns are compatible with reverse causation and abstainer misclassification, including sick-quitter effects [36,55]. A separate dose-response meta-analysis on alcohol consumption and death by suicide reported increasing risk at higher intakes, with steeper dose-related increases in women at comparable levels of exposure [35].

Clinical implications for internal medicine and primary care extend beyond counselling about 'units'. Validated instruments for hospital and primary care settings are available, and a Rational Clinical Examination systematic review provides an evidence-based approach to bedside identification of alcohol use disorder [45,46]. Brief interventions in primary care reduce alcohol consumption among hazardous drinkers, supporting their use as part of routine preventive care [17]. Electronic and digitally delivered interventions may extend reach in non-treatment-seeking populations and trauma-linked pathways, although effects are generally modest and implementation barriers remain substantial [19,21,47,49,65]. Consistent with preventive guidance, structured screening coupled with brief behavioural counselling should be routine for unhealthy alcohol use in adults, with clear referral pathways for more severe disorders [66]. For patients with established alcohol use disorder, the present umbrella synthesis should be interpreted alongside dedicated pharmacotherapy reviews and consensus statements that sit outside the retained Q1-Q37 corpus. These external sources support oral naltrexone and acamprosate as first-line pharmacotherapies and, in some European settings, sodium oxybate; they also suggest that selected off-label agents, including topiramate, gabapentin and baclofen, may be considered for carefully chosen patients, although the supporting evidence is more limited and heterogeneous. Such pharmacotherapy should be integrated with psychosocial care, and nutritional support - including thiamine when clinically indicated - remains an important adjunct in relevant patients [67–75].

At the population level, the synthesis supports a graded rather than uniform policy message. Umbrella and systematic review evidence suggested directionally beneficial effects for pricing and taxation measures, including minimum unit pricing, and for some availability restrictions, particularly where changes were substantial and sustained [22,50]. By contrast, evidence for marketing restrictions and warning labels was more limited or heterogeneous, whereas drink-driving measures appeared more effective when enforcement was sustained and intensive [51–53]. WHO's global alcohol action plan nevertheless provides an internationally endorsed implementation framework, emphasising structural 'best buys' such as pricing measures, availability restrictions and marketing controls [54]. For the clinician, these policy levers matter because they shape the baseline risk environment in which individual counselling and treatment operate [1,54].

This umbrella review has strengths that increase confidence in its overall message. It was guided by pre-specified research questions and eligibility criteria documented in a protocol archived on OSF, employed structured overlap management to reduce redundancy, and focused on clinically actionable questions relevant to internal medicine practice. At the same time, several limitations should temper interpretation of

precise thresholds or causal claims. The included corpus was methodologically heterogeneous and comprised not only systematic reviews/meta-analyses but also two WHO documents and one primary cross-sectional study, retained because not all questions were adequately covered by contemporary review evidence. Across reviews, AMSTAR 2 confidence was often low or critically low; although some downgrading reflected reporting/transparency deficits, other reviews had limitations more likely to affect effect estimates. Many primary studies relied on self-reported alcohol measures that are vulnerable to under-reporting, changes in intake over time and misclassification of former drinkers as abstainers [13,36]. In addition, some endpoints required pre-2015 sentinel syntheses when no newer definitive review existed, policy evidence was largely observational and context-dependent, and some residual overlap among primary studies across reviews is unavoidable despite the anchor/support approach. English and Italian predominance may also have limited capture of some non-English evidence [16,22,36,55].

Future research should prioritise designs and measurement strategies that reduce bias in low-dose drinking estimates (e.g., improved lifetime drinking history, repeated measures, triangulation with biomarkers and genetic instruments) and should expand evidence on vulnerable clinical subgroups commonly managed in internal medicine (e.g., advanced liver disease, cardiometabolic multimorbidity, and pregnancy) [16,42]. Pragmatic trials and implementation evaluations in hospital and outpatient settings are also needed to determine whether reductions in alcohol consumption translate into hard clinical and service outcomes, and to clarify how screening, brief interventions and pharmacotherapy can be integrated into routine pathways at scale, particularly in socioeconomically disadvantaged populations where the alcohol harm paradox is most evident [3,56,66–68,75–76]. Emerging work on precision treatment for alcohol use disorder - including biomarker-informed and craving-domain approaches - may help identify which patients are most likely to respond to specific interventions and sustain a lower-risk trajectory [77,78]

In conclusion, across most outcomes and settings, lower alcohol consumption and avoidance of heavy episodic drinking were associated with lower risk, whereas apparent low-dose benefits were not robust to bias-aware analyses. This overarching message should be interpreted as a direction-of-evidence conclusion rather than as uniform high-certainty evidence across all endpoints. For clinicians, this supports a pragmatic counselling approach centred on reduction, supported by opportunistic screening, brief intervention and clear treatment pathways for alcohol use disorder; at the population level, structural policies remain important complements to clinical prevention.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Members of the “Alcohol Research” Group: Mariangela Antonelli, Alberto Tosoni, Claudia Tarli, Francesco Mancarella, Rachele Caprari, Giorgia Spagnolo, Marialisa Mastrangioli, Emilio Palmieri, Matteo Sirignano, Domitilla Picozzi, Umberto Russo, Irene Orzella, Gabriele Angelo Vassallo, Giovanni Camardese.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2026.106837.

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