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Update of Canada's Low-Risk Alcohol Drinking Guidelines: Evidence Review Technical Report

August 2022

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This document was published by the Canadian Centre on Substance Use and Addiction (CCSA).

Suggested citation: Levesque, C., Sanger, N., Edalati, H., & Paradis, C. (2022). *Update of Canada's Low-Risk Alcohol Drinking Guidelines: Evidence review technical report*. Ottawa, Ont.: Canadian Centre on Substance Use and Addiction.

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Production of this document has been made possible through a financial contribution from Health Canada. The views expressed herein do not necessarily represent the views of Health Canada.

This document can also be downloaded as a PDF at www.ccsa.ca

Ce document est également disponible en français sous le titre :

Rapport technique du projet d'actualisation des Directives de consommation d'alcool à faible risque du Canada : examen des données probantes

ISBN 978-1-77178-986-8

Table of Contents

Abbreviations

AAWC	Australian Alcohol Working Committee
ADOLOPMENT	Adaptation, Adoption, De Novo Development
AMSTAR	A measurement tool to assess systematic reviews
CCSA	Canadian Centre on Substance Use and Addiction
CI	Confidence interval
ERWG	Evidence Review Working Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazards ratio
LRDG	Low-Risk Alcohol Drinking Guidelines
PECO	Population, Exposure/Comparison, Outcome
OR	Odds ratio
RoB	Risk of bias
RR	Relative risk
SGBA+	Sex and gender-based analysis
SR	Systematic review

Executive Summary

Key Messages

- Between January 2017 and February 2021, 5,915 systematic reviews on the effects of alcohol use on physical health, mental health and social harms were published internationally.
- Two independent investigators from the Evidence Review Working Group followed a strict screening and quality assessment process using GRADE, an internationally recognized methodology to review the evidence.
- A total of 16 systematic reviews were retained and considered most appropriate to inform the development of updated Low-Risk Alcohol Drinking Guidelines.
- High quality systematic reviews about alcohol and mental health and social issues such as violence are greatly in need. Not a single high quality systematic review on these topics was identified.
- With a view to refining and improving guidance on alcohol and health, more work on establishing causality between alcohol use and physical health outcomes such as various cancers is needed.
- The updated guidelines will inform people living in Canada so that they can make healthy choices about their consumption of alcohol.

This report was produced by the Evidence Review Working Group (ERWG) of the Canadian Centre on Substance Use and Addiction (CCSA) for the project to update Canada's Low-Risk Alcohol Drinking Guidelines (LRDGs). Its purpose is to review and update the evidence on the effects of alcohol use on physical health, mental health and social harms. This review forms the basis for further analyses and modelling that will address this project's research questions and inform the development of updated guidelines. It is intended for members of the LRDG Scientific Expert Panels and those interested in understanding in detail the process followed in developing the new guidelines, such as policy makers, healthcare professionals, and alcohol scientists.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE)-Adaptation, Adoption, De Novo Development (ADOLOPMENT) approach was used to produce the report, informed by the already existing guidelines from Canada, the United Kingdom and Australia, with evidence updated for the period of January 2017 to February 2021. For more details see *Update of Canada's Low-Risk Alcohol Drinking Guidelines: Evaluation of Selected Guidelines* and *Update of Canada's Low Risk Alcohol Drinking Guidelines: Source Guidelines*, both available with further documentation on the LRDG Project 2022 web page.

A total of 5,915 systematic reviews on alcohol, health and harms were initially retrieved. A subset of 780 systematic reviews were screened for title and abstract and 239 systematic reviews were subsequently screened for full-text eligibility. In the end the ERWG found that 16 systematic reviews fulfilled all the inclusion criteria for the project and recommended them for use in the mathematical modelling. Specifically, two reviews focus on the short-term health risks and benefits of alcohol consumption (i.e., road injury, and intentional and unintentional injuries). The remaining fourteen reviews examine outcomes associated with the long-term health risks and benefits of alcohol consumption. These include liver cirrhosis, ischæmic heart disease, hypertensive heart disease, breast cancer, liver cancer, pancreatitis, lower respiratory infections, epilepsy, ischæmic stroke, intracerebral haemorrhage, subarachnoid hemorrhage, atrial fibrillation, colon and rectum cancers,

diabetes mellitus, larynx cancer, mouth and oropharynx cancers, esophagus cancer, and tuberculosis. The quality of these systematic reviews was assessed with the international standards tools AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) and GRADE. Systematic reviews were also evaluated for the inclusion of sex- and gender-based analysis.

The strategy enabled the ERWG to identify the latest, most high-quality evidence available that examines the relationship between alcohol consumption and physical health outcomes. Through this work, the ERWG also identified areas (e.g., mental health, violence) where high-quality systematic reviews are currently missing and for which the LRDG experts agreed to commission additional reviews to complete the LRDG update.

Introduction

Canada's first Low-Risk Alcohol Drinking Guidelines (LRDGs) were published in November 2011 (Butt et al., 2011). They provided people living in Canada with advice on how to minimize the relative long-term risk of serious diseases caused by the consumption of alcohol over a number of years, and the relative short-term risk of injury or acute illness due to the overconsumption of alcohol on a single occasion (Stockwell et al., 2012). Additionally, they provided specific recommendations for situations and individual circumstances that are particularly hazardous and for which abstinence or only occasional light intake was advised.

The 2011 LRDGs have been a significant step in disseminating consistent information and messaging to minimize the risks associated with drinking alcohol. They have been the cornerstone for a variety of health promotion, prevention and education initiatives across the country (Paradis, 2016). Since 2011, many studies have been produced to establish that the consumption of alcohol often results in physical and social harms. Updating the Canadian LRDGs for the first time in more than 10 years is highly warranted.

As noted in the first LRDG technical report (Butt et al., 2011), there were important limitations with the research evidence used in developing the 2011 LRDGs. When publishing the report, the working group noted the under-reporting of personal alcohol use in self-reported surveys, the failure to take account of heavy drinking episodes, the misclassification of people who used to consume alcohol and people who occasionally drink alcohol as lifetime abstainers, and the failure to control for the confounding effects of personality and lifestyle factors independent of alcohol. As ten years have passed since the release of the original LRDGs, it is timely to review and update the LRDGs to ensure they reflect the most current and high-quality evidence.

During the past 10 years, there have been significant developments in knowledge about alcohol-related mortality and morbidity (International Agency for Research on Cancer, 2012; Lu et al., 2017; Rehm et al., 2017a). Substantial percentages of deaths due to cancer, digestive conditions and injuries have been reported by people living in Canada who complied with the LRDGs (Sherk et al., 2020). Moreover, evolving research has demonstrated that consuming alcohol contributes to social harms, such as injury and violence from others (Laslett et al., 2019). The United Kingdom (UK Chief Medical Officers, 2016) and Australia (National Health and Medical Research Council, 2020) recently reviewed new evidence on alcohol and health, and released updated guidelines with weekly limits significantly different from the 2011 Canadian LRDGs (Butt et al., 2011).

In early 2019, representatives of the Canadian Centre on Substance Use and Addiction (CCSA), Health Canada and the Public Health Agency of Canada and members of the 2011 LRDG working group engaged in discussions about updating the guidelines. In July 2020, Health Canada confirmed funding to CCSA to update the guidelines. CCSA established an Executive Committee to provide project oversight and advice, three Scientific Expert Panels to analyze and assess the evidence in specific areas, and one Evidence Review Working Group (ERWG) tasked with the preparation and technical aspects of the guideline's development.

The purpose of this report, prepared by CCSA's ERWG, is to review and update the evidence on the effects of alcohol use on physical health, mental health, and social harms. This review is primarily intended for Scientific Expert Panels members and will form the basis for further analyses and modelling that will address this project's research questions and inform the development of updated guidelines.

Methods

Defining Research Questions

The LRDG update is informed by one general research question: **to minimize the risk of experiencing alcohol-related physical and mental health issues and social harms, which level or pattern of use of alcohol should be recommended to people living in Canada?**

With the view to guiding the identification of systematic reviews, facilitating interpretation of the findings and informing the formulation of recommendations, three more specific research questions were developed. Using the PECO (Population, Exposure/Comparison, Outcome) criteria, these questions specify 1) the target populations for the exposure; 2) the exposures and comparators being considered; and 3) the outcomes that are most relevant to assess (for more information, see Canadian Centre on Substance Use and Addiction, 2021a).

1. What are the short-term risks and benefits (physical and mental health, and social impact) associated with varying levels of alcohol consumption (including no alcohol use), in different contexts, associated with a single episode of drinking in the general population?
2. What are the long-term risks and benefits (physical and mental health, and social impact) associated with varying levels and patterns of alcohol consumption (including no alcohol consumption) in the general population?
3. What are the risks and benefits (physical and mental health, and social impact) associated with varying levels and patterns of alcohol consumption (including no alcohol consumption) by women who are pregnant or breastfeeding, for fetal, infant and child development?

GRADE-ADOLOPMENT Approach

For this project, the internationally recognized Grading of Recommendations Assessment, Development and Evaluation (GRADE)-Adaptation, Adoption, De Novo Development (ADOLOPMENT) approach (Schünemann et al., 2017) for guideline development was used to ensure that the latest and best scientific evidence is correctly and appropriately collected, analyzed, interpreted and reported in a transparent manner.

An initial step of any GRADE-ADOLOPMENT project is to search for recent and relevant guidelines that cover the same topics and questions that the new guidelines aim to address. For this project, CCSA's mandate from Health Canada required that the update guidelines be informed by the 2011 Canadian LRDGs (Butt et al., 2011), the 2016 guidelines from the United Kingdom (UK Chief Medical Officers, 2016) and the 2020 Australian Guidelines to Reduce Health Risks from Drinking Alcohol (National Health and Medical Research Council, 2020). Quality assessments of these guidelines were performed by the ERWG. With regards to methodology for identifying and selecting evidence on the risks and benefits associated with alcohol consumption, the Australian guidelines received top ratings (for more information, see Canadian Centre on Substance Use and Addiction, 2021b). This led to the recommendation to adapt the results of systematic searches and associated evaluations conducted by the Australian Alcohol Working Committee (AAWC). The current project would not start from scratch, but would build upon the high-quality work previously done by the AAWC.

Updating the Evidence

The AAWC provided clear and detailed methods for each step of their guideline development process. The following sections describe the process followed by the ERWG to update the evidence collected by the AAWC from January 1, 2007, to January 5, 2017. It is a three-step process that includes 1) the identification of systematic reviews published after the search period covered by the AAWC, and 2) the screening and 3) appraisal of the reviews.

Identification of Systematic Reviews

One evidence search was carried out for all three research questions. This method ensured that all studies, regardless of the population, the exposure (i.e., the pattern or level of alcohol use) or the outcomes, would be identified. To capture all possible outcomes associated with alcohol consumption, both risks and benefits, specific outcomes were not included as search terms.

Nine databases were searched: PubMed, PsycNET, Embase, Cochrane Library, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, International Health Technology Assessment Database, Joanna Briggs Institute, Database of Abstracts of Reviews of Effects, and Epistemonikos. The search was limited to systematic reviews and meta-analyses published from January 6, 2017, to February 17, 2021. Variations of search terms related to alcohol were used to encompass the full range of possible systematic review in this field. The detailed search strategy is presented in Table 1. A comprehensive search of the grey literature was also undertaken on sixteen websites (see Table 2).

Once the search was complete, an Information Specialist removed duplicates and articles that, based on titles and abstracts, were clearly outside of the scope of the project. The remaining articles were passed on to the ERWG for screening. Because they represent the best evidence available prior to the current literature search, the systematic reviews previously retained by the AAWC were also passed on the ERWG to go on to the next stage of the updating process: the screening.

Table 1. Detailed search strategy

Database	Search terms
Pubmed	((((((("Alcohol Drinking"[Mesh]) OR "Alcoholism"[Mesh]) OR "Alcohol-Related Disorders"[Mesh]) OR "Alcoholic Intoxication"[Mesh]) OR "Binge Drinking"[Mesh]) OR "Fetal Alcohol Spectrum Disorders"[Mesh]) or (alcohol*[Title/Abstract]) Filters applied: Meta-Analysis, Systematic Review, Humans, MEDLINE, from 2017/1/6–2021/2/17.
PsycNET	((title: (alcohol*)) OR (abstract: (alcohol*))) OR ((IndexTermsFilt: ("Alcohol Drinking Patterns") OR IndexTermsFilt: ("Binge Drinking") OR IndexTermsFilt: ("Social Drinking") OR IndexTermsFilt: ("Underage Drinking") OR IndexTermsFilt: ("Alcoholic Beverages") OR IndexTermsFilt: ("Beer") OR IndexTermsFilt: ("Liquor") OR IndexTermsFilt: ("Wine") OR IndexTermsFilt: ("Alcoholism") OR IndexTermsFilt: ("Alcoholic Psychosis") OR IndexTermsFilt: ("Acute Alcoholic Intoxication") OR IndexTermsFilt: ("Chronic Alcoholic Intoxication") OR IndexTermsFilt: ("Fetal Alcohol Syndrome"))) AND Methodology: Systematic Review OR Meta Analysis AND Peer-Reviewed Journals only AND Year: 2017 to 2021
Embase	#1 'drinking behavior'/exp OR 'alcoholic beverage'/exp OR 'alcoholism'/exp OR 'alcohol intoxication'/exp OR 'binge drinking'/exp OR 'fetal alcohol syndrome'/exp

	#2 alcohol*:ab,ti #3 #1 OR #2 #4 #3 AND (2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py) AND ('meta analysis'/de OR 'systematic review'/de)
Epistemonikos	title:(title:(alcohol*)) + Systematic reviews + Custom date range 2017 to 2021
Database of Abstracts of Reviews of Effects	Search not conducted: no new records added after March 31, 2015
Health Technology Assessment Database	Title: alcohol* + Date range: 2017–2018
International Health Technology Assessment Database	alcohol* OR drinking (All fields) + Date range: 2017–2021
Cochrane Library	alcohol* (Title, abstract, keyword) + Custom date range: January 1, 2017–February 23, 2021
Joanna Briggs Institute	alcohol in Title, Abstract or Keywords OR alcoholism in Title, Abstract or Keywords OR alcoholic in Title, Abstract or Keywords OR alcoholics in Title, Abstract or Keywords OR drinking in Title, Abstract or Keywords + Systematic review

Table 2. Search of the grey literature

Database	Search terms
Register of Australian Drug and Alcohol Research: https://catalogue.nla.gov.au/Record/2978698	Alcohol* [title]
National Drug and Alcohol Research Centre: http://ndarc.med.unsw.edu.au/	Alcohol
National Drug Research Institute: http://ndri.curtin.edu.au/	Alcohol*
Australian Centre for Addiction Research: http://www.acar.net.au/	No specific search; browsed website
National Institute of Health and Care Excellence: https://www.nice.org.uk/	alcohol*
Agency for Healthcare Research and Quality: http://www.ahrq.gov/	Alcohol*
Centers for Disease Control and Prevention: https://www.cdc.gov/	Alcohol*
World Health Organization: http://www.who.int/en/	Alcohol
National Institute on Alcohol Abuse and Alcoholism: https://www.niaaa.nih.gov/	No specific search; browsed website
International Prospective Register of Systematic: Reviews http://www.crd.york.ac.uk/PROSPERO/	MeSH DESCRIPTOR Alcohol-Related Disorders EXPLODE ALL TREES MeSH DESCRIPTOR Alcohol Drinking EXPLODE ALL TREES AND (Systematic Review OR Meta-Analysis):RT MeSH DESCRIPTOR Alcoholic Beverages EXPLODE ALL TREES AND (Systematic Review OR Meta-Analysis):RT

	MeSH DESCRIPTOR Alcoholism EXPLODE ALL TREES AND (Systematic Review OR Meta-Analysis):RT MeSH DESCRIPTOR Alcoholic Intoxication EXPLODE ALL TREES AND (Systematic Review OR Meta-Analysis):RT MeSH DESCRIPTOR Binge Drinking EXPLODE ALL TREES AND (Systematic Review OR Meta-Analysis):RT MeSH DESCRIPTOR Fetal Alcohol Spectrum Disorders EXPLODE ALL TREES AND (Systematic Review OR Meta-Analysis):RT
Health Evidence Canada: http://www.healthevidence.org/	Limit: Date = Published from 2017 to 2021 Topic Area = Addiction/Substance Use -> Alcohol Abuse/Use
U.S. Preventive Services Task Force: https://www.uspreventiveservicestaskforce.org/	alcohol*
Public Health England: https://www.gov.uk/government/organisations/public-health-england	alcohol* in Research and Statistics
Indigenous HealthInfoNet: http://www.healthinfonet.ecu.edu.au/	Browsed Alcohol and Other Drugs Knowledge Centre Alcohol
International Agency for Research on Cancer: https://www.iarc.fr/	Alcohol
World Cancer Research Fund: https://www.worldwidecancerresearch.org/	Alcohol*

Screening of Systematic Reviews

Two independent investigators from the ERWG went through the titles and abstracts of the remaining studies from the updated search to identify which systematic reviews should be assessed in full text, along with the studies already selected by the AAWC. Throughout the screening process, disagreements between the two investigators were resolved through discussions between them. Full-text screening was done in four steps, as presented in Figure 1.

Step 1: PECO and Study Design Criteria

Selected full text systematic reviews were assessed against the PECO and study design criteria. To be considered for inclusion, a study needed to be a systematic review published in either English or French with alcohol use as the main exposure of interest. Systematic reviews that did not assess at least three varying levels of alcohol use were excluded as dose–response risk ratio calculation would not be possible. Systematic reviews that only focused on one type of alcoholic beverage such as wine or beer were also excluded because in these studies, people who do not consume alcohol from a specific beverage could consume other types of alcoholic beverages. Populations deemed not relevant to the context of people living in Canada were also excluded. For example, a systematic review that focused exclusively on people living in India would be excluded because it does not reflect the multicultural context of people living in Canada. Systematic reviews had to include cohort, case–control or case-crossover studies to be eligible for inclusion. Where other types of studies were included in the systematic review, such as cross-sectional studies, the results from the cohort, case–control or case-crossover studies had to be reported separately for the review to be considered.

Step 2: Methodological Quality Criteria

For the second screening step, the remaining systematic reviews were assessed against four methodological quality criteria, modelled on the Australian approach. This was to ensure that the included systematic reviews met the threshold for minimum methodological quality. A systematic review had to meet at least two of the four criteria described below to be considered for inclusion.

1. Comprehensive literature search

   The systematic reviews had to search two or more databases, specify which ones, provide the timeframe when the search was conducted and the search strategy that was used (key words and MESH terms). Reference lists of the included primary studies also needed to be screened.

2. Characteristics of included studies in systematic reviews

   The systematic reviews had to report the age and sex of the participants and any confounding variables included in the primary studies. They also had to state and describe the exposure, comparator and study design of the included primary studies.

3. Quality assessment of included studies in systematic reviews

   The systematic reviews had to use a pre-determined quality assessment tool to review the quality of every primary study included in the review.

4. Inclusion and exclusion criteria

   The systematic reviews had to report their inclusion and exclusion criteria along with specific descriptions and rationales for the criteria. This includes the rationales for the population, exposure and outcome.

Step 3: Methods of Analysis Criteria

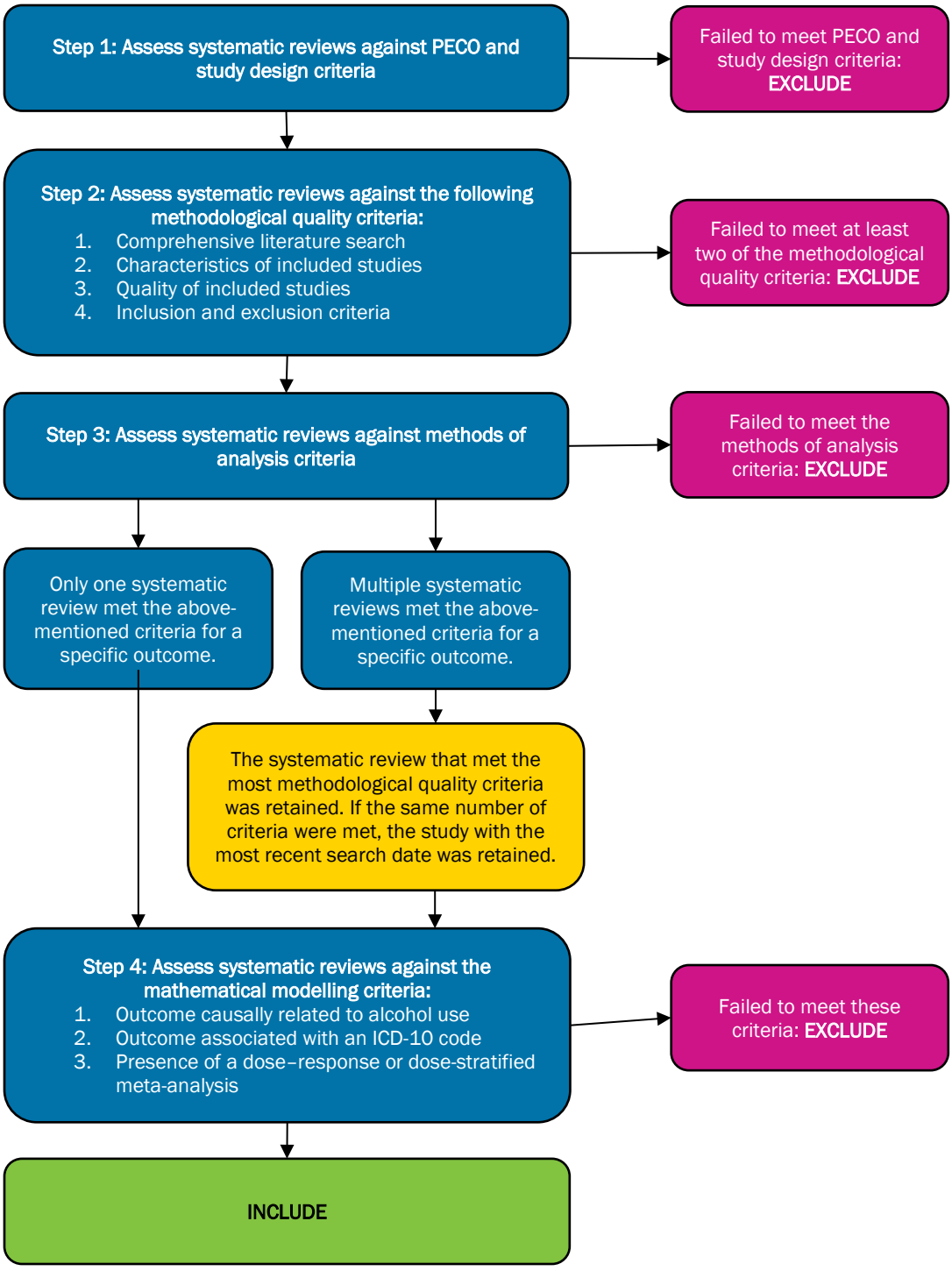
To be considered for inclusion, the systematic reviews also needed to provide a clear description and justification of the methodology used to analyze the individual studies. Analytical methods had to be sufficient to allow for reliable extraction and interpretation of the results. The use of inappropriate analytical methods led to the exclusion of a systematic review.

Systematic reviews that met all the selection criteria were then submitted to the mathematical modellers to estimate the health impact of alcohol consumption on an individual. However, as mathematical modelling only allows for one systematic review for each outcome, if there was more than one systematic review for the same outcome, the review that met the most methodological quality criteria was retained. In the case where the same number of criteria were met, the study that had the most recent search date was retained.

Step 4: Mathematical Modelling Criteria

Mathematical modellers assessed the retained systematic reviews against the following criteria: 1) the outcome is considered causally related to alcohol use as determined by the Institute for Health Metrics and Evaluation, the World Health Organization or the International Agency for Research on Cancer; 2) the outcome is associated with an International Classification of Disease, version 10 (ICD-10) code; and 3) a dose–response or dose-stratified meta-analysis of relative risks (RRs), odds ratios (ORs) and hazards ratios (HRs) is available. Systematic reviews that did not met these criteria were excluded. All the remaining systematic reviews were included in the mathematical modelling for the updated LRDGs.

Figure 1. Screening steps for selecting the included systematic review for each outcome



Appraisal of Systematic Reviews

The quality of all included systematic reviews was assessed by two independent investigators from the ERWG using A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2; Shea et al., 2017), and the Grading of Recommendations, Assessment, Development and Evaluations system (GRADE; Schünemann et al., 2013). The use of sex- and gender-based analysis (SGBA) was also appraised.

AMSTAR and GRADE Assessments

AMSTAR 2 is comprised of 16 items covering domains that can affect the validity of a systematic review such as the risk of bias, the publication bias, the literature search strategy and the appropriateness of meta-analytical methods. Each item is coded as yes, partial yes or no (for more details, see Shea et al., 2017).

The GRADE system allows a judgment to be made on the quality of evidence of the included systematic reviews. According to the GRADE system, the quality of evidence falls into one of the following categories: high, moderate, low or very low. The judgments depend on the type of study design, as randomized controlled trials typically start out with high-quality evidence and observational studies with low-quality evidence. However, it is recognized that prospective cohort studies are the best and most appropriate study design to answer PECO questions related to public health guidelines (Harder et al., 2015). Therefore, for the current project, all included systematic reviews comprised of observational studies were considered to start out as "moderate" instead of "low" quality. The quality of the evidence may be downgraded or upgraded according to eight factors (see Table 3 and the Appendix for more details). Although GRADE does not recommend upgrading levels if downgrading has occurred for an outcome, it was determined that for the purpose of the current project it was important to do so to differentiate the different levels of evidence quality. The adjustments made to GRADE followed the methodology adopted by AAWC.

Table 3. Reasons for downgrading or upgrading the quality of evidence

GRADE factor	Consequence
Risk of bias	Downgraded by 1 or 2 levels
Inconsistency of results	Downgraded by 1 or 2 levels
Indirectness of evidence	Downgraded by 1 or 2 levels
Imprecision	Downgraded by 1 or 2 levels
Publication bias	Downgraded by 1 level
Large effect size	Upgraded by 1 or 2 levels
All plausible confounding would reduce the demonstrated effect or increase the effect if no effect was observed	Upgraded by 1 level
Dose–response gradient	Upgraded by 1 level

Finally, because the current project is building upon the work previously done by the AAWC, GRADE assessments were only conducted for newly included systematic reviews. The assessments of previously selected studies by the AAWC have been used and are included in the present report. However, since the AAWC used a previous version of AMSTAR to evaluate the quality of their systematic reviews, AMSTAR 2 assessments were performed for both newly included systematic reviews and previously selected studies by the AAWC.

Sex- and Gender-Based Analysis (SGBA)

Sex- and gender-related factors are involved in patterns of alcohol use, alcohol metabolization and its impact on health and social harms (British Columbia Centre of Excellence for Women's Health, n.d.). Consequently, the Scientific Expert Panels members recommended that all the systematic reviews to be included in the LRDGs update be evaluated for the inclusion of sex- and gender-based analysis. Hence, the included systematic reviews were evaluated using four items adapted from Brabete and colleagues, namely intentional and accurate use of language, use of sex and gender in the aim and research questions, study design and reporting results, and interpretation of sex and gender findings (Brabete et al., 2020).

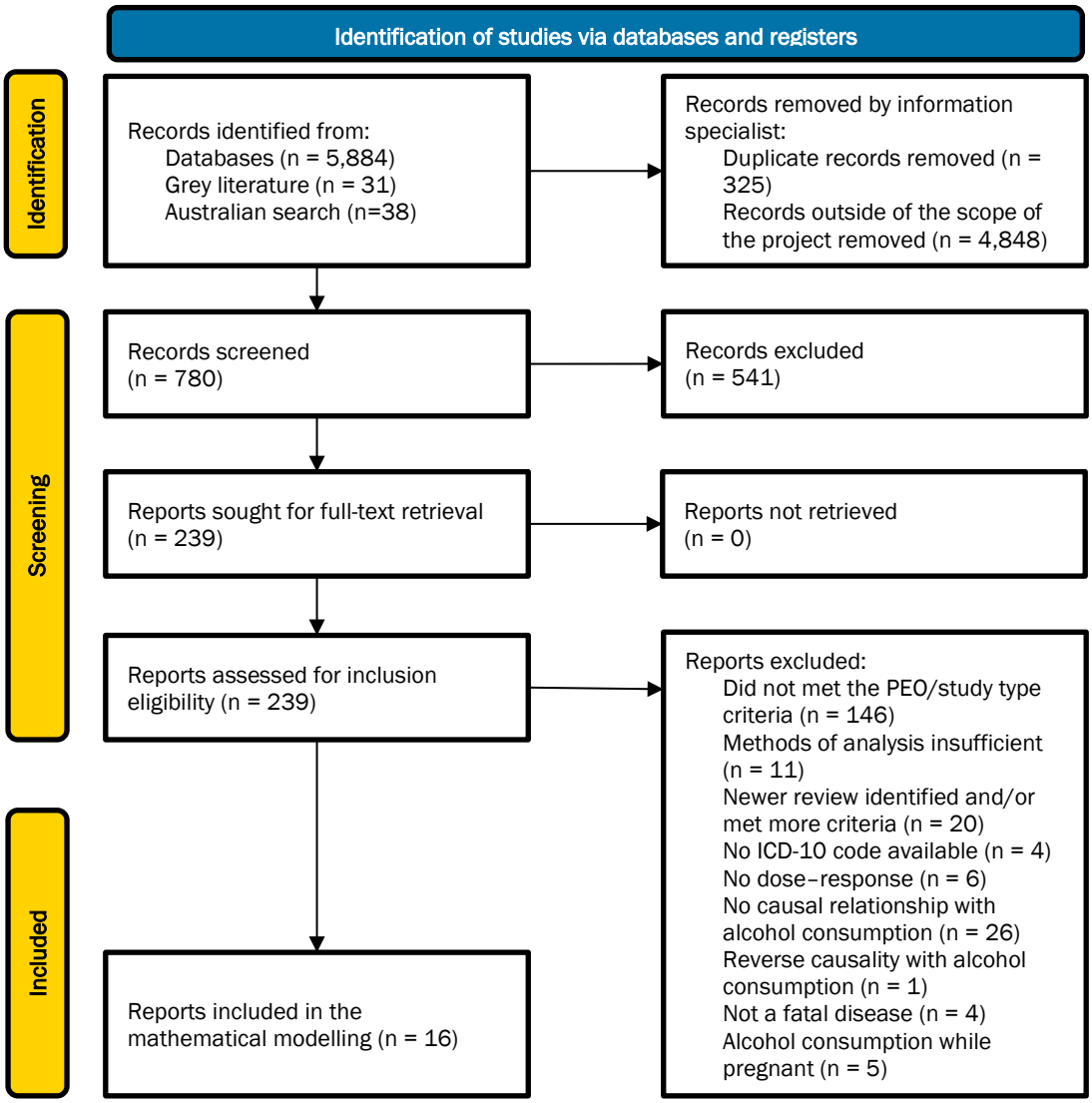
Results

In addition to the 38 systematic reviews already identified by the AAWC, a total of 5,915 systematic reviews were initially retrieved through the updated search. The ERWG used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standard for selecting from this large number of reviews those that warranted inclusion in the mathematical modelling for this project. PRISMA is an evidence-based minimum set of items to help in reporting on systematic reviews and meta-analyses. After removing duplicates and any articles that were outside of the scope of the project, a subset of 780 systematic reviews were screened for title and abstract and 239 systematic reviews were subsequently screened for full-text eligibility. Details of the full-text assessments are presented in the sections below. In the end, a total of 16 systematic reviews fulfilled all the inclusion criteria for this project and were included in the mathematical modelling. The PRISMA flow diagram is presented in Figure 2.

Caveat

Please note that the ERWG recognizes that some terms used in the results, such as "drinkers" and "smokers," are stigmatizing. However, for the results in the tables in which information was extracted from the full text articles, the information referring to the population and outcomes was reported according to the terms used by the original authors. In future work, authors should use less stigmatizing language such as "people who consume alcohol" and "people who smoke." Similarly, some authors used the terms "men" and "women" instead of "male" and "female" to describe biological sex differences. The ERWG have reported the results in the terms used by the authors. In future studies, authors may make distinctions that would better inform the evidence.

Figure 2. PRISMA flow diagram



Question 1: Short-Term Risks and Benefits

Injuries

For injuries, two systematic reviews were included in the mathematical modelling: Taylor et al. (2010) and Taylor & Rehm (2012). The details of the selection process are presented below.

Six new systematic reviews were identified that dealt with the association between alcohol consumption and injuries. Results of the updated search are presented in Table 4. Ding et al.'s (2017) systematic review on traumatic brain injury was the only one that met steps 1 to 3 inclusion criteria. This study, however, was not included in the mathematical modelling because this specific outcome does not have a corresponding ICD-10 code needed for the dose–response model for low-risk drinking guidelines.

Although the systematic review from Zeisser et al. (2013) on injury was identified as evidence by the AAWC in their update of the guidelines, this study was not used to model alcohol-attributable injuries in the current project as it did not examine a dose–response relationship. This study was therefore replaced by the systematic review from Taylor et al. (2010) on the association between alcohol use and non-motor vehicle accident. Taylor and Rehm's (2012) systematic review on the association between alcohol consumption and motor vehicle injury was also included from the evidence identified by the AAWC.

AMSTAR 2 and GRADE assessments of both Taylor et al. (2010) and Taylor and Rehm's (2012) systematic reviews are presented in Tables 5 to 8. A summary of these studies' findings can also be found in Tables 6 and 8, respectively. The systematic review from Taylor et al. (2010) received a low-quality score, while Taylor and Rehm's (2012) systematic review received a very low-quality score. As demonstrated by the AMSTAR 2 and the GRADE assessments, the systematic reviews did not assess risk of bias in individual studies that were included in their review. Case–control studies were also included, which are susceptible to the introduction of more bias. The quality of the systematic reviews was also downgraded according to the level of heterogeneity observed (Taylor et al., 2010: Moderate heterogeneity, $I^2 = 51$; Taylor & Rehm, 2012: Substantial heterogeneity, $I^2 = 99.4\%$). Publication bias was evaluated and detected in both systematic reviews. However, the presence of a dose–response gradient was identified, which improves the quality attributed to the evidence. Large effect size was also identified in both studies.

Table 4. Full text screening for injuries

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Included as evidence by the Australian guideline											
Taylor et al., 2010	Adults (not just in the ED)	Alcohol consump-tion	Injury	Case-crossover Case–control	Yes	Nov-2008	Yes	Partial - age and sex not stated	No	Yes	Yes
Taylor & Rehm, 2012	General population	Alcohol consump-tion	Motor vehicle injury	Cohort Case–control	Yes	Dec-2010	Yes	Yes	No	Yes	Yes
Zeisser et al., 2013	Patients in the ED with injury.	Self-reported alcohol consump-tion within 6 hours of injury	Injury	Case–control Case-crossover	Yes	2009	Yes	No - age, sex, confound-ers not stated.	Partial	Yes	Yes
Updated search for Canada's LRDG 2022											
Baraúna Magno et al., 2019	Children, adolescent, or adults	Alcohol and illicit drugs consump-tion	Traumatic dental injuries	Cross-sectional, cohort	No	Nov-2018	N/A	N/A	N/A	N/A	N/A
Borges et al., 2017	General population	Acute alcohol use	Suicide attempt	Case–control, Case-crossover	No	1996-2015	N/A	N/A	N/A	N/A	N/A
Bunker et al., 2017	General population	Alcohol consumption	Rates of emergency department	Any	No	2013	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
			presentations for alcohol-related injuries that occurred "at home" (compared to alcohol-related injuries that occurred at licensed venues)								
Ding et al., 2017	Patients with traumatic brain injury	Alcohol consump-tion at the time of injury (different blood alcohol concentra-tion levels (low, moderate or high BAC)	Mortality rate of traumatic brain injury patients	Cohort, case–control	Yes	Nov-2015	Yes	Partial - age of participants and confounders are not specified.	Yes	Yes	Yes
Hamilton et al., 2018	People engaged in recreational aquatic activities	Alcohol use prior to or during activities	Unintentional fatal or non-fatal drowning death or injury	Cohort, case–control, cross-sectional, case series	No	31 Jan-2017	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Mathias & Osborn, 2018	Adults with a sustained non-penetrating Traumatic brain injury	Day-of-injury blood alcohol levels (BALs): BAL+ vs. BAL− and/or BALhigh vs. BALlow	Cognitive, psychologi-cal, and functional/ medical outcomes after traumatic brain injury	Cross-sectional; case–control	No	Mar-2015	N/A	N/A	N/A	N/A	N/A

Note: Systematic reviews that meet steps 1 to 3 inclusion criteria but were not included for mathematical modelling purposes are represented in yellow, while systematic reviews included in mathematical modelling are represented in green.

Table 5. AMSTAR 2 assessment for Taylor et al., 2010

Item	Result
Did the research questions and inclusion criteria for the review include the components of PECO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
Did the review authors use a comprehensive literature search strategy?	Partial yes
Did the review authors perform study selection in duplicate?	Not reported
Did the review authors perform data extraction in duplicate?	Not reported
Did the review authors provide a list of excluded studies and justify the exclusions?	No
Did the review authors describe the included studies in adequate detail?	Partial yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No
Did the review authors report on the sources of funding for the studies included in the review	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes

Item	Result
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No, did not assess RoB
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No, did not assess RoB
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No

Table 6. GRADE assessment for Taylor et al., 2010

Outcome	No of reviews (SRs) (No. unique studies and no. participants)	Narrative summary of results	GRADE	GRADE reasons for downgrading or upgrading	Quality of evidence
Non-motor vehicle accident	1 SR (25 case–control and case-crossover studies)	1 SR (Taylor et al., 2010), including 25 case–control and case-crossover studies with unknown risk of bias. Dose–response relationship detected with the odds ratio (OR) of a non-MVA injury increase by 1.30 (95% CI: 1.26–1.34) for every 10-gram increase in alcohol consumption. At 140 grams of pure alcohol consumption prior to injury, a maximum odds ratio of 24.2 (95% CI: 16.2 – 36.2) for non-MVA injury was calculated.	Risk of bias: -2 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: -1 Dose response: +1 Effect size: +2	Risk of bias: Included studies at unknown risk of bias and included studies of case–control and case-crossover design. Inconsistency: Heterogeneity detected but reasons for heterogeneity not explored enough. Indirectness: Nil. Imprecision: Nil. Publication bias: Detected Dose response: Detected. Effect size: Very large.	⨁⨁◯◯

Note: SR = systematic review; MVA = Motor vehicle accident; OR = odds ratio; CI = confidence interval.

Table 7. AMSTAR 2 assessment for Taylor & Rehm, 2012

Item	Result
Did the research questions and inclusion criteria for the review include the components of PECO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No

Item	Result
Did the review authors explain their selection of the study designs for inclusion in the review?	No
Did the review authors use a comprehensive literature search strategy?	Partial yes
Did the review authors perform study selection in duplicate?	Not reported
Did the review authors perform data extraction in duplicate?	Not reported
Did the review authors provide a list of excluded studies and justify the exclusions?	No
Did the review authors describe the included studies in adequate detail?	Partial yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No
Did the review authors report on the sources of funding for the studies included in the review	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No, did not assess RoB
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No, did not assess RoB
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Table 8. GRADE assessment for Taylor & Rehm, 2012

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	GRADE reasons for downgrading or upgrading	Quality of evidence
Fatal motor vehicle injury	1 SR (5 case–control, cases n=3272, control n=96,657)	One SR (Taylor & Rehm, 2012), including 5 case–control studies with an unknown risk of bias, reported OR = 1.74 (95% CI: 1.43–2.14) for every 0.02% increase in BAC, in a random effects meta-analysis. A dose response analysis was also undertaken that reported that at	Risk of bias: -2 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: -1 Dose response: +1 Effect size: +1	Risk of bias: Included studies at unknown risk of bias. Inconsistency: Heterogeneity detected but reasons for heterogeneity not explored enough. Indirectness: Nil. Imprecision: Nil. Publication bias: Detected.	⨁◯◯◯

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	GRADE reasons for downgrading or upgrading	Quality of evidence
		a BAC level of 0.08 OR = 13.0 (95% CI: 11.1–15.2) compared with no blood alcohol. At a BAC level of 0.02 OR = 3.64 (95% CI: 3.37–3.94) (p number for dose–response analysis not reported in the systematic review).		Dose response: Detected. Effect size: Large.	

Note: BAC = blood alcohol content; SR = systematic review; OR = odds ratio; CI = confidence interval.

Source: Adapted from National Health and Medical Research Council, https://www.nhmrc.gov.au/about-us/publications/australian-guidelines-reduce-health-risks-drinking-alcohol. Attribution 4.0 International (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/

Other Conditions

No other systematic reviews were included in the mathematical modelling. The details are presented below.

Although nineteen systematic reviews on various other outcomes emerged in the updated search, none of these studies met the inclusion criteria (see Table 9). The AAWC identified the systematic review from Mostofsky et al. (2016) as evidence on the association between alcohol consumption and short-term risks of ischemic stroke, myocardial infarction and hemorrhagic stroke. However, because the systematic reviews from Larsson et al. (2016) and Zhao et al. (2017) reflect both short- and long-term risks of alcohol use for the same outcomes (see Table 15), these latter studies have been included in the mathematical modelling to generate one risk curve.

Table 9. Full text screening for other conditions

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis
Included as evidence by the Australian guideline											
Mostofsky et al., 2016	General population	Alcohol consumption in the week prior to the event	Ischemic stroke, myocardial infarction,	Case–control Case-crossover	Yes	Mar-2015	Partial - Keywords not stated	yes	Partial - some factors considered	Yes	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
			hemorrhagic stroke						- no tool used		
Updated search for Canada's LRDG 2022											
Alexandre et al., 2019	Human in situations of alcohol abuse submitting to a dopamine emission tomography scan	Alcohol abuse	Dopamin-ergic system	Observa-tional	No	Mar-2018	N/A	N/A	N/A	N/A	N/A
Berry & Johnson, 2018	General population	Alcohol intoxica-tion	HIV sexual risk behaviour	Not specified	No	Oct-2016 to Jan-2017	N/A	N/A	N/A	N/A	N/A
Burgos-Sanchez et al., 2020	General population	Alcohol consump-tion prior to sleep	Occurrence and severity of snoring and obstructive sleep apnea	Cohort (controlled interven-tion)	No	Jul-2018	N/A	N/A	N/A	N/A	N/A
Capito et al., 2017	Social drinkers	Acute alcohol consump-tion	Facial expres-sions of induced positive and negative emotions	Laboratory studies with controls	No	May-2017	N/A	N/A	N/A	N/A	N/A)
Charlton et al., 2020	People with type 1	Acute effects of alcohol	Blood glucose	Any studies	No	Jun-2019	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
	diabetes mellitus			including reviews							
Crane et al., 2017	Females	Acute alcohol use compared to placebo or no alcohol	Female aggression	Experimental	No	Mar-2015	N/A	N/A	N/A	N/A	N/A
Fairbairn et al, 2021	Human participants	Acute alcohol intoxication	Event-related brain potentials	Randomized controlled trials	No	May-2020	N/A	N/A	N/A	N/A	N/A
Gunn et al., 2018	General population (healthy human adults (18+ years of age))	Heavy alcohol consumption measured using blood alcohol concentration	Cognition-next-day effects of heavy alcohol consumption on cognition	Laboratory studies with controls	No	May-2018	N/A	N/A	N/A	N/A	N/A
Hirst et al., 2017	People with diabetes	Alcohol use	Glycaemic control	Controlled trials	No	1946 to 5 May-2015	N/A	N/A	N/A	N/A	N/A
Huang et al., 2021	COVID-19 patients	Ethanol exposure	Severe acute respiratory syndrome coronavirus 2	7 transcriptomic studies, one proteomic and metabolomic study, 6	No	June to August 2020	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
				studies on risk factors and treatment, 7 studies on clinical characteriz-ation, and 7 studies regarding molecular mechanisms, biomarker identification, and various perspectives on COVID-19							
Irwin et al., 2017	Adult (≥18 years of age) participants with no known medical conditions or indication of recent psychoactive drug use	Acute alcohol consumption (vs. "no alcohol" or "placebo alcohol" ingestion) - drinking but only in a laboratory setting	Measures of simulated driving perform-ance	Repeated measures experi-mental designs	No. Incorrect exposure and study type included.	Jun-2016	N/A	N/A	N/A	N/A	N/A
Kolla et al., 2018	Human subjects	Acute alcohol consump-tion (any	Breathing parameter s during sleep	Cross-over	No	Nov-01-2017	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
		vs. placebo)									
Kuypers et al., 2020	General population	Acute use of alcohol, cocaine, and ampheta-mines	Aggressive behaviour and cognitive processes potentially contribut-ing to aggressive behaviour	Experiment al	No	2017	N/A	N/A	N/A	N/A	N/A
Kwok et al., 2019	Healthy popula-tions	Alcohol consump-tion	Food energy intake	Randomized controlled trials, randomized crossover, non-randomized crossover trials	No	February 2018	N/A	N/A	N/A	N/A	N/A
Okoro et al., 2019	People living in Nigeria	Alcohol consump-tion	Risky sexual behaviours and HIV	Not stated.	No-population is not relevant	Dec-2014	N/A	N/A	N/A	N/A	N/A
Przybyla et al., 2018	People living with HIV	Alcohol consumption (any alcohol consumption, binge/ problematic drinking, and	Sero discordant condom-less sex	Cohort; cross-sectional	No	Sep-30-2014	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
		alcohol in a sexual context)									
Roerecke et al., 2017	Adults	Reduction in average alcohol consump-tion that lasted at least 7 days	Change in blood pressure	Crossover, parallel arm	No	Jul-13-2016	N/A	N/A	N/A	N/A	N/A
Tasnim et al., 2020	Healthy and hyper-tensive adults over 18 years of age	Alcohol consump-tion (single dose of alcohol versus placebo)	Blood pressure and heart rate	RCT-experiment al	No-incorrect exposure (not on a single episode of drinking)	Mar-2019	N/A	N/A	N/A	N/A	N/A
Thompson et al, 2017	Human adult participant s	Alcohol consump-tion (measured alcohol dosages vs. no-alcohol)	Response to noxious stimulation (decrease in experiment ally induced pain)	Controlled experi-ments	No-incorrect exposure (not on a single episode of drinking)	Apr-04-2016	N/A	N/A	N/A	N/A	N/A

Note: Systematic review that meets steps 1 to 3 inclusion criteria but was not included for mathematical modelling purposes is represented in yellow.

Question 2: Long-Term Risks and Benefits

Digestive Diseases

For digestive diseases, two systematic reviews were included in the mathematical modelling: Roerecke et al. (2019) and Samokhvalov et al. (2015). The details of the selection process are presented below.

Five new systematic reviews were identified that dealt with the association between alcohol consumption and digestive diseases. Results of the updated search are presented in Table 10. The systematic review from Roerecke et al. (2019) on liver cirrhosis was the only one that met all the inclusion criteria. This systematic review replaced the evidence identified by the AAWC (Rehm et al., 2010) as it accounts for more recent data on liver cirrhosis. This study, however, received a very low-quality score when evaluated by AMSTAR 2 and GRADE (see Tables 13 and 14, respectively). The quality score was lowered because of the presence of moderate to high risk of bias in individual studies, along with the inclusion of case–control studies in the systematic review. Substantial heterogeneity was also detected amongst various drinking categories (I^2 ranged from 70% to 98%). The large effect sizes for some of the drinking categories, however, helped to improve the quality of the evidence.

Evidence for the link between alcohol consumption and pancreatitis was identified by the AAWC (Samokhvalov et al., 2015). AMSTAR 2 and GRADE assessments (see Tables 11 and 12, respectively) revealed a low evidence quality score. This systematic review did not assess risk of bias but had less than 25% of the population from case–control studies. Moderate to substantial heterogeneity was also detected (I^2 ranged from 46.5% to 88.8%) but insufficiently explored. However, the presence of a dose–response gradient and a large effect size for higher levels of alcohol consumption were detected, which improves the quality attributed to the evidence.

Table 10. Full text screening for digestive diseases

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Included as evidence by the Australian guideline											
Rehm et al., 2010	General population	3 or more categories of alcohol consumption	Cirrhosis	Cohort Case–control	Yes	Jan-2008	MEDLINE, EMBASE, CINAHL, PsychINFO, Web of	Partial - confounders and age not stated	No	Yes	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
							Science, ETOH, Google Scholar				
Samokhvalov et al., 2015	General population	Two levels or more of alcohol consumption compared to abstainers	Pancrea-titis	Cohort Case–control (specifical-ly excluded cross-sectional)	Yes	May-2015	Yes	No - number of each sex not stated. Confound-ers stated. Age not stated for all studies.	No	Yes	Yes
Updated search for Canada's LRDG 2022											
Ajmera et al., 2017	Patients with non-alcoholic fatty disease	Moderate alcohol use	Cardiovas-cular and liver disease	Cross-sectional, cohort	No	Not specified	N/A	N/A	N/A	N/A	N/A
Llamosas-Falcon et al., 2020	People with hepatitis C virus infection	Alcohol use disorders (AUDs)	Progres-sion of liver disease	Cohort or case–control	No	Dec-22-2019	N/A	N/A	N/A	N/A	N/A
Pan et al., 2019	People with gastro-esophageal reflux disease	Alcohol consump-tion (grams of ethanol per day for dose–	Gastro-esophageal reflux disease	Cross-sectional, case–control	Yes	Dec-2017	Partial-not checked the references in the primary	Partial-alcohol consump-tion categories (exposure)	Yes	Yes	No

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
		response analysis)					studies identified	were not predefined			
Parker et al., 2019	People with biopsy-proven alcohol related liver disease	Alcohol consump-tion	Prevalence, progression, and mortality in alcohol related liver disease	Cohort (not clearly stated)	No	May-31-2018	N/A	N/A	N/A	N/A	N/A
Roerecke et al., 2019	General population (sex-specific)	Alcohol consumption (at least two quantitatively defined categories of average alcohol consumption in relation to non-drinkers, or data for former drinkers in relation to long-term abstainers)	Cirrhosis of the liver	Cohort; case–control	Yes	Mar-6-2019	Yes-keywords in supplemen tary table	Yes	No	Yes	Yes

Note: Systematic reviews included in mathematical modelling are represented in green.

Table 11. AMSTAR 2 assessment for Samokhvalov, 2015

Item	Result
Did the research questions and inclusion criteria for the review include the components of PECO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
Did the review authors explain their selection of the study designs for inclusion in the review?	No
Did the review authors use a comprehensive literature search strategy?	Partial yes
Did the review authors perform study selection in duplicate?	Yes
Did the review authors perform data extraction in duplicate?	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	No
Did the review authors describe the included studies in adequate detail?	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No
Did the review authors report on the sources of funding for the studies included in the review	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No, did not assess RoB
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No, did not assess RoB
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Table 12. GRADE assessment for Samokhvalov, 2015

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	GRADE reasons for downgrading or upgrading	Quality of evidence
Pancreatitis (acute and chronic)	1 SR (5 Case–control, 2 Cohort, n=157,026, cases=3,186)	One systematic review with an unknown risk of bias reported a dose–response relationship for alcohol consumption and risk of pancreatitis. For risk of chronic pancreatitis, it reported for 25g per day of alcohol a RR=1.58 (95% CI 1.32-1.90) and that for 100g per day this increased to RR=6.29 (95% CI 3.04-13.02). There was no evidence of non-linearity for chronic pancreatitis (p=0.091). For acute pancreatitis there was a separate dose–response meta-analysis for men and women in which there was no evidence of non-linearity (p=0.396) but significant evidence of non-linearity for women (p<0.001). The categorical meta-analysis for acute pancreatitis <40g per day reported no difference in men RR=1.10 (95% CI 0.69-1.74) and a decreased risk for women RR=0.76 (95% CI 0.60-0.97) in comparison to abstainers.	Risk of bias: -1 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose response: +1 Effect size: +1	Risk of bias: Included studies at unknown risk of bias. Less than 25% of participants from case–control studies. Inconsistency: Moderate to high heterogeneity was detected and insufficiently explored. Indirectness: Nil. Imprecision: Nil. Publication bias: None detected. Dose response: Detected. Effect size: Large.	⨁⨁◯◯

Note: N = number of participants; SR = systematic review; CI = confidence interval; g = grams.

Table 13. AMSTAR 2 assessment for Roerecke, 2019

Item	Result
Did the research questions and inclusion criteria for the review include the components of PECO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
Did the review authors explain their selection of the study designs for inclusion in the review?	No
Did the review authors use a comprehensive literature search strategy?	Partial yes
Did the review authors perform study selection in duplicate?	Yes
Did the review authors perform data extraction in duplicate?	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	No
Did the review authors describe the included studies in adequate detail?	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
Did the review authors report on the sources of funding for the studies included in the review	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Table 14. GRADE assessment for Roerecke, 2019

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	GRADE reasons for downgrading or upgrading	Quality of evidence
Cirrhosis of the liver	1 SR (7 cohort studies and 2 case–control studies) with a total of 2,629,272	1 SR, including 7 cohort studies and 2 case–control studies with moderate to serious risk of bias reported a pooled RR of 1.11	Risk of bias: -2 Inconsistency: -2 Indirectness: 0	Risk of bias: Risk of bias was assessed using ROBINS-I and 8 studies included moderate risk of bias whereas one had serious risk of	⨁◯◯◯

	participants, n= 5,505 cases of liver cirrhosis	(95%CI: 0.77–1.59), I^2=70.6% for occasional drinkers, 1.40 (95%CI: 1.00–1.97), I^2=78.2% for 1 drink/day, 3.02 (95%CI: 1.95–4.70), I^2=91.7% for 2 drinks/day, 3.27 (95%CI: 0.90–11.87), I^2=98.6% for 3-4 drinks/day, 6.26 (95%CI: 2.38–16.50), I^2=96.7% for 5-6 drinks/day and 10.70 (95%CI: 2.95–38.78, I^2=98.3% for 7 or more drinks/day compared with long-term abstainers.	Imprecision: 0 Publication bias: 0 Effect size: +1	bias. Included case–control study designs. Inconsistency: High heterogeneity was detected amongst various drinking categories (I^2 ranged from 70%-98%). Sensitivity analyses were conducted, but heterogeneity was not explored enough. Indirectness: Nil. Imprecision: Nil. Publication bias: None detected. Effect size: Large.	

Note: N = number of participants; SR = systematic review; CI = confidence interval.

Cardiovascular Diseases

For cardiovascular diseases, four systematic reviews were included in the mathematical modelling: Larsson et al. (2014), Larsson et al. (2016), Liu et al. (2020), and Zhao et al. (2017). The details of the selection process are presented below.

Fifteen new systematic reviews that dealt with the association between alcohol consumption and cardiovascular diseases were identified by the updated search. The results are presented in Table 15. Seven of these systematic reviews met the steps 1 to 3 inclusion criteria, but only two were retained for mathematical modelling purpose (Liu et al., 2020; Zhao et al., 2017).

Specifically, the systematic review from Yoon et al. (2020) on cardiovascular diseases was not retained for mathematical modelling as it includes many disease categories, and it was decided that disease-specific relative risks should be used. The systematic review from Chen et al. (2020b) on venous thromboembolism and the systematic review from Spencer et al. (2017) on abdominal aortic aneurysm were also excluded because no causal relationship between alcohol use and these outcomes has been established. In addition, as modelling low-risk drinking guidelines requires a dose–response risk curve, the systematic review from Gallagher et al. (2017) was not used to model alcohol-attributable atrial fibrillation. This systematic review was replaced by Larsson's et al. (2014) study, which was identified by the AAWC. Based on AMSTAR 2 and GRADE assessments, the systematic review from Larsson et al. (2014) received a moderate quality score (see Tables 16 and 17, respectively). This systematic review includes studies at unknown risk of bias although limited to prospective cohort studies. Nonetheless, the presence of a dose–response gradient was identified as a strength for this specific study. The systematic review from Zhu et al. (2017) on the association between alcohol use and myocardial infarction was also not retained for the mathematical modelling as myocardial infarction is a subcategory of ischemic heart disease, which is covered by the systematic review from Larsson et al. (2016), identified by the AAWC. The quality of Larsson's et al. (2016) systematic review was deemed to be very low (see Tables 18 and 19, respectively). The included studies presented a moderate risk of bias although limited to prospective cohort studies. Moderate heterogeneity was also detected for both intracerebral (I^2 ranging from 0% to 57.3%) and subarachnoid haemorrhage. Furthermore, for ischaemic stroke and subarachnoid haemorrhage, small study bias was identified for low alcohol consumption.

The systematic review from Briasoulis et al. (2012) on the association between alcohol consumption and hypertension, which was identified by the AAWC, was replaced by a newer systematic review by Liu et al. (2020). As demonstrated by the AMSTAR 2 and the GRADE assessments (see Tables 20 and 21, respectively), the systematic review from Liu et al. (2020) received a high-quality score. This systematic review only included high-quality cohort study design and the risk of bias in individual studies was evaluated using the Newcastle-Ottawa Scale. High-heterogeneity was detected (I^2 = 76.4%), although sensitivity analyses were performed to explore the source of heterogeneity. The presence of a dose–response relationship between alcohol consumption and hypertension increases the confidence in this evidence. Alongside Liu's et al. (2020) study, the systematic review from Zhao et al. (2017) on ischaemic heart disease was also retained to be part of the mathematical modelling. Based on AMSTAR 2 and GRADE assessments, this study was deemed to be low quality evidence (see Tables 22 and 23, respectively). Although limited to prospective studies, the risk of bias in individual studies that were included in the review was not assessed. There was also significant heterogeneity observed across individual studies for all drinking categories confirmed by the I^2 estimates (all above 38%).

The systematic review from Larsson et al. (2015) on the association between alcohol consumption and heart failure was identified as evidence by the AAWC. This study was not retained in the current mathematical modelling as no causal relationship between alcohol use and heart failure has yet been established. As the low-risk drinking guidelines only consider diseases and injuries causally related to alcohol use, the systematic review from Larsson et al. (2015) was not used to model alcohol-attributable heart failure.

Table 15. Full text screening for cardiovascular diseases

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Included as evidence by the Australian guideline											
Briasoulis et al., 2012	General population	Three or more categories of alcohol consumption	Hypertension	Prospective cohort	Yes	May-2012	Yes	No-confounders not stated	No	Yes	Yes
Larsson et al., 2014	Population and hospital based	Alcohol consumption	Atrial fibrillation incidence	Prospective cohort	Yes	Jan-2010	Partial – searched PubMed only	Yes	No	Yes (3 or more categories of alcohol	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
			or atrial flutter				but keywords defined.			consump-tion)	
Larsson et al., 2015	General population	At least 3 different non-overlap-ping levels of drinking categories	Heart failure	Prospec-tive cohort	Yes	Sep-2014	Partial - one database searched	Yes	No	Yes	Yes
Larsson et al., 2016	General population	Alcohol consumpti on	Ischaemic stroke, subarachnoid hemorrhage, intracerebral hemorrhage	Prospec-tive cohort	Yes	Sep-2016	Partial - only PubMed searched.	Yes	Yes	Yes	Yes
Updated search for Canada's LRDG 2022											
Ajmera et al., 2017	Patients with non-alcoholic fatty disease	Moderate alcohol use	Cardio-vascular and liver disease	Cross-sectional, cohort	No	Not specified	N/A	N/A	N/A	N/A	N/A
Chen et al., 2020b	General population	Alcohol consump-tion-at least three levels of alcohol intake (dose–response)	Venous thrombo-embolism	Cohort, nested case–control, random-ized trial	Yes	Feb-2020	Yes	Yes	Yes	Yes	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Cheng et al., 2019	Patients with a diagnosis of alcohol use disorder	Alcohol use disorder	Parasym-pathetic function	Cross-sectional case–control, clinical trial, cohort	No	Sept-2018	N/A	N/A	N/A	N/A	N/A
Gallagher et al., 2017	General population	Chronic alcohol intake	Incident atrial fibrillation	Prospec-tive studies	Yes	1 Feb-2016	Yes	Yes	Partial - Only publication bias was evaluated.	Yes	Yes
Larsson et al., 2018	General population	Alcohol consumption (unit of drinks not standardized)	Heart failure	Prospec-tive	No	Jan-01-2017	N/A	N/A	N/A	N/A	N/A
Liu et al., 2020	Adults (consider-ing the effect of sex and race)	alcohol consump-tion (examining at least three levels of ethanol consump-tion)	Hypertensi on	Cohort	Yes	Sep-07-2019	Yes	Yes	Yes	Yes	Yes
Okojie et al., 2020	Patients with hyper-tension	Alcohol consump-tion	Primary or secondary hyper-tension	Not stated.	No	Not stated.	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis
Peng et al., 2020	General population	Alcohol consumption	Outcome of intracerebral hemorrhage	Cohort, case–control	No	Aug-2019	N/A	N/A	N/A	N/A	N/A
Raheja et al., 2018	Patients with acute alcohol intoxication, without pre-existing alcohol or non-alcohol related cardiac conditions	Acute alcohol intoxication (not clearly defined)	Electrocardiogram changes	Case control; crossover	No	Jan-2017	N/A	N/A	N/A	N/A	N/A
Rehm et al., 2017b	General population	Alcohol consumption (dose–response)	Cardiomyopathy	Meta-analyses; any other type of studies	No	Nov-2016	N/A	N/A	N/A	N/A	N/A
Roerecke et al., 2018	People without hypertension at baseline	Alcohol consumption	Hypertension	Cohort	Yes	Apr-03-2017	Yes	Yes	Yes	Yes	No
Spencer et al., 2017	Adults with no abdominal aortic aneurysm diagnosis at the	Alcohol consumption (at least three categories of quantified alcohol intake or analysis of	Abdominal aortic aneurysm	Cohort, case–control, cross-sectional, RCTs	Yes	Jan-2017	Yes	Yes	Yes	Yes	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
	beginning of the study	alcohol as a continuous variable)		(separate analysis)							
Yoon et al., 2020	People living in the local community	Alcohol consump-tion (dose–response)	Incidence of cardio-vascular diseases	Cohort; case–control	Yes	Dec-2017	Partial-Not checked the references in the primary studies identified	Yes	Yes	Yes	Partial-no sensitivity test was done.
Zhao et al., 2017	Human subjects of all ages	Alcohol consump-tion (Level of daily alcohol use in grams of ethanol)	Coronary heart disease	Cohort	Yes	Jun-30-2016	Yes-MESH terms available on PubMed link	Partial-A clear description of the outcomes is not provided	Partial-a specific quality assess-ment tool is not used. Only publication bias is assessed	Partial-clear descrip-tions/ inclusion criteria of the outcome is not provided	Yes
Zhu et al., 2017	Individuals with myocardial infarction conditions	Alcohol consumpti on (dose–response)	Myocardial infarction	Cohort	Yes	May-2016	Partial - Not checked the references in the primary studies identified	Partial-A clear description of the outcomes is not provided.	Yes	Partial-clear descriptions/ inclusion criteria of the outcome is not provided	Yes

Note: Systematic reviews that meet steps 1 to 3 inclusion criteria but were not included for mathematical modelling purposes are represented in yellow, while systematic reviews included in mathematical modelling are represented in green.

Table 16. AMSTAR 2 assessment for Larsson, 2014

Item	Result
Did the research questions and inclusion criteria for the review include the components of PECO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviationsfrom the protocol?	No
Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
Did the review authors use a comprehensive literature search strategy?	No
Did the review authors perform study selection in duplicate?	Not reported
Did the review authors perform data extraction in duplicate?	Not reported
Did the review authors provide a list of excluded studies and justify the exclusions?	No
Did the review authors describe the included studies in adequate detail?	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No
Did the review authors report on the sources of funding for the studies included in the review	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No, did not assess RoB
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No, did not assess RoB
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Table 17. GRADE assessment for Larsson, 2014

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	GRADE reasons for downgrading or upgrading	Quality of evidence
Atrial Fibrillation (AF) incidence or atrial flutter	One SR (7 prospective cohort, n=198,485, cases=11,419)	One SR including 7 prospective cohort studies, reported a dose–response relationship between alcohol consumption and risk of AF. The linear dose–response analysis reported that for every 12g per day of ethanol consumption the RR increased by 1.08 (95% CI: 1.06 to 1.10) (p linearity <0.001).	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose response: +1	Risk of bias: Included studies at unknown risk of bias but limited to prospective cohort studies only. Inconsistency: Nil. Indirectness: Nil. Imprecision: Nil. Publication bias: None detected Dose response: Detected.	⨁⨁⨁◯

Note: SR = systematic review; RR = relative risk; AF = atrial fibrillation; CI = confidence interval; g = grams; n = number of participants.

Table 18. AMSTAR 2 assessment for Larsson, 2016

Item	Result
Did the research questions and inclusion criteria for the review include the components of PECO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviationsfrom the protocol?	No
Did the review authors explain their selection of the study designs for inclusion in the review?	No
Did the review authors use a comprehensive literature search strategy?	No
Did the review authors perform study selection in duplicate?	Yes
Did the review authors perform data extraction in duplicate?	Not reported
Did the review authors provide a list of excluded studies and justify the exclusions?	No
Did the review authors describe the included studies in adequate detail?	Partial yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
Did the review authors report on the sources of funding for the studies included in the review	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes

If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Table 19. GRADE assessment for Larsson, 2016

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	GRADE reasons for downgrading or upgrading	Quality of evidence
Ischaemic stroke	1 SR (25 prospective cohorts, cases=19,302)	One SR including 25 prospective cohort studies reported a decreased risk at ≤2 drink per day, but an increased risk for >2 drink per day for ischaemic stroke when compared to the reference group (non-drinkers, never drinkers, or occasional drinkers).	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: -1	Risk of bias: Risk of bias was assessed using NOS and scores ranged from 4-9 out of 9. The included studies are at a lower risk of bias due to restriction of inclusion to only prospective cohort studies. Inconsistency: Low or none detected. Indirectness: Nil. Imprecision: Nil. Publication bias: Small study bias was identified for low alcohol consumption for ischaemic stroke (P=0.04).	⨁◯◯◯
Intracerebral haemorrhage	1 SR (11 prospective cohorts, cases=2,359)	One SR including 11 prospective cohort studies reported no difference in risk of intracerebral haemorrhage for ≤4 drinks/day but an increased risk at >4 drinks/day when compared to the reference group (non-drinkers, never drinkers, or occasional drinkers).	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: 0	Risk of bias: Risk of bias was assessed using NOS and scores ranged from 4-9 out of 9. The included studies are at a lower risk of bias due to restriction of inclusion to only prospective cohort studies. Inconsistency: Moderate heterogeneity detected but not explored enough. Indirectness: Nil. Imprecision: Nil.	⨁◯◯◯

				Publication bias: Nil.	
Subarachnoid haemorrhage	1 SR (11 prospective cohorts, cases=1164)	One SR including 11 prospective cohort studies reported no difference in risk of subarachnoid haemorrhage for ≤4 drinks/day but an increased risk at >4 drinks/day when compared to the reference group (non-drinkers, never drinkers, or occasional drinkers).	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: -1	Risk of bias: Risk of bias was assessed using NOS and scores ranged from 4-9 out of 9. The included studies are at a lower risk of bias due to restriction of inclusion to only prospective cohort studies. Inconsistency: Moderate heterogeneity detected but not explored enough. Indirectness: Nil. Imprecision: Nil. Publication bias: Small study bias was identified for low alcohol consumption for subarachnoid haemorrhage (P=0.01).	⊕◯◯◯

Note: NOS = Newcastle-Ottawa Scale SR = systematic review; RR = relative risk; CI = confidence interval.

Source: Adapted from the National Health and Medical Research Council, https://www.nhmrc.gov.au/about-us/publications/australian-guidelines-reduce-health-risks-drinking-alcohol. Attribution 4.0 International (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/

Table 20. AMSTAR 2 assessment for Liu, 2020

Item	Result
Did the research questions and inclusion criteria for the review include the components of PECO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
Did the review authors explain their selection of the study designs for inclusion in the review?	No
Did the review authors use a comprehensive literature search strategy?	Partial yes
Did the review authors perform study selection in duplicate?	No reported
Did the review authors perform data extraction in duplicate?	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
Did the review authors describe the included studies in adequate detail?	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
Did the review authors report on the sources of funding for the studies included in the review	No

Item	Result
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Table 21. GRADE assessment for Liu, 2020

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	GRADE reasons for downgrading or upgrading	Quality of evidence
Hypertensive heart disease	1 SR (22 articles, 31 independent cohort studies with a total of 414,477 participants, n= 89,734 cases of hypertension	1 SR including 31 cohort studies with Newcastle-Ottawa Scale risk of bias. For each increase of 10g/day of ethanol consumption, reported a pooled RR for hypertension of 1.06 (95% CI: 1.05-1.08), I2=76.4% in comparison to non-drinkers. Dose–response relationship showed that hypertension increased linearly with alcohol consumption. For 50 g/day of ethanol consumption, the pooled RR was 1.35 (95% CI: 1.25, 1.45) in comparison to non-drinkers	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose response: +1	Risk of bias: All of the studies included in the meta-analysis were cohort studies and had high quality. Inconsistency: High heterogeneity was detected (I^2 = 76.4%). Sensitivity analyses conducted and heterogeneity explored. Indirectness: Nil. Imprecision: Nil. Publication bias: None detected Dose response: Detected	⨁⨁⨁⨁

Note: N = number of participants; SR = systematic review; RR = relative risk CI = confidence interval; g = grams.

Table 22. AMSTAR 2 assessment for Zhao, 2017

Item	Result
Did the research questions and inclusion criteria for the review include the components of PECO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviationsfrom the protocol?	Partial yes
Did the review authors explain their selection of the study designs for inclusion in the review?	No
Did the review authors use a comprehensive literature search strategy?	Yes
Did the review authors perform study selection in duplicate?	Yes
Did the review authors perform data extraction in duplicate?	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	No
Did the review authors describe the included studies in adequate detail?	Partial yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No
Did the review authors report on the sources of funding for the studies included in the review	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No, did not assess RoB
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No, did not assess RoB
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Table 23. GRADE assessment for Zhao, 2017

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	GRADE reasons for downgrading or upgrading	Quality of evidence
Ischaemic heart disease	1 SR (45 cohort studies) with a total of 2,913,140 participants, and n=65,476 deaths	1 SR including 45 cohort studies with unknown risk of bias. Significantly reduced Coronary heart disease mortality was reduced for current low-volume drinkers with a RR=0.80, (95% CI 0.69, 0.93) and all current drinkers RR = 0.88, (95% CI 0.78, 0.99)	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0	Risk of bias: Included studies at unknown risk of bias but limited to prospective cohort studies only. Inconsistency: Heterogeneity was detected I^2 was greater than 38%. Further analyses were conducted and explored heterogeneity. Indirectness: Nil. Imprecision: Nil. Publication bias: None detected	⨁⨁◯◯

Note: N = number of participants; SR = systematic review; RR = relative risk CI = confidence interval.

Diabetes Mellitus

For diabetes mellitus, one systematic review was included in the mathematical modelling: Knott et al. (2015). The details of the selection process are presented below.

Three new systematic reviews of the association between alcohol consumption and diabetes mellitus were identified by the updated search. The results are presented in Table 24. Only one of these studies met steps 1 to 3 inclusion criteria (Huang, 2017), but unfortunately could not be retained for mathematical modelling purpose. The systematic review from Huang et al. (2017) did not examine a dose–response relationship required to model alcohol-attributable diabetes mellitus. The systematic review from Knott et al. (2015), identified by the AAWC, was therefore kept as evidence for the current project.

This specific systematic review was evaluated by both AMSTAR 2 and GRADE (see Tables 25 and 26, respectively), and received a very low-quality score. The systematic review from Knott et al. (2015) included studies at low to high risk of bias, although less than 25% of participants came from case–control studies. Considerable between-study heterogeneity was also detected (first-order polynomial: I^2 = 75%; second-order polynomial: I^2 = 50%). Stratified and sensitivity analyses were conducted but heterogeneity was insufficiently explored. The authors also reported potential publication bias.

Table 24. Full text screening for diabetes mellitus

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis
Included as evidence by the Australian guideline											
Knott et al., 2015	Adults aged 16 and over	Three or more categories of alcohol consumption, including never or non-drinking	Diabetes	Cohort Case–control Case–cohort Nested case–control	Yes	Feb-18-2014	Medline, EMBASE, CINAHL, ETOH. Reference lists searched Free-text keywords and combinations stated	Yes	Yes Newcastle-Ottawa Scale	Yes	Yes
Updated search for Canada's LRDG 2022											
Chen et al., 2020a	General population as well type 1 diabetes mellitus, type 2 diabetes mellitus, or mixed patients	Any alcohol intake	Diabetic retinopathy	Cohort, case–control, cross-sectional (separate analysis)	No	Nov-2019	N/A	N/A	N/A	N/A	N/A
Huang et al., 2017	General population	Alcohol consumption (g per day)	Type 2 diabetes	Cohort	Yes	Jan-1966 to Feb-2016	Yes	Yes	Yes	Yes	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Neuensch-wander et al., 2019	Adults	Dietary factors including alcohol consump-tion	Incidence of type 2 diabetes	Umbrella review of systematic reviews with meta-analyses of prospective observational studies	No	Aug-2018	N/A	N/A	N/A	N/A	N/A

Note: Systematic review that meets steps 1 to 3 inclusion criteria but was not included for mathematical modelling purposes is represented in yellow, while the systematic review included in mathematical modelling is represented in green.

Table 25. AMSTAR 2 assessment for Knott, 2015

Item	Result
Did the research questions and inclusion criteria for the review include the components of PECO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviationsfrom the protocol?	No
Did the review authors explain their selection of the study designs for inclusion in the review?	No
Did the review authors use a comprehensive literature search strategy?	Partial yes
Did the review authors perform study selection in duplicate?	Yes
Did the review authors perform data extraction in duplicate?	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	No
Did the review authors describe the included studies in adequate detail?	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
Did the review authors report on the sources of funding for the studies included in the review	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes

Item	Result
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Table 26. GRADE assessment for Knott, 2015

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	GRADE reasons for downgrading or upgrading	Quality of evidence
Type II diabetes	1 SR (37 cohort, 1 nested case–control, n= 1,902,605)	One SR including 37 cohort and 1 nested case–control study with a moderate risk of bias, reported in a dose–response analysis a decreased risk of type II diabetes with alcohol consumption <63 g/day, compared to current and lifetime abstainers, with considerable heterogeneity. Stratified and sensitivity analysis were conducted. One was conducted on different referent groups (current abstention = 33 studies, lifetime abstention = 5 studies) and reported no risk decrease at any level of alcohol consumption when compared to lifetime abstainers, but a risk decrease at <59g/day when compared to current abstainers. (P nonlinearity <0.001). Sex-stratified analysis across all included studies reported that women had a decreased risk at	Risk of bias: -1 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: -1	Risk of bias: Included studies at low to high risk of bias (NOS 3-9, median 6). Less than 25% of participants from case–control studies. Inconsistency: Considerable heterogeneity detected however stratified and sensitivity analyses were conducted but insufficiently explored heterogeneity. Indirectness: Nil. Imprecision: Nil. Publication bias: Potential publication bias reported.	⨁◯◯◯

		<71 g/day, but in men there was no decrease in risk even at low levels. This trend was still present when only including lifetime abstainers as the reference group, with a decreased risk at <61 g/day, but in men there was no decrease in risk even at low levels. For case ascertainment (participant self-report (n = 11), objective ascertainment (n = 21), combination (n = 6)) there was a greater decrease in risk for objective ascertainment than self-reported. For multivariable-adjusted analyses (n=24) compared to unadjusted analyses (n=14), multivariable-adjusted analyses showed a less pronounced decrease in risk than unadjusted analyses at moderate levels of consumption.			

Note: SR = systematic review; n = number of participants; g = grams.

Source: Adapted from the National Health and Medical Research Council, https://www.nhmrc.gov.au/about-us/publications/australian-guidelines-reduce-health-risks-drinking-alcohol. Attribution 4.0 International (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/

Respiratory Infections and Infectious and Parasitic Diseases

For respiratory infections and infectious and parasitic diseases, two systematic reviews were included in the mathematical modelling: Imtiaz et al. (2017) and Samokhvalov et al. (2010a). The details of the selection process are presented below.

Six new systematic reviews on the association between alcohol consumption and respiratory infections as well as infectious and parasitic diseases were identified by the updated search. The results are presented in Table 27. Three of these systematic reviews met the steps 1 to 3 inclusion criteria, but only one was retained for mathematical modelling purpose (Imtiaz et al., 2017). Specifically, both Simou's et al. (2018a; 2018c) systematic reviews on tuberculosis and pneumonia did not explore dose–response relationships needed to model alcohol-attributable outcomes. These studies were therefore replaced by the systematic reviews from Imtiaz et al. (2017) and Samokhvalov et al. (2010a), respectively, for the current project. The systematic review from Imtiaz et al. (2017) also replaced the evidence identified by the AAWC (Lönnroth et al., 2008) as it accounts for more recent data on tuberculosis.

AMSTAR 2 and GRADE assessments for Imtiaz's et al. (2017) systematic review revealed a very low evidence-quality score (see Tables 30 and 31, respectively). Case–control studies were included in this systematic review and risk of bias in individual studies was not reported. Substantial heterogeneity was also detected (I^2 = 83%) and sufficiently explored. However, the presence of a dose–response gradient was identified, which contributes to the quality of the evidence. Regarding the association between alcohol consumption and pneumonia, AMSTAR 2 and GRADE assessments (see Tables 28 and 29, respectively) revealed a low-quality evidence score for the systematic review from Samokhvalov et al. (2010a). This systematic review included studies at unknown risk of bias, although less than 25% of participants came from case–control studies.

Table 27. Full text screening for respiratory infections and infectious parasitic diseases

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Included as evidence by the Australian guideline											
Lönnroth et al., 2008	General population	Amount of alcohol intake or alcohol use disorder	Tuberculosis	Cohort Case–control	Yes	Not stated	Partial - one database searched and private WHO collection, search dates not stated	Partial - no age or sex reported	No	Yes	Yes
Samokhvalov et al., 2010a	General population	Three or more categories of alcohol consumption	Pneumonia	Cohort Case–control (specifically excluded cross-sectional)	Yes	Aug-2009	Yes	Partial – no age reported	No	Yes	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Updated search for Canada's LRDG 2022											
Imtiaz et al., 2017	General population	Alcohol consumption (alcohol use, alcohol dosage and alcohol-related problems)	Tuber-culosis	Cohort, case–control	Yes	January 2007 to June 2016	Yes	Yes	Yes	Yes	Yes
Ragan et al., 2020	Participants receiving standard treatment regimens for tuberculosis disease	Alcohol consump-tion (highest vs. lowest levels)	Tuber-culosis treatment outcomes	cohort, case–control, random-ized controlled trial	Yes	May-2018	Yes-search terms in the supple-mentary materials	Partial-Potential confound-ers are not included	Partial - did not use a specific quality assessment tool but considered quality in a narrative way	Yes	No, only included highest vs. lowest
Rajarajan et al., 2019	Not stated	Alcohol consump-tion	Tuberculosis progression and treatment response	Observatio nal; experiment al	No	Not stated	N/A	N/A	N/A	N/A	N/A
Simou et al., 2018a	Adults aged >18 years	Alcohol consumption (studies with at least three exposure categories included in the dose–	Tuberculo sis	Cohort/ longitudi-nal, case–control, cross-sectional	Yes	Apr-2018	Yes	Yes	Yes	Yes	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
		response analyses)									
Simou et al., 2018c	Adult populations (≥18 years)	Alcohol consumption (studies with at least three different categories of exposure, standardised for dose–response analysis to grams per day)	Com-munity-acquired pneu-monia	longitudi-nal, cohort, case–control, cross-sectional (separate analysis for cross-sectional)	Yes	Dec-2017	Yes	Yes	Yes	Yes	Yes
Simou et al., 2018d	Adults aged 18 years and over	Prior alcohol intake (including two categories)	Acute respira-tory distress syndrome	longitudi-nal/cohort, case control, cross-sectional	No-cross-sectional studies not separated from others in the analyses	Dec-2015	N/A	N/A	N/A	N/A	N/A

Note: Systematic reviews that meet steps 1 to 3 inclusion criteria but were not included for mathematical modelling purposes are represented in yellow, while systematic reviews included in mathematical modelling are represented in green.

Table 28. AMSTAR 2 assessment for Samokhvalov 2010a

Item	Result
Did the research questions and inclusion criteria for the review include the components of PECO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviationsfrom the protocol?	No

Did the review authors explain their selection of the study designs for inclusion in the review?	No
Did the review authors use a comprehensive literature search strategy?	Partial Yes
Did the review authors perform study selection in duplicate?	No reported
Did the review authors perform data extraction in duplicate?	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	No
Did the review authors describe the included studies in adequate detail?	Partial Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No
Did the review authors report on the sources of funding for the studies included in the review	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No, did not assess RoB
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No, did not assess RoB
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Table 29. GRADE assessment for Samokhvalov 2010a

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	GRADE reasons for downgrading or upgrading	Quality of evidence
Pneumonia (morbidity and/or mortality)	1 SR (2 Cohort (n=108,658), 3 Case–control (n=3,442), n cases=2371))	One systematic review with an unknown risk of bias found an increased risk of CAP morbidity or mortality of RR=1.06 (95% CI 1.01–1.11) per standard drink (12g pure alcohol) per day compared with non-drinkers. For those with AUD compared to people without AUD the risk was RR=8.22, (95% CI 4.85–13.95). P number for dose–response	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0	Risk of bias: Included studies at unknown risk of bias. Less than 25% of participants from case–control studies. Inconsistency: Nil. Indirectness: Nil. Imprecision: Nil. Publication bias: None detected.	⨁⨁◯◯

		analysis not reported in the systematic review.			

Note: AUD = alcohol use disorders; n = number of participants; SR = systematic review; RR = relative risk CI = confidence interval; CAP = community-acquired pneumonia.

Table 30. AMSTAR 2 assessment for Imtiaz, 2017

Item	Result
Did the research questions and inclusion criteria for the review include the components of PECO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviationsfrom the protocol?	No
Did the review authors explain their selection of the study designs for inclusion in the review?	No
Did the review authors use a comprehensive literature search strategy?	Yes
Did the review authors perform study selection in duplicate?	No
Did the review authors perform data extraction in duplicate?	No
Did the review authors provide a list of excluded studies and justify the exclusions?	No
Did the review authors describe the included studies in adequate detail?	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No
Did the review authors report on the sources of funding for the studies included in the review	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No, did not assess RoB
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No, did not assess RoB
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Table 31. GRADE assessment for Imtiaz, 2017

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	GRADE reasons for downgrading or upgrading	Quality of evidence
Tuberculosis	1 SR (8 cohort studies, and 28 case–control studies)	1 SR including 8 cohort studies and 28 case–control studies with an unknown risk of bias, found that the RR for alcohol use was 1.35 (95% CI 1.09–1.68; I^2: 83%). Concerning alcohol dosage, tuberculosis risk rose as ethanol intake increased, with evidence of a threshold effect. Alcohol consumption caused 22.02 incident cases (95% CI 19.70–40.77) and 2.35 deaths (95% CI 2.05–4.79) per 100000 people from tuberculosis in 2014. Dose–response meta-analysis was conducted. Tuberculosis risk rose as ethanol intake in grams per day increased.	Risk of bias: -2 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose response: +1	Risk of bias: Case–control study design was included, and risk of bias was not reported. The number of participants from case–control or cohort studies is also not reported. Inconsistency: Substantial heterogeneity detected. Sensitivity analyses were conducted, but heterogeneity not explored enough. Indirectness: Nil. Imprecision: Nil. Publication bias: None detected. Dose response: Detected.	⨁◯◯◯

Note: SR = systematic review, RR = relative risk, CI = confidence interval

Neurological Conditions

For neurological conditions, one systematic review was included in the mathematical modelling: Samokhvalov et al. (2010b). The details of the selection process are presented below.

Nineteen new systematic reviews on the association between alcohol consumption and neurological conditions were identified by the updated search. The results are presented in Table 32. Three of these systematic reviews met the steps 1 to 3 inclusion criteria, but none were retained for mathematical modelling purpose. More precisely, while alcohol consumption may be associated with long-term cognitive function (Brennan et al., 2020) and cognitive deficits (Ran et al., 2020), these conditions are considered symptoms, not diseases. These studies were therefore excluded from the modelling process as mortality and morbidity data are coded using the ICD-10 coding system and symptoms cannot be used to model lifetime alcohol-attributable risk curves. Moreover, a causal relationship between alcohol use and dementia at lower levels of alcohol consumption (i.e., for those without alcohol use disorder) has not been established yet. As the low-risk drinking guidelines only consider diseases and injuries causally related to alcohol use, it was not possible to include the systematic review from Xu et al. (2017) in the mathematical modelling, nor Anstey's et al. (2009) systematic review that was identified by the AAWC.

The systematic review from Samokhvalov et al. (2010b) on the association between alcohol use and epilepsy, which was identified by the AAWC, was included for mathematical modelling purposes. The quality of Samokhvalov's et al. (2010b) systematic review was deemed to be very low based on AMSTAR 2 and GRADE assessments (see Tables 33 and 34, respectively). This systematic review included case–control studies at unknown risk of bias. Although no significant heterogeneity was detected, clinical heterogeneity is suspected due to inclusion of different outcome measures. Indeed, this study pooled together the outcomes of unprovoked seizures and epilepsy, in addition to having a very small number of cases and studies included.

Table 32. Full text screening for neurological conditions

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Included as evidence by the Australian guideline											
Anstey et al., 2009	General population	Alcohol consumption	Dementia and cognitive decline	Prospective cohort	Yes	Jun-2007	Yes	Confounders not stated.	No	Yes	Yes
Samokhvalov et al., 2010b	General population	Three or more categories of alcohol consumption	Unprovoked seizures epilepsy morbidity	Cohort Case–control	Yes	Sep-2008	Yes	Partial - no age or sex reported	No	Yes	Yes
Updated search for Canada's LRDG 2022											
Brennan et al., 2020	General population and subgroups	Different levels of alcohol consumption, patterns of alcohol consumption, or both;	Long-term cognitive function	Cohort, nested case–control	Yes	Apr-2018	Yes - the search terms available in appendix	Yes	Yes	Yes	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
		and dose–response									
Carbia et al., 2018	Healthy adolescent and young adults (13 to 30 years old) with a binge drinking pattern	Consumption of large quantity of alcohol on one occasion leading to a blood alcohol concentration (BAC) of at least 0.08 g/dl	Neuropsychological consequences of binge drinking	Observational, cross-sectional	No	01 Jan-2000 to 16 Dec-2016	N/A	N/A	N/A	N/A	N/A
Coppens et al., 2019	Alcohol use disorder patients	Alcohol use disorder-related inflammation	Decreased cognitive functioning	Not stated	No	Oct-2018	N/A	N/A	N/A	N/A	N/A
Davis & Bajaj, 2018	Cirrhosis patients with and without hepatic encephalopathy	Chronic alcohol use	Brain	Not stated	No - Not a systematic review.	Not stated	N/A	N/A	N/A	N/A	N/A
de Goede et al., 2021	Adolescents and young adults ranging between 12	Any alcohol consumption compared to less or no	Measures of brain structure and activity, cognitive	Longitudinal studies, cohort	No	May-2018	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
	and 24 years of age at baseline	alcohol consump-tion	functioning, educational achievement, or alcohol use disorder								
Jiménez-Jiménez et al., 2019	General population	Alcohol consump-tion (2 categories)	Parkin-son's disease	Case–control, cohort	No	Jul-07-2018	N/A	N/A	N/A	N/A	N/A
Julian et al., 2019	Human	Chronic alcohol consump-tion	Alcohol-related peripheral neuropathy	Case–control, cohort, control trials, cross-sectional, population-based	No	June 2018	N/A	N/A	N/A	N/A	N/A
Julian et al., 2020	Human subjects consuming ethanol in excess	Chronic alcohol consump-tion	Autonomic dysfunc-tion	Cross-sectional, case–control, cohort, case series	No	June 2018	N/A	N/A	N/A	N/A	N/A
Kyriacou et al., 2021	Healthy adult participants (16 years and over)	Alcohol consump-tion	Prospective memory	Randomized controlled trials, cross-sectional	No	Jul-2019	N/A	N/A	N/A	N/A	N/A
Lao et al., 2021	General population	Alcohol consump-tion	Develop-ment of mild	No-Incorrect	No-it's a protocol for	No - Incorrect	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
			cognitive impair-ment into dementia	study type included.	systematic review	study type included					
Maurage et al., 2021	Participants with excessive alcohol consump-tion	Excessive alcohol exposure	Eye tracking indexes of cognitive and affective processes	Interven-tional; observa-tional; cross-sectional	No	Jul-01-2019	N/A	N/A	N/A	N/A	N/A
Maurage et al., 2020	Participants with acute alcohol consump-tion	Acute alcohol exposure	Eye tracking indexes of cognitive processes	Interven-tional; observa-tional; cross-sectional	No	Sep-10-2018	N/A	N/A	N/A	N/A	N/A
Platt et al., 2019	Users of common recreational drugs who were not intoxicated during testing	Recrea-tional drugs including alcohol (low, moderate and high lifetime exposure to a specific drug)	Prospectiv e memory performan ce	Parallel group design with a control condition and experi-mental condition - did not include any cohort, case–control or case-crossover	No-Incorrect study design	Mar-2017	N/A	N/A	N/A	N/A	N/A
Ran et al., 2021	Subjects without	Alcohol/ coffee/	Cognitive deficits	Prospec-tive cohort	Yes	Jun-04-2020	Partial - not checked the	Yes	Yes	Yes	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
	cognitive deficits at baseline	tea consump-tion (daily dose)		studies, nested case–control			references in the primary studies identified				
Rehm et al., 2019	General population	Alcohol use	Dementia	Systematic reviews	No	Oct-2017; updated search in Mar-2018	N/A	N/A	N/A	N/A	N/A
Stephan et al., 2017	Adult alcohol-dependent former users	Alcohol consump-tion in the past	Subcompon-ents of executive functioning and impulsivity	Not clearly stated	No	Jan-2015	N/A	N/A	N/A	N/A	N/A
Wilson et al., 2017	Humans	Problematic alcohol use (alcohol using group vs. a no or minimal alcohol using group)	Hippo-campal volume	Any empirical studies including cross-sectional	No	Dec-2015	N/A	N/A	N/A	N/A	N/A
Xu et al., 2017	General population (adults)	Alcohol consumption (dose–response)	Dementia	Prospect-ive cohort; prospect-ive nested case–control	Yes	Oct-07-2016	Partial -Not checked the references in the primary studies identified	Yes	Yes	Partial-clear descriptions /inclusion criteria of the population and outcome are not provided	Partial-no sensitivity test was done

Note: Systematic reviews that meet steps 1 to 3 inclusion criteria but were not included for mathematical modelling purposes are represented in yellow, while the systematic review included in mathematical modelling is represented in green.

Table 33. AMSTAR 2 assessment for Samokhvalov 2010b

Item	Result
Did the research questions and inclusion criteria for the review include the components of PECO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviationsfrom the protocol?	No
Did the review authors explain their selection of the study designs for inclusion in the review?	No
Did the review authors use a comprehensive literature search strategy?	Partial Yes
Did the review authors perform study selection in duplicate?	Not reported
Did the review authors perform data extraction in duplicate?	Not reported
Did the review authors provide a list of excluded studies and justify the exclusions?	No
Did the review authors describe the included studies in adequate detail?	Partial Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No
Did the review authors report on the sources of funding for the studies included in the review	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No, did not assess RoB
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No, did not assess RoB
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Table 34. GRADE assessment for Samokhvalov 2010b

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	GRADE reasons for downgrading or upgrading	Quality of evidence
Seizures (co-morbidity)	1 SR (6 case–control (cases n=934, controls n=1,398))	One systematic review including 6 case–control studies with an unknown risk of bias examined the association between alcohol consumption and epilepsy/unprovoked seizures. The risk of epilepsy/unprovoked seizures for <50g daily average consumption of pure alcohol reported RR = 1.29 (95% CI: 1.03-1.61) compared with non-drinkers (4 studies). A dose–response analysis reported that consumption of 12, 48, 72, and 96g of alcohol per day had RRs of 1.17 (95% CI: 1.13–1.21), 1.81 (95% CI: 1.59–2.07), 2.44 (95% CI: 2.00–2.97), and 3.27 (95% CI: 2.52–4.26), respectively, relative to abstainers (p = 0.787).	Risk of bias: -2 Inconsistency: -1 Indirectness: -1 Imprecision: -1 Publication bias: 0	Risk of bias: Unknown risk of bias. Inconsistency: No statistically heterogeneity detected however clinical heterogeneity is suspected due to inclusion of different outcome measures. Indirectness: indirectness for outcome due to definition being both unprovoked seizures and epilepsy. Imprecision: Moderate. Small sample sizes. Publication bias: None detected.	⨁◯◯◯

Note: N = number of participants; SR = systematic review; CI = confidence interval; RR = relative risk; g = grams.

Source: National Health and Medical Research Council, https://www.nhmrc.gov.au/about-us/publications/australian-guidelines-reduce-health-risks-drinking-alcohol. Attribution 4.0 International (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/

Malignant Neoplasms

For malignant neoplasms, four systematic reviews were included in the mathematical modelling: Bagnardi et al. (2015), the World Cancer Research Fund (WCRF, 2018e), Sun, Xie et al. (2020), and Vieira et al. (2019). The details of the selection process are presented below.

Thirty new systematic reviews on the association between alcohol consumption and malignant neoplasms were identified by the updated search. The results are presented in Table 35. Fifteen of these systematic reviews met the steps 1 to 3 inclusion criteria, but only two were included for mathematic modelling (Sun, Xie et al., 2020; Vieira et al., 2019). Most of the excluded studies included a specific type of cancer for which there is not yet an established causal relationship with alcohol use: stomach cancer in Deng et al. (2021); melanoma in

Gandini et al. (2018); gastric cancer in Han et al. (2017); gastric cancer morbidity and mortality in He et al. (2017); prostate cancer in Hong et al. (2020); follicular lymphoma in Odutola et al. (2020); hematological malignancies and subtypes in Psaltopoulou et al. (2018); bladder cancer in Vartolomei et al. (2019); nonmelanoma skin cancer in Yen et al. (2017); and endometrial cancer in Zhou et al. (2017).

Moreover, as the low-risk drinking guidelines are intended for use by the general population, systematic reviews that focus on the general population as opposed to cancer patients were prioritized. For that reason, the systematic review from Kim et al. (2019) on the association between alcohol consumption and colorectal cancer was replaced by the systematic review from Vieira et al. (2017). This latter study also replaced the World Cancer Research Fund's (2018c) systematic review identified by the AAWC. Based on AMSTAR 2 and GRADE assessments, the systematic review from Vieira et al. (2019) received a moderate quality score (see Tables 42 and 43, respectively). This systematic review includes studies at unknown risk of bias although limited to cohort studies. Only low or no heterogeneity was detected (I^2 = 24.5%). Publication bias was also evaluated but not detected. The presence of a dose–response gradient was identified as a strength for this study.

The systematic review by Park et al. (2020) on the association between alcohol use and liver cancer did not examine a dose–response relationship that was required for the mathematical modelling. This study was therefore replaced by the World Cancer Research Fund's (2018e) systematic review, which is an updated version of the 2015 study identified by the AAWC. As demonstrated by the AMSTAR 2 and the GRADE assessments (see Tables 38 and 39, respectively), the WCRF's (2018e) systematic review received a low-quality score. Included studies were prospective cohorts that are at lower risk of bias than other observational study designs. However, due to lack of explicit risk of bias assessment, the quality of the evidence was downgraded. Although substantial heterogeneity was detected (I^2 = 64%), it was sufficiently explored and explained by small effect size. Publication bias was evaluated and detected. The presence of a dose–response gradient was identified, which improves the quality attributed to the evidence.

The systematic review from Yu et al. (2020) on the association between alcohol use and squamous cell carcinoma and adenocarcinoma was also not included in the final model as this study did not provide a risk function for esophageal cancer in general. Indeed, mortality and morbidity data for Canada are coded by ICD-10 codes and these codes do not provide data on the sub-types of esophageal cancer, namely squamous cell carcinoma and adenocarcinoma. Therefore, the systematic review from Yu et al. (2020) was replaced by Bagnardi's et al. (2015) study, which was identified by the AAWC. In addition to esophageal cancer, the systematic review from Bagnardi et al. (2015) was also used to model mouth and pharynx cancer as well as larynx cancer. As demonstrated by the AMSTAR 2 and the GRADE assessments (see Tables 36 and 37, respectively), Bagnardi's et al. (2015) systematic review received a very low-quality score. In addition to including case–control study design, this systematic review did not report the risk of bias of their included individual studies. Moderate to substantial heterogeneity was detected (mouth and pharynx cancer: I^2 ranging from 26% to 77%; larynx cancer: I^2 ranging from 39% to 77%; esophageal cancer: I^2 ranging from 68% to 91%;) and not otherwise explored. Publication bias was not statistically explored. However, a dose–response relationship between alcohol consumption and these outcomes increases the confidence in this evidence. A large effect size was also found for mouth and pharynx cancer.

The World Cancer Research Fund's (2018a) systematic review on the association between alcohol consumption and breast cancer, which was identified by the AAWC, was replaced by a newer systematic review by Sun, Xie et al. (2020). AMSTAR 2 and GRADE assessments of the Sun, Xie et al. (2020) systematic review are presented in Tables 40 and 41, respectively. Sun, Xie et al. (2020) systematic review received a

high-quality score. Risk of bias was assessed using the Newcastle-Ottawa Scale (Wells et al., 2013) and scores ranged from 7 to 9 out of 9. The included studies are at a lower risk of bias due to restriction of inclusion to only prospective cohort studies. Substantial heterogeneity was detected ($I^2 = 64.7\%$); however, when assessing heterogeneity in subgroup analyses, the heterogeneity disappeared. Publication bias was evaluated, but none was detected. The presence of a dose–response gradient was identified, which improves the quality attributed to the evidence.

Nine systematic reviews identified by the AAWC were excluded as no relationship between alcohol use and these specific type of cancer has been establish yet: brain cancer, cervical cancer, lung cancer, lymphoma and melanoma in Bagnardi et al. (2015); multiple myeloma in Psaltopoulou et al. (2015); leukemia in Rota et al. (2014b); thyroid cancer in Wang, Cheng et al. (2016); pancreatic cancer in Wang, Gou et al. (2016); bladder cancer in World Cancer Research Fund, (2018b); gallbladder cancer in World Cancer Research Fund (2018d); renal cell carcinoma incidence and kidney cancer mortality in Xu et al. (2015); ovarian cancer in Yan-Hong et al. (2015).

Table 35. Full text screening for malignant neoplasms

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Included as evidence by the Australian guideline											
Bagnardi et al., 2015	General population	At least two levels of alcohol consumption vs non-drinkers and/or occasional drinkers	All cancers (mouth and oropharynx cancers, esophagus cancer, larynx cancer)	Case–control, cohort, or nested case–control	Yes	Sep-01-2012	Yes	Partial Included table of study characteris-tics but pooled by cancer site (review includes 572 studies)	No	Yes	Yes
Bagnardi et al., 2015	General population	At least two levels of alcohol consumption vs non-drinkers	All cancers (brain cancer, cervical cancer, lung	Case–control, cohort, or nested case–control	Yes	Sep-01-2012	Yes	Partial Included table of study characteris-tics but	No	Yes	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
		and/or occasional drinkers	cancer, lymphoma, melanoma)					pooled by cancer site (review includes 572 studies)			
Psaltopoulou et al., 2015	General population	Alcohol consump-tion	Multiple myeloma	Case–control, cohort	Yes	Dec-31-2013	Partial - searched PubMed only	Yes	Yes	Yes	Yes
Rota et al., 2014b	General population	Alcohol consump-tion	Leukaemia	Case–control, cohort	Yes	Aug-31-2013	Yes	Yes	No	Yes	Yes
Wang, Cheng et al., 2016	General population	Alcohol consump-tion	Thyroid cancer	Cohort or case–control	Yes	Aug-2015	Partial	Partial	Yes	Yes	Yes
Wang, Gou et al., 2016	General population	Alcohol intake	Pancreatic cancer	Prospect-ive cohorts	Yes	Aug-01-2015	Yes	Yes	Yes	Yes	Yes
WCRF, 2018a (revised version of the 2017 report)	General population	All exposures related to food, nutrition, and physical activity	Breast cancer	Randomized controlled trial, cohort, case–cohort or nested case control, pooled studies	Yes	Apr-30-2015	Partially searched PubMed only (justified)	Yes	Partially - study quality considered in report	Yes	Yes
WCRF, 2018c (revised version of	General population	All exposures related to food,	Colorectal cancer	Randomized controlled trial, prospective	Yes	Apr-30-2015	Partially Searched PubMed	Yes	Partially Study quality	Yes	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
the 2017 report)		nutrition, and physical activity		cohort, nested case–control, historical cohort study, case–cohort			only (justified)		considered in report		
WCRF, 2018b (revised version of the 2015 report)	General population	All exposures related to food, nutrition and physical activity	Bladder cancer	Randomized controlled trial, group randomized controlled trial, prospective cohort, nested case–control study, case–cohort study, or historical cohort study	Yes	Jul-31-2013	Partial - searched PubMed only (justified)	Yes	Partial - study quality considered in report	Yes	Yes
WCRF, 2018d (revised version of the 2015 report)	General population	All exposures related to food, nutrition and physical activity	Gallbladder cancer	Randomized controlled trial, group randomized controlled trial, prospective cohort, nested case–control study, case–cohort study,	Yes	Mar-31-2013	Partial - searched PubMed only (justified)	Yes	Partial - study quality considered in report	Yes	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
				or historical cohort study							
WCRF, 2018e (revised version of the 2015 report)	General population	All exposures related to food, nutrition and physical activity	Liver cancer	Randomized controlled trial, cohort studies	Yes	Mar-31-2013	Partial - searched Medline only (justified)	Yes	Partial - study quality considered in report	Yes	Yes
WCRF, 2018g (revised version of the 2016 report)	General population	All exposures related to food, nutrition and physical activity	Gastric/ stomach cancer	Randomized controlled trial, group randomized controlled trial, prospective cohort, nested case–control study, case–cohort study or historical cohort study	Yes	Feb-28-2014	Partially Searched PubMed only (justified)	Yes	Partial - study quality considered in report	Yes	Yes
WCRF, 2018f (revised version of the 2016 report)	General population	All exposures related to food, nutrition and physical activity	Oesophageal squamous cell carcinomas and oesophageal adenocarcinomas	Randomized controlled trial, group randomized controlled trial, prospective cohort, nested	Yes	Feb-28-2014	Partial - searched PubMed only (justified)	Yes	Partial - study quality considered in report	Yes	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
				case–control study, case–cohort study or historical cohort study							
Xu et al., 2015	General population	Alcohol drinking	Renal cell carcinoma incidence and kidney cancer mortality	Cohort studies or nested case–control	Yes	Feb-01-2015	Yes	Yes	Yes	Yes	Yes
Yan-Hong et al., 2015	General population	Alcohol intake	Ovarian cancer	Prospect-ive study (cohort or nested case–control)	Yes	May-01-2014	Yes	Yes	Yes	Yes	Yes
Zhao et al., 2016	General population	At least three levels of alcohol consump-tion	Prostate cancer	Case–control or cohort studies	Yes	Dec-01-2014	Yes	Yes	Partially Results analysed using different measures of bias	Yes	Yes
Updated search for Canada's LRDG 2022											
Brunner et al., 2017	Men with prostate cancer and controls	Alcohol consump-tion	Prostate cancer incidence and survival	Data from 25 studies in within the genome (PRACTICAL) consortium-	No. Not a systematic review.	Not stated	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
				Mendelian randomiza-tion study							
Caprio et al., 2020	General population	Alcohol consump-tion	Risk of cancer developme nt	Meta-analyses	No	2014-2019	N/A	N/A	N/A	N/A	N/A
Choi et al., 2018	General healthy popula-tions	Alcohol drinking	Risk of cancer	Cohort	Yes	31 March-2016	Yes	Partial age of the participants is not specified	Yes	Yes	Yes
Deng et al., 2021	Participants with pathological-ly confirmed stomach cancer compared to controls	Alcohol consump-tion (drinkers and non-drinkers; grams per day)	Stomach cancer	Cohort, case–control	Yes	Sep-2019	Partial - only one database was searched	Partial age of the participants is not specified	Partial-no tool used; only publication bias is calculated	Yes	Yes
Du et al., 2019	Patients with naso-pharyngeal carcinoma vs. controls (cancer free)	Alcohol consump-tion	Nasopharyn-geal carcinoma	Cohort, case–control	Yes	Aug-2018	Yes	Yes	Yes	Yes	No
Gandini et al., 2018	Human	Alcohol intake	Melanoma	Cohort, case–control	Yes	30 Jun-2017	Yes	Partial - age and gender of participants are not	Yes	Yes	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
								reported. No detailed description of the exposure			
Han et al., 2017	General population	Alcohol consump-tion (dose–response)	Gastric cancer	Cohort	Yes	Dec-2016	Yes	Yes	Yes	Partial-clear description of the population is not provided.	Yes
He et al., 2017	Adult participants (18 years or older)	Alcohol consump-tion	Gastric cancer morbidity and mortality	Cohort	Yes	Apr-2017	Yes	Yes	Yes	Yes	Yes
Hong et al., 2017	General population	Alcohol intake	Thyroid cancer	Cross-sectional, case–control, cohort	Yes	May-2015	Yes	Yes	Yes	Partial-clear descriptions/ inclusion criteria of the outcome and exposure is not provided	No
Hong et al., 2020	Men in general population	Alcohol intake	Prostate cancer (non-aggressive and aggressive)	Cohort	Yes	Apr-2020	Yes	Yes	No	Partial-clear descriptions/ inclusion criteria of the outcome is not provided	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis
Kim et al., 2019	Patients with colorectal cancer	Alcohol consumption	Colorectal cancer–specific mortality	Cohort	Yes	December 2018	Yes	Partial - gender of the participant is not reported	Yes	Yes	Yes
Ma et al., 2017	Patients with gastric cancer & persons with non-gastric cancer	Alcohol consumption	Gastric cancer	Case–control	Yes	2015	Partial - not checked the references in the primary studies identified	Partial-age and confounders not stated	Partial-no tool used; only publication bias is calculated	Yes	Yes
Matejcic et al., 2017	Humans	Alcohol intake	Oesophageal cancer	case–control, prospective cohort, meta-analyses, pooled analysis	No	Nov-2016	N/A	N/A	N/A	N/A	N/A
McMenamin et al., 2017	Gastrointestinal cancer patients	Smoking and alcohol consumption	Prognosis/survival in gastrointestinal cancer	Interventional; observational	No	May-2016	N/A	N/A	N/A	N/A	N/A
Miyazaki et al., 2017	Cigarette smokers and consumers of alcohol	Smoking and drinking cessation	Risk of esophageal cancer	Observational (cohort, case–control)	No	Aug-2016	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
O'Sullivan et al., 2021	Individuals with CRC diagnosed before the age of 50 and healthy individuals younger than the age of 50	Nongenetic risk factors including alcohol consump-tion (highest study defined category compared with never drinkers)	Early-onset colorectal cancer	Observation-al (prospective or retrospective cohort, case–control, cross-sectional)	No	Aug-05-2020	N/A	N/A	N/A	N/A	N/A
Odutola et al., 2020	General population	Modifiable lifestyle factors including alcohol consump-tion	Follicular lymphoma	Cohort; case–control	Yes	Jan-01-2020	Yes - search terms/ MESH terms in the Supplement-ary materials	Partial-clear description of outcome is not provided	Yes	Partial-clear description/ inclusion criteria for the population is not provided	Yes
Psaltopoulou et al., 2018	Adult populations	Alcohol consump-tion in three levels (light; moderate; heavy drinkers)	Hemato-logical malignancies and subtypes	Cohort	Yes	Aug-31-2016	Partial-only one database was searched	Partial - age of participants is not stated	Yes	Yes	Yes
Park et al., 2020	General population	Alcohol consumption (at least two	Liver cancer	Nested case–	Yes	Jul-31-2019	Yes	Yes	Yes	Yes	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
		levels of alcohol consumption vs non-drinkers and/or occasional drinkers)		control, cohort							
Si et al., 2017	General population	Dietary patterns including alcohol consump-tion (two categories)	Endo-metrial cancer	Cohort; case–control	Yes	May-2015	Yes	Yes	Yes	Yes	No
Sun, Yan et al., 2020	Patients with esophageal cancer	Dietary factors including alcohol consumption (comparing the highest with the lowest categories of intake)	All-cause mortality, esophageal cancer-specific mortality and esophageal cancer recurrence	Cohort	No	Oct-2019	N/A	N/A	N/A	N/A	N/A
Sun, Xie et al., 2020	General population	Alcohol consumption (the dose–response analysis of different	Breast cancer	Cohort	Yes	Dec-01-2018	Yes - search terms in the supplemen-tary materials	Yes	Yes	Partial - clear description for the population	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
		alcoholic beverages)								is not provided	
Vartolomei et al., 2019	General population (all genders, males or females) or compared with a control group of individuals without bladder cancer	Alcohol consump-tion (moderate or heavy dose, compared to non-drinkers)	Bladder cancer	Observatio nal cohorts; case–control	Yes	May-2018	Partial - not checked the references in the primary studies identified	Partial - a clear description of the outcomes is not provided	Yes	Partial-clear description /inclusion criteria of the outcome is not provided	Partial-only two categories of alcohol use compared in each analysis (moderate vs. none and heavy vs. none) but no levels of alcohol consumption
Veettil et al., 2021	Adults	Dietary patterns including alcohol	Colorectal cancer	Umbrella review of meta-analyses of prospective observation-al studies	No - incorrect study type	Sep-2019	N/A	N/A	N/A	N/A	N/A
Vieira et al., 2017	General populations	Foods and beverages intake including alcohol consumption (continuous intake levels)	Colorectal, colon and rectal cancer	Randomize controlled trial or prospective studies with cohort, case–cohort or nested	Yes	May-31-2015	Partial-key words and/or MESH terms not provided	Partial-a clear description of the outcomes is not provided	No	Partial - clear descriptions of the population and outcomes are not provided	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
				case–control design							
Vingeliene et al., 2017	General population	Dietary and anthropo-metric factors including alcohol consumption (in grams)	Esophageal cancer risk	Cohort, nested case–control or case–cohort	Yes	Jan-10-2017	Partial-key words and/or MESH terms not provided	Partial - age is not included. A clear description of the outcomes is not provided	No	Partial - clear description of the population is not provided	Yes
Wang, Xiao et al., 2017	General population	Alcohol consumption (in grams-dose–response)	Gastric cancer risk	Cohort; case–control; nested case–control	Yes	Dec-31-2016	Partial-only one data base is searched. Not checked the references in the primary studies identified	Partial - age is not specified. A clear description of the outcomes is not provided	Yes	Partial - clear descriptions/ inclusion criteria of the population and outcome are not provided	Yes
Yen et al., 2017	General population	Alcohol intake (dose–response)	Non-melanoma skin cancer	Cohort; case–control	Yes	Oct-30-2016	Yes - key words search are in supplement-ary materials	Partial - a clear description of the outcomes is not provided.	Partial - a specific quality assessmen t tool is not used.	Partial-clear descriptions /inclusion criteria of the population and outcome are not provided.	Yes
Yu et al., 2020	General population	Alcohol consumption including	Esophageal cancer by histological	Cohort; case–control	Yes	Dec-2019	Yes	Yes	Yes	Partial-clear descriptions/ inclusion	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
		different alcoholic beverages (dose–response)	type (esophageal squamous cell carcinoma and esophageal adeno-carcinoma)							criteria of the population and outcome are not provided	
Zhou et al., 2017	General population	Alcohol intake (dose–response)	Endometrial cancer	Cohort; case–control	Yes	Jan-05-2016	Partial -not checked the references in the primary studies identified	Partial-A clear description of the outcomes is not provided	Yes	Partial-clear descriptions/ inclusion criteria of the population and outcome are not provided	Yes

Note: Systematic reviews that meet steps 1 to 3 inclusion criteria but were not included for mathematical modelling purposes are represented in yellow, while systematic reviews included in mathematical modelling are represented in green.

Table 36. AMSTAR 2 assessment for Bagnardi, 2015

Item	Result
Did the research questions and inclusion criteria for the review include the components of PECO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviationsfrom the protocol?	No
Did the review authors explain their selection of the study designs for inclusion in the review?	No
Did the review authors use a comprehensive literature search strategy?	Partial Yes
Did the review authors perform study selection in duplicate?	No
Did the review authors perform data extraction in duplicate?	Not reported

Did the review authors provide a list of excluded studies and justify the exclusions?	No
Did the review authors describe the included studies in adequate detail?	Partial yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No
Did the review authors report on the sources of funding for the studies included in the review	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No, did not assess RoB
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No, did not assess RoB
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Table 37. GRADE assessment for Bagnardi, 2015

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	GRADE reasons for downgrading or upgrading	Quality of evidence
Mouth and pharynx cancer	1 SR (5 cohort, 47 case–control, n=13,895 cases)	1 SR including 5 cohort and 47 case–control studies with unknown risk of bias, reported a summary RR of 1.13 (95%CI: 1.00–1.26), I^2=26%) for low consumption (≤12.5g per day), 1.83 (95%CI: 1.62–2.07), I^2=72%) for moderate consumption (≤50g per day) and 5.13 (95%CI: 4.31–6.10), I^2=77%) for heavy (>50g per day) alcohol consumption compared with non-drinkers. P number for dose–response analysis not reported in the systematic review.	Risk of bias: -2 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: -1 Dose response: +1 Large effect: +1	Risk of bias: Downgraded by 2 as case–control study design was included and risk of bias was not reported in the SR. The number of participants from case–control or cohort studies is not reported. Inconsistency: Moderate heterogeneity detected and not otherwise explained. Indirectness: Nil. Imprecision: Nil. Publication bias: No test undertaken, therefore downgraded by 1 as it is considered likely. Dose response: Detected, therefore upgraded by 1.	⨁◯◯◯

				Effect size: Large, therefore upgraded by 1.	
Larynx cancer	1 SR (3 cohort, 38 case–control, n=7,059 cases)	1 SR including 3 cohort and 38 case–control studies with unknown risk of bias, reported a summary RR of 0.87 (95%CI: 0.68–1.11), I^2=39%) for low consumption (≤12.5g per day), 1.44 (95%CI: 1.25–1.66), I^2=61%) for moderate consumption (≤50g per day) and 2.65 (95%CI: 2.19–3.19, I^2=77%) for heavy (>50g per day) alcohol consumption compared with non-drinkers. P number for dose–response analysis not reported in the systematic review.	Risk of bias: -2 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias: -1 Dose response: +1	Risk of bias: Downgraded by 2 as case–control study design was included and risk of bias was not reported in the SR. The number of participants from case–control or cohort studies is not reported. Inconsistency: Moderate heterogeneity detected and not otherwise explained. Indirectness: Nil. Imprecision: Nil. Publication bias: No test undertaken, therefore downgraded by 1 as it is considered likely. Dose response: Detected, therefore upgraded by 1.	⊕◯◯◯
Esophagus cancer	(13 cohort studies, 41 case–control studies, n=10,633 cases)	1 SR including 13 cohort and 41 case–control studies with unknown risk of bias, reported a summary RR of 1.26 (95%CI: 1.06–1.50), I^2=68%) for low consumption (≤12.5g per day), 2.23 (95%CI: 1.87–2.65), I^2=85%) for moderate consumption (≤50g per day) and 4.95 (95%CI: 3.86–6.34, I^2=91%) for heavy (>50g per day) alcohol consumption compared with non-drinkers. P number for dose–response analysis not reported in the systematic review.	Risk of bias: -2 Inconsistency: -2 Indirectness: 0 Imprecision: 0 Publication bias: -1 Dose response: +1	Risk of bias: Downgraded by 2 as case–control study design was included and risk of bias was not reported in the SR. The number of participants from case–control or cohort studies is not reported. Inconsistency: Substantial heterogeneity detected and not otherwise explained. Indirectness: Nil. Imprecision: Nil. Publication bias: No test undertaken, therefore downgraded by 1 as it is considered likely. Dose response: Detected, therefore upgraded by 1.	⊕◯◯◯

Note: SR = systematic review, RR = relative risk, CI = confidence interval

Table 38. AMSTAR 2 assessment for WCRF, 2018e

Item	Result
Did the research questions and inclusion criteria for the review include the components of PECO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviationsfrom the protocol?	Yes
Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
Did the review authors use a comprehensive literature search strategy?	No
Did the review authors perform study selection in duplicate?	Yes
Did the review authors perform data extraction in duplicate?	Not reported
Did the review authors provide a list of excluded studies and justify the exclusions?	No
Did the review authors describe the included studies in adequate detail?	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No
Did the review authors report on the sources of funding for the studies included in the review	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No, did not assess RoB
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No, did not assess RoB
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No

Table 39. GRADE assessment for World Cancer Research Fund, 2018e

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	GRADE reasons for downgrading or upgrading	Quality of evidence
Liver cancer	1 SR (14 cohort, n=5,650 cases)	1 SR including 14 cohort studies with unknown risk of bias, reported a summary RR of 1.04	Risk of bias: -1 Inconsistency: 0	Risk of bias: Included studies were prospective cohorts which are at lower risk of bias than other	⨁⨁◯◯

		(95% CI: 1.02-1.06; I^2=64.0%) per 10g of ethanol increase per day in dose–response analysis).	Indirectness: 0 Imprecision: 0 Publication bias: -1 Dose response: +1	observational study designs, however due to lack of explicit risk of bias assessment, it was downgraded by 1. Inconsistency: Inconsistency detected (I^2=64%) but explained by small effect size. Indirectness: Nil. Imprecision: Nil. Publication bias: Detected. Dose response: Strong dose response, upgraded by 1.	

Note: SR = systematic review, RR = relative risk, CI = confidence interval.

Table 40. AMSTAR 2 assessment for Sun, Xie, et al., 2020

Item	Result
Did the research questions and inclusion criteria for the review include the components of PECO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviationsfrom the protocol?	No
Did the review authors explain their selection of the study designs for inclusion in the review?	No
Did the review authors use a comprehensive literature search strategy?	Partial Yes
Did the review authors perform study selection in duplicate?	Not reported
Did the review authors perform data extraction in duplicate?	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	No
Did the review authors describe the included studies in adequate detail?	Partial yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
Did the review authors report on the sources of funding for the studies included in the review	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No

Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Table 41. GRADE assessment for Sun, Xie, et al., 2020

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	GRADE reasons for downgrading or upgrading	Quality of evidence
Breast cancer	1 SR (22 cohort studies, n=45,350 cases)	1 SR including 22 cohort studies with low risk of bias, found that with every 20 g total alcohol increase, the magnitude of the estimated RR ranged from a 22% (95%CI = 1.17-1.27) increase in breast cancer to 23.3% (95%CI = 1.18–1.29) increase in postmenopausal breast cancer in dose–response analysis. For alcohol type, every extra 20 g/day ethanol in wine increased the incidence by 18.6% (95%CI = 1.08–1.30). No statistical evidence was found for beer and spirits specifically.	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose response: +1	Risk of bias: Risk of bias was assessed using NOS and scores ranged from 7 to 9 out of 9. The included studies are at a lower risk of bias due to restriction of inclusion to only prospective cohort studies. Inconsistency: Substantial heterogeneity was detected; however, when assessing heterogeneity in subgroup analyses, the heterogeneity is not substantial. Indirectness: Nil. Imprecision: Nil. Publication bias: None detected. Dose response: Detected.	⨁⨁⨁⨁

Note: SR = systematic review, RR = relative risk, CI = confidence interval, NOS = Newcastle-Ottawa Scale

Table 42. AMSTAR 2 assessment for Vieira, 2017

Item	Result
Did the research questions and inclusion criteria for the review include the components of PECO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviationsfrom the protocol?	Yes
Did the review authors explain their selection of the study designs for inclusion in the review?	No
Did the review authors use a comprehensive literature search strategy?	Partial yes
Did the review authors perform study selection in duplicate?	Yes

Did the review authors perform data extraction in duplicate?	Not reported
Did the review authors provide a list of excluded studies and justify the exclusions?	No
Did the review authors describe the included studies in adequate detail?	Partial yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No
Did the review authors report on the sources of funding for the studies included in the review	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No, did not assess RoB
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No, did not assess RoB
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Table 43. GRADE assessment for Vieira, 2017

Outcome	No of reviews (SRs) (No. unique studies and No. participants)	Narrative summary of results	GRADE	GRADE reasons for downgrading or upgrading	Quality of evidence
Colorectal cancer	1 SR (16 cohort studies, n=15,896 cases)	1 SR including 16 cohort studies with an unknown risk of bias, found that each increase of 10 g/day of alcohol intake (as ethanol in alcoholic beverages) was associated with an increased risk of colorectal cancer (RR = 1.07 (95% CI = 1.05–1.09, I^2 = 25%, *ph* = 0.21).	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Dose response: +1	Risk of bias: Included studies at unknown risk of bias but limited to cohort studies only. Inconsistency: Low or none detected. Indirectness: Nil. Imprecision: Nil. Publication bias: None detected. Dose response: Detected.	⨁⨁⨁◯

Note: SR = systematic review, RR = relative risk, CI = confidence interval

Mental Health and Substance Use Disorders

No systematic reviews for mental health and substance use disorders were included in the mathematical modelling. The details are presented below.

Seven new systematic reviews were identified on the association between alcohol consumption and mental health and substance use disorders. Results from the updated search are presented in Table 44. The systematic review from Li et al. (2020) on depressive symptoms was the only one that met the steps 1 to 3 inclusion criteria. This study, however, was not included in the mathematical modelling because the relationship between alcohol use and depression is biased by reverse causality. That is, alcohol use may increase the risk of having depression, but having depression may also increase the risk of consuming alcohol. This reverse causality is not accounted for in the current lifetime risk of alcohol mortality and morbidity models.

Table 44. Full text screening for mental and substance use disorders

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Included as evidence by the Australian guideline											
Evaluated some systematic reviews, but none were included											
Updated search for Canada's LRDG 2022											
Amiri & Behnezhad, 2020b	General population	Alcohol consumption (any intake)	Suicide	Cohort longitudinal	No	May-2018	N/A	N/A	N/A	N/A	N/A
Azevedo et al., 2020	Women with binge eating disorder who consume alcoholic beverages	Alcohol consumption	Binge eating	Longitudinal, cross-sectional, cohort, case–control	No	2015-2019	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Bresin & Mekawi, 2020	General population	Alcohol use (alcohol use frequency or alcohol use disorder diagnosis)	Non-suicidal self-injury	Not stated	No	Aug-2019	N/A	N/A	N/A	N/A	N/A
Cruise & Becerra, 2018	General population	Problem-atic alcohol use	Alexithymia	Any design including cross-sectional	No	Nov-7-2016	N/A	N/A	N/A	N/A	N/A
Hakulinen & Jokela, 2019	General population	Alcohol use	Personality trait change	Cohort	No	Not specified	N/A	N/A	N/A	N/A	N/A
Li et al., 2020	General population	Alcohol use disorders and alcohol intake levels	Depressive symptoms	Cohort	Yes	Apr-15-2019	Yes	Yes	Yes	Yes	Yes
Newton et al., 2018	General population & subgroups	Alcohol consump-tion	Several mental health outcomes (depression, suicide, anxiety	Prospect-ive cohort; cross-sectional; case–control	No	2017	N/A	N/A	N/A	N/A	N/A

Note: Systematic review that meets steps 1 to 3 inclusion criteria but was not included for mathematical modelling purposes is represented in yellow.

Other Conditions

No other systematic reviews were included in the mathematical modelling. The details are presented below.

Thirty-nine new systematic reviews on various outcomes were identified in the updated search (see Table 45). Although five of these studies met the steps 1 to 3 inclusion criteria, none were included in the mathematical modelling. Only diseases and injuries causally related to alcohol can be modelled for the low-risk drinking guidelines. Because there are no established causal relationships between alcohol use and gallstone disease (Cha et al., 2019), chronic kidney damage (Li et al., 2019), and systemic lupus erythematosus (Wang et al., 2021), it was not possible to include these outcomes in the model. Moreover, while alcohol may be related to fecundability (Fan et al., 2017) and rheumatoid arthritis (Ye et al., 2021), these diseases are not considered fatal. As disability from both fecundability and rheumatoid arthritis is not specifically measured by the Institute for Health Metrics and Evaluation (i.e., the data source for morbidity data), it was not possible to use these systematic reviews to model the lifetime risk of an alcohol-attributable death.

Two of the three systematic reviews identified by the AAWC were also excluded from the mathematical modelling for the same reason. Indeed, osteoporosis (Berg et al., 2008) and gout (Wang et al., 2016) are also not considered fatal. The third systematic review identified by the AAWC on the association between alcohol consumption and all-cause mortality (Stockwell et al., 2016) was also excluded. Disease and injury-specific relative risks were used instead of the broader category of all-cause mortality.

Table 45. Full text screening for other conditions

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Included as evidence by the Australian guideline											
Berg et al., 2008	General population	Alcohol consumption compared to non-drinkers	Osteoporosis	Experimental (none included) Cohort case–control	Yes	May-14-2007	Yes	Yes	Yes	Yes	Yes
Stockwell et al., 2016	General population	Alcohol consumption	All-cause mortality	Cohort	Yes	Feb-25-2015	Yes	Yes	Partial	Yes	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Wang et al., 2013	General population	Alcohol where non/ occasional drinking is the reference group	Gout	Cohort Case–control	Yes	Jan-2013	Partial - PubMed, Web of Science, Google Scholar and Wanfang Med Online searched - Reference lists searched - MESH terms/ search strategy not stated	Yes	Yes	Yes	Yes
Updated search for Canada's LRDG 2022											
Amiri & Behnezhad, 2020a	General population	Alcohol consumption (any intake)	Sick leave	Cohort	No	Nov-2018	N/A	N/A	N/A	N/A	N/A
Barbhaiya et al., 2017	Women followed in the Nurses' Health Study cohorts	Alcohol consump-tion	Systemic lupus erythema-tosus	Selected cohorts	No - not a systematic review.	Not stated	N/A	N/A	N/A	N/A	N/A
Cha et al., 2019	General population	Alcohol consump-tion-grams	Gallstone disease	Case–control, cohort	Yes	Mar-01-2018	Yes-the search terms	Yes	Yes	Yes	Partial-no sensitivity

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
		of ethanol per day (categories & dose–response)					available in Appendix 1				test was done.
Cheraghi et al., 2019	General population	Alcohol consump-tion	Osteo-porosis	Cohort, case–control, cross-sectional	No	Jun-2018	N/A	N/A	N/A	N/A	N/A
Chiaffarino et al., 2017	General population	Alcohol consump-tion (ever and current versus never alcohol)	Incidence of uterine myoma	Case–control, cohort	No	May-2017	N/A	N/A	N/A	N/A	N/A
Cummings et al., 2020	Humans	Alcohol consump-tion (single occasion and frequency)	Dietary intake (carbo-hydrate, fat, and protein intake)	Experiment al and observa-tional, including cross-sectional design	No-Incorrect study type included.	Mar-2019	N/A	N/A	N/A	N/A	N/A
Cunningha m et al., 2017	Adoles-cents with psychiatric disorders	Alcohol use (lifetime and current (i.e., prior six months) and alcohol	Sexual risk behaviours	Any design	No	Feb-2015	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
		abuse and/ or depend-ence									
Davis-Martin et al., 2017	Human participants with a diagnosis of migraine or tension-type headache	Alcohol use disorders and alcohol consump-tion (any)	Primary headache	Any including cross-sectional	No	May-6-2015	N/A	N/A	N/A	N/A	N/A
de Vries et al., 2019	Selected groups	Gene-alcohol inter-actions	Lipid Levels	Not stated	No	Not stated-Not a systematic review	N/A	N/A	N/A	N/A	N/A
Fan et al., 2017	Females	Alcohol consumption (dose–response for total and specific types of alcohol consumption beverage)	Fecund-ability	Case–control, cohort	Yes	Nov-01-2016	Yes	Yes	Yes	Yes	Yes
Fernández et al., 2018	Women	Alcohol consumption (any intake, heavy drinking)	Pre-menstrual syndrome	Case–control, cohort, cross-sectional	No	May-2017	N/A	N/A	N/A	N/A	N/A
Ge et al., 2018	Adults living with human	Alcohol use	Risk of developing adverse	Longitudi-nal, cross-sectional	No	2005 to 2015	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
	immunodeficiency virus		health outcomes								
Grochowski et al., 2019	Patients with a history of chronic alcohol abuse	Alcoholism	Fluctuations in the concentration of iron, magnesium, copper and manganese	Not stated	No	Not stated	N/A	N/A	N/A	N/A	N/A
Holton et al., 2017	Older adults	Concurrent use of alcohol and alcohol-interactive medicines	Adverse outcomes	Cross-sectional	No	Jun-2016	N/A	N/A	N/A	N/A	N/A
Hu N et al., 2020	General community population	Alcohol consumption	Incidence of sleep disorder	Cohort	Yes	Mar-2020	Partial -not checked the references in the primary studies identified	Partial confounders are not specified	Yes	Yes	No
Huang et al., 2017	Adults without pre-existing cardiovascular disease	Moderate alcohol consumption (current alcohol use with a comparison	Atherosclerosis	Controlled intervention study	No	Sep-2016	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
		group of no alcohol use)									
Ijaz et al., 2017	Homeless problem-drinking populations	Problematic drinking	Nutritional deficiencies	Surveys, case reports, intervention study	No	November 2016	N/A	N/A	N/A	N/A	N/A
Jaruvongvanich et al., 2017	General population	Alcohol intake	Diverticulosis and diverticular bleeding	Cross-sectional; cohort	No	February-2017	N/A	N/A	N/A	N/A	N/A
Jores et al., 2019	General population	Alcohol consumption (BAC) levels	Witness testimony	Experimental	No	Not stated	N/A	N/A	N/A	N/A	N/A
Kojima et al., 2018	Middle-aged or older population in the community	Alcohol consumption (amount of pure alcohol in grams)	Incident frailty	Cohort	Yes	2000 to July 2016	Yes	Yes	Yes	Yes	No
Kwon et al., 2019	Adolescents residing in North America, aged between 10 and 21 years old	Substance use including alcohol consumption (any)	Sleep disturbances	Any design including cross-sectional	No	Sep-2018	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Li et al., 2019	Subjects free of kidney diseases at baseline	Alcohol drinking	Chronic kidney damage	Cohort	Yes	March-2019	Yes	Yes	Yes	Yes	Yes
Litwinowicz et al., 2020	Individuals of any age with alcohol use disorders	Alcohol use disorders	Intestinal micro-biome alterations	Cross-sectional, longitud-inal; prospect-ive	No	Jan-17-2019; updated on Sep-15-2019	N/A	N/A	N/A	N/A	N/A
Lubis et al., 2020	Patients with age-related macular degenera-tion	Alcohol consump-tion	Early age-related macular degenera-tion	Prospect-ive-not clear	No	May-2020	N/A	N/A	N/A	N/A	N/A
Mantzourani et al., 2018	Patients with inflam-matory bowel diseases	Alcohol and narcotics use	Inflammatory bowel diseases (prevalence, develop-ment, symptoms)	Any type including cross-sectional	No	Mar-2016	N/A	N/A	N/A	N/A	N/A
Mello et al., 2019	Humans	Synergistic consump-tion of alcohol and tobacco	Occur-rence of oral squamous cell carcinoma	Cohort; case–control;	No	Jul-01-2018	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis
Meyrel et al., 2020	Human participants	Different stages of alcohol use)	Circadian rhythms	Any type	No	Jul-2018	N/A	N/A	N/A	N/A	N/A
Nie & Zhao, 2017	People with ulcerative colitis diagnosis	Alcohol and other beverage consumption (highest versus the lowest consumption level)	Development of ulcerative colitis	Case–control; Prospective cohort	Yes	Aug-01-2017	Yes	Partial-alcohol consumption categories (highest versus the lowest level) were not predefined	Yes	Yes	No
Ohlsson, 2017	General population	Smoking and alcohol intake	Functional gastrointestinal disorders	Not clearly stated	No	Not clearly stated	N/A	N/A	N/A	N/A	N/A
Probst et al., 2020	General adult population (aged ≥15 years)	Alcohol use and drinking patterns	Socioeconomic inequalities in mortality	Longitudinal (data linkage), cohort	No	Jun-30-2019	N/A	N/A	N/A	N/A	N/A
Pulikkotil et al., 2020	Adults	Alcohol consumption (highest versus lowest/non-alcohol)	Presence/occurrence of periodontitis	Observational including longitudinal and cross-sections-not separated	No	Nov-30-2018	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Rehm et al., 2017a	General population	Alcohol consump-tion	Disease or injury	Reviews; meta-analyses	No	Oct-2016	N/A	N/A	N/A	N/A	N/A
Simou et al., 2018b	Adults aged 18 years and over	Alcohol consump-tion	Sleep apnoea	Longitud-inal, cohort, case control, cross-sectional	No-cross-sectional studies not separated from others in the analyses	Dec-2015	N/A	N/A	N/A	N/A	N/A
Stockwell et al., 2018	General population	Extent of under-estimation of alcohol consump-tion	All-cause mortality	Cohort	No - This article used results from a previous systematic review (Stockwell et al, 2016)	Dec-31-2016	N/A	N/A	N/A	N/A	N/A
Wang et al., 2017	General population	Alcohol consump-tion (categories & in grams for dose–response)	Gallstone disease	Cohort; case–control	Yes	May-2016	Yes	Partial - a clear description of the outcomes is not provided	Partial - no tool used; only publication bias is calculated	Partial - inclusion criteria of the population and outcome are not provided	Yes
Wang et al., 2021	General population or systemic lupus	Alcohol intake at various levels	Systemic lupus erythemat osus	Cohort; case–control	Yes	Mar-2020	Yes	Yes	Yes	Partial-clear description /inclusion	Partial-only two categories of alcohol

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
	erythe-matosus patients with matched controls									criteria of the outcome is not provided.	use included in each analysis
Ye et al., 2021	US adults	Non-genetic risk factors including alcohol use (dose–response)	Incidence of rheuma-toid arthritis	Cohort; case–control; nested case–control	Yes	Mar-31-2019	Partial - Not checked the references in the primary studies identified	Partial - A clear description of the outcomes is not provided	Yes	Partial-clear descriptions/ inclusion criteria of the outcome are not provided	Yes
Yoon BH et al., 2017	Adults (Japanese popula-tions)	Alcohol intake (habits (never, former, or current), average drinking consumption (g/week) and cumulative drinking consumption (drink-years))	Osteo-necrosis of the femoral head	Case–control	No - population is not relevant	Jan-2016	N/A	N/A	N/A	N/A	N/A
Ziembicki et al., 2017	Female partici-pants	Alcohol consumpti on	Percent breast density	Cross-sectional;	No	Nov-30-2015	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
				case–control							

Note: Systematic reviews that meet steps 1 to 3 inclusion criteria but were not included for mathematical modelling purposes are represented in yellow.

Question 3: Pregnancy and Child Development Risks and Benefits

No systematic reviews were included in the mathematical modelling for pregnancy and child development risks and benefits. The details are presented below.

Twenty-two new systematic reviews were identified in the updated search about the risks and benefits associated with alcohol consumption by women who are pregnant or breastfeeding, for fetal, infant and child development. These results are presented in Table 46. Only two of these studies (San Martin Porter et al., 2019; Zhang et al., 2020) met the steps 1 to 3 inclusion criteria, although none were included in the mathematical modelling as the lifetime risk of alcohol-attributable mortality and morbidity curves do not take into consideration alcohol consumption while pregnant. The three systematic reviews identified by the AAWC (Bay & Kesmodel, 2011; O'Keeffe et al., 2014; Patra et al., 2011) were also excluded from the mathematical modelling for the same reason.

Table 46. Full text screening for women who are pregnant or breastfeeding, for fetal, infant and child development

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Included as evidence by the Australian guideline											
Bay & Kesmodel, 2011	Pregnant women	Daily, moderate and binge drinking	Child motor function	Yes	Case–control cohort	Feb-10	Yes	Yes	Partial - not reported for	Yes	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
									individual studies		
O'Keeffe et al., 2014	Pregnant women	Prenatal alcohol consump-tion	Communi-cation delay Communi-cation development	Yes	Case–control cohort	Mar-12	Yes	Yes	Yes	Yes	Yes. No meta-analysis but justified.
Patra et al., 2011	Pregnant women	Maternal alcohol consump-tion	Low birth, preterm birth, and small for gestational age	Yes	Case–control cohort	Aug-09	Yes	Partial - age of participant is not specified.	Partial - publication bias only	Yes	Yes
Updated search for Canada's LRDG 2022											
Brown et al., 2018	Breast-feeding mothers	Maternal drug use including any alcohol use	Lactation	No	Any	Not stated	N/A	N/A	N/A	N/A	N/A
Easey et al., 2019	Pregnant women and their offspring	Low levels of prenatal alcohol exposure (not properly defined)	Offspring mental health at age 3 or older	No	Any design	Mar-15-2017	N/A	N/A	N/A	N/A	N/A
Garrison et al., 2019	Human	Prenatal alcohol exposure	Neuro-development and behaviour	No	Cohort	Jan-1980 to July-2018	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis
Halling-Overgaard et al., 2018	Pregnancy alcohol users	Alcohol use	Atopic dermatitis	No	Cross-sectional, cohort, case–control	Dec-2016	N/A	N/A	N/A	N/A	N/A
Hendricks et al., 2019	From infancy (birth to 2 years old) up to preschool age (6 years)	Prenatal alcohol exposure	Language, speech and communication development	No	Cohort studies with at least 2 time-points	Not specified	N/A	N/A	N/A	N/A	N/A
Hu et al., 2021	Pregnant women	Maternal alcohol use (yes vs. no)	Gestational diabetes mellitus	No	Cross-sectional, cohort, or case–control;	Mar-25-2020	N/A	N/A	N/A	N/A	N/A
Karalexi et al., 2017	Parents and their offspring	Paternal consumption during preconception and maternal consumption during pregnancy (dose–response)	Leukemia in childhood (0–14 years)	Yes	Case–control, cohort	Feb-14-2016	Partial-only one database was searched.	Yes	Yes	Yes	No
Khoury et al., 2018	Children and adolescents with prenatal	Prenatal alcohol exposure	Internalizing and	No	Not stated	Jan-2018	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
	alcohol exposure to non- or light-exposed controls and attention-deficit/hyper-activity disorder samples		externaliz-ing behaviour outcomes								
Mamluk et al., 2017	Pregnant women or women trying to conceive with prospective assessment of prenatal alcohol exposure (before birth)	Low level of maternal alcohol consumption (up to 32 g/week) versus abstinence	Several pregnancy and offspring outcomes	No. Incorrect study type included.	Quasi-experiment al; negative control; Mendelian randomiza-tion	Jul-11-2016	N/A	N/A	N/A	N/A	N/A
Mamluk et al., 2020	Pregnant women or women trying to conceive with prospective assessment of prenatal alcohol exposure (before birth)	Prenatal alcohol exposure	Several pregnancy and offspring outcomes	No	RCT; Mendelian randomiza-tion; natural experiment	Jun-21-2018	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
McQuire et al., 2020	Pregnant women and their offspring	Prenatal alcohol exposure and other risk factors	Fetal alcohol spectrum disorders (FASDs)	No	Systematic reviews; other sources	Mar-02-2016; Supplement-ary searches were concluded on Dec-22-2017.	N/A	N/A	N/A	N/A	N/A
Müller-Schulte et al., 2018	Target population of neonates and children <19 years of age	Intake of alcohol, tobacco smoking and/or consump-tion of illicit drugs during pregnancy	Risk of neuro-blastoma in the child	No	Case–control	Feb-2017	N/A	N/A	N/A	N/A	N/A
Pereira et al., 2019	Pregnant women or women trying to conceive	Maternal alcohol consump-tion (assessed dichoto-mously)	Low birthweight	No	Retrospect ive cohort, Prospect-ive cohort, case–control, systematic reviews	Jan-2017	Yes	Partial description of the exposure and compara-tor(s) are not provided	Yes	Partial-clear descriptions for the population and exposure(s) are not provided	No
Reid et al., 2019a	Offspring of women with prenatal alcohol exposure	Prenatal alcohol exposure	Cardio-vascular and renal outcomes	No	Clinical, preclinical (using animals)	Dec-2017 (extracted from resources provided)	N/A	N/A	N/A	N/A	N/A

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Reid et al., 2019b	Offspring of women with prenatal alcohol exposure	Prenatal alcohol exposure	Immune-related outcomes	No	cohort; case–control; longitudinal-preclinical studies were not analyzed in the review	Dec-2017	N/A	N/A	N/A	N/A	N/A
Römer et al., 2020	Pregnant women and their offspring-excluding clinical samples and pregnant women who abused substances	Low and moderate amounts of prenatal alcohol and nicotine exposure	Early child develop-ment within the first 2 years of life	No	Cohort, case–control, cross-sectional	Dec-2019	N/A	N/A	N/A	N/A	N/A
Roozen et al., 2018	Pregnant women and their offspring	Maternal alcohol consump-tion	Fetal alcohol spectrum disorders	No	Retrospect ive	Aug-2018	N/A	N/A	N/A	N/A	N/A
San Martin Porter et al., 2019	Individuals aged 2–17 years (with prenatal alcohol exposure)	Low-to-moderate prenatal alcohol exposure (gram/ week)	Attention-deficit hyper-activity disorder (ADHD) or ADHD-like symptoms/	Yes	Prospect-ive cohort	Not provided	Partial-not provided the search end date. Not checked the references in the	Yes	Yes	Yes	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
			behaviours in offspring				primary studies identified				
Subramoney et al., 2018	Pregnant women and their offspring	Alcohol consump-tion during pregnancy	Early child develop-ment from birth to 5 years	No	Case–control, follow-up	Oct-31-2017	N/A	N/A	N/A	N/A	N/A
Sundermann et al., 2019	Pregnant women	Alcohol exposure during pregnancy (number of drinks per week).	Mis-carriage	Yes	Cohort; case–control	Jan-2019	Yes	Yes	Yes	Partial - clear description for the population is not provided	No
Yin et al., 2019	Offspring of women with maternal alcohol consump-tion	Maternal alcohol consump-tion during the first trimester	Non-syndromic oral cleft in offspring	No-exposure not clearly defined.	Cohort; case–control	Mar-2019	N/A	N/A	N/A	N/A	N/A
Zhang et al., 2020	Offspring of parents with alcohol consump-tion during the peri-conception period	Parental alcohol consumption during the peri-conception period (three months before the pregnancy	Congenital heart diseases (CHD) and specific CHD pheno-types in offspring	Yes	Cohort; case–control	Jul-24-2019	Yes	Partial-age and gender of offspring are not specified	Yes	Partial-clear descriptions/ inclusion criteria of the population and outcome are not provided	Yes

Study (first author, date)	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in systematic review?	Criteria 3: Quality assess-ment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
		and the first trimester of pregnancy-dose–response)									

Note: Systematic reviews that meet steps 1 to 3 inclusion criteria but were not included for mathematical modelling purposes are represented in yellow.

Grey Literature

A comprehensive search of the grey literature was undertaken on various websites. Thirty-one reports were screened, although they were excluded as PECO and study design criteria were not met. More specifically, most of the reports were found to be informative brochures, reports, fact sheets and books (see Table 47).

Table 47. Full text screening for grey literature

Reference	Source	URL	Popula tion	Expo-sure	Out-come	Study type	Meets PEO /study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character istics of included studies in system-atic review?	Criteria 3: Quality assess-ment of included studies in system-atic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
National Institute on Alcohol Abuse and Alcoholism (2021a)	Fetal Alcohol Exposure, National Institute on Alcohol Abuse and Alcoholism	https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/fetal-alcohol-exposure	Pregnant women	Preg-nancy alcohol consump tion	Fetal alcohol spectrum disorder	Informa-tion Brochure	No	N/A	N/A	N/A	N/A	N/A	N/A

Reference	Source	URL	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis
National Institute on Alcohol Abuse and Alcoholism (2021b)	Underage Drinking, National Institute on Alcohol Abuse and Alcoholism	https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/underage-drinking	Underage population	Underage drinking	General Information about risks	Information Brochure	No	N/A	N/A	N/A	N/A	N/A	N/A
National Institute on Alcohol Abuse and Alcoholism (2021c)	Women and Alcohol, National Institute on Alcohol Abuse and Alcoholism	https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/women-and-alcohol	Women	Alcohol use and misuse	General Information about risks	Information Brochure	No	N/A	N/A	N/A	N/A	N/A	N/A
National Cancer Institute (2021)	Alcohol and Cancer Risk, National Cancer Institute	https://www.cancer.gov/about-cancer/causes-prevention/risk/alcohol/alcohol-fact-sheet	General population	Alcohol consumption	Cancer risk	Information Brochure	No	N/A	N/A	N/A	N/A	N/A	N/A
World Health Organization (2018)	Global status report on alcohol and health 2018, World Health Organization	https://www.who.int/publications/i/item/9789241565639	General population	Alcohol consumption	Risks and Harms	Global Drug Report	No	N/A	N/A	N/A	N/A	N/A	N/A

Reference	Source	URL	Population	Exposure	Outcome	Study type	Meets PEO /study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis
World Health Organization (n.d.)	Harms and Consequences, World Health Organization	https://www.who.int/data/gho/data/themes/topics/topic-details/GHO/harms-and-consequences	General population	Alcohol consumption	Harms and Consequence	Alcohol Use Reports	No	N/A	N/A	N/A	N/A	N/A	N/A
World Health Organization (2022)	Alcohol, World Health Organization	https://www.who.int/news-room/fact-sheets/detail/alcohol	General population	Alcohol consumption	General information	Fact Sheet	No	N/A	N/A	N/A	N/A	N/A	N/A
Esser et al. (2020)	Deaths and Years of Potential Life Lost from Excessive Alcohol Use — United States, 2011–2015, Centers for Disease Control and Prevention	https://www.cdc.gov/mmwr/volumes/69/wr/mm6939a6.htm	General population	Excessive alcohol use	Death	Fact Sheet	No	N/A	N/A	N/A	N/A	N/A	N/A
Centers for Disease Control and Prevention (2020a)	Excessive Alcohol Use is a Risk to Men's Health, Centers for Disease Control and Prevention	https://www.cdc.gov/alcohol/fact-sheets/mens-health.htm	Men	Alcohol consumption	General information	Fact Sheet	No	N/A	N/A	N/A	N/A	N/A	N/A

Reference	Source	URL	Population	Exposure	Outcome	Study type	Meets PEO /study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis
Centers for Disease Control and Prevention (2020b)	Excessive Alcohol Use is a Risk to Women's Health. Centers for Disease Control and Prevention	https://www.cdc.gov/alcohol/fact-sheets/womens-health.htm	Women	Alcohol consumption	General information	Fact Sheet	No	N/A	N/A	N/A	N/A	N/A	N/A
Centers for Disease Control and Prevention (2020c)	Alcohol-Related Disease Impact (ARDI) Application, Centers for Disease Control and Prevention	https://nccd.cdc.gov/DPH_ARDI/default/default.aspx	General population	Alcohol consumption	Death	Fact Sheet	No	N/A	N/A	N/A	N/A	N/A	N/A
National Institute for Health and Care Excellence (2019)	The percentage of patients with one or more of the following conditions: CHD, atrial fibrillation, chronic heart failure, stroke or TIA, diabetes or dementia who have been screened for hazardous drinking using the FAST or AUDIT-C tool in the preceding 2 years. National	https://www.nice.org.uk/standards-and-indicators/qofindicators/the-percentage-of-patients-with-one-or-more-of-the-following-conditions-chd-atrial-fibrillation-chronic-heart-failure-stroke-or-tia-diabetes-or-dementia-who-have-been-screened-for-unsafe-drinking-	CHD, atrial fibrillation, chronic heart failure, stroke or TIA, diabetes or dementia	Hazardous drinking	General information about risks	Fact Sheet	No	N/A	N/A	N/A	N/A	N/A	N/A

Reference	Source	URL	Population	Exposure	Outcome	Study type	Meets PEO /study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis
	Institute for Health and Care Excellence	using-the-fast-or-audit-c-tool-in-the-preceding-2-years											
National Institute on Health and Care Excellence (2010)	The percentage of patients with schizophrenia, bipolar affective disorder and other psychoses who have a record of alcohol consumption in the preceding 15 months, National Institute for Health and Care Excellence	https://www.nice.org.uk/standards-and-indicators/qofindicators/the-percentage-of-patients-with-schizophrenia-bipolar-affective-disorder-and-other-psychoses-who-have-a-record-of-alcohol-consumption-in-the-preceding-15-months	Schizophrenia, bipolar disorder	Alcohol Consumption	General Information about risks	Fact Sheet	No	N/A	N/A	N/A	N/A	N/A	N/A
Wilkinson (2018)	*Older Australians: Trends and Impacts of Alcohol and Other Drug Use.* National Drug Research Institute	https://ndri.curtin.edu.au/ndri/media/documents/publications/T281.pdf	General population	Alcohol consumption	Alcohol, illicit, and pharmaceutical misuse-related harms	Drug Report	No	15 July 2017 and closed on 15 Sept. 2017	N/A	N/A	N/A	N/A	N/A

Reference	Source	URL	Population	Exposure	Outcome	Study type	Meets PEO /study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Lensvelt et al. (2018)	*Estimated alcohol-attributable deaths and hospitalisations in Australia, 2004 to 2015. National Alcohol Indicators Project, Bulletin No. 16.* National Drug Research Institute	https://ndri.curtin.edu.au/ndri/media/documents/naip/naip016.pdf	General population	Alcohol consumption	Deaths and hospitalizations	Bulletin	No	N/A	N/A	N/A	N/A	N/A	N/A
Davey & Sprigings (2018)	Diagnosis and Treatment in Internal Medicine.	https://oxfordmedicine.com/view/10.1093/med/9780199568741.001.0001/med-9780199568741	General population	Alcohol consumption	Alcohol-related damage	Book	No	N/A	N/A	N/A	N/A	N/A	N/A
Smith & Mattick (2018)	Are there sex differences in the relationship between heavy alcohol use and disinhibition? A meta-analysis, National Drug & Alcohol Research Centre	https://ndarc.med.unsw.edu.au/resource/are-there-sex-differences-relationship-between-heavy-alcohol-use-and-disinhibition-meta	General population	Heavy alcohol consumption	Cognition and disinhibition	Cross-sectional	No	Nov-17	N/A	N/A	N/A	N/A	N/A

Reference	Source	URL	Population	Exposure	Outcome	Study type	Meets PEO /study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Darke (2019)	How death provides insights into alcohol-related harm [webinar] National Drug & Alcohol Research Centre	https://ndarc.med.unsw.edu.au/resource/how-death-provides-insights-alcohol-related-harm	General population	Alcohol consumption	Death	Webinar	No	N/A	N/A	N/A	N/A	N/A	N/A
Anstey (2019)	Drugs, alcohol, and late-life cognitive outcomes [webinar] National Drug & Alcohol Research Centre	https://ndarc.med.unsw.edu.au/resource/drugs-alcohol-and-late-life-cognitive-outcomes	Older adults	Alcohol consumption	Cognition	Webinar	No	N/A	N/A	N/A	N/A	N/A	N/A
Leung (2020)	All-cause and cause-specific mortality in a cohort of individuals with an emergency or inpatient presentation for an alcohol-related problem – an Australia data-linkage study [poster] National Drug & Alcohol Research Centre	https://ndarc.med.unsw.edu.au/resource/all-cause-and-cause-specific-mortality-cohort-individuals-emergency-or-inpatient	General population	Alcohol consumption	Mortality	Poster	No	N/A	N/A	N/A	N/A	N/A	N/A

Reference	Source	URL	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis
Yuen (2020)	Patterns of Transitions Across Physiological and Psychosocial Alcohol-related Harms in Adolescence [poster] National Drug & Alcohol Research Centre	https://ndarc.med.unsw.edu.au/resource/patterns-transitions-across-physiological-and-psychosocial-alcohol-related-harms	Adolescents	Alcohol consumption	Physiological and psychological health	Poster	No	N/A	N/A	N/A	N/A	N/A	N/A
Sullivan & English (2019)	Is alcohol and energy drink consumption associated with antisocial behaviour? *Trends & issues in crime and criminal justice* no. 573	https://www.aic.gov.au/publications/tandi/tandi573	Police detainees	Alcohol consumption	Criminal activity and behaviour	Not specified	No	N/A	N/A	N/A	N/A	N/A	N/A
Australian Institute of Health and Welfare (2018)	Impact of alcohol and illicit drug use on the burden of disease and injury in Australia: Australian Burden of	https://www.aihw.gov.au/reports/burden-of-disease/impact-alcohol-illicit-drug-use-on-burden-disease/contents/table-of-contents	General population	Alcohol consumption	Burden	Report	No	N/A	N/A	N/A	N/A	N/A	N/A

Reference	Source	URL	Population	Exposure	Outcome	Study type	Meets PEO /study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis
	Disease Study 2011, Australian Institute of Health and Welfare												
McLean (2021)	Understanding the impacts of Fetal Alcohol Spectrum Disorder (FASD) on child mental health, Emerging Minds	https://emergingminds.com.au/resources/understanding-the-impacts-of-fetal-alcohol-spectrum-disorder-fasd-on-child-mental-health/	Children	Pregnancy alcohol consumption	Fetal alcohol spectrum disorder	Fact sheet	No	N/A	N/A	N/A	N/A	N/A	N/A
National Health and Medical Research Council (2020)	Australian guidelines to reduce health risks from drinking alcohol, National Health and Medical Research Council	https://www.nhmrc.gov.au/about-us/publications/australian-guidelines-reduce-health-risks-drinking-alcohol	General population	Alcohol consumption	Health risks	National guidelines	No	N/A	N/A	N/A	N/A	N/A	N/A
Grisel (2019)	Never enough: the neuroscience and experience of addiction / Judith Grisel (see chapter 5	https://catalogue.nla.gov.au/Record/8053953?lookfor=(title:alcohol*)%20AND%20(date:[2017%20TO%202021])&offset=86&max=92	Alcohol use disorder	Alcohol consumption	General information	Personal book chapter	No	N/A	N/A	N/A	N/A	N/A	N/A

Reference	Source	URL	Population	Exposure	Outcome	Study type	Meets PEO/study type criteria?	Search date	Criteria 1: Comprehensive literature search?	Criteria 2: Characteristics of included studies in systematic review?	Criteria 3: Quality assessment of included studies in systematic review?	Criteria 4: Inclusion/exclusion criteria?	Methods of analysis
Department of Transport, U.K. (2020)	Reported road casualties in Great Britain, final estimates involving illegal alcohol levels: 2018, Public Health England	https://www.gov.uk/government/statistics/reported-road-casualties-in-great-britain-final-estimates-involving-illegal-alcohol-levels-2018	General population	Alcohol consumption	Road casualties	Report	No	N/A	N/A	N/A	N/A	N/A	N/A
Northern Ireland Statistics and Research Agency (2019)	Alcohol-Specific Deaths 2008-2018, Public Health England	https://www.gov.uk/government/statistics/alcohol-specific-deaths-2008-2018	General population	Alcohol consumption	Death	Report	No	N/A	N/A	N/A	N/A	N/A	N/A
Burton et al (2016)	The public health burden of alcohol: evidence review, Public Health England	https://www.gov.uk/government/publications/the-public-health-burden-of-alcohol-evidence-review	General population	Alcohol consumption	Health risks	Evidence review	No	N/A	N/A	N/A	N/A	N/A	N/A

Reference	Source	URL	Population	Expo-sure	Out-come	Study type	Meets PEO /study type criteria?	Search date	Criteria 1: Compre-hensive literature search?	Criteria 2: Character-istics of included studies in system-atic review?	Criteria 3: Quality assess-ment of included studies in system-atic review?	Criteria 4: Inclusion/ exclusion criteria?	Methods of analysis
Harford-Mills (2019)	Plain language review of the harmful use of alcohol among Aboriginal and Torres Strait Islander people, Indigenous	https://aodknowledgecentre.ecu.edu.au/healthinfonet/getContent.php?linkid=620817&title=Plain+language+review+of+the+harmful+use+of+alcohol+among+Aboriginal+and+Torres+Strait+Islander+people&contentid=36281_1	Aboriginal and Torres Strait Islander people	Alcohol consump-tion	Risks and Harms	Plain language review of a report	No	N/A	N/A	N/A	N/A	N/A	N/A
Gray et al. (2019)	Review of the harmful use of alcohol among Aboriginal and Torres Strait Islander people	https://aodknowledgecentre.ecu.edu.au/key-resources/publications/35532/?title=Review%20of%20the%20harmful%20use%20of%20alcohol%20among%20Aboriginal%20and%20Torres%20Strait%20Islander%20people%20%5BeBook%5D&contentid=35532_1	Aboriginal and Torres Strait Islander people	Alcohol consump-tion	Risks and harms	eBook	No	N/A	N/A	N/A	N/A	N/A	N/A

Sex and Gender-Based Analysis (SGBA)

From the 16 studies identified from the included systematic reviews, 13 conducted sex- and gender-based analyses and three explored sex and gender differences. Most of the reviews (n=9) did not use sex- and gender-related terms in their research questions or in the aims of the systematic review or the review protocol. None of the studies only used gender terms, two studies used sex and gender interchangeably, 11 studies used sex- and gender-related terms interchangeably, although they were only referring to biological sex, and three used only sex-related terms, which were used appropriately. Five studies did not report any findings related to sex and gender, whereas the remaining 11 reviews that conducted sex analyses pooled meta-analyses by sex and its association to alcohol consumption. Half of the studies (n=8) did not discuss the sex- and gender-related findings in their interpretation of the data and its implications. Table 48 provides a summary of the SGBA analysis.

Table 48. Summary of the sex- and gender-related analysis

Authors, Date	Outcome	SGBA Categorization (intentional and accurate use of language)	Sex/Gender in the Research Question: Yes or No (use of sex and gender in the aim and research questions)	Results (study design and reporting results)	Interpretation of Sex/Gender Findings: Yes or No (interpretation of sex/gender findings)	Use of Terminology	Findings Related to Sex and Gender
Imtiaz et al., 2017	Tuber-culosis	Sex- and gender-based analyses	No	Sex by risk relations from categorical meta-analyses of alcohol use as a risk factor for tuberculosis was analyzed.	No	Use only sex	Risk relations for males from categorical meta-analyses of alcohol use (versus no alcohol use) as a risk factor for tuberculosis for all included studies was RR 1.12, 95% CI (0.73 - 1.71). For females from categorical meta-analyses of alcohol use (versus no alcohol use) as a risk factor for tuberculosis for all studies was RR 1.20, 95% CI (0.54 - 2.67).
Bagnardi et al., 2015	Larynx cancer	Sex- and gender-based analyses	No	Conducted pooled analyses by sex for larynx cancer and its association to alcohol consumption	Yes	Sex and gender used interchange-ably although only examined sex	For larynx cancer, in men the pooled RR for light drinkers is 0.85, 95% CI (0.61–1.19), moderate drinkers 1.50 95% CI (1.23–1.83) and heavy drinkers is 2.77 95% CI (2.15–3.57) in comparison to non-drinkers. For

Authors, Date	Outcome	SGBA Categorization (intentional and accurate use of language)	Sex/Gender in the Research Question: Yes or No (use of sex and gender in the aim and research questions)	Results (study design and reporting results)	Interpretation of Sex/Gender Findings: Yes or No (interpretation of sex/gender findings)	Use of Terminology	Findings Related to Sex and Gender
						(biological) differences	larynx cancer; in women the pooled RR for light drinkers is 0.89 95% CI (0.62–1.29), moderate drinkers 1.59 95% CI (1.06–2.38) and heavy drinkers is 1.55 95% CI (0.45–5.34) in comparison to non-drinkers.
	Mouth and oro-pharynx cancers	Sex- and gender-based analyses	No	Conducted pooled analyses by sex for oral cavity and pharynx cancer and its association to alcohol consumption	Yes	Sex and gender used interchange-ably although only examined sex (biological) differences	For oral cavity and pharynx cancer, in men the pooled RR for light drinkers is 1.20 95% CI, (1.06–1.35), moderate drinkers 2.01 95% CI (1.69–2.40) and heavy drinkers is 5.33 95% CI (4.28–6.63) in comparison to non-drinkers. In women the pooled RR for light drinkers is 1.00 95% CI (0.78–1.27), moderate drinkers 1.67 95% CI (1.25–2.22) and heavy drinkers is 5.70 95% CI (3.75–8.66) in comparison to non-drinkers.
	Eso-phagus cancer	Sex- and gender-based analyses	No	Conducted pooled analyses by sex for oesophageal cancer and its association to alcohol consumption	Yes	Sex and gender used interchange-ably although only examined sex (biological) differences	For oesophageal cancer, in men the pooled RR for light drinkers is 1.39 95% CI (1.11–1.74), moderate drinkers 2.25 95% CI (1.78–2.85) and heavy drinkers is 4.69 95% CI (3.49–6.31) in comparison to non-drinkers. In women the pooled RR for light drinkers is 1.14 95% CI (0.87–1.49), moderate drinkers 2.18 95% CI (1.42–3.35) and heavy drinkers is 8.32 95% CI (2.95–

Authors, Date	Outcome	SGBA Categorization (intentional and accurate use of language)	Sex/Gender in the Research Question: Yes or No (use of sex and gender in the aim and research questions)	Results (study design and reporting results)	Interpretation of Sex/Gender Findings: Yes or No (interpretation of sex/gender findings)	Use of Terminology	Findings Related to Sex and Gender
							23.45) in comparison to non-drinkers.
Knott et al., 2015	Diabetes mellitus	Sex- and gender-based analyses	Yes	Conducted sex-specific differences in the dose–response relationship between average daily alcohol consumption and incident cases of type 2 diabetes.	Yes	Sex and gender used interchange-ably although only examined sex (biological) differences	For males, the RR increased to 1.01 at 25 g/day and 1.04 at 50g/day, compared to females that had a protective effect with a RR of 0.67 and 0.66 at 25 g/day and 50 g/day respectively.
Vieira et al., 2017	Colon and rectum cancers	Sex- and gender-based analyses	Yes	Meta-analysis of the association between colorectal cancer and alcohol	No	Sex and gender used interchange-ably although only examined sex (biological) differences	The RR for men was 1.08, 95% CI (1.06-1.10) and for women was 1.04 95% CI (1.00-1.08) for 10g/day
Larsson et al., 2014	Atrial fibrillation	Sex- and gender-based analyses	Yes	Extracted information from studies about sex and looked at interaction	No	Sex and gender used interchange-ably although only examined sex (biological) differences	No specific analyses for men and women were conducted as the association between alcohol consumption and AF did not differ by sex (p for interaction = 0.74).
Larsson et al., 2016	Ischaemic stroke	Sex- and gender-based analyses	No	Conduct analyses examining the sex-specific association between average	No	Sex and gender used interchange-ably although only	For men that have 2 or less drinks a day, the RR is 0.94, 95% CI (0.88–1.00) and for more than 2 drinks a day is 1.11 95% CI (1.00–1.23). For women that have 2 or

Authors, Date	Outcome	SGBA Categorization (intentional and accurate use of language)	Sex/Gender in the Research Question: Yes or No (use of sex and gender in the aim and research questions)	Results (study design and reporting results)	Interpretation of Sex/Gender Findings: Yes or No (interpretation of sex/gender findings)	Use of Terminology	Findings Related to Sex and Gender
				alcohol consumption and Ischaemic stroke		examined sex (biological) differences	less drinks a day, the RR is 0.88, 95% CI (0.83–0.95) and for more than 2 drinks a day is 1.15 95% CI (0.96–1.36).
	Intra-cerebral haemor-rhage	Sex- and gender-based analyses	No	Conduct analyses examining the sex-specific association between average alcohol consumption and Intracerebral haemorrhage	No	Sex and gender used interchange-ably although only examined sex (biological) differences	For men that have 2 or less drinks a day, the RR is 0.98 95% CI (0.78–1.24) and for more than 2 drinks a day is 1.35 95% CI (1.06–1.72). For women that have 2 or less drinks a day, the RR is 0.95, 95% CI (0.76–1.19) and for more than 2 drinks a day is 2.23 95% CI (1.47–3.38).
	Sub-arachnoid hemor-rhage	Sex- and gender-based analyses	No	Conduct analyses examining the sex-specific association between average alcohol consumption and Subarachnoid hemorrhage	No	Sex and gender used interchange-ably although only examined sex (biological) differences	For men that have 2 or less drinks a day, the RR is 1.06 95% CI (0.69–1.60) and for more than 2 drinks a day is 1.48 95% CI (0.96–2.28). For women that have 2 or less drinks a day, the RR is 2.38, 95% CI (1.04–1.85) and for more than 2 drinks a day is 1.90 95% CI (1.16–3.13).
Samokhvalov et al., 2010a	Lower respir-atory infections	Sex- and gender differences	No	Extracted information from studies about sex	No	Use only sex	Did not report and sex or gender findings
Samokhvalov et al., 2010b	Epilepsy	Sex- and gender differences	No	Extracted information from studies about gender	No	Use only sex	Did not report and sex or gender findings

Authors, Date	Outcome	SGBA Categorization (intentional and accurate use of language)	Sex/Gender in the Research Question: Yes or No (use of sex and gender in the aim and research questions)	Results (study design and reporting results)	Interpretation of Sex/Gender Findings: Yes or No (interpretation of sex/gender findings)	Use of Terminology	Findings Related to Sex and Gender
Samokhvalov et al., 2015	Pancrea-titis	Sex- and gender-based analyses	Yes	Examine the association between alcohol consumption and risk of pancreatitis by sex	Yes	Sex and gender used interchange-ably although only examined sex (biological) differences	There was a significant decrease in risk (RR = 0.76, 95%CI: 0.60–0.97) of acute pancreatitis in women below the threshold of 40 g/day in comparison to abstainers. There was no significant association found for men (RR = 1.1, 95%CI: 0.69–1.74).
Taylor & Rehm, 2012	Road injury	Sex- and gender differences	No	Extracted information from studies about sex	No	Sex and gender used interchange-ably	Did not report and sex or gender findings
WCRF, 2018e	Liver cancer	Sex- and gender-based analyses	No	Conducted pooled analyses examining the relationship between risk of liver cancer and alcohol consumption	Yes	Sex and gender used interchange-ably although only examined sex (biological) differences	The RR for men was 1.03, 95% CI (1.01-1.05) and for women was 1.19 95% CI 1.04-1.35 for 10g/day.
Sun, Xie et al., 2020	Breast cancer	Sex- and gender-based analyses	No	Conducted analysis for postmenopausal women only	Yes	Sex and gender used interchange-ably although only examined sex (biological) differences	For postmenopausal women, the risk increases by 11.1% (RR = 1.11, 95%CI = 1.09–1.13) with every 10 g of total alcohol increase.
Liu et al., 2020	Hyper-tensive heart disease	Sex- and gender-based analyses	Yes	Conduct analyses examining the sex-specific association between alcohol	Yes	Sex and gender used interchange-ably although	The hypertension risk differed between men (RR: 1.14, 95% CI: 1.07, 1.20) and women (RR: 0.98, 95% CI: 0.89, 1.06) at 10 g/d.

Authors, Date	Outcome	SGBA Categorization (intentional and accurate use of language)	Sex/Gender in the Research Question: Yes or No (use of sex and gender in the aim and research questions)	Results (study design and reporting results)	Interpretation of Sex/Gender Findings: Yes or No (interpretation of sex/gender findings)	Use of Terminology	Findings Related to Sex and Gender
				consumption and hypertension		only examined sex (biological) differences	
Zhao et al., 2017	Ischaemic heart disease	Sex- and gender-based analyses	Yes	Conduct analyses examining the sex-specific association between alcohol consumption and ischaemic heart disease	Yes	Sex and gender used interchange-ably although only examined sex (biological) differences	There was significantly decreased risk of CHD mortality among male drinkers who drank 1.3–44.99 g per day (RR = 0.86 and 0.84, t test $p < .05$) and female drinkers who drank 1.3–24.99 g per day (RR = 0.81, t test $p < .05$) compared with abstainers
Roerecke et al., 2019	Cirrhosis of the liver	Sex- and gender-based analyses	Yes	Conduct analyses examining the sex-specific association between average alcohol consumption and liver cirrhosis	Yes	Sex and gender used interchange-ably although only examined sex (biological) differences	Drinking ≥5 drinks per day was associated with a substantially increased risk in both women (RR = 12.44, 95% CI: 6.65 – 23.27 for 5–6 drinks, and RR = 24.58, 95% CI: 14.77 – 40.90 for ≥7 drinks) and men (RR = 3.80, 95% CI: 0.85 – 17.02, and RR = 6.93, 95% CI: 1.07 – 44.99, respectively)
Taylor et al., 2010	Intention-al and uninten-tional Injuries	Sex- and gender differences	No	Extracted information from studies about sex	No	Sex and gender used interchange-ably	Did not report and sex or gender findings

Conclusion and Future Directions

Sixteen systematic reviews were retained to be included in the mathematical modelling that will inform the LRDGs update. Two reviews focus on the short-term health risks and benefits of alcohol consumption, road injury (Taylor & Rehm, 2012), and intentional and unintentional injuries (Taylor et al. 2010). The remaining fourteen reviews examine outcomes associated with the long-term health risks and benefits of alcohol consumption, such as liver cirrhosis (Roerecke et al., 2019), ischæmic heart disease (Zhao et al., 2017), hypertensive heart disease (Liu et al., 2020), breast cancer (Sun, Xie et al., 2020), liver cancer (World Cancer Research Fund, 2018), pancreatitis (Samokhvalov et al., 2015), lower respiratory infections (Samokhvalov et al., 2010a), epilepsy (Samokhvalov et al., 2010b), ischaemic stroke (Larsson et al., 2016), intracerebral haemorrhage (Larsson et al., 2016), subarachnoid hemorrhage (Larsson et al., 2016), atrial fibrillation (Larsson et al., 2014), colon and rectum cancers (Vieira et al., 2017), diabetes mellitus (Knott et al., 2015), larynx cancer (Bagnardi et al., 2015), mouth and oropharynx cancers (Bagnardi et al., 2015), esophagus cancer (Bagnardi et al., 2015), and tuberculosis (Imtiaz et al., 2017). No systematic reviews were retained for the risks and benefits associated with alcohol consumption by women who are pregnant or breastfeeding, for fetal, infant and child development.

Retained systematic reviews used PECO questions and clearly presented inclusion criteria. All were based on strong and rigorous methods for statistical combination of their results. Retained reviews also examined dose-dependent relationships through pooled analyses, which is indicative of high-quality methods. The majority of retained reviews also described the included studies with a good amount of detail justifying their inclusion. The review search strategies were detailed and many of the studies conducted the screening steps in duplicate. Most of the retained reviews had no imprecision and indirectness according to GRADE. However, many of the retained reviews did not assess risk of bias. Heterogeneity was also reported for many of the reviews and, despite conducting sensitivity analyses, the source for heterogeneity was seldom identified. Hence, the overall quality score of most retained reviews was low but this was expected.

Tools used to assess the quality of identified systematic reviews consider randomized clinical trials the gold standard. However, for examining the association between alcohol consumption and health, this study design is neither practical nor ethical. For example, it would be unethical to randomize one group of females to drink alcohol on a daily basis for 10 years and another one to abstain, and then test who develops breast cancer. In fact, in the field of alcohology most evidence is derived from cohort and observational studies that have inherent limitations that explain why many systematic reviews retained for this project did not receive a high-quality score. However, in no way does this mean that the quality of evidence is insufficient to provide guidance on alcohol and health to people living in Canada. In fact, there is a high level of confidence among members of the Scientific Expert Panels and the ERWG that the identified reviews covered in this report are the latest and most high-quality evidence available to examine this public health issue. Furthermore, the methodology used to select these systematic reviews is based on the Australian guidelines that received a top score according to a previous evaluation made by the ERWG (for more information, see Canadian Centre on Substance Use and Addiction, 2021b), which strengthens our certainty that our results are based on the highest quality evidence.

The current evidence review did not identify high quality-evidence systematic reviews on alcohol use and mental health, nor on alcohol use and violence. Not a single review met all the selection criteria. This is unfortunate as these are issues of increasing concern. The impact of drinking alcohol on mental health was identified by people living in Canada as the top priority for the updated LRDGs in a

recent public consultation (for more information, see Canadian Centre on Substance Use and Addiction, 2021c). Therefore, the LRDG experts agreed to commission additional systematic reviews on these topics to complete the LRDG update. The scientific community should take notice that high-quality systematic reviews about alcohol, mental health and social issues like violence are needed.

Moreover, the current evidence review could not retain systematic reviews on key outcomes like gastric and stomach cancers because even if a causality between alcohol and these cancers is suspected, it has not been firmly established. Therefore, with a view to refine and improve guidance on alcohol and health, more work on establishing causality between alcohol use and various outcomes is also needed.

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Appendix: Grade Domains

GRADE Domain 1: Risk of Bias

Risk of bias in GRADE refers to limitations in the primary studies in regard to the study design or the execution of the studies (Guyatt et al., 2011e). Typically, the risk of bias is evaluated using a risk of bias tool such as the Cochrane Risk of Bias (Higgins et al., 2011) or the Newcastle-Ottawa Scale (Wells et al., 2013). There are various study limitations that can be identified. For example, one common limitation is not controlling for confounding variables or only adjusting for age and sex. This reduces the certainty of evidence of the systematic review and corresponding meta-analysis as the inability to adequately control confounding variables in individual studies could increase bias in the results.

If the systematic review did not assess risk of bias but only included prospective cohort studies, the quality of evidence was downgraded by 1, instead of by 2. This remained true if the systematic review had less than 25% of the population from case–control studies. Moreover, if risk of bias or any quality assessment was completed and the results depicted a low risk of bias, but the review included case–control studies, the quality of evidence was downgraded by 1. The reason for this is due to case–control study designs having a higher risk of bias. Indeed, in etiological research questions, prospective cohort studies are thought to have a quality of evidence than case–control study designs. Thus, the confidence in the results of the identified systematic reviews that only include prospective cohort studies compared to the reviews that include both case–control and cohort studies in their meta-analysis is higher.

GRADE Domain 2: Inconsistency of Results

GRADE defines inconsistency as unexplained heterogeneity of results and refers to the following ranges for heterogeneity using the I^2 statistic: 0-40% may indicate low heterogeneity, 30-60% may indicate moderate heterogeneity, 50-90% may indicate substantial heterogeneity, and 75%-100% is high heterogeneity (Guyatt et al., 2011d). The quality of evidence was downgraded by 1 or 2, depending on the level of heterogeneity present, if any was detected. The highest level of heterogeneity that was detected was used to qualify the heterogeneity of the systematic reviews' individual studies, which resulted in the reduction of the evidence quality. For example, if one subgroup had a high level of heterogeneity while other subgroups had a low or moderate level, the score was reduced by 2 as it represents the highest level of heterogeneity. However, if heterogeneity was explored through subgroup or sensitivity analyses and adequately discussed, the quality of evidence was not downgraded.

GRADE Domain 3: Indirectness of Evidence

GRADE defines indirectness as a difference in the population, exposure or outcome of the systematic review's PECO as compared to the PECO of the current project (Guyatt et al., 2011c). For example, the quality of evidence was downgraded if indirectness was present in the population, due to potential residual confounding that may influence the reported results. The quality of evidence was also downgraded if the systematic review pooled together two outcomes (e.g., unprovoked seizures and epilepsy),

GRADE Domain 4: Imprecision

Imprecision in GRADE refers to the confidence in the estimates of effect, which is examined using confidence intervals (CI), typically 95% (Guyatt et al., 2011b). Pre-determined optimal information size (OIS) or default OIS are usually set to assess this domain. However, as the effect sizes for alcohol are normally dose-dependent, it would not be appropriate to have a pre-set or default OIS. Therefore, for this specific domain, the quality of evidence was downgraded by 1 or 2 if the CIs were wide and lacked precision, especially if the CIs crossed the line of no effect. Furthermore, even if CIs appear satisfactory, the quality of evidence was downgraded if the effect was large and the sample size was small.

GRADE Domain 5: Publication Bias

Publication bias refers to the phenomenon that a scientific study may not get published if it does not produce statistically significant results, leading to an over- or under-estimation of the underlying beneficial or harmful effect of an outcome (Guyatt et al., 2011a). This can lead to misrepresentation of included studies in a systematic review. This can also occur if the topic of interest does not have a lot of literature available for synthesis at the time the systematic review was undertaken.

If publication bias was assessed and detected in the systematic review, the evidence quality was downgraded. In addition, if the systematic review did not assess publication bias, the evidence quality was also downgraded as the possibility that publication bias may be present cannot be excluded. Furthermore, if the search strategy only included one database, the quality of evidence was downgraded unless appropriate justification was provided.