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ALCOHOL CLINICAL & EXPERIMENTAL RESEARCH ISBRA

CRITICAL REVIEW

A systematic review of relative risks for the relationship between chronic alcohol use and the occurrence of disease

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Abstract

Alcohol use is causally linked to the development of and mortality from numerous diseases. The aim of this study is to provide an update to a previous systematic review of meta-analyses that quantify the sex-specific dose–response risk relationships between chronic alcohol use and disease occurrence and/or mortality. An updated systematic search of multiple databases was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria to identify meta-analyses published from January 1, 2017, to March 8, 2021, which quantified the risk relationships between chronic alcohol use and the risk of disease occurrence and/or mortality. This systematic review was not preregistered. The comparator was people who have never consumed at least one standard drink of alcohol. Measurements included relative risks, odds ratios, and hazard ratios of disease occurrence and/or mortality based on long-term alcohol intake measured in grams per day. The systematic search yielded 5953 articles, of which 14 were included in the narrative review. All diseases showed an increased risk of occurrence as alcohol use increased. At all doses examined, alcohol had a significant detrimental effect on tuberculosis, lower respiratory infections, oral cavity and pharyngeal cancers, esophageal cancer, colorectal cancer, liver cancer, laryngeal cancer, epilepsy, hypertension, liver cirrhosis, and pancreatitis (among men). For ischemic heart disease, ischemic stroke, and intracerebral hemorrhage, protective effects from low-dose chronic alcohol use among both men and women were observed. Low-dose alcohol consumption also had a protective effect for diabetes mellitus and pancreatitis among women (approximately to 50 g/day and 30 g/day, respectively). Alcohol use increases the risk of numerous infectious and noncommunicable diseases in a dose–response manner. Higher levels of alcohol use have a clear detrimental impact on health; however, at lower levels of use, alcohol can have both disease-specific protective and detrimental effects.

KEYWORDS
alcohol, chronic drinking, infectious diseases, noncommunicable diseases, systematic review

Christine Levesque and Nitika Sanger are shared first authorship.

INTRODUCTION

The consumption of alcohol is causally linked to the development of and mortality from numerous infectious and noncommunicable diseases (Griswold et al., 2018; IARC Working Group, 2012; World Health Organization, 2018). Furthermore, at the population level, alcohol use leads to a substantial burden of death and disability worldwide (Shield et al., 2020) and is the number one risk factor for the burden of disease among people 15–49 years of age (Griswold et al., 2018). There are multiple dimensions of alcohol use, which lead to risk, including the chronic volume of EtOH consumed, acute alcohol consumption, patterns of alcohol use, and the context of consumption (Rehm et al., 1996). Chronic use of alcohol has been linked to numerous disease categories, including infectious diseases, cancers, gastrointestinal diseases, and cardiovascular diseases (Rehm et al., 2017).

Chronic alcohol use impacts health and disease occurrence based on the volume of alcohol consumed. This impact is typically measured as an increase in the relative risks (RRs), odds ratios (ORs), and hazards ratios (HRs) of disease occurrence. Alcohol RRs, ORs, and HRs are necessary information for individuals and for policymakers to understand the impact of alcohol use, to address drinking behaviors, and to guide policy decisions at the individual and population levels. At the population level, alcohol RRs, ORs, and HRs are used in conjunction with alcohol use and population statistics to model the hospitalizations, burden of disease, and social costs attributable to alcohol use as well as to model changes, which might be expected to hospitalizations, the burden of disease, and social costs attributable to alcohol use if alcohol public health policies were changed. At the individual level, alcohol RRs, ORs, and HRs are used in conjunction with burden of disease statistics to estimate the health impact of alcohol consumption on an individual and the potential health improvements if the individual decreased their alcohol use. Furthermore, such information can be used to formulate low-risk drinking guidelines and other policy recommendations.

There are numerous systematic reviews and meta-analyses which quantify the alcohol RRs, ORs, and HRs of diseases associated with alcohol consumption; however, these reviews and analyses vary in terms of their publication dates, inclusion and exclusion criteria, and methods used to combine alcohol RRs, ORs, and HRs. The aims of this study were to systematically search for and review meta-analyses which reported alcohol dose–response curves between different levels of average daily alcohol use and disease outcomes, and to assess if the RRs, ORs, and HRs differ by sex. Therefore, to ensure the study's aims were achieved, this review selected the highest quality systematic reviews and meta-analyses from our search using a standard set of quality criteria.

METHODS

Our review acts as an update of the 2020 Australian Guidelines to Reduce Health Risks from Drinking Alcohol (2007–2020) by the National Health and Medical Research Council (NHMRC) (Alcohol Guidelines Project Team, 2020). The systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009), and was not preregistered. Our review synthesizes new literature that assessed the relationship between chronic alcohol use and the risk of disease, published between 2017 and 2022. The disease categorizations used for this study were based on those reported by the Institute for Health Metrics and Evaluation (IHME; Griswold et al., 2018) and the World Health Organization (WHO, 2018). Based on these disease categorizations, a total of 18 disease categories were identified as causally related to alcohol use (as per IHME; Griswold et al., 2018), the WHO (World Health Organization, 2018), and the International Agency for Research on Cancer (IARC; IARC Working Group, 2012).

Search strategy

A systematic electronic search was performed using PubMed, PsycNET, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, Joanna Briggs Institute (JBI) Database of Systematic Reviews, and Epistemonikos. The search was limited to articles published from January 1, 2017, to March 8, 2021. All articles included in the systematic review that described studies performed as part of the process to formulate the Australian Guidelines to Reduce Health Risks from Drinking Alcohol were also included in this review (Alcohol Guidelines Project Team, 2020). Full details of the systematic search strategy, including keywords used and all gray literature sources examined, can be found in the Appendix S1.

Inclusion and exclusion criteria

Articles were included if the following criteria were met: (a) a systematic review of epidemiological studies, (b) published in either English or French, (c) the primary exposure of interest was chronic alcohol use, (d) the comparator was people who have never consumed at least one standard drink of alcohol (i.e., lifetime abstention), (e) the primary outcome was disease occurrence and/or mortality from a disease; (f) the disease was considered causally related to alcohol use as determined by the IHME (Griswold et al., 2018), the WHO (World Health Organization, 2018), or the IARC (IARC Working Group, 2012); (g) the confounding factor of age was adjusted for in the underlying risk estimates; and (h) a dose–response or dose-stratified meta-analysis of RRs, ORs, and/or HRs was performed.

Data extraction, quality assessment, and selection of the most relevant systematic reviews

An information specialist screened the search results and removed duplicates and any articles that were clearly outside the scope of the project based on titles and abstracts. Two investigators independently assessed the articles for title and abstract inclusion, and, subsequently, both assessed the articles for full text eligibility; any discrepancies were resolved through discussion between the two investigators. Each investigator extracted data, which was then cross-checked by the other investigator.

From each relevant article, we extracted authors' names, publication date, study design, sex of study participants, number of studies included in the systematic review, the systematic review's inclusion and exclusion criteria, ascertainment of alcohol consumption, measures of association (RR, OR, and/or HR), reference group used to measure the RR, OR, and/or HR, and the 95% confidence intervals. Continuous RR functions were extracted from the reviews when provided. If continuous RR functions were not provided, then categorical RR estimates were extracted. When risk functions were graphed but not provided, authors were contacted for further details.

All full-text studies were assessed for eligibility through the Population, Exposure, Comparator, and Outcomes (PECO) framework. If an identified systematic review met the PECO criteria, it was screened for its methodological quality using the criteria from the A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2) and Risk of Bias in Systematic Reviews (ROBIS) tools. The quality of the 14 included systematic reviews was evaluated using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system, and AMSTAR 2 instrument to rate the evidence for an association between alcohol and disease occurrence (Balshem et al., 2011). If a particular disease was considered by more than one systematic review and/or meta-analysis which met the GRADE and AMSTAR 2 criteria, our systematic review selection prioritized the most recent systematic review which adjusted for the most potential confounding factors, had a large number of cohort studies, and reported cohort studies where participants were younger in age at baseline. The systematic reviews that met the inclusion, exclusion, and GRADE criteria, but which were not selected, are listed in the Supplement (see Table S1).

Relative risk estimates

The RR estimates were extracted for each of the disease categories examined from the selected 14 meta-analyses. In each study, the extracted RR estimates were modeled either based on categories of alcohol use or based on a continuous distribution. RRs based on a continuous distribution were based on either a RR for an incremental amount of alcohol consumed (e.g., a RR for every 10g increase in average daily consumption) or a RR that was modeled based on polynomials or splines to account for a curvilinear RR. Each RR estimate compares the relative changes in risk from a certain level of average drinking against the risk of a lifetime abstainer (Rehm et al., 2001). The reference group of lifetime abstention instead of abstention is often selected as the abstention group includes lifetime abstainers and former drinkers (Rehm et al., 2008). The RRs presented in this manuscript are based on data directly extracted from the manuscript and no transformations or imputations were applied to these RRs.

All tables and figures were constructed using the statistical program R. The R code used to produce all figures and tables presented in this manuscript is attached to this manuscript as Appendix S1.

RESULTS

From the original review by the National Health and Medical Research Council (NHMRC) (Alcohol Guidelines Project Team, 2020), we extracted 38 studies (of which 13 mapped on to disease categories from the WHO and IHME). The updated search resulted in 5953 references (after the removal of duplicate references); after screening of titles and abstracts, 239 full-text reviews were assessed for eligibility. Articles that did not meet quality inclusion criteria or did not examine the impact of alcohol use in a dose–response manner on infectious and noncommunicable diseases were excluded from the review. Of the 239 studies, a total of 50 studies fulfilled the eligibility criteria for this overview. Among these studies, 14 were selected as the highest quality systematic reviews (see Table 1 and Figure 1). Table S1 in the Appendix S1 outlines the rationale for the selection of each of the 14 studies.

An overview of the conditions that evaluated the effects of chronic alcohol consumption and the number of meta-analyses found for each disease category are presented in Table 1. Results are presented by major disease categories causally related to alcohol use. Tables 2–4 present for each systematic review the search date, exposure definitions, outcome definitions, statistical analysis, sex-specific analysis, and the number of studies included in the analysis. The OR and RR functions and categorical estimates extracted from each paper are also presented in Tables 2–4. The inclusion and exclusion criteria of each study are listed in Table S2 in the Appendix S1. Across all meta-analyses, a total of 364 studies were included in the underlying analyses (208 cohort studies and 155 case–control studies; see Table S2). These tabulations count once those studies which are sex-specific RRs (i.e., studies that provide sex-specific RRs are counted as one unique study and not two studies). The increases and decreases in risk per gram of alcohol consumed are presented in Table 5 as well as in Figures S1–S4 in the Appendix S1.

Communicable, maternal, perinatal, and nutritional conditions

The systematic review for tuberculosis by Imtiaz et al. (2017b) met all GRADE and AMSTAR 2 criteria and thus was selected for inclusion. The systematic review for lower respiratory infections by Samokhvalov et al. (2010b) was limited in its reporting of the characteristics of the studies included (the review did not include the ages of participants in the underlying studies) and did not undertake a quality assessment of the studies included in the systematic review; however, the Samokhvalov study did meet all other quality criteria and, thus, was selected for inclusion. Both systematic reviews reported dose–response RRs, but did not report sex-specific RRs (Imtiaz et al., 2017; Samokhvalov et al., 2010b).

TABLE 1 Major disease categories causally related to alcohol, International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes, and the systematic reviews identified upon full-text review.

Outcome	ICD 10 codes	No. of meta-analyses examined	At least one study met GRADE criteria
Communicable, maternal, perinatal, and nutritional conditions			
Infectious and parasitic diseases			
Tuberculosis	A15-19, B90	5	Imtiaz et al. (2017b)
Respiratory infections			
Lower respiratory infections	J09-22, P23, U04	3	Samokhvalov, Irving, & Rehm (2010)
Noncommunicable diseases			
Malignant neoplasms			
Mouth and oropharynx cancers			
Lip and oral cavity and other pharyngeal cancers	C00–08; C09–10, C12–14	1	Bagnardi et al. (2015)
Esophageal cancer	C15	7	Bagnardi et al. (2015)
Colon and rectum cancers	C18–21	5	Vieira et al. (2017)
Liver cancer	C22	2	World Cancer Research Fund/American Institute for Cancer Research (2018)
Breast cancer	C50	2	Sun et al. (2020)
Larynx cancer	C32	1	Bagnardi et al. (2015)
Diabetes mellitus	E10–14 (minus E10.2–10.29, E11.2–11.29, E12.2, E13.2–13.29, E14.2)	4	Knott et al. (2015)
Neurological conditions			
Epilepsy	G40–41	1	Samokhvalov, Irving, Mohapatra, & Rehm (2010)
Cardiovascular diseases			
Hypertensive heart disease	I10–15	4	Liu et al. (2020)
Ischemic heart disease	I20–25	1	Zhao et al. (2017)
Stroke			
Ischemic stroke	G45–46.8, I63–63.9, I65–66.9, I67.2–67.848, I69.3–69.4	2	Larsson et al. (2016)
Intracerebral hemorrhage	I61-I62, I62.9, I69.0-I69.298	2	Larsson et al. (2016)
Subarachnoid hemorrhage	I60-I60.9, I67.0-I67.1	2	Larsson et al. (2016)
Atrial fibrillation and flutter	I48	2	Larsson et al. (2014)
Digestive diseases			
Cirrhosis of the liver	K70, K74	5	Roerecke et al. (2019)
Pancreatitis	K85–86	1	Samokhvalov et al. (2015)

The risk of tuberculosis and lower respiratory infections increased with higher levels of alcohol consumption, with the risk of tuberculosis rapidly increasing to a RR of 1.57 at 25 g/day and 2.46 at 50 g/day (Imtiaz et al., 2017) compared to a RR of 1.13 and 1.27 for lower respiratory infections at 25 g/day and 50 g/day, respectively (Samokhvalov et al., 2010b).

Noncommunicable diseases

The systematic review by Bagnardi et al. (2015) was selected for oropharyngeal cancer, esophageal cancer, and larynx cancer. The systematic review was limited as it did not include a table of study characteristics by cancer site; however, it did meet all other inclusion criteria. The systematic review by Vieira et al. (2017) was selected for colorectal cancer. This review was limited as it did not provide the key words and/or MESH terms used to provide the systematic search, did not provide a clear description of the outcomes examined, did not undertake a quality assessment for the articles examined, and did not provide a clear description of the population studied. The systematic review by the World Cancer Research Fund International was selected for liver cancer (World Cancer Research Fund/American Institute for Cancer Research, 2018). This review was limited as only PubMed was searched for relevant articles. For breast cancer, the

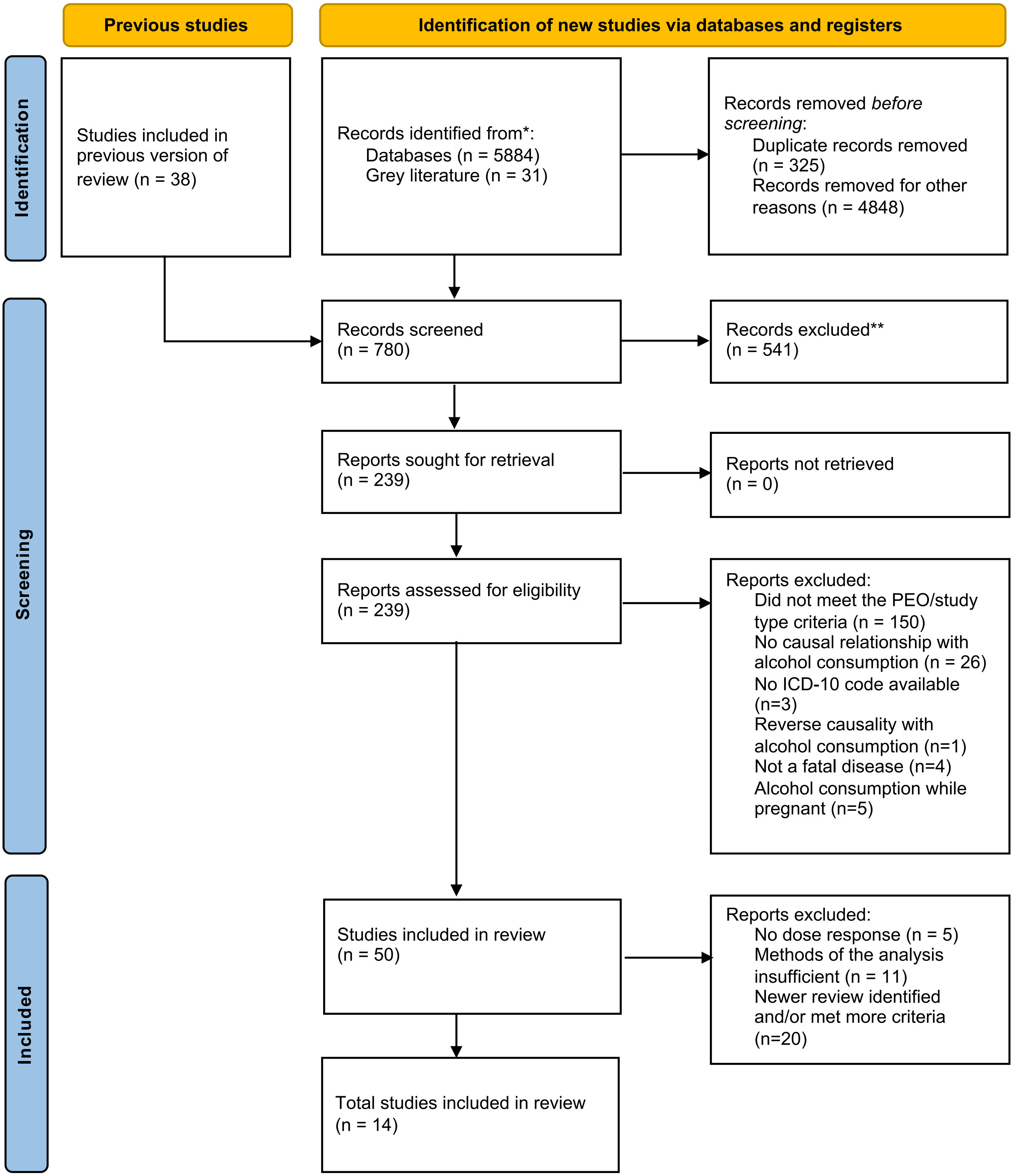

FIGURE 1 Systematic search flow diagram.

systematic review by Sun et al. (2020) was selected for inclusion. This review was limited as it did not provide a clear description of the populations it covered. All systematic reviews reported dose–response RRs and sex-specific RRs (except for lip and oral cavity and other pharyngeal cancers, or for esophageal or larynx cancers; Bagnardi et al., 2015; Sun et al., 2020; Vieira et al., 2017; World Cancer Research Fund/American Institute for Cancer Research, 2018).

The risk of oral cavity and pharyngeal cancers increased the most rapidly with higher levels of alcohol consumption, with the risk increasing to a RR of 1.81 at 25 g/day and 3.12 at 50 g/day (Bagnardi

TABLE 2 Relative risks for alcohol use for infectious diseases, malignant neoplasms, diabetes, epilepsy, liver cirrhosis, and pancreatitus as reported by the selected systematic reviews.

Study	Disease	Search date	Exposure	Outcome	Statistical analysis	Sex- specific analysis	No. of studies included in the analysis	Relative risk (RR) / odds ratio (OR)
Imtiaz et al. (2017b)[d]	Tuberculosis	Jan 2007 to June 2016	Alcohol dosage categorized into >0–24, 25–60 and >60 g/day[a]	Tuberculosis incidence (as defined by ICD-10 codes A15–19, as well as corresponding ICD-8 and ICD-9 codes)	Continuous: DerSimonian and Laird's random-effects meta-regression	No	4 (3 cohort studies; 1 case–control)	RR = exp(β1*x) β1 = 0.0179695 x = alcohol intake in g/day
Samokhvalov et al. (2010b)[d]	Lower respiratory infections	Jan 1980 to Aug 2009	Alcohol dosage in average grams per day[a]	Community-acquired pneumonia morbidity and/ or mortality diagnosed as 480–486 in ICD-8, 481–486 in ICD-9 and J10–J18 in ICD-10.	Continuous: DerSimonian and Laird's random-effects meta-regression (using fractional polynomial models)	No	5 (2 cohort and 3 case–control)	RR = exp(β1 * ((x + 0.0399999618530273) / 100)) β1 = 0.4764038 x = alcohol intake in g/day
Bagnardi et al. (2015)[d]	Lip and oral cavity and other pharyngeal cancers	1956 to Sept 2012	Alcohol dosage in average grams per day[b]	Lip and oral cavity cancer incidence and mortality (no additional information provided on diagnosis)	Continuous: DerSimonian and Laird's random-effects meta-regression	No	52 (4 cohort, 47 case–control)	RR = exp(x*β1 + x^2*β2) β1 = 0.02474 β2 = −0.00004 x = alcohol intake in g/day
	Esophageal cancer	1956 to Sept 2012	Alcohol dosage in average grams per day[b]	Esophageal cancer incidence and mortality (no additional information provided on diagnosis)	Continuous: DerSimonian and Laird's random-effects meta-regression	No	79 (17 cohort and 62 case–control)	RR = exp(x*β1 + x^3*β2) β1 = 0.02474 β2 = −0.00004 x = alcohol intake in g/day
	Larynx cancer	1956 to Sept 2012	Alcohol dosage in average grams per day[b]	Laryngeal cancer incidence and mortality (no additional information provided on diagnosis)	Continuous: DerSimonian and Laird's random-effects meta-regression	No	41 (3 cohort, 38 case–control)	RR = exp(x*β1 + x^2*β2) β1 = 0.01462 β2 = −0.00002 x = alcohol intake in g/day

(Continues)

TABLE 2 (Continued)

Study	Disease	Search date	Exposure	Outcome	Statistical analysis	Sex- specific analysis	No. of studies included in the analysis	Relative risk (RR) / odds ratio (OR)
Vieira et al. (2017)	Colon and rectum cancers	Jan 2006 to May 31 2015	Alcohol dosage in 10 g/day increments[c]	Colorectal cancer incidence or mortality (no information on diagnostic criteria provided)	Continuous: DerSimonian and Laird's random-effects meta-analysis	Male	14 (all cohort)	RR = 1.08 (95%CI: 1.06, 1.10) per 10 g/day increment
						Female	10 (all cohort)	RR = 1.04 (95%CI: 1.00, 1.08) per 10 g/day increment
World Cancer Research Fund/ American Institute for Cancer Research (2018)	Liver cancer	Mar 01 2013	Alcohol dosage in 10 g/day increments[c]	Liver cancer incidence or mortality (no information on diagnostic criteria provided)	Continuous: DerSimonian and Laird's random-effects meta-analysis	Male	8 (all cohort)	RR = 1.03 (95%CI: 1.01, 1.05) per 10 g/day increment
						Female	4 (all cohort)	RR = 1.19 (95% CI: 1.04, 1.35) per 10 g/day increment
Sun et al. (2020)	Breast cancer	1990 to Dec 01 2018	Alcohol dosage 20 g/day increments (no information on the transformation of categorical estimates was provided)[c]	Breast cancer incidence (no information on diagnostic criteria provided)	Continuous: DerSimonian and Laird's random-effects meta-analysis	Female	22 (all cohort)	RR: 1.20 (95% CI: 1.17, 1.27) per 20 g/day increment

[a]Alcohol intake midpoints for this study were calculated from categorical estimates. Midpoints for open-ended estimates were estimated using three-quarters of the second-highest category's range that was added to the lower limit of open-ended categories.

[b]Alcohol intake midpoints for this study were calculated from categorical estimates. Midpoints for the open-ended upper category alcohol use were assumed to be 1.2 times the lower bound of this category.

[c]Alcohol intake midpoints for this study were calculated from categorical estimates. Midpoints for the open-ended upper category alcohol use assuming the width of this category were the same as the adjacent alcohol intake category.

[d]Relative risks are presented in a graph and the relative risk functions were provided by the authors of this article.

TABLE 3 Relative risks for alcohol use for cardiovascular diseases as reported by the selected systematic reviews.

Study	Disease	Search date	Exposure	Outcome	Statistical analysis	Sex-specific analysis	No. of studies included in the analysis	Relative risk (RR) /odds ratio (OR)
Liu et al. (2020)	Hypertensive heart disease	Sept 07 2019	Alcohol dosage in average grams per day[a]	Incident cases of hypertension (defined as SBP140 mm Hg or DBP 90 mm Hg or taking antihypertensive drugs or when participants reported hypertension diagnosed by a physician.)	Continuous: DerSimonian and Laird random effects meta-regression	Male	13 (all cohort)	RR (≥0 to <10 g/day) = exp(β1*x) RR (≥10 to <30 g/day) = exp(β1*10 + β2*(x-10)) RR (≥30 g/day) = exp(β1*10 + β2*(20) + β3*(x-30)) β1 = 0.013976194 β2 = 0.00689349 β3 = 0.002942025 x = alcohol intake in g/day
						Female	8 (all cohort)	RR (≥0 to <10 g/day) = exp(β1*x) RR (≥10 to <30 g/day) = exp(β1*10 + β2*(x-10)) RR (≥30 g/day) = exp(β1*10 + β2*(20) + β3*(x-30)) β1 = 0.005826891 β2 = 0.005362277 β3 = 0.005605865 x = alcohol intake in g/day
Zhao et al. (2017)	Ischemic heart disease	June 30 2016	Alcohol dosage categorized into >0 to 1.3, 1.3 to <25, 25 to <45 a45 to <65 and ≥ 65 g/day[a]	Presence or absence of mortality from CHD in individual studies (ICD-10: I20–I25)	Categorical: Mixed-effects regression analyses (drinking groups and control variables were treated as fixed effects with a random study effect). The analysis for cohorts with a mean age 19 to 55 years at baseline and fully adjusted RRs was extracted.	No	14 (all cohort)	Occasional (>0 to <1.30 g/day) RR = 1.44 (95% CI: 1.09, 1.89) Low volume (1.30 to <25 g/day) RR = 0.95 (95% CI: 0.75, 1.21) Medium volume (25 to <45 g/day) 1.04 (95% CI: 0.81, 1.34) High volume: (45 to <65 g/day) RR = 1.07 (95% CI: 0.83, 1.39) Higher volume (≥65 g/day): RR = 1.15 (95% CI: 0.86, 1.52)

TABLE 3 (Continued)

Study	Disease	Search date	Exposure	Outcome	Statistical analysis	Sex-specific analysis	No. of studies included in the analysis	Relative risk (RR) /odds ratio (OR)
Larsson et al. (2016)	Ischemic stroke	Sept 01 2016	Alcohol dosage categorized into light (<12 g/day), moderate (12 to 24 g/day), high (>24 to 48 g/day), and heavy (>48 g/day) alcohol consumption[b]	Incidence or mortality from ischemic stroke (no diagnostic criteria were stated)	Categorical: DerSimonian and Laird random effects meta-analysis	No	25 (all cohort)	Light (<12 g/day): RR = 0.90 (95%CI: 0.85 to 0.95) Moderate (12 to 24 g/day): RR = 0.92 (95%CI: 0.87 to 0.97) High (>24 to 48 g/day): RR = 1.08 (95%CI: 1.01 to 1.15) Heavy (>48 g/day): RR = 1.14 (95%CI: 1.02 to 1.28)
	Intracerebral hemorrhage	Sept 01 2016	Alcohol dosage categorized into light (<12 g/day), moderate (12 to 24 g/day), high (>24 to 48 g/day), and heavy (>48 g/day) alcohol consumption[b]	Incidence or mortality from intracerebral hemorrhage (no diagnostic criteria were stated)	Categorical: DerSimonian and Laird random effects meta-analysis	No	11 (all cohort)	Light (<12 g/day): RR = 0.92 (95%CI: 0.77 to 1.10) Moderate (12 to 24 g/day): RR = 0.99 (95%CI: 0.82 to 1.18) High (>24 to 48 g/day): RR = 1.25 (95%CI: 0.93 to 1.67) Heavy (>48 g/day): RR = 1.67 (95%CI: 1.25 to 2.23)
	Subarachnoid hemorrhage	Sept 01 2016	Alcohol dosage categorized into light (<12 g/day), moderate (12 to 24 g/day), high (>24 to 48 g/day), and heavy (>48 g/day) alcohol consumption	Incidence or mortality from intracerebral hemorrhage (no diagnostic criteria were stated)	Categorical: DerSimonian and Laird random effects meta-analysis	No	11 (all cohort)	Light (<12 g/day): RR = 1.21 (95%CI: 0.96 to 1.52) Moderate (12 to 24 g/day): RR = 1.11 (95%CI: 0.80 to 1.53) High (>24 to 48 g/day): RR = 1.39 (95%CI: 0.94 to 2.07) Heavy (>48 g/day): RR = 1.82 (95%CI: 1.18 to 2.28)
Larsson et al. (2014)	Atrial fibrillation and flutter	Jan 10 2014	Alcohol dosage in average drinks (12 g) per day	Incidence of AF or AF and AFL combined	Aggregation of RR estimates for a 12 g/day increase: Random effects meta-analysis.	No	7 (all cohort)	RR = 1.08 (95% CI:1.06 to 1.10) per 12 g/day increment

[a]Alcohol intake midpoints for this study were calculated from categorical estimates. Midpoints for open-ended estimates were estimated using three-quarters of the second-highest category's range that was added to the lower limit of open-ended categories.

[b]Categories were based on alcohol intake measured in drinks, where 1 drink contained 12 grams per day.

TABLE 4 Relative risks for alcohol use for diabetes, epilepsy, liver cirrhosis, and pancreatitus as reported by the selected systematic reviews.

Study	Disease	Search date	Exposure	Outcome	Statistical analysis	Sex-specific analysis	No. of studies included in the analysis	Relative risk (RR)/odds ratio (OR)
Knott et al. (2015)[c]	Diabetes mellitus	Feb 18 2014	Alcohol dosage in average grams per day[a]	Incident type 2 diabetes (based on all historic World Health Organization recommendations, doctor-reported diagnosis, antidiabetic medication prescription or linkage to clinical registry data)	Continuous: DerSimonian and Laird's random-effects meta-regression	Male	33 (all cohort)	$RR = exp(\beta1*(x/100)^2 + \beta2*(x/100)^3)$ $\beta1 = 0.1763703$ $\beta2 = -0.0728256$ x = alcohol intake in g/day
						Female	23 (all cohort)	$RR = exp(\beta1*(x/100)^{0.5} + \beta2*(x/100))$ $\beta1 = -1.3133910$ $\beta2 = 1.0142390$ x = alcohol intake in g/day
Samokhvalov, Irving, Mohapatra, & Rehm (2010)[c]	Epilepsy	Jan 1960 to Sept 01 2008	Alcohol dosage in average grams per day[b]	Epilepsy derived from the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) (at least one unprovoked seizure or epilepsy as their outcomes)	Continuous: DerSimonian and Laird's random-effects meta-regression	No	6 (all case–control)	$RR = exp(\beta1*(x + 0.5) / 100)$ $\beta1 = 1.22861$ x = alcohol intake in g/day
Roerecke et al. (2019)[c]	Cirrhosis of the liver	Mar 6 2019	Alcohol dosage in average grams per day[b]	Incidence of liver cirrhosis (ICD-7: 581; ICD-8: 571; ICD-10: K70, K73, K74) and unspecified liver cirrhosis (ICD-8: 571.9, 456.0, 785.3; ICD-10: I85.0, I85.9, K74.6, R18.9)	Continuous: Random effects, inverse-variance weighting DerSimonian–Laird meta-regression random-effect models	Male	6 (4 cohort; 2 case–control)	$RR (<1 g/day) = 1 + x * (exp((\beta1 + \beta2) * (1 + 0.1699981689453125) / 100) - 1)$ $RR = exp((\beta1 + \beta2) * (x + 0.1699981689453125) / 100)$ $\beta1 = 1.687111$ $\beta2 = 1.106413$ x = alcohol intake in g/day
						Female	7 (5 cohort; 2 case–control)	$RR (<1 g/day) = 1 + x * (exp(\beta1 + \beta2) * ((1 + 0.1699981689453125) / 100) - 1)$ $RR (>1 g/day) = exp((\beta1 + \beta2) * sqrt(x + 0.1699981689453125) / 100)$ $\beta1 = 2.351821$ $\beta2 = 0.9002139$ x = alcohol intake in g/day

(Continues)

TABLE 4 (Continued)

Study	Disease	Search date	Exposure	Outcome	Statistical analysis	Sex-specific analysis	No. of studies included in the analysis	Relative risk (RR)/odds ratio (OR)
Samokhvalov et al. (2015)[c]	Pancreatitis	January 2009 to May 2015	Alcohol dosage in average grams per day[b]	Diagnoses of acute pancreatitis (ICD-10 codes (K85.x)). For earlier studies, the corresponding ICD-8 and ICD-9 codes were used (577.0)	Continuous: Random effects, inverse-variance weighting DerSimonian–Laird meta-regression random-effect models	Male	3 (1 cohort; 2 case–control)	RR = exp(β1*x) β1 = 0.0173451 x = alcohol intake in g/day
						Female	3 (1 cohort; 2 case–control)	RR (<3 g/day) = exp(β1*x) RR (≥3 to <15 g/day) = exp(β1*x + β2*((x-3)^3/(40–3)^2)) RR (≥15 to <40 g/day) = exp(β1*x + β2*((x-3)^3–1/(40–15)*(x-15)^3*(40-3))/(40-3)^2) RR (≥40 tg/day) = exp(β1*x + β2*(((x-3)^3–1/(40–15)*((x-15)^3*(40-3)-(x-40)^3*(15-3)))/(40-3)^2)) β1 = −0.0272886 β2 = 0.0611466 x = alcohol intake in g/day

Note: This study used averages for alcohol consumption categories. Where averages were not reported for each exposure category, this study used the medians of the lower and upper limits were selected. Alcohol intake is in grams per day. Where averages were not reported for each exposure category, the medians of the lower and upper limits were selected. For categories with no upper limit, median values were defined as 1.5 times the lower limit of the category. Where averages were not reported for each exposure category, the medians of the lower and upper limits were selected. For categories with no upper limit, median values were defined as 1.5 times the lower limit of the category.

[a]Alcohol intake midpoints for this study were calculated from categorical estimates. Midpoints for open-ended estimates were estimated using three-quarters of the second-highest category's range that was added to the lower limit of open-ended categories.

[b]This study calculated alcohol intake midpoints from categorical estimates. Midpoints for open-ended estimates were estimated using three-quarters of the second-highest category's range that was added to the lower limit of open-ended categories.

[c]Relative risks are presented in a graph and the relative risk functions were provided by the authors of this article.

TABLE 5 Increases and decreases in risk per gram of alcohol consumed by disease and sex.

Chronic condition (source)	Sex	Alcohol intake (g/day) 5	10	15	20	25	30	35	40	45	50
Tuberculosis (Imtiaz et al., 2017b)	Total	1.09 (1.02, 1.18)	1.20 (1.04, 1.38)	1.31 (1.06, 1.63)	1.43 (1.08, 1.91)	1.57 (1.10, 2.25)	1.71 (1.12, 2.64)	1.88 (1.15, 3.11)	2.05 (1.17, 3.66)	2.24 (1.19, 4.30)	2.46 (1.21, 5.05)
Lower respiratory infections (Samokhvalov et al., 2010b)	Total	1.02 (1.01, 1.05)	1.05 (1.01, 1.09)	1.07 (1.02, 1.14)	1.10 (1.02, 1.19)	1.13 (1.03, 1.25)	1.15 (1.03, 1.30)	1.18 (1.04, 1.36)	1.21 (1.04, 1.42)	1.24 (1.05, 1.48)	1.27 (1.05, 1.55)
Oral cavity and pharynx cancer (Bagnardi et al., 2015)	Total	1.13 (1.11, 1.15)	1.28 (1.24, 1.32)	1.44 (1.37, 1.51)	1.61 (1.52, 1.72)	1.81 (1.68, 1.95)	2.03 (1.86, 2.22)	2.26 (2.05, 2.51)	2.52 (2.25, 2.83)	2.81 (2.48, 3.18)	3.12 (2.73, 3.58)
Esophageal cancer (Bagnardi et al., 2015)	Total	1.07 (1.06, 1.07)	1.14 (1.13, 1.15)	1.22 (1.21, 1.23)	1.30 (1.28, 1.32)	1.39 (1.36, 1.42)	1.48 (1.45, 1.52)	1.58 (1.54, 1.63)	1.69 (1.64, 1.74)	1.80 (1.75, 1.87)	1.93 (1.86, 2.00)
Colorectal cancer (Vieira et al., 2017)	Men	1.04 (1.03, 1.05)	1.08 (1.06, 1.10)	1.12 (1.09, 1.15)	1.17 (1.13, 1.21)	1.21 (1.16, 1.27)	1.26 (1.19, 1.33)	1.31 (1.23, 1.40)	1.36 (1.27, 1.47)	1.41 (1.30, 1.54)	1.47 (1.34, 1.61)
	Women	1.02 (1.00, 1.04)	1.04 (1.00, 1.08)	1.06 (1.00, 1.13)	1.08 (1.00, 1.17)	1.10 (1.00, 1.22)	1.12 (1.00, 1.27)	1.15 (1.00, 1.32)	1.17 (1.00, 1.38)	1.19 (1.00, 1.43)	1.22 (0.99, 1.49)
Liver cancer (World Cancer Research Fund/American Institute for Cancer Research, 2018)	Men	1.01 (1.01, 1.02)	1.03 (1.01, 1.05)	1.05 (1.02, 1.08)	1.06 (1.02, 1.10)	1.08 (1.03, 1.13)	1.09 (1.03, 1.16)	1.11 (1.04, 1.19)	1.13 (1.04, 1.22)	1.14 (1.05, 1.25)	1.16 (1.05, 1.28)
	Women	1.09 (1.02, 1.17)	1.19 (1.04, 1.36)	1.30 (1.07, 1.58)	1.42 (1.09, 1.84)	1.54 (1.11, 2.15)	1.69 (1.14, 2.50)	1.84 (1.16, 2.92)	2.01 (1.19, 3.40)	2.19 (1.22, 3.96)	2.39 (1.24, 4.61)
Larynx cancer (Bagnardi et al., 2015)	Total	1.08 (1.06, 1.09)	1.16 (1.11, 1.20)	1.24 (1.18, 1.30)	1.33 (1.24, 1.42)	1.42 (1.31, 1.54)	1.52 (1.38, 1.67)	1.63 (1.45, 1.82)	1.74 (1.53, 1.97)	1.85 (1.62, 2.13)	1.98 (1.70, 2.29)
Diabetes Mellitus (Knott et al., 2015)	Men	1.00 (1.00, 1.00)	1.00 (1.00, 1.01)	1.00 (0.99, 1.02)	1.01 (0.98, 1.03)	1.01 (0.98, 1.05)	1.01 (0.97, 1.06)	1.02 (0.97, 1.08)	1.02 (0.97, 1.09)	1.03 (0.97, 1.10)	1.04 (0.97, 1.11)
	Women	0.78 (0.72, 0.85)	0.73 (0.65, 0.82)	0.7 (0.61, 0.80)	0.68 (0.59, 0.79)	0.67 (0.57, 0.79)	0.66 (0.55, 0.78)	0.66 (0.54, 0.79)	0.65 (0.53, 0.80)	0.65 (0.53, 0.81)	0.66 (0.52, 0.81)
Epilepsy (Samokhvalov, Irving, Mohapatra, & Rehm, 2010)	Total	1.07 (1.06, 1.09)	1.14 (1.11, 1.17)	1.21 (1.16, 1.26)	1.29 (1.22, 1.36)	1.37 (1.28, 1.47)	1.45 (1.35, 1.59)	1.55 (1.41, 1.71)	1.64 (1.48, 1.85)	1.75 (1.56, 1.99)	1.86 (1.64, 2.15)
Hypertension (Liu et al., 2020)	Men	1.07 (1.04, 1.10)	1.15 (1.09, 1.22)	1.19 (1.13, 1.26)	1.23 (1.16, 1.32)	1.28 (1.20, 1.37)	1.32 (1.23, 1.43)	1.34 (1.25, 1.46)	1.36 (1.27, 1.48)	1.38 (1.28, 1.50)	1.40 (1.30, 1.53)
	Women	1.03 (1.00, 1.05)	1.06 (1.01, 1.11)	1.09 (1.03, 1.15)	1.12 (1.05, 1.19)	1.15 (1.06, 1.24)	1.18 (1.07, 1.30)	1.21 (1.10, 1.34)	1.25 (1.12, 1.39)	1.28 (1.14, 1.43)	1.32 (1.16, 1.50)

(Continues)

TABLE 5 (Continued)

Chronic condition (source)	Sex	Alcohol intake (g/day) 5	10	15	20	25	30	35	40	45	50
Ischemic heart disease[a] (Zhao et al., 2017)	Total	0.95 (0.75, 1.21)	0.95 (0.75, 1.21)	0.95 (0.75, 1.21)	0.95 (0.75, 1.21)	1.04 (0.81, 1.34)	1.04 (0.81, 1.34)	1.04 (0.81, 1.34)	1.04 (0.81, 1.34)	1.07 (0.83, 1.39)	1.07 (0.83, 1.39)
Ischemic stroke[a] (Larsson et al., 2016)	Total	0.90 (0.85, 0.95)	0.90 (0.85, 0.95)	0.92 (0.87, 0.97)	0.92 (0.87, 0.97)	1.08 (1.01, 1.15)	1.08 (1.01, 1.15)	1.08 (1.01, 1.15)	1.08 (1.01, 1.15)	1.08 (1.01, 1.15)	1.14 (1.02, 1.28)
Intracerebral hemorrhage[a] (Larsson et al., 2016)	Total	0.92 (0.77, 1.10)	0.92 (0.77, 1.10)	0.99 (0.82, 1.18)	0.99 (0.82, 1.18)	1.25 (0.93, 1.67)	1.25 (0.93, 1.67)	1.25 (0.93, 1.67)	1.25 (0.93, 1.67)	1.25 (0.93, 1.67)	1.67 (1.25, 2.23)
Subarachnoid hemorrhage[a] (Larsson et al., 2016)	Total	1.21 (0.96, 1.52)	1.21 (0.96, 1.52)	1.11 (0.80, 1.53)	1.11 (0.80, 1.53)	1.39 (0.94, 2.07)	1.39 (0.94, 2.07)	1.39 (0.94, 2.07)	1.39 (0.94, 2.07)	1.39 (0.94, 2.07)	1.82 (1.18, 2.38)
Atrial fibrillation and flutter (Larsson et al., 2014)	Total	1.03 (1.02, 1.04)	1.07 (1.05, 1.08)	1.10 (1.08, 1.13)	1.14 (1.10, 1.17)	1.17 (1.13, 1.22)	1.21 (1.16, 1.27)	1.25 (1.19, 1.32)	1.29 (1.21, 1.37)	1.33 (1.24, 1.42)	1.38 (1.27, 1.48)
Liver cirrhosis (Roerecke et al., 2019)	Men	1.16 (1.13, 1.18)	1.33 (1.28, 1.38)	1.53 (1.45, 1.62)	1.76 (1.63, 1.90)	2.02 (1.84, 2.22)	2.32 (2.08, 2.60)	2.67 (2.35, 3.05)	3.07 (2.66, 3.57)	3.53 (3.00, 4.19)	4.06 (3.39, 4.91)
	Women	2.09 (1.89, 2.31)	2.82 (2.44, 3.24)	3.55 (2.98, 4.20)	4.31 (3.52, 5.23)	5.11 (4.07, 6.35)	5.97 (4.65, 7.56)	6.88 (5.26, 8.88)	7.85 (5.90, 10.32)	8.90 (6.56, 11.89)	10.01 (7.27, 13.58)
Pancreatitis (Samokhvalov et al., 2015)	Men	1.09 (1.05, 1.13)	1.19 (1.10, 1.28)	1.30 (1.16, 1.44)	1.41 (1.21, 1.63)	1.54 (1.27, 1.85)	1.68 (1.34, 2.09)	1.84 (1.40, 2.36)	2.00 (1.47, 2.67)	2.18 (1.54, 3.02)	2.38 (1.62, 3.41)
	Women	0.87 (0.78, 0.98)	0.77 (0.62, 0.97)	0.72 (0.53, 0.99)	0.72 (0.50, 1.05)	0.76 (0.51, 1.15)	0.85 (0.55, 1.31)	0.98 (0.62, 1.56)	1.15 (0.69, 1.94)	1.35 (0.75, 2.45)	1.58 (0.82, 3.17)

Note: Red: RR > 1.5; Orange: RR = 1.0–1.5; Green: RR < 1.

[a]Risk estimates are based on categorical RRs.

et al., 2015), compared to a RR of 1.39 and 1.93 for esophageal cancer (Bagnardi et al., 2015), 1.42 and 1.98 for larynx cancer (Bagnardi et al., 2015), 1.18 and 1.40 for colorectal cancer (Vieira et al., 2017), 1.10 and 1.22 for liver cancer (World Cancer Research Fund/ American Institute for Cancer Research, 2018b), and 1.26 and 1.58 for breast cancer (women only; Sun et al., 2020), for each at 25 g/day and 50 g/day, respectively.

Diabetes

For diabetes mellitus, the systematic review by Knott et al. (2015) was selected, and it reported dose–response RRs and sex-specific RRs. The systematic review by Knott et al. (2015) met all GRADE and AMSTAR 2 criteria. Among males, the risk of diabetes mellitus gradually increased to a RR of 1.01 at 25 g/day and 1.04 at 50 g/day, compared to females where alcohol consumption had a protective effect with a RR of 0.67 and 0.66 at 25 and 50 g/day, respectively.

Neurological conditions

For neurological conditions, one systematic review was identified upon full-text review on the association between alcohol consumption and epilepsy. The systematic review for epilepsy by Samokhvalov et al. (2010c) was limited in its reporting of the characteristics of the studies included (it did not include the ages of participants in the underlying studies) and did not undertake a quality assessment of the studies included in the systematic review; however, this study met all other quality criteria and, thus, was selected for inclusion. Samokhvalov et al. (2010c) reported dose–response RRs, but did not report sex-specific RRs. The risk of epilepsy increased with higher levels of alcohol consumption, with a RR of 1.37 at 25 g/day and 1.86 at 50 g/day (Samokhvalov, Irving, Mohapatra, & Rehm, 2010).

Cardiovascular diseases

The systematic reviews selected for hypertension (Liu et al., 2020) and for ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage (Larsson et al., 2016) met all GRADE and AMSTAR 2 criteria and, thus, were selected for inclusion. The study by Larsson et al. (2014) for atrial fibrillation and flutter was limited as only PubMed was searched for relevant studies; however, all other quality criteria were met and, thus, this study was selected for inclusion. The systematic review by Zhao et al. (2017) for ischemic heart disease was limited as a clear description of the outcomes was not provided, and no specific quality assessment tool for studies included in the review was used; however, all other quality criteria were met and, thus, this study was selected for inclusion (Zhao et al., 2017).

The systematic review by Larsson et al. (2014) for atrial fibrillation and by Liu et al. (2020) for hypertension provided a dose–response RRs. The systematic review by Liu et al. (2020) for hypertension provided sex-specific RRs. The risk of atrial fibrillation increased with higher levels of alcohol consumption, with a RR of 1.17 at 25 g/day and 1.38 at 50 g/day (Larsson et al., 2014). For the association between hypertension and alcohol consumption, the risk of hypertension increased with higher levels of alcohol consumption, with a RR of 1.28 at 25 g/day and 1.40 at 50 g/day among men, compared to a RR of 1.15 and 1.32 among women at 25 g/day and 50 g/day, respectively (Liu et al., 2020).

The systematic review by Zhao et al. (2017) for ischemic heart disease and by Larsson et al. (2016) provided categorical RR estimates and did not provide RR estimates by sex. For the risk of ischemic heart disease, a protective effect was seen at lower levels of alcohol use (<25 g/day), with a RR of 0.95 (Zhao et al., 2017); however, the risk of ischemic heart disease increased with higher levels of alcohol consumption, with a RR of 1.04 at 25 to <45 g/day, a RR of 51.07 at 45 to <65 g/day, and a RR of 1.15 at 65 g/day or more (Zhao et al., 2017). The risk of ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage increased with higher levels of alcohol consumption. For ischemic stroke, the RR was 0.90, 0.92, 1.08, and 1.14 for people who consumed <12. 12 to 24, >24 to 48, and ≥ 48 g/day of alcohol, respectively (Larsson et al., 2016). For intracerebral hemorrhage, the RR was 0.92, 0.99, 1.25, and 1.67 for people who consumed <12. 12 to 24, >24 to 48, and ≥ 48 g/day of alcohol, respectively (Larsson et al., 2016). For subarachnoid hemorrhage, the RR was 1.21, 1.11, 1.39, and 1.82 for people who consumed <12. 12 to 24, >24 to 48, and ≥ 48 g/day of alcohol, respectively (Larsson et al., 2016).

Digestive diseases

The systematic review for liver cirrhosis by Roerecke et al. (2019) was limited as it did not provide a clear description of the population covered by the systematic review; however, the review met GRADE and AMSTAR 2 criteria and, thus, was selected for inclusion (Roerecke et al., 2019). The systematic review for pancreatitis by Samokhvalov et al. (2015) was limited as it did not report the number of males and females from each study or the ages of the participants included in each study, but it did meet GRADE and AMSTAR 2 criteria and, thus, was selected for inclusion. Both systematic reviews reported dose–response RRs and sex-specific RRs (Roerecke et al., 2019; Samokhvalov et al., 2015). The risk of liver cirrhosis increased with higher levels of alcohol consumption, with the risk of rapidly increasing to a RR of 5.11 at 25 g/day and 10.01 at 50 g/day among women, compared to a RR of 2.02 and 4.06 among men at 25 g/day and 50 g/day, respectively (Roerecke et al., 2019). As for pancreatitis, the risk increased with higher levels of alcohol consumption among men, with the risk rapidly increasing to a RR of 1.54 at 25 g/day and 2.38 at 50 g/day, compared to a RR of 0.76 at 25 g/day (a protective effect) and 1.58 at 50 g/day among women (Samokhvalov et al., 2015).

Sex-specific dose–response risks

Sex is a modifier of the dose–response relationships between alcohol consumption and some chronic diseases and conditions. Sex-specific RRs were available for colorectal cancer, liver cancer, diabetes mellitus, hypertension, liver cirrhosis, and pancreatitis. Higher RRs are currently seen among men for colorectal cancer, diabetes mellitus, hypertension, and pancreatitis (see Table 5). Among women, higher levels of alcohol consumption increase the risk of breast cancer, while protective effects are seen for diabetes mellitus. However, the statistical significance of these differences was not assessed. With pancreatitis, while a protective effect is seen among women at lower alcohol intake levels (≤35 g/day), the risk of pancreatitis increases to a RR of 1.58 at 50 g/day (Samokhvalov et al., 2015). Further, the risk of liver cirrhosis among women is more than double (RR: 5.11 at 25 g/day; 10.01 50 g/day) the risk among men (RR: 2.02 at 25 g/day; 4.06 at 50 g/day; Roerecke et al., 2019). Similarly the RR of liver cancer per gram of alcohol consumed is higher among women when compared to men.

DISCUSSION

This review indicates that alcohol use increases the risk of multiple diseases in a dose–response manner. There is a clear detrimental impact on health from higher levels of alcohol consumption. Although statistical significance of sex differences was not assessed, it was observed that men had a higher risk of developing colorectal cancer, diabetes mellitus, hypertension, and pancreatitis per gram of alcohol consumed compared to women. The reason for this elevated risk is not clear and further research is necessary to fully understand the complex interplay between sex, alcohol consumption, and these health outcomes. One potential explanation is that men may have a greater tendency to engage in heavy episodic drinking (Rehm et al., 2017). However, other factors such as differences in alcohol metabolism may also contribute to the observed sex differences in the noted relative risks (Rehm et al., 2017).

This review only considered those diseases which are coded using the ICD-10 coding system and which are fatal, or if nonfatal are monitored by either the WHO or the IHME. Accordingly, a total of 18 diseases and conditions were included where there was a quantification of the dose–response risk relationship between chronic alcohol consumption and the occurrence of and/or mortality from these infectious or noncommunicable diseases. Unfortunately, the quantification of causality is difficult for other categories in which alcohol consumption is a component cause. Other disease categories identified but not included within this review include osteoporosis, gout, dementia, cognitive decline/function, depression, sexually transmitted diseases, fertility, gallstone disease, lupus, and chronic kidney damage. Specifically for osteoporosis (ICD 10 code: M81) and gout (ICD 10 code: M10), alcohol may be related to these diseases, but they are not considered fatal, and therefore, these disease categories could not be used to model the lifetime risk of an alcohol-attributable death. For other disease categories, gallstone disease (ICD 10 code: K80), lupus (ICD 10 code: M32), and chronic kidney damage (ICD 10 code: N18), a causal relationship between alcohol use and the disease has not been established. As for the other disease categories, alcohol may be related, but as mortality and morbidity data are coded using the ICD-10 coding system, we were not able to consider symptoms when modeling lifetime alcohol-attributable risk curves. In addition, within the evidence base of the 14 meta-analyses included in the review, 10 were published in or before 2016. Thus, these results indicate a need for more studies to fill the research gaps in order to provide the most up-to-date and robust evidence on the associations between alcohol consumption and various chronic diseases and conditions.

The reference group selected was lifetime abstention instead of abstention, as the abstention group includes lifetime abstainers and former drinkers. Lifetime abstainers and former drinkers have different risk levels, and if combined as a reference group, more curvilinear relationships will result, which may underestimate the risk and indicate the lowest risk at low to moderate levels of drinking (Rehm et al., 2008). Research indicates curvilinear dose–response relationships overestimate the protective effect or falsely create a curvilinear curve, when in actuality it should be a monotonous relationship (Sarich et al., 2019; Zhao et al., 2017). This does not indicate, however, that there are no curvilinear relationships between alcohol use and disease outcomes, as there are known protective effects of light to moderate drinking on ischemic heart disease, ischemic stroke, diabetes mellitus (women only), and pancreatitis (women only), as mentioned above.

Limitations

The RRs included in the review are also limited by numerous biases. This review also focused on RRs for total volume of alcohol use; however, chronic alcohol use impacts health and disease occurrence based on two dimensions, namely, overall levels of consumption and patterns of drinking. The measurement of chronic alcohol use is performed using cross-sectional self-reported measurements of alcohol use, thus introducing some biases. This one-time baseline measurement is followed up years later creating regression dilution bias as the time interval impacts the magnitude of the underestimation of the real association (Clarke et al., 1999). The self-reporting of alcohol use in research is subject to social desirability bias, which may lead to an underestimation of alcohol use in medical epidemiology studies (Stockwell et al., 2018).

The selection of only one review per outcome may be a limitation as for some outcomes there were multiple reviews that met the minimum criteria for inclusion. As this was not a scoping review, we included the highest quality review based on the currency and quality.

This study is also limited depending upon the recency of the systematic review. For example, the reviews of how alcohol use impacts cardiovascular outcomes do not include recent studies, some of which used a Mendelian-randomization methodology, which accounts for the potential confounding effects of genetic factors (Koellinger & De Vlaming, 2019). In contrast to the reviews included in this systematic review, these Mendelian-randomization studies do not observe a significant protective effect of low-level alcohol consumption on cardiovascular disease (Larsson et al., 2020; van de Luitgaarden et al., 2021).

What this study adds to the previous systematic review

Compared to the previous systematic review, the current systematic review updates the RRs for liver cirrhosis (from Rehm et al., 2010 to Roerecke et al., 2019), hypertension (from Briasoulis et al., 2012 to Liu et al., 2020), breast cancer (from World Cancer Research Fund/American Institute for Cancer Research, 2018b to Sun et al., 2020), colorectal cancer (from World Cancer Research Fund/American Institute for Cancer Research, 2018 to Vieira et al., 2017), and tuberculosis (from Lönnroth et al., 2008 to Imtiaz et al., 2017). The currents systematic review adds RRs for stroke by subtype (Larsson et al., 2016), ischemic heart disease (Zhao et al., 2017), and lower respiratory infections (Samokhvalov, Irving, & Rehm, 2010), which were not included in the previous systematic review (see Table S1). The systematic reviews for Larsson et al. (2016) and Samokhvalov, Irving, and Rehm (2010) were published before 2017, were identified through gray literature search, and were not identified during the previous systematic search. Accordingly, this article presents updated information on the risk relationships between alcohol use and disease occurrence and/or mortality for a numerous of additional disease categories when compared to the previous systematic review. In particular, the addition of RRs for ischemic heart disease and stroke are vital to modeling the impact of alcohol on health as alcohol may have a protective effect on these diseases at low levels of consumption.

Public health relevance

The findings of this study have multiple clinical and public health applications. Firstly, this study updates the systematic review by NHMRC and provides a updated list of RR estimates for the relationships between chronic alcohol use and disease occurrence/mortality. It is critical to know dose–response relationships based on overall levels of consumption in order to estimate the burden of disease attributable to alcohol use (i.e., the burden of disease that would not occur in a given year if everyone was a lifetime abstainer; World Health Organization, 2018) and to formulate low-risk drinking guidelines (in particular, the RRs outlined in this study were used in a mathematical model to determine the 2022 update of Canada's Low-Risk Drinking Guidelines (LRDGs; Paradis et al., 2023)). It is also critical to know dose–response relationships based on overall levels of consumption to model the impact on health of potential treatments for alcohol use (see: Rehm et al., 2013 for an example) and to model the potential impacts of public health policies on population health (see: Rovira et al., 2021 for an example). In clinical practice, the RRs can help physicians communicate to their patients the impact of alcohol use on disease risk. In particular, the RRs presented in this article can be combined with the disease occurrence among lifetime abstainers to estimate the statistic of "number needed to harm" (i.e., the fraction of people who consume alcohol who will also either develop and/or die from a disease in a given time period; Berry et al., 2006).

Secondly, this review has implications on our knowledge of the impact on health of low volume alcohol use. This review calls into question the public's perception of the health benefits of low volume alcohol use. Men who consumed 10 g/day (1 WHO standard drink) experienced a significant protective effect for ischemic stroke; however, significant increases in health risks were observed for tuberculosis, lower respiratory infections, oral cavity and pharynx cancer, esophageal cancer, colorectal cancer, liver cancer, larynx cancer, diabetes mellitus, epilepsy, hypertension, atrial fibrillation and flutter, liver cirrhosis, and pancreatitis at this drinking level. Women who consumed 10 g/day experienced a significant protective effect on diabetes, ischemic stroke, and pancreatitis risk; however, significant increases in health risk were observed for tuberculosis, lower respiratory infections, oral cavity and pharynx cancer, esophageal cancer, colorectal cancer, liver cancer, breast cancer, larynx cancer, epilepsy, hypertension, atrial fibrillation and flutter, and liver cirrhosis at this drinking level. While an individual's overall health risk depends on their alcohol use and co-occurring risk factors, this study demonstrates that there are significant health risks for numerous diseases among both men and women at lower levels of alcohol consumption.

The health risks of alcohol at lower levels of consumption are of particular concern given the public's lack of knowledge on the topic. For example, despite the magnitude of the cancer health burden caused by alcohol, and the fact that alcohol has been designated a carcinogen by both the IARC Monograph program (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012) and the World Cancer Research Fund Continuous Update Project (World Cancer Research Fund/American Institute for Cancer Research, 2018a), to a great extent the public is not aware that alcohol use causes cancer, and drinkers, racial/ethnic minorities, and those with lower levels of education are even less likely to be aware of the link between alcohol use and cancer (Scheideler & Klein, 2018). Accordingly, information on the risks of alcohol use and its impact on health are vital to health promotion efforts.

Conflicting health messages relating to alcohol use lead to confusion, not only for alcohol users but also for family practitioners who provide patients with health advice and for policy makers who set public health policies. As stated above, research has unequivocally shown that the consumption of even small amounts of alcohol can lead to negative health effects. Therefore, there is a need for a consensus as to unequivocal public health messaging regarding alcohol use so that people understand that less consumption of alcohol is better for their health.

CONCLUSIONS

Alcohol increases the risk of infectious and noncommunicable diseases in a dose–response manner. Higher levels of alcohol consumption have a clear, detrimental impact on health; however, lower levels of use can have both disease-specific protective as well as detrimental effects on health. Future research is required to fully understand the modifiers of dose–response relationships, including sex, age, socio-economic status, and genetic constitution.

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CONFLICT OF INTEREST STATEMENT

None to declare.

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REFERENCES

Alcohol Guidelines Project Team. (2020) *Australian guidelines to reduce health risks from drinking alcohol*. Commonwealth of Australia: Canberra.

Bagnardi, V., Rota, M., Botteri, E., Tramacere, I., Islami, F., Fedirko, V. et al. (2015) Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *British Journal of Cancer*, 112, 580–593.

Balshem, H., Helfand, M., Schunemann, H.J., Oxman, A.D., Kunz, R., Brozek, J. et al. (2011) GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology*, 64, 401–406.

Berry, D.C., Knapp, P. & Raynor, T. (2006) Expressing medicine side effects: assessing the effectiveness of absolute risk, relative risk, and number needed to harm, and the provision of baseline risk information. *Patient Education and Counseling*, 63, 89–96.

Briasoulis, A., Agarwal, V. & Messerli, F.H. (2012) Alcohol consumption and the risk of hypertension in men and women: a systematic review and meta-analysis. *The Journal of Clinical Hypertension*, 14, 792–798.

Clarke, R., Shipley, M., Lewington, S., Youngman, L., Collins, R., Marmot, M. et al. (1999) Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *American Journal of Epidemiology*, 150, 341–353.

Griswold, M., Fullman, N., Hawley, C.N., Arian, N., Zimsen, S.R.M., Tymeson, H.D. et al. (2018) Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the global burden of disease study 2016. *The Lancet*, 392, 1015–1035.

IARC Working Group. (2012) *IARC monographs on the evaluation of carcinogenic risks to humans. Human Papillomaviruses: 1995*. Lyon: International Agency for Research on Cancer.

IARC Working Group on the Evaluation of Cacrinogenic Risks to Humans. (2012) Personal habits and indoor combustions. Volume 100 E. a review of human carcinogens. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, 100, 1–538.

Imtiaz, S., Shield, K.D., Roerecke, M., Samokhvalov, A.V., Lönnroth, K. & Rehm, J. (2017) Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease. *European Respiratory Journal*, 50, 1700216.

Knott, C., Bell, S. & Britton, A. (2015) Alcohol consumption and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of more than 1.9 million individuals from 38 observational studies. *Diabetes Care*, 38, 1804–1812.

Koellinger, P.D. & De Vlaming, R. (2019) *Mendelian randomization: the challenge of unobserved environmental confounds*, Vol. 48. Oxford: Oxford University Press, pp. 665–671.

Larsson, S.C., Burgess, S., Mason, A.M. & Michaëlsson, K. (2020) Alcohol consumption and cardiovascular disease: a mendelian randomization study. *Circulation: Genomic and Precision Medicine*, 13, e002814.

Larsson, S.C., Drca, N. & Wolk, A. (2014) Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. *Journal of the American College of Cardiology*, 64, 281–289.

Larsson, S.C., Wallin, A., Wolk, A. & Markus, H.S. (2016) Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis. *BMC Medicine*, 14, 1–11.

Liu, F., Liu, Y., Sun, X., Yin, Z., Li, H., Deng, K. et al. (2020) Race-and sex-specific association between alcohol consumption and hypertension in 22 cohort studies: a systematic review and meta-analysis. *Nutrition, Metabolism, and Cardiovascular Diseases*, 30, 1249–1259.

Lönnroth, K., Williams, B.G., Stadlin, S., Jaramillo, E. & Dye, C. (2008) Alcohol use as a risk factor for tuberculosis–a systematic review. *BMC Public Health*, 8, 1–12.

Moher, D., Liberatie, T.J. & Altman, D.G. (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of Internal Medicine*, 151, 264–269.

Paradis, C., Butt, P., Shield, K., Poole, N., Wells, S., Naimi, T. et al. (2023) *Canada's guidance on alcohol and health: final report*, Ottawa, Canada.

Rehm, J., Ashley, M.J., Room, R., Single, E., Bondy, S., Ferrence, R. et al. (1996) On the emerging paradigm of drinking patterns and their social and health consequences. *Addiction*, 91, 1615–1621.

Rehm, J., Gmel, G.E.S., Gmel, G., Hasan, O.S., Imtiaz, S., Popova, S. et al. (2017) The relationship between different dimensions of alcohol use and the burden of disease — an update. *Addiction*, 112, 968–1001.

Rehm, J., Irving, H., Ye, Y., Kerr, W.C., Bond, J. & Greenfield, T.K. (2008) Are lifetime abstainers the best control Group in Alcohol Epidemiology? On the stability and validity of reported lifetime abstention. *American Journal of Epidemiology*, 168, 866–871.

Rehm, J., Monteiro, M., Room, R., Gmel, G., Jernigan, D., Frick, U. et al. (2001) Steps towards constructing a global comparative risk analysis for alcohol consumption: determining indicators and empirical weights for patterns of drinking, deciding about theoretical minimum, and dealing with different consequences. *European Addiction Research*, 7, 138–147.

Rehm, J., Shield, K., Gmel, G., Rehm, M. & Frick, U. (2013) Modeling the impact of alcohol dependence on mortality burden and the effect of available treatment interventions in the European Union. *European Neuropsychopharmacology*, 23, 89–97.

Rehm, J., Taylor, B., Mohapatra, S., Irving, H., Baliunas, D., Patra, J. et al. (2010) Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis. *Drug and Alcohol Review*, 29, 437–445.

Roerecke, M., Vafaei, A., Hasan, O.S.M., Chrystoja, B.R., Cruz, M., Lee, R. et al. (2019) Alcohol consumption and risk of liver cirrhosis: a systematic review and meta-analysis. *The American Journal of Gastroenterology*, 114, 1574–1586.

Rovira, P., Kilian, C., Neufeld, M., Rumgay, H., Soerjomataram, I., Ferreira-Borges, C. et al. (2021) Fewer cancer cases in 4 countries of the WHO European region in 2018 through increased alcohol excise taxation: a modelling study. *European Addiction Research*, 27, 189–197.

Samokhvalov, A., Irving, H. & Rehm, J. (2010) Alcohol consumption as a risk factor for pneumonia: a systematic review and meta-analysis. *Epidemiology and Infection*, 138, 1789–1795.

Samokhvalov, A.V., Irving, H., Mohapatra, S. & Rehm, J. (2010) Alcohol consumption, unprovoked seizures, and epilepsy: a systematic review and meta-analysis. *Epilepsia*, 51, 1177–1184.

Samokhvalov, A.V., Rehm, J. & Roerecke, M. (2015) Alcohol consumption as a risk factor for acute and chronic pancreatitis: a systematic review and a series of meta-analyses. *eBioMedicine*, 2, 1996–2002.

Sarich, P., Canfell, K., Banks, E., Paige, E., Egger, S., Joshy, G. et al. (2019) A prospective study of health conditions related to alcohol consumption cessation among 97,852 drinkers aged 45 and over in Australia. *Alcoholism: Clinical and Experimental Research*, 43, 710–721.

Scheideler, J.K. & Klein, W.M. (2018) Awareness of the link between alcohol consumption and cancer across the world: a review. *Cancer Epidemiology, Biomarkers & Prevention*, 27, 429–437.

Shield, K., Manthey, J., Rylett, M., Probst, C., Wettlaufer, A., Parry, C.D. et al. (2020) National, regional, and global burdens of disease from 2000 to 2016 attributable to alcohol use: a comparative risk assessment study. *The Lancet Public Health*, 5, e51–e61.

Stockwell, T., Zhao, J., Sherk, A., Rehm, J., Shield, K. & Naimi, T. (2018) Underestimation of alcohol consumption in cohort studies and implications for alcohol's contribution to the global burden of disease. *Addiction*, 113, 2245–2249.

Sun, Q., Xie, W., Wang, Y., Chong, F., Song, M., Li, T. et al. (2020) Alcohol consumption by beverage type and risk of breast cancer: a dose-response meta-analysis of prospective cohort studies. *Alcohol and Alcoholism*, 55, 246–253.

van de Luitgaarden, I.A., van Oort, S., Bouman, E.J., Schoonmade, L.J., Schrieks, I.C., Grobbee, D.E. et al. (2021) Alcohol consumption in relation to cardiovascular diseases and mortality: a systematic review of Mendelian randomization studies. *European Journal of Epidemiology*, 37, 655–669.

Vieira, A., Abar, L., Chan, D., Vingeliene, S., Polemiti, E., Stevens, C. et al. (2017) Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR continuous update project. *Annals of Oncology*, 28, 1788–1802.

World Cancer Research Fund/American Institute for Cancer Research. (2018) *Continous update porject expert report 2018. Diet, nutirition, physical activity and bladder cancer*, London, United Kingdom.

World Health Organization. (2018) *Global status report on alcohol and health 2018*. Geneva: World Health Organization.

Zhao, J., Stockwell, T., Roemer, A., Naimi, T. & Chikritzhs, T. (2017) Alcohol consumption and mortality from coronary heart disease: an updated meta-analysis of cohort studies. *Journal of Studies on Alcohol and Drugs*, 78, 375–386.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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